Chapter

Bladder Cancer Variant Histologies: Epidemiology, Diagnosis, Treatment and Prognosis

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Abstract

Bladder cancer (BC) is an increasingly frequent cancer worldwide, being currently the sixth most frequent tumor and the thirteenth leading cause of cancer death. Among all BC cases, pathologists have identified several histomorphologies different from the conventional urothelial carcinoma. Although rare, these histologic variants have a distinct growth pattern, an altered cell differentiation and an unusual clinical behavior, especially concerning clinical presentation at diagnosis, response to the standard treatment and prognosis. Therefore, an updated review of this topic should be useful to aid clinicians in a better evidence-based decision-making. This chapter aims to summarize the current literature on the most common histologic variants regarding their epidemiology, clinical presentation at diagnosis, treatment options and prognosis. This includes both non-muscle invasive BC and muscle invasive BC as well as metastatic disease. A special focus will be placed on the role of neoadjuvant chemotherapy and early cystectomy and its prognostic implications.

Keywords: Bladder, Cancer, Histologic, Variants, Prognosis, Treatment

1. Introduction

Bladder cancer is an entity characterized by a wide range of different histomorphologies as well as distinct clinical courses. Approximately 75% of tumors are classified as pure urothelial carcinoma (transitional cell carcinoma), the remaining 25% consist of other histological variants. Several histological variants have been identified throughout the years, based on morphological features [1]. During the past decade, there is a trend of increasing evidence of the clinical relevance of histological variants, some them with data showing adverse pathological features and poor prognosis [2]. The acknowledgment of this information has been changing the clinical reasoning and disease management in patients with BC.

Pure non-urothelial bladder cancer comprises only a small minority (about 5%) of all bladder cancers. They include squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and mixed histology tumors, with squamous and adenocarcinoma comprising the most frequent morphologies. Non-urothelial histologic subtypes were generally thought to have a worse prognosis compared to urothelial

BC [3], however, once corrected for stage and patient-related factors, a significant proportion of them may have a similar prognosis.

On other hand, urothelial tumors with a variant histology component are more frequent than non-urothelial tumours. The classification of histologic variants is mainly based on morphologic features, being each differentiation pattern characterized by a distinct biological behavior, such as propensity for local recurrence and metastasis [4]. Non-muscle invasive BC with variant histology most likely remains underdiagnosed, as it seems challenging to identify its presence on TURB specimens. Current data suggests that variant histologies confer high-risk status to non-muscle invasive tumors, despite some studies had demonstrated similar progression rates in comparison with pure urothelial carcinomas (UC) associated with high risk factors [5]. Therefore, the question arises, does variant histology justify an aggressive treatment approach with early radical cystectomy?

The treatment of BC has evolved throughout the years such that clinical markers of risk are now used to guide us through algorithms that incorporate transurethral surgery, intravesical chemotherapy and immunotherapy, radical cystectomy, systemic combination chemotherapy, and sometimes radiation therapy. Therefore, the optimal risk stratification may include variant histology as a relevant factor in clinical decision making [6].

This chapter focuses on most common histological variants and discusses different treatment options and their prognostic value.

2. Histologic variants of Urothelial Carcinoma

Urothelial carcinoma (UC) is remarkable for displaying a wide range of diversity in its morphological appearance, which may reflect its molecular heterogeneity. Urothelial tumors with divergent differentiation are the most common histology variant within urothelial carcinomas [7]. The term refers to tumors that present some degree of typical urothelial carcinoma (invasive or *in situ*) with other histomorphologies such as squamous or glandular differentiation.

Squamous and Glandular differentiation are most common histology variants [8, 9]. UCs with squamous or glandular differentiation are distinct entities and should be distinguished from both pure squamous cell carcinoma (SCC) and or adenocarcinoma (AC) which do not include any urothelial components and subsequently present different clinical behavior. Other subtypes of UC variants include rarer differentiations including trophoblastic and small cell differentiation.

Urothelial carcinomas with divergent differentiation were previously thought to present at a more advanced stage at diagnosis and early reports indicated a poorer survival rate. More recently, studies have shown that, if standardized for stage, patients with either squamous or glandular UCs have survival rates comparable with those with pure UC.

Yet, current guidelines still categorize UC with variant histology in the highest risk category in which early radical cystectomy should be considered [8].

2.1 Urothelial carcinomas with squamous differentiation

Urothelial carcinomas with squamous differentiation are found in up to 40% of UCs and the inclusion of keratinization and/or intercellular bodies (**Figure 1**) are their main histological hallmarks [7]. The distinction between UC with squamous differentiation and pure squamous cell carcinomas (SCC) of the bladder remains a challenge for pathologists, especially in transurethral resection (TUR) specimens, because both tend to share most of the same immunohistochemical components.

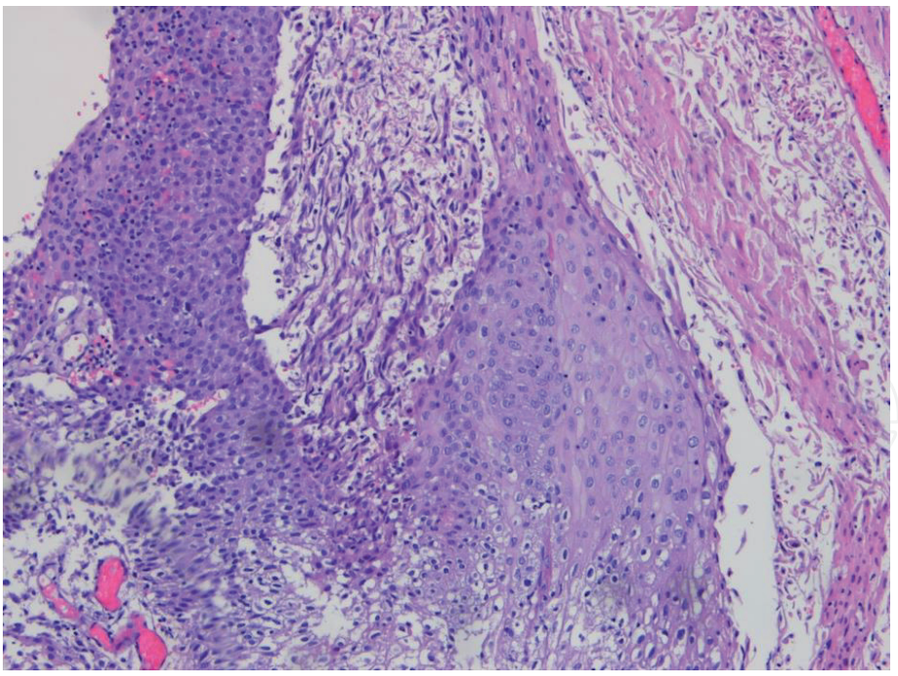

Figure 1.
Squamous differentiation is characterized by the presence of both urothelial carcinoma and keratin clusters and intercellular bodies (HE × 100).

