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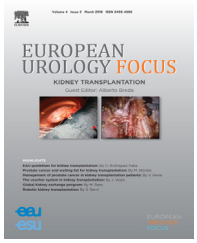

Review – Bladder Cancer

# What Is the Significance of Variant Histology in Urothelial Carcinoma?

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**Abstract**

*Context:* Urothelial carcinoma can exhibit a wide range of variant morphologies. Many variants present diagnostic challenges and carry clinical implications that inform prognosis and treatment decisions.
*Objective:* To provide an overview of the diagnostic, therapeutic, and prognostic significance of histological variants of urothelial carcinoma.
*Evidence acquisition:* A PubMed/MEDLINE-based literature search was conducted using the key terms “urothelial carcinoma”, “variant histology”, “nested”, “micropapillary”, “microcystic”, “sarcomatoid”, “squamous differentiation”, “glandular differentiation”, “clear cell”, “plasmacytoid”, “lymphoepithelioma-like carcinoma”, “squamous cell carcinoma”, “small cell carcinoma”, “adenocarcinoma”, “radiotherapy”, “neoadjuvant chemotherapy”, and “adjuvant chemotherapy”.
*Evidence synthesis:* The incidence of variant histology is increasing due to improved recognition. Nonetheless, diagnosis can pose challenges due to sampling limitations and interobserver variability. Although associated with advanced disease at presentation, survival outcomes for most variants do not differ significantly compared with pure urothelial carcinoma of the same stage. Controversy exists regarding optimal management due to the low quality of available evidence. For most cases, radical cystectomy with pelvic lymph node dissection (with neoadjuvant chemotherapy when appropriate) represents the standard of care. Small cell carcinoma and lymphoepithelioma-like carcinoma appear to be particularly chemosensitive.

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Plasmacytoid urothelial carcinoma
Lymphoepithelioma-like carcinoma
Squamous cell carcinoma
Small cell carcinoma
Adenocarcinoma

**Conclusions:** Accurate identification of variant histological subtypes is an important part of risk stratification, as these variants exhibit aggressive biological behaviour. Variant histology tumours are associated with advanced disease at presentation, which must be considered when counselling patients regarding survival outcomes. Optimal management remains to be defined but in most cases; neoadjuvant chemotherapy and radical cystectomy with pelvic lymph node dissection remains the mainstay of treatment.

**Patient summary:** It is important to recognise histological variants of urothelial carcinoma as they indicate aggressive disease. When compared with patients with pure urothelial carcinoma of the same disease stage, survival does not appear to be significantly worse. In most cases, patients with invasive variant histology should be treated with neoadjuvant chemotherapy and radical cystectomy.



## 1. Introduction

Approximately 75% of bladder cancers are classified as pure urothelial carcinoma (UC), with histological variants accounting for the remaining 25%. Several variant morphologies are recognised in the 2016 World Health Organization classification of urothelial tract tumours (Table 1). These are divided into urothelial and nonurothelial subtypes, with classification based predominantly on morphological features on haematoxylin and eosin–stained pathological sections. Urothelial variants often show urothelial differentiation mixed with specific morphological phenotypes, whereas nonurothelial variants exhibit independent features.

The apparent rise in the incidence of variant histology is largely due to the increased awareness, recognition, and improved reporting by pathologists. Literature from several academic units has shown that the presence of variant histology is a major area of inconsistency; up to 30% of urothelial cancer diagnoses changed upon re-review by an expert genitourinary pathologist [1]. In one study, re-review of 589 transurethral resection of the bladder (TURBT) specimens by expert genitourinary pathologists found that the presence of variant histology had not been reported by community pathologists in 44% of cases [2].

Variant histology carries important diagnostic, prognostic, and therapeutic implications. Accurate diagnosis allows risk stratification, determines prognosis, and directs treatment decisions particularly where treatment of variant histology might differ from that of pure UC. Published data come from small retrospective series and extrapolation of data from pure UC; this is due to the rarity of certain histological subtypes, but also because, in general, patients with variant histology have been excluded from clinical trials as these require UC to be the predominant (>50%) histology. This review presents an overview of the most current data regarding the diagnosis and management of UC with variant histology.

## 2. Evidence acquisition

A nonsystematic literature review was conducted using the PubMed/MEDLINE databases using the key terms “urothelial carcinoma”, “non-urothelial carcinoma”, “variant histology”, “nested”, “micropapillary”, “microcystic”, “sarcomatoid”, “squamous differentiation”, “glandular differentiation”, “clear cell”, “plasmacytoid”, “lymphoepithelioma-like carcinoma”, “squamous cell carcinoma”, “small cell carcinoma”, “adenocarcinoma”, “radiotherapy”, “neoadjuvant chemotherapy”, and “adjuvant chemotherapy”. The reference lists of relevant publications were also cross-referenced for supplementary information. Owing to the rarity of variant histology, no time restrictions were applied and meeting abstracts were also considered for inclusion. Only studies in English were included. Studies on variant histology in non–muscle-invasive bladder cancer were excluded.

