Modern Pathology (2009) 22, S70–S95
 0893-3952/09 $32.00
www.modernpathology.org

Staging and reporting of urothelial carcinoma of the urinary bladder

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Significant progress has been made in the standardization of bladder neoplasm classification and reporting. Accurate staging using the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM system is essential for patient management, and has been reinforced by clinical evidence in recent years. It is now recognized that 'superficial' bladder carcinomas are a heterogenous group of tumors with diverse biological and clinical manifestations. The term 'superficial,' therefore, is no longer used for bladder tumor nomenclature. Recognition of diagnostic pitfalls associated with lamina propria invasion is critical for the evaluation of bladder tumor specimens. Neither the 1973 nor the 2004 WHO grading system appears to be useful for predicting the clinical outcome of invasive urothelial carcinoma. This review will discuss recent progress and controversial issues on the staging and substaging of bladder carcinomas. Essential elements for handling and reporting of bladder tumor specimens will also be discussed.
Modern Pathology (2009) **22,** S70–S95; doi:10.1038/modpathol.2009.1

Keywords: urinary bladder; TNM staging; pT1 substaging; neoplasia classification; specimen handling and reporting

Bladder cancer is a significant cause of cancer morbidity and mortality, accounting for an estimated 68 810 new cases and 14 100 cancer deaths in the United States in 2008.[1] Pathological stage is the most important determinant of prognosis and treatment for bladder cancer.[2–6] An ideal staging system should accurately reflect the natural history of cancer at this site, describe the total cancer burden, assess the extent of spread at the time of diagnosis, and stratify patients into prognostic groups for treatment planning. Adoption of a uniform staging system permits comparison of therapeutic interventions among different institutions.

Historically, the term 'superficial bladder cancer' has been used to describe tumors that have not invaded into muscularis propria. This designation includes noninvasive papillary urothelial carcinoma (pTa), carcinoma *in situ* (CIS) (pTis), and tumor invading into the lamina propria (pT1). It is now recommended that the term 'superficial' be entirely eliminated from bladder tumor nomenclature.[7,8] The 2002 revision of the American Joint Committee on Cancer/International Union Against Cancer/Union Internationale Contre le Cancer (AJCC/UICC) TNM system is the most widely used staging system at this time (Table 1).[9] This review will focus on recent progress and controversial issues related to bladder cancer staging. Practical diagnostic issues, such as lymphovascular invasion, surgical margins, specimen handling, and cancer reporting, will also be discussed.

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Received 8 January 2009; accepted 9 January 2009

Stage pT0 carcinoma

Stage pT0 tumor is a condition in which there is no evidence of residual carcinoma in the cystectomy specimen after an initial cancer diagnosis in the biopsy or transurethral resection (TUR) specimens. The incidence of stage pT0 bladder carcinoma is approximately 10%.[5,10–14] Unlike stage pT0 cancer of the prostate (so called 'vanishing cancer phenomenon'), the clinical outcome among patients with stage pT0 bladder cancer is variable. In the largest series of pT0 carcinomas (120 patients), the 5-year

Table 1 The 2002 TNM Staging System for Bladder Carcinoma

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumor invades subepithelial connective tissue (lamina propria)
T2	Tumor invades musclularis propria bladder wall
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, and abdominal wall
T4a	Tumor invades prostate, uterus, or vagina
T4b	Tumor invades pelvic or abdominal wall
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in a single lymph node, 2 cm or less in greatest dimension
N2	Metastases in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

recurrence-free, cancer-specific, and overall survivals were 84, 88, and 84%, respectively.[11] Multivariate analysis showed that lymphovascular invasion and carcinoma-*in situ* in the TUR specimens were independent predictors of adverse clinical outcome.[11] The 5-year overall survival for patients with lymphovascular invasion was 70%, compared with 89% for those patients without lymphovascular invasion.[11] The incidence of lymph node metastasis among pT0 patients is 3 to 7%.[10,13]

Stage pTa carcinoma

pTa carcinoma is defined by the 2002 TNM (tumor, lymph node, and hematogenous metastasis) staging system as noninvasive papillary carcinoma (Table 1). It should be distinguished from pT1 cancer by the absence of lamina propria invasion (see discussion below). Histological grading is considered one of the most important prognostic factors for pTa bladder tumors.[15]

Stage pT1 carcinoma

pT1 carcinoma is defined by invasion into lamina propria, but not into muscularis propria (Figure 1).

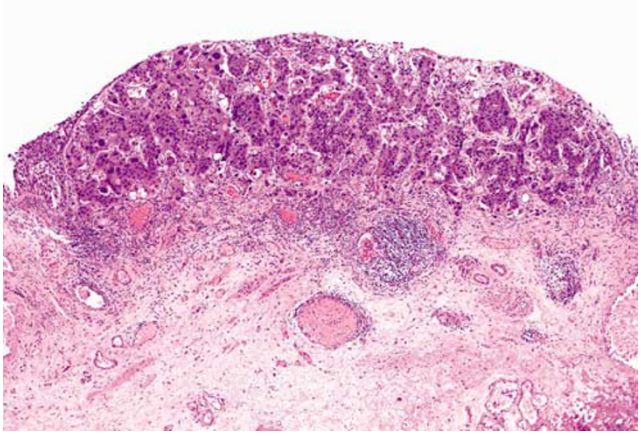

Figure 1 pT1 urothelial carcinoma invading into the lamina propria. Wisps of muscularis mucosae, thin-walled vessels, and inflammatory infiltrate are present at the deepest penetration of the tumor.

Recognition of lamina propria invasion is challenging. Pathologists should be aware of various diagnostic pitfalls, including tangential section, poor specimen orientation, obscuring inflammation, thermal injury, deceptively bland cytology in some variants of urothelial carcinoma and pseudoinvasive nests of benign proliferative urothelial cells.[16] pT1 carcinomas often invade the underlying stroma as single cells or irregularly shaped nests of tumor cells (Figure 2). Sometimes tentacular or finger-like extensions arise from the base of the papillary tumor (Figure 3). Retraction artifact provides an important clue for the diagnosis of early invasion (Figure 4). The invading nests appear cytologically different from cells at the base of the noninvasive component. Invasive tumor cells often have more abundant cytoplasm and less nuclear pleomorphism than *in situ* carcinoma. In some cases, particularly in microinvasive carcinoma, the invasive tumor cells acquire abundant eosinophilic cytoplasm. At low to medium power magnification, these microinvasive cancer cells appear to be more differentiated than the overlying noninvasive tumor cells, a feature known as paradoxical differentiation (Figure 5).

Tumor cells involving von Brunn's nests, either by pagetoid spread or by direct extension from adjacent tumor, can be confused with lamina propria invasion. This is especially problematic when von Brunn's nests are prominent, or when they have been distorted by inflammation or cautery artifact. When urothelial carcinoma involves von Brunn's nests, the basement membrane preserves a regular contour (Figure 6). If this smooth delineation is absent, there may be true lamina propria invasion. A parallel array of thin-walled vessels often line the basement membrane of noninvasive nests; whereas these vessels are usually absent next to invasive nests. Thermal injury or cautery artefact can produce severely distorted morphology, rendering accurate diagnosis of invasion difficult. Immuno-

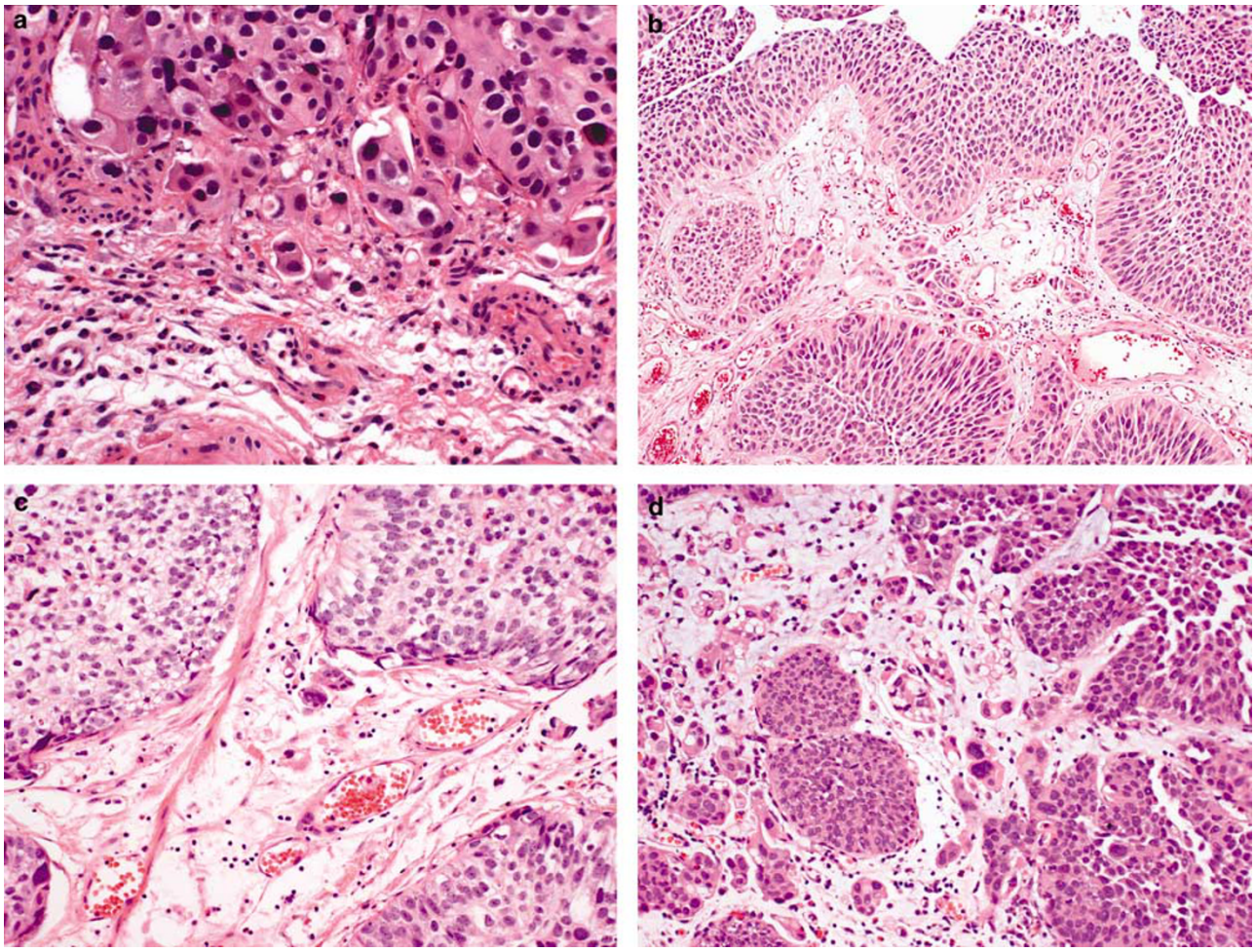

Figure 2 pT1 urothelial carcinoma with different invasive patterns. (**a**) The smooth contour of basement membrane is disrupted in infiltrating tumor cells. (**b** and **c**) Irregular small clusters of tumor cells invading the stroma. (**d**) Variably sized nests with single cells and irregular clusters of invading cells.

histochemistry with pan-cytokeratin may be helpful in these cases by highlighting invasive tumor cells.[17] Papillary urothelial carcinoma may be tangentially sectioned in multiple planes, resulting in isolated nests of noninvasive tumor cells surrounded by connective tissue. Smooth, round, and regular contours favor tangential sectioning, whereas irregular, jagged nests containing haphazardly arranged cells favor stromal invasion.

Assessment of different stromal growth patterns may provide important diagnostic clues to minimally invasive carcinoma.[17,18] A stromal response to invading carcinoma, however, is not uniformly present with urothelial carcinoma. Thus, the diagnosis of invasion may rely predominantly on characteristics of the invading epithelium. When present, the stromal reaction of lamina propria to invasive tumor may be myxoid, fibrous, pseudosarcomatous, desmoplastic or inflammatory (Figure 7). Urothelial carcinoma may show brisk inflammation at the epithelial–stromal interface. This cellularity and distortion obscure isolated cells or small nests of invasive tumor. Immmunostaining with anti-cytokeratin antibodies can facilitate the diagnosis of invasion in cases with prominent inflammation obscuring the interface between epithelium and stroma (Figure 8a and b). Microinvasive carcinoma may have only subtle signs of stromal response. In some cases, retraction artifact around superficially invasive individual tumor cells may mimic vascular invasion. This finding is often focal and may itself be an early sign of lamina propria invasion. Retraction artifact may be distinguished from true vascular invasion using CD31 and CD34 immunohistochemistry. Identification of vascular invasion has recently been considered an important prognostic feature.[19]

Invasive urothelial carcinoma may have a cellular stroma with spindled fibroblasts and variable collagenization, or it may have a hypocellular stroma with myxoid background. Rarely, the tumor induces an exuberant proliferation of fibroblasts, which display alarming cellular atypia similar to giant cell cystitis. This feature, although a helpful clue to invasion, should not be mistaken for the spindle cell

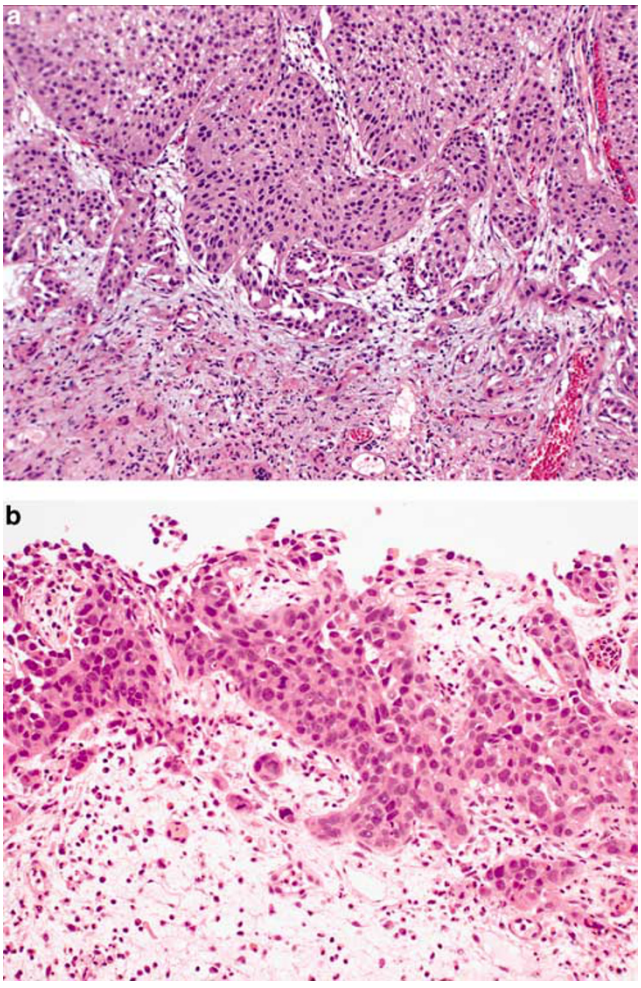

Figure 3 pT1 urothelial carcinoma. (**a**) Invading fronts of the neoplasm show tentacular or finger-like extensions with myxoid reaction of the stroma. (**b**) Smooth contours of basement membrane are lost and irregular clusters or single cells are present in the lamina propria.

