Histologic subtypes of urothelial carcinoma: an update

Dilek Ertoy-Baydar

Purpose of review
The biological significance of urothelial carcinoma subtypes/divergent differentiation (S/DD) and clinical approach to them remain challenging issues. This review aims to summarize the most relevant recent information on urothelial carcinoma subtypes/divergent differentiation.

Recent findings
The urothelial carcinoma S/DDs have variable histologies and different genetic alterations. They are considered as high-grade by WHO-2022 system, but they still have prognostic variances and should not be pooled into a single clinicopathological group. Studies confirm that sarcomatoid, micropapillary, plasmacytoid and neuroendocrine forms follow more aggressive course even after other clinicopathological variables are matched. Their higher volume is associated with upstaging and decreased survival. The presence and extent of any S/DD should be documented in all specimens submitted to pathology without a cutoff threshold. Optimal treatment for the aggressive forms is controversial including the use of neoadjuvant chemotherapy. Somatic alterations, some of which are likely oncogenic and targetable, occur in urothelial carcinomas with markedly variable frequency among different subtypes.

Summary
The role of intravesical treatment, neoadjuvant or adjuvant chemotherapy has not been well characterized for most subtypes, and prospective data are inadequate. Understanding detailed molecular biology of these tumors, development of personalized biomarkers and design of clinical trials focusing specifically on S/DDs with worse prognosis are needed to improve patient care.

Keywords
divergent differentiation, subtype, urothelial carcinoma

INTRODUCTION

Urothelium undergoing neoplastic transformation has pronounced plasticity, thus urothelial carcinoma may show morphologic and molecular heterogeneity along with variability in patient outcome. It can exist in a pure or classical form, but about 25% have components of either subtype histology or divergent differentiation (Table 1). A subtype refers to specific histological features that are urothelial in appearance but have distinct architectural or cellular hallmarks. These tumors retain expression of usual markers of urothelium. In contrast, divergent (aberrant) differentiation alludes to the histology where it is no longer urothelial but exhibits a different histogenesis such as squamous, glandular or trophoblastic. These components usually express the markers of their new lineage. The most commonly encountered divergent/subtype morphologies in TUR and cystectomy materials are squamous differentiation (30–32%), micropapillary (12–15%), nested (8–13%), glandular differentiation (8–13%) and sarcomatoid (3–6%) [1▪]. They can be mixed in 3–9.9% of cases. Regions of mixed histology generally share clonal origins, but exceptions do occur. Although some forms may have bland cellular features, the last classification by WHO (2022) recommends that all invasive subtype histology/divergent differentiation should be considered high grade because they have behavior at least equal to or worse than invasive conventional urothelial carcinoma.

This review presents a brief summary of recent information on the histological subtypes of urothelial carcinoma excluding the sarcomatoid form, as it is the subject of another review article in this issue of the journal.

KUTTAM, Koc University Research Center for Translational Medicine, Istanbul, Turkiye

Correspondence to Dilek Ertoy-Baydar, MD, Koc University School of Medicine, Department of Pathology, Istanbul 34010, Turkiye.
Tel: +90 533 552 2830; e-mail: dertoy@kuh.ku.edu.tr

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KEY POINTS

- Urothelial epithelium has extreme plasticity to give rise to tumor subtypes with a wide variety of morphological appearances.
- The presence of any urothelial carcinoma subtype or divergent differentiation should be reported by the pathologist regardless of its extent and type of specimen.
- Subtypes and divergent differentiations are not homogenous in terms of behavior and treatment response, they should not be lumped into one clinicopathological group.
- Marked variations are observed between different subtypes in terms of oncogenic and targetable somatic molecular alterations.
- To improve the value of clinical recommendations and patient care, well designed prospective studies are needed.

HISTOLOGY AND SIGNIFICANT MOLECULAR FEATURES

The incidence of subtype histology/divergent differentiation seems in rise due to the increased awareness and recognition by the pathologists [2]. The record of histological variations is required as some types are associated with a different clinical outcome and/or may invoke different therapeutic approach. In the others, however, cognizance of the peculiar pattern can be important in avoiding diagnostic misinterpretation (Fig. 1).