Among NMIBC cases, UCs with squamous differentiation are frequently associated with high-grade and high-stage tumors at diagnosis and tend to have a less favorable response to intravesical chemotherapy or BCG instillations [10]. In the MIBC disease setting, studies have shown that response rate of neoadjuvant chemotherapy may be similar to conventional UC [11], although with a poor prognosis [2].

2.2 Urothelial carcinomas with glandular differentiation

Glandular differentiation comprises approximately 10% of all UCs and is characterized by true gland formation (**Figure 2**), resembling colonic adenocarcinoma, signet ring carcinoma or mucinous/colloid carcinoma. It may be associated with UC in situ or less frequently with in situ UC with glandular differentiation. Pseudo glandular aspects with mucin expression may be observed in conventional UC and should not be confused with either UC with glandular differentiation or bladder adenocarcinoma, although the lack of immunohistochemical markers makes the distinction challenging [12]. Telomerase reverse transcriptase (TERT) mutations are seen in the majority of UCs with glandular differentiation and not in adenocarcinomas of the bladder [13]; nevertheless, this marker is yet to be implemented in routine clinical use.

In terms of clinical significance of this differentiation, it tends to present at a higher stage, but it is not a predictor of adverse prognosis in stage-matched patients, showing similar rates of recurrence-free and overall survival when compared to conventional UC [5].

It is important to note that data from studies has showed that intravesical BCG treatment might play a key role in patients with UC with glandular differentiation, with this therapy presenting reasonable response rates [14, 15].

2.3 Urothelial Carcinomas with Trophoblastic Differentiation

UC with trophoblastic differentiation is a rare entity with only a few cases reported, and it is characterized by the expression of the beta subunit of the human chorionic gonadotropin (ßhCG) (**Figure 3**). This subtype must be distinguished from

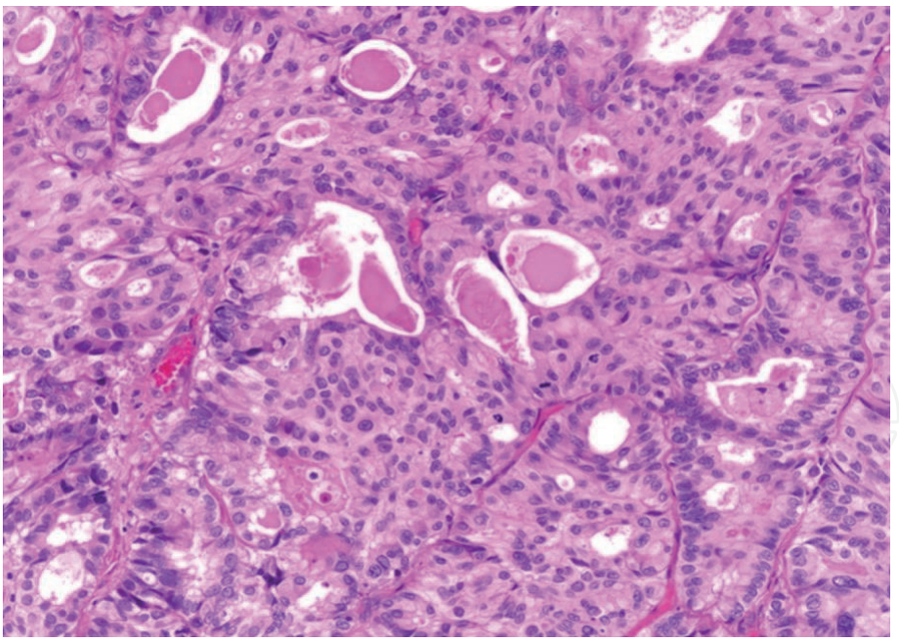

Figure 2.
Glandular differentiation encompasses gland-like lumina or fully developed adenocarcinoma with intestinal morphology (HE × 100).

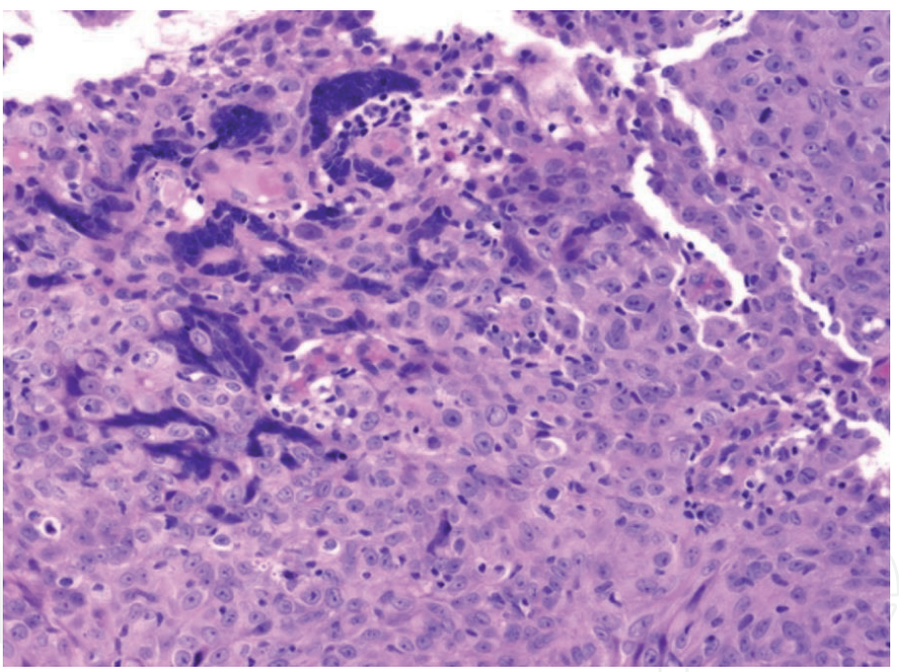

Figure 3.
The image shows a cluster of syncytiotrophoblastic giant cells enclosed by high-grade urothelial carcinoma (HE × 100).

pure choriocarcinoma which requires the demonstration of the isochromosome 12p, a hallmark of germ cell tumors. The percentage of ßhCG-immunoreactive cells is associated with higher stage and grade of the disease. Elevated secretion of ßhCG into the serum may be associated with an observable poorer response to chemotherapy and radiation, and it can be used as a marker in the follow-up of these patients [2].