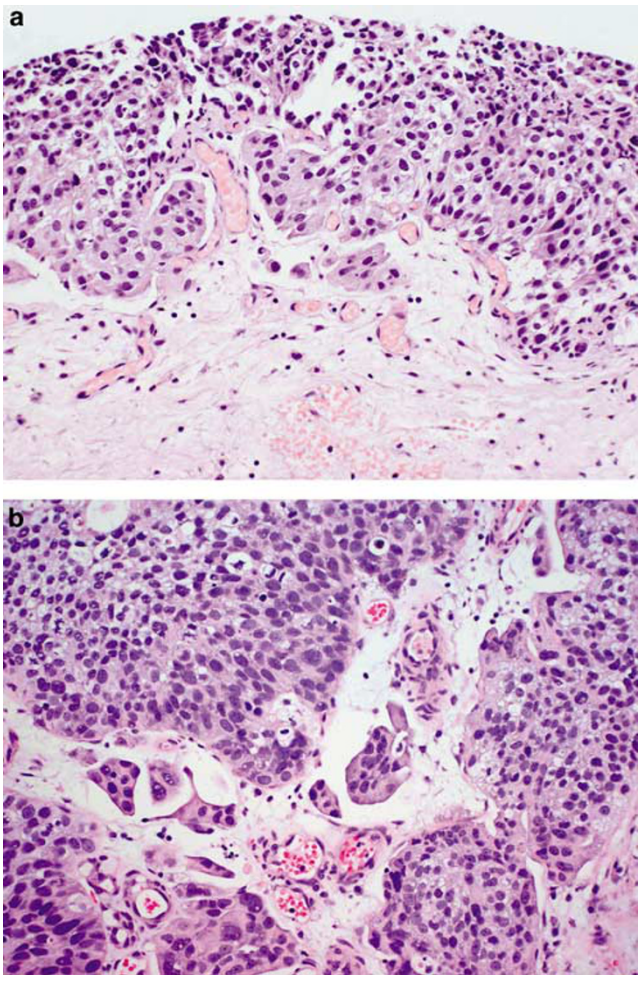

Figure 4 pT1 urothelial carcinoma with retraction artifact. (**a**) Retraction artifact around invasive clusters is a useful feature for diagnosing stromal invasion. (**b**) The appearance of clusters with retraction artifact should not be mistaken for lymphovascular invasion.

component of sarcomatoid urothelial carcinoma. Immunostains for cytokeratin are helpful in difficult cases. Pathologists, however, should be aware of the caveat that aberrant keratin expression can also be seen in myofibroblastic cells (Figure 8c and d).[20] Attention to spindle cell morphology and normal cytology of myofibroblastic cells will help to avoid misinterpretation of staining results. The proliferating stroma associated with invasion is usually nonexpansile, being limited to areas around the neoplasm and composed of cells whose nuclei have a degenerate or smudged appearance.

Interobserver variability in diagnosing lamina propria invasion is substantial. In one study, 35% of carcinomas initially diagnosed as stage pT1 were downstaged to pTa, and 3% were upstaged as pT2-4 carcinomas.[21] In another study, there was complete interobserver agreement on pT1 stage among reviewers in 80% of cases, which rose to 88% after a second review.[22] Of the 63 tumors originally diagnosed as stage pT1, the consensus diagnosis by experienced genitourinary pathologists resulted in downstaging of 35 (56%) to pTa and upstaging of 8 (13%) to pT2–pT3 tumors.[22] Progression was more common in the 20 consensus confirmed stage pT1 cases (25%) than in the 55 pTa and pT1 cases (20%).[22] Tumors that were downstaged to pTa showed less frequent progression than stage pT1 tumors (17 versus 25%), confirmed by review. It was concluded that prognostic variation resulting from observer variability in staging and grading is considerable with significant implications for patient management.[22] The high rate of congruence between trained observers also implies that interobserver variation can be reduced by agreement on criteria for invasion.

Understaging of T1 bladder carcinoma is of greatest concern.[23–26] It is recommended that the second TUR be performed within 2–4 weeks of the initial resection and diagnosis of T1 bladder carcinoma.[27–29]

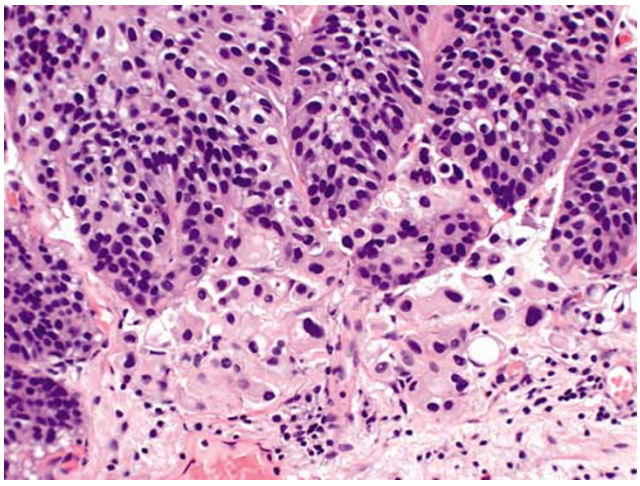

Figure 5 Paradoxical differentiation in pT1 urothelial carcinoma. The invasive tumor cells often acquire abundant eosinophilic cytoplasm and appear to be more differentiated than overlying noninvasive tumor cells.

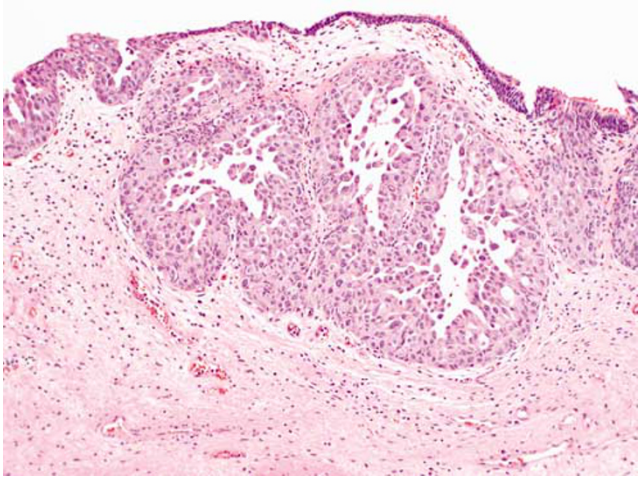

Figure 6 Urothelial carcinoma may involve von Brunn's nests. The smooth regular contour of basement membrane, however, is preserved. Definite stromal invasion is not seen.

Substaging of pT1 Bladder Carcinoma

Recurrence and progression rates for pT1 tumors are highly variable.[16,23–25,27,30] This is probably due to intrinsic difficulty in assessing the presence and extent of invasion. An accurate, easy-to-use, reproducible substaging system is needed to stratify pT1 patients into prognostically distinct groups. Elderly patients with bladder cancer frequently have comorbid conditions that make conservative management preferable for early invasive urothelial carcinomas. Several studies have explored the utility of evaluating the spatial relationship of invasive tumor to the muscularis mucosae for subclassification of pT1 urothelial carcinomas.[16,31–37] Muscularis mucosae consists of thin and wavy fascicles of smooth muscle frequently associated with large, thin-walled blood vessels (Figure 9). Muscularis mucosae can be identified in 15–83% of biopsy specimens;[16,24,25,31–36,38–42] however, 6% of radical cystectomy specimens do not have discernable muscularis mucosae.[41] Thus, the large associated vessels have been used as a surrogate marker for muscularis mucosae in all published studies of substaging based on muscularis mucosae invasion. For example, Angulo *et al*[31] were able to identify muscularis mucosae fascicles in 39% of their cases, and used the blood vessel landmark in another 26%. Thus, in 35% of their cases, substaging could not T1 be performed because neither muscularis mucosae nor large vessels were found. Platz *et al*[35] identified muscularis mucosae in only 33% of their cases and found no significant prognostic value in substaging pT1 cancer using this criterion. With median follow-up of 71 months, Kondylis *et al*[43] found no difference in recurrence and progression rates between patients with T1a and T1b cancer using muscularis mucosae invasion for substaging. Cancer progression rates were 78 and 71% for T1a and T1b cancer, respectively. Furthermore, significant topographical variation of muscularis mucosae in different regions of the bladder has recently been documented.[44] These problems raise concerns about the practicality and validity of substaging pT1 carcinomas based on muscularis mucosae invasion, and currently this practice is not universally advocated.[45] Nevertheless, when feasible, pathologists should provide assessment for the extent of lamina propria invasion. Substaging of pT1 urothelial carcinoma arising from the trigone region is even more problematic (Figure 10).

Substaging of pT1 carcinoma based on ocular micrometer measurement of tumor invasion is an alternate strategy to provide information for the management of pT1 cancer (Figure 11).[24,25,38] Using an ocular micrometer to measure the depth of invasion from the mucosal basement membrane, investigators have found a significant correlation between depth of invasion in the biopsy specimens and final pathological stage at cystectomy.[38,46] A 1.5 mm depth of invasion predicted advanced-stage bladder carcinoma at cystectomy with a sensitivity of 81%, a specificity of 83%, and positive and negative predictive values of 95 and 56%, respectively. Ninety-five percent of patients with the depth of invasion $\geq$1.5 mm at TUR specimens have advanced stage ($\geq$pT2) bladder carcinoma at cystectomy.[38] Applying this criterion to 83 consecutive patients diagnosed with pT1 bladder cancer, the investigators found a 5-year progression-free survival of 67% with tumor invasion greater than 1.5 mm.[25] When the depth of invasion was less than 1.5 mm, the 5-year survival rate was 93%.[25] More recently, Andius *et al*[19] identified solid tumor growth pattern and vascular invasion as adverse prognostic indicators for patients with T1 bladder cancer.

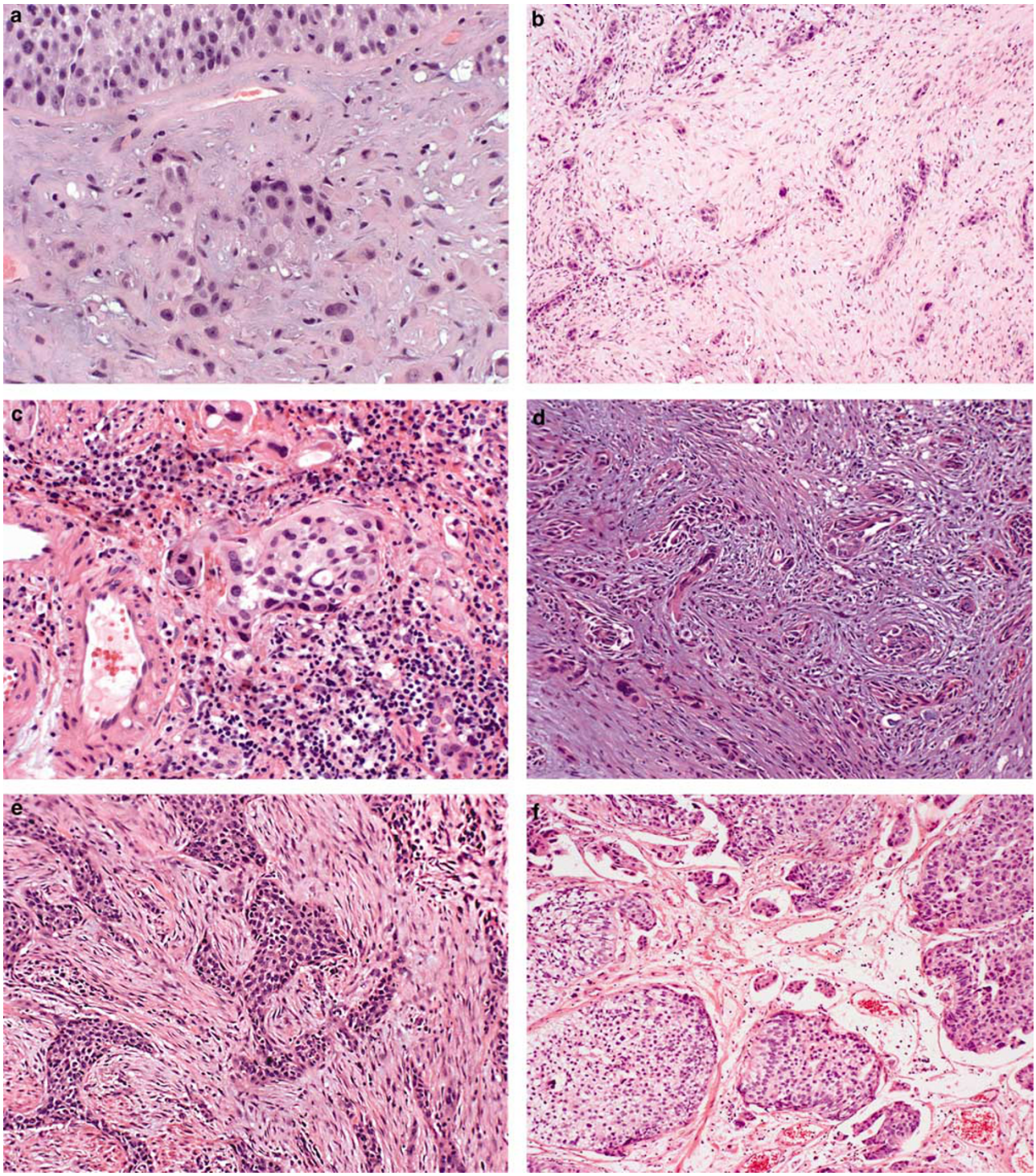

Figure 7 Stromal responses in invasive urothelial carcinoma. The stromal reaction to invasive tumor may be (**a**) myxoid; (**b**) fibrous; (**c**) inflammatory; (**d**) pseudosarcomatous; or (**e**) desmoplastic. (**f**) Retraction artifact is also common adjacent to early invasive carcinoma, an important diagnostic clue for stromal invasion.