Table 1. Urothelial carcinoma: histological subtypes and divergent differentiation

Conventional
Plasmacytoid
Micropapillary
Nested (including large nested)
Microcystic and tubular
Clear cell
Lipid rich
Giant cell
Lymphoepithelioma-like
Poorly differentiated
Sarcomatoid
Urothelial carcinoma with divergent differentiation squamous glandular trophoblastic neuroendocrine

Plasmacytoid subtype

The plasmacytoid subtype is composed of individual tumor cells with abundant eosinophilic cytoplasm and eccentric nuclei, resembling plasma cells that can grow in linear cords, as single cells or solid sheets (Fig. 2). Signet ring-like features with intracellular mucin can occur in the absence of extracellular mucin. It is not unusual that the neoplastic cells invade the bladder wall transmurally with minimal stromal reaction and spread to the perivesical fat causing peritoneal carcinomatosis. Plasmacytoid carcinomas are enriched for immune infiltration in more than 70% of cases. A recent study showed frequent PD-L1 expression (53% had tumor proportion score $\geq$1% and 66% showed combined positive score $\geq$1%) and/or high tumor mutational burden (TMB) (median 10.3 mut/Mb) suggesting a potential for intervention with immune check-point inhibitors [3].

CDH1 mutations can be identified in 61% of plasmacytoid carcinomas. Truncating somatic mutations of the *CDH1* that result in nonfunctional E-cadherin protein, is a hallmark molecular alteration of plasmacytoid urothelial carcinoma, and this is reflected as negative immunohistochemical E-cadherin staining in tumor tissue. Loss of E-cadherin function is believed to correlate with a discohesive infiltrative growth and aggressive tumor behavior. Thus, plasmacytoid urothelial carcinoma have a higher chance for surgical margin positivity (up to 5$\times$) and recurrence in the retroperitoneum. Other frequently mutated genes in the plasmacytoid subtype include *TP53, RB1, ARID1A, CDKN1A* and *ERBB2*. Alterations in *TP53* and *RB1* are higher in plasmacytoid urothelial carcinoma than those in conventional urothelial carcinoma (76% versus 48% for *TP53*, and 55% versus 17% for *RB1*). In addition, 15% of the tumors harbor mutations in DNA damage repair genes, including *ERCC2, ATM, BRCA2* and *RECQL4* [4▪▪].

Studies at mRNA and protein levels show that plasmacytoid carcinomas are mainly luminal in nature, expressing high levels of luminal markers such as FOXA1, KRT20 and GATA3, although expression of basal markers can be observed at low levels.

Micropapillary subtype

This subtype is characterized by small tumor cell aggregates lying in lacunar cyst-like retraction spaces,

