AJCC Staging of Bladder Cancers

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Introduction

Bladder cancer is one of the major causes of cancer morbidity and mortality in men, accounting for an estimated 80,470 new cases and 17,670 cancer deaths in the United States in 2019 [1]. Among many prognostic determinants, pathologic stage is the most crucial factor in risk stratification, management, and surveillance follow-up for bladder cancer [2–6]. As with other hollow visceral organs, bladder tumor (T) stage categories are defined by the depth of invasion (extent of wall invasion). However, assigning pT stage category is sometimes problematic due to regional and individual histoanatomic variation. An ideal and uniform staging system would permit accurate reflection of the natural history of cancer, the extent of disease spread, the stratification of prognostic groups and comparison of therapeutic interventions among different hospitals. Staging guidelines from the International Union Against Cancer (UICC) were released in 2016 [7, 8], and on January 1, 2018, utilization of the eighth edition of the AJCC staging manual was implemented [9]. However, the UICC failed to incorporate new data considered in the new eighth edition of AJCC, and there are many differences between the staging recommendations of recent UICC and AJCC staging systems. Thus, this chapter will discuss the current staging recommendations of the AJCC staging manual eighth edition.

Stage pT0 Carcinoma

Stage pT0 carcinoma is assigned when there is no evidence of residual urothelial carcinoma in the cystectomy specimen, according to the eighth AJCC staging system [9]. The incidence of stage pT0 carcinoma is approximately 10% [10–15]. Recently, the incidence of pT0 carcinoma has been increasing due to the use of neoadjuvant chemotherapy [16–18]. The presence of variant histology is associated with a decreased rate of complete pathologic response (ypT0) [19]. The clinical outcome of patients with ypT0 carcinoma is variable. The 5-year recurrence-free, cancer-specific, and overall survival rates were 84%, 88% and 84%, respectively [11]. In one study, the presence of lymphovascular invasion and concomitant carcinoma in situ in the transurethral resection (TUR) specimen were the only significant prognostic factors associated with shorter overall

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survival and recurrence-free survival in patients with ypT0 carcinoma [11]. The incidence of lymph node metastasis of patients with ypT0 carcinoma was 3–7% [12, 14].

Stage pTa Carcinoma

There are two types of noninvasive carcinomas with one pTa and the other with pTis. Stage pTa carcinoma is defined as noninvasive papillary carcinoma that lacks invasion, according to the eighth AJCC staging system [9]. pTa carcinoma should be distinguished from pT1 carcinoma by the absence of lamina propria or submucosal invasion.

Stage pTis Carcinoma

Stage pTis carcinoma is assigned when urothelial carcinoma in situ without stromal invasion is present in the cystectomy specimen, according to the eighth AJCC staging system (Fig. 18.1) [9]. pTis carcinoma is often associated with concurrent invasive urothelial carcinoma, but it can be present alone in about 10% of cystectomy specimens [20].

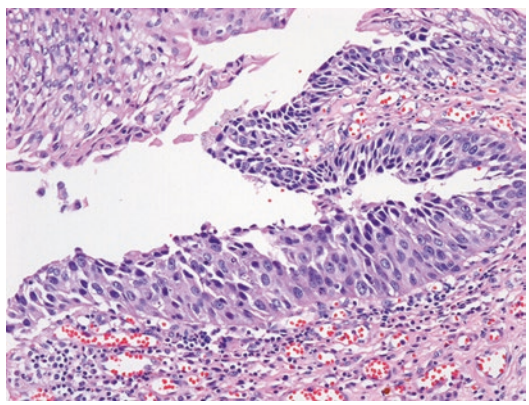


Fig. 18.1 Urothelial carcinoma in situ. Flat proliferation of urothelial cells characterized by loss of polarity, marked nuclear enlargement, irregularity, and hyperchromasia with full-thickness involvement of the urothelium. Mitoses are frequently observed

Stage pT1 Carcinoma

pT1 carcinoma is defined when a tumor invades the lamina propria/submucosa but not the proper muscle layer, according to the eighth AJCC staging system [9].

Topographic Variation of the Lamina Propria (Submucosa, Submucosal Connective Tissue Layer)

The lamina propria/submucosa (LP/SM) is composed predominantly of loose connective tissue stroma with a collection of thin smooth muscle fibers, vascular plexuses, nerves, and occasional adipose tissue between the mucosa and muscularis propria (MP) layer [21]. In the bladder, LP and SM are interchangeably used; however, the proper designation of LP and SM is available when muscularis mucosae (MM) is present: LP is the layer above MM, and SM is the layer below MM. Therefore, the proper term in the bladder is submucosal connective layer over LP or SM. In this chapter the term LP is used. The LP depth is more pronounced at the dome (0.98–3.07 mm), similar at the anterior, posterior, and lateral walls and relatively thinner at the bladder neck and trigone (0.46–1.58 mm) (Fig. 18.2) [21]. The mean tumor depth of pT1 carcinoma is 1.1–1.5 mm (range, 0.1–5 mm) [22, 23].

The MM in the urinary bladder LP layer was first described by Dixon and Gosling [24] in 1983, and Ro et al. later underlined its importance in the pathologic staging of bladder cancer [25]. The MM is usually at about the mid- to upper LP and forms a discernible layer in up to 40% of cystectomy specimens, varying by region but more common in the dome (75%) and less common in the trigone (~10%) [21]. Typically, the MM forms individual or small groups of slender and wavy fascicles or wispy fibers with (a) dispersed/scattered (71%), (b) discontinuous/interrupted (20%), or (c) continuous (3%) muscle layers (Fig. 18.3) [25]. The MM also has a focal to rarely extensive hyperplastic appearance with

