



REVIEW

Staging of bladder cancer

Martin J Magers,¹ Antonio Lopez-Beltran,^{2,3} Rodolfo Montironi,^{4,5} Sean R Williamson,^{6,7} Hristos Z Kaimakliotis⁸ & Liang Cheng^{1,8}

Departments of ¹Pathology and Laboratory Medicine, ²Urology, Indiana University School of Medicine, Indianapolis, IN, USA, ³Department of Pathology, ⁴Faculty of Medicine, Department of Surgery, Unit of Anatomical Pathology, Cordoba, Spain, ⁵Champalimaud Clinical Center, Lisbon, Portugal, ⁶Institute of Pathological Anatomy and Histopathology, School of Medicine, Polytechnic University of the Marche Region (Ancona), United Hospitals, Ancona, Italy, ⁷Department of Pathology and Laboratory Medicine and Henry Ford Cancer Institute, Henry Ford Health System, Detroit, MI, USA, and ⁸Department of Pathology, Wayne State University School of Medicine, Detroit, MI, USA

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Urothelial carcinoma of the urinary bladder is a heterogeneous disease with multiple possible treatment modalities and a wide spectrum of clinical outcome. Treatment decisions and prognostic expectations hinge on accurate and precise staging, and the recently published American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition, should be the basis for staging of urinary bladder tumours. It is unfortunate that the International Union Against Cancer (UICC) 8th edition failed to incorporate new data which is considered in the AJCC 8th edition. Thus, the AJCC 8th edition is the focus of this review.

Keywords: urinary bladder, urothelial carcinoma/neoplasia, staging classification, prognosis, T1 substaging, metastasis

Several critical changes and clarifications are made by the AJCC 8th edition relative to the 7th edition. Although the most obvious changes in the 8th edition are in the N (i.e. perivesical lymph node involvement now classified as N1) and M (i.e. M1 is subdivided into M1a and M1b) categories, several points are clarified in the T category (e.g. substaging of pT1 should be attempted). Further optimisation, however, is required. No particular method of substaging pT1 is formally recommended. In this review, these modifications are discussed, as well as points, which require further study and optimisation.

Introduction

Urothelial carcinoma is the most common cancer of the urinary bladder, and is a heterogenous disease with multiple possible treatment modalities, ranging from surveillance to radical cystectomy.¹ Patients with urinary bladder cancer are stratified by tumour grade and by tumour stage, according to the recently

published American Joint Committee on Cancer (AJCC) Staging Manual 8th edition.² These parameters guide treatment decisions, and it is important for surgical pathologists to be aware of current staging guidelines for urinary bladder cancer.^{1,3} Unfortunately, a point of confusion in regard to accurate tumour grading and staging may arise due to conflicting and confusing recommendations made by the International Union Against Cancer (UICC) 8th edition, which was published in 2016.^{4,5} The UICC 8th edition failed to incorporate new data which was taken into consideration in the AJCC 8th edition. For example, the UICC retained the old term ‘transitional

Address for correspondence: Liang Cheng, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, 350 West 11th Street, IUHPL Room 4010, Indianapolis, IN 46202, USA. e-mail: liang_cheng@yahoo.com

cell carcinoma', the UICC does not indicate which grading system should be used for grading of urothelial neoplasms and the UICC still recommends different stages for *in-situ* involvement of the prostatic urethra (i.e. Tis pu) and prostatic duct involvement (Tis pd), even though there is no prognostic difference between these groups.⁵

Furthermore, the UICC recommendations for pT2 and pT4 tumours are incomplete and confusing. The UICC recommendations for pT2 staging are not stated clearly, as they refer to inner muscle and outer muscle invasion, and the inner muscle invasion could be confused to mean muscularis mucosa invasion rather than the inner half of the muscularis propria. Regarding pT4 tumours, the UICC fails to discuss the route of invasion by urothelial carcinoma into prostatic stroma (i.e. direct invasion from the bladder into prostatic stroma or invasion from the prostatic urethra).

Thus, this review will discuss current staging recommendations made by the AJCC Staging Manual 8th edition, with emphasis on problematic decision points and areas which need further refinement in future staging systems (Figure 1).

Stage pT0 carcinoma

Pathological stage pT0 is assigned when there is no residual urothelial carcinoma (non-invasive or invasive) in the cystectomy specimen (Table 1). This occurs typically following a diagnosis of muscle invasive bladder carcinoma in the biopsy or transurethral resection (TUR) specimen(s) and completion of neoadjuvant chemotherapy (NAC), although some patients are stage pT0 at radical cystectomy without undergoing NAC.⁶ NAC should be designated in the pathological stage with the modifier 'y' (e.g. ypT0).

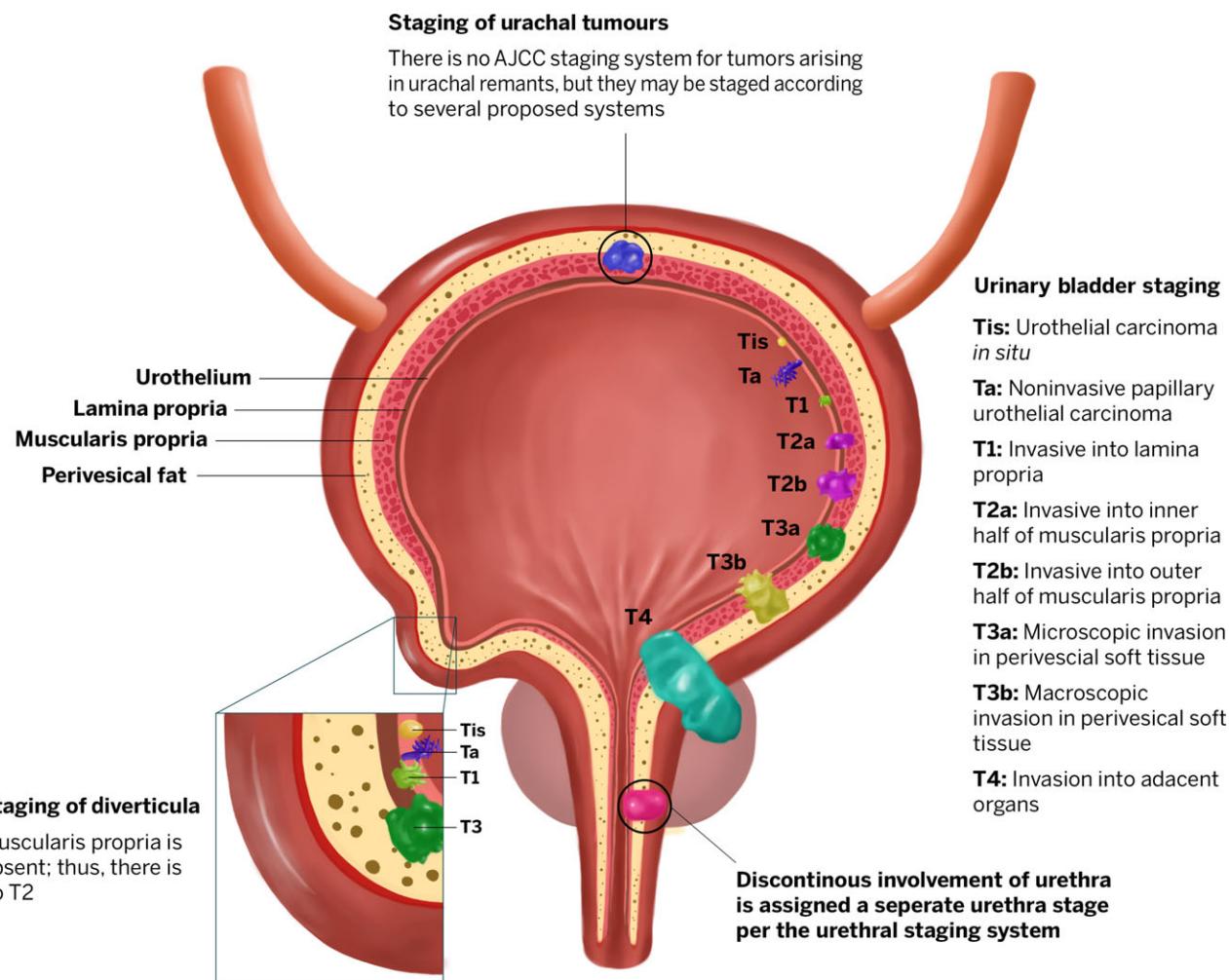


Figure 1. Overview of staging of tumours arising from the urinary bladder, diverticulum and urachal remnants.

