Pathology

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Introduction

The urinary tract from the renal pelvis to the proximal portion of the urethra is lined by a multilayered epithelial lining called *urothelium* (formerly referred to as transitional epithelium). The thickness of the urothelium varies depending on the extent of bladder distention and can therefore range from 4 to 7 cells thick. A number of conditions can alter the thickness and the shape of the urothelium such as inflammatory and reactive conditions and may make the histologic evaluation of bladder tissue more challenging.

Approximately 98% of malignant tumors arising in the urinary bladder are of epithelial (urothelial) origin, of which the overwhelming majority, approximately 90%, is "usual" urothelial carcinoma (formerly referred to as transitional cell carcinoma). Most urothelial carcinomas (UCs) at initial diagnosis are papillary and superficial and in approximately 70% of cases, multiple recurrences following local resection without tumor progression will develop. Pathologic features that have been reported associated with recurrence and progression include the depth of invasion, if any at presentation, multifocality, a history of prior urothelial tumors, tumor size, and grade [1–3].

Flat Urothelial Carcinoma In Situ (CIS)

CIS represents high-grade neoplasia of the bladder that often shows characteristic features such as markedly enlarged nuclei (often >4X the size of a lymphocyte), hyperchromasia, disorganization, loss of nuclear polarity, loss of cohesion, and frequent mitotic activity, that may be atypical and extends to the upper portion of the urothelium. Loss of cellular cohesion contributes to the higher rate of detecting these high-grade lesions on urine cytologic examination compared to other papillary neoplasms. CIS is often relatively straightforward to diagnose, although a number of morphologic variants may be challenging due to their rarity [4].

Papillary Neoplasms

Papillary (exophytic) neoplasms of the bladder, based on their cellularity and degree of atypia, may be either benign (urothelial papilloma) or malignant (papillary urothelial neoplasms of low-malignant potential - PUNLMP, low-grade

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papillary urothelial carcinoma - LGPUC, and high-grade papillary urothelial carcinoma - HGPUC) [5]. Generally, the highest grade component of the papillary lesion is assigned to the neoplasm with the exception that if the high-grade component is minimal (<5%), an overall low-grade can be assigned with a note referring to the presence of a focal high-grade morphology.

Urothelial Papilloma

Urothelial papilloma is a rare, benign condition typically occurring as a small, isolated growth seen primarily (but not exclusively) in younger patients. Morphologically, it is a discrete, exophytic papillary growth with a central fibrovascular core lined by urothelium of normal thickness and cytology with prominent umbrella cells [5, 6]. Inverted urothelial papillomas are similarly rare and benign neoplasms, differing only in that the epithelial cords are endophytic and consequently more closely packed. Both exophytic and inverted papillomas generally follow a benign course and have recently been reported to harbor activating RAS pathway alterations (primarily activating *KRAS* and *HRAS* mutations) and lack the more common genomic features of urothelial carcinoma [7].

Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

PUNLMP is a papillary urothelial neoplasm with an orderly papillary proliferation of urothelial cells with minimal architectural abnormalities and minimal nuclear atypia. Generally, the papillae are lined by thickened urothelium [5]. When strictly defined, PUNLMP does not progress to invasive disease but recurrence is common [8, 9].

Low-Grade Papillary Urothelial Carcinoma (LGPUC)

LGPUC is characterized by an overall orderly appearance but have variability in architecture or cytologic features such as variability in nuclear polarity, nuclear size, shape, and chromatin texture. Mitotic figures may be frequently identified but are generally not atypical and are limited to the lower half of the neoplastic urothelium [5]. The majority of these lesions will recur, but progression is not common (ranging from 2.4% to 8%) [8, 9].

High-Grade Papillary Urothelial Carcinoma (HGPUC)

HGPUC is characterized by disorderly appearance due to marked architectural and cytologic abnormalities typically in the form of nuclear pleomorphism, clumped chromatin, increased mitosis, including atypical forms, and apoptosis [5]. They are commonly associated with invasive disease at the time of initial presentation. The adjacent mucosa may show evidence of CIS, and in some cases, prominent cellular discohesion and denudation may be present. Tumor recurrence occurs in the majority of cases and disease progression may occur in up to a third of cases [10, 11].