## 3. Evidence synthesis

### 3.1. Diagnosis

Variant histology is prone to being under-recognised or misclassified for several reasons [3]. Tumours are heterogeneous, and undersampling can compromise recognition of variant histology. This is reflected in the variable concordance rates between TURBT and radical cystectomy (RC) specimens reported in the literature; whilst some studies demonstrate relatively poor concordance [4,5], others report rates as high as 83.6% [6]. Warrick et al [7] recently described intratumoural heterogeneity in RC specimens, observing significant molecular intratumoural heterogeneity between variant histologies. This shows that different regions of a tumour are genetically distinct, and therefore, if an area of genomically aggressive tumour is not sampled, a patient could be incorrectly assigned to a lower-risk group.

Other reasons for misdiagnosis of variant histology include fixation artefacts, high interobserver variability, changing criteria for diagnostic inclusion, and lack of supplementary tests to confirm variant diagnosis [1]. Future diagnostic paradigms will use molecular profiling to define variants rather than simply relying on their histological appearance.

### 3.2. Urothelial Variants

#### 3.2.1. Urothelial carcinoma with divergent differentiation

Urothelial carcinoma with divergent differentiation is the most common variant of histology. The term refers to tumours in which some degree of typical UC is present together with other morphologies including squamous and glandular differentiation. Squamous differentiation is

**Table 1 – Variants of urothelial carcinoma.**

| | Estimated incidence | Histology | Differential diagnoses | Recommendations for management |
|---|---|---|---|---|
| Urothelial variants | | | | |
| UC with divergent differentiation | Squamous differentiation 20–40% | Squamous differentiation | Squamous cell carcinoma | More aggressive behaviour is usually due to the higher-grade concomitant UC |
| | Glandular differentiation 18% | • Intercellular bridges and/or keratinisation | | Manage as for UC of the same stage |
| | | Glandular differentiation | Adenocarcinoma | |
| | | • Intratumoural tubular or enteric gland-like spaces | | |
| Micropapillary | 2–5% | Resembles papillary serous carcinomas of the ovary | Papillary nephrogenic adenoma | Less responsive to intravesical BCG; clinical understaging common |
| | | Small tumour nests surrounded by empty or lacunar spaces | Invasive UC with stromal retraction | Manage as for UC of the same stage |
| Microcystic | 1.2% | Bland histological appearance | Nested UC | Manage as for UC of the same stage |
| | | Round to oval cysts of varying sizes (1–2 mm), which often contain intraluminal secretions and are lined by cuboidal or flattened urothelial cells | Bladder adenocarcinoma | |
| | | | Cystitis glandularis | |
| | | | Cystitis cystica | |
| Nested | <1% | Bland histological appearance | Nephrogenic adenoma | Deceptively bland in appearance |
| | | A large number of discrete to confluent small nests of urothelial cells infiltrating the lamina propria and muscularis propria | Cystitis cystica | Manage as for UC of the same stage |
| | | | Von Brunn's nests | |
| Lymphoma | | Lymphoepithelioma-like carcinoma Chemosensitive | <1% | Resembles nasopharyngeal LELC |
| | | Small aggregates of poorly differentiated tumour cells with large nuclei, prominent nucleoli, and indistinct cell membranes | Solitary inflammatory nodule | Consider bladder-sparing options |
| | | Dense infiltrate of lymphoid or inflammatory cells | Poorly differentiated squamous cell carcinoma | |
| Plasmacytoid | 1–3% | Discohesive cells with eccentrically placed nuclei and abundant eosinophilic cytoplasm | Melanoma | Uniformly poor prognosis |
| | | | Lymphoma | Currently to be managed as for UC of the same stage |
| | | | | Wide resection important since high rates of margin positivity |
| Sarcomatoid | <1% | High-grade spindle tumour cells | Postoperative spindle cell nodules | Chemoresistant |
| | | | Inflammatory myofibroblastic tumour | Upfront RC |
| | | | Primary bladder sarcoma | |
| Clear cell | <1% | Cells with glycogen-rich cytoplasm | Clear cell adenocarcinoma of the bladder and female genital tract | Treatment strategies poorly defined |
| | | | Metastatic clear cell renal cell carcinoma | Manage as for UC of the same stage |
| Non-urothelial variants | | | | |
| Small cell carcinoma | <1% | Nests or sheets of small tumour cells with enlarged nuclei, evenly dispersed 'salt and pepper' chromatin and scant cytoplasm | Lymphoma | Early neoadjuvant chemotherapy (cisplatin/carboplatin + etoposide) followed by radical radiotherapy or radical cystectomy |
| | | | | High propensity for brain and bone metastases—imaging needed |

