The impact of histological variants on bladder cancer outcomes

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Abstract: Pure urothelial carcinoma is the most common histology of bladder cancer, consisting of about 75% of all cases. The remaining cases are represented by histological variants (HVs). Despite an apparent and recent rise in the incidence of variant histology (VH) in pathological reports, the real epidemiology, presentation and prognostic value on oncological outcomes are still not well established. Pathological identification of HVs indeed is challenging and at risk of under-recognition and misclassification, both at transurethral resection (TUR), due to the lack of a standardized technique, and at definitive histology after cystectomy because of the need for dedicated genitourinary pathologists. Genomic sequencing has led to identify molecular subtypes of bladder cancer eventually related to HVs and potentially implicated in the management of bladder cancer. The aim of this review is to present an overview of the literature regarding the impact of VH and molecular subtypes on bladder cancer outcomes. A narrative review of the literature was conducted applying several terms and combinations of them regarding HVs and molecular subtypes. The main findings are that HVs are indicative of a more aggressive disease, often advanced at presentation. When matched for stage and grade, the oncological outcomes are similar with pure urothelial carcinoma, except for pure squamous cell and signet ring cell carcinoma variants that invariably portend a poor prognosis. Radical cystectomy (RC) remains the treatment of choice and should be considered even in non-muscle-invasive cases if some forms of VH are present. Neoadjuvant chemotherapy is recommended in chemo-sensitive variants. Molecular composition could be related to the expression of specific VH and new subtypes could be identified with further investigations. Future developments in TUR procedures, genomic techniques and dedicated genitourinary pathologists will lead to a better definition of each HV, along with related prognosis and response to treatments.

Keywords: Bladder cancer; urothelial; variant histology (VH); molecular subtypes; oncological outcomes

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Background

Pure urothelial carcinoma is the most common histology of bladder cancer, consisting of about 75% of all cases (1). The remaining cases are represented by variant histology (VH), divided into urothelial and non-urothelial subtypes.

Histological variants (HVs) can arise in variable proportion in bladder cancer, as part of urothelial carcinoma or in pure forms.

The 2016 World Health Organization (WHO) classification of tumours in the urinary tract stressed out the need to mention the presence and percentage of VH in the pathological report (2), as commonly associated, like in upper urinary tract neoplasm, with advanced disease and correlated with clinical implications affecting the prognosis

of patients and guiding the treatment algorithm (3,4).

Pathological identification of VH is challenging, with high risk of under-recognition and misclassification due to several reasons (5), both at transurethral resection (TUR) and radical cystectomy (RC) levels.

The techniques for TUR of bladder tumours are quite heterogeneous and still poorly standardized, with great variability in quality and quantity of specimens retrieved: a resection in multiple specimens is often a "puzzling challenge" for histological report due to cautery damage and lack of spatial orientation (6). An "*en-bloc*" resection could be preferable to recognize HVs, even if present in small percentage (7).

Few studies in literature evaluated the accuracy of initial TUR in the identification of VH compared to RC, with conflict results. While Abufaraj *et al*. demonstrated similar accuracy in VH reporting between TUR and RC, up to 84% (8), other three studies showed poor concordance between the two specimens, depending on the type of HVs (9-11).

Moreover, several studies highlighted the importance of the analysis of TUR specimens by expert and dedicated genitourinary pathologists. In particular, Shah *et al*. demonstrated that HVs had not been reported in 44% of cases evaluated by non-dedicated pathologists (12).

Despite an apparent and recent rise in the incidence of VH in pathological reports, probably due to the increased awareness by pathologists, the real epidemiology, presentation and prognostic value on oncological outcomes are still not well established. Literature is still based principally on case reports or retrospective studies, even for the exclusion of patients with HVs from clinical trials.

Latest researches postulated that the phenotype of different HVs could be the expression of underlying diversity in molecular composition of the tumour, through a process of progressive dedifferentiation as observed in other organs (13).