Invasive Urothelial Carcinoma

The histopathological features of invasive UC can be variable, except when a specific variant histology is present (see more details about variant histology later in the chapter). Most invasive UC show cohesive irregular nests or solid sheets of cells with moderate to abundant cytoplasm. The nuclei are generally large hyperchromatic and pleomorphic commonly associated with irregular nuclear contours and occasionally prominent nucleoli. Mitotic figures are generally readily identifiable. Changes in underlying stroma (of the lamina propria and beyond) can aid in assessing the presence of invasion. Such changes include retraction, desmoplastic reaction, fibrosis, or inflammation. Once invasion is established, assessing the depth and extent of invasion becomes very important. A very important finding in this regard is the presence of invasion into the detrusor muscle of the bladder (muscularis propria) which would in general

determine if the patient should be offered conservative/localized or more radical surgical treatment. The terminology applied in this setting, such as "muscle invasion" without further qualification may be misleading as it does not distinguish between invasions of the muscularis mucosae (a component of the lamina propria) or the muscularis propria. Also, the term "superficial bladder cancer" is not precise and does not reflect a uniform disease state as it refers to biologically different lesions in noninvasive flat (in situ) or papillary (low or high grade) urothelial carcinoma and carcinoma with lamina propria invasion. Therefore, invasion into the muscularis propria should be reserved to when tumor infiltrates thick and organized smooth muscle bundles, which should be distinguished from the generally thin, loose, wispy, and sometimes branching muscle fibers of the muscularis mucosae.

There are useful morphologic criteria that can be applied to determine invasion of lamina propria invasion, which include the presence of: (1) urothelial nests, clusters, or single cells within the lamina propria, (2) prominent retraction artifact, (3) abundant eosinophilic cytoplasm of the infiltrating tumor, and (4) the presence of desmoplastic or inflammatory stromal response to the tumor.

When tumors invade the lamina propria (pT1), it is recommended to provide details about the extent of invasive disease. A number of methods have been studied and attempts to subclassify pT1 tumors based on their depth of invasion have been successful only in some cases and provided predictive or prognostic value for disease progression. This includes measuring the depth or width of the invasive disease, or whether invasion of the muscularis mucosae is present [12–14].

Lymphovascular invasion (LVI) is an important histological finding that should be reported when present. It is defined by the presence of tumor within endothelium-lined spaces. Numerous studies have documented the clinical importance of LVI as an important prognostic marker of upstaging, lymph node involvement, recurrence, and decreased overall survival, underscoring the importance of identifying and reporting such finding [15–18].

Pathologic Features of Invasive Urothelial Carcinomas (Including Divergent Differentiation)

The microscopic features of invasive UC are variable and nonspecific, consisting of cohesive nests of cells with moderate to abundant cytoplasm and large hyperchromatic nuclei, nuclear pleomorphism, irregular nuclear contours, and occasionally prominent nucleoli. Urothelial carcinomas, however, may show divergent differentiation (Table 4.1), particularly high-grade tumors, can be seen in approximately one-third of cystectomy specimens, but less frequently in transurethral resection specimens (approximately 7%). Although divergent differentiation/variant histology is commonly associated with locally advance disease, it can be identified in a subset of lamina propria-invasive tumors which may impact treatment selection and require a more radical surgical approach [19]. It is recommended to report variant histology anytime it is identified regardless of specimen type (biopsy, TUR, cystectomy) or tumor stage (NMIBC or MIBC) [20] [20].

The most frequently encountered variant histology is invasive UC with divergent differentiation, most commonly in the form of *squamous* and *glandular differentiation.* **Squamous differentiation (SqD)** is the most common variant histology identified in UC occurring in up to 40% of cases [21, 22]. *Glandular differentiation* is less common ranging from 8% to 18% [21, 23–25] and morphologically includes areas that

Table 4.1 WHO classification of tumors of the urothelial tract

Invasive urothelial tumors
Infiltrating urothelial carcinoma (with divergent differentiation)
Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid/signet ring cell/diffuse
Sarcomatoid
Giant cell
Poorly differentiated
Lipid-rich
Clear-cell

Adopted with modification from reference [38]

resemble adenocarcinomas of other organs such as enteric/colonic, mucinous, or a variety of mixed types.

Nested (including large nested), small tubular, and microcystic variants have been grouped under the heading of deceptively bland carcinomas due to their appearance and low-grade features, which can sometimes be difficult to distinguish from benign entities especially when examining superficial biopsy samples where frank invasion may not be easy to establish. It is debatable whether to grade these variants knowing that they tend to present at an advanced stage despite their deceptively bland histopathologic features. These tumors generally consist of well-demarcated medium-sized to large nests closely resembling von Brunn nests but they typically infiltrate the *lamina propria* or deeper within the bladder wall [26–29]. Mitoses are generally rare, and the nuclei show minimal or no atypia particularly in the superficial component of the tumor, but may display more atypia in the deeper and more invasive part of the tumor.