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**Table 1 (*Continued*)**

| | Estimated incidence | Histology | Differential diagnoses | Recommendations for management |
|---|---|---|---|---|
| Squamous cell carcinoma | 2–5% | Keratin pearl formation and intracytoplasmic keratin granules | UC with squamous differentiation | RC preferred as radical radiotherapy yields poor outcomes<br>Insufficient data regarding neoadjuvant/adjuvant chemotherapy<br>Preoperative radiotherapy in locally advanced cases |
| Adenocarcinoma | <2% | Several subtypes including intestinal, papillary, signet ring cell, clear cell, and mixed | Secondary adenocarcinoma from the prostate, colon, endometrium, cervix, and lung | RC but consider partial cystectomy in urachal AC |
| Urachal | | | | Insufficient data regarding neoadjuvant/adjuvant chemotherapy |
| Nonurachal | | | | |

AC = adenocarcinoma; BCG = bacillus Calmette-Guerin; LELC = lymphoepithelioma-like carcinoma; RC = radical cystectomy; UC = urothelial carcinoma.

found in up to 40% of invasive UCs and characterised histologically by the presence of intercellular bridges and/or keratinisation [8]. Glandular differentiation is the second most common variant and occurs in up to 18% of invasive tumours, where it is defined by the presence of intratumoural tubular or enteric gland-like spaces [9].

*3.2.1.1. Implications for diagnosis.* Urothelial carcinoma with squamous or glandular differentiation must be distinguished from pure squamous cell carcinoma (SCC) or pure adenocarcinoma (AC), which are separate histological entities lacking urothelial components.

*3.2.1.2. Implications for management.* Urothelial carcinoma with divergent differentiation presents at an advanced disease stage compared with pure UC [10–13]. Although early reports indicated inferior survival outcomes [10,11], more recent studies have shown that, when controlled for disease stage, patients with squamous and glandular differentiation have similar survival rates to those with pure UC [13,14].

The literature regarding the role of neoadjuvant chemotherapy (NAC) is conflicting. Whilst some studies demonstrate downstaging after NAC [15], others show a poor response [16]. The best available evidence in favour of NAC comes from the SWOG-directed Intergroup Study (S8710). This showed that patients with squamous/glandular differentiation had a better response to NAC than patients with pure UC, with these patients also demonstrating improved overall survival with NAC [17].

There is a paucity of data regarding the role of trimodality therapy (TMT) in the management of variant UC. Outcomes are limited to a retrospective single-institution study of 303 patients, of whom 49 had squamous/glandular differentiation [18]. In this study, there was no significant difference in 5- and 10-yr disease-specific and overall survival between patients with pure UC and variant UC treated with TMT. This finding is, perhaps, unsurprising given that the majority of patients with variant histology in this cohort had squamous/glandular differentiation and, as already discussed, survival outcomes between these variants and pure UC are not significantly different.

Overall, although patients with divergent differentiation present at a higher stage than pure UC, survival outcomes are similar and, therefore, should be managed as would be appropriate for UC of the same stage.

### *3.2.2. Micropapillary*

Micropapillary urothelial carcinoma (MPUC) is an aggressive variant that accounts for 2–5% of all UCs. It is characterised by small tumour nests surrounded by empty or lacunar spaces, which often invades the bladder wall deeply [19]. Multiple small nests and papillae without fibrovascular cores are frequently seen in one single lacuna, resembling papillary serous carcinomas of the ovary (Fig. 1A).

*3.2.2.1. Implications for diagnosis.* MPUC typically presents at an advanced stage with high rates of lymphovascular invasion, carcinoma in situ, and lymph node involvement [20–22]. Failure to recognise this variant, therefore, has