Microinvasive Carcinoma

George Farrow, beginning in 1976, defined microinvasive carcinoma as a tumor invading into the lamina propria to a depth up to 5 mm from the basement membrane[47–49] (Figure 12). Farrow reviewed cystectomy specimens with urothelial CIS that were totally embedded and identified cases with extensive CIS involving at least 25% of the bladder. Of these 70 cases, there were 24 (34%), which contained microinvasion. Of the patients with microinvasion, 5.8% had lymph node metas-

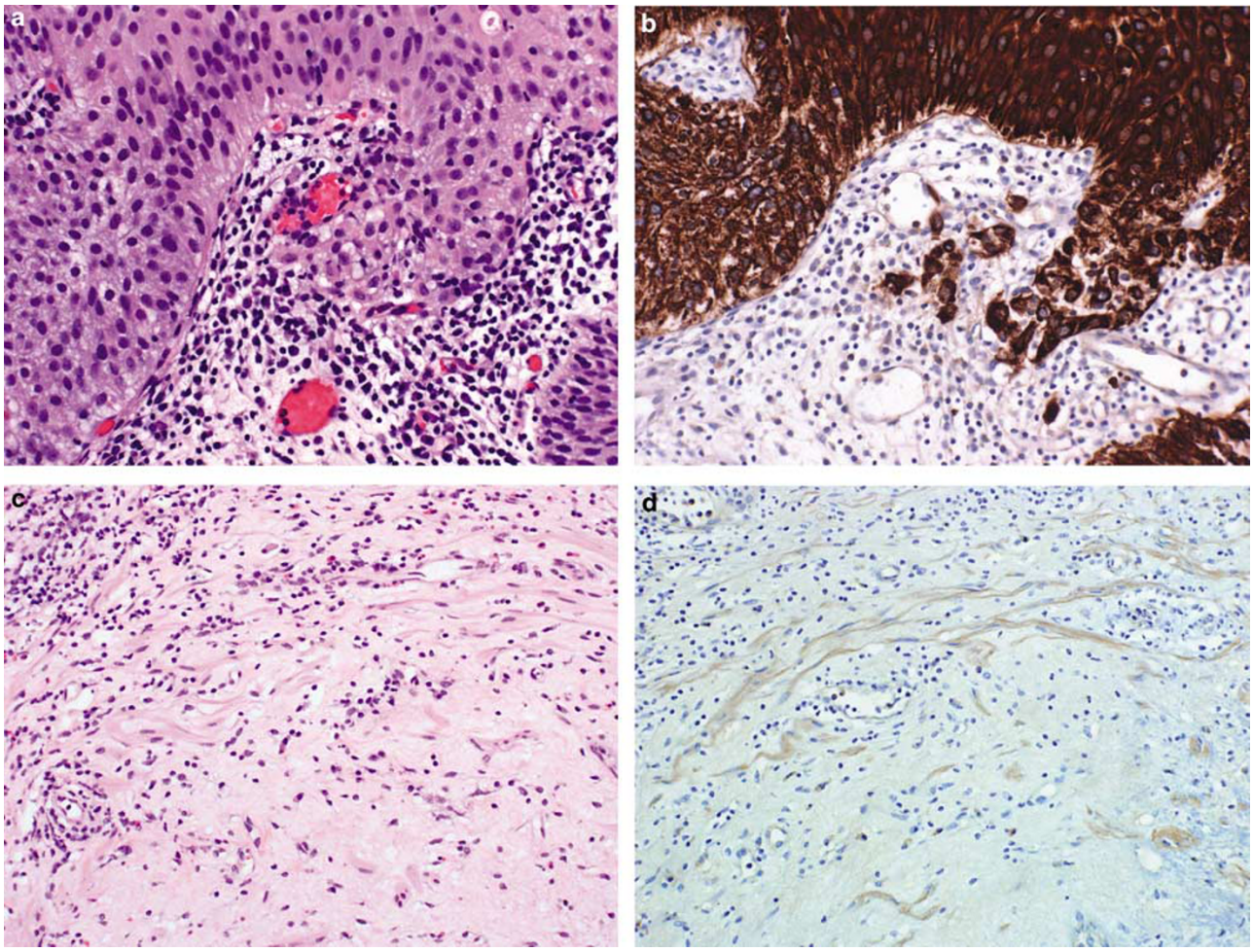

Figure 8 (**a**) Prominent inflammation at the epithelial–stromal interface may obscure isolated cells or small nests of invasive carcinoma. (**b**) Immmunostaining with anti-cytokeratin antibodies highlights the tumor cells. (**c** and **d**) Myofibroblasts and smooth muscle cells may show positive cytokeratin immunoreactivity. The intensity of staining, however, is weak and the nuclei are small with indistinct smudged chromatin.

tasis and all of them died of cancer. The study of McKenney *et al*[50] suggested a depth of 2 mm to assign the microinvasive category. More recently, Lopez-Beltran *et al*[51] again refined the criteria for microinvasion. They proposed that the microinvasive component into the lamina propria should consist of no more than 20 invading cells, as measured from the stromal–epithelial interface.[51] Further investigation is warranted to define the clinical significance of this diagnostic category.

Stage pT2 carcinoma

Stage pT2 carcinoma is defined by tumor invasion into muscularis propria (Figure 13). The 2002 TNM staging system subclassifies pT2 carcinoma into two categories: cancer invading less than one-half of the depth of muscular propria (pT2a) and cancer invading greater than one-half of the muscle wall.[9] The clinical utility of pT2 tumor substaging has been questioned.[25]

Current subclassification of T2 carcinomas is based on the work by Jewett[52] in 1952. In a study of 18 patients with muscle-invasive carcinoma, from 5 T2a (B1) cases and 13 T2b (B2) urothelial carcinomas, the authors found that 80% of T2a bladder carcinoma patients survived, whereas only 8% of those with stage T2b survived.[52] Data that have accumulated in the 47 years since this original publication do not appear to support the subdivision of T2 by depth of muscularis propria invasion (Table 2).[5,53–86] During a mean follow-up of 8.3 years, Cheng *et al*[85] found no survival difference between pT2a and pT2b cancer (Figure 14). Ten-year cancer specific survival rates were 82 and 81%, respectively, for patients with pT2a and pT2b bladder cancer.[85] In contrast, tumor size (the largest tumor dimension) was predictive of distant metastasis-free and cancer-specific survival in patients with muscularis propria invasion.[85] Ten-year cancer-specific survival rates were 94 and 73%, respectively, for patients with cancers <3 cm and patients with cancer ≥ 3 cm in greatest dimension.[85] In a recent

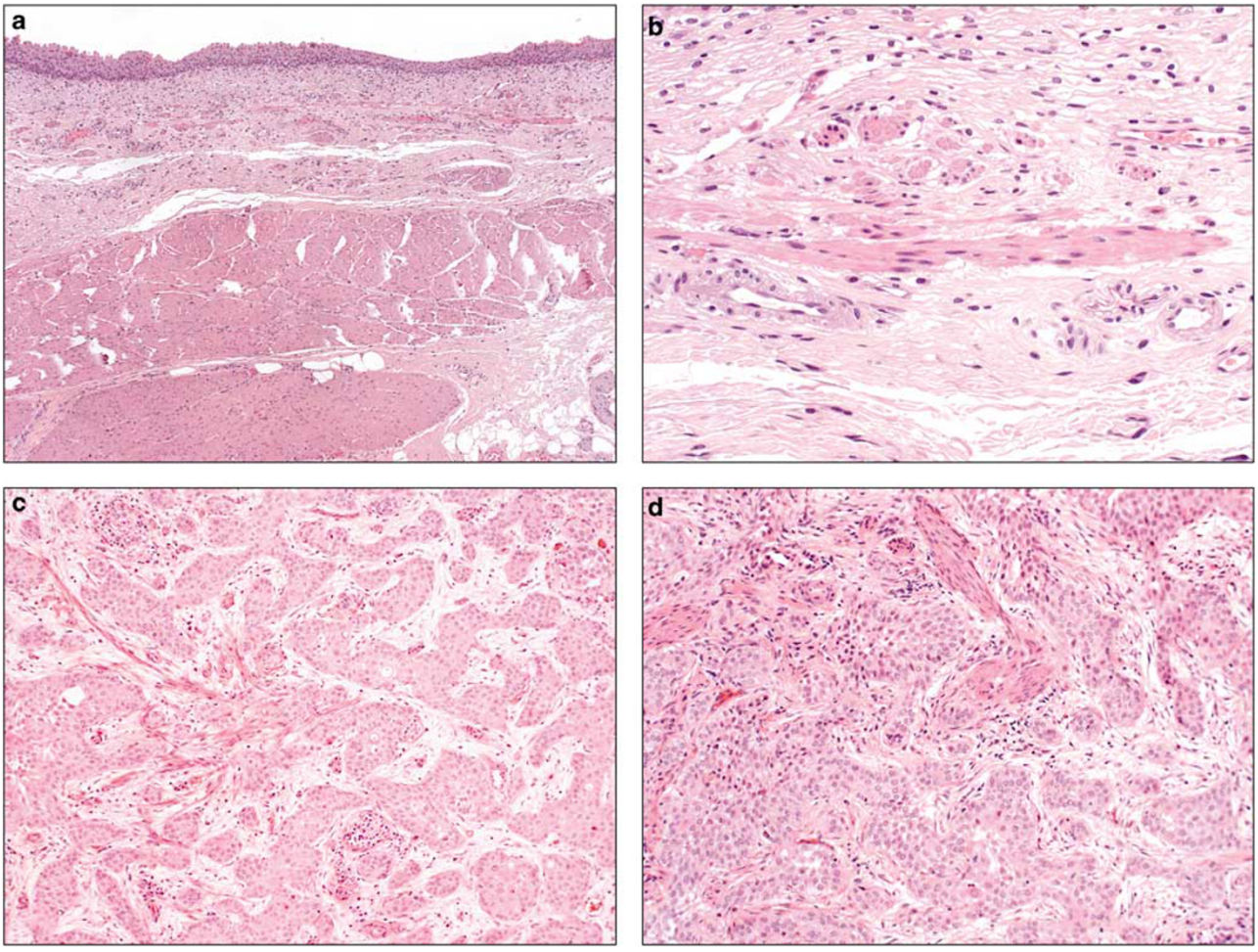

Figure 9 Muscularis mucosae and muscularis mucosae invasion. (**a**) Muscularis mucosae is composed of thin and wavy fascicles of smooth muscle in the submucosa of the bladder wall. (**b**) Muscularis mucosae is characterized by thin, often interrupted, bands of smooth muscle cells at high power. (**c**) Muscularis mucosae invasion. (**d**) Hyperplastic muscularis mucosae may be difficult to be distinguished from muscularis propria.

study of 311 patients with pT2 bladder cancer, Yu *et al*[81] found no significant difference in clinical outcome between pT2a and pT2b cancers after controlling for lymph node status. Ten-year recurrence-free survival rates were 84 and 72%, respectively, for pT2a and pT2b lymph node-negative bladder cancers. Among lymph node-positive bladder cancer patients, 10-year recurrence-free survival was 50% for pT2a carcinoma and 48% for pT2b carcinoma.[81]

In 1978, Jewett[87] concluded, 'it seems probable that our arbitrary dividing line drawn 30 years ago at the halfway level to separate B1 (pT2a) from B2 (pT2b) tumors was too superficial.' Substaging of T2 bladder carcinoma based on the level of muscularis propria invasion is of limited value for stratifying patients into prognostic groups and should be eliminated from future TNM classification. Tumor size may be a more pertinent parameter for the subclassification of T2 bladder cancer.