Lymphoepithelioma-like carcinoma is another variant that is sometimes difficult to recognize due to the presence of a dense immune cell infiltrate surrounding and infiltrating nests of, or single, tumor cells. It is important to recognize this variant as it may be mistaken for lymphoma and when present in pure form (i.e., not associated with classic urothelial carcinoma), may follow a less-aggressive clinical course [30, 31].

Micropapillary UC (MPUC) is a rare variant whose diagnosis requires the application of strict morphologic criteria. The tumor is characterized by the presence of small and tight tumor clusters lacking true fibrovascular cores and located within clear "lacunar" spaces. This arrangement is likely due to reverse cellular orientation or polarization and lack of cohesion between the tumor and the adjacent stroma [21, 32, 33]. These tumors have strong propensity for lymphovascular invasion [34]. Despite the increasing recognition of MPUC, there is generally lack of good interobserver agreement, particularly when strict diagnostic criteria are not applied [35]. This has significant clinical implication particularly that some clinicians advise early cystectomy for patients with MPUC even in the absence of invasion into the muscularis propria [36, 37].

Plasmacytoid UC is a rare and aggressive variant that exhibits a diffuse and infiltrating pattern of discohesive, individual, or small clusters of cells, generally with minimal stromal reaction. Tumor cells contain eccentrically located nuclei resembling plasma cells and in the vast majority of cases, tumor cells contain intracytoplasmic vacuoles that give the appearance of signet ring cells [39–41]. Of all the variants of UC, PUC is most likely to be encountered in its pure form, but can occasionally be seen in association with usual UC or other variants [38]. Clinically, PUC is characterized by advanced stage at presentation, high mortality rate, high propensity for relapse, and frequent peritoneal carcinomatosis despite sometimes the apparent initial response to chemotherapy [39–43]. Recent analysis by next-generation sequencing identified the presence of *CDH1* truncating mutations, and less frequently CDH1 promoter hypermethylation, as the defining molecular feature of PUC [39]. Truncating somatic *CDH1* mutations were identified in 84% of PUC and were specific to this histologic variant.

The sarcomatoid variant of UC, formerly known as carcinosarcoma, is rare and generally presents at advanced stage. Despite morphological similarities with sarcomas, molecular analyses have shown a common clonal origin for the carcinomatous and sarcomatous components, suggesting that these spindle cell areas strictly derive from the underlying epithelial malignancy. Giant cell, undifferentiated, clear cell, and lipid-rich variants are exceedingly rare and have poor outcome [38]. Tumors with pure non-urothelial features include squamous cell carcinoma and adenocarcinoma, in which no urothelial component (invasive of in-situ) should be recognized. Primary small cell carcinoma of the bladder is an uncommon neoplasm and resembles small cell carcinoma of any other organ. Neuroendocrine immunohistochemical markers, such as synaptophysin and chromogranin, may aid in the diagnosis if needed. These tumors seem to correspond to the neuronal tumors described recently in the molecular

classification and display frequently loss of wild-type *TP53* and *RB* [44, 45].

En Bloc Resection

The role of transurethral resection of the bladder tumors (TURBT) is to remove the visible tumor (therapeutic) and provide tissue to establish diagnosis and stage (diagnostic). It is crucial for diagnostic histopathologic interpretation that there be minimal to no artefacts. One of the major criticisms of TURBT is that when cutting the tumor, a dissemination of the tumor material is possible. Instead of resecting with an electrical wire-loop, the en bloc resection (EBR) has been suggested. This technique allows to resect the entire tumor including the detrusor muscle, limits tumor scattering, and displays no cautery artefacts. EBR is supposed to improve the resection quality, lowering perioperative complication rates, and decreasing recurrence rates and might even lower the frequency of second resections [46]. This technique is especially useful in case of smaller tumors <1 cm, as it has been suggested by the NMIBC panel of the EAU [47]. Several recent studies demonstrated that EBR is a safe technique associated with high rates of recurrence-free survival after 2 years (85%) [48]. In many of the more recent publications, detrusor muscle was found in 100% of the specimens, which allows for correct staging [49]. Nevertheless, ERB cannot be performed for every bladder cancer. Not all patients are suitable for ERB, as some might harbor big tumors (>3 cm), tumors in locations that are difficult to reach or resect (anterior wall, bladder neck, etc.), or tumors which have an endophytic and infiltrating growth [46, 50].