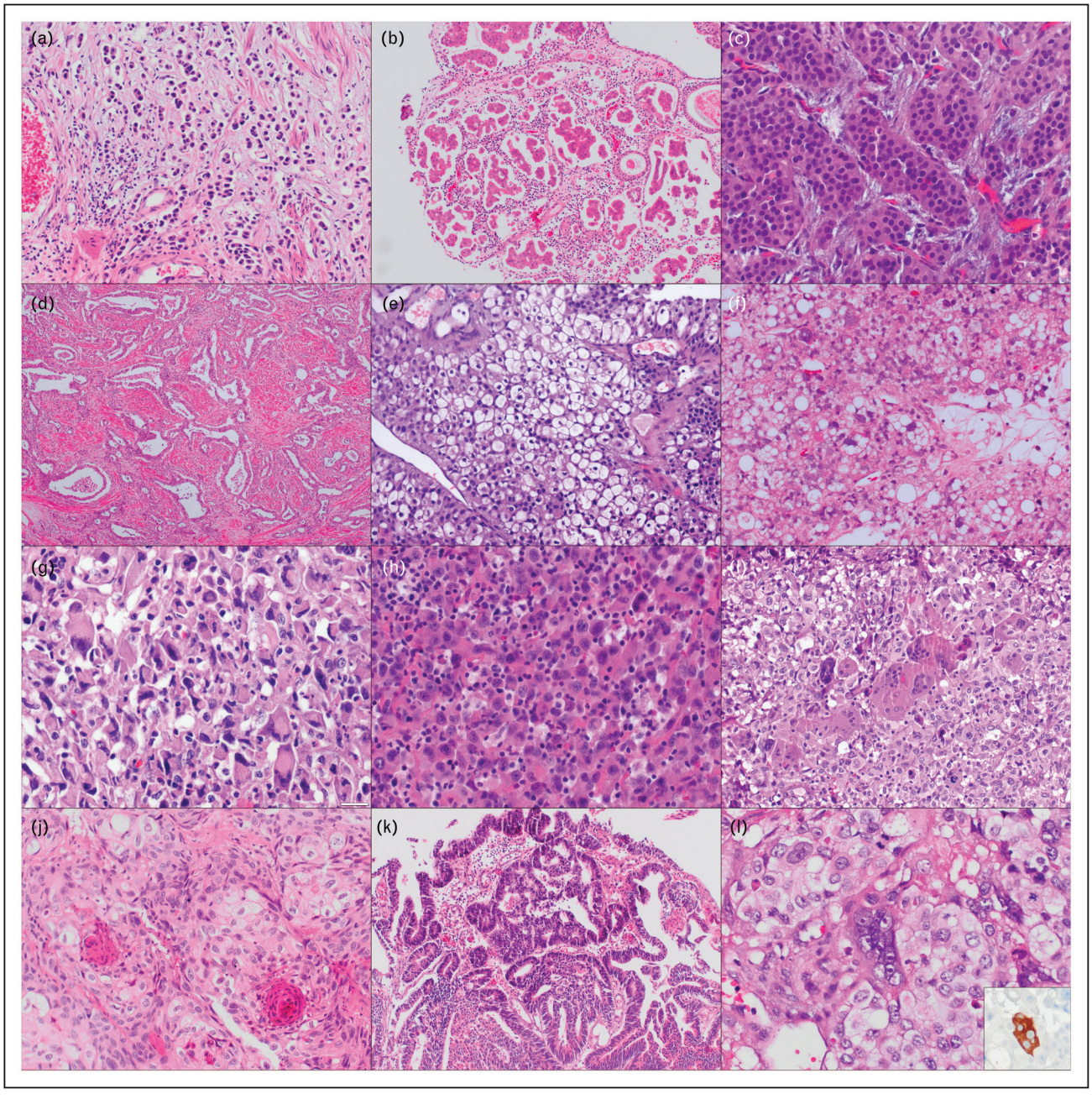

FIGURE 1. Subtypes of urothelial carcinoma. (a) Plasmacytoid subtype of urothelial carcinoma (H&E, 100*x*). (b) Micropapillary subtype of urothelial carcinoma (H&E, 40*x*). (c) Nested subtype of urothelial carcinoma (H&E, 200*x*). (d) Microcystic subtype of urothelial carcinoma (H&E, 40*x*). (e) Clear cell subtype of urothelial carcinoma (H&E, 200*x*). (f) Lipid-rich subtype of urothelial carcinoma (H&E, 200*x*). (g) Giant cell subtype of urothelial carcinoma (H&E, 400*x*). (h) Lymphoepithelioma-like subtype of urothelial carcinoma. (H&E, 400*x*). (i) Poorly differentiated osteoclast-rich subtype of urothelial carcinoma (H&E, 200*x*). (j) Urothelial carcinoma with squamous differentiation (H&E, 200*x*). (k) Urothelial carcinoma with glandular differentiation (H&E, 40*x*). (l) Urothelial carcinoma with trophoblastic differentiation. Inset shows a syncytiotrophoblast in the tumor, expressing βhCG (H&E, 400*x; inset:* Immunohistochemistry, antiβhCG Ab, 200*x*).

which may mimic lymphovascular space invasion (Fig. 3). The tumor nests lack fibrovascular cores, and they are often densely packed in a back-to-back pattern, nuclei are peripherally oriented. Characteristic neoplastic cells have cytoplasmic vacuoles causing nuclear indentation (referred to as "ring forms"). Micropapillary tumors are enriched in immune infiltration in around 40% of cases. They