2.4 Urothelial Carcinomas with Small Cell Differentiation

UC can exhibit neuroendocrine differentiation in the form of small cell carcinoma. These tumors are usually treated similarly to their counterpart in the lungs.

2.5 Nested Urothelial Carcinoma

Based on the 2016 WHO classification, the nested variant includes UC with small tubules and microcysts (**Figure 4**). This histologic variant can often resemble benign cytology [16]. It is characterized by disorderly proliferation of confluent nests, with minimal cell atypia [17], which can often delay the definitive diagnosis.

Nested UCs usually present as high stage disease and may be associated with a worse prognosis compared with pure nested variants [14]. It shares similar immunohistochemical features and clinical outcomes with the conventional UC, with little to no difference in recurrence rate or survival when treated with RC in either NMIBC and MIBC [17].

2.6 Microcystic Urothelial Carcinoma

The microcystic UC variant, like the nested UCs, is characterized by a benign cytologic resemblance features. It is constituted by oval cysts, lined by urothelial, low columnar or flattened epithelium (**Figure 5**) and focal conventional UC may be present in up to 40% of tumors [18]. Foci of high-grade UC are seen in up to 40% of cases, which may help distinguish this variant form benign mimicking tumors [14].

Differential diagnosis includes benign proliferations such as florid polypoid cystitis cystica and glanduraris and adenocarcinoma [19].

There is very limited information about prognostic implications of microcystic histology in BC, only a few case reports and case series have been published. The largest study to date (N = 20) reported 55% of patients died at a mean follow-up of 30 months after radical cystectomy (RC). However, when controlled for stage, there was no statistically significant difference in survival compared with patients with pure UC [20].

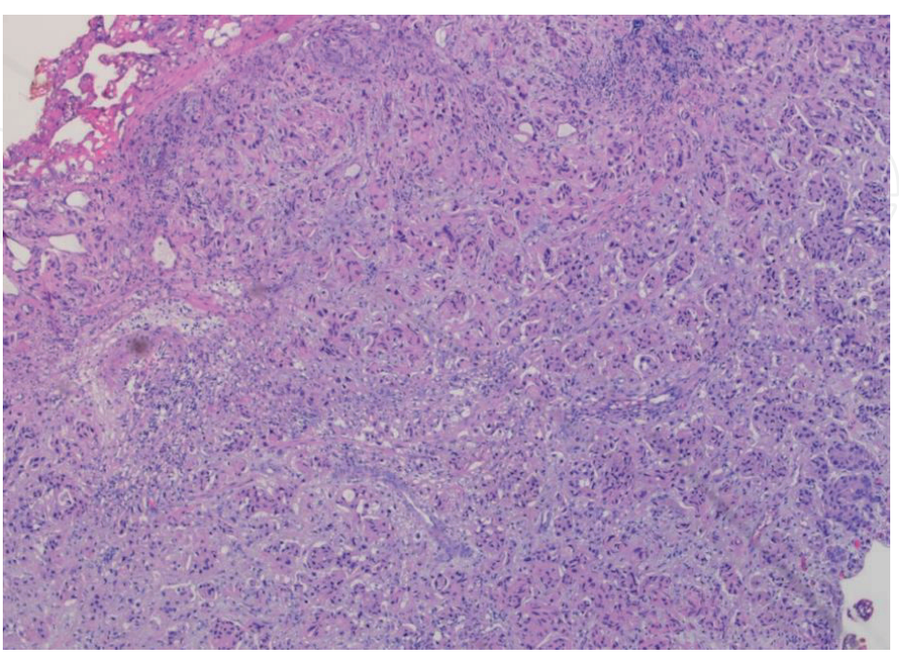

Figure 4.
The nested variant of urothelial carcinoma consists of small, discrete nests with bland morphology distributed irregularly in the lamina propria. The size of nests is much smaller than von Brunn's nests of normal urothelium (HE × 40).

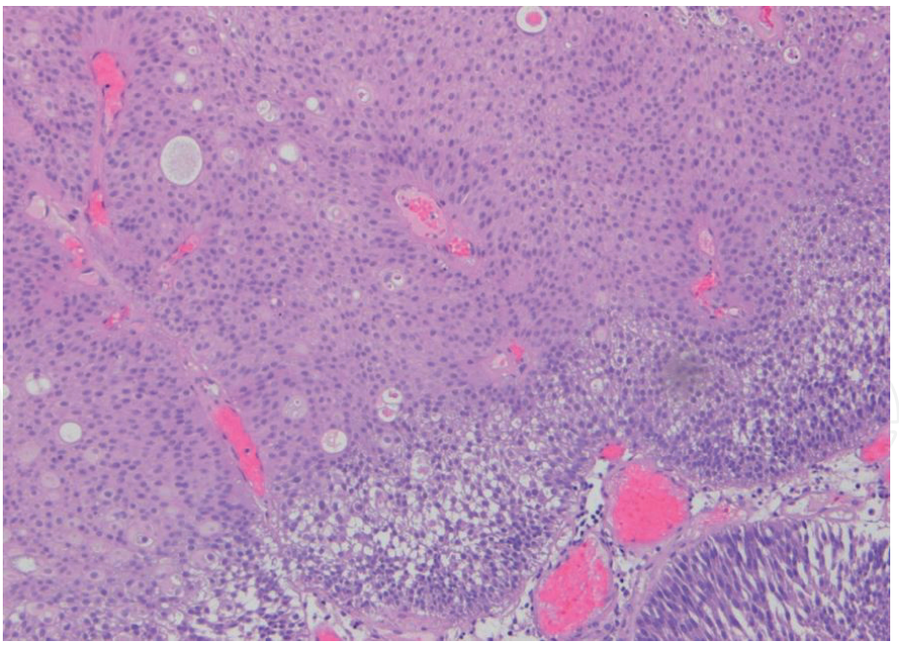

Figure 5.
Characterized by the formation of microcysts which may mimic cystitis cystica in small specimens. Cytologic atypia is minimal or entirely absent (HE × 100).