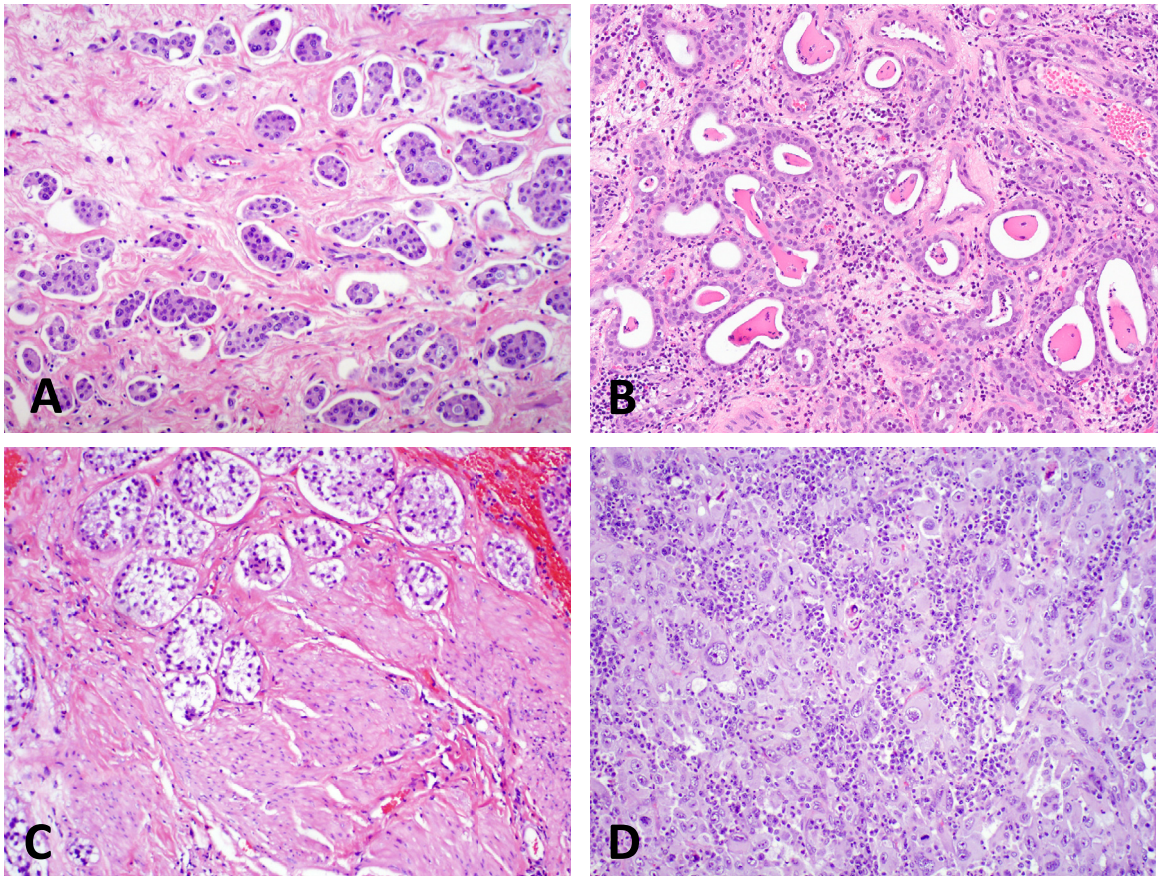


**Fig. 1 – (A) Micropapillary variant is characterised by small nests of tumour cells in lacunar spaces. (B) Microcystic variant shows small infiltrative cysts with intraluminal secretion. (C) Nested variant shows muscle-invasive small tumour nests with minimal cytological atypia. (D) Lymphoepithelioma-like variant shows tumour cells with marked nuclear atypia and indistinct cell borders, and a dense lymphocytic infiltrate.**

serious implications due to its high potential for metastases.

Results from retrospective single-institution series and population-based registries demonstrate worse outcomes in patients with MPUC than in those with pure UC [23,24]. However, more recent evidence suggests that this may not be the case when outcomes are controlled for disease stage [20–22]. Indeed, a recent meta-analysis of seven studies showed that patients harbouring a micropapillary component at RC were not associated with worse recurrence-free, cancer-specific, or overall survival compared with those with pure UC [25].

*3.2.2.2. Implications for management.* It is important to recognise that non–muscle-invasive MPUC is associated with high rates of progression to muscle-invasive disease and even metastatic disease. For this reason, early RC is considered the standard of care over intravesical therapy with bacillus Calmette-Guerin in most centres [24,26,27]. Nonetheless, some series have reported reasonable outcomes with bladder preservation therapies in highly selected patients where the micropapillary component is relatively small [26,28].

With regard to muscle-invasive disease, there is a lack of clarity regarding the role of NAC, with some advocating immediate RC and others recommending NAC and RC. The MD Anderson Cancer Center compared patients who underwent immediate RC or NAC, and found that there was no significant difference in 5-yr overall survival between groups (63% vs 71%) [27]. However, patients treated with NAC had higher rates of non–organ-confined disease (68.7% vs 34.8%, $p = 0.016$). In contrast to these findings, the group from the Memorial Sloan-Kettering Cancer Center reported downstaging to pT0 in 45% (13/29) patients with MPUC receiving NAC compared with 13% who underwent RC alone ($p = 0.049$). However, at 2 years, there was no significant difference between the groups with regard to recurrence, and overall or cancer-specific survival rates [29]. Similarly, in the meta-analysis by Abufaraj et al [25], use of NAC was associated with downstaging in RC specimens for a significant number of patients, but this did not translate into a significant improvement in survival outcomes. This result could be explained by the aggressive biological behaviour of this variant, small patient numbers, and short follow-up duration. Another possible explanation is the absence of risk stratification in most studies. To address this, Fernandez et al [30] identified three distinct risk groups for survival, and observed a beneficial effect of NAC in patients with muscle-invasive disease without hydronephrosis in contrast to patients with cT1 disease and those with tumour-associated hydronephrosis. Ultimately, the current data suggest that platinum-based NAC