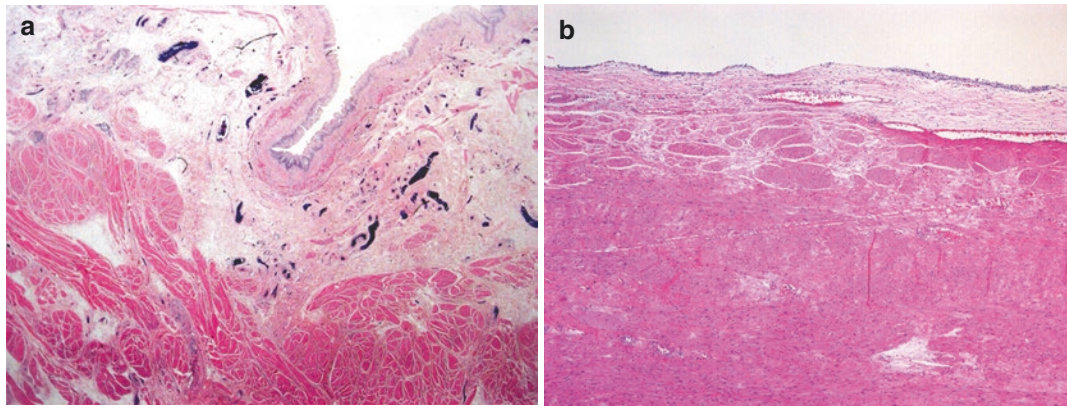


Fig. 18.2 Variable thickness of the lamina propria based on anatomical location. The lamina propria is more prominent in the dome (**a**) than in the trigone (**b**)

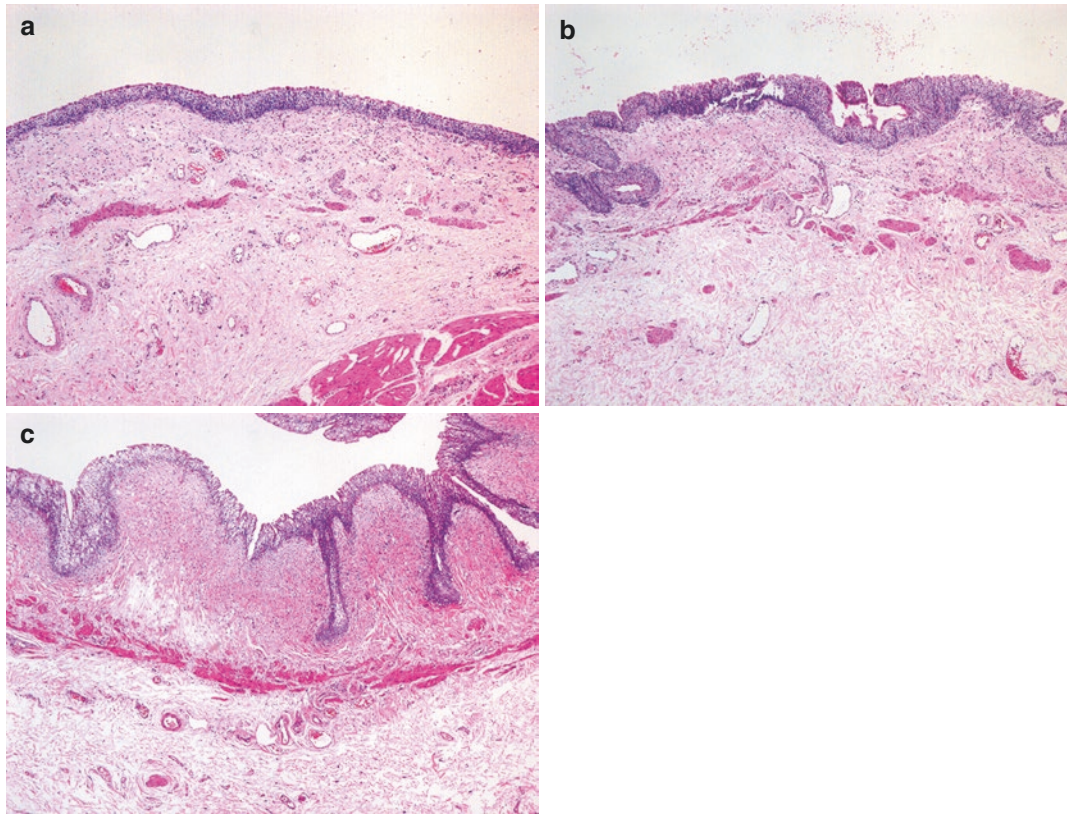
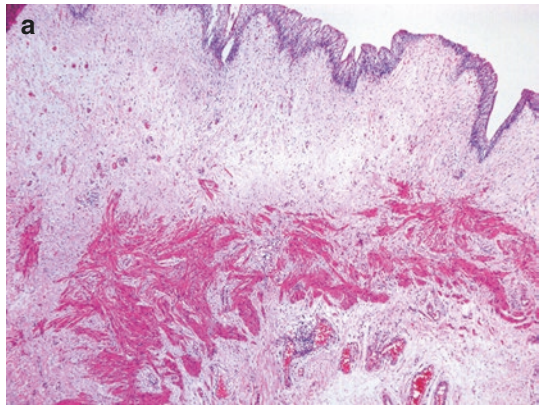


Fig. 18.3 The muscularis mucosae is composed of individual or small groups of slender and wavy fascicles or wispy fibers with variable patterns as follows: (**a**) dispersed/scattered, (**b**) discontinuous/interrupted, (**c**) continuous

two recognizable patterns of aggregates of hyperplastic MM with haphazard outlines and hyperplastic compact MM with parallel muscle fibers and a regular outline arranged singly or in small groups that sometimes mimics the muscularis propria (MP) (Fig. 18.4) [21]. Hyperplastic MM is relatively more common in the dome and less frequent in the trigone [21]. Awareness of



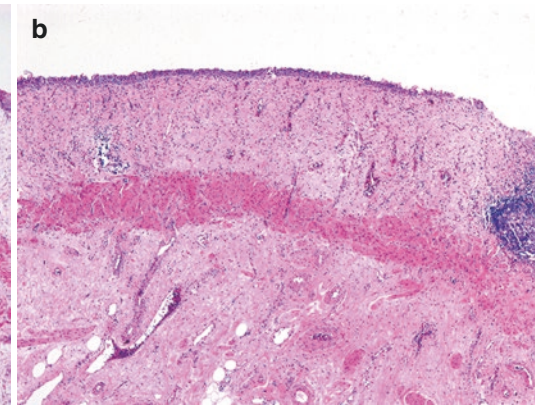


Fig. 18.4 The muscularis mucosae shows a variable hyperplastic appearance ranging from focal to rarely extensive with two discernible patterns: (**a**) haphazardly arranged hyperplastic muscularis mucosae with irregular outlines and (**b**) hyperplastic compact muscularis mucosae with parallel muscle fibers and regular outline arranged singly or in small groups. This pattern of the muscularis mucosae should be distinguished from the muscularis propria, especially in transurethral resection specimens