In recent years, the increasing spread of research in genomic next-generation sequencing has led to identify specific molecular subtypes of bladder cancer. Most of classification systems differentiate urothelial tumours in major subtypes luminal and basal, respectively characterized by the expression of urothelial or basal cell/squamous differentiation markers, and in additional subtypes (14-17). Moreover, evidences from molecular analysis of some histologically defined variants, like squamous differentiation or neuroendocrine tumour, led to identify specific mutations present also in neoplasms lacking classic histologic hallmarks (18).

Molecular classification has potential implications in the management of bladder cancer, both for therapeutic and prognostic purposes: recent studies demonstrated different survival and response to chemotherapies and target therapies for the different subtypes of urothelial carcinoma (19).

Therefore, the optimal management of bladder cancer with VH is already not established, with a general recommendation by international guidelines for early RC also in non-muscle-invasive cases (20,21).

The aim of this review is to present an up-to-date overview of the literature regarding the impact of VH and molecular subtypes on bladder cancer outcomes in relation to the actual standard of care treatment options for muscle-invasive (RC, perioperative neoadjuvant or adjuvant chemotherapy and trimodality therapy) and non-muscle-invasive (intravesical immunotherapy and early RC) urothelial carcinoma.

Methods

A non-systematic review of the literature was performed in October 2019, using the PubMed/MEDLINE database applying the following terms and combinations: "bladder cancer", "bladder tumour", "variant histology", "histological variants", "urothelial carcinoma", "non-urothelial carcinoma", "nested", "micropapillary", "signet ring cell carcinoma", "microcystic", "sarcomatoid", "squamous differentiation", "glandular differentiation", "clear cell", "plasmacytoid", "lymphoepithelioma-like carcinoma", "squamous cell carcinoma", "small cell carcinoma", "large cell carcinoma", "neuroendocrine", "adenocarcinoma", "mixed variants", "radical cystectomy", "radiotherapy", "neoadjuvant chemotherapy", "adjuvant chemotherapy", "molecular subtypes", "basal", "luminal". Meta-analysis, original articles, reviews, case reports and case series were selected. Only English-language papers were included.

Due to the rarity of VH, no time restriction was applied and studies on non-muscle-invasive bladder cancer were not excluded.

Urachal adenocarcinoma, endometrioid carcinoma, melanocytic tumours, mesenchymal tumours, haematopoietic and lymphoid tumours were excluded.

Results

The characteristics and oncological outcomes for each VH, related to each treatment option, are summarized in *Table 1*.

Table 1 Variant histology outcomes for treatment option, compared with pure urothelial carcinoma, and molecular subtypes

Variant	Outcomes after RC (adjusted for stage): inferior/similar/superior/variable	Outcomes after perioperative CT: beneficial/no effect/no data/not preferred	Outcomes after trimodality therapy: inferior/similar/superior/no data/not preferred	Outcomes after intravesical therapy with BCG (NMIBC): inferior/similar/superior/variable/no data	Molecular subtype: luminal/basal/unknown
Nested	Similar	No data	No data	Inferior	Luminal/basal
Microcystic	Similar	No data	No data	No data	Luminal/basal
Micropapillary	Similar/inferior	Beneficial/no effect	No data	Inferior	Luminal
Lymphoepithelioma-like	Superior	Beneficial	No data	No data	Basal
Plasmacytoid/signet ring cell	Similar/inferior	Beneficial/no effect	Inferior (Signet ring cell)	No data	Luminal
Sarcomatoid	Inferior/similar	No benefit	No data	No data	Basal
Clear cell	Variable	No data/not preferred	No data	No data	Luminal/basal
Mixed variants	Similar	Beneficial (MVAC)	Similar	Similar (glandular)	Luminal (glandular)/basal (squamous)
Neuroendocrine tumours	Inferior/similar	Beneficial (Etoposide)	No data	No data	Basal
Adenocarcinoma	Similar	No benefit	No data	No data	Unknown
Pure squamous cell carcinoma	Inferior	No benefit	No data	No data	Unknown

RC, radical cystectomy; CT, chemotherapy; BCG, bacillus Calmette-Guerin; NMIBC, non-muscle-invasive bladder cancer; MVAC, methotrexate vinblastine adriamycin cisplatin.