2.7 Micropapillary Urothelial Carcinoma

Micropapillary Urothelial Carcinoma (MPUC) is a variant seen most commonly in males, being characterized by small tumour nests surrounded by lacunar spaces (**Figure 6**). It is a clinically aggressive variant that usually presents at an advanced stage that accounts for 2–5% of UCs [14, 21]. ERBB2 (HER2) amplification by FISH is seen more commonly in patients with MPUC versus conventional UC, such expression has been related to worse cancer-specific survival although it also provides a potential role for HER2 targeted therapy [22]. Single institution case-series

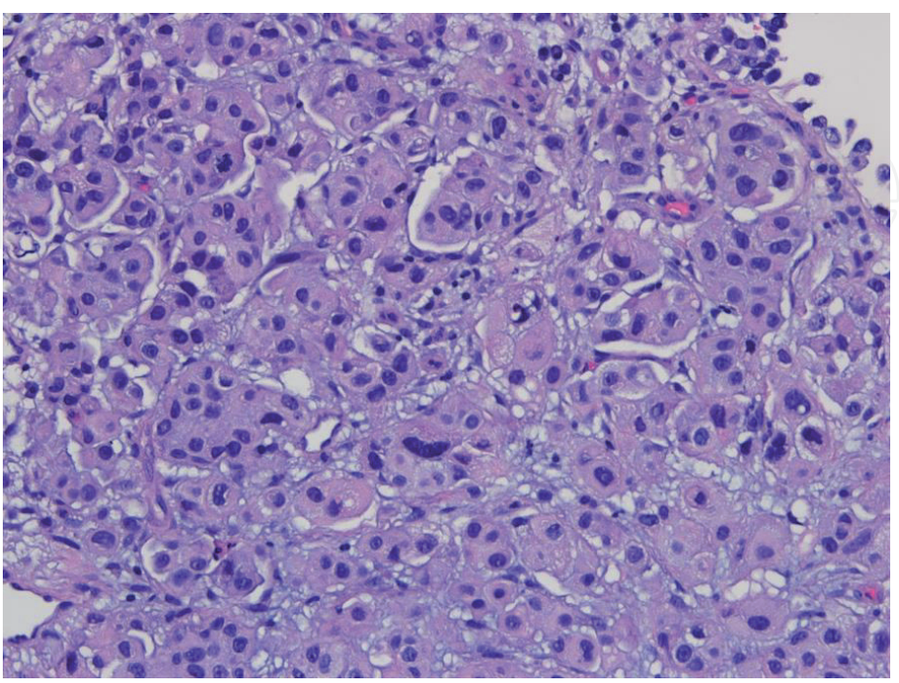

Figure 6.
Infiltrating tumors cells with slender filiform processes without fibrovascular cores and multiple small tumor nests within a single lacunar space, mostly not enclosing a true fibrovascular core (HE × 200).

have demonstrated poorer outcomes in patients with MPUC than those with pure UC [23]. However, more recent studies demonstrated that, when controlled for stage, this may not be the case.

Non muscle-invasive MPUC is characterized by high rates of progression to muscle-invasive and metastatic BC. A case series with 44 patients with non-muscle invasive MPUC, amongst those treated with BCG, 67% showed cancer progression with 22% developing metastatic disease, only 19% remained alive at the end of follow-up (10-yeat) without RC. Patients who underwent delayed RC after BCG treatment failure presented a median disease-specific survival (DSS) of 62% at 10 years. On the other hand, patients treated with early RC had a 10-year median DSS of 72% [24].

Patients with UC with a micropapillary component doing upfront RC were not associated with worse recurrence-free, cancer specific or overall survival, when compared to those with pure UC [25].

Therefore, early RC has been considered the standard of care in most centers, however, there have been reports of reasonable outcomes in series in which bladder preservation therapies were applied in highly selected patients with a relatively small micropapillary component [26].

Although there is still scarce evidence regarding muscle-invasive MPUC and the role of Neo-adjuvant chemotherapy (NAC) in opposition to early RC, there have been reports showing no statistically significant differences in overall survival (OS) between the group who have undergone NAC plus RC vs. RC only [27]. A recent study analyzed the impact of adjuvant chemotherapy (AC) in the OS among patients with MPUC and the results demonstrated that, in contrast to pure UC, no survival benefit was observed in patients with this histology subtype [28]. Nevertheless, although these results could be explained by the more aggressive clinical behavior of this histologic variant, they can also be a consequence of small samples size, short follow-up periods and lack of risk stratification in most studies.

2.8 Lymphoepithelioma-like UC

Lymphoepithelioma-like UC (LLUC) resembles lymphoepithelioma of the nasopharynx and is characterized by a prominent lymphoid stroma (**Figure 7**) with T (predominantly CD3) and B lymphocytes, plasma cells, histiocytes, neutrophils and eosinophils. Major differential diagnosis comprises poorly differentiated UC with lymphoid inflammatory response or lymphoma [29, 30].

This histologic variant has been found to have a similar prognosis to conventional UC as well as similar chemosensitivity and response to immunotherapy [31].

2.9 Plasmocytoid

Plasmacytoid UC is a rare histopathological variant of UC, comprising 1–3% of all UCs and is characterized by the presence of discohesive cells with eccentrically placed nuclei surrounded by abundant eosinophilic cytoplasm (**Figure 8**). This variant usually displays a diffusely infiltrative growth pattern, inducing minimal stromal reaction [32]. This morphology is not exclusive to UC, thus plasmacytoid UC (PUC) must be distinguished from melanoma and lymphoma. Immunohistochemical markers such as CK7, CK20 uroplakin II, and GATA-3 can be useful in the differentiation in doubtful situations [33]. It is also characterized by a distinct growth pattern in which tumour cells can manifest distant from macroscopic disease with the absence of a desmoplastic reaction making it more challenging to determine the plane between the tumour and normal tissue. A wide margin of resection is therefore mandatory to ensure an adequate resection at the time of RC [32].