Table 1. The American Joint Committee on Cancer (AJCC) Staging System (8th edition, 2017)

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria
pT2a	Tumour invades superficial muscularis propria (inner half)
pT2b	Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostatic stroma, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall
Regional lymph nodes (N)	
NX	Lymph nodes cannot be assessed
NO	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Historically, the incidence of stage pT0 bladder carcinoma was approximately 10%.^{7–12} With increased utilisation of NAC, however, the incidence of stage pT0 bladder carcinoma may be increasing. A recent meta-analysis found an incidence of pT0 of nearly 30%; another recent meta-analysis found that NAC achieved higher rates of pT0 than radical cystectomy alone, and a primary benefit of NAC may be that it

increases a patient's chance of achieving stage pT0.^{13–15} Even so, most patients do not achieve a stage pT0 following NAC. A possible predictor of likelihood of pT0 at cystectomy following NAC is the presence or absence of variant histology, and this should be included in the surgical pathology report. Demonstrating this, a recent study of 50 patients with and without pT0 at cystectomy found that any variant histology (e.g. squamous or sarcomatoid differentiation) in the TUR specimen decreases the likelihood of achieving pT0 compared to patients with pure urothelial carcinoma lacking variant histology.¹⁶ Achieving pT0 portends a significantly better prognosis for the patient, particularly when the patient has a complete pathological response (pTONOMO), as these patients had better overall survival and recurrence-free survival than patients without a complete pathological response in the aforementioned recent meta-analysis.¹³

Although prognosis is much improved relative to higher stage bladder carcinoma, the clinical outcome of patients with stage pT0 bladder carcinoma remains somewhat variable, as 5-year recurrence-free, cancer-specific and overall survivals were 84, 88 and 84%, respectively, in a large study of 120 patients, due probably to extravesical spread prior to cystectomy.⁹ Thus, identifying and reporting parameters which can stratify stage pT0 patients is important. Multivariate analysis demonstrated that independent predictors of outcome include lymphovascular invasion (LVI) and carcinoma *in situ* (CIS) in the TUR specimen(s); the 5-year overall survival for patients with LVI was 70%, while the overall survival for patients without LVI was 89%.⁹ LVI is clearly an important prognostic factor in some patients, and standardisation of reporting of LVI with possible formal incorporation into staging systems may be necessary.¹⁷

Lymph node metastases in patients with stage pT0 bladder carcinoma occur rarely, with 3–7% of patients developing nodal metastases and, as discussed above, these patients may have a worse prognosis.^{8,11}

In summary, pT0 urinary bladder cancer is increasing in incidence due to utilisation of NAC and prognosis is generally very good, particularly in patients with a complete pathological response, but death can occur in patients with metastatic disease.

Stage pTa carcinoma

Papillary urothelial carcinoma which lacks invasion is assigned stage pTa, according to the AJCC Staging

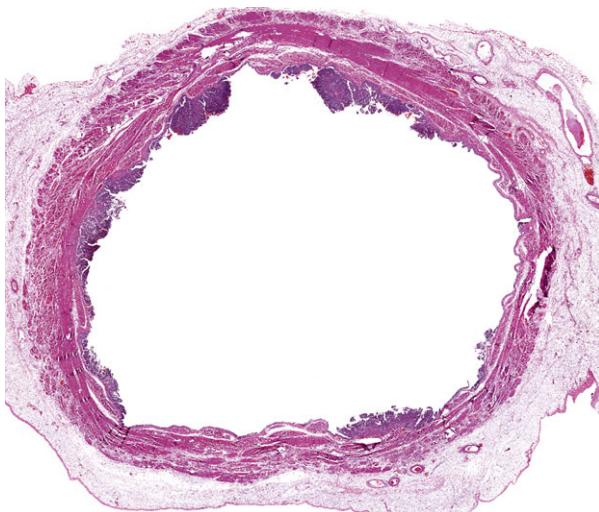


Figure 2. Whole mount view of non-invasive papillary urothelial carcinoma (pTa).

Manual 8th edition (Figure 2).² Histological grade should be designated in the surgical pathology report and is an important prognostic factor for pTa bladder tumours.¹⁸ Any invasion removes a tumour from the category of pTa. Conversely, if a flat urothelial lesion (i.e. urothelial CIS) is truly present, it should also be reported, as this can have important prognostic implications. Caution should be taken when diagnosing CIS in the presence of high-grade papillary urothelial carcinoma, however, as the 'shoulder' or base of the papillary lesion may appear flat. While no consensus guidelines for this situation exist, the authors of this review recommend that (1) the CIS be located remotely from the papillary tumour or present in an entirely different tissue fragment; (2) if present in the same tissue fragment, a strip of normal (i.e. non-neoplastic) urothelium is present between the CIS and the papillary tumour; or (3) the CIS looks histologically distinct from the papillary tumour. If both a papillary tumour and CIS are present, the AJCC Staging Manual 8th edition is not entirely clear regarding what is the correct stage assignment.² One approach, which is recommended by the authors, is to assign both pTa and pTis (i.e. pTa/pTis).

Stage pTis carcinoma

Urothelial carcinoma *in situ* is a flat urothelial lesion composed of atypical, enlarged urothelial cells with hyperchromasia, nuclear pleomorphism, high nuclear to cytoplasm ratio and frequent mitotic figures which lack invasion (Figure 3). It is often associated with

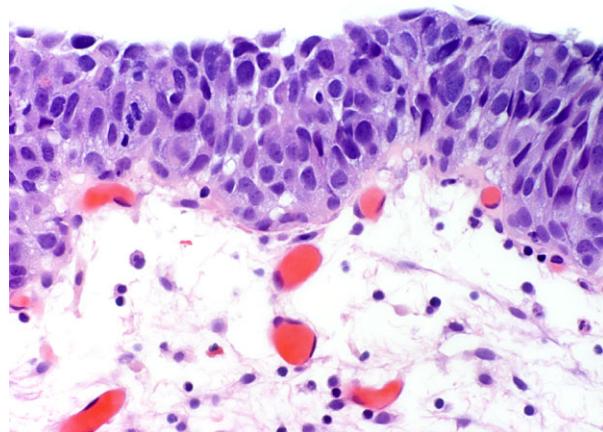


Figure 3. Urothelial carcinoma *in situ* (pTis).

invasive urothelial carcinoma or high-grade papillary urothelial carcinoma, but it can also be present alone. Cystectomy specimens possessing urothelial CIS without an invasive component are assigned pathological stage pTis, according to the AJCC Staging Manual 8th edition.² Urothelial CIS is present without concomitant invasive urothelial carcinoma (i.e. pTis) in approximately 10% of radical cystectomy specimens.¹⁹

Urothelial CIS may be resistant to chemotherapy and can progress to invasion,^{20–22} and CIS is often present in the cystectomy specimen following NAC, either alone or in association with residual invasive urothelial carcinoma. Urothelial CIS is not only critical to identify when it is the 'worst' pathological finding (i.e. pTis), but it is also an important prognostic indicator in patients with an invasive tumour (i.e. pT1-2) with associated CIS.

The presence of urothelial CIS in association with stage pT0–pT2 bladder carcinoma is associated with worse cancer-specific mortality compared to patients with stage pT0–pT2 bladder carcinoma lacking urothelial CIS.²³ Cancer-specific mortality of patients with stage pT3–pT4 bladder carcinoma, however, is unaffected by the presence of urothelial CIS.²³

Stage pT1 carcinoma

Invasion of lamina propria by urothelial carcinoma without extension into muscularis propria is assigned stage pT1 (Figure 4).² Additionally, the AJCC Staging Manual 8th edition strongly recommends substaging pT1 tumours to stratify patients and separate a small focus of invasion from extensive invasion, but it does not fully endorse any method for doing so. Thus,

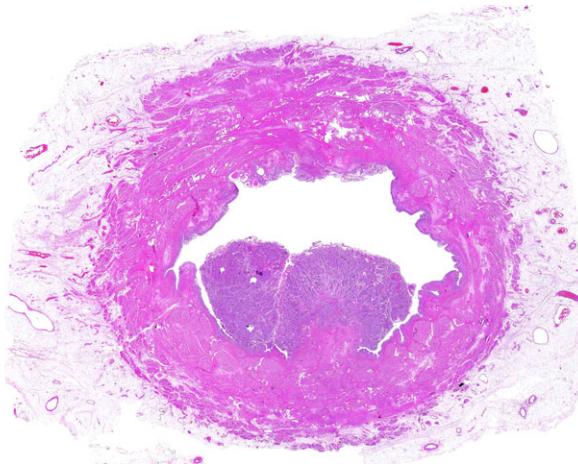


Figure 4. Whole mount view of pT1 papillary urothelial carcinoma.

there are currently no officially recognised categories for pT1 substaging.

CHALLENGES OF DIAGNOSING LAMINA PROPRIA INVASION

Identification of lamina propria invasion may be challenging in some situations, particularly in cases which are superficially or focally invasive. Factors which add to this difficulty are problems with embedding the tissue (e.g. tangential sectioning or poorly orientated tissue fragments), procedural artefact (e.g. thermal injury or cautery artefact) and tumour-induced changes (e.g. severe inflammation at the interface of the tumour and non-neoplastic tissue).^{1,24} Additionally, some variants of invasive urothelial carcinoma are deceptively bland (e.g. nested variant of urothelial carcinoma), and proliferative von Brunn nests may mimic invasion.²⁵ Neoplastic cells may also involve von Brunn nests via either pagetoid spread or direct extension from adjacent tumour, and this can be confused with lamina propria invasion. In this situation, the basement membrane typically remains smooth with a regular contour, and a parallel array of thin-walled vessels often lines the basement membrane (Figure 5A). Morphological features which may aid in identification of lamina propria invasion include identifying infiltrative single cells or irregularly shaped nests, jagged basement membrane contour without a linear array of thin-walled vessels, tentacular or finger-like extensions arising from the base of papillary tumours (Figure 5B), retraction artefact surrounding irregular nests and paradoxical maturation of invasive cells (i.e. invasive cells gain

eosinophilic cytoplasm and appear less pleomorphic than overlying *in-situ* neoplastic cells) (Figure 5C).

