Clinical Significance of Histologic Variants of Bladder Cancer

Joshua I. Warrick, MD

Abstract

Pathologists have identified many “histologic variants” of bladder cancer (BCA): histologic patterns that differ from conventional urothelial carcinoma (transitional cell carcinoma). Several of these are biologically aggressive, and their identification may aid in clinical decision-making. This article reviews several histologic variants and their value in deciding management of cT1 disease and predicting response to neoadjuvant chemotherapy (NAC). Diagnostic issues are also addressed, such as interobserver variability among pathologists. For example, although stage cT1 conventional urothelial carcinoma is usually managed conservatively, cT1 micropapillary carcinoma has high mortality following conservative management, and early cystectomy may reduce mortality. Similarly, plasmacytoid and small cell cancers are remarkably aggressive, and those diagnosed as stage cT1 at transurethral resection are likely understaged; conservative management thus greatly risks undertreatment. As an example of response, NAC dramatically reduces mortality in patients with small cell BCA, and is thus the standard of care, even in stage cT1 disease. Although identification of histologic variants may inform on optimal management, diagnostic issues challenge their incorporation into clinical practice. For example, interobserver reproducibility is only moderate for the diagnosis of micropapillary BCA. Studies have identified specific histologic issues underlying this diagnostic irreproducibility, and ongoing work aims to remedy this issue. In summary, histologic variants are emerging as potentially useful biomarkers in the management of BCA. Although issues remain unresolved, pathologists and treating physicians will benefit from understanding these variants and their prognostic and therapeutic implications.

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Pathologists have identified many bladder cancer (BCA) histomorphologies that differ from conventional urothelial carcinoma (UC; also known as *transitional cell carcinoma*). Several of these histologic variants are biologically aggressive, and their identification may aid in clinical decision-making.

Tumor stage drives BCA management. Treatment is typically conservative in patients with non-muscle-invasive (NMI) tumors diagnosed on biopsy or transurethral resection, including noninvasive cancers (stage cTa and cTis) and invasive cancers limited to the lamina propria (stage cT1).¹ Conservative treatment entails transurethral resection of all cystoscopically visible tumor, often followed by intravesical therapy, such as bacillus Calmette-Guérin (BCG); morbidity is minimal, bladder function is preserved, and overall mortality is low. However, although mortality is very low (<5%) in

patients with low-risk NMI BCA,² mortality is considerably higher in those with high-risk NMI tumors, a group that includes all stage cT1 cases. Approximately 30% of conservatively managed patients with high-risk cancers will die of the disease on long-term follow-up (10–15 years), and only a quarter will maintain an intact, functional bladder in the long term.³ Definitive treatment of patients with cT1 disease is radical cystectomy (early cystectomy), which improves mortality compared with conservative management.³ However, cystectomy entails considerable functional morbidity. Treatment of cT1 disease is thus a difficult balance between preventing mortality and preserving the patient’s normal urinary tract function.

BCA that invades the muscularis propria (≥stage cT2) kills most patients if managed conservatively.⁴ Patients with such muscle-invasive cancers are thus

From the Departments of Pathology and Surgery, Division of Urology, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania.

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Correspondence: Joshua I. Warrick, MD, Department of Pathology, Penn State Health Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17033. E-mail: jwarrick@pennstatehealth.psu.edu

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managed definitively, typically with radical cystectomy, which improves survival.⁴ Survival is further improved by the addition of neoadjuvant chemotherapy (NAC), usually gemcitabine and cisplatin, or MVAC (methotrexate/vinblastine/doxorubicin/cisplatin).⁵ However, the survival benefit is largely limited to patients in whom the tumor histologically responds to chemotherapy, typically defined as a *complete pathologic response* (cPR)—the complete absence of cancer on histologic examination of the cystectomy specimen.⁵ Only 30% to 40% of patients experience cPR, and 3.7 patients must receive NAC to save 1 life.⁵ NAC also delays surgery by several months and has its own risks, including potential nephrotoxicity and neurotoxicity. Many patients thus endure a delay in definitive management that is nonbeneficial and potentially harmful.