Stage pT3 carcinoma

Stage pT3 bladder carcinoma is defined by tumor invasion into perivesical soft tissue (Figure 15). The presence of intramural adipose tissue is well documented in the bladder.[88] The appearance of fat invasion in a biopsy or TUR specimen, therefore, does not necessarily indicate invasive pT3 carcinomasr. As a consequence, it is not feasible to document pT3 cancer in biopsy or TUR specimens. Nevertheless, in one study of 90 patients, the investigators found that depth of invasion in the TUR specimen was predicative of the final pathological stage.[46] Patients with a bladder cancer depth of invasion greater than 4 mm in the TUR of the bladder (TURB) specimen are likely to have extravesical extension. On the basis of a 4.0-mm cutoff point, the sensitivity, specificity, positive predictive value and negative predictive value for extravesical extension were 54, 90, 81, and 72%, respectively.[46] The overall accuracy of invasion depth for

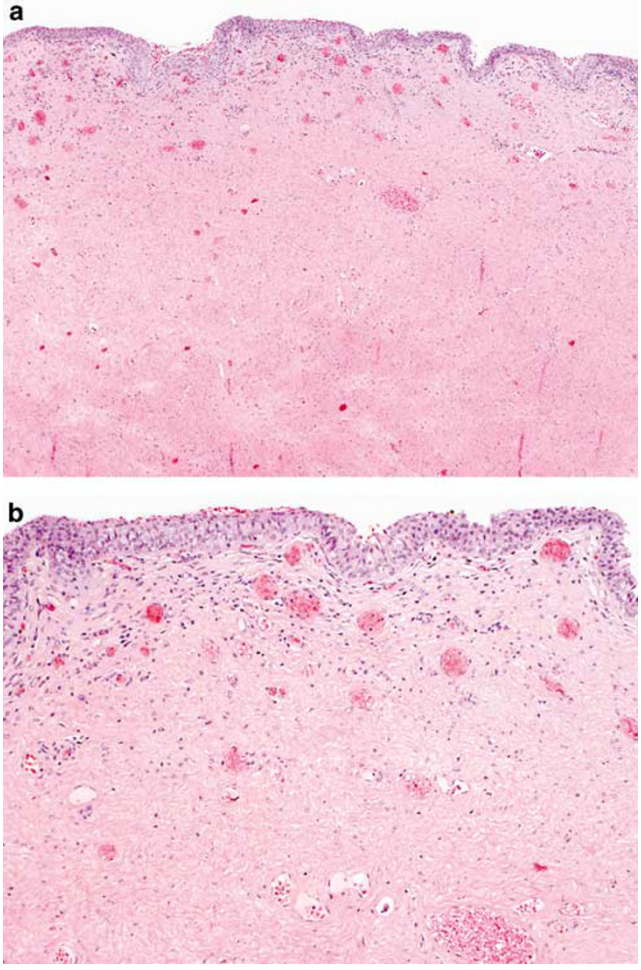

Figure 10 The trigone of the urinary bladder. (**a**) The lamina propria is thin in the trigone area, and merges imperceptibly into the muscularis propria wall. (**b**) Higher magnification view of the trigone area. Substaging of pT1 bladder carcinoma is particularly challenging for tumors arising from the trigone.

predicting extravesical extension, measured by the area under the receiver operating curve, was 0.81 (s.e. 0.045). Eighty-one percent of patients with an invasion depth >4 mm in the TUR specimen have pT3 (extravesical extension) or higher stage bladder cancer at cystectomy.[46]

The subdivision of pT3 tumors into pT3a (tumors with microscopic extravesical extension) and pT3b (tumors with gross extravesical extension) is controversial. Quek *et al*[89] examined 236 patients with pT3 bladder carcinoma. With a median follow-up of 8.9 years, there was no difference in recurrence or survival rates between patients with pT3a and pT3b tumors. Lymph node metastasis and surgical margin status were the only factors to significantly impact patient prognosis in this study.[89] A more recent study, however, has found that macroscopic perivesical fat invasion on gross examination (pT3b) is associated with increased risk of cancer recurrence and cancer death.[90] The presence or absence of macroscopic perivesical fat invasion, therefore, should be reported.

Stage pT4 carcinoma

Stage pT4 bladder cancer is defined by tumor invasion into an adjacent organ, including the uterus, vagina, prostate, pelvic wall or abdominal wall. In the 2002 AJCC/UICC bladder cancer staging guidelines, pT4a includes invasion of prostate (Figure 16), uterus or vagina, and pT4b indicates pelvic or abdominal wall invasion. The designation of prostate invasion by bladder carcinoma as stage pT4 cancer has been debated.[91] Donat *et al*[92] identified three pathways for prostatic stromal invasion by urothelial carcinoma. These include extravesical, intraurethral, and bladder neck invasion.[92] However, the prognostic significance of stromal invasion through these different pathways is uncertain. Esrig *et al*[93] studied 143 bladder cancers with prostatic involvement, dividing them into two groups. Group I penetrated the full thickness of bladder wall to involve the prostate, and group II involved the prostate by extension from the prostatic urethra.[93] Five-year overall survival rates were 21 and 55% for group I and group II patients, respectively. Among group II patients, the presence of prostatic stromal invasion was associated with a worse prognosis than for patients in whom urothelial cancer was confined to the urethral mucosa only.[93] Similarly, Pagano *et al*[94] found that 5-year survival was only 7% among group I patients, compared with 46% among group II patients. In group II cases, all patients with urethral mucosal involvement only were alive and free of cancer after 5 years, compared with 40–50% survival among patients with prostatic stromal invasion.[94] In a detailed mapping study of 214 radical cystoprostatectomy specimens with prostatic involvement by urothelial carcinoma, 26% of invasive bladder carcinomas resulted from direct infiltration of the prostate from the bladder. In the remaining 74% of cases, the prostate was invaded by urothelial carcinoma extending from the prostatic urethra.[95] More recently, Montironi *et al*[96] reported a detailed histopathological analysis of 248 consecutive prostates from cystoprostatectomies for muscle-invasive bladder carcinoma, using the whole mount technique. Involvement by bladder cancer was present in 38% of the prostates. Incidental prostate cancer was also seen in 50% of the specimens, but 81% of these prostate cancers were clinically insignificant.[96] These findings emphasize the importance of thorough sampling and histological evaluation of the prostate for cystoprostatectomy specimens removed for bladder carcinoma.

Direct perivesical tumor extension involving the seminal vesicles was associated with poor prognosis similar to that of pT4b bladder cancer.[97,98] Five-year

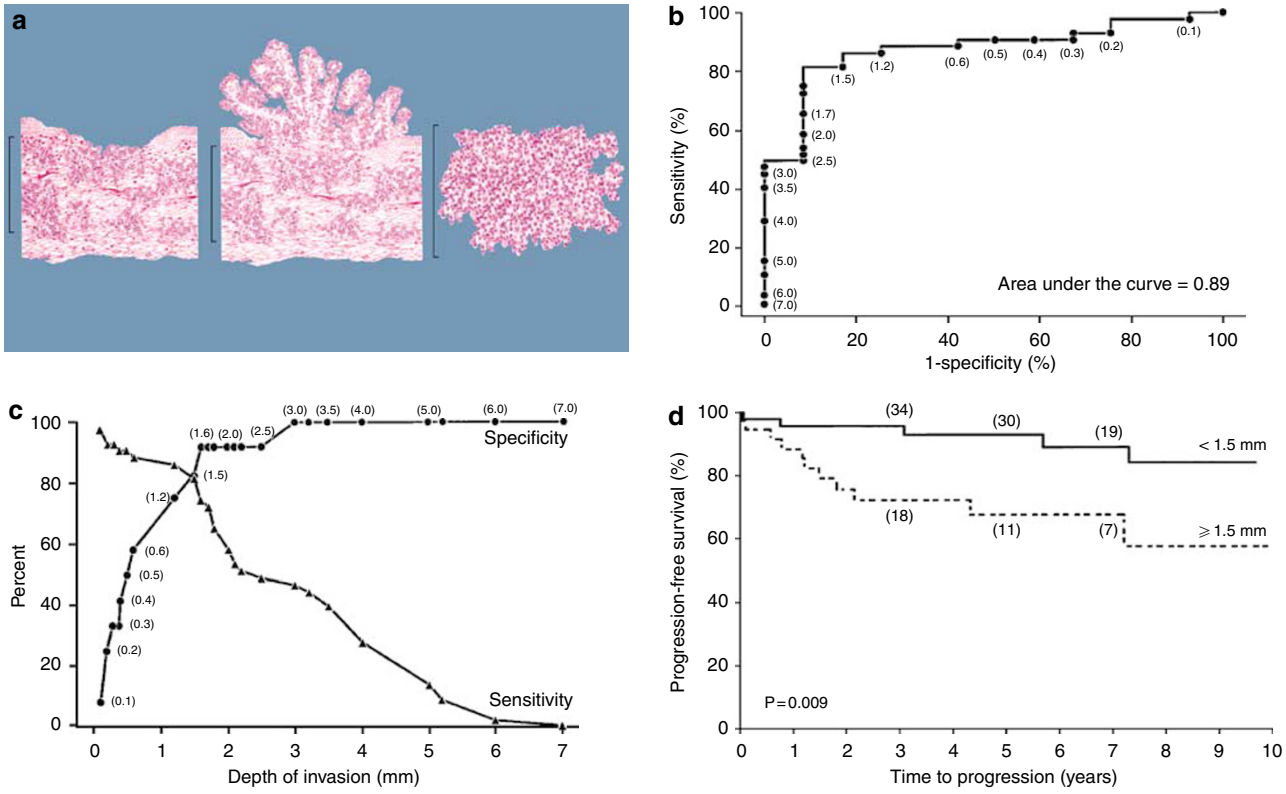

Figure 11 Depth of invasion in pT1 urothelial carcinoma is a powerful predictor of clinical outcome. (**a**) The depth of stromal invasion in the transurethral resection or biopsy specimens is measured from the basement membrane of the bladder mucosa to the deepest invasive cancer cells using an ocular micrometer, whether the lesion is flat (AI) or papillary (AII). When tissue fragments contained cancer without adjacent basement membrane or when the specimen is not oriented, the depth of invasion is the shortest dimension of an intact tumor fragment to avoid overestimation of the depth of invasion (AIII). (**b**) Receiver operating characteristic (ROC) analysis of invasion depth as a predictor of advanced stage (≥T2) bladder carcinoma. The area under the ROC curve was 0.89. (**c**) Sensitivity and specificity of invasion depth as a predictor for advanced stage (≥T2) bladder carcinoma. The optimal depth of invasion (for maximizing both sensitivity and specificity in predicting advanced stage bladder carcinoma is 1.5 mm. (**d**) Cancer progression-free survival curves comparing invasion depth <1.5 and ≥1.5 mm in transurethral resection specimens. Progression consisted of muscle-invasive or more advanced stage carcinoma, of distant metastasis or of death from bladder cancer (from Cheng *et al*[38]: Substaging of T1 bladder carcinoma based on the depth of invasion as measured by micrometer: a new proposal. *Cancer* 1999; 86:1035; and Cheng *et al*[46]: Predicting extravesical extension of bladder carcinoma. *Urology* 2000; 55:668, with permission).

overall survival for these patients was only 10%, similar to pT4b cancer (7%). The five-year overall survival for patients with prostatic stromal involvement was 38%.[97] However, the prognostic significance of seminal vesicle invasion through intraepithelial extension from the prostate is less certain and should be reported separately.[99]

The prognostic significance of different prostatic involvement patterns is uncertain. The prostatic urethra may be involved by urothelial carcinoma, with or without stromal invasion. CIS involving the prostatic urethra should not be designated as pT4a cancer. Similarly, prostatic ducts and acini may be involved by urothelial carcinoma without stromal invasion. Prostatic stromal invasion is usually associated with poor clinical outcome and should be clearly stated. Seminal vesicle involvement by direct perivesical tumor extension is a poor prognostic indicator.[97,98]

Nodal classification (N staging)

The 2002 TNM staging system categorizes nodal status based on the number and size of positive lymph nodes. The rationale for using 2 and 5 cm as thresholds for substaging is uncertain and questionable (Table 1). Recent studies have emphasized the importance of lymph node density for nodal staging.[100–103] Lymph node density is defined by the ratio of positive lymph nodes to the total number of lymph nodes sampled. In an analysis of 248 patients with positive nodal metastasis, Kassouf *et al*[101] found that lymph node density was an independent predictor of cancer survival. The 5-year cancer-specific survival for patients with lymph node density >20% was 15%, compared with 55% 5-year cancer-specific survival among patients with lymph node density ≤20%.[101] However, the minimum number of lymph nodes in the

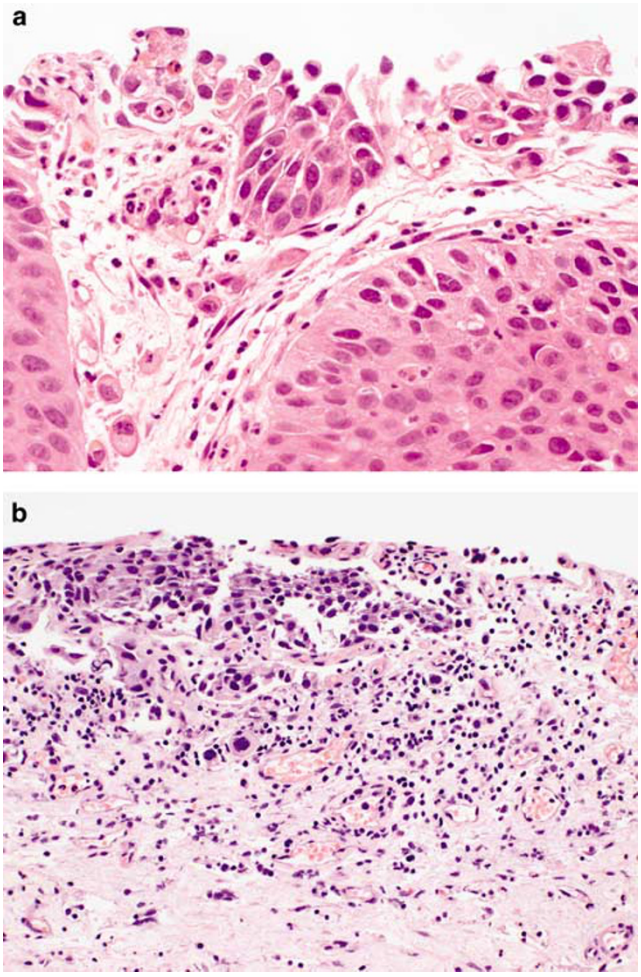

Figure 12 Microinvasive carcinoma arising from urothelial carcinoma *in situ*. (**a**) Individual single cells permeate the stroma adjacent to von Brunn's nests containing carcinoma *in situ*. (**b**) Prominent stromal inflammatory response may obscure the presence of individual tumor cells. Retraction artifact is a useful clue for the diagnosis of invasion.