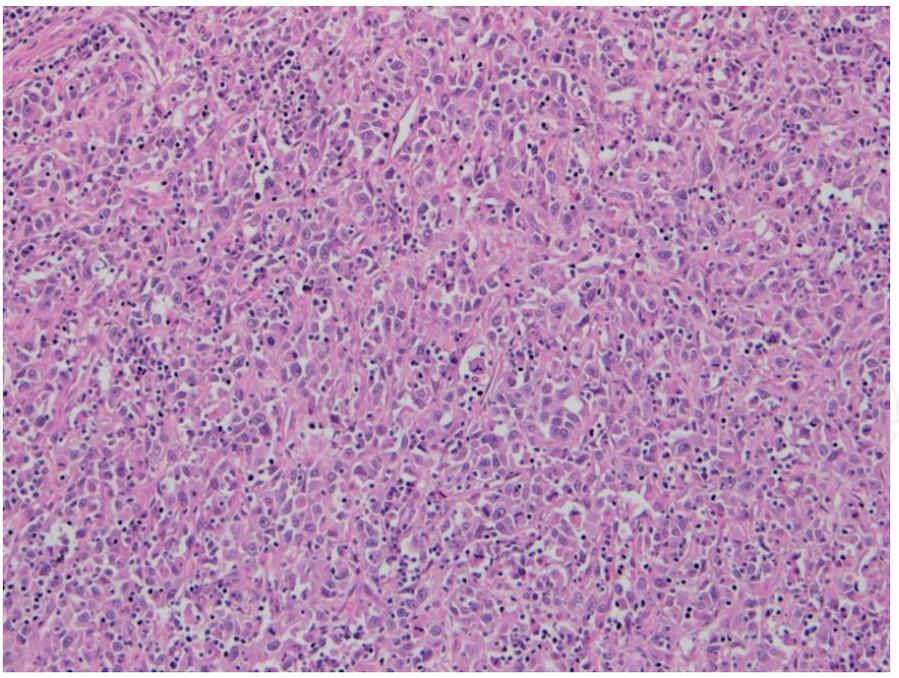

Figure 7.
Characterized by syncytial sheets of tumor cells and a prominent chronic inflammatory infiltrate in the stroma. The infiltrate is composed largely of lymphocytes, plasma cells, eosinophils, and other inflammatory cells which may create an appearance of chronic cystitis or malignant lymphoma (HE × 100).

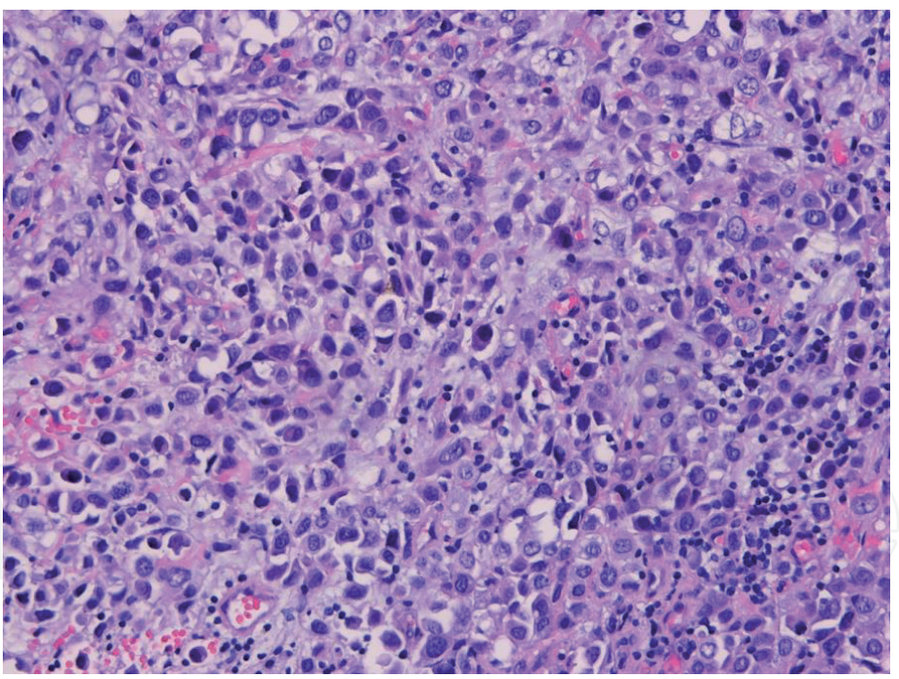

Figure 8.
PUC usually displays single tumor cells with plasmacytoid features infiltrating loose myxoid stroma. It shows discohesive tumour cells with eccentrically located nuclei and abundant eosinophilic cytoplasm (HE × 200).

Mutations in CDH1 are pathognomonic of PUC and result in the loss of E-cadherin expression in its tumour cells, this is thought to explain the higher rates of tumour cell migration observed [34, 35].

Plasmacytoid UC response to intravesical BCG has not been clearly defined yet but given the fact that these tumors display a strong predilection for recurrence, especially in peritoneal lining, even in cases when non-muscle invasiveness is encountered, early RC seems to provide a more effective control of the disease [36].

The role of NAC/AC is still unclear in PUC, although initial evidence suggested this histologic variant was chemosensitive, more recent data suggests that platin based regimens confer no survival enhancement and that even in patients who achieve pT0 stage after cystectomy after RC, poor prognosis is maintained in PUC [36, 37].

2.10 Sarcomatoid

Sarcomatoid UC accounts for approximately 0.3% of all UCs. This histologic variant is characterized highly variable morphology exhibiting both epithelial and mesenchymal differentiation with high-grade spindle cells (**Figure 9**). Previous exposure to radiotherapy (RT) and intravesical cyclophosphamide are known risk factors [38].

Sarcomatoid differentiation has been associated with a very poor prognosis, since it usually presents at an advanced stage [38]. However recent series demonstrated no differences in comparison with same stage pure UC, regarding disease-specific, all-cause mortality and overall survival [28]. A survival benefit was not found in patients undergoing NAC or AC, suggesting this variant might be particularly resistant to chemotherapy [39].