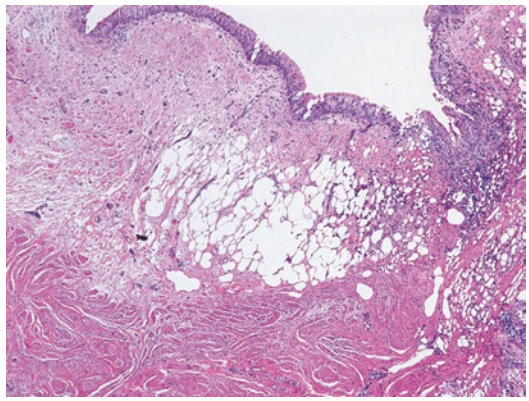


Fig. 18.5 Adipose tissue within the lamina propria. Adipose tissue is seen in the deep aspect of the lamina propria, which faces the superficial border of the muscularis propria. The presence of adipose tissue can be often misinterpreted as perivesical soft tissue in transurethral resection specimens, resulting in unnecessary overtreatment

these occasional hyperplastic MM patterns and distributions of hyperplastic MM is crucial to avoid overstaging of bladder cancer.

Adipose tissue within the LP is seen in about 50% of cystectomy specimens and typically located at the deep aspect near the superficial border of the MP (Fig. 18.5) [21, 26]. It is more often focal (35%), mostly situated in the dome (32%), and rare in the trigone (5%) [21]. Considering the high frequency of adipose tissue within the LP, care should be taken to avoid misinterpretation of pT1 carcinoma as perivesical soft tissue involvement (pT3 carcinoma) in TUR specimens to prevent inappropriate aggressive treatment.

Substaging of pT1 Bladder Carcinoma

A reproducible, easy-to-use, and accurate substaging system is essential to stratify pT1 carcinomas into prognostically distinct subgroups. There are two main approaches: histoanatomic and micrometric substaging. Histoanatomic substaging using the MM and/or vascular plexus as histologic landmarks is the most studied approach for pT1 carcinomas. Both two-tiered and three-tiered systems have been utilized. However, the size and distribution of the MM varies depending on anatomical location. Micrometric substaging of pT1 carcinoma involves measuring the depth of invasion from the mucosal basement membrane using an ocular micrometer with different linear cut-offs. However, the LP depth varies depending on location. The eighth edition of the AJCC staging manual recommends subcategorization of pT1, but no specific methods have been endorsed yet [9], and pT1 substages are not currently recommended to officially implement to use.

Histoanatomical Substaging

This method uses the MM and/or vascular plexus as landmarks to divide the extent of LP invasion [27–30]. The MM is usually at about the mid- to upper LP and disperses or forms a discernable layer as a discontinuous or infrequently near-continuous layer in only about 40% of cystectomy sections [21]. In cases that lack the MM, the vascular plexus has been proposed as a surrogate, because it is typically situated at about the same level of the accompanying MM. However, the location of the vascular plexus sporadically varies from the suburothelial to the deep LP region, being above, below, and/or at the plane of the MM [21]. Therefore, some cases cannot be properly staged using this method because of absent or incomplete MM and variable locations of the vascular plexus either above or below the MM [21].

These problems may cause concern about the feasibility of pT1 substaging. However, many studies have applied histoanatomical staging in pT1 carcinomas in relation to the MM and/or vascular plexus using either the three-tiered [above (T1a), into (T1b), and below (T1c)] or a two-tiered [above and into (T1a) and below (T1b)] approach, and substaging was feasible in 43–100% (median, 93%) of the tumors [22, 23, 27, 29–56].

Micrometric Substaging

Substaging pT1 carcinoma can also be carried out by measuring the depth of invasion using an ocular micrometer, and measurement of the depth of invasion from the mucosal basement membrane in biopsy specimens correlates well with the final pathologic stage at cystectomy [57, 58]. The most studied method uses a 0.5 mm (1 high power field) cut-off to divide pT1 into pT1m (microinvasive) and pT1e (extensive) [28, 56, 59]. In contrast to the histoanatomical method, micrometric pT1 substaging using a 0.5 mm cut-off was feasible in all (100%) tumors studied [29, 34, 35, 55, 56, 59]. Other studies have also proposed different cut-offs to divide pT1, including 1 mm, 1.5 mm, 3 mm, and 6 mm [22, 23, 29, 35]. Several studies have also suggested that measuring the aggregate linear length of invasive carcinoma in TUR fragments is a superior quantification approach for pT1 substaging [60, 61].

Microinvasive Carcinoma

Microinvasive carcinoma was originally defined as tumor extending up to 5 mm from the basement membrane (Fig. 18.6) [62]. Since then, several criteria has been proposed to define microinvasive carcinoma, and the cut-off has been lowered to the proposed 0.5 mm [59]. Alternatively, Lopez-Beltran et al. suggested using 20 infiltrating tumor cells within the LP as the cut-off rather than a linear measurement [63]. The 0.5 mm cut-off is currently proposed in pT1 substaging because it has been shown to be widely attainable and correlates with outcome in the majority of studies [29, 34, 35, 55, 56, 59]. Lawless et al. compared tumors with stalk-only invasion, base-focal invasion, and base-extensive invasion and suggested that patients with base-extensive invasion had worse prognosis [64]. They proposed that the site as well as the extent of the LP invasion matters in patient stratification for risk of progression [64].