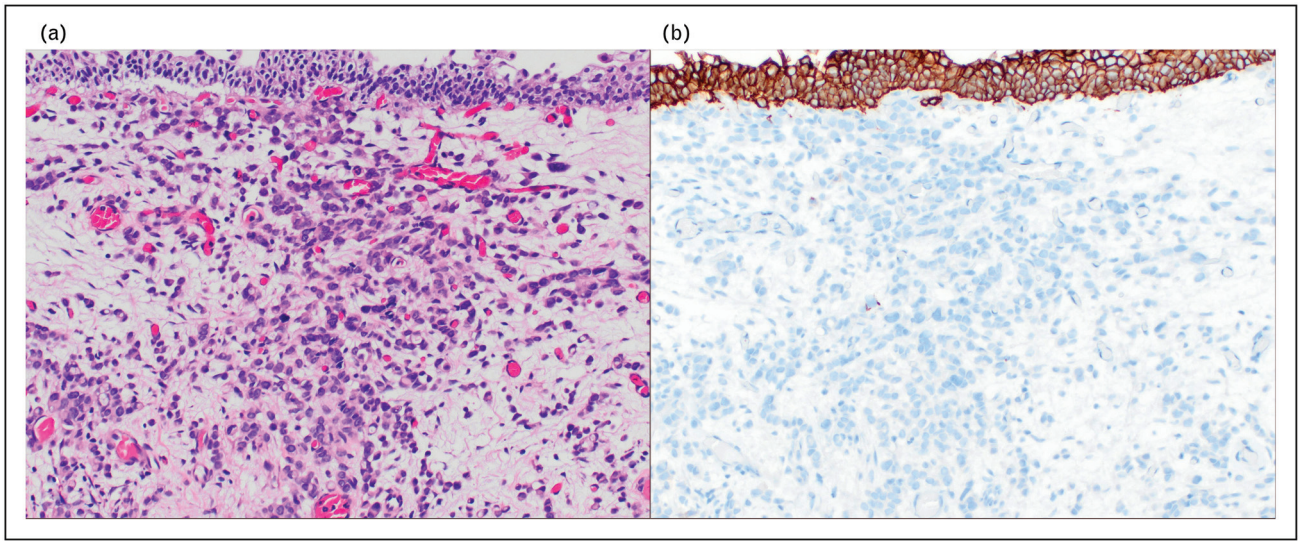

FIGURE 2. Plasmacytoid urothelial carcinoma with loss of E-cadherin. (a) Discohesive plasmacyte-like small neoplastic cells infiltrating superficial lamina propria in the form of cords or single cells (H&E, 200*x*). (b) Same tumor showing negative E-cadherin staining immunohistochemically, a clue for *CDH1* mutation in the tumor (Immunohistochemistry, anti-E-cadherin Ab, 200*x*).

have high TMB without microsatellite instability-high phenotype [4▪▪].

Downregulation of miR-296 and activation of the RUVBL1 pathway seem to drive the expression signature of micropapillary cancer. The most common mutations in micropapillary urothelial carcinoma involve *TP53* (67%), *ERBB2* (*HER2*, 40%), *MCL1* (33%), *RB1* (33%) and *ARID1A* (27%). Activating mutations in the extracellular domain of *ERBB2* gene and *ERBB2* amplifications are seen substantially enriched in micropapillary cancer. This brings the potential that *ERBB2* can be a therapeutic target in this subtype. The identical *TERT* promoter mutations are found in both micropapillary and conventional areas of the same tumor (and also in areas of glandular/squamous differentiation, if present) supporting their link in clonality. *ERBB2* amplification on the other hand, was found as an acquired alteration, detected both in the primary and metastatic micropapillary sites, but absent in the conventional urothelial carcinoma region of the primary tumor [4▪▪].

Micropapillary subtype exhibits molecular features of luminal-type urothelial carcinoma. All paired conventional urothelial carcinomas adjacent to

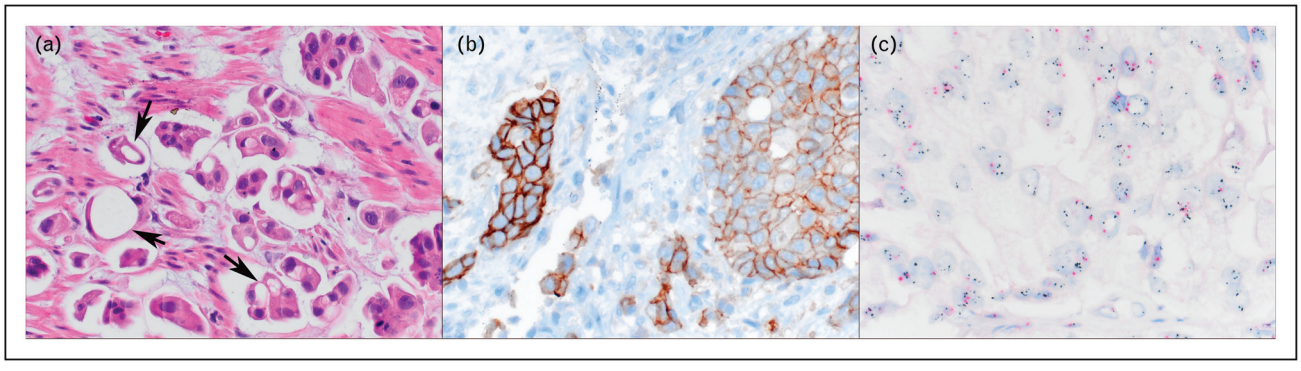

FIGURE 3. Micropapillary urothelial carcinoma with *HER2* amplification. (a) Nests of tumor cells in lacunar spaces . Typical "ring form" cells were pointed by arrows (H&E, 200*x*). (b) Tumor cells showed moderate to strong membranous HER2 staining (Immunohistochemistry, anti-HER2 antibody, 400*x*). (c) Chromogenic in-situ hybridization (ISH) revealed *HER2* (*ERBB2*) amplification in neoplastic cells. Black signals mark the *HER2* gene and show increased copy numbers whereas red dots highlight chromosome 17 centromere (HER2 Dual ISH DNA Probe Cocktail, 600*x*).

micropapillary areas of the same tumor also appear of luminal type, further evidence of evolution from a precursor luminal tumor.