2.11 Clear cell

Clear cell UC is a very rare variant of UC characterized by tumour cells with glycogen-rich cytoplasm (**Figure 10**). It is crucial to do the correct differential diagnosis among clear cell UC, clear cell adenocarcinoma of the bladder, metastatic clear cell renal cell carcinoma or clear cell carcinoma of the female genital tract [28].

Only a few case reports are available for this rare histologic variant. The evidence suggests a high progression rate to muscle-invasive and metastatic BC, and although treatment strategy is poorly defined, an aggressive approach with early RC is advocated [40].

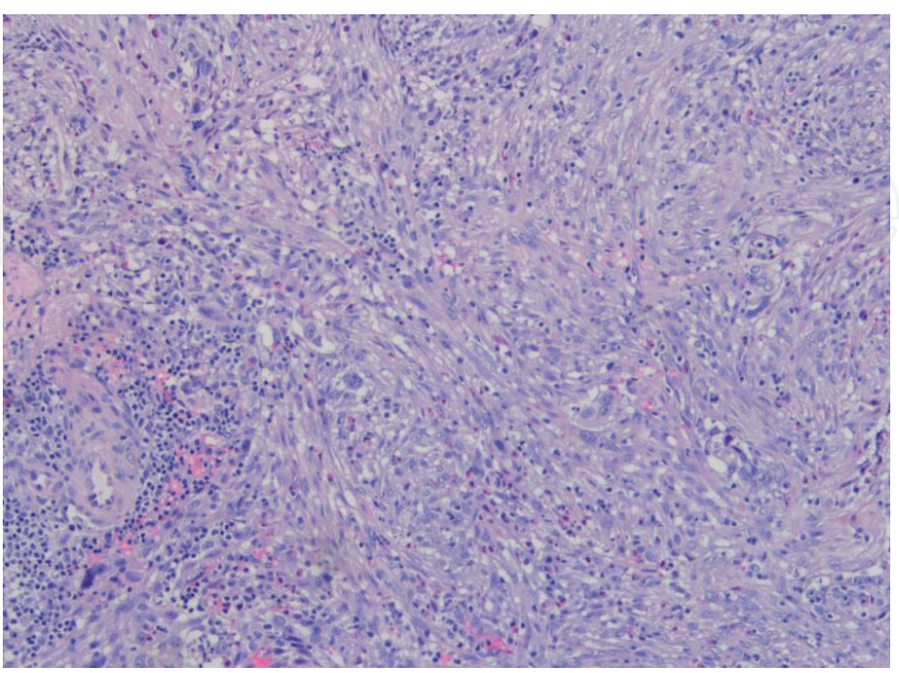

Figure 9.
It contains both carcinoma as well as sarcomatous areas usually with high-grade urothelial carcinoma on the surface and a high-grade undifferentiated sarcoma underneath in the lamina propria (HE × 100).

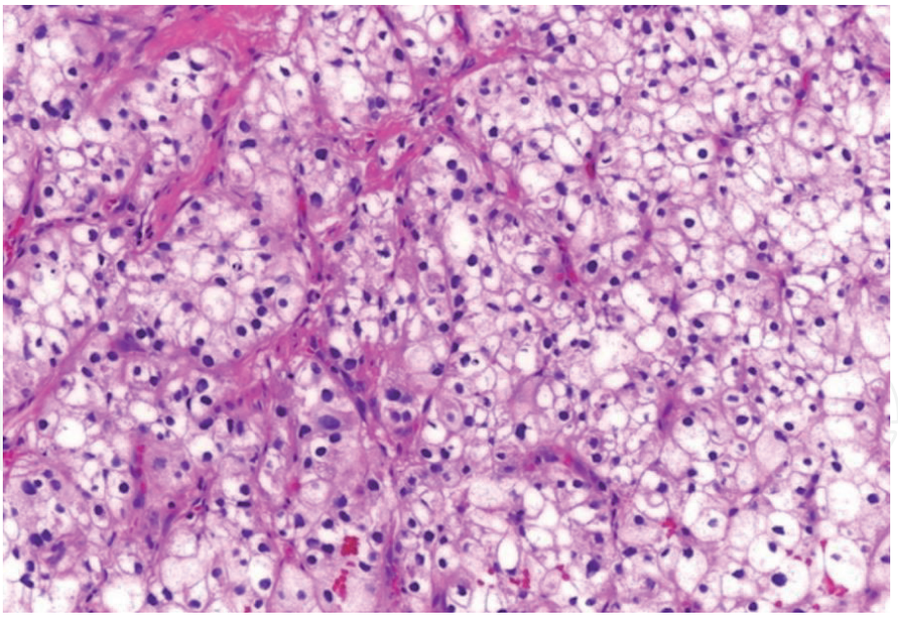

Figure 10.
Clear cell variant of urothelial carcinoma consists of abundant clear cytoplasm due to glycogen content and it is characterized by large nests of tumour cells with high- grade nuclear atypia and clear cytoplasm (HE × 200).

3. Non-Urothelial Variants

Non-urothelial BC can be categorized as epithelial and non-epithelial tumors. Approximately 90% are epithelial, including squamous cell carcinoma, adenocarcinoma and small-cell carcinoma. Non-epithelial tumors are rare, and include sarcoma, corinosarcoma, paraganglioma, melanoma and lymphoma [41]. In this section we will restrict our description to the most common subtypes.

4. Squamous Cell Carcinoma

Squamous Cell Carcinoma (SCC) represents the most common non-urothelial histologic variant, accounting for almost 2–5% of all BC in the western world and approximately 30% in endemic regions (Egypt and other parts of Africa) due to the parasite *Schistosoma haematobium* infection, which causes bilharzial SCC [42]. Non-bilharzial SCC is associated with chronic inflammation of the urothelium as a result of chronic urinary tract infection, long-term indwelling catheters and bladder calculi. In contrast to UC, the relationship between SCC and cigarette smoking in not clearly established [43].

In terms of histological characteristics, SCC contains keratin pearl inclusions and granules (**Figure 11**). Moreover, microscopic analysis shows that most SCC tumors are moderately to poorly differentiated tumors.