Diagnostic Pitfalls

Factors in Superficially or Focally Invasive pT1 Carcinomas

Because pT1 carcinomas often invade the LP as single cells or irregularly shaped small nests, the identification of pT1 carcinoma can be sometimes challenging when problems are encoun-

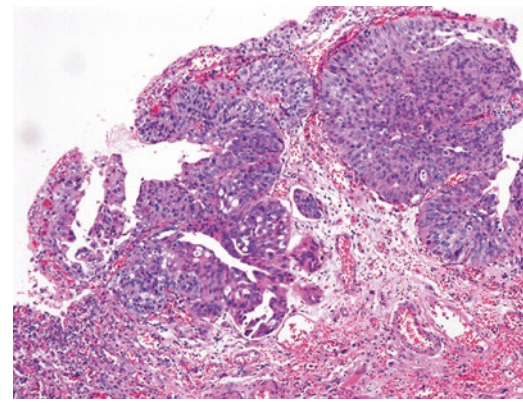


Fig. 18.6 Microinvasive carcinoma. Tumor cells microscopically invade the lamina propria with a depth less than 0.5 mm

tered such as improper tissue embedding (tangential cut or poor orientation), procedural artifacts (thermal injury or cautery artifact), or tumoral responses (obscuring due to inflammation) [65].

Bland Cytology and von Brunn Nests

Some variant histology such as nested variants show deceptively bland cytology, and florid von Brunn nests mimic invasion (Fig. 18.7) [65]. Tumor cells involving von Brunn nests either by pagetoid spread or direct extension from the adjacent tumor can be confusing and especially problematic when the involved von Brunn nests are distorted by inflammation or cautery artifact [66]. True LP invasion can be distinguished from pseudoinvasion of von Brunn nests by identifying the smooth linear contour of the basement membrane (Fig. 18.8).

Helpful Histological Features in Identifying Invasive Carcinoma

Histological features that can be helpful in identification of LP invasion include identifying single cells or irregularly shaped small nests, absence of parallel arrays of thin-walled vessels that often line the basement membrane of noninvasive nests, presence of retraction artifacts, stromal reaction, and paradoxical maturation, where invasive tumor cells obtain abundant eosinophilic cytoplasm [66]. Retraction is a helpful clue, but it sometimes mimics lymphovascular invasion, which can be distinguished from true lymphovascular invasion using immunohistochemical stains (CD34, CD31, and D2–40) [66, 67]. A stromal reaction may be helpful in identifying invasion but is not always present [68]. It may be hypocellular with myxoid background, cellular with spindle-shaped fibroblasts and variable collagenization, pseudosarcomatous, desmoplastic, or inflammatory (Fig. 18.9) [66, 67].

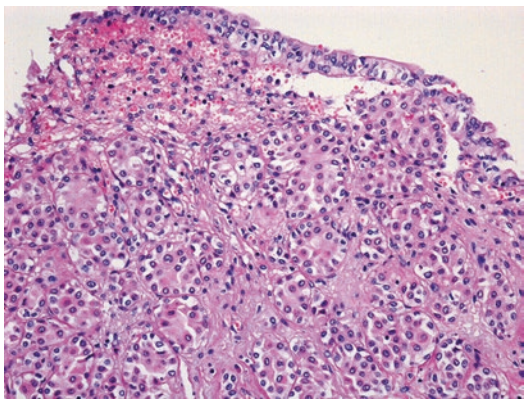


Fig. 18.7 Nested variant urothelial carcinoma. Tumor cells are arranged in tightly packed nests separated by fine collagenous stroma. Tumor cells exhibit deceptively bland cytology that often makes it difficult to distinguish nested variant urothelial carcinoma from florid von Brunn's nests

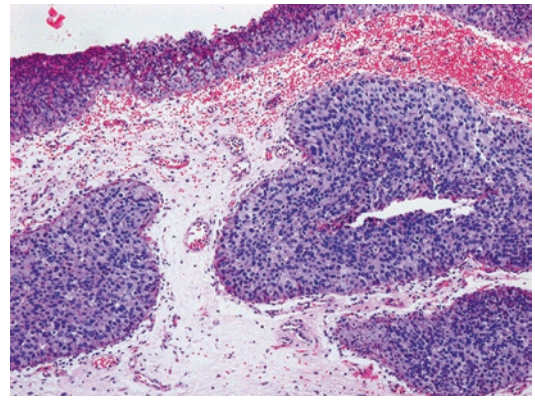


Fig. 18.8 Urothelial carcinoma in situ involving von Brunn's nests, which should not be misinterpreted as invasive carcinoma nests

Early Cystectomy

Proper muscle invasion in TUR specimens is the major indication for more aggressive treatment (radical cystectomy with bilateral pelvic lymphadenectomy, neoadjuvant chemotherapy or chemoradiation). However, early radical cystectomy can be considered when pT1 carcinoma is associated with other high-risk features such as concurrent carcinoma in situ, multiple or large tumor size (>3 cm), and repeated pT1 on re-TUR and variant histologies, particularly for micropapillary carcinoma [3, 5].