This article serves 2 purposes. First, it reviews the therapeutic and prognostic significance of histologic variants of BCA, with specific emphasis on the decisions to perform early cystectomy in cT1 disease and to give NAC in muscle-invasive disease (Table 1). Second, it reviews diagnostic issues with histologic variants, such as interobserver variability among pathologists. Seven histologic variants are reviewed: micropapillary, plasmacytoid, small cell, squamous, glandular, nested, and lymphoepithelioma-like (Figure 1). A few general observations apply to these variants and will constrain the discussion. First, with the exception of squamous morphology, these histologic variants are uncommon, each accounting for <10% of BCA diagnoses.⁶ Studies with large cohorts are thus difficult to assemble, and most evidence comes from smaller retrospective studies.

Second, these variants often co-occur with conventional UC. Tumors with pure squamous and pure glandular morphology have been designated “pure squamous cell carcinoma” and “pure adenocarcinoma,” respectively, for many years,⁷ and this review adheres to this convention. Studies of lymphoepithelioma-like cancer have also consistently distinguished between cancers with focal variants and those with pure or predominant variants, and this review recognizes this distinction. However, for the remaining variants, several studies have shown that mixed cases (histologic variant with conventional UC) have similar clinical behavior to pure histologic variants.^{8–11} This is somewhat of an oversimplification. For example, increasing fraction of micropapillary morphology in a given case is associated with worse outcome.¹² However, for the sake of uniformity, this article does not distinguish mixed from pure variants for micropapillary, plasmacytoid, small cell, or nested carcinomas. Third, specific variants have specific clinical and management associations. Many prior studies considered all histologic variants as a single category. This review focuses on studies that separate specific variants. Fourth, histomorphologic descriptions in this review are somewhat abbreviated, because the aim is to discuss the clinical significance of histologic variants. Excellent reviews and book chapters have been written on the histomorphologic details of these variants,^{13–15} and this article will not reproduce their work. Lastly, this review is limited to invasive cancers arising from the bladder proper; noninvasive neoplasia and urachal neoplasia will not be covered.

Table 1. Optimal Treatment of Histologic Variants of Bladder Cancer

	Early Cystectomy in cT1 Cancer	Neoadjuvant Chemotherapy Benefit in Muscle-Invasive Disease
Micropapillary	Controversial ^a	Probable ^b
Plasmacytoid	Yes	Unknown
Small cell	Yes	Yes
Pure squamous cell carcinoma	Yes	Unknown
UC with squamous differentiation	No	Yes
Pure adenocarcinoma	Yes	Unknown
UC with glandular differentiation	No	Yes
Nested	Unknown	Unknown

Abbreviation: UC, urothelial carcinoma.

^aOpinions differ on the appropriate management of cT1 micropapillary bladder cancer, particularly given diagnostic reproducibility issues (see “Micropapillary” discussion, page 1270).

^bEvidence shows micropapillary cancer histologically responds to neoadjuvant chemotherapy, suggesting improved survival, though survival benefit has not directly been shown.

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Figure 1. Hematoxylin-eosin–stained sections of histologic variants. (A) Micropapillary morphology (original magnification, x200) appears as small invasive nests with surrounding tissue retraction. (B) Plasmacytoid cancer (x400) seen as infiltrative single cells. (C) Small cell cancer (x400) has high nuclear-to-cytoplasmic ratio, nuclear molding, and numerous mitotic figures. (D) Squamous carcinoma (x400) seen as keratin formation within invasive carcinoma. (E) Glandular morphology (x400) appears as formation of true glandular structures within invasive cancer. (F) Nested cancer (x400) consists of infiltrative small nests of tumor cells with minimal cytologic atypia.

Histologic Variants

Micropapillary

Micropapillary morphology describes invasive small cancer nests with surrounding tissue retraction.^{7,12} This variant is clinically aggressive, typically presenting with high tumor stage and lymph node metastasis.^{16,17} The 5- and 10-year overall survival rates are 54% and 27%, respectively, with standard treatment.¹⁶ Patients with stage cT1 micropapillary BCA frequently die from disease, and mortality may be reduced by early cystectomy. In the largest single-institution study of stage cT1 micropapillary carcinoma to date (n=72), Willis et al¹⁸ showed that patients receiving early cystectomy had 100% 5-year disease-specific survival (DSS) compared with 60% 5-year DSS in conservatively managed patients ($P=.006$). Similarly, using data from the National Cancer Data Base, Sui et al¹⁹ showed that cystectomy improves survival compared with bladder-conserving

surgery in stage cT1 micropapillary BCA, although this finding only approached statistical significance ($P=.057$). Separate, smaller studies have not corroborated a mortality reduction with early cystectomy, although they support that stage cT1 micropapillary carcinoma has high mortality even on short-term follow-up.^{20,21} Given these data, many advocate early cystectomy in stage cT1 micropapillary cancers,^{17,18,22} although this recommendation is not universal.