specimen for optimal lymph node density estimation is yet to be established. Moreover, the best cutoff for lymph node density has not been determined in a systematic way. In a multivariate analysis of 101 lymph node-positive bladder carcinomas, using 20% as the cutoff, lymph node density was not a significant predictor of survival.[104] In another series of 154 node-positive patients, only the number of positive nodes was an independent predictor of survival.[105] Each level of increase by one positive node increased the risk of cancer death by 20%.[105]

Additional factors, such as the largest dimension of metastasis, extranodal extension, and anatomic location of positive nodes, may also be important (Figure 17). Fleischmann *et al*[104] found that extranodal extension was the strongest predictor of clinical outcome. The incidence of extranodal extension in 101 patients with pelvic node metastases was 58%.[104] During a median follow-up of 21 months, patients with extranodal extension had significantly worse recurrence-free (median, 12 months) and overall (median, 16 months) survival, as compared with those without extranodal extension (median, 60 months for both recurrence and overall survival).[106]

Occult lymph node metastasis may be present but undetectable by routine H&E examinations. The detection of lymph node micrometastasis by molecular methods is a promising technique to overcome this limitation. The reverse transcriptase-polymerase chain reaction (RT-PCR) assay for uroplakin II was more sensitive than cytokeratin 20 for detecting occult lymph node metastasis.[107] Of 66 pelvic lymph node samples without histological evidence of metastasis, uroplakin II was detected in 6 (10%), whereas cytokeratin 20 was not detected in any samples.[107] The incidence of positive RT-PCR for uroplakin II mRNA was 25% in Seraj *et al*'s analysis of 27 patients with hisotologically negative lymph nodes.[108] Copp *et al*[109] found positive uroplakin II RNA transcripts in 33% of pelvic lymphadeectomy specimens without morphologic evidence of lymph node metastasis. The investigators found that only 5% of histologically and RT-PCR node-negative patients had cancer recurrence, whereas 91% of histologically and RT-PCR node-positive patients recurred after a mean follow-up of 6 months.[109] Using the quantitative real-time RT-PCR approach, Marin-Aguilera *et al*[110] found positive RT-PCR results in 21% of histologically negative lymph nodes. However, there was no survival difference between RT-PCR-positive and RT-PCR-negative groups during a median follow-up of 35 months.[110] The use of cytokeratin immunohistochemistry for detection of occult metastasis appeared to be of no practical value.[111]

Specimen handling

Efforts have been made to standardize the handling and reporting of bladder specimens.[16,99,112–120] The most common bladder specimens are endoscopic biopsies and TURB. Other specimens include cystectomy (partial or total), cystoprostatectomy, pelvic exenteration (*en bloc* resection), and diverticulum resections. Surgical excision of an urachal carcinoma usually includes the bladder dome, urachus, and umbilicus.

Biopsy and TUR Specimens

Small, noninvasive papillary neoplasms are often excised using biopsy with cold-cup forceps, diathermy forceps or a small diathermy loop. To avoid tissue distortion, these specimens should be transferred to fixative with minimal handling. Larger neoplasms are often sampled by TURB with a diathermy loop that produces strips of tissue approximately 6 mm in width and of variable length.

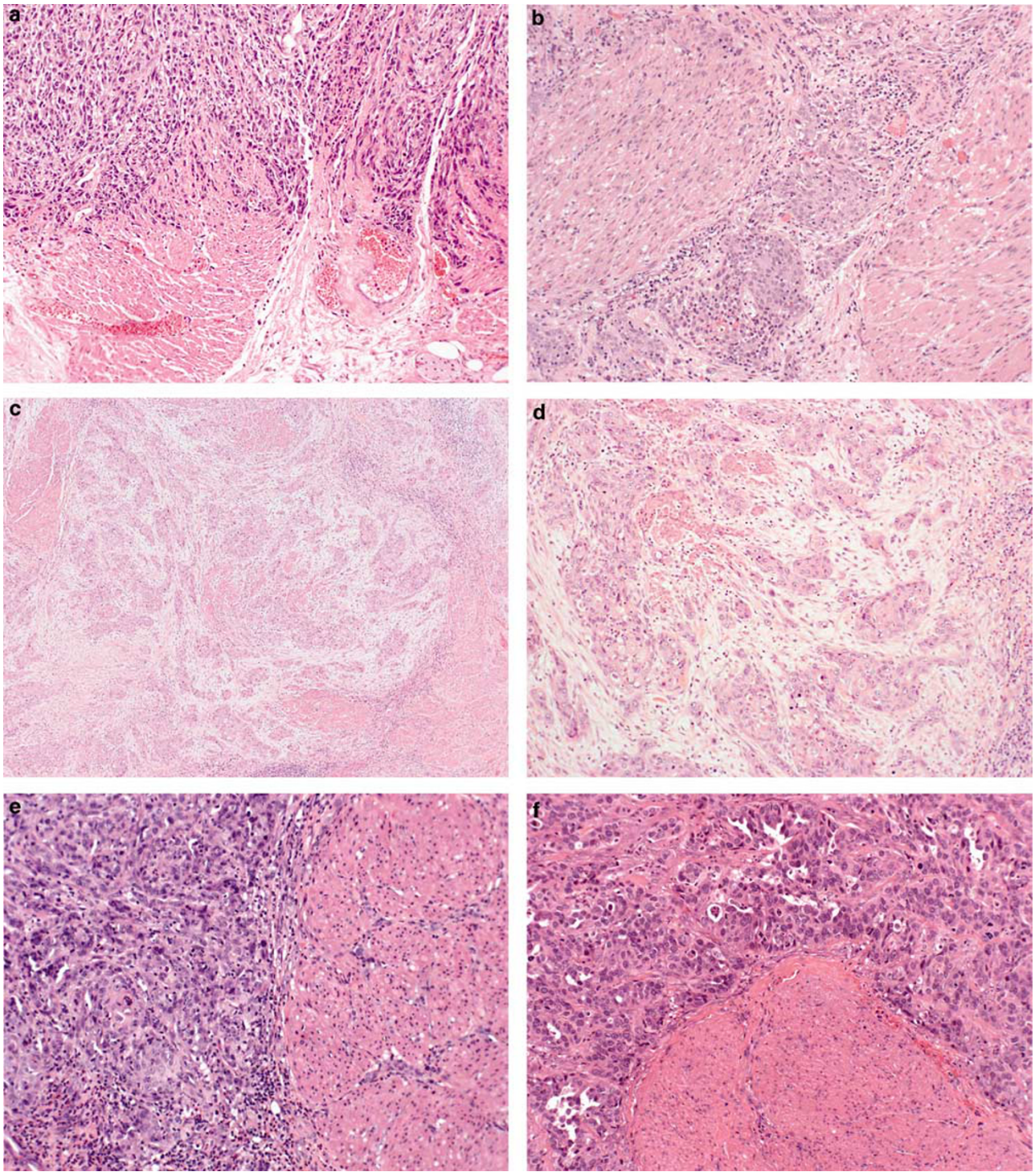

Figure 13 pT2 urothelial carcinoma. (**a**) pT2 urothelial carcinoma invades into muscularis propria. Infiltrating tumor cells permeate the thick muscularis propria wall. (**b**) Sometimes it is difficult to ascertain the presence of muscularis propria invasion when columns and nests of tumor cells widely separate bundles of detrusor muscle. (**c** and **d**) Extensive destruction of muscularis propria may result in fragmentations of detrusor muscle, mimicking muscularis mucosae invasion. (**e**) It is not uncommon for tumor cells to abut, but not penetrate bundles of mucularis propria. The muscle–tumor interface may even have a smooth contour. (**f**) Even without direct invading into muscularis propria wall, tumor cells immediately adjacent to broad smooth muscle fibers should be categorized as pT2 carcinoma.

Additional resection of the tumor base may be obtained to assess the level of invasion (muscularis propria invasion). Any erythematous or velvety area of urothelium is sampled to exclude CIS. Random biopsies are also taken from cystoscopically normal urothelium remote from the tumor site to determine

Table 2 Comparison of clinical outcome between pT2a and pT2b bladder carcinomas

Authors	*Number of cases (T2a and T2b)*	*5-year survival (%)*	
		T2a	*T2b*
Jewett[52]	18	80	8
Bowles and Cordonnier[60]	40	52	50
Cox *et al*[61]	75	45	40
Sorensen *et al*[74]	38	7	0
Pomerance[68]	46	15	29
Utz *et al*[75]	73	47	40
Cordonnier[65]	76	52	40
Richie *et al*[71]	58	40	40
Pearse *et al*[78]	26	64	50
Prout[69]	112	31	31
Boileau *et al*[62]	67	38	52
Bredael *et al*[64]	61	54	48
Mathur *et al*[66]	18	86	64
Skinner *et al*[83]	33	53	39
Beahrs *et al*[63]	61	42	35
Montie *et al*[79]	27	62	63
Pagano *et al*[80]	95	63	50
Roehrborn *et al*[72]	145	65	61
Wishnow *et al*[77]	35	75	78
Pollack *et al*[67]	140	78	77
Cuesta *et al*[84]	50	73	67
Cheng *et al*[85]	64	62	56
Dalbagni *et al*[5]	58	62	58
Girgin *et al*[82]	75	84	66
Yu *et al*[81]	242[a]	87	75
	69[b]	50	50
Tokgoz[86]	57	44	43

[a]Lymph node-negative patients.
[b]Lymph node-positive patients.

the extent of urothelial involvement. It has been suggested that random biopsy samples be obtained from predetermined sites in four quadrants of the urinary bladder.[121] Some urologists also submit biopsy specimens of the urethra to assess the extent of disease.

Bladder biopsy and/TUR specimens are to provide diagnostic and prognostic information for urologists to plan surveillance and treatment, and to predict tumor response to therapy. Tissues from biopsy specimens should be entirely embedded for histological examination. These biopsy specimens obtained through the cystoscope often vary in size. At least two levels of sectioning should be obtained on each small biopsy. Proper orientation of bladder tumor biopsy specimens is difficult, even with a dissecting microscope. It may be necessary to re-embed and reorient the tissue to facilitate assessment of the depth of invasion.

Transurethral resection of the bladder specimens should be weighted in aggregate. Papillary tumors may be grossly recognizable in these specimens. The number of tissue chips with involvement and gross tumor size should be recorded. At least one block per centimeter of tumor diameter, up to 10 cassette blocks, should be submitted at the initial sampling. Overfilling of specimen cassettes should be avoided. If the tumor is noninvasive, submitting any residual specimen may be necessary to firmly rule out stromal invasion. If there is invasion into the lamina propria in the initial sampling, then additional sampling is recommended to rule out muscularis propria invasion. We recommend that the urologist submit superficial and deep tumor-base specimens

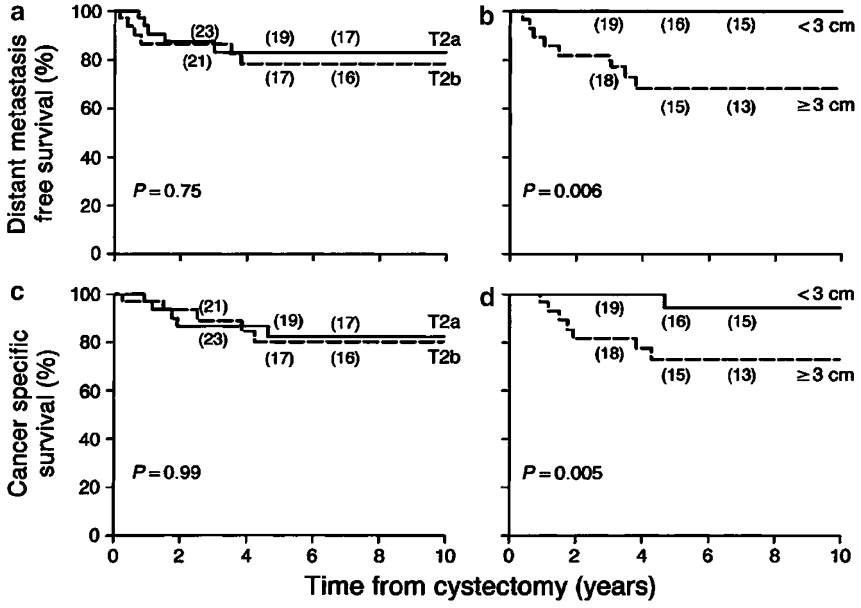

Figure 14 Substaging of pT2 urothelial carcinoma. Distant metastasis-free (**a** and **b**) and cancer-specific (**c** and **d**) survivals for patients with pT2 urothelial carcinoma. Tumor size (**b** and **d**) was more clinically relevant than the pT2 substaging (pT2a versus pT2b) (**a** and **c**) (from Cheng *et al*[85] Tumor size predicts the survival of patients with pathologic stage T2 bladder carcinoma: a critical evaluation of the depth of muscle invasion. *Cancer* 1999; 85:2638, with permission).