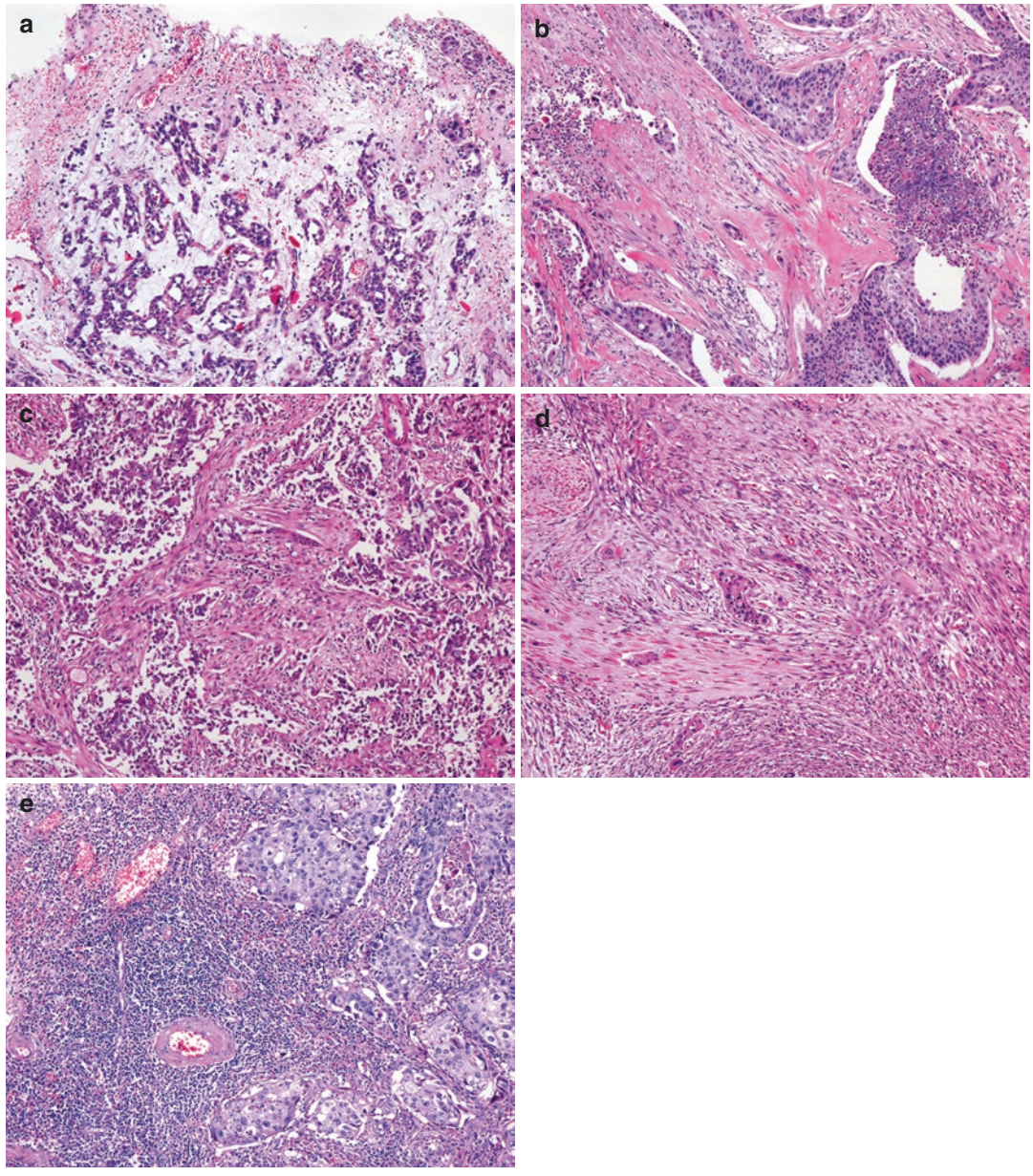


Fig. 18.9 Diverse stromal reaction seen in urothelial carcinomas. (**a**) Tumor cells infiltrate into hypocellular and loose stroma with a myxoid background. (**b**) Tumor cells are surrounded by cellular stroma composed of an admixture of spindle-shaped fibroblasts and variable collagenization. (**c**) Tumor cells are intermingled with fibrous stroma containing atypical spindle cells and lacking overt malignant histological features (i.e., increased mitotic activity, necrosis). (**d**) Tumor cells infiltrate in cords and single cells with abundant fibrous stroma. (**e**) Tumor cells are embedded in a rich inflammatory stroma with variable inflammatory cells, including lymphocytes, plasma cells, neutrophils, and eosinophils

Stage pT2 Carcinoma

Stage pT2 carcinoma is defined as tumor extending into the MP. The urinary bladder MP serves as a key anatomic landmark in the evaluation of depth of invasion and is most often the critical intersection between conservative and aggressive treatment. Diagnosing pT2 carcinomas in TUR specimens is essential for aggressive treatment, including radical cystectomy. Therefore, distinction between the MM and MP invasion is mandatory. The MP layer is composed predominantly of smooth muscle bundles, fibroconnective tissue, adipose tissue, and vessels in between the muscle bundles. A definite pT2 carcinoma is defined by infiltration into MP muscle bundles, but tumors situated in between MP muscle bundles within the MP layer are also typically staged as pT2 carcinoma [6].

Helpful Morphologic Features in Diagnosing pT2 Carcinoma

Hyperplastic MM

The MM is occasionally hyperplastic and could mimic the MP, obscuring pT1/pT2 [21, 28]. Helpful morphologic clues for the MM include thin and slender muscle bundles, superficial location, nonjuxtaposition to adipose tissue, closeness to the surface epithelium, or association with the vascular plexus [28].

LP-Inner MP Boundary and MP-Perivesical Boundary

The inner boundary of the MP can be irregular due to disconnected muscle bundles that vary in size. Therefore, the principle of defining the LP-inner MP boundary (junction of pT1 vs. pT2) is not clear. Traditionally, the outermost extent of the MP was considered the boundary distinguishing the outer MP from perivesical tissue. However, the criteria defining the outer boundary of the MP is unclear due to no clear defined boundary and aggregates of adipose tissue randomly separating MP bundles without a clear demarcation line and is different among expert pathologists. It is reasonable to follow the common approach in defining the outer MP-perivesical tissue boundary [28, 69]. A common criterion in defining the inner and outer boundary of the MP can be used. In a recent study, three general methods were reviewed by expert genitourinary pathologists without consensus, although one method (multiple boundary lines between variable outer bands of the MP) resulted in the highest level of interobserver reproducibility [69].

Staging pT2 Carcinoma in TUR Specimens

Definite pT2 carcinoma can be diagnosed by identifying tumor infiltrating into MP muscle bundles. Therefore, MP presence is considered a surrogate marker for good TUR quality [70–73]. In contrast to cystectomy specimens, the clear line of demarcation of the LP-inner MP boundary cannot be drawn in TUR specimens, where tissue fragmentation is common. Therefore, the diagnosis of pT2 carcinoma in TUR specimens is generally recommended to be restricted to cases where definite muscle invasion is present (Fig. 18.10). However, the MP can be often fractured and separated by carcinomas into small muscle bundles, masquerading pT1 carcinoma invading into the MM. Diagnosis of pT2 carcinoma is preferred when invasive carcinoma nests are surrounded by MP muscle bundles or invasive carcinoma nests are surrounding an MP muscle bundle, even without direct MP muscle invasion (Fig. 18.11) [6]. The diagnosis of pT3 carcinoma in TUR specimens is generally not recommended, because adipose tissue in the MP layer may be mistakenly considered to be perivesical adipose tissue (Fig. 18.12), complicating the distinction between pT2b and pT3a disease.