Retraction artefact is helpful as a clue in identifying invasive carcinoma (Figure 5D), but it can also be problematic when assessing for lymphovascular invasion (LVI). Immunohistochemistry for endothelial markers (e.g. CD31 and CD34) may be helpful in separating retraction artefact (i.e. negative for endothelial markers) from true LVI (i.e. positive for endothelial markers). This is increasingly important, as LVI has been identified as an important prognostic feature.²⁶

Additionally, a stromal reaction may also aid in identifying invasive carcinoma (Figure 6), but this is not always present.²⁷ When a stromal response is present, it may be hypocellular with a myxoid background; cellular with spindle-shaped fibroblasts and variable collagenisation; pseudosarcomatous; desmoplastic; or inflammatory. Immunohistochemistry using a pan-keratin cocktail may be helpful in identifying invasive carcinoma.²⁸ This, however, should be performed with caution, as aberrant keratin expression may be seen in reactive myofibroblastic cells, and not everything that is keratin-positive in the lamina propria is carcinoma.²⁹ The spindled morphology with myofibroblastic features and lack of frankly malignant features (e.g. cytological atypia or atypical mitotic figures) can help to avoid misinterpretation of immunohistochemical results.

INTEROBSERVER VARIABILITY OF DIAGNOSING LAMINA PROPRIA INVASION

Underscoring the difficulty of assessing lamina propria invasion is substantial interobserver variability. While the majority of changes in staging from pT1 occurs in downstaging (15–56% of pT1 cases), a substantial number of cases are also upstaged (3–13% of pT1 cases).^{30–34} Change of stage by experienced or expert genitourinary pathologists appears prognostically important, as confirmed pT1 tumours have a greater likelihood for progression or recurrence than those tumours which are downstaged.^{30,31,34} Further demonstrating this variability, Compérat *et al.* found that when eight expert genitourinary pathologists annotated invasive areas on virtual slides from cases diagnosed initially, as pT1 cancer full agreement was present in only 47% of cases ($\kappa = 0.47$).³⁴

Interobserver variability in diagnosing pT1 cancer clearly has important clinical consequences, and striving for higher reproducibility in assessing staging categories, particularly pT1, is important. Bol *et al.* found that while complete interobserver agreement

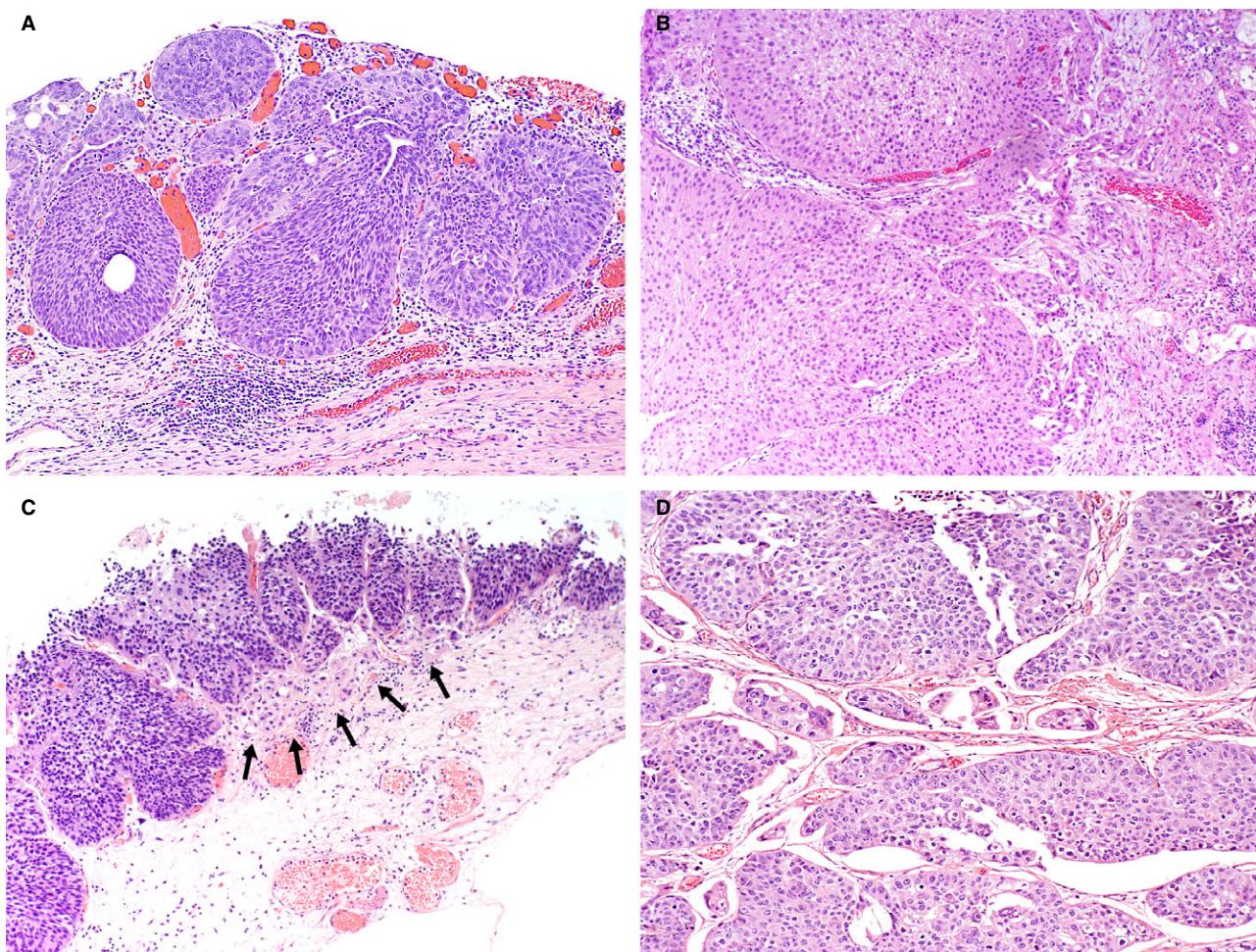


Figure 5. Histopathological evaluation of lamina propria invasion. A, Urothelial carcinoma involving the von Brunn nests. Note parallel arrays of thin-walled vessels surrounding von Brunn nests. B, pT1 urothelial carcinoma with ragged irregular borders. C, pT1 urothelial carcinoma with paradoxical differentiation (arrows). D, pT1 urothelial carcinoma with retraction artefact.

on stage pT1 stage cases among reviewers was only 80%, after a second review this increased to 87.7%.³⁰ Thus, consensus review and agreement on criteria for invasion may at least partially ameliorate interobserver disagreement of stage pT1 cases. Furthermore, substaging of pT1 is probably valuable in separating cases which are superficially invasive and borderline non-invasive from cases which are clearly invasive and borderline muscularis propria-invasive.

TUMOUR GRADE

Current recommendations for grading urothelial carcinoma are to assign either low- or high-grade as part of a two-tier grading scheme, and invasive urothelial carcinoma is almost invariably considered high-grade. Prior to adoption of this system, the 1973 WHO grading classification stratified urothelial

carcinoma into three tiers: grades 1, 2 and 3. Tumours that are now considered high-grade urothelial carcinoma would previously have been considered grades 2 or 3 urothelial carcinoma.³⁵ The previous system acknowledges the morphological spectrum of tumour grade, and Pellucchi *et al.* demonstrated that application of the 1973 grading system can stratify patients with lamina propria invasion.³⁶ Recurrence-free and progression-free survival were significantly worse in the grade 3 group compared to the grade 2 group. These data suggest that application of the 1973 grading system may be useful for substaging pT1 cancers.^{20,35,37}

MICROINVASIVE CARCINOMA

One subset of pT1 cancers which merit discussion is so-called 'microinvasive carcinoma'. Beginning in