Upper Urinary Tract Biopsies

Confirming the diagnosis of an upper tract tumor can be readily achieved by ureteroscopic biopsy of the ureter or renal pelvis and can be complemented by urine cytology from upper tract in select cases [51]. Contrary to the bladder, ureteroscopic biopsy can be more difficult to obtain, and the material may be sparse, superficial, and with crush or thermal artefact. Although interpretation of the small amounts of tissue may be challenging to pathologists, evaluation of ureteroscopic biopsies can provide accurate assessment of grade and stage in the majority of cases, especially by combining biopsy and cytology material [51, 52]. As biopsy techniques continue to evolve, the quality and quantity of biopsy material obtained ureteroscopically continue to improve as a result, as has been shown in a number of recent studies comparing standard versus newer biopsy forceps and basket devices [53, 54]. The challenge that remains, however, is how representative these small ureteroscopic biopsies are of the entire upper tract tumor especially when the tumor is large and may be heterogeneous. An alternative to ureteroscopic biopsy may be a CT-guided percutaneous approach to sampling upper tract tumors, which has been shown to be safe and provided high diagnostic yield and concordance [55].

Pathology Report

Several items need to be mentioned in a pathology report. The International Collaboration on Cancer Reporting (ICCR) produces common, internationally validated, and evidence-based pathology datasets for cancer reporting with the aim to encourage uniform pathology reporting standard across the world and utilize these reports as a guide to improve cancer patient outcomes and management worldwide [20]. Not only does it ensures that the same histological elements are reported, it also allows for more accurate comparison of different studies conducted in different institutions or countries. The American Urological Association (AUA) and Society of Urologic Oncology (SUO) published guidelines that provide risk stratification, and clinical framework for the management of nonmuscle-invasive and muscle-invasive urothelial bladder cancer [56, 57]. Similar guidelines are also provided by the European Association of Urology (EAU) [58, 59]. However, for standardized reports to provide meaningful information, clear and reproducible

histological criteria defining different elements should be strictly followed. The World Health Organization (WHO) classification provides detailed description of different entities and histological elements and is regarded as a very useful guide [22]. Elements to be included in pathology report can be required or recommended. Required elements are those which are prognostically important and on which clinical management is based. These elements are mandatory reporting items that should be included in every pathology report. In comparison, recommended elements are clinically important and reporting them is considered to be good practice but are not yet validated or regularly used in patient management.

These guidelines generally agree on including the following elements in pathology reports: Clinical information, specimen site, additional specimens submitted, operative procedure, histological tumor type, the presence and extent of variant histology, presence of noninvasive carcinoma, associated epithelial lesions, histological grade, extent of invasion, the presence of muscularis propria (in TURBT specimens), tumor focality, substaging T1 disease (when possible) and lymphovascular invasion. In cystectomy specimens, additional elements may be included such as response to neoadjuvant therapy, margin status, lymph node status, and pathologic stage.