Nested subtype

It may occur as a small nested or less frequently as a large nested form. The neoplastic cells that form nests and sometimes tubules, appear bland without atypia or mitotic activity in the superficial portions of the tumor while atypia and occasional mitoses may be seen at deeper levels. The differential diagnosis between nested urothelial carcinoma and benign proliferative lesions such as von Brunn islands or cystitis cystica/glandularis can be extremely challenging in superficial tissue samples. Identification of *TERT* promoter mutations in the lesion can be used to support the neoplastic nature in such cases.

TP53, *JAK3* and *CTNNB1* are among the most frequently mutated genes identified by next generation sequencing (NGS). *TSC1* and *MDM2* mutations were found enriched in the nested subtype (each 20%), while the frequency of *FGFR3* mutations was similar to that in conventional urothelial carcinoma [4▪▪]. Most nested urothelial carcinomas express luminal markers. But at the same time, they also show CK5/6 (a basal marker) expression which is distinctly localized to the basal layers of tumor nests. Gene expression profiling seems to be needed to better define the correct place of nested subtype in the molecular classification model of urothelial carcinoma.

Microcystic/tubular subtype

This subtype is characterized by tubular structures along with macro- and microcysts lined by urothelial cells which are typically bland and cuboidal although focal higher-grade areas can occur. The lumina may contain calcifications and secretions. It can be seen admixed with the nested subtype. *TERT* promoter mutations are frequent in microcystic tumors as in the other types of urothelial carcinoma, and can be used in ruling out benign lesions if differential diagnosis is problematic.

Clear cell subtype

This is a rare subtype that resembles clear cell carcinomas of kidney. It consists of cells with voluminous clear cytoplasm. The clear appearance is due to cytoplasmic glycogen.

Lipid-rich subtype

This is an infrequent subtype of urothelial carcinoma characterized by lipid vacuoles in the neoplastic cells, which can indent the nucleus and cause a lipoblast-like appearance resembling liposarcoma.

Giant cell subtype

Giant cell urothelial carcinoma (GCUC) is a rare and aggressive variant of undifferentiated urothelial carcinoma characterized by the aggregates or sheets of highly pleomorphic and bizarre tumor giant cells, frequent multinucleation, necrosis and atypical mitoses. Available data on the pathological characteristics and clinical behavior of GCUC are limited. In a recent series consisting of 23 patients, the prognosis was poor with 50% dying within 1 year of diagnosis [5]. Tumor cells expressed markers of urothelial-lineage including uroplakin-II (focal), GATA3, CK20, CK7 and S100P in addition to nuclear p53 (mutant type). Two cases showed PD-L1 expression with tumor proportion scores of 10 and 20, were treated with pembrolizumab and radiotherapy combination, and remained alive with the disease for 20 and 22 months.

Lymphoepithelioma-like subtype

This subtype resembles pharyngeal lymphoepithelioma, but has no association with Epstein–Barr virus. Tumor consists of sheets or nests of large pleomorphic cells with indistinct cell borders. Cells are arranged in a syncytial manner, and they possess large nuclei and prominent nucleoli. An intense inflammatory infiltrate comprising lymphocytes, histiocytes, plasma cells and polymorphonuclear leukocytes is present on and around the tumor islands. These tumors have high PD-L1 expression and high TMB with the mean and median values of 46.5 and 39.1 mutations/Mb in one study [6]. Mismatch repair protein deficiency has not been detected.

Most common pathogenic mutations were found in chromatin-modifying genes: *KMT2C* (100%), *CHD2* (44%), *EP300* (33%) and *KMT2D* (22%). Seventy-eight percent of patients had *TP53* mutations [6]. Studies suggest that lymphoepithelioma-like UCs are basal type tumors.

Poorly differentiated subtype

These are rare tumors that exhibit high grade morphology, lack morphological features of urothelial origin but has evidence of urothelial-lineage by immunohistochemistry.

Osteoclast-rich undifferentiated carcinoma of the urinary tract is a rare biphasic tumor composed of mononuclear and giant cell components resembling osteoclastic giant cell tumor of bone, and currently classified under the "poorly differentiated urothelial carcinoma" subtype. NGS of 14 such

tumors in one study revealed mutations consistent with conventional urothelial carcinoma [7].

Urothelial carcinoma with squamous differentiation

It is the most frequent type of divergent histology seen in approximately 30% of high-grade urothelial carcinomas. The presence of keratinization and intercellular bridges are requirements to determine squamous differentiation. *CDK2NA* alterations were most frequently found in squamous urothelial carcinomas among other subtype histologies, with a rate of 46% [4▪▪]. *PIK3CA* and *PTEN* were noted as other altered genes, near to 30% and 10% respectively. The frequency of *FGFR3* mutations in squamous subtype was similar to that in usual urothelial carcinoma. These tumors fall into basal group within the molecular urothelial carcinoma classification schema.