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may be utilised in patients with muscle-invasive MPUC, but further drug development is needed (eg, HER2-based therapy). With regard to adjuvant chemotherapy, only one study exists, and this reported higher tumour recurrence rates in MPUC patients receiving AC compared with those with pure UC [31].

Molecular subtyping studies have shown that MPUC exhibits a luminal subtype; the variant is also characterised by HER2 overexpression and activation of *miR-296* and *RUVBL1* target genes, all of which represent future therapeutic targets [32].

#### 3.2.3. Microcystic

Microcystic UC is characterised by the presence of round to oval cysts of varying sizes (1–2 mm) which often contain intraluminal secretions and are lined by cuboidal or flattened urothelial cells with bland cytology (Fig. 1B) [33]. This variant is usually deeply infiltrative and involves the muscularis propria.

*3.2.3.1. Implications for diagnosis.* Microcystic UC has a deceptively benign appearance and shares histological similarities with nested UC, bladder AC, cystitis glandularis, and cystitis cystica. Foci of high-grade UC are seen in 40% of cases, and this may help distinguish the variant from benign mimickers, as does the presence of a TERT promoter mutation [34].

*3.2.3.2. Implications for management.* Outcomes for patients with microcystic UC are limited to a few case reports and two small case series, but it is clear that the variant is associated with a poor prognosis. In the largest study of 20 patients, 55% had died following RC at a mean follow-up of 30 mo. However, when controlled for stage, there was no difference in survival outcomes when compared with pure UC [35].

#### 3.2.4. Nested

Nested UC is a rare variant characterised by a large number of discrete to confluent small nests of urothelial cells infiltrating the lamina propria and muscularis propria (Fig. 1C). The tumour cells have a bland appearance, and the tumour nests show a haphazard, infiltrative distribution [36].

*3.2.4.1. Implications for diagnosis.* The variant's deceptively benign histological appearance can present diagnostic difficulties, as it may be mistaken for benign lesions such as von Brunn's nests, cystitis cystica, and nephrogenic adenoma. Features that may help distinguish variant from benign entities include the deeply invasive nature with involvement of the muscularis propria, an infiltrative growth pattern at the tumour base, and the confluence of small tumour nests.

*3.2.4.2. Implications for management.* Nested UC demonstrates high rates of muscle invasion, extravesical disease, and a propensity for metastases [37,38]. In a comparison of 52 nested variant cases undergoing RC with stage-matched pure UC controls, the nested variant was associated with a very high rate of locally advanced disease at RC (pT3–4 in 69%). However, when matched stage for stage, there was no significant difference in recurrence-free or cancer-specific survival between cohorts at a median follow-up of almost 11 yr [38].

#### 3.2.5. Lymphoepithelioma-like carcinoma

Lymphoepithelioma-like carcinoma (LELC) of the bladder is so named because of its histological resemblance to nasopharyngeal lymphoepithelioma. It accounts for <1% of all UCs and is composed of small aggregates of poorly differentiated tumour cells with large nuclei, prominent nucleoli, and indistinct cell membranes (Fig. 1D). A dense infiltrate of lymphoid or inflammatory cells is a characteristic feature [39].

*3.2.5.1. Implications for diagnosis.* This variant is unusual in that the tumour cells may be masked by intense infiltration of polyclonal T and B cells [40]. At low magnification, these lesions may mimic a lymphoma or a solitary inflammatory nodule. However, at high magnification, the diagnosis is evident due to the presence of syncytial sheets of tumour cells. Other differential diagnoses include poorly differentiated SCC.

*3.2.5.2. Implications for management.* LELC in its pure form appears to have a very favourable response to platinum-based chemotherapy and a low metastatic potential [40]. In mixed form, the prognosis is associated with the other variant present in the tumour. In a systematic review of 140 cases of LELC, RC was associated with the highest disease-free survival rate (67.8%) compared with partial cystectomy or TURBT alone [41].

#### 3.2.6. Plasmacytoid

Plasmacytoid UC is characterised by the presence of discohesive cells with eccentrically placed nuclei and abundant eosinophilic cytoplasm (Fig. 2A) [42]. A number of tumour cells may show morphology of signet ring cells. This variant usually displays a diffusely infiltrative growth pattern but induces minimal stromal reaction.