References

1. Kassouf W, et al. Follow-up in non-muscle-invasive bladder cancer-International Bladder Cancer Network recommendations. Urol Oncol. 2016;34(10):460–8.
2. Sylvester RJ, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49(3):466–5; discussion 475–7.
3. van Rhijn BW, et al. Recurrence and progression of disease in non-muscle-invasive bladder cancer: from epidemiology to treatment strategy. Eur Urol. 2009;56(3):430–42.
4. McKenney JK, et al. Morphologic expressions of urothelial carcinoma in situ: a detailed evaluation of its histologic patterns with emphasis on carcinoma in situ with microinvasion. Am J Surg Pathol. 2001;25(3):356–62.
5. Epstein JI, et al. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. Am J Surg Pathol. 1998;22(12):1435–48.
6. McKenney JK, Amin MB, Young RH. Urothelial (transitional cell) papilloma of the urinary bladder: a clinicopathologic study of 26 cases. Mod Pathol. 2003;16(7):623–9.
7. Isharwal S, et al. Genomic landscape of inverted urothelial papilloma and urothelial papilloma of the bladder. J Pathol. 2019;248(3):260–5.
8. Holmang S, et al. Recurrence and progression in low-grade papillary urothelial tumors. J Urol. 1999;162(3 Pt 1):702–7.
9. Herr HW, Donat SM, Reuter VE. Management of low-grade papillary bladder tumors. J Urol. 2007;178(4 Pt 1):1201–5; discussion 1205.
10. Holmang S, et al. Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. J Urol. 2001;165(4):1124–8; discussion 1128–30.
11. Miyamoto H, et al. Non-invasive papillary urothelial neoplasms: the 2004 WHO/ISUP classification system. Pathol Int. 2010;60(1):1–8.
12. Leivo MZ, et al. Analysis of T1 bladder cancer on biopsy and transurethral resection specimens: comparison and ranking of T1 quantification approaches to predict progression to muscularis propria invasion. Am J Surg Pathol. 2018;42(1):e1–e10.
13. Roupret M, et al. Prognostic interest in discriminating muscularis mucosa invasion (T1a vs T1b) in nonmuscle-invasive bladder carcinoma: French national multicenter study with central pathology review. J Urol. 2013;189(6):2069–76.
14. Brimo F, et al. Prognostic factors in T1 bladder urothelial carcinoma: the value of recording millimetric depth of invasion, diameter of invasive carcinoma, and muscularis mucosa invasion. Hum Pathol. 2013;44(1):95–102.
15. Lotan Y, et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. J Clin Oncol. 2005;23(27):6533–9.
16. Quek ML, et al. Prognostic significance of lymphovascular invasion of bladder cancer treated with radical cystectomy. J Urol. 2005;174(1):103–6.
17. Resnick MJ, et al. Longitudinal evaluation of the concordance and prognostic value of lymphovascular invasion in transurethral resection and radical cystectomy specimens. BJU Int. 2011;107(1):46–52.
18. Kim HS, et al. Presence of lymphovascular invasion in urothelial bladder cancer specimens after transurethral resections correlates with risk of upstaging and survival: a systematic review and meta-analysis. Urol Oncol. 2014;32(8):1191–9.

19. Porten SP, Willis D, Kamat AM. Variant histology: role in management and prognosis of nonmuscle-invasive bladder cancer. Curr Opin Urol. 2014;24(5):517–23.
20. International Collaboration on Cancer Reporting - Urinary / Male Genital. International Collaboration on Cancer Reporting [cited 2019]. Available from http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital.
21. Amin MB. Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. Mod Pathol. 2009;22(Suppl 2):S96–S118.
22. Moch H, et al. WHO classification of tumours of the urinary system and male genital organs. In: Bosman FT, et al., editors. World Health Organization classification of tumours. 4th ed. Lyon: International Agency for Research on Cancer; 2016.
23. Wasco MJ, et al. Urothelial carcinoma with divergent histologic differentiation (mixed histologic features) predicts the presence of locally advanced bladder cancer when detected at transurethral resection. Urology. 2007;70(1):69–74.
24. Linder BJ, et al. The impact of histological reclassification during pathology re-review--evidence of a Will Rogers effect in bladder cancer? J Urol. 2013;190(5):1692–6.
25. Shah RB, et al. Variant (divergent) histologic differentiation in urothelial carcinoma is under-recognized in community practice: impact of mandatory central pathology review at a large referral hospital. Urol Oncol. 2013;31(8):1650–5.
26. Beltran AL, et al. Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder. Virchows Arch. 2014;465(2):199–205.
27. Cox R, Epstein JI. Large nested variant of urothelial carcinoma: 23 cases mimicking von Brunn nests and inverted growth pattern of noninvasive papillary urothelial carcinoma. Am J Surg Pathol. 2011;35(9):1337–42.
28. Comperat E, et al. Large nested variant of urothelial carcinoma: a clinicopathological study of 36 cases. Histopathology. 2017;71(5):703–10.
29. Mai KT, et al. Nested and microcystic variants of urothelial carcinoma displaying immunohistochemical features of basal-like urothelial cells: an immunohistochemical and histopathogenetic study. Pathol Int. 2014;64(8):375–81.
30. Tamas EF, et al. Lymphoepithelioma-like carcinoma of the urinary tract: a clinicopathological study of 30 pure and mixed cases. Mod Pathol. 2007;20(8):828–34.
31. Williamson SR, et al. Lymphoepithelioma-like carcinoma of the urinary bladder: clinicopathologic, immunohistochemical, and molecular features. Am J Surg Pathol. 2011;35(4):474–83.
32. Nassar H, et al. Pathogenesis of invasive micropapillary carcinoma: role of MUC1 glycoprotein. Mod Pathol. 2004;17(9):1045–50.
33. Luna-More S, et al. Invasive micropapillary carcinoma of the breast. A new special type of invasive mammary carcinoma. Pathol Res Pract. 1994;190(7):668–74.
34. Johansson SL, Borghede G, Holmang S. Micropapillary bladder carcinoma: a clinicopathological study of 20 cases. J Urol. 1999;161(6):1798–802.
35. Sangoi AR, et al. Interobserver reproducibility in the diagnosis of invasive micropapillary carcinoma of the urinary tract among urologic pathologists. Am J Surg Pathol. 2010;34(9):1367–76.
36. Kamat AM, et al. The case for early cystectomy in the treatment of nonmuscle-invasive micropapillary bladder carcinoma. J Urol. 2006;175(3 Pt 1):881–5.
37. Willis DL, et al. Micropapillary bladder cancer: current treatment patterns and review of the literature. Urol Oncol. 2014;32(6):826–32.
38. Humphrey PA, et al. The 2016 WHO classification of tumours of the urinary system and male genital organs-part B: prostate and bladder tumours. Eur Urol. 2016;70(1):106–19.
39. Al-Ahmadie HA, et al. Frequent somatic CDH1 loss-of-function mutations in plasmacytoid variant bladder cancer. Nat Genet. 2016;48(4):356–8.
40. Keck B, et al. The plasmacytoid carcinoma of the bladder--rare variant of aggressive urothelial carcinoma. Int J Cancer. 2011;129(2):346–54.
41. Nigwekar P, et al. Plasmacytoid urothelial carcinoma: detailed analysis of morphology with clinicopathologic correlation in 17 cases. Am J Surg Pathol. 2009;33(3):417–24.
42. Dayyani F, et al. Plasmacytoid urothelial carcinoma, a chemosensitive cancer with poor prognosis, and peritoneal carcinomatosis. J Urol. 2013;189(5):1656–61.
43. Kaimakliotis HZ, et al. Plasmacytoid bladder cancer: variant histology with aggressive behavior and a new mode of invasion along fascial planes. Urology. 2014;83(5):1112–6.
44. Robertson AG, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell. 2017;171(3):540–56. e25.
45. Chang MT, et al. Small cell carcinomas of the bladder and lung are characterized by a convergent but distinct pathogenesis. Clin Cancer Res. 2017;
46. Kramer MW, et al. Current evidence for transurethral en bloc resection of non-muscle-invasive bladder cancer. Minim Invasive Ther Allied Technol. 2014;23(4):206–13.
47. Babjuk M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol. 2017;71(3):447–61.
48. Hurle R, et al. "En Bloc" resection of nonmuscle-invasive bladder cancer: a prospective single-center study. Urology. 2016;90:126–30.
49. Liang H, et al. En bloc resection improves the identification of muscularis mucosae in non-muscle- invasive bladder cancer. World J Urol. 2019;37(12):2677–82.
50. Bach T, et al. Technical solutions to improve the management of non-muscle-invasive transitional cell carcinoma: summary of a European Association of Urology Section for Uro-Technology (ESUT) and Section for Uro-Oncology (ESOU) expert meet-