NAC often induces cPR in micropapillary BCA, although a direct survival benefit has not been demonstrated.^{23,24} In the largest single-institution study to date (n=103), Fernandez et al²³ showed cPR in 52% of micropapillary carcinomas treated with NAC compared with 19% of micropapillary carcinomas treated with immediate cystectomy ($P=.002$). The 5-year DSS rate was 96% in patients with cPR compared with 45% in patients without such response ($P<.001$). However, superior survival was not directly reported in the NAC group. In a study using the National Cancer Data Base, no survival benefit was found in micropapillary BCA.¹⁹ The combined data provide an unclear answer as to the value of NAC in micropapillary BCA, although the frequency of cPR to chemotherapy and the improved survival in such patients suggest that it is appropriate for this variant.

Diagnostic reproducibility of micropapillary carcinoma is only moderate among pathologists.²⁵ Specifically, although diagnostic reproducibility is high in cases of classic micropapillary carcinoma (seen as small nests with surrounding tissue retraction), diagnostic reproducibility is low in cases composed of “admixed large and small cell nests with retraction.”²⁵ Some consider this pattern as micropapillary, whereas others do not. In the cystectomy setting, high rates of nodal metastasis are seen in both classic micropapillary BCA and invasive carcinoma with “admixed large and small cell nests with retraction,” suggesting that both patterns similarly inform on tumor behavior.²⁶ However, no study has evaluated invasive carcinoma with “admixed large and small cell nests with retraction” in the transurethral resection setting. Thus, it remains unclear whether such cases should receive early cystectomy, and ongoing work aims to clarify this issue.

Plasmacytoid

Plasmacytoid morphology describes a pattern of infiltrative, individual tumor cells, morphologically

similar to lobular breast cancer and gastric signet-ring cancer.^{7,27} In keeping with this aggressive histology, plasmacytoid BCA is clinically aggressive, with approximately 90% of cases extending outside the bladder at diagnosis.²⁸ The 5-year survival rate is <30%.²⁸ This variant has a unique propensity for peritoneal spread.^{29,30} Plasmacytoid morphology is likewise associated with worse disease-free and overall survival compared with conventional UC, even when controlling for tumor stage and nodal status.³⁰

Approximately 80% of cT1 plasmacytoid BCAs are upstaged to $\geq$ pT3 disease at cystectomy.³¹ Conservative management of cT1 plasmacytoid cancer thus greatly risks undertreatment, and early definitive management is prudent.

NAC appears less effective in plasmacytoid carcinoma than conventional UC. For example, Keck et al³² showed that plasmacytoid carcinoma has worse median overall survival (27.4 months) than both micropapillary carcinoma (64.2 months) and conventional UC (62.6 months) ($P=.013$) when treated with NAC and cystectomy. In keeping with this, Dayyani et al²⁹ showed that although patients with plasmacytoid cancers may experience a cPR to NAC, recurrence is common. The NAC group in this study was small, however, comprising only 5 patients. Presently, no well-powered study has specifically addressed survival in patients with plasmacytoid cancer treated with immediate cystectomy versus NAC plus cystectomy.

Diagnostic interobserver variability has not been studied in plasmacytoid carcinoma to the author's knowledge.

Small Cell

Small cell carcinoma morphology in BCA describes a high-grade neuroendocrine carcinoma, morphologically like small cell lung cancer. Like its pulmonary cognate, small cell BCA is aggressive, frequently presenting with lymph node metastasis and high tumor stage.³³ Patients with small cell BCA historically had a 5-year survival rate of <30%.^{8,9} However, this tumor type responds uniquely well to NAC. In the largest study to date ($n=95$ patients), Lynch et al³⁴ showed that patients with small cell BCA receiving NAC have markedly improved 5-year DSS compared with patients receiving upfront cystectomy (79% vs 20%; $P<.001$). NAC is thus the standard of care for this variant, as reflected in the NCCN Clinical Practice Guidelines in Oncology (NCCN