VH of bladder cancer

Urothelial variants

Nested

Nested is a rare HV, representing the 0.3% of invasive bladder cancers. It usually presents with high rates of muscle invasion (70%), locally advanced disease and metastases (22).

The morphological appearance of nested variant resembles benign von Brunn nests or nephrogenic adenoma on the surface but demonstrates focal high-grade cytological atypia within the base, with a disordered and infiltrative proliferation (23).

In two cohort studies, patients with nested variant showed similar oncological outcomes, in terms of 5-year recurrence-free survival (RFS) and cancer-specific survival (CSS), compared to patients with pure urothelial carcinoma when treated with RC and matched for stage (5,23).

No data exists on the impact of perioperative chemotherapy (neoadjuvant or adjuvant) or trimodality therapy in patients harbouring nested variant.

The use of intravesical immunotherapy in non-muscle-invasive nested variant is reported in only one study in literature: in seven patients treated with bacillus of Calmette-Guerin (BCG) the RFS, progression-free survival (PFS), CSS and overall survival (OS) were significantly inferior compared to patients with pure urothelial carcinoma (24).

Microcystic

Microcystic variant has an incidence around 1% of bladder tumours (25) and it is histologically composed of varying sizes cysts with intraluminal secretions, usually lined by transitional cells or low columnar cells with mucinous differentiation. It is deeply infiltrative, with early invasion of muscularis propria and usually associated with high-grade urothelial carcinoma (26).

Poor and limited data exists in literature on microcystic variant, mostly case reports and small case series, the biggest counting 20 patients. This VH is associated with poor prognosis but, when matched for stage, no difference in oncological outcomes after RC is observed compared with pure urothelial carcinoma (27).

No data exists on the use of perioperative chemotherapy or trimodality therapy, neither on the use of intravesical

therapy in patients with microcystic variant.

Micropapillary

Micropapillary is an aggressive urothelial carcinoma variant that accounts for 2% to 5% of all bladder cancers. It histologically presents with multiple small nests and papillae in lacunar spaces and it is usually diagnosed at advanced stage, with high rates of carcinoma in situ and regional lymph node metastases (28-30).

For its behaviour of rapid progression to muscle invasion and metastases, early cystectomy in non-muscle-invasive micropapillary carcinoma is advocated as the optimal management over intravesical immunotherapy in many centres (31-33).

Nevertheless, bladder preserving strategies were explored in other studies for non-muscle-invasive stage, with a non-inferior OS in selected patients harbouring small percentage of micropapillary component (32,34).

Data from National Cancer Data Base (NCDB) and single-centre retrospective studies showed inferior OS in patients with micropapillary variant compared to patients with pure urothelial carcinoma (31,35), nevertheless when matched for disease stage, OS is similar (11,28-30).

Despite a single report of Monn *et al*. showing inferior OS for micropapillary variant (36), a recent meta-analysis of seven studies demonstrated that patients with this variant have similar RFS, CSS and OS to patients with pure urothelial carcinoma after RC (37).

The role of neoadjuvant chemotherapy remains unclear due to conflicting results reported in literature.

In a comparative study on 100 consecutive patients treated with RC with or without neoadjuvant chemotherapy, despite a 61% of pathological downstaging, no benefit on 5-year OS was observed in the neoadjuvant chemotherapy group, which experienced a higher non-organ-confined disease rate (33).

Same results were showed by a similar study on 82 patients (38) and by a recent meta-analysis (37): despite a higher rate of downstaging to pT0, no significant differences were noted in RFS, CSS and OS (38).

The MD Anderson Cancer Center experience on 103 patients with micropapillary variant was reviewed accounting for possible selection bias, showing a beneficial effect of neoadjuvant chemotherapy in those with muscle-invasive disease and absence of tumour-associated hydronephrosis (39).

Only one study explored the role of adjuvant chemotherapy in micropapillary variant, showing a higher recurrence rate compared to pure urothelial carcinoma (40), but did not evaluate if adjuvant chemotherapy could give an advantage with respect to no adjuvant treatment.