Substaging of pT2 Bladder Carcinoma

pT2 carcinoma is subdivided into tumor extending into the superficial (i.e., inner half) MP (pT2a) and tumor extending into the deep (i.e., outer half) MP (pT2b). The clinical implication of this substaging is still uncertain [66], although several recent large studies have shown the clinical utility of this approach [74–77]. Using the

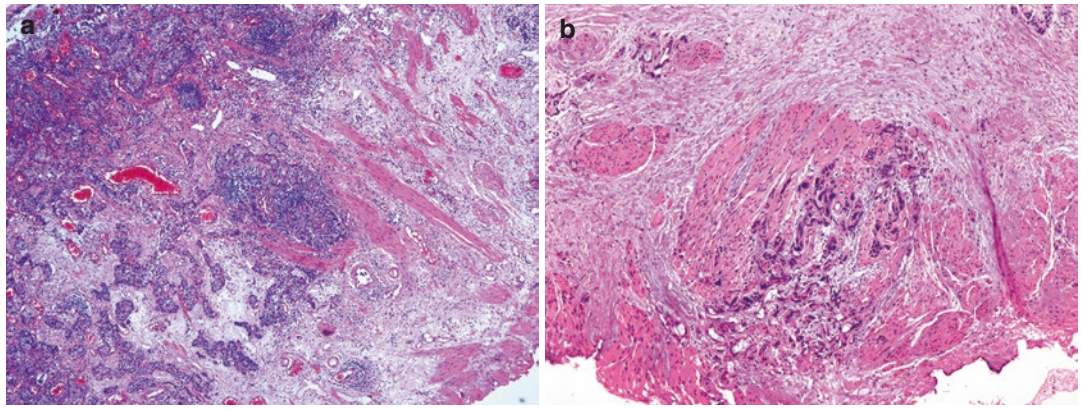


Fig. 18.10 Distinguishing between hypertrophic muscularis mucosae and muscularis propria can be problematic in transurethral resection specimens. (**a**) Tumor cell nests infiltrate into hypertrophic muscularis mucosae composed of thin and slender smooth muscle fibers (pT1). (**b**) Tumor cell nests invade into aggregates of thick muscular bundles (pT2)

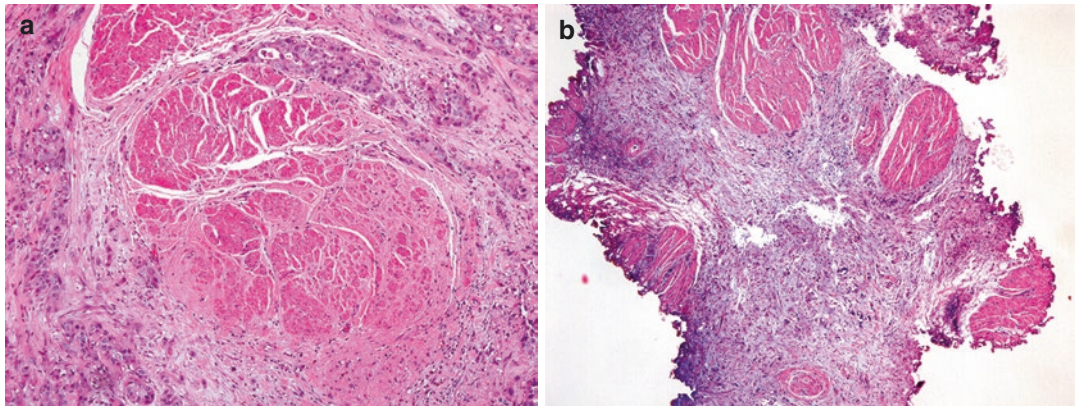


Fig. 18.11 Staging pT2 carcinoma in transurethral resection specimens. The diagnosis of pT2 urothelial carcinoma is favored when tumor cells surround some muscle bundles of the muscularis propria (**a**) or tumor cells are surrounded by muscle bundles of the muscularis propria (**b**) in transurethral resection specimens

middle of the MP as the cut-off seems to be profitable in pT2 substaging [67]. However, this substage is not recommended on TUR specimens.

Stage pT3 Carcinoma

pT3 carcinoma is defined by tumor extending into perivesical soft tissue. The outer boundary of the MP is not well delineated, confounding the distinction between T2b and T3a carcinomas. However, distinguishing pT2b from pT3a disease is critical, because pT3 disease is usually treated with adjuvant chemotherapy [69, 78, 79]. Subclassification of muscle invasive tumors (>pT2) should be made only in cystectomy specimens. It is usually not feasible to document pT3a carcinoma in biopsy or TUR specimens because the outer MP boundary is irregular, with discontinuous MP muscle bundles separated by adipose tissue or fibroconnective tissue [26].

The MP outer boundary is irregular due to discrete muscle bundles that vary in size. Therefore,

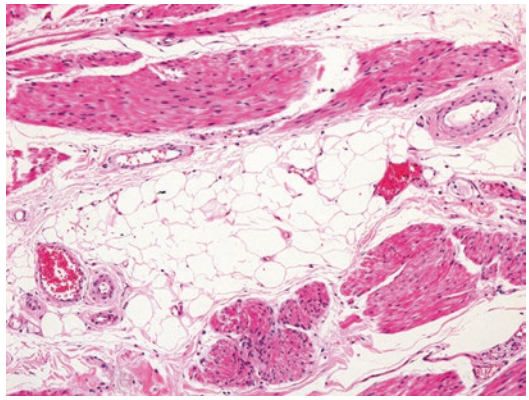


Fig. 18.12 Adipose tissue within the muscularis propria. Adipose tissue is frequently detected between the layers of the muscularis propria

the clear line of demarcation of the outer MP boundary (junction of pT2b vs. pT3a) cannot be delineated, and the criteria of definition vary among expert pathologists. In an interobserver study tasked to assign stage on equivocal cases, three categories for delineating the outer MP boundary were used as follows: (1) drawing a straight horizontal line using the outermost MP bundle edges as reference for the MP-perivesical tissue boundary, (2) drawing multiple discontinuous lines between the outermost MP bundle edges, and (3) making a curved line along every outermost MP muscle bundle edges. The most commonly used approach was by interconnecting the outermost MP bundles edges with multiple straight lines [69]. The presence of lymphovascular invasion alone in perivesical soft tissue should not be considered pT3a, although this is not mentioned in the eighth edition of AJCC TNM staging manual [9, 67].