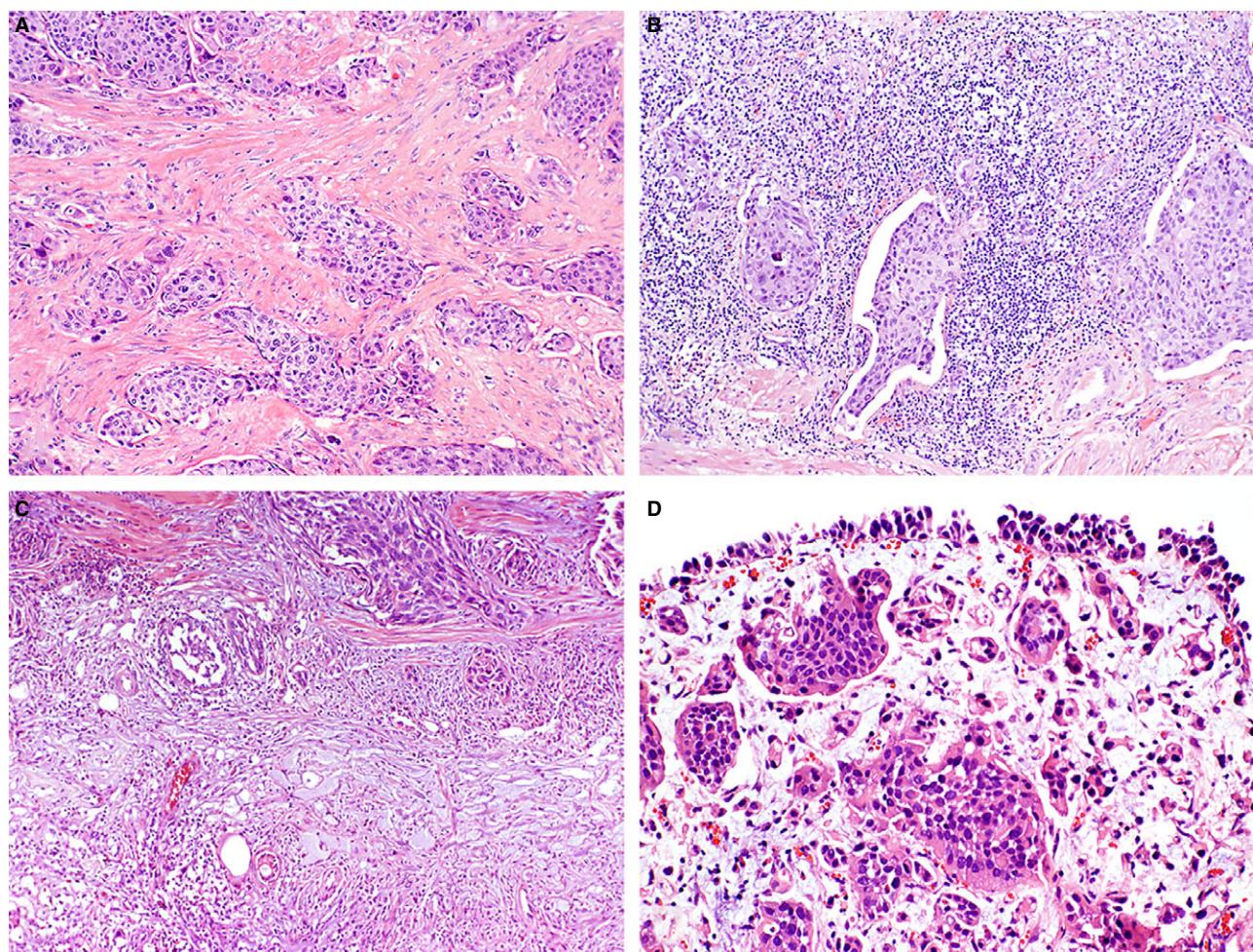


Figure 6. Different patterns of stromal response. A, Desmoplastic. B, Inflammatory. C, Myxoid. D, Mucinous/pseudosarcomatous.

1976 with the study by Farrow *et al.*, several criteria for microinvasion have been proposed.^{38–44} Farrow *et al.* initially defined microinvasion as tumour extending up to 5 mm from the basement membrane.^{38,39,44} With this definition in mind, Farrow examined cystectomy specimens that were entirely embedded and identified cases which possessed extensive urothelial CIS involving at least 25% of the bladder. Of these 70 cases, 24 cases (34%) possessed microinvasion, and 5.8% of patients with microinvasion had a lymph node metastasis and died of their disease.⁴⁴

Amin *et al.* and McKenney *et al.* subsequently proposed a 2-mm cut-off and, more recently, a 0.5-mm cut-off, which is pragmatically equivalent to one high-power field, was proposed by van der Aa *et al.*^{40,42,43} The 0.5-mm/one high-power field cut-off has been shown to be widely feasible and, in the majority of studies, correlated with outcome.^{42,45–50}

Alternatively, Lopez-Beltran *et al.* proposed the cut-off to be 20 infiltrating tumour cells within the lamina propria rather than a linear measurement.⁴¹ Specifically, with regard to papillary urothelial carcinoma, Lawless *et al.* compared tumours with stalk-only invasion and focal tumour base invasion to tumours with extensive tumour base invasion, and found significantly worse outcomes in patients with extensive invasion.⁵¹

Further investigation and clinical validation is necessary to confirm the presence of microinvasion as a distinct substage of pT1 cancer and to determine the optimum cut-off.

HISTO-ANATOMICAL SUBSTAGING OF PT1

Microinvasive tumours excluded, pT1 remains a heterogeneous group with highly variable recurrence and progression rates.^{25,52–56} Thus, reproducible and

accurate substaging of pT1 tumours with more than microinvasion is necessary to stratify pT1 patients into prognostically and clinically distinct groups. The two main strategies which have been attempted toward this goal are substaging based on anatomical relationships (e.g. invasion relative to muscularis mucosae) and substaging based on linear depth of invasion (e.g. utilising a cut-off of 3 mm), both of which have some merits as well as difficulties.

Muscularis mucosae is composed of thin, wavy fascicles of smooth muscle which are frequently associated with large, thin-walled blood vessels (Figure 7A). It is present in the mid to upper lamina propria in the majority of radical cystectomy specimens, but a minority of radical cystectomy specimens do not have discernable muscularis mucosae (approximately 6%).⁵⁷ In biopsy specimens, muscularis mucosae is variably present (15–83%).^{25,53,54,57–66} In cases which lack muscularis mucosae, a vascular plexus typically associated with the muscularis mucosae has been proposed as a substitute landmark.^{25,58–62,67,68} However, some cases are still unable to be staged using this criterion, as Angulo *et al.* was unable to identify muscularis mucosae or the associated vascular plexus in 35% of their cases.⁶⁹ Furthermore, the location of the vascular plexus can vary greatly either above or below the muscularis mucosae, particularly in the trigone, making the use of the vascular plexus questionable.⁶⁹ Nonetheless, beginning in 1990 with Younes *et al.*,⁶² many studies have investigated pT1 substaging relative to the muscularis mucosae and/or vascular plexus with mixed, but generally positive, results.^{26,45–49,54,58–60,67–86}

Some of these studies substaged pT1 into three categories (i.e. above, into or below the muscularis mucosae/vascular plexus), while others utilised only two substages (i.e. above or below the muscularis mucosae/vascular plexus) (Figure 7B). Overall, substaging was usually possible (median = 93%; range = 43–100%), and the majority of the studies found pT1 substaging to be predictive of outcome (68% of the studies; 48% by multivariate analysis and 19% by univariate analysis).⁸⁷ Not all studies, however, found utility in substaging based on muscularis mucosae/vascular plexus. For example, Platz *et al.* found muscularis mucosae in only 33% of cases, and they identified no significant prognostic value in utilising the muscularis mucosae/vascular plexus cut-off.⁶⁹ Similarly, Kondylis *et al.* found no significant difference in recurrence and progression in their study, with a median follow-up of 71 months.⁷³ Conversely, in the largest of these studies, involving 587 pT1 patients from six hospitals and median follow-up

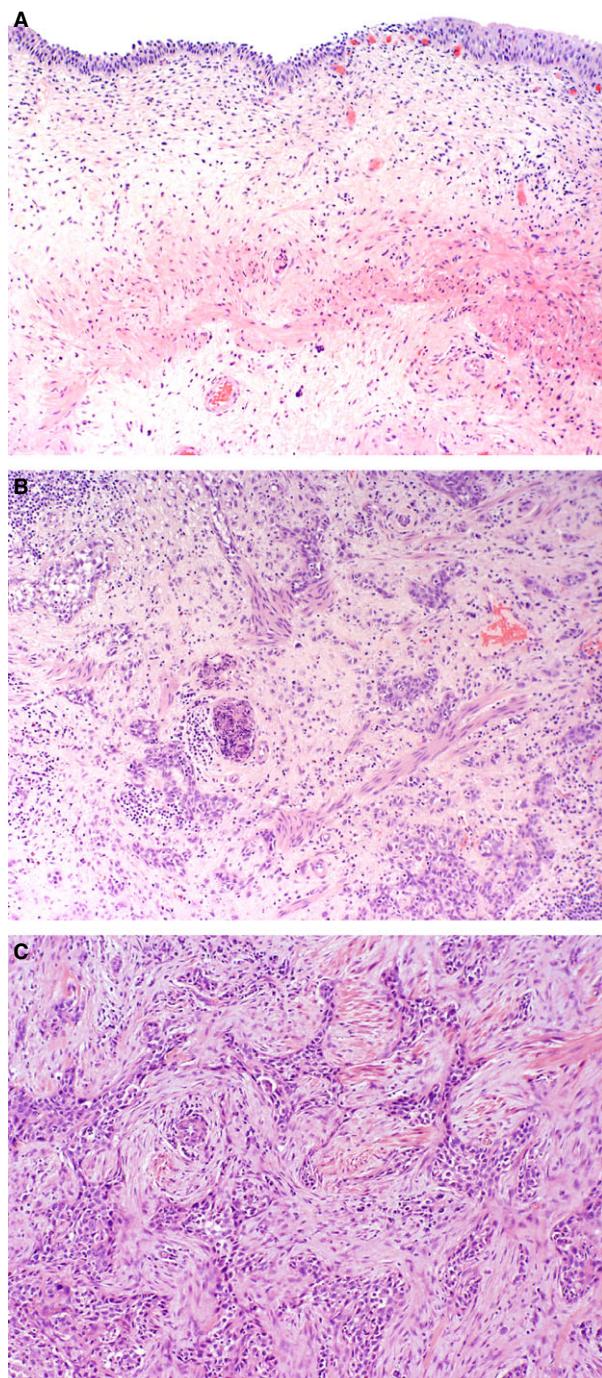


Figure 7. Histopathological evaluation of muscularis mucosae invasion. A, normal muscularis mucosae of the urinary bladder. B, pT1 urothelial carcinoma with muscularis mucosae invasion. C, Extensively invasive urothelial carcinoma. It would be difficult to distinguish between muscularis mucosae and muscularis propria.

of 35 months, Rouprêt *et al.* identified significantly worse recurrence-free survival, progression-free survival and cancer-specific survival in patients with

invasion beyond the muscularis mucosae.⁸² Furthermore, in the only prospective study of the group, Orsola *et al.* studied 200 patients with median follow-up of 71 months and found invasion beyond the muscularis mucosae to be an independent risk for progression.⁸⁶ Thus, although the data are somewhat mixed, there is substantial evidence that suggests substaging based on the muscularis mucosae/vascular plexus has clinical utility, although it is not always possible to do so due to histo-anatomical variance. In cases of extensively invasive urothelial carcinoma, it may be difficult or impossible to distinguish between muscularis mucosae and muscularis propria (Figure 7C).