Urothelial carcinoma with glandular differentiation

Tumors form glandular structures that may have the enteric histology, resembling a colonic-type adenocancer. Other forms may show features of mucinous type carcinoma with extracellular mucin that contain floating glands and/or signet ring cells. The cells may acquire expression of CK20 and CDX2, typical of enteric lesions, with or without co-expression of urothelial markers. Urothelial carcinoma with glandular differentiation was found as the second most common subtype showing *ERBB2* alterations at a rate of 22% after micropapillary urothelial carcinoma [4▪▪]. They align with luminal tumors in the molecular classification of urothelial carcinomas.

Urothelial carcinoma with trophoblastic differentiation

The morphologic spectrum is wide in these tumors where it ranges from scattered isolated cells with trophoblastic differentiation to pure choriocarcinoma. Beta-HCG is the used immunohistochemical marker to highlight trophoblastic cells, but it commonly stains urothelial component of the tumor as well. Expression of hydroxyl-δ-5-steroid dehydrogenase is reported more sensitive and more specific, staining 100% of the cases and limited to trophoblasts in the vast majority. Urothelial carcinoma with trophoblastic differentiation has been associated with high grade and high stage disease.

Neuroendocrine differentiation

These tumors, similar to pulmonary neuroendocrine carcinoma are composed of poorly differentiated round cells with scant cytoplasm and a high nuclear/cytoplasmic ratio growing in solid sheets. The nuclei are small and round with characteristic "salt and pepper" granular chromatin, and have very high mitotic rate. Tumor cells express neuroendocrine markers such as CD56, synaptophysin and chromogranin in addition to keratin. They are believed to originate from urothelial cell through divergent differentiation, and approximately half are associated with conventional urothelial carcinoma and/or areas of glandular or squamous differentiation. Despite this, WHO classification lists neuroendocrine carcinoma of urothelial tract as a separate entity rather than a urothelial carcinoma subtype, since the treatment algorithm can be significantly different.

They exhibit lower levels of immune cell infiltration than most conventional urothelial carcinoma despite high TMB [4▪▪]. Inactivating *TP53* mutations are found in almost all cases and co-inactivating *RB1* mutations in 50–75% of them. Transcription factors involved in neural crest development, pro-neural stem-cell differentiation and cell proliferation are upregulated. *PTEN* mutations were most commonly found (near 15%) in neuroendocrine carcinoma when compared with other subtypes. They contain activating *TERT* promoter mutations, which is a significant deviation from pulmonary neuroendocrine carcinoma. *FGFR3* mutations are not a feature of neuroendocrine bladder tumors.

Neuroendocrine carcinomas lose expression of urothelial-lineage markers, and are uniformly double negative for basal and luminal markers. Molecularly, they are thought to develop via the basal pathway.

Emerging subtypes not listed in current WHO classification

There are other proposed rare subtypes of urothelial carcinoma not included in the 2022 WHO classification. These are urothelial carcinoma with pseudoangiomatous features and urothelial carcinoma with chordoid and myxoid (UC-CM) features. The pseudoangiomatous subtype is characterized by discohesive acantholytic tumor cells (GATA3 and CK7 positive, CD31 and CD34 negative) creating pseudovascular formations within variably dense collagen matrix.

UC-CM subtype exhibits distinctive elongated nests and cords of tumor cells floating within a prominent myxoid/mucinous stroma. Interestingly, they are associated with low-grade papillary urothelial carcinoma that may be invasive in 50% of the cases. A study on nine such tumors showed a similar molecular profile to typical of conventional urothelial carcinoma, with recurrent alterations in *TERT*

promotor (7/9), chromatin remodeling genes (8/9) and cell cycle pathway genes (8/9) in addition to a high rate of alterations in DNA damage repair (DDR) genes (6/9) [8▪]. Five of nine cases were shown to harbor recurring alterations in RAS/RAF pathway genes showing a genomic profile with mixed urothelial and adenocarcinoma features. These findings suggest possible alternative therapies for these patients with potentially actionable targets in the RAS/RAF and DDR pathways.

Whether emerging subtype urothelial carcinomas exhibit basal or luminal molecular features is unknown. A study involving eight cases of UC-CM morphology demonstrated mixed results after utilizing immunohistochemical markers for basal and luminal urothelial carcinoma [9]. Authors also note that one case displayed a molecular and immunohistochemical profile consistent with plasmacytoid urothelial carcinoma, suggesting that myxoid and chordoid features may occur as a pattern in previously recognized histologic subtypes. The 5-year overall survival (OS) rate of patients with UC-CM morphology was 75% in that study.