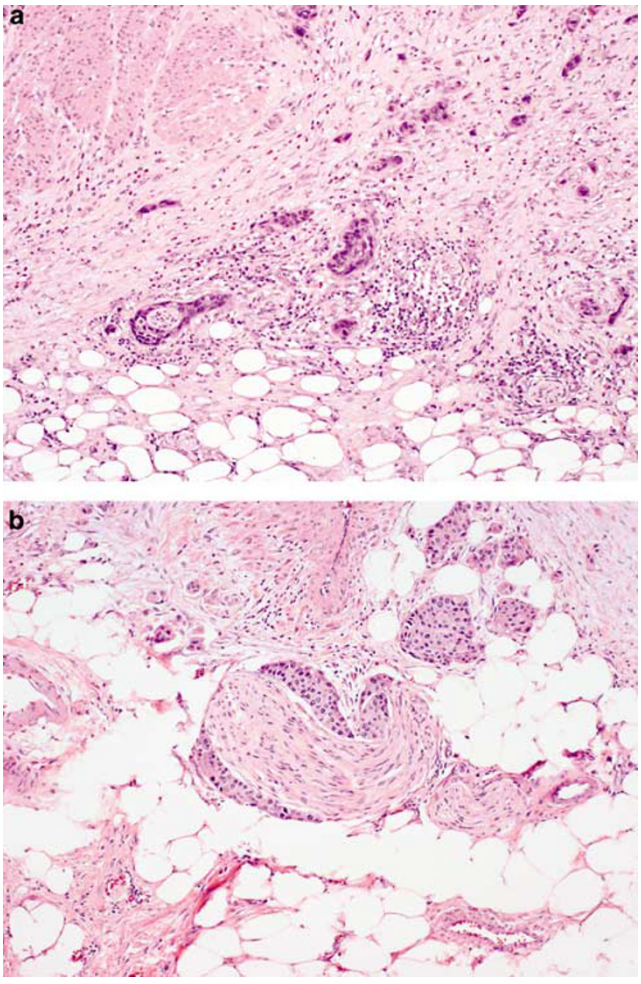

Figure 15 pT3 urothelial carcinoma. (**a**) Tumor invades into perivesical adipose tissue. (**b**) Perineural invasion is present. The prognostic significance of perineural invasion is uncertain.

in separate containers to facilitate the detection of deep muscle invasion.

Cystectomy, Cystoprostatectomy and Pelvic Exenteration (*en Bloc* Resection) Specimens

Processing of these specimens may be summarized in three steps: (1) orientation of the specimen and identification of relevant anatomic structures (eg, ureters), (2) fixation of the specimen and (3) dissection of the specimen. Peritoneum covering the surface of the bladder is a reliable anatomic landmark. In both male and female patients, the peritoneum descends further along the posterior wall of the bladder than it does along the anterior wall. Other pelvic organs, if present, may also be used to orient the specimen. In the male, the bladder adjoins the rectum and seminal vesicles posteriorly, the prostate inferiorly, and the pubis and peritoneum anteriorly. In the female, the vagina is located posteriorly, and the uterus is located superiorly. Once the specimen is oriented, both ureters and, when present, the vasa deferentia should be identified. Location and dissection of the ureters is easier after fixation. The outer dimensions of the urinary bladder, as well as the length and diameter of ureters, should be recorded. The external surface of the bladder should be inked.

Proper fixation of the specimen is a prerequisite for adequate histological evaluation. We recommend that large bladder specimens be fixed in formalin overnight. Some prefer to expand the bladder with formalin. Injection of formalin into the urinary bladder cavity is accomplished either through the urethra by a Foley catheter or through the bladder dome using a large-gauge needle after the urethra has been clamped. We prefer to open the bladder before formalin fixation. It should be opened anteriorly from the urethra to the bladder dome. Thus the bladder mucosa may be everted for close examination. Any subtle alteration of the mucosa, such as granularity, ulceration, hemorrhage, or erythema, is documented. If a grossly visible tumor is identified, the size, location, configuration (flat, papillary, solid/nodular, sessile, exophytic, endophytic or ulcerated), color and consistency of the tumor should be documented.

After the specimen is well fixed, the dissection is resumed by shaving the margins from each ureter and the urethra. When the specimen includes the prostate, the distal urethral margin is the distal end of the prostate at the apex. The ureters are opened at their trigone orifices, and examined for strictures, dilatations, ulcerations, diverticulae or exophytic lesions. If a tumor is identified in the bladder, a full-thickness cut through the tumor and bladder wall should be made. The tumor should be generously sampled for accurate staging, grading and histological typing. For a large tumor, at least one section should be taken for each centimeter of tumor diameter. Sections are taken in such a way as to show the relationship of tumor to adjacent urothelium, its maximal level of penetration, and external soft tissue margin. For large exophytic tumors, several sections are taken from the tumor base to adequately assess the extent of invasion. Normal appearing mucosa is also sampled to detect occult multifocal carcinomas due to the field effect of bladder carcinogenesis. The entire bladder is transversely step-sectioned at 5-mm intervals from the bladder neck to the dome. Perivesical fat is carefully searched for lymph nodes. The presence or absence of gross fat invasion should be documented.

The minimum number of sections to be taken are as follows: tumor (3); bladder neck (1), trigone (2), anterior wall (2), posterior wall (2), lateral walls (2), dome (2), ureteral orifices (including intramural portion), margins (ureteral, urethral and perivesical soft tissue), any abnormal appearing bladder mucosa and any perivesical lymph nodes[122] (Figure 18).

Preoperative treatments or repeat TUR may render residual tumors grossly invisible. As TUR

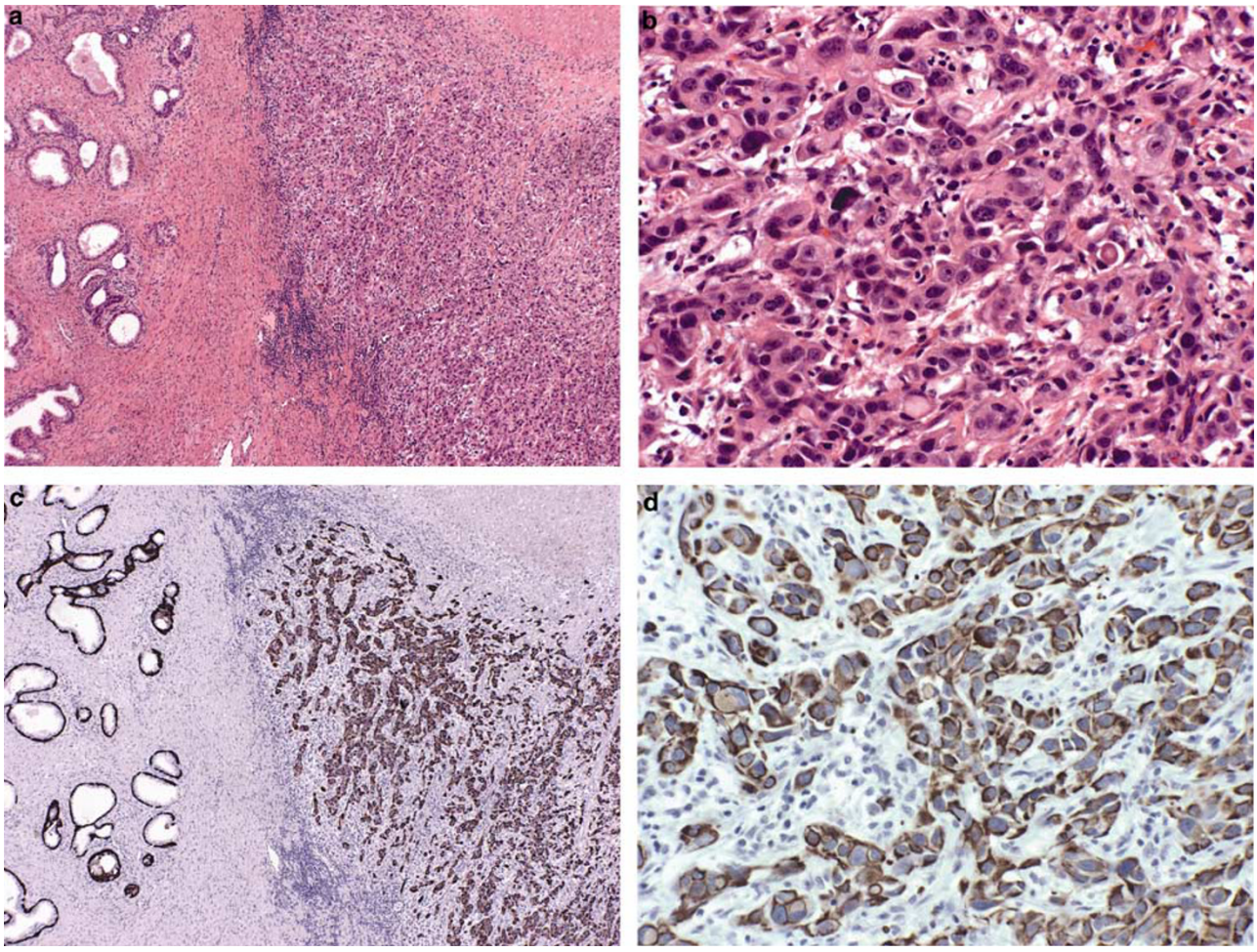

Figure 16 Urothelial carcinoma invading into prostatic stroma (pT4a urothelial carcinoma). (**a**) Urothelial carcinoma often elicits a strong inflammatory response, unusual for prostatic adenocarcinoma. (**b**) Tumor cells invading prostatic stroma are usually highly pleomorphic. (**c** and **d**) Immunostaining for high molecular weight cytokeratins is diffusely and strongly positive in urothelial carcinoma. The basal cells in the adjacent prostatic glands show positive stainings for high molecular weight cytokeratin (**c**).

techniques have improved, there is increasing incidence of pT0 carcinoma at cystectomy. For such cases, the bladder should be extensively sampled with particular attention to abnormal appearing mucosa and to sites of previously documented tumor resection.

For a cystoprostatectomy specimen (Figure 18), the bladder is opened anteriorly by an incision from the prostatic urethra to the dome. The urethral mucosa is carefully examined for evidence of tumor extension into the prostatic urethra. The prostate should be examined by the established protocol for pathological evaluation and reporting of radical prostatectomy specimens. The prostate is transversely sectioned from apex to base at 5-mm intervals with the plane of the sections perpendicular to the posterior surface of the gland. If a tumor is grossly visible, it is important to document whether the tumor arises centrally from the prostatic urethra or more peripherally in the common location for prostate cancer (peripheral zone). It is important to take sections from the bladder neck, as this is an important route for urothelial carcinoma to invade prostatic stroma.[92] Recent whole mount analysis of large numbers of cystoprostatectomy specimens emphasizes the importance of thorough prostate sampling.[96]

For pelvic exenteration specimens, the rectum, uterus and vagina should be evaluated according to the standardized protocols for these organs. Pelvic soft tissue margins should be documented. As the uterus and rectum are located posterior to the bladder, an anterior opening of the bladder is preferred to facilitate documentation of urothelial tumors and to evaluate the tumor's relationship to these other organs for staging. Sections should be taken to confirm the presence of each pelvic organ, and to show the relationship between the tumor and each of these structures. These sections also document the resection margins for each organ and examine each organ for primary disease.

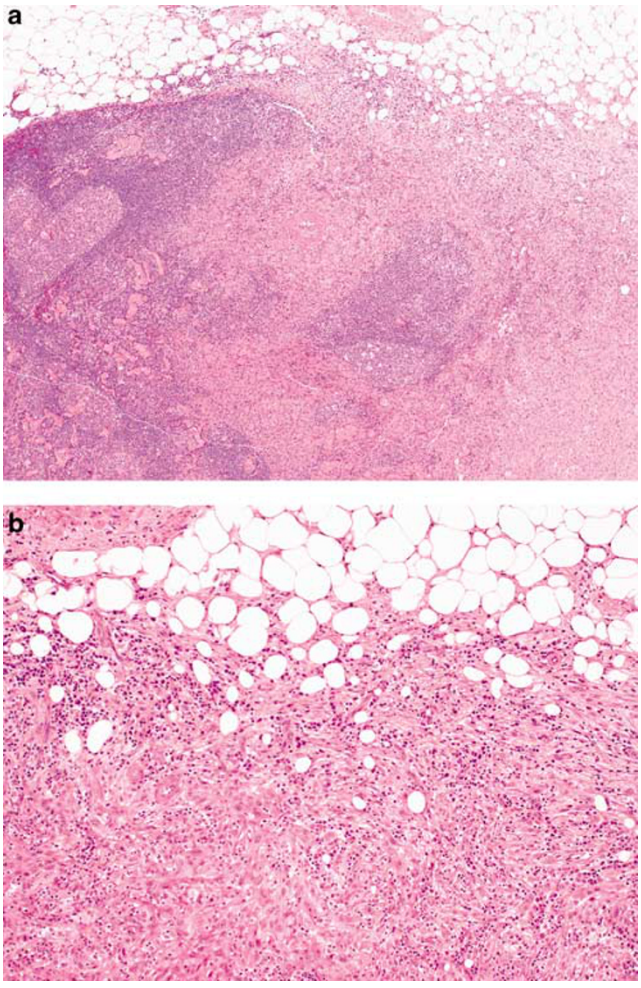

Figure 17 Lymph node metastasis from urothelial carcinoma. Extranodal extension is present at low power (**a**) and is confirmed on high power examination (**b**).

Partial Cystectomy and Urachal Resection Specimens

Partial cystectomy specimens (including resections of diverticula) should be fixed and dissected according to the guidelines of radical cystectomy (see earlier discussion). The edges of the specimen are inked because these represent the surgical margins of the bladder wall. A variation of the partial cystectomy is performed for resections of urachal tract neoplasms. These specimens consist of the dome of the bladder in continuity with the urachal tract including the umbilicus. After inking the soft tissue margin, the urachal tract should be serially sectioned at right angles to the long axis from the bladder to the umbilicus. Submit for histology a number of these urachal tract cross-sections, as well as the standard bladder sections. Appropriate samples of the soft tissue margin surrounding the urachus and of the skin margin around the umbilicus should be submitted for histology.