LINEAR DEPTH SUBSTAGING OF PT1

An alternative to substaging with muscularis mucosae is to substage pT1 tumours by measuring the depth of invasion using an ocular micrometer.^{47,49,53,54,63,70,88} Measurement of depth of invasion from the mucosal basement membrane correlates with the final pathological stage at cystectomy.^{63,89} This is a similar approach to that discussed above for microinvasion (i.e. 0.5 mm cut-off), but the cut-off is greater. Some investigators have evaluated a 1-mm cut-off with varied success. Two studies identified significantly worse clinical outcomes in the tumours with > 1 mm compared to tumours with ≤ 1 mm invasion, while a third study showed no difference in the two groups.^{47,49,63} The study which failed to show a difference using the 1-mm cut-off demonstrated prognostic significance using a cut-off of 1.5 mm, as 95% of patients with invasion ≥ 1.5 mm in TUR had advanced stage (≥ pT2) bladder carcinoma at cystectomy (sensitivity 81%; specificity 83%; positive predictive value 95%; negative predictive value 56%).⁶³ Furthermore, although Chang *et al.*⁴⁷ recommended a 1-mm cut-off, they also found clinical significance in the 1.5-mm cut-off. Using this criterion, of 83 consecutive pT1 patients, the 5-year progression-free survival was significantly worse in tumours with ≥ 1.5 mm (67 versus 93%).⁵⁴ Finally, Brimo *et al.*⁷⁰ found that quantifying invasion using cut-offs for depth of 3 mm and diameter of 6 mm significantly correlated with outcome and, very recently, Leivo *et al.*⁹⁰ recommended using a cut-off of ≥ 2.3 mm as the best predictor of progression. In practical terms, 2.3 mm is approximately equivalent to one ×10 microscopic field.

The cumulative data of these studies clearly weighs in favour of the utility of a linear cut-off to substage

pT1 tumours. The optimal cut-off point and whether linear measurement should be used instead of the muscularis mucosae/vascular plexus are, however, debatable. This is the reason for the current recommendation by the AJCC Staging Manual 8th edition to attempt some strategy of pT1 substaging without specifying which method and cut-off should be used.² Future staging systems will need to bring clarity to this hotly debated issue.

Stage pT2 carcinoma

Stage pT2 urinary bladder cancer is defined as tumour invasion into the muscularis propria (Figure 8A). This is subdivided further into tumour invading the superficial (i.e. inner half) muscularis propria (pT2a) and tumour invading the deep (i.e. outer half) muscularis propria (pT2b). The clinical utility of this subdivision is still questionable.¹

In 1952, Jewett found that patients with what is now considered stage pT2b disease had worse survival ($n = 13$, 8% survival) than patients with what is now considered pT2a disease ($n = 5$, 80%).⁹¹ Many subsequent, larger studies have failed to support these initial findings.^{7,92–103} Cheng *et al.* found no survival difference between stage pT2a and pT2b tumours in 64 patients, with a median follow-up of 8.3 years.⁹⁷ Although depth of muscularis propria invasion demonstrated no difference in outcome, tumour size (i.e. largest tumour dimension) was predictive of outcome in pT2 patients.⁹⁷ Patients with a pT2 tumour <3 cm had better 10-year cancer-specific survival compared to patients with a pT2 tumour ≥3 cm (94 versus 73%, respectively).⁹⁷ Additionally, Yu *et al.* studied 311 patients with a pT2 tumour and, when controlling for lymph node status, found no significant difference in outcome between superficial and deeply invasive tumours.¹⁰¹ Similarly, in studies of 790 pT2NO patients and 148 pT2NO patients, there were no significant differences in outcome between pT2a and pT2b patients.^{99,100} Indeed, even in 1978 enough evidence weighing against the utility of pT2a/b subdivision had mounted that Jewett determined: 'it seems probable that our arbitrary dividing line drawn 30 years ago at the halfway level to separate B1 (pT2a) from B2 (pT2b) tumours was too superficial'.¹⁰⁴

This admission of error by Jewett may have been premature, however, as several recent, large studies found clinical utility in the current pT2a/b staging classification.^{105–108} Gakis *et al.* studied 252 patients with pT2 tumours and found a significant difference

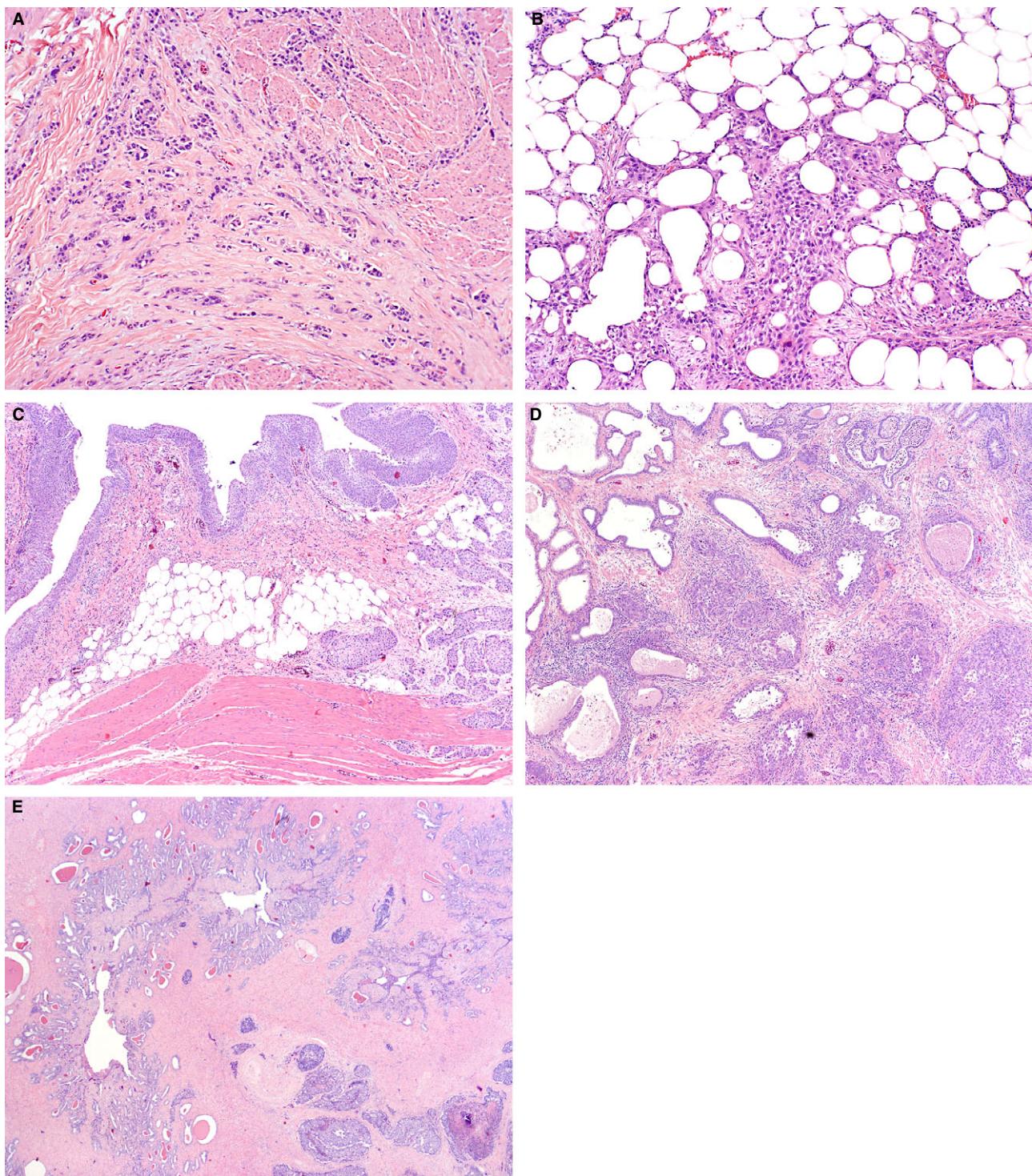


Figure 8. Advanced stage urothelial carcinoma. A, T2 invasive urothelial carcinoma. B, pT3 urothelial carcinoma with perivesical fat invasion. C, Adipose tissue can be seen in the lamina propria. Fat invasion in the transurethral resection specimen does not indicate pT3 cancer. D, pT4 urothelial carcinoma invading into the prostate. E, pT4 urothelial carcinoma invading into the seminal vesicles.

in recurrence-free survival (85.9 versus 37.5%, respectively) and cancer-specific survival (84.8 versus 59.6%, respectively) between pT2aN0 and pT2bN0

patients.¹⁰⁸ Additionally, pT2 substratification was the only risk factor of recurrence and cancer-specificity.¹⁰⁸ Similarly, Tilki *et al.* studied 565 pT2

tumours from six different institutions and found significantly better recurrence-free survival (73.2 versus 58.7%, respectively) and cancer-specific survival (78.0 versus 65.1%, respectively) in pT2a versus pT2b patients.¹⁰⁵ Another multi-institutional study by Sonpavde *et al.* included 707 pT2NO patients from nine different institutions found that recurrence-free survival was worse in pT2b patients compared to pT2a patients.¹⁰⁶ Finally, a study by Ghoneim *et al.* found significantly better 5- and 10-year survival in pT2a patients than pT2b patients, both with and without lymph node metastases, although this cohort included a relatively large number of squamous cell carcinomas (54%) and adenocarcinomas (11%).¹⁰⁷

In summary, of the studies regarding pT2 subclassification there may be utility in using the middle of the muscularis propria as the cut-off. This, however, is not definite, and future studies should elucidate this point further. Alternative methods of subclassifying pT2, such as tumour size, should also be explored further.