SCC tends to appear in the seventh decade of life, except for spinal cord injured patients which can present at younger ages and is characterized by a slight male predominance with a higher proportion of non-Caucasians [44]. SCC is associated with more advanced disease at presentation compared to UC, with 70% of cases showing muscle-invasiveness at time of diagnosis, with a higher propensity for nodal involvement and metastatic disease [45]. Even in patients with T1 staging at diagnosis, pure SCC has been identified as an independent predictor of mortality in patients who did not undergo early cystectomy [46]. However, data from studies has also reported that, in cases in which the tumor was confined to the bladder wall and the bladder was surgically removed as part of the initial treatment, SCC histologic features were not associated with increased mortality when compared to UC [41, 47].

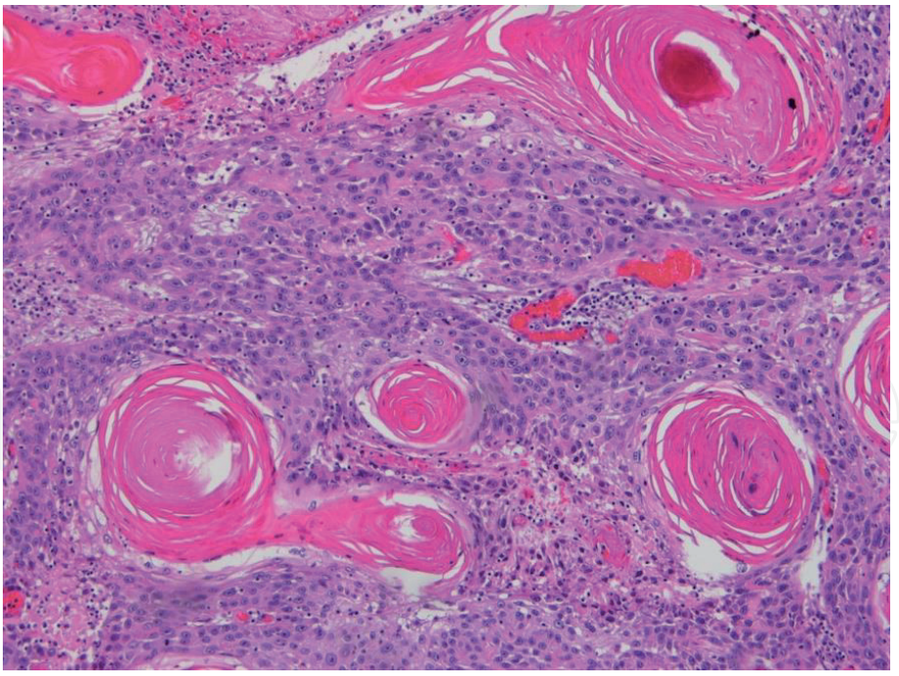

Figure 11.
The image shows presence of keratin pearls and copious keratin production, unequivocal for squamous differentiation (HE × 100).

This histological subtype has been associated with poorer OS, even when adjusted for stage. However, bilharzial-associated SCC, which usually presents at a younger age, is associated with lower stages at diagnosis, and a more indolent disease course with subsequent better survival outcomes [48].

In opposition to UC, NAC has not demonstrated a statistically significant improvement in OS among patients with the SCC histology, treated with RC [49].

Regarding radiation therapy, there is some evidence that treatment with pre-operative RT may improve disease-free survival comparing with RC alone [49]. Moreover, since SCC histology subtype is notoriously chemo-resistant to most regiments used for metastatic UC, radiotherapy can have an important therapeutic role [50]. This data was, however, obtained from retrospective studies with a very limited number of cases, suggesting that conclusions must be further evaluated.

Based on the best published evidence, early RC remains the mainstay therapy in patients with high-risk SCC, even when non-muscle invasive staging is observed [28]. It is important to note that, unlike other histologic subtypes, pelvic lymph node dissection (PLND) was associated with an improvement in OS [51].

5. Adenocarcinoma

Adenocarcinoma (AC) of the bladder can be primary or secondary [if it results from a contiguous invasion from other organs such as prostate, colon or uterus (endometrium and cervix), or metastatic spread (lung)]. Primary AC accounts for roughly 2% of all BCs and is divided into two subtypes: Urachal (10%) and nonurachal AC. There are also different types of adenocarcinomas that have been described, including glandular (**Figure 12**), colloid, papillary, signet ring and clear cell. Known risk factors include bilharziasis, chronic inflammation and bladder exstrophy (even in patients who have undergone correction in the neonatal period) [43, 51]. The diagnosis of primary AC of the bladder should only be made if secondary involvement from other organs is excluded. This entity has been shown to be more common in females, with a higher proportion among non-caucasians [52].

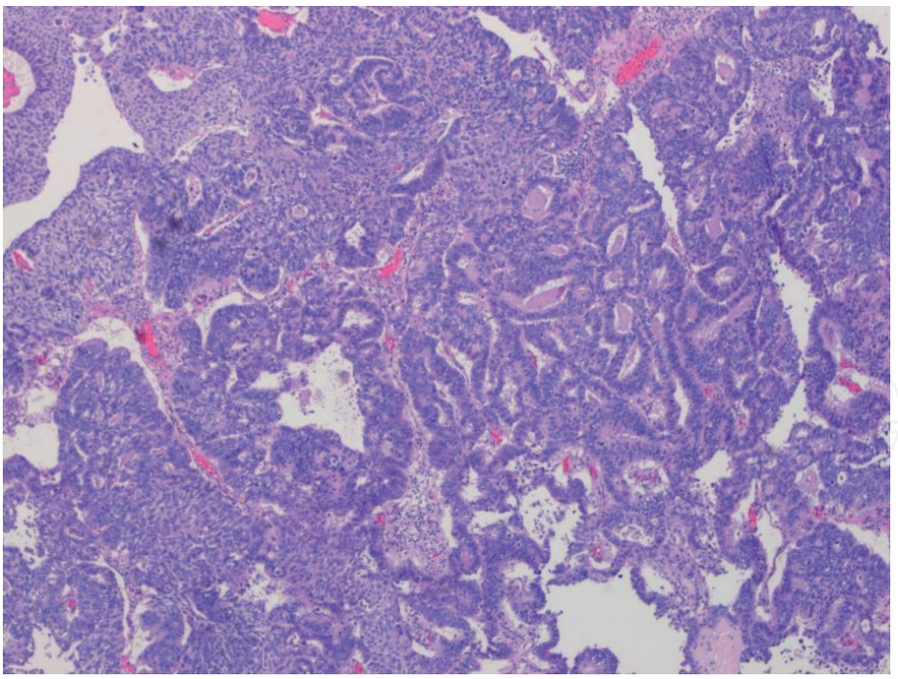

Figure 12.
Intestinal-type adenocarcinoma shows malignant colonic glands with high-grade columnar cells and necrosis in the lumens (HE × 40).