*3.2.6.1. Implications for diagnosis.* Plasmacytoid morphology is not exclusive to UC, and so plasmacytoid urothelial carcinoma must be differentiated from other plasmacytoid neoplasms in the bladder such as melanoma and lymphoma. The presence of concomitant UC is usually diagnostic, but a panel of immunohistochemical stains for CK7, CK20 uroplakin II, and GATA-3 can be useful if in doubt [43].

Accurate preoperative identification of plasmacytoid UC is imperative as the variant is associated with a high rate of positive surgical margins on extirpative surgery [44,45]. This, in part, is due to the variant's advanced stage at presentation, but also because it exhibits a characteristic pattern of spread. Tumour cells invade in single file, with malignant cells manifesting distant from macroscopic disease. There is also a lack of desmoplastic reaction such that the plane between the tumour and normal tissue is difficult to determine surgically. Identification of plasmacytoid

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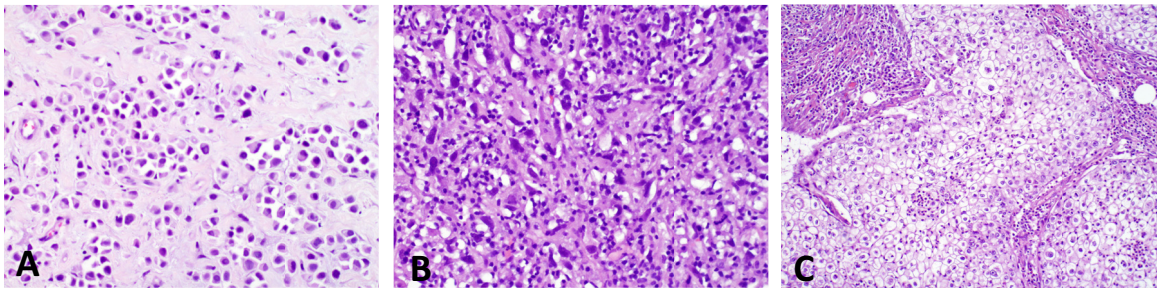


**Fig. 2 – (A) Plasmacytoid variant shows discohesive tumour cells with eccentrically located nuclei and abundant eosinophilic cytoplasm. (B) Sarcomatoid variant is characterised by high-grade spindle tumour cells. (C) Clear cell variant is characterised by large nests of tumour cells with high-grade nuclear atypia and clear cytoplasm.**

morphology is therefore important to ensure wide and adequate resection by the surgeon at the time of RC.

Given the high rate of surgical margin positivity, it is no surprise that recurrence rates are high [44]. Furthermore, peritoneal carcinomatosis is frequently seen [45,46] and is thought to occur due to truncating mutations of CDH1. These mutations are pathognomonic of plasmacytoid UC and result in the loss of E-cadherin expression, which is associated with enhanced tumour cell migration [47].

*3.2.6.2. Implications for management.* Multiple studies demonstrate that plasmacytoid UC is associated with locally advanced disease at presentation and a propensity for lymph node involvement [42,44,45,48,49]. However, when matched stage for stage to pure UC, there does not appear to be any difference in survival outcomes [44,45].

The role of NAC/adjuvant chemotherapy is unclear because current data come from small retrospective single-institution series with differing chemotherapy regimens. Although early studies indicated that tumours were chemosensitive [46], more recent data suggest that cisplatin-based chemotherapy confers no survival benefit and prognosis remains poor even in those achieving pT0 on RC specimens [48,49].

#### *3.2.7. Sarcomatoid*

Sarcomatoid UC is estimated to represent 0.3% of all urothelial cancers. The variant is composed of high-grade spindle tumour cells, and exhibits morphological and/or immunohistochemical evidence of both epithelial and mesenchymal differentiation (Fig. 2B). Risk factors include previous exposure to radiotherapy and intravesical cyclophosphamide [50].

*3.2.7.1. Implications for diagnosis.* The diagnosis of sarcomatoid UC may be challenging, as its morphology is highly variable and can mimic nonepithelial neoplasms [50]. Differential diagnoses include postoperative spindle cell nodule, inflammatory myofibroblastic tumour, and primary bladder sarcoma. Sarcomatoid tumours often overexpress epithelial-mesenchymal transition markers including FoxC2, SNAIL, ZEB1, and vimentin, and identification of these may aid diagnosis [51].

*3.2.7.2. Implications for management.* Sarcomatoid UC is associated with a poor prognosis as it frequently presents at an advanced stage and is associated with worse overall survival when compared with pure UC [50–53].