Guidelines) for BCA.³⁵ Notably, the guidelines state that patients with small cell BCA (including those with a component of conventional UC) should receive neoadjuvant cisplatin and etoposide, agents used for primary therapy in small cell lung cancer, instead of the chemotherapeutic regimens typically used for conventional UC.^{35,36}

Stage cT1 small cell BCA is rare,⁸ and cases diagnosed with stage cT1 disease at transurethral resection are often understaged.³⁴ Given the high risk of understaging and aggressive biology of this variant, definitive treatment with NAC is the standard of care for small cell BCAs, regardless of stage, including cT1 cases (per NCCN Guidelines).³⁵

Small cell BCA has a similar morphology to small cell lung cancer, although interobserver variability is not studied to the author's knowledge. Importantly, conventional UC may at times have a "small cell" pattern. These must be distinguished from true small cell BCA. The immunophenotypes of these tumors differ, and immunohistochemistry can resolve most challenging cases.³⁷

Squamous

Squamous differentiation appears histologically as keratin or intercellular bridges in invasive BCA.^{7,13} Squamous differentiation may be incomplete, termed *UC with squamous differentiation* (UC-SD). This is common, seen in up to 40% of conventional UCs.⁷ Squamous differentiation may also involve the entire tumor, termed *pure squamous cell carcinoma* (SCC) of the bladder. This is classically seen in countries with endemic schistosomiasis, a well-described risk factor.⁷ It is also seen in Western countries,³⁸ particularly in patients with chronic catheterization.³⁹ UC-SD and pure SCC of the bladder are typically considered separate entities.⁷

UC-SD tends to be high stage at diagnosis, although survival does not differ between UC-SD and conventional UC when controlling for tumor stage and patient age.⁴⁰ To the author's knowledge, no study has shown that stage cT1 UC-SD responds worse to conservative management than conventional UC. Therefore, treatment decisions in cT1 disease are challenging. On one hand, UC-SD is often high-stage, suggesting that patients with cT1 disease are at great risk of understaging, and should thus be treated aggressively. On the other hand, squamous differentiation is present in a large frac-

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tion of invasive BCAs, and no study has shown that patients with UC-SD will do worse than those with conventional UC following conservative management. A reasonable approach is to consider patients with stage cT1 UC-SD as candidates for conservative management, provided staging is thorough and they have no other risk factors for progression and death from disease.⁴¹

Pure SCC of the bladder typically presents at high stage, and is thus treated aggressively.⁴² However, management of cT1 pure SCC is less clear, largely because it is rare.^{38,43} Using SEER data to address this, Scosyrev et al⁴⁴ showed that patients with stage cT1 pure SCC had higher 2-year mortality than patients with cT1 conventional UC, if managed conservatively ($P<.001$). In contrast, mortality did not differ between pure SCC and conventional UC if patients with stage cT1 disease were treated with cystectomy. Based on this study and others showing high mortality and risk of recurrence in pure SCC, many clinicians advocate early cystectomy in stage cT1 pure SCC.

Data on the impact of squamous differentiation on chemotherapy response have been contradictory. Older studies of SCC of the bladder showed poor response to chemotherapy compared with pure UC.⁴⁵ For a time, BCAs with squamous differentiation were thus considered largely chemoresistant. However, more recent studies have shown that patients with BCA with squamous differentiation may benefit from chemotherapy. For example, Scosyrev et al⁴⁶ showed neoadjuvant MVAC reduces mortality in “mixed tumors,” defined as BCA with either squamous and/or glandular differentiation, in a retrospective study. Others have reproduced this finding.⁴⁷ Current evidence thus indicates NAC is appropriate in patients with UC-SD. No evidence shows that NAC improves survival in pure SCC of the bladder, as reflected in current NCCN Guidelines.³⁵

The distinction between UC-SD and pure SCC may be difficult. Partial sampling of UC-SD at transurethral resection may give the false impression of pure SCC if only the squamous component is sampled. Additionally, some cases are difficult to confidently classify as pure SCC or UC-SD based on histologic review, particularly poorly differentiated carcinomas with extensive squamous differentiation. Given the treatment differences between pure SCC and UC-SD, diagnosis and treatment are best decided by a multidisciplinary team, in which histology

and clinical data are synthesized into a cogent diagnosis and management plan. For example, a patient found to have muscle-invasive BCA with complete squamous differentiation on transurethral resection should not necessarily be diagnosed with pure SCC, given the potential for undersampling, especially in the absence of risk factors for pure SCC. Such a patient could be a candidate for NAC if the full clinicopathologic picture pointed more toward UC-SD.