Substaging of pT3 Bladder Carcinoma

pT3 carcinoma is subdivided further into pT3a (i.e., microscopic invasion of perivesical soft tissue) and pT3b (i.e., macroscopic invasion of perivesical soft tissue). To date, pT3 substaging counts entirely on meticulous gross examination of perivesical soft tissue. Even in a tertiary institution, the presence or absence of macroscopic perivesical soft tissue involvement was not documented in 17% of pT3 cystectomy specimens [80]. Moreover, there is considerable debate about the prognostic significance of pT3 substaging [81–86]. However, it was adopted for use in the AJCC 2010 system [87]. An alternative approach has also been proposed to subdivide pT3 by measuring the depth of invasion into the perivesical soft tissue from the base of the MP (>4.5 mm) [88], but this approach remains to be clarified due to inconsistency in defining the MP base (outer boundary of the MP) [69].

Stage pT4 Carcinoma

pT4 carcinoma is defined as extravesical tumor directly invading adjacent organs or structures and is subcategorized into pT4a (direct invasion into the prostatic stroma, uterus, or vagina) and pT4b (direct invasion into the pelvic or abdominal wall) [9]. Overall, 11.7–19.2% and 1.9–4.4% of patients with radical cystectomy harbor pT4a or pT4b disease, respectively, according to recent studies [89, 90].

Substaging of pT4 Bladder Carcinoma

Prostatic Stromal Invasion

Prostatic stromal invasion by bladder cancer may occur by transmural extravesical, transmural bladder neck, and superficially intraurethral invasion [91–93]. Among these routes, transmural direct invasion of the prostatic stroma through extravesical fat or the bladder neck merits classification as pT4a. However, the third pathway of invasion of the prostate, superficially intraurethral invasion, has been a matter of debate. Cases with superficially intraurethral invasion of the prostatic stroma are not as aggressive as a true pattern of transmural invasion [92, 94–98]. Thus, the prior 2010 AJCC staging manual excluded intraurethral spread from pT4a [87], and Patel et al. validated this revision by showing that cases with subepithelial prostatic stromal invasion had more favorable outcomes compared to transmu-

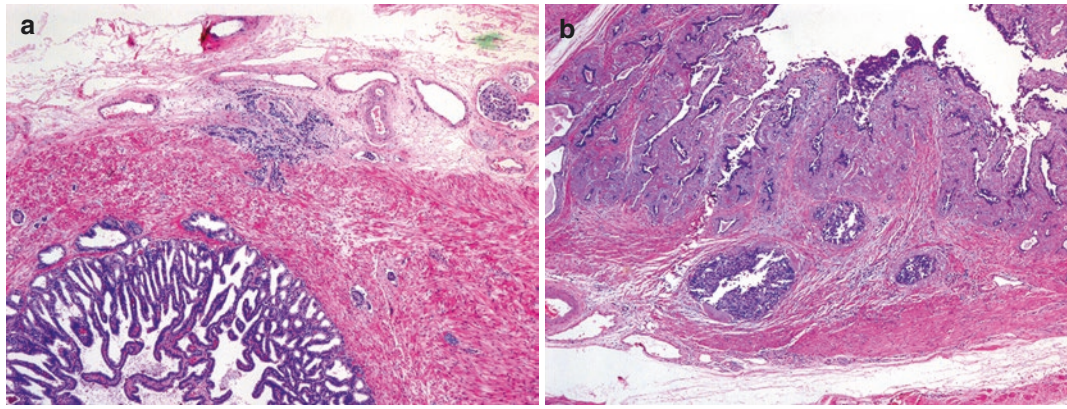


Fig. 18.13 Two distinct patterns of seminal vesicle involvement. (**a**) Direct perivesical tumor extension into the seminal vesicle. (**b**) Intramucosal pagetoid spread of urothelial carcinoma in situ

ral pT4a disease [99]. Because of the ambiguity of defining prostatic stromal invasion in the previous AJCC staging manual [87], the new eighth edition AJCC staging manual clarified that intraurethral spread of urothelial carcinoma with prostatic stromal invasion should be assigned as pT2 according to urethral cancer staging and not bladder cancer staging, and the bladder tumor should be staged separately per bladder cancer staging [9]. Therefore, providing two separate pT stages is advocated. In cases of prostatic TUR specimens, rendering a definite pT stage is not recommended. In the absence of direct prostatic stromal invasion, explanatory comments should be given and the tumor staged at least as pT2 unless otherwise specified.

Seminal Vesicle Invasion

Seminal vesicle invasion may occur via direct bladder transmural perivesical soft tissue or intraepithelial extension from the prostate, and both have similarly poor prognosis (Fig. 18.13) [100]. However, the significance of seminal vesicle invasion through an intraurethral prostatic route is uncertain [101]. Direct seminal vesicle invasion is staged as pT4 according to the current eighth AJCC staging manual, but there is no further subclassification [9]. Studies demonstrate that seminal vesicle invasion has a more unfavorable effect on survival than prostatic stromal invasion alone and argue a prognosis comparable with pT4b tumor [100, 102, 103].