No data regarding the use of trimodality therapy is available.

Lymphoepithelioma-like

Named for its histological similarities to nasopharyngeal lymphoepithelioma, this variant represents less than 1% of all urothelial carcinomas (41).

Its peculiar characteristics are represented by poorly differentiated tumour cells with nuclear atypia and indistinct cell borders, with a massive infiltration of polyclonal T and B cells (42).

In a systematic review of 140 cases, Yang *et al*. demonstrated a higher disease-free survival (DFS) for patients harbouring this variant when treated with RC compared to partial cystectomy or TUR alone (43).

In its pure form, this variant has a high response rate to platinum-based chemotherapy and a low metastatic potential. In mixed forms, the prognosis mostly depends by the other associated variants (42).

The optimal management of this VH should be therefore RC with neoadjuvant chemotherapy.

No data is available regarding intravesical or trimodality therapy.

Plasmacytoid and signet ring cell

Plasmacytoid and signet ring cell carcinoma are classified in the same group by the 2016 WHO update (2).

Data from recent series estimates that plasmacytoid variant represents 1% to 4.9% of urothelial carcinoma and a specific differential diagnosis with other plasmacytoid bladder neoplasms, such as melanoma and lymphoma, is mandatory (44).

Plasmacytoid variant is histologically characterized by discohesive cells with eccentrical nuclei and eosinophilic cytoplasm (45) and has a characteristic pattern of invasion, with distant microscopic satellite lesions associated with a lack of desmoplastic reaction between normal and neoplastic tissues. These characteristics determine a difficult surgical resection and a consequent high risk of positive surgical margins at RC, with high rates of recurrence (46).

This variant is frequently associated to peritoneal carcinomatosis probably related to loss-of-function mutations of E-cadherin, conferring enhanced cell migration activity to the tumour (47-49).

Despite multiple studies in literature showed that

plasmacytoid variant is associated with locally advanced disease and lymph node metastases (44,45,49-51), when matched for stage OS is similar to pure urothelial carcinoma (46,50).

Nevertheless, in a single centre comparative study including patients with plasmacytoid variant underwent RC, Monn *et al.* found that this variant was independently associated with an increased mortality risk. Considering its aggressive nature, early RC should be suggested even in non-muscle-invasive cases (36).

Promising initial data on the chemo-sensitivity of plasmacytoid variant (47) was not confirmed by recent experiences that failed to demonstrate a benefit from neoadjuvant chemotherapy in OS, even if pT0 is achieved (51,52).

Considering all these findings, no study regarding the role of trimodality therapy on this variant is available.

Based on data from the 685 patients with signet ring cell carcinoma of the Surveillance Epidemiology and End Results (SEER) database and from the NCDB, signet-ring variant is associated with inferior OS after RC compared to pure urothelial carcinoma (53,54), with a 5-year CSS of 24.8% (55).

Nevertheless, RC guarantees better outcomes when compared to bladder-preserving strategies including trimodality therapy (56).

No data on neoadjuvant or adjuvant chemotherapy is available.

Sarcomatoid

Sarcomatoid variant represents 0.3% of all urothelial neoplasms. The peculiar characteristic of this VH is the presence of high-grade spindle tumour cells and both epithelial and mesenchymal differentiation. Previous pelvic irradiation and intravesical cyclophosphamide exposure are two established risk factors (57).

Differential diagnosis is challenging as this variant can mimic the morphology of a variety of other neoplasms.

Sarcomatoid variant presents usually at advanced stages and is associated with poor prognosis and inferior OS compared to pure urothelial carcinoma when treated with RC (57-60).

Only Moschini *et al.* (11) and Monn *et al.* (36) did not found sarcomatoid variant as an independent predictor of worse OS.

Based on data from NCDB, neoadjuvant chemotherapy seems to offer no significant benefit on OS in patients with sarcomatoid variant (61-63).

In their study, Sui *et al.* analysed the role of trimodality therapy, demonstrating a worse OS when compared to RC with or without neoadjuvant chemotherapy (61).