In the largest series of 489 patients, 41.1% and 15.3% presented with clinical T2 and T3 disease, respectively, and the median overall survival was 18.4 mo following diagnosis [54]. Survival in the RC cohort was not significantly different from those receiving either NAC or adjuvant chemotherapy. The apparent lack of benefit from chemotherapy on overall survival has been confirmed by other studies [55,56].

#### *3.2.8. Clear Cell*

Clear cell UC is an exceedingly rare variant characterised by cells with glycogen-rich cytoplasm (Fig. 2C).

*3.2.8.1. Implications for diagnosis.* This variant can be either focal or extensive in the tumour component, and needs to be distinguished from clear cell AC of the bladder, or metastatic clear cell renal cell carcinoma, or clear cell carcinoma of the female genital tract [57].

*3.2.8.2. Implications for management.* Given the rarity of this variant, prognosis and treatment strategies are poorly defined. Data from case reports and a single case series suggest that there is rapid progression to muscle invasion and metastases [58,59]. As such, aggressive management is warranted with upfront RC.

### *3.3. Nonurothelial variants*

#### *3.3.1. Small cell carcinoma*

Small cell carcinoma (SmCC) of the bladder is an aggressive neuroendocrine tumour, accounting for 0.5–0.7% of all bladder tumours. It histologically resembles its pulmonary counterpart and frequently coexists with conventional UC, SCC, and AC. The tumour is composed of nests or solid sheets of small tumour cells with enlarged nuclei, evenly dispersed "salt and pepper" chromatin, and scant cytoplasm (Fig. 3A).

*3.3.1.1. Implications for diagnosis.* Accurate diagnosis of SmCC is critical as, unlike conventional UC, this variant exhibits rapid growth with a predilection for early metastases to

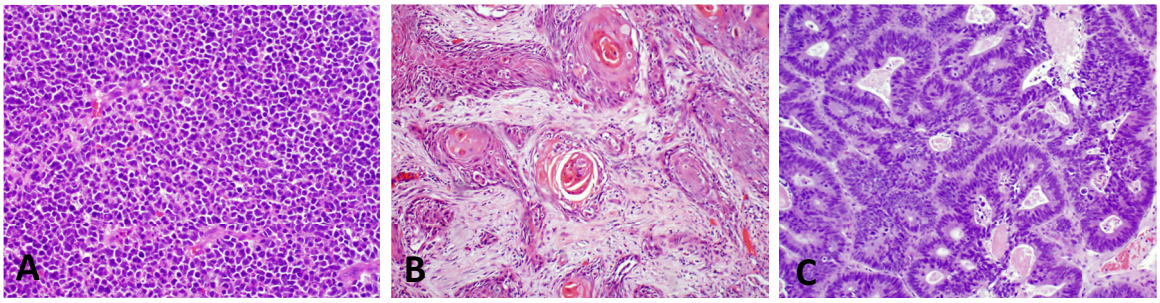


**Fig. 3 – (A) Small cell carcinoma shows a solid sheet of poorly differentiated tumour cells with a high nuclear/cytoplasmic ratio. (B) Well-differentiated squamous cell carcinoma shows abundant keratin production. (C) Intestinal-type adenocarcinoma shows malignant colonic glands with high-grade columnar cells and necrosis in the lumens.**

sites including brain and bone [60–62]. Differential diagnoses include poorly differentiated UC and metastatic SmCC from other organs, especially the prostate. Most, but not all, bladder SmCCs express neuroendocrine markers such as chromogranin, synaptophysin, and CD56. However, SmCCs do not express urothelial markers, thus distinguishing them from poorly differentiated UC.

Owing to the high propensity for brain metastases, a diagnosis of bladder SmCC mandates central nervous system imaging because, as seen in the MD Anderson series, patients had a 50% incidence of brain metastases in bulky, high-stage (≥T3b, N + or M+) tumours [63].

*3.3.1.2. Implications for management.* Early use of NAC (typically cisplatin/carboplatin and etoposide) followed by local control (either surgery or radiotherapy) represents the optimal management for bladder SmCC. There is clear evidence for the chemosensitivity of these tumours, with many studies demonstrating a survival benefit with NAC [55,61,64]. This favourable response may be because some of these tumours express a basal molecular subtype, which has been shown to predict chemosensitivity [61].

When compared with pure UC at a similar stage, survival outcomes are similar with appropriate use of chemotherapy, except in the setting of metastatic disease where SmCC harbours a worse prognosis [61].

### 3.3.2. Squamous cell carcinoma

SCC is the most common nonurothelial variant, representing approximately 5% of all bladder cancers in western countries [65] and up to 30% in endemic countries such as Egypt and Sudan [66]. It may occur de novo or in individuals infected with the parasite *Schistosoma haematobium*. Nonbilharzial SCC develops as a result of chronic inflammation of the urothelium from sources including chronic urinary tract infection, long-term catheters, and bladder calculi. Histologically, SCC is characterised by classical squamous features such as keratin pearl formation and intracytoplasmic keratin granules (Fig. 3B).