ing and current and future perspectives. BJU Int. 2015;115(1):14–23.
51. Williams SK, et al. Correlation of upper-tract cytology, retrograde pyelography, ureteroscopic appearance, and ureteroscopic biopsy with histologic examination of upper-tract transitional cell carcinoma. J Endourol. 2008;22(1):71–6.
52. Keeley FX, et al. Diagnostic accuracy of ureteroscopic biopsy in upper tract transitional cell carcinoma. J Urol. 1997;157(1):33–7.
53. Lama DJ, et al. Multi-institutional valuation of upper urinary tract biopsy using backloaded cup biopsy forceps, a nitinol basket, and standard cup biopsy forceps. Urology. 2018;117:89–94.
54. Kleinmann N, et al. Ureteroscopic biopsy of upper tract urothelial carcinoma: comparison of basket and forceps. J Endourol. 2013;27(12):1450–4.
55. Hendrickson AC, et al. Percutaneous ureteral biopsy: safety and diagnostic yield. Abdom Radiol (NY). 2019;44(1):333–6.
56. Diagnosis and treatment of non-muscle-invasive bladder cancer: AUA/SUO joint guideline (2016). 2016 [cited 2020]. Available from https://www.auanet.org/guidelines/bladder-cancer-non-muscle-invasive-guideline.
57. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline (2017). 2017 [cited 2020]. Available from https://www.auanet.org/guidelines/bladder-cancer-non-metastatic-muscle-invasive-guideline.
58. Babjuk M, et al. European Association of Urology guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) – 2019 update. Eur Urol. 2019;76(5):639–57.
59. Alfred Witjes J, et al. Updated 2016 EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol. 2017;71(3):462–75.