INTERNATIONAL SOCIETY OF UROLOGIC PATHOLOGY RECOMMENDATIONS

ISUP [1▪] recommends that the presence of urothelial carcinoma subtype histology/divergent differentiation should be reported in all types of specimens (biopsy, transurethral resection and cystectomy). In tumors with combined morphologies, all distinct subtypes must be noted with their extent without a cutoff threshold. ISUP points into the potential heterogeneity of subtypes and divergent differentiations in terms of behavior and response to therapy. It is important that different entities should not be pooled into a single clinicopathological group.

CLINICAL OUTCOMES

Subtypes and divergent differentiations are generally thought to have poorer prognosis. But in fact, poorer outcomes in some morphologies are primarily attributable to higher stage presentation. In a total of 616 primary bladder carcinoma, muscle invasive disease was present in 64.1% of patients with subtype histology in comparison to 20.6% with pure urothelial carcinoma [10]. Similarly, frequency of nodal involvement and metastatic disease were significantly higher within the subtype histology group. Urothelial carcinoma with squamous and/or glandular differentiation, nested, microcystic and lymphoepithelioma-like urothelial carcinoma have outcomes comparable to conventional urothelial carcinoma when other clinicopathological factors such as stage, lymph node status, lymphovascular invasion, positive margins and chemotherapy are matched.

Yet, there are several subtypes of urothelial carcinoma that follow a more aggressive clinical course with worse cancer-specific survival (CSS) than patients with pure urothelial histology even after adjusting for other clinicopathological variables, and these are mainly sarcomatoid, micropapillary, plasmacytoid and neuroendocrine forms. In a recent analysis of 3052 patients with radical cystectomies including 1841 subtype histologies, the highest cumulative incidence rates for cancer-specific death (CSD) at 5 years were found in plasmacytoid (42%), sarcomatoid (51%), micropapillary (35%) and squamous (35%) urothelial carcinomas [4▪▪]. Hazard ratios for CSD were significantly higher for sarcomatoid, plasmacytoid, micropapillary and mixed subtypes [1.76 (95% confidence interval (95% CI) 1.17–2.65], 1.5 (95% CI 1.01–2.27), 1.43 (95% CI 1.05–1.95) and 1.42 (95% CI 1.17–1.73) respectively] when adjusted for pathologic stage in multivariable analysis. Jojima *et al.* [11] reported that all of their seven micropapillary urothelial carcinomas (2 $\leq$cT1, 2 cT2 and 3 $\geq$cT3) which were treated by immediate radical cystectomy and pelvic lymph node dissection without neoadjuvant treatment relapsed with a median of 14 months despite adjuvant chemotherapy given to six. In a cohort of 32 plasmacytoid urothelial carcinoma, median OS was 13.0 months with death rate of 65.6% [3].

A meta-analysis recently explored the impact of histological SH/DD on the outcomes of upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy, and found that clinicopathological and oncological results were associated with more advanced/aggressive features similar to bladder tumors [12]. Patients with subtype histology/divergent differentiation had significantly worse CSS (hazard ratio 1.65, 95% CI 1.39–1.96), OS (hazard ratio 1.84, 95% CI 1.52–2.22) and recurrence-free survival (hazard ratio 1.64, 95% CI 1.43–1.87).

The extent of aggressive subtype histology is an important parameter as higher volume is often associated with upstaging and survival outcomes. At least 25% micropapillary urothelial carcinoma in T1 disease is more likely to progress during BCG therapy and have nodal metastasis. Micropapillary urothelial carcinoma fraction greater than or equal to 30% was an independent predictor of pathologic lymph node positivity in both cT1 and $\geq$cT2 patients with an overall odds ratio of 4.0 [13]. Thus, quantification of each SH/DD morphology in the surgical specimens by the pathologist is justified.

Urothelial carcinoma with trophoblastic differentiation, giant cell urothelial carcinoma and poorly

differentiated urothelial carcinoma are also suggested to be very aggressive tumors, but no comparison studies with conventional urothelial carcinoma is yet available for these tumors. Urothelial carcinoma with pure or predominant lymphoepithelioma-like subtype on the other hand, appears to have better outcomes being more chemosensitive than urothelial carcinoma with mixed or minor lymphoepithelioma-like component, with more disease-free status after treatment.

The subtypes known for their unfavorable prognoses are not uniform among themselves in terms of clinical behavior. But more data are needed to compare and potentially stratify them by outcome and therapy response.