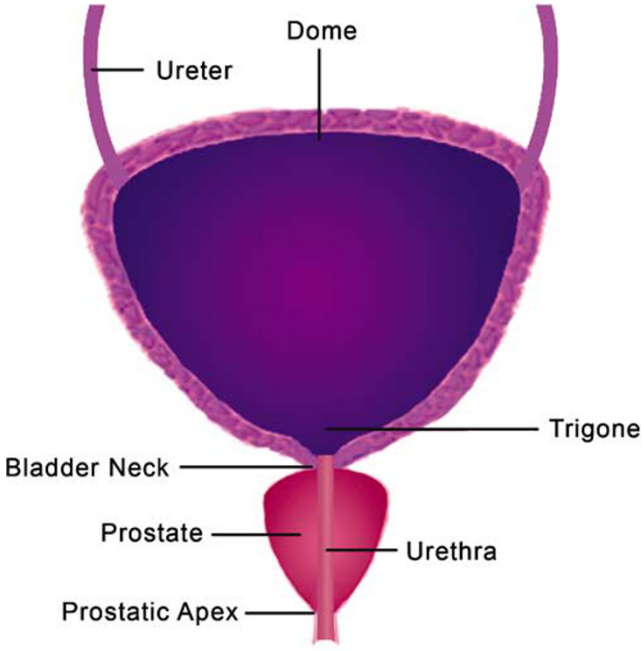

Figure 18 Illustration of a cystoprostatectomy specimen. Sections should be taken from tumor, bladder neck, trigone, anterior wall, posterior wall, lateral walls, dome, ureteral orifices (including intramural portion), margins (ureteral, urethral, and perivesical soft tissue), and any abnormal appearing bladder mucosa. The prostate should be sampled using the standard protocol for radical prostatectomy specimens.

Lymph Node Dissection

The regional lymph nodes of the bladder are the pelvic lymph nodes below the bifurcation of the common iliac arteries. These include the hypogastric, obturator, iliac (internal, external, not otherwise specified), perivesical, pelvic (not otherwise specified), sacral (lateral, sacral promontory) and presacral lymph nodes. The common iliac nodes are considered sites of distant metastasis and are coded as M1[9]. Current nodal classification is based on the number and size of positive nodes. Recent studies have emphasized the importance of lymph node density[101] and we recommend that the number of lymph nodes sampled should be clearly stated. Unlike colon cancer, the minimum number of lymph nodes that should be sampled has not been established. We recommend that at least eight lymph nodes be sampled. In difficult cases, a clearing solution may be used to aid in detection of lymph nodes. These may, on occasion, be detected in the perivesical fat, so a thorough search should be made of this area in addition to other pelvic node-bearing structures.

Pathology reporting

The pathology report should include clinically relevant historical information as well as clinically useful

Table 3 Reporting of bladder biopsy/transurethral resection specimens

Gross findings
- Cold-cup biopsy
  - The estimated number of tissue fragments, aggregate dimensions
  - The presence or absence of papillary growth
  - All tissue fragments should be submitted
- Transurethral resection of the bladder (TURB)
  - The estimated number of tissue fragments, aggregate dimensions
  - Total weight of resected tissue fragments
  - The proportion of tissue embedded, if not completely embedded
    - *We recommend that a minimum of 10 block cassettes be submitted for initial evaluation. If lamina propria invasion is identified, the entire specimen may be submitted to rule out muscularis propria invasion and to further assess the extent of invasion.

Microscopic findings
- General assessment
  - Epithelial surface (intact, ulcerated, denuded)
  - The presence or absence of muscularis propria (detrusor muscle)
  - Comment on cautery artifact if it compromises evaluation
- Tumor assessment
  - Anatomic location (if available)
  - Histological diagnosis
    - Specify invasive or noninvasive urothelial carcinoma
  - Histologic grade
  - Overall architecture (eg, papillary or flat)
  - Pattern of invasion (nodular, trabecular, or infiltrative)
  - The presence or absence of lymphovascular invasion
  - Extent of invasion (specify if stromal invasion is present or not and the level of invasion)
    - Invasion into lamina propria
      - Extent and/or depth of invasion should be provided
        Reporting of muscularis mucosae invasion is optional, as muscularis mucosae is not uniformly present in the biopsy specimens
    - Invasion into muscularis propria (detrusor muscle)
      - T2 substaging (pT2a versus T2b) cannot be performed on biopsy specimens
    - Statements of tumor stage should provided (eg, at least T1, or T2)
      - Comment that accurate staging may require complete resection of the tumor
      - T2 substaging (pT2a versus T2b) cannot be performed on biopsy specimens
      - Fat invasion in biopsy is not necessarily indicative of extravesical invasion (pT3), as fat is present throughout the bladder wall
- Findings in the adjacent mucosa
  - The presence or absence of dysplasia, carcinoma *in situ*
  - Other findings: intestinal metaplasis, cystitis glandularis, keratinizing squamous metaplasia etc.

gross and microscopic information.[99,112–117,119,120] Bladder cancer reports must include the specimen type, anatomic location of the tumor, tumor size, histological type, histological grade, tumor growth pattern, surgical margin status, treatment effect, and any other intraepithelial lesions (Tables 3 and 4). These parameters are listed in Tables 3 and 4, which illustrate synoptic formats for biopsy and cystectomy cancer specimen reports.

For biopsy and TUR specimens, it is particularly important to mention the presence or absence of lymphovascular invasion and to comment on certain histological variants, such as micropapillary and nested variants of urothelial carcinoma (Figure 19).[123] Aggressive therapies may be considered for those patients with lymphovascular invasion, micropapillary variant, or nested variant of urothelial carcinoma.

The presence or absence of muscularis propria (detrusor muscle), regardless of whether there is invasion, should also be reported as an indication of resection adequacy.[16,124,125] However, designation of mere muscle invasion in the report is inappropriate. The type of muscle being invaded, whether muscularis mucosae (T1 carcinoma) or detrusor muscle invasion (T2 carcinoma), should be clearly stated. Although staging based on the level of muscularis mucosae invasion is not recommended,[45] an indication of the extent of invasion is of clinical interest and should be reported. The use of an ocular micrometer to measure the depth of invasion may be considered.[24,25,38] Patients with invasion less than 1.5 mm have a better prognosis than other T1 bladder cancer patients.[25]

Substaging of T2 bladder cancer (T2a verrus T2b) is not feasible in bladder biopsy or TURB specimens, as the entire thickness of the detrusor muscle is not present. The term 'superficial muscle invasion' in the pathology report leads to confusion. Therefore, it should be avoided. For biopsy and TUR of invasive bladder carcinoma, some urologists prefer a statement of pathological stage (T1 or T2) in the report. In such an instance, we recommend that tumor stage be indicated as 'at least' pT1 or pT2.

Adipose tissue is present in the lamina propria and muscularis propria of the bladder wall (Figure 20). Therefore, the presence of fat invasion in the biopsy or TUR specimen does not necessarily

Table 4 Reporting of cystectomy specimens

Gross findings
- Fresh or fixed specimen
- Nature of the specimen: partial cystectomy, radical cystectomy, cystoprostatectomy, pelvic exenteration
- Three-dimensional measurements of recognizable anatomic structures, and of tumors or other recognizable lesions
  - Site of involvement
  - Growth pattern (papillary, ulcerated, solid, nodular, infiltrative)
  - Gross assessment of invasion (into lamina propria or muscularis propria)
  - Gross extravesical fat extension
  - Gross invasion into adjacent organs, such as prostate, ureter, urethra, uterus, vagina, pelvic, and abdominal wall
  - Gross assessment of margin status
- Lymph nodes
  - Location and the number of lymph nodes sampled
    - Report if the lymph nodes are bisected or completely embedded
    - Report if the lymph nodes are grossly involved by cancer

Microscopic findings
- Anatomic location of the tumor
- Histological diagnosis
- Tumor size and multifocality
- Histological grade
- Pattern of invasion (nodular, trabecular, or infiltrative)
- Extent of invasion (pathological staging)
  - No invasion (pTa or pTis)
  - Invasion into the lamina propria (pT1)
  - Invasion into inner or outer half of muscularis propria (pT2)
  - Invasion into perivesical soft tissue (pT3)
  - Tumor arising in a diverticulum (specify whether detrusor muscle is present)
- Surgical margins
  - Ureteral margin
  - Urethral margins
  - Perivesical soft tissue margin
  - Pelvic soft tissue margin (or pelvic exenteration specimens)
- The presence or absence of lymphovascular invasion
- Other intraepithelial abnormalities
  - The presence or absence of dysplasia and carcinoma *in situ* in adjacent mucosa
  - Location and multifocality
  - Other findings such as intestinal metaplasia, therapeutic treatment effects etc.
- Extent of tumor invasion into adjacent organs
  - Prostate
    - a. Involvement of the prostatic urethra with or without stromal invasion
    - b. Involvement of prostatic ducts/acini without stromal invasion
    - c. Prostatic stromal invasion
    - d. Direct extension into the prostate from carcinoma through the bladder neck
    - e. Direct extravesical extension into the prostatic parenchyma
    - f. Seminal vesicle invasion through intraprostatic epithelium or by direct perivesical extension
  - Ureter and urethra
    - a. Report any dysplastic/neoplastic change of the mucosa, including pagetoid spread of carcinoma *in situ*
    - b. Report invasion into adjacent lamina propria or muscularis propria
  - Seminal vesicles
    - Report spread of carcinoma in these organs either through epithelium or by direct extension of an infiltrative carcinoma
  - Vagina/uterus
    - Report direct extension or metastases to either organ
  - Rectum, pelvic and abdominal wall
    - Report direct extension or metastases

Lymph node status
- Report the number of lymph nodes sampled
- Report the presence or absence of metastases
  - If metastases are present, state the followings in the report
    - The number of positive nodes
    - The overall size the largest positive (<2, 2.1–5, >5 cm) (for N staging)
    - The diameter of the largest metastasis
    - The presence or absence of extranodal extension
- Final pathological staging (using the most current TNM staging)
- Results of ancillary studies (if performed)
- Correlation with frozen section diagnosis (if performed)

indicate higher stage (pT3) cancer. Currently, there was no reliable method to predict extravesical extension with a TUR specimen.[26] However, a tumor with a 4 mm or greater depth of invasion in the TURB specimen is most likely to have extravesical extension.[46]

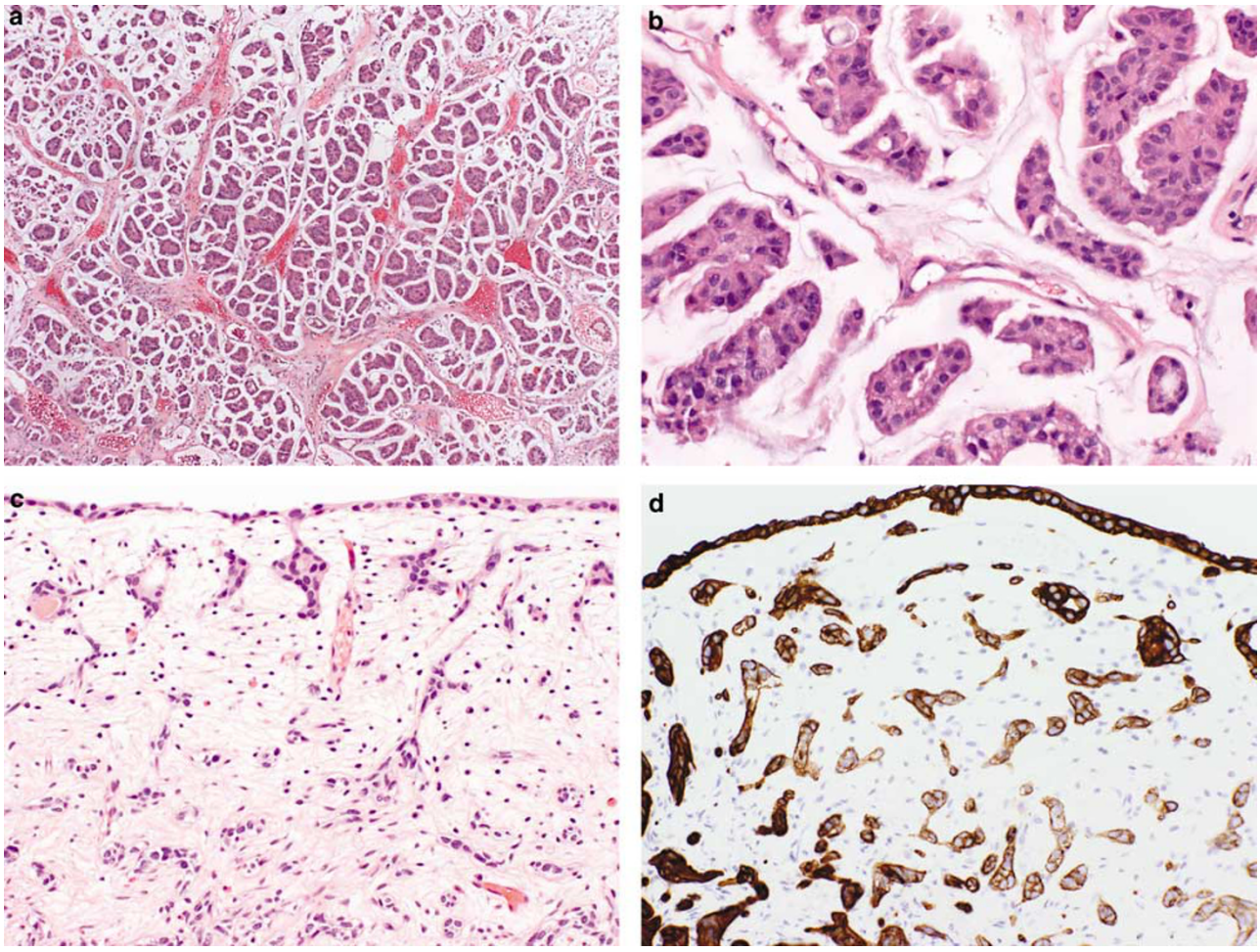

Figure 19 Micropapillary (**a** and **b**) and nested (**c** and **d**) variants of urothelial carcinoma. These variants are associated with poor prognosis and aggressive treatment is warranted. Retraction artifact is common in micropapillary variant (**a**). The tumor cells of nested variant may appear to be bland (**c**), yet immunostaining for cytokeratin highlights the aggressively infiltrative nature of these cancer cells (**d**).