*3.3.2.1. Implications for diagnosis.* Although some bladder tumours may present with mixed urothelial and squamous components, the diagnosis of bladder SCC implies that it is the only histology.

*3.3.2.2. Implications for management.* Patients with SCC present with more advanced disease, with approximately 70% having muscle-invasive disease at diagnosis. Furthermore, SCC carries a worse prognosis on both an overall and a stage-for-stage basis [67]. Even in the absence of distant metastases, prognosis remains poor because of a tendency for locoregional recurrence [68].

RC is the mainstay of treatment, as radiotherapy alone appears to be less effective. Surveillance, Epidemiology, and End Results (SEER) database analysis of 5018 SCC cases from 1973 to 2013 demonstrated a significant difference in cancer-specific and overall survival favouring the cystectomy group compared with the radiotherapy or no treatment group [69]. Furthermore, a recent analysis of 79 SCC cases from the National Cancer Database showed that following chemoradiotherapy, patients with SCC had worse overall survival than their counterparts with UC [70]. However, these findings must be interpreted cautiously, as they are limited by their retrospective design, small patient numbers, and differences in treatment regimen. Neither NAC nor adjuvant chemotherapy appears to confer a survival advantage on patients with pure SCC [55,56,67,71]. However, preoperative radiotherapy can be used in locally advanced cases, combined with intraoperative radiotherapy as appropriate, to reduce the incidence of local recurrence.

### 3.3.3. Adenocarcinoma

ACs of the bladder are either primary or secondary depending on the presence of a direct spread from other organs. Secondary AC represents the most common form and originates from the prostate, colon, endometrium, cervix, and lung. Primary AC accounts for approximately 2% of all bladder cancers and is broadly divided into two subtypes: urachal and nonurachal carcinoma. Risk factors include bilharziasis, chronic irritation, nonfunctioning bladders, and bladder exstrophy.

Urachal AC develops from the urachal remnant and accounts for a third of primary ACs involving the bladder. It usually presents as a solitary polypoid mass in the bladder dome, although it can be seen anywhere along the anterior midline. Urachal AC shows a male preponderance and an earlier age of diagnosis compared with nonurachal AC [9,72].

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*3.3.3.1. Implications for diagnosis.* Histologically, AC can present as intestinal, papillary, signet-ring cell, clear cell, or mixed subtypes (Fig. 3C). The diagnosis of primary bladder AC should be made only when secondary involvement from other organs has been excluded, as this is the main differential diagnosis.

*3.3.3.2. Implications for management.* The majority of ACs present with locally advanced or metastatic disease; SEER analysis of 215 AC patients from 2004 to 2013 reported that only 35% of tumours were organ confined [73]. When matched for stage, primary AC appears to have similar outcomes to UC [74]. RC is, therefore, the standard of care for all localised primary bladder ACs.

Several studies demonstrate superior survival outcomes for urachal ACs compared with nonurachal tumours [72,75]. These patients can be managed with partial cystectomy with en bloc resection of the bladder dome, urachal ligament, and umbilicus. However, RC may be necessary for some as negative margins are essential and salvage surgery has poor outcomes [76].

The role of radiotherapy is unclear. Although one study observed improved disease-specific survival in patients receiving adjuvant radiotherapy [76], recent analysis of the National Cancer Database demonstrated inferior survival outcomes in patients undergoing radiotherapy or cystectomy with radiotherapy compared with cystectomy alone [77]. Current data are insufficient to support the use of NAC/adjuvant chemotherapy in bladder AC, but the available evidence suggests that neither confers a survival benefit [55,56].

## 4. Conclusions

In the management of bladder cancer, accurate identification of variant histology forms an important part of risk stratification. Variant histology not only presents diagnostic challenges, but also has clinical implications that affect patient prognosis and inform treatment decisions. Although associated with advanced disease at presentation, when treated appropriately, survival outcomes are comparable with that of stage-matched pure urothelial carcinomas. Controversy exists regarding optimal management as current recommendations are predominantly based on small retrospective series as well as extrapolation of data from pure urothelial carcinoma. While the survival benefit of cisplatin-based chemotherapy remains often discussed, current evidence is not robust enough to preclude its use. Therefore, NAC and RC with pelvic lymph node dissection remains the mainstay of treatment for most cases of variant histology. Small cell carcinoma and lymphoepithelioma-like carcinoma appear to be especially chemosensitive, and in these patients, chemotherapy is essential. Emerging genomic information will change treatment paradigms for variant histology by predicting response to treatment and leading to the development of new targeted therapies.

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