Stage pT3 carcinoma

Stage pT3 urinary bladder cancer is defined as tumour invading perivesical soft tissue (i.e. tumour invades perivesical fat outside of the muscularis propria) (Figure 8B). This is subdivided further into pT3a (i.e. microscopic invasion of perivesical soft tissue) and pT3b (i.e. macroscopic invasion of perivesical soft tissue).

A challenge in determining extravesical extension is the irregular arrangement of muscularis propria muscle bundles and admixture of adipocytes within the muscularis propria, which result in the border between the muscularis propria and the perivesical soft tissue being ill-defined. A recent survey of problematic pT2b versus pT3a cases conducted by Ananthanarayanan *et al.* demonstrated merely fair interobserver agreement ($\kappa = 0.286$) among 17 expert urological pathologists.¹⁰⁹ This study also highlighted three distinct approaches to defining the outer boundary of the muscularis propria: (1) the precise edge of the muscle bundle; (2) an irregular, imaginary line between adjacent muscle bundles; and (3) a straight, imaginary line along the outermost muscle bundle. Approximately half (nine of 17, 53%) of expert urological pathologists utilise the irregular, imaginary line between adjacent muscle bundles, and application of this definition results in higher median agreement ($\kappa = 0.696$). LVI alone should be not considered pT3a, although this is not specified in the

AJCC Staging Manual 8th edition.² The distinction of pT2b versus pT3a has important therapeutic implications, and a clear, consistent definition of microscopic extravesical extension is needed.^{110,111} The ambiguity of pT2b versus pT3a is a probable cause of the conflicting results of outcome studies between the two groups.^{100,112–114}

Adipose tissue is always present within the muscularis propria and is found frequently within the lamina propria (Figure 8C).¹¹⁵ Thus, the presence of tumour admixed with fat in a biopsy or TUR specimen does not necessarily indicate extravesical extension, or even muscle invasion, and stage pT3 should not be assigned to these transurethral specimens. Even so, it may be possible to identify patients at risk for extravesical extension based on a TUR or biopsy. For example, in a study of 90 patients the depth of invasion in the TUR specimen was found to be predictive of extravesical extension, with a depth of invasion > 4 mm from the basement membrane of the surface urothelium having a sensitivity, specificity, positive predictive value, and negative predictive value of 54, 90, 81 and 72%, respectively, for predicting stage pT3b.¹¹⁵ The overall accuracy of invasion depth for predicting extravesical extension, measured by the area under the receiver operating curve, was 0.81 [standard error (SE) = 0.045]. Zarei *et al.* demonstrated similar findings in a study of 206 patients with pT3NO following radical cystectomy,¹⁰⁰ as patients with < 4.5 -mm tumour invasion from the base of the muscularis propria had significantly better cancer-specific survival than patients with ≥ 4.5 -mm tumour invasion (53 versus 40%). It may be that a more objective parameter, such as measurement of thickness of invasive disease from the basement membrane of the surface urothelium or base of the muscularis propria, stratifies patients with pT2 and/or pT3 disease more clearly, and application of this measurement to TUR may be clinically valuable.

The prognostic significance of pT3 substaging as pT3a or pT3b has been a matter of debate, with numerous studies demonstrating conflicting results. For example, Quek *et al.* examined 236 patients (median follow-up = 8.9 years) with pT3 urinary bladder cancer and found no significant difference in recurrence or survival rates between patients with pT3a and pT3b tumours;¹¹⁶ lymph node and surgical margin status were the only factors to impact patient prognosis significantly among pT3 patients. Other studies have also demonstrated similar findings.^{100,117,118} Conversely, several recent, large studies have found that pT3b is associated with worse

outcome compared to pT3a.^{112–114,119} For example, Tilki *et al.*¹²⁰ included 808 patients who underwent radical cystectomy with stage pT3 and found that although there was no significant difference overall in outcome of pT3a versus pT3b patients, of the patients without lymph node metastasis (pN0) pT3b was associated with significantly worse 5-year recurrence-free survival (47.9 versus 60.7%) and cancer-specific survival (55.0 versus 64.4%) compared to pT3apN0 patients. Thus, careful assessment of the presence or absence of macroscopic perivesical invasion should be performed and report.

Although gross diagnosis of macroscopic perivesical soft tissue invasion is a critical component of the AJCC Staging Manual 8th edition and appears to have prognostic implications in a subset of pT3 patients, it is not always straightforward and hinges heavily on the thoroughness and accuracy of the prosector.² Unfortunately, assessment of extravesical extension of the tumour is not always documented in the prosector's gross description, and a recent study from a large tertiary care academic institution found that this was missing in 17% of reports.¹²¹ Most of these cases were staged as pT3a, and it is plausible that failure to document macroscopic extension resulted in understaging these tumours. Importantly, the authors also found that educational intervention increased the rate of reporting presence or absence of extravesical extension. Conversely, extravesical extension can also be mimicked macroscopically by reactive changes (e.g. inflammation and fibrosis), and microscopic confirmation is necessary. Because of these difficulties, it is not unexpected that the data regarding pT3a/pT3b may be muddled by inexact or incomplete gross descriptions. Another reason for these disparate findings may be that some patients

receive neoadjuvant or adjuvant chemotherapy.¹¹³ In a study of 903 patients, Neuzillet *et al.* found no significant difference in outcome between patients with pT3apN0 and pT3bpN0 who had received adjuvant chemotherapy while patients with pT3bpN0 had significantly worse metastasis-free survival compared to pT3apN0 (42 versus 68%, respectively).¹¹³

Stage pT4 carcinoma

According to the AJCC Staging Manual 8th edition, stage pT4 urinary bladder cancer is defined as extravesical tumour directly invading adjacent organs.² This is subdivided further into pT4a (i.e. direct invasion into prostatic stroma, uterus, or vagina) and pT4b (i.e. direct invasion into pelvic wall or abdominal wall).

PROSTATIC INVASION

Invasion of the prostate by urinary bladder urothelial carcinoma (Figure 8D) may occur in three ways: (1) intra-urethral, (2) extravesical and (3) bladder neck invasion.^{122–124} Spread of urothelial carcinoma through the urethra with subsequent invasion into prostatic stroma is not considered direct invasion of the prostate; rather, this situation is staged using the urethral cancer staging system for the urethral/prostatic tumour and a separate stage for the urinary bladder tumour (Table 2). The extravesical and bladder neck pathways into the prostate occur less frequently than intra-urethral spread.^{123–130} The reported incidence of direct involvement of the prostate by urinary bladder cancer is somewhat variable, due probably to differences in patient populations and

Table 2. Involvement of prostate by urothelial carcinoma

	Route of spread	
	Directly from prostate through bladder neck or soft tissue	Intraurethral
Tumour cells within prostatic glands	Bladder component: pT4a Urethral component: NA	Bladder component: pTX Urethral component: pTis
Tumour invasive into subepithelial connective tissue underlying urethra	Bladder component: pT4a Urethral component: NA	Bladder component: pTX Urethral component: pT1
Into prostatic stroma	Bladder component: pT4a Urethral component: NA	Bladder component: pTX Urethral component: pT2
Into periprostatic tissue	Bladder component: ≥ pT4a Urethral component: NA	Bladder component: pTX Urethral component: ≥ pT3

NA, not applicable.

method of processing the cystoprostatectomy specimens, but it is not rare, occurring in 7–38% of male patients who underwent radical cystoprostatectomy.^{123–130} The distinction between invasion of prostatic stroma by a urethral tumour (i.e. pT2) versus invasion of prostatic stroma by a urinary bladder tumour is critical (i.e. pT4a), due to significantly worse outcomes in the latter group.^{123,125,127–129,131,132} This is best achieved by correlation with the clinical and gross findings. For example, if a tumour is grossly present in the urethra, it is probably a urethral tumour invading the prostatic stroma. If, however, no urethral tumour is present and a urinary bladder mass, perhaps arising in the trigone or bladder neck, is grossly deeply invasive into the prostate or perivesical soft tissue, it is probably a urinary bladder tumour invading the prostatic stroma.