Bladder AC usually presents at an advanced stage, with muscle-invasive or metastatic disease. For localized disease, RC is currently the treatment of choice. However, when matched for stage, primary AC appears to have similar outcomes to UC [53]. In patients with NMIBC disease, a SEER analysis reports that, in non-urachal AC, transurethral resection (TUR) alone increased mortality risk, compared with early cystectomy [54]. There is currently no evidence available regarding the effect of immuno- or chemotherapy.

Urachal AC seems to present more favorable prognosis compared with non-urachal AC. Partial cystectomy (with en bloc resection of the bladder dome and umbilical ligament) is an alternative option to RC, in selected patients [55, 56]. Although urachal AC also seems more likely to present as metastatic disease in comparison to UC, the previous mentioned better prognosis is most probably partly due to be diagnosed among younger patients, with less co-morbidities [28].

Current data about NAC or AC in adenocarcinoma patients, although very scarce, suggests that neither therapy confers an improvement in survival [57].

5.1 Small Cell Carcinoma

The urinary bladder is the most common site for genitourinary extra-pulmonary neuroendocrine/small cell carcinomas. Small cell carcinoma (SmCC) accounts for less than 1% of BCs. It is a neuroendocrine tumour characterized by nests or solid sheets of small cells with enlarged nuclei, evenly dispersed chromatin with a "salt and pepper" pattern (**Figure 13**), with abundant resemblance to its pulmonary counterpart. It often co-exists with conventional UC, SCC and AC. Neuroendocrine markers such as chromogranin, synaptophysin and CD56 are expressed in SmCC [43]. Mean age presentation sits in the seventh-decade of life, with a strong male predominance (5:1) [55]. SmCC also shows similar characteristics to small cell carcinomas of the lung including ectopic hormone production, which can lead to clinically relevant hyperkalemia and hypophosphatemia [56, 58].

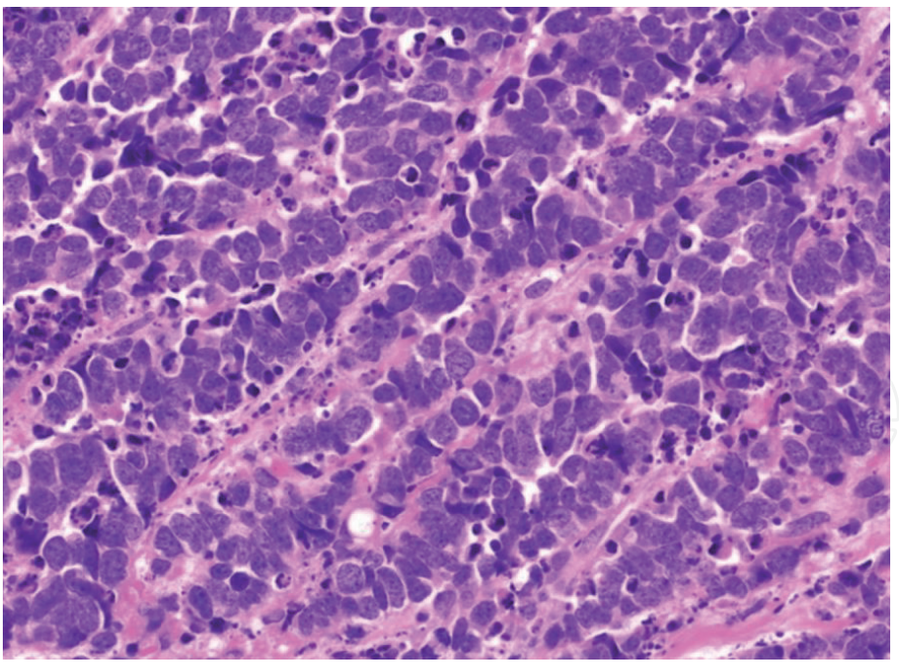

Figure 13.
Small cells with artifacts that make it difficult to distinguish between cytoplasm and nucleus (HE × 100).

This histologic variant is also characterized by its aggressiveness, exhibiting rapid growth with a predilection for early metastases, and a particularly high propensity for brain metastasis [59].

Contrarily to many of other histologic variants, a treatment strategy based on NAC followed by RC or RT represents the optimal strategy, based on several studies that demonstrated the chemosensitivity (with platinum-based therapy) of SmCC with an improvement in survival [59].

In terms of prognosis, SmCC presents a similar outcome to pure UC at same stages, except in the setting of diffuse metastatic disease in which it presents worse outcomes [60].

6. Conclusions

Bladder cancer with UC variants and non-urothelial subtypes have been classically described as tumors with a worse prognosis in comparison with pure UCs. However, the latter is mostly explained by a higher stage at the diagnosis among non-pure UC, since data from case-series and retrospective studies seems to suggest that, among the majority of variants, the prognosis is similar to pure UC, after adjustment for the disease stage.

Current diagnosis of variant histology in BC provides clinically relevant information to the physician and a novel framework to stratify patients according to prognosis, risk of recurrence and expected response to a given therapy. However, the management of this conditions remains challenging. Currently, RC preceded, in some tumors by NAC, constitutes the recommended treatment approach for resecable disease; AC is most commonly unsuccessful and data on immunotherapy is still scant. Regarding immunotherapy, it appears that drugs active in the PD-1 pathway are independent of histology [60].

Additionally, molecular alterations unique to these variants could be of use, in the future, as targeted therapies could emerge as a treatment option. However, further investigation is still needed to understand more clearly the diagnostic criteria

to be applied in these entities. Multicenter, international, prospective collaborative efforts are needed in order to clarify the distinct prognosis of these patients and to determine optimal therapy regimens.

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