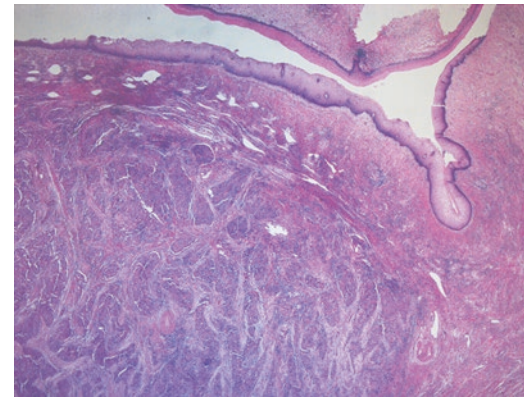


Fig. 18.14 Vaginal invasion of urothelial carcinoma. Tumor cell nests extend into the muscular layer of the vaginal wall

Gynecological Tract Invasion

Direct invasion of the uterus or vagina by bladder cancer is regarded as stage pT4a (Fig. 18.14) [9], and the incidence is relatively rare (3–6% of female cystectomy specimens) compared to prostatic stromal invasion (7–38% of male cystoprostatectomy specimens) [91–97, 104–110]. The involvement of urothelial carcinoma in the female gynecological tract either via pagetoid or metastatic spread would not be considered stage pT4a [9].

Pelvic or Abdominal Wall Invasion

Direct invasion of urinary bladder carcinoma into the pelvic or abdominal wall is assigned as stage

pT4b [9]. Stage pT4b is uncommon due to the limited number of patients with this stage disease, constituting only 1.9–4.4% of all patients with radical cystectomy [89, 90].

Regional Nodal Staging (N Staging)

In the AJCC staging manual eighth edition, regional nodal staging in bladder cancer is determined by the number and location of positive lymph nodes, not by the number and size of positive lymph nodes [9]. In the previous edition, regional lymph nodes included the obturator, iliac (internal and external), sacral (lateral and sacral promontory), and common iliac lymph nodes [87]. In the current AJCC staging manual, perivesical lymph nodes are included as formal regional lymph nodes [9]. Regional nodal staging is classified as follows: (1) lymph nodes cannot be assessed (pNX); no lymph node metastasis (pN0); single regional lymph node metastasis in the true pelvis (pN1); multiple regional lymph node metastasis in the true pelvis (pN2); and metastasis to common iliac lymph nodes (pN3) [9]. Although reporting perinodal extension is not included in the AJCC staging manual eighth edition, it is recommended to report the presence or absence of extranodal extension as well as the total number of lymph nodes examined [9]. However, the minimum number of lymph nodes necessary to determine adequate pN staging has not been clarified yet for bladder cancer.

M Staging

Stage pM1 was previously designated for both non-regional lymph node metastasis and distant non-lymph node metastasis (Fig. 18.15) [87]. However, stage pM1 is now subdivided into non-regional lymph node metastasis (pM1a) and distant non-lymph node metastasis (pM1b) in the AJCC staging manual eighth edition [9] because patients with non-regional lymph node metastasis (pM1a) have a better clinical outcome than patients with distant non-lymph node metastasis (pM1b) [111].

Staging of Bladder Carcinoma Arising in a Diverticulum

The AJCC staging manual eighth edition provides formal recommendations regarding tumors arising in a diverticulum (Fig. 18.16). Most bladder diverticula are acquired and lack an MP layer [112]. Thus, the tumor moves directly from pT1 carcinoma into pT3 carcinoma without invading the MP [112–117]. The AJCC staging manual eighth edition advises skipping the pT2 stage [9].

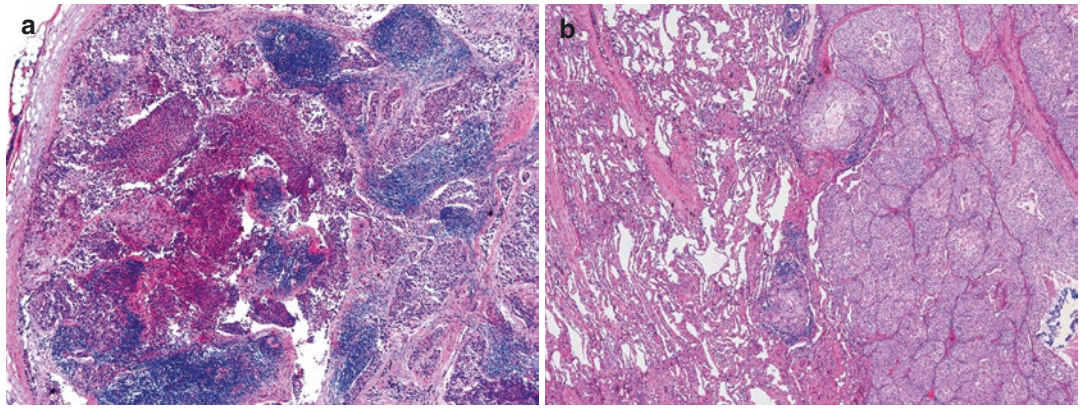


Fig. 18.15 Distant metastasis of urothelial carcinoma. (**a**) Non-regional lymph node metastasis. (**b**) Distant non-lymph node metastasis (lung metastasis)

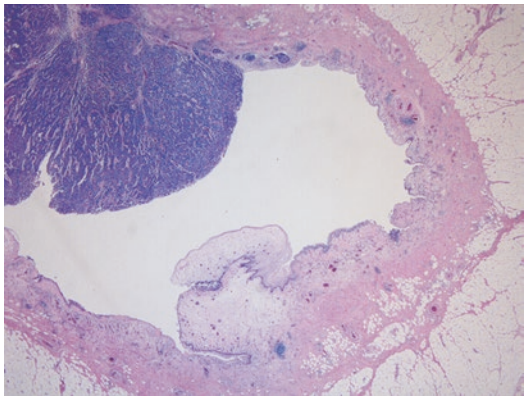


Fig. 18.16 Urothelial carcinoma arising from a diverticulum of the urinary bladder. The diverticulum, a mucosal outpouching without a muscle layer, is in direct contact with perivesical soft tissue in the deep portion. Infiltrating urothelial carcinoma that developed in a diverticulum invades into subepithelial connective tissue. Squamous metaplasia is noted in the non-tumoral epithelium within the diverticulum

In conclusion, this chapter provides a comprehensive review with regard to bladder cancer staging including a reliable substaging method of each stage based on histoanatomic characteristics. In addition, confounding factors or diagnostic pitfalls in the staging of bladder cancer were discussed. The accurate staging is crucial to determine the prognosis and the prompt treatment option of bladder cancer patients. This chapter will offer a standardized guideline for bladder cancer staging to reduce disagreement in staging among pathologists and to define the optimal treatment for bladder cancer patients.

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