Glandular

Glandular differentiation is morphologically defined as areas of carcinoma with the appearance of gland-forming adenocarcinoma.⁷ Similar to squamous differentiation, BCAs with complete glandular differentiation are considered pure adenocarcinoma, whereas those with admixed UC and gland-forming carcinoma are considered UC with glandular differentiation.⁷ Pure adenocarcinoma of the bladder is rare, and enriched in patients with schistosomiasis and bladder extrophy.⁷

Although glandular differentiation in UC is associated with high-stage disease, it is not predictive of survival when accounting for tumor stage and patient age.⁴⁰ To the author's knowledge, glandular differentiation in cT1 BCA has not been shown to predict poor outcomes with conservative management. As with squamous differentiation, glandular differentiation alone does not appear to be an indication for early cystectomy in patients with cT1 BCA, provided staging is thorough and there are no other risk factors.⁴¹ That stated, this situation is uncommon.

Pure adenocarcinoma of the bladder typically presents at high stage, and is associated with high rates of local recurrence and metastasis.⁴⁸ Treatment is thus radical cystectomy in most cases. Management is not well-studied in cT1 bladder adenocarcinoma because it is rare.^{48,49} However, given the association between adenocarcinoma and aggressive disease, many advocate definitive cystectomy in early-stage nonurachal bladder adenocarcinoma.⁴¹

As stated earlier, NAC reduces mortality in BCA with squamous or glandular differentiation, indicating that glandular differentiation is not a contraindication to NAC.^{46,47} No strong evidence shows that NAC improves survival in pure adenocarcinoma of the bladder, as reflected in current NCCN Guidelines.³⁵

As with squamous differentiation in BCA, distinguishing pure adenocarcinoma from UC with

extensive glandular differentiation may be difficult in some cases because of sampling issues and when the histologic patterns are difficult to interpret. Diagnosis and treatment are best decided by a multidisciplinary team, in which histology and clinical information are used together to determine the best diagnosis and treatment plan.

Nested

Nested carcinoma tends to be high stage at presentation, but is not an independent predictor of survival when accounting for tumor stage.⁵⁰ The current value in recognizing nested carcinoma lies in preventing misdiagnosis. Nested carcinomas are histologically seen as invasive cancer nests with minimal cytologic atypia^{7,51} and therefore may appear deceptively similar to benign Vonn Brunn nests, particularly on superficial biopsies.⁵² Likewise, the invasive “large nested” variant of UC may appear deceptively similar to non-invasive low-grade papillary UC.⁵³ No study to the author’s knowledge has addressed outcomes in conservatively managed stage cT1 nested cancers, nor has a study investigated NAC response in this variant.

Lymphoepithelioma-Like

The lymphoepithelioma-like variant describes BCA with a histology similar to nonkeratinizing nasopharyngeal carcinoma, specifically undifferentiated carcinoma with large pleomorphic nuclei, prominent nucleoli, and indistinct cell borders, associated with a prominent lymphocytic proliferation.⁷ Lymphoepithelioma-like BCAs are typically high-stage, like other histologic variants.^{54–58} Despite histologic similarity, lymphoepithelioma-like BCA lacks association with Epstein-Barr virus infection, a known association in nasopharyngeal carcinoma.^{57–59}

Several small studies (<10 cases) have suggested that patients with high-stage BCA with pure or predominant lymphoepithelioma-like histology may be adequately treated with chemotherapy and transurethral resection of the tumor, foregoing cystectomy.^{54–56} Although these studies are compelling, a larger study (n=28) showed that patients with lymphoepithelioma-like bladder cancer treated with cystectomy had similar survival to those with muscle-invasive conventional UC, and that those treated with chemotherapy and transurethral resection may experience recurrence.⁵⁷ Although it is possible that a subset of patients with pure lymphoepithelioma-like BCA may be safely treated with chemotherapy and transurethral resection, the data are insufficient to justify this as a treatment recommendation. Diagnostic reproducibility among pathologists is also not studied in the lymphoepithelioma-like variant, and will be important if this variant is ultimately used to guide therapy.

Conclusions

Histologic variants of BCA are emerging as valuable biomarkers for clinical decision-making. Although several issues remain unresolved, pathologists and treating physicians will benefit from understanding these variants and their specific prognostic and therapeutic indications.

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