No study regarding effectiveness of intravesical therapy is available in literature. The optimal management for this VH remains therefore RC even in non-muscle-invasive cases.

Clear cell

Clear cell is an extremely rare VH composed of cells with glycogen-rich cytoplasm. Literature is sparse with only 16 case reports, so poor data exists on prognosis and oncological outcomes. This variant seems to have a male sex predisposition (male to female ratio of 16:1) and to be associated with an aggressive behaviour, as fast progression to muscle invasion and metastases.

Differential diagnosis includes clear cell adenocarcinoma of the bladder, clear cell carcinoma of the female genital tract or metastatic clear cell carcinoma from other organs (64).

Perioperative chemotherapy was rarely used with upfront RC as preferred treatment with wide variable oncological outcomes (65-67).

No data regarding trimodality therapy is available.

Urothelial carcinoma with squamous and/or glandular divergent differentiation (mixed variant)

Urothelial carcinoma with divergent differentiation, also known as mixed variant, is the most common VH of bladder cancer. The term "mixed variant" refers to those tumours that harbour urothelial carcinoma and squamous and/or glandular differentiation in variable proportion.

Squamous is the most common divergent differentiation, counting up to 40% of invasive urothelial carcinoma, while glandular differentiation occurs in up to 18% of invasive tumours.

Mixed variants are morphologically characterized by the presence of intercellular bridges or keratinization in squamous differentiation and intratumoural tubular or enteric gland-like spaces in glandular differentiation.

These entities must be distinguished from pure squamous cell carcinoma and pure adenocarcinoma of the bladder, which are different HVs without urothelial component, with different behaviour and prognosis.

Mixed variant usually presents with locally advanced disease and lymph node metastases (68-73).

While earlier reports showed inferior OS (71,72), Mitra *et al.* and Kim *et al.* demonstrated a similar 5-year OS and CSS after RC for patients with mixed variant compared to

those with pure urothelial carcinoma in two single-centre studies (68,69).

Data regarding the benefits of neoadjuvant chemotherapy remains conflicting.

Despite Zargar-Shoshtari *et al*. reported a significant pathological downstaging after neoadjuvant chemotherapy (74), Minato *et al*. showed poorer response to this treatment (75).

The strongest evidences for neoadjuvant chemotherapy come from a secondary analysis of the Southwest Oncology Group (SWOG)-directed intergroup randomized trial S8710 of neoadjuvant platinum-based chemotherapy (with MVAC: methotrexate, vinblastine, doxorubicin and cisplatin): 32 of 59 patients with VH that received neoadjuvant chemotherapy showed a large survival benefit in multivariate analysis (70).

Available data is scarce regarding the role of trimodality therapy in patients with mixed HVs. In a retrospective single centre study, patients treated with trimodality therapy showed similar 5- and 10-year CSS and OS when compared with patients with pure urothelial carcinoma (76).

The only data available regarding the use of intravesical therapy in mixed variants derives from a small case series of 24 patients with glandular divergent differentiation: six patients were successfully treated with BCG (77).

The optimal management of mixed variant remains RC with or without neoadjuvant chemotherapy but, in case of glandular divergent differentiation, intravesical therapy with BCG can be considered (78).

Non-urothelial variants

Neuroendocrine tumours (small/large cell)

Neuroendocrine tumours of the bladder, especially small cell VH, represent 0.5–0.7% of bladder cancer.

Bladder neuroendocrine small cell tumour is histologically similar to pulmonary small cell carcinoma, characterized by small poorly differentiated cells with high atypia, and is frequently present together with urothelial carcinoma, squamous cell carcinoma and adenocarcinoma of the bladder.

Small cell carcinoma is an extremely aggressive tumour with early metastases to multiple sites including bone and brain, rarely affected in urothelial carcinoma (79-81).

In a phase II trial on neoadjuvant chemotherapy in patients with small cell carcinoma of the bladder, a strong association between advanced disease stage (≥T3b, N+ or M+) and brain metastases was observed, with an increased incidence up to 50% (82).