Distinction between pT2 urethral cancer and pT4a urinary bladder cancer is critical, because assignment of a pathological stage to a TUR specimen is problematic. Assignment of stage \geq pT2 with an accompanying note describing the difference between urethral pT2 and urinary bladder pT4a is appropriate.⁸⁷

SEMINAL VESICLE INVASION

Seminal vesicle invasion by urinary bladder cancer is staged as pT4 in the AJCC Staging Manual 8th edition, but the staging manual does not subclassify it as pT4a or pT4b (Figure 8E).² Nonetheless, compared to prostatic stromal invasion (i.e. pT4a), seminal vesicle invasion by urinary bladder cancer is associated with a worse prognosis.^{133–136} In one large study of 1682 patients who underwent radical cystectomy and pelvic lymphadenectomy for urinary bladder cancer, 5-year survival for patients with seminal vesicle invasion was 10%, similar to pT4b patients (7%) and significantly worse than patients with prostatic stromal invasion (38%).¹³³ Seminal vesicle invasion by urinary bladder urothelial carcinoma is a poor prognostic indicator and portends a prognosis similar to stage pT4b patients, even if current staging systems do not subclassify it as such.

INVASION OF THE FEMALE GYNAECOLOGICAL TRACT

Anatomical differences between males and females necessitate differences in staging. In females, invasion of the uterus or vagina by a urinary bladder cancer warrants a stage of pT4a (Figure 9). When extravesical extension is present in females, the most commonly involved organs are the vagina and uterus.¹⁰⁷ Relative

to prostatic involvement by urinary bladder urothelial carcinoma, direct invasion of the vagina or uterus (i.e. without urethral involvement) is rare, occurring in approximately 3–6% of females undergoing radical cystectomy.^{137–141} In addition to direct invasion by urinary bladder carcinoma, the female gynaecological tract may be involved by urothelial carcinoma either via pagetoid or metastatic spread and, although this would not be considered stage pT4a, is associated with poor outcomes.¹⁴² Anatomical differences in staging also result ultimately in differences in outcomes following radical cystectomy. Several studies have demonstrated worse recurrence-free survival and cancer-specific survival in pT4a females following radical cystectomy compared to pT4a males.^{22,143,144}

INVASION OF THE PELVIC OR ABDOMINAL WALL

Direct invasion of urinary bladder urothelial carcinoma into the pelvic wall or abdominal wall is

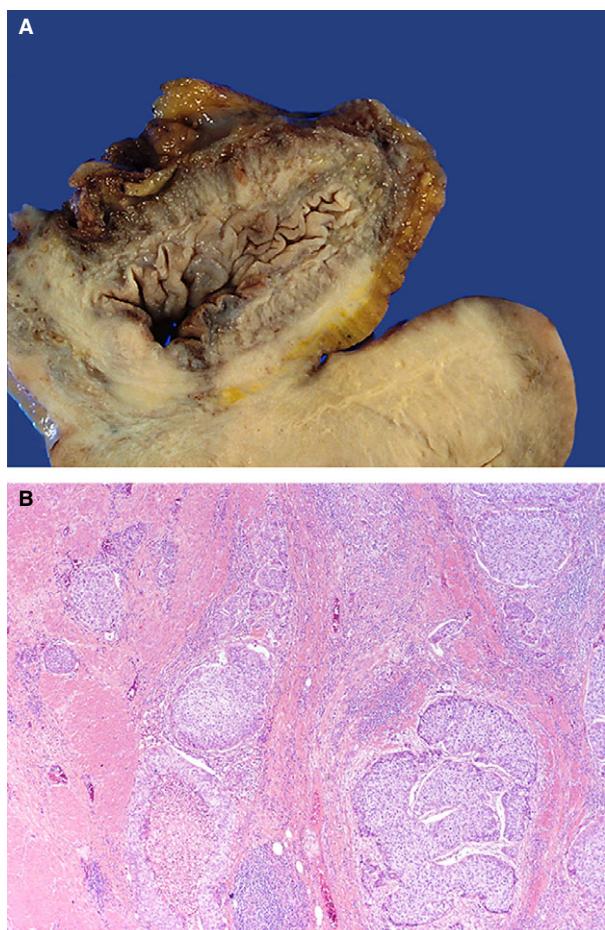


Figure 9. pT4 urothelial carcinoma invading into the uterus. A, gross appearance. B, microscopic appearance.

regarded as stage pT4b. Stage pT4b is a rare finding at radical cystectomy, accounting for only 14% of pT4 tumours and 2% of all resected tumours, probably because many of these patients are not surgical candidates.¹⁴⁵ Although rarely present at radical cystectomy, pT4b tumours are associated with significantly worse outcomes than pT4a tumours.^{145–147} Liberman *et al.* found that 5-year cancer-specific mortality in pT3, pT4a and pT4b patients is 53.9, 57.6 and 81.7%, demonstrating the drastic increase in mortality when comparing pT4b versus pT4a patients relative to the same comparison in pT4a versus pT3 patients.¹⁴⁶

Lymph node staging

In the AJCC Staging Manual 8th edition, regional lymph node staging is categorised as: lymph nodes cannot be assessed (Nx); no lymph node metastasis (N0); single regional lymph node metastasis in the true pelvis (N1); multiple regional lymph node metastasis in the true pelvis (N2); and lymph node metastasis to the common iliac lymph nodes (N3) (Table 1).² Metastases to lymph nodes beyond the iliac lymph nodes are considered distant metastases and assigned M1a. Regional lymph nodes include perivesical, obturator, iliac (internal and external), sacral (lateral and sacral promontory) and common iliac lymph nodes. The inclusion of perivesical lymph nodes in what are formally considered regional lymph nodes is the only change in lymph node staging relative to the previous edition. Although not part of the formal staging system, the AJCC Staging Manual 8th edition also recommends reporting the presence or absence of extranodal extension as well as the total number of lymph nodes present. Extranodal extension has been found by some to be associated with reduced disease-specific survival and recurrence-free survival, but others have not found any prognostic difference (Figure 10A).^{148–150} Agreed-upon criteria for the minimum number of lymph nodes identified do not currently exist, and the number of lymph nodes identified in a case varies based on the surgical procedure performed (e.g. *en bloc* resection of lymph nodes with the urinary bladder versus separate pelvic lymph node dissection) as well as the meticulousness of the gross dissection.¹⁵¹ Nonetheless, multiple studies demonstrate that a greater number of dissected lymph nodes is associated with improved outcome, even in pN0 disease.^{152–156} Specifically, Herr *et al.* recommended removal of ≥ 9 lymph nodes, while Wright *et al.* found that removal of >10 lymph nodes is

ideal.^{152,155} In the opinion of the authors, removal of at least 12 lymph nodes, which parallels recommendations made for colorectal tumours and meets the minimum criteria of the studies discussed above, is probably adequate. Some investigators recommended that a minimum of 25 lymph nodes should be obtained in radical cystectomy with bilateral pelvic lymphadenectomy.^{151,157}

The presence of lymph node metastasis is associated with markedly worse prognosis compared to patients without lymph node metastasis, but a subset of patients experience long-term survival following resection of lymph nodes possessing metastatic tumour.^{89,148,158–161} Thus, stratification of patients with nodal disease is vital. The AJCC Staging Manual 7th edition staged nodal disease based on the anatomical location and number of positive lymph nodes rather than based on size, as the AJCC Staging Manual 6th edition had previously done.^{162,163} This change occurred following reports outlining the inefficiency in stratifying patients based on size.^{148,164} This was maintained in the 8th edition, and it accurately stratifies many patients, particularly with respect to pN1 disease, although pN3 disease remains relatively heterogeneous and may not be significantly different to pN2.¹⁶⁵

Indeed, there is evidence that better separation of prognostic groups may occur using only the number of lymph nodes involved, irrespective of anatomical location. Pedrosa *et al.* demonstrated recently that in 244 patients with metastases to lymph nodes who underwent radical cystectomy and pelvic lymph node dissection, a three-tiered classification system of: N1 = metastasis in a single lymph node; N2 = metastasis in two to five lymph nodes; and N3 = metastasis in more than five lymph nodes was able to stratify patients with statistical significance.¹⁶⁶ Thus, it is clear that the current AJCC Staging Manual recommendations are improved relative to previous schema, but further refinement is necessary.

Distant metastasis

Distant metastases are now subdivided into M1a and M1b, according to the AJCC Staging Manual 8th edition (Table 1).² Distant metastases limited to lymph nodes beyond the common iliac lymph nodes are considered M1a, and non-lymph node metastases are considered M1b (Figure 10B). This distinction is important, as patients with metastases limited to non-regional lymph nodes have a significantly better outcome than patients with visceral or bone metastases.¹⁶⁷