Histological Grading

Histological grading for invasive bladder carcinoma is of limited utility, as the majority of these tumors are high-grade or grade 3 urothelial carcinoma.[26] Either the 1973[126,127] or 2004[126,127] WHO grading system may be used for this purpose. Laboratories accredited by the College of American Pathologists are required to use the CAP cancer reporting guidelines.

Tumor Growth Pattern

Jimenez *et al*[128] proposed a classification of invasive bladder tumors based on pattern of growth. They noted three common patterns: nodular, trabecular, and infiltrative. In the infiltrative pattern, there are narrow cords or single cells permeating the stroma (Figure 21). These tumor cells are either highly pleomorphic or small and undifferentiated. Desmoplasia and necrosis are common with this pattern. Tumors with an infiltrative growth pattern are associated with a worse prognosis (median survival of 29 months) than tumors displaying a noninfiltrative (nodular or trabecular) growth pattern (median survival of 85 months).[128] The significance of assessing tumor growth pattern has been highlighted in a recent study.[129] The 5-year metastasis-free survival rates for urothelial carcinoma with nodular, trabecular, and infiltrative invasion pattern were 94, 74, and 12%, respectively.[129]

Tumor Size

The pathology report should include the largest tumor dimension and information about multifocality. In an analysis of 249 patients with stage Ta and T1 cancer, Heney *et al*[130] found that tumor size was a significant predictor of cancer progression. Thirty-five percent of patients with tumor size ≥ 5 cm developed muscularis propria invasion or metastasis. On the other hand, only 9% of patients with

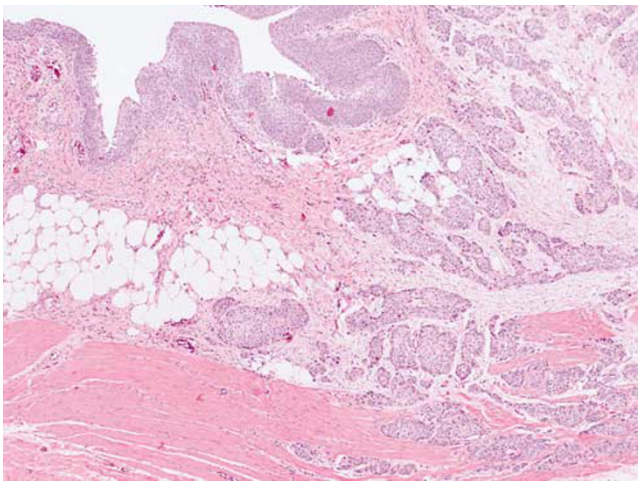

Figure 20 Adipose tissue may be present in both the lamina propria and muscularis propria. Thus, the presence of fat in a biopsy or TUR specimen does not necessarily indicate extravesical extension (pT3 carcinoma).

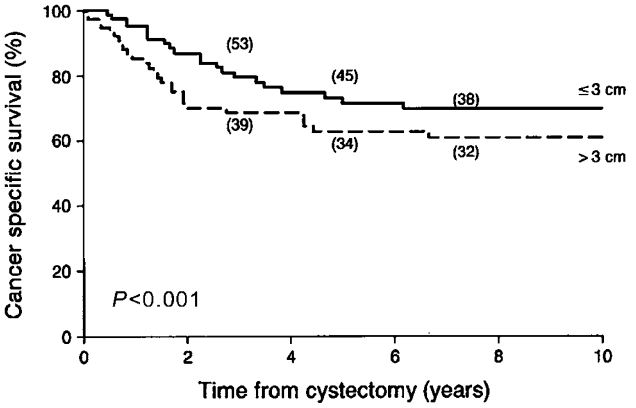

Figure 22 Cancer-specific survival according to tumor size. Tumor size was independent predictor of clinical outcome when comparing tumors with maximum dimension ≤ 3 or >3 cm ($P<0.001$) (from Cheng *et al*:[3] Predicting the survival of bladder carcinoma patients treated by radical cystectomy. *Cancer* 2000; 88:2326, with permission).

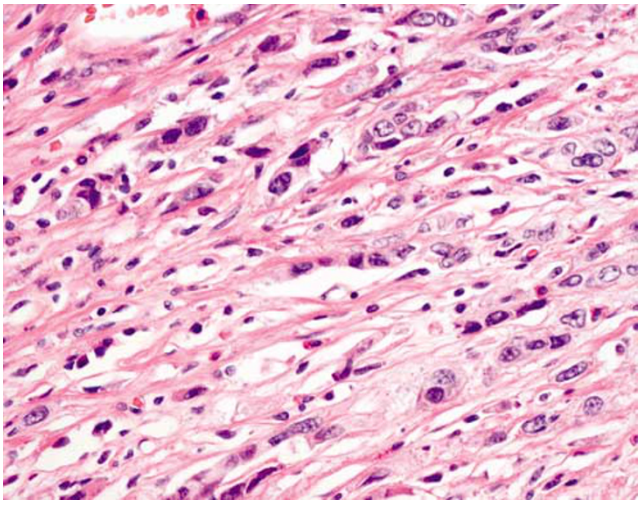

Figure 21 Infiltrative growth pattern in invasive urothelial carcinoma. The tumor is composed of highly pleomorphic and anaplastic cells in narrow cords or as individual cells permeating the stroma.

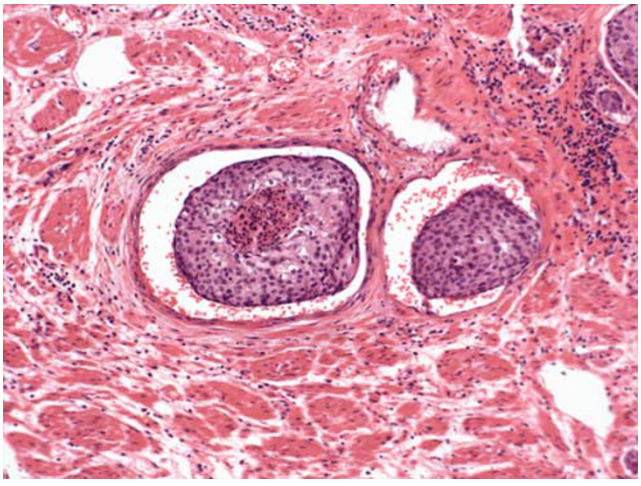

Figure 23 Lymphovascular invasion of urothelial carcinoma. In some cases, endothelial cells are identified on routing H&E sections, eliminating the need for CD31 or CD34 staining.

tumor size <5 cm developed cancer progression.[130] One study found that tumor size was an independent predictor of distant metastasis-free survival, but not of overall survival.[131] In recent cystectomy series, tumor size was an independent predictor of distant metastasis-free survival, cancer-specific survival, and overall survival (Figure 22).[3,85] The use of a 3 cm largest tumor diameter cutoff appeared to stratify patients into distinct prognostic groups.[3,85]

Tumor Multifocality

Development of multifocal tumors in the same patient, either synchronous or metachronous, is a common characteristic of urothelial malignancy.[132–135] Premalignant changes, such as dysplasia or CIS, often are found in urothelial mucosa aside from an invasive bladder cancer.[136,137] Studies of urothelial genetic alterations and atypia mapping in cystectomy specimens confirm the importance of field cancerization in the development of multifocal urothelial tumors, especially in early stage cancer. There is evidence that multifocal urothelial carcinoma can arise through independent concurrent genetic events at multiple locations in the lower urinary tract.[138,139] Other studies, however, have suggested a monoclonal origin for multifocal urothelial carcinoma.[140,141] In cases with multifocal cancer, the location and size of each tumor should be documented in the gross description. Some studies have suggested that tumor multifocality

is associated with poor outcome for patients with urothelial carcinoma.[130,134,135,142] Cohorts in these studies were limited to early stage (Ta and T1) bladder cancer. In a recent study of cystectomy specimens, which included more advanced cancers, tumor multifocality did not have prognostic significance.[3]

Lymphovascular Invasion

The incidence of lymphovascular invasion is variable and has been reported to be as high as 42% (Figure 23).[143] The presence of lymphovascular invasion predicts poor outcome, and this finding should be included in the pathology report.[143–147] The 5-year cancer-specific survival was 87 and 65%, respectively, for those without and with lymphovascular invasion.[145] In another study of 283 radical cystectomy specimens, vascular invasion, pathological stage, and lymph node metastasis were independent predictors of cancer-specific survival.[144] In the most recent study of radical cystectomy specimens with stratification for lymphovascular invasion, this parameter was the most significant predictor of cancer-specific survival (HR 2.3, $P=0.009$), surpassing even pT stage (HR 1.26, $P=0.03$).[146]

Identification of lymphovascular invasion is often difficult due to artifactual clefting around nests of invasive carcinoma.[148] Retraction artifact is prominent and almost uniformly present in the micropapillary variant of urothelial carcinoma (Figure 19a and b).[123] In suspicious cases, endothelial lined vessels can be highlighted by immunohistochemical staining for CD31 or CD34. The presence of vascular or lymphatic invasion, and whether immunohistochemical stains assisted in identifying this finding, should be included in the report. Immunohistochemical studies directed against endothelial cells have found that fewer than 40% of cases with purported vascular invasion on routine H&E examination are definitively confirmed.[116]

Perineural Invasion

The incidence of perineural invasion is high in advanced stage bladder carcinoma. Leissner *et al*[144] found perineural invasion in 47% of 283 radical cystectomy specimens. Perineural invasion is often present at the fronts of fatty infiltration by urothelial carcinoma (Figure 15b). The prognostic significance of perineural invasion is uncertain. In multivariate analyses, perineural invasion was not an independent predictor of patient outcome.[144,149]

Surgical Margins

Tumor present at the resection margin is assumed to indicate residual tumor in the patient. A positive margin should be classified as macroscopic or microscopic according to the findings at gross examination and at microscopic study of inked margins (Figure 24). The incidence of positive soft tissue margins is 4% in modern series, and a positive soft tissue margin is associated with poor cancer survival.[3,150] Five-year cancer-specific survival rates of 32 and 72% were found for those with and without positive surgical margins, respectively (Figure 25).[150] None of the patients with positive margins survived after 10 years.[3]

The resection margins should be individually specified in the pathology report, especially when positive. The following margins should be reported separately: ureteral (right and left), urethral, perivesical soft tissue, and pelvic soft tissue margins (for pelvic exenteration specimens). In cases of urachal adenocarcinoma in which partial cystectomy with excision of the urachal tract and umbilicus is performed, the margins of the urachal tract, that is, the soft tissue surrounding the urachus and

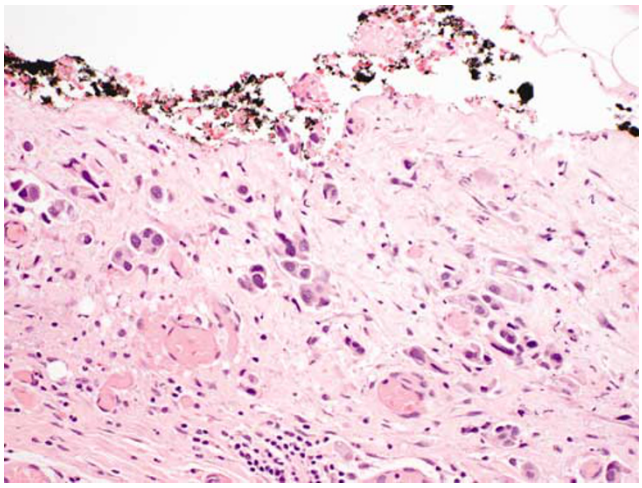

Figure 24 Positive soft tumor margins. Tumor cells are present at the inked perivesical soft tissue margin.

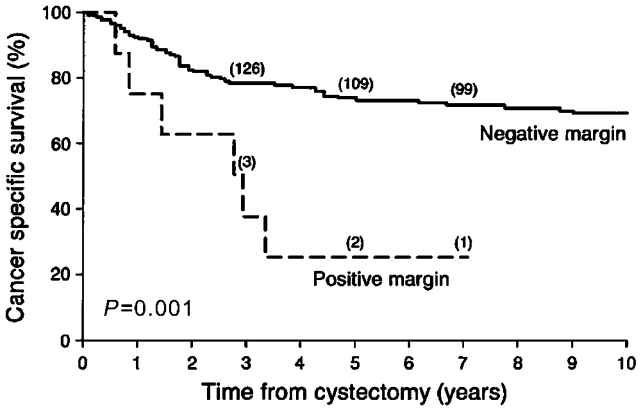

Figure 25 Cancer-specific survival according to margin status. Positive margins were associated with poor clinical outcome ($P=0.001$) (from Cheng *et al*:[85] Tumor size predicts the survival of patients with pathologic stage T2 bladder carcinoma: a critical evaluation of the depth of muscle invasion. *Cancer* 1999; 85:2638, with permission).

the skin around the umbilical margin, should be specified.

Consistent and standardized pathological evaluation is essential for comparison of treatment results between clinical trials and for translational research endeavors.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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