TREATMENT

Management of nonmuscle invasive forms of aggressive subtypes presents a controversy for clinicians trying to balance oncologic control while minimizing treatment morbidity. On multivariate analysis by Minato *et al.* [14], presence of subtype histology in <pT2 disease independently predicted progression to muscle invasion and metastasis. The rates and median time of progression to muscle invasion were 6.9% and 22.5 months in the pure urothelial carcinoma group, and 22.9% and 10.0 months in the subtype histology UC group. All of the recent clinical guidelines published by the American Urologic Association, National Comprehensive Cancer Network (NCCN), and the European Association of Urology recommend early radical cystectomy as either the preferred or equivalent treatment strategy for patients with cT1 sarcomatoid, micropapillary or plasmacytoid urothelial carcinoma. Nonetheless, there are also studies which report acceptable oncological outcomes with intravesical BCG [14].

The meta-analyses on muscle invasive bladder cancer show a significant survival benefit in favor of neoadjuvant chemotherapy (NAC). Concurrent chemoradiotherapy or NAC followed by local treatment (radical cystectomy or radiation therapy) is recommended for any patient with small cell neuroendocrine component with localized disease, regardless of stage (including nonmuscle invasive state) [15,16]. However, the clinical benefit of NAC to other subtype histologies or divergent differentiation is inconsistent. The guidelines do not clearly indicate the therapeutic efficacy of NAC for subtype histology/divergent differentiation except for small cell neuroendocrine subtype. Even for the neuroendocrine carcinomas, the optimal chemotherapy regimen is undefined and long-term survival results are poor. These tumors are initially highly responsive to cisplatin plus etoposide combination chemotherapy, but responses are not durable. Chu *et al.* [4▪▪] report more frequent chemorefractory disease in subtype histologies in comparison to not otherwise specified urothelial carcinoma (56 versus 43%) with squamous urothelial carcinoma and mixed subtypes having the highest odds ratios after adjusting for clinical stage. On the other hand, the posthoc analysis of the VESPER trial [17▪▪] which included 177 patients with more than 10% variant histology or divergent differentiation among 300 patients who underwent NAC, showed that the presence of subtype histology/divergent differentiation was not associated with the inferior pathological response and progression-free survival (PFS). However, PFS was shortened in the patients with at least 50% squamous differentiation and at least 50% micropapillary when compared with pure urothelial carcinoma. Recently, the NIAGARA trial showed that event-free survival and OS in the subtype histology/divergent differentiation group had lower hazard ratios with the use durvalumab before and after radical cystectomy in addition to NAC [18▪].

Adjuvant CT is variably used among patients with histologic subtype bladder cancer. A query on the National Cancer Database included patients with nonmetastatic bladder cancer who underwent radical cystectomy ($n=45\,797$), and revealed that adjuvant CT was associated with significantly longer OS (hazard ratio = 0.69) for squamous, sarcomatoid and micropapillary subtypes [19].

There are not much data on the outcomes of radiation-based therapy for histologic subtypes of urothelial cancer at muscle invasive stage. A multicenter retrospective study of muscle invasive 864 cases, who underwent curative-intent radiation-based therapy to the bladder, did not find statistically different survival outcomes between groups of subtype histology and pure urothelial carcinoma [20]. Sixty-one percent of subtype histologies were squamous and/or glandular differentiation, and complete response rate in subtype histology group was 63% versus 69% in pure urothelial carcinoma ($P>0.05$).

Lymphoepithelioma-like urothelial carcinoma is an important exception to the majority of other urothelial carcinoma subtypes in terms of prognosis. It has a favorable outcome and response to platinum-based chemotherapy when it is in pure form. However, when coexistent with usual urothelial carcinoma, prognosis is determined by the conventional component. Lymphoepithelioma-like urothelial carcinoma is likely to show a favorable response also to immunotherapy as they are highly positive for PD-1/PD-L1 [6].

CONCLUSION

Urothelial carcinoma is a heterogeneous disease due to epithelial plasticity leading to development of morphologically and molecularly different tumor subtypes along with variability in patient outcome.

Urothelial carcinoma subtypes have distinct patterns of genomic alterations although no single gene is pathognomonic. The clinicopathological importance of each subtype has not been fully elucidated yet, but it is generally accepted that sarcomatoid, micropapillary, plasmacytoid and neuroendocrine morphologies are associated with highly aggressive clinical behavior. Data on neoadjuvant treatment, bladder preservation, adjuvant treatment and the impact of new therapies are limited for these tumors. Somatic alterations which may be targetable by novel agents have been shown primarily in the *PIK3CA, PTEN, TSC1, KRAS, FGFR3* and *ERBB2* genes, with varying frequencies in different subtypes. That could be the basis to design prospective clinical trials of investigational as well as standard therapies with the incorporation of personalized biomarkers for individual histologic subtypes. For these reasons, recognition and uniform reporting of subtype histology/divergent differentiation in urothelial carcinoma is essential for developing treatment strategies and improving patient outcomes.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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