For this reason, it is mandatory an imaging evaluation of central nervous system at the preoperative diagnosis, even in asymptomatic patients.

Due to its aggressive behaviour, differential diagnosis is crucial and includes poorly differentiated high-grade urothelial carcinoma and bladder metastases of small cell carcinoma from other organs (especially from prostate).

Data on small cell carcinoma comes mostly from comparative studies based on SEER database and NCDB, and shows inferior OS when patients are treated with only RC compared to pure urothelial carcinoma (11,53,54,83).

Nevertheless, Kaushik *et al*. demonstrated no significant 5-year CSS differences compared to pure urothelial carcinoma when adjusted for stage and lymph node status (84).

Like its pulmonary counterpart, data from literature demonstrates the chemo-sensitivity of small cell carcinoma of the bladder when platinum- and etoposide-based chemotherapy is used, and three studies on neoadjuvant chemotherapy demonstrated a significant survival benefit (62,80,85).

Early neoadjuvant chemotherapy and extent radical surgery should be considered therefore the optimal treatment for this VH, even in non-muscle-invasive disease (78).

Adenocarcinoma

While secondary adenocarcinoma interesting the bladder by direct or distant spread from other organs (prostate, gastrointestinal tract, endometrium, cervix, lung) is the most frequent form, primary adenocarcinoma is a rare variant of bladder cancer, representing 2% of all bladder neoplasms.

It has to be distinguished from urachal adenocarcinoma that develops from the urachal remnant, which usually shows a less aggressive behaviour and a favourable prognosis and could be treated with bladder preserving techniques (86).

Bladder exstrophy and non-functioning neurogenic bladder are well established risk factors for adenocarcinoma of the bladder.

Primary adenocarcinoma exists in different morphologies including intestinal, papillary, signet ring cell, clear cell or mixed. It usually presents at advanced stages with local invasion or distant metastases.

Data from SEER database shows that 75% of adenocarcinomas were locally advanced at the time of surgery (87), however when stage- and grade-adjusted, cancer specific mortality after RC is similar to urothelial carcinoma (88).

Recent multivariable analysis of data from patients

treated with RC from NCDB and SEER database confirmed comparable outcomes (53,54).

Owing the radio-sensitivity of adenocarcinoma histology, the role of radiotherapy was explored, but at present is still not well established. Although a previous report on the beneficial effect on 5-year DFS, CSS and lower local failure of adjuvant radiotherapy (89), more recent data from NCDB failed to confirm these results, showing worse outcomes for patients receiving radiotherapy alone or after RC (90).

Data on the role of perioperative chemotherapy in patients with adenocarcinoma is still scarce, with apparent no beneficial effects on OS (62,63).

RC with or without adjuvant radiotherapy remains therefore the standard of care for patients harbouring primary adenocarcinoma of the bladder.

Pure squamous cell carcinoma

Pure squamous cell carcinoma is the most common non-urothelial variant, accounting 5% of all bladder cancers in western countries and reaching 30% in *Schistosoma haematobium* endemic regions like Egypt and Sudan (91).

Risk factors for squamous cell carcinoma, other than schistosomiasis, are represented by causes of chronic inflammation of the bladder, including permanent/intermittent catheterization, urinary tract infections and bladder calculi.

It is microscopically characterized by abundant keratin production as pearl formations and intracytoplasmic granules.

Approximatively 70% of pure squamous cell carcinomas are muscle-invasive at initial diagnosis, with high rate of local recurrence (92).

Based on data from NCDB, OS in squamous cell carcinoma remains inferior compared to urothelial carcinoma, even when adjusted for grade and stage (83,93).

SEER database analysis showed that patients treated with RC have a significant superior CSS and OS compared to patients treated with only radiotherapy or to untreated patients (94), but pure squamous cell variant remains an independent predictor of inferior CSS and OS compared to pure urothelial carcinoma.

Moreover, bladder preserving techniques including trimodality therapy showed worse OS in patients with pure squamous cell carcinoma compared to those with pure urothelial histology (95).