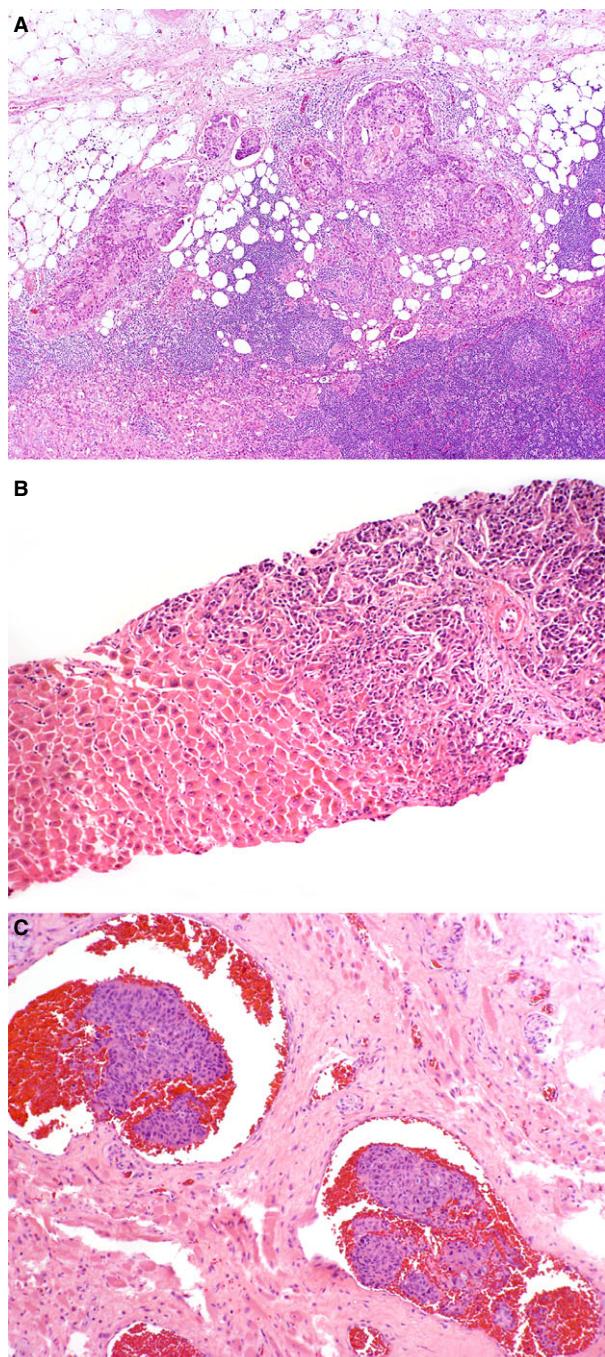


Figure 10. A, Lymph node metastasis with extranodal extension. B, Distant (liver) metastasis. C, Lymphovascular invasion.

Lymphovascular invasion

Lymphovascular invasion (LVI) is the unequivocal presence of neoplastic cells within a lymphatic or blood vessel (Figure 10C).¹ It is not a formal component of the AJCC Staging Manual 8th edition, but it has been associated with worse outcomes in

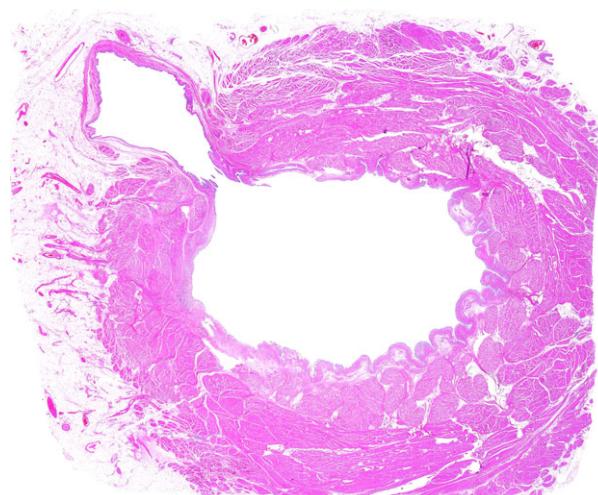


Figure 11. Diverticulum. Note the absence of muscularis propria.

Table 3. Staging of urothelial carcinoma arising in a diverticulum

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Not applicable
T3	Tumour invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostatic stroma, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall

invasive tumours, and incorporation of LVI into future staging systems may help to guide therapeutic decisions.^{2,26,168,169} For example, patients with LVI present in a TURBT specimen may receive aggressive treatment, such as early radical cystectomy or peri-operative chemotherapy (e.g. neoadjuvant chemotherapy).¹⁷

Identification of LVI, however, is often difficult, owing to the propensity of urothelial carcinoma to demonstrate stromal retraction artefact. The use of

Table 4. Staging of urachal carcinoma

	Sheldon system	Mayo system	Ontario system
Confined to urachus, bladder and perivesical soft tissue	I. Confined to urachal mucosa II. Invasion confined to urachus III. Extension into bladder	I. Confined to urachus and/or bladder II. Extension beyond urachus and/or bladder	T1. Invasion limited to submucosa T2. Invasion limited to muscularis propria of urachus and/or bladder
Spread beyond urachus, bladder and perivesical soft tissue	IIIB. Extension into abdominal wall IIIC. Extension into peritoneum IIID. Extension into viscera other than the bladder IVA. Metastasis to regional lymph nodes IVB. Metastasis to distant sites	III. Involvement of regional lymph nodes IV. Involvement of non-regional lymph nodes and/or distant sites	T3. Invasion into peri-urachal or perivesical soft tissue T4. Invasion into adjacent organs including abdominal wall

histochemistry (e.g. elastica van Gieson) and immunohistochemistry (e.g. antibodies to CD31, CD34 and podoplanin) can often resolve this dilemma, but these are not performed routinely.^{170,171} Additionally, the sensitivity of TURBT to detect LVI may be limited by the specimen's relatively small size, with reported rates of sensitivity ranging from 18 to 79%.^{172,173} Nonetheless, finding LVI in a TURBT does correlate well with finding LVI at radical cystectomy, with specificity rates ranging from 62 to 90%.^{172,173} Thus, LVI should be reported when present in order to stratify patients for appropriate management, particularly in patients with stage pT1 urothelial carcinoma.²⁶

Tumour arising in a diverticulum

Approximately 1% of all urinary bladder tumours occur within a diverticulum, and up to 14% of diverticula harbour a malignancy.^{174,175} Most urinary bladder diverticula are acquired and lack muscularis propria (Figure 11).¹⁷⁶ Thus, intradiverticular tumours invade directly from the subepithelial connective tissue (i.e. pT1) into the perivesicular soft tissue (i.e. pT3) without invading muscularis propria, and the AJCC Staging Manual 8th edition formally recommends excluding pT2 as a staging category for intradiverticular tumours (Figure 1, Table 3).^{2,174,177–179} Essentially, staging for intradiverticular tumours is the same as for non-diverticular tumours, with the exception of the exclusion of muscularis propria invasion (i.e. pT2a/b) as a category.

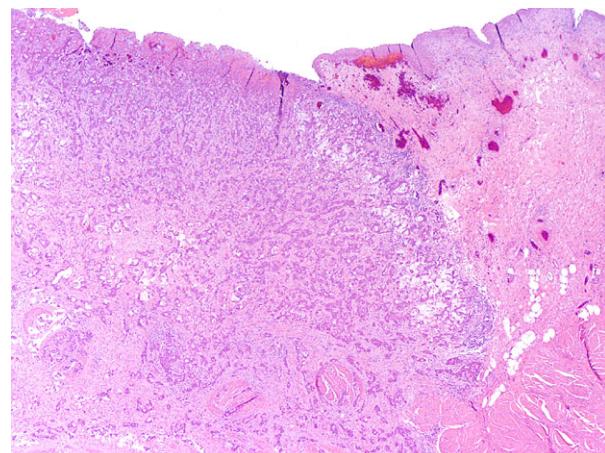


Figure 12. Urachal adenocarcinoma involving full thickness of the bladder wall.

There are limited data comparing outcome of intradiverticular tumours with non-diverticular tumours, but their outcomes appear similar based on the few studies available.^{177,180}

Tumour arising in a urachal remnant

The AJCC Staging Manual 8th edition does not include a formal staging system for tumours which arise within a urachal remnant, although several urachal-specific staging systems have been proposed (Figure 1, Table 4).^{2,181–185} Recently, the nomenclature and classification regarding urachal neoplasms has been updated and generally accepted.^{24,186,187}

The first staging system for urachal carcinoma was proposed in 1984 by Sheldon *et al.*¹⁸⁵ (the Sheldon system). A major detriment of this system is that the majority of tumours are at least stage III, with little stratification of urachal carcinoma among different stage groups, because of the indistinct boundary between the urachus and urinary bladder (Figure 12). Subsequently, Ashley *et al.*¹⁸³ (Mayo system) and Pintus *et al.*¹⁸⁴ (Ontario system) both published alternative staging systems. The Ontario system parallels the AJCC staging system for urinary bladder cancer, while the Mayo system achieves the greatest stratification of cases into stages I or II by considering urachal carcinoma limited to the urachus and/or urinary bladder to be stage I and extension of urachal carcinoma beyond the muscular layer of the urachus or urinary bladder to be stage II.^{2,183,184} While some data suggest that these systems have value, the major distinction appears to be whether the tumour is confined to the resection specimen (i.e. confined to the urachus, urinary bladder and perivesical soft tissue) or has spread to the peritoneum and/or other organs.^{181–184,188–190} Thus, although no particular staging system has been formally recommended, the Mayo system can be easily utilised to stratify cases into either stages I and II (i.e. lacking spread beyond the perivesical soft tissue) or stages III and IV (i.e. with spread beyond the perivesical soft tissue including regional lymph nodes).¹⁸³

Summary

Bladder cancer is a heterogeneous disease with a spectrum of clinical outcomes, ranging from extremely favourable (i.e. pT0 tumours) to extremely poor (i.e. pT4). Therapeutic decisions and prognostic expectations are based largely on the stage of the tumour in a biopsy, transurethral and/or cystectomy specimen. For example, the presence of muscularis propria invasion or LVI are indicative of aggressive disease, and early radical cystectomy or NAC may be considered in these patients. The AJCC Staging Manual 8th edition provides a basis for staging bladder cancer, but further refinement, such as for pT1 sub-staging and possible incorporation of LVI, is necessary. Incorporation of molecular and genomic information into treatment algorithms and possibly staging systems is also likely to occur in the future.

Conflicts of interest

No conflicts of interest are declared.

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