From analyses based on NCDB patients, perioperative both neoadjuvant and adjuvant chemotherapy seem to confer no beneficial effects on OS in patients with pure squamous cell carcinoma. In patients underwent only neoadjuvant chemotherapy no downstaging effect was observed, with poorer OS (62,63,93,96).

The standard of care for squamous cell carcinoma remains therefore RC even for pT1 disease (97).

Molecular subtypes and VH

Four classification methods, University of North Carolina (UNC), MD Anderson Cancer Center (MDA), The Cancer Genome Atlas (TCGA) and Lund University, have identified at least five different molecular profiles for muscle-invasive bladder cancer: luminal, luminal-papillary/uroA, luminal-infiltrated/p53-like, basal-squamous, basal-neuronal (98,99).

Another molecular subtype has been recently identified as a basal mesenchymal-like/claudin-low type, different from either basal-squamous or neuronal (100).

Basal subtypes, both squamous and neuronal, seem to have a more aggressive behavior than luminal subtypes, with a tendency to early invasion and metastases. However, Seiler *et al*. demonstrated that basal-squamous is the most chemo-sensitive subtype, with a significative improvement in prognosis after neoadjuvant cisplatin-based chemotherapy (19). Neuronal tumours are only initially chemo-sensitive, especially to etoposide-platinum combined chemotherapy, but with short-term responses (101). Therefore, new therapeutic approaches are under study, in particular immune checkpoint inhibitors due to the high tumour mutational burdens of neuronal subtypes (98).

Claudin-law subtype has the worst outcome, with no beneficial effect from neoadjuvant chemotherapy (19).

Luminal-papillary subtype is associated with the best survival outcomes, regardless the low likelihood of response to platinum-based chemotherapy (19). This subtype is also described as an "immune desert" phenotype for its low expression of immune markers and nonimmune-infiltrated nature. For this reason, luminal-papillary tumours do not respond to immunotherapy (102). Nevertheless, the high rates of FGFR3 mutations may be a target for therapies based on FGFR inhibitors.

Instead, luminal-infiltrated is the most chemo-resistant but immunosensitive subtype (19,102).

Luminal subtype is clinically aggressive, but it seems to be sensitive to chemotherapy and immunotherapy (18).

Recent studies suggested that some HVs tend to have specific molecular subtypes (13,103), as reported in *Table 1*.

Micropapillary, plasmacytoid/signet ring cell variants and glandular divergent differentiation express typically luminal and luminal-infiltrated biomarkers (104,105). Lymphoepithelioma-like, sarcomatoid and neuroendocrine variants and squamous divergent differentiation express instead basal molecular mutations.

Conclusions

Accurate pathological identification and report of VH is crucial for a precise risk stratification of patients with bladder cancer, in order to choose the optimal management and improve the oncological outcomes.

The presence of HVs is indicative of a more aggressive disease, often advanced at presentation. Nevertheless, when matched for stage and grade, the oncological outcomes are similar with pure urothelial carcinoma, except for pure squamous cell and signet ring cell carcinoma variants which have the worst prognosis.

RC remains the treatment of choice and should be considered even in non-muscle-invasive cases if some forms of VH are present, in particular micropapillary, pure squamous, plasmacytoid and sarcomatoid. Further studies are necessary to fully explore the role of early RC in non-muscle-invasive HVs. Neoadjuvant chemotherapy is recommended in chemo-sensitive variants, in particular for neuroendocrine tumour and lymphoepithelioma-like carcinoma. Adjuvant radiotherapy could be considered in pure adenocarcinoma.

Basal molecular subtype relates to a more aggressive disease, with poor survival outcomes but high response to neoadjuvant chemotherapy. Luminal subtype has instead a better prognosis but low response to chemotherapy. Recent evidences suggest that molecular composition could be related to the expression of specific HVs and new subtypes could be identified with further investigations.

Improvement in TUR procedures, dedicated genitourinary pathologists and emerging genomic techniques for molecular subtyping will lead to a better definition of each HV, along with related prognosis and response to treatments.

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