Variants of Urothelial Carcinoma

A. Lopez-Beltran

Variants of Bladder Cancer: The Pathologist’s Point of View

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Table 1 – Histologic variants of infiltrating urothelial carcinoma according to World Health Organization Classification of Tumors of the Urinary Tract [3]

<table>
<thead>
<tr>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial carcinoma with divergent differentiation</td>
</tr>
<tr>
<td>with squamous cell differentiation</td>
</tr>
<tr>
<td>with glandular differentiation</td>
</tr>
<tr>
<td>with lymphoepithelial differentiation</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Nested urothelial carcinoma (including large nested)</td>
</tr>
<tr>
<td>Microcystic urothelial carcinoma</td>
</tr>
<tr>
<td>Micropapillary urothelial carcinoma</td>
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<tr>
<td>Papillary Francesco-lei urothelial carcinoma</td>
</tr>
<tr>
<td>Plasmacytoid/serous neo plasmacytoid urothelial carcinoma</td>
</tr>
<tr>
<td>Sarcomatoid urothelial carcinoma</td>
</tr>
<tr>
<td>Gland cell urothelial carcinoma</td>
</tr>
<tr>
<td>Urothelial carcinoma with clear cell differentiation</td>
</tr>
<tr>
<td>Poorly differentiated urothelial carcinoma</td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

Table 3 – Histologic variations and variants of urothelial carcinoma not included in the current World Health Organization classification of tumors of the urinary tract [4]

<table>
<thead>
<tr>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial carcinoma, inverted growth (inverted papilloma-like)</td>
</tr>
<tr>
<td>Urothelial carcinoma with unusual internal architecture</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
</tr>
<tr>
<td>General carcinoma</td>
</tr>
<tr>
<td>General metastases</td>
</tr>
<tr>
<td>Osteosarcoma-like cells</td>
</tr>
<tr>
<td>Prominent lymphocytic infiltration</td>
</tr>
<tr>
<td>Prostate adenocarcinoma (prostate-like) urothelial carcinoma</td>
</tr>
<tr>
<td>Urothelial carcinoma with mixed mesenchymal</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
</tr>
<tr>
<td>Undifferentiated carcinoma with stromal features</td>
</tr>
<tr>
<td>Undifferentiated carcinoma NOS</td>
</tr>
<tr>
<td>Undifferentiated carcinoma NOS with stromal features</td>
</tr>
<tr>
<td>NOS = not otherwise significant</td>
</tr>
</tbody>
</table>
### Classification of Bladder and Urinary Tract Cancer

**WHO 2016**

#### WHO classification of tumours of the urothelial tract

<table>
<thead>
<tr>
<th>Urothelial tumours</th>
<th>Neuroendocrine tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubating urothelial carcinoma</td>
<td>Small cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
<tr>
<td>Neoplasms, including large clear-cell carcinoma</td>
<td>Clear cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
<tr>
<td>Monophasic</td>
<td>Small cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
<tr>
<td>Lymphoepithelioma-like</td>
<td>Small cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
<tr>
<td>Plasmacytoid / signet ring cell / diffuse</td>
<td>Small cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>Small cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
<tr>
<td>Giant cell</td>
<td>Small cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>Small cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
<tr>
<td>Clear cell</td>
<td>Small cell neuroendocrine carcinoma with nested clear-cell carcinoma</td>
</tr>
</tbody>
</table>

#### Histologic variants of invasive urothelial carcinoma:
- Changes in terminology
- Better definition criteria
- New entries

#### WHO 2016
- Histologic variants of bladder cancer:
- Histologic patterns that differ from conventional urothelial carcinoma.
One key factor in such risk stratification appears to be the presence of variant histologic patterns in the bladder tumor. All of the variant histologies portend a worse prognosis than pure urothelial carcinoma.
The Response of Variant Histology Bladder Cancer to Intravesical Immunotherapy Compared to Conventional Cancer.

Gofrit ON.

**INTERPRETATION:**
- A patient with variant bladder cancer treated with intravesical immunotherapy has a 27% chance of dying from this disease within 5 years compared to 7.5% chance for a patient with conventional high-grade UC.

Abstract
- biologically aggressive, and their identification may aid in clinical decision-making.
- management of cT1 disease and predicting response to neoadjuvant chemotherapy (NAC).
- For example, although stage cT1 micropapillary carcinoma has high mortality following conservative management, and early cystectomy may reduce mortality.
- plasmacytoid and small cell cancers are remarkably aggressive, and those diagnosed as stage cT1 at transurethral resection are likely understaged.
- Although identification of histologic variants may inform on optimal management, diagnostic issues challenge their incorporation into clinical practice.
- >> example, interobserver reproducibility is only moderate for the diagnosis of micropapillary BCA.
• Monn MF et al.
  MPV and PCV were independently associated with twice the risk of all-cause mortality compared with nonvariant.

• Monn MF et al.
  BJU Int. 2015 Aug;116(2):236-40. The changing reality of urothelial bladder cancer: should non-squamous variant histology be managed as a distinct clinical entity?
  While SQD behaves similarly to NV, non-SQD variant histology portends worse OS and disease-specific survival regardless of neoadjuvant or adjuvant chemotherapy and pathological stage.

• Moschini M et al.
  30% of specimens. In this setting, the presence of a pure variant but not the presence of mixed variant with urothelial carcinoma is related to a detrimental effect on survival outcomes after RC.

• Pokuri VK et al.
  The presence of pure UC favored a pT0 response to NAC compared with those with variant histologic features or mixed tumors.

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**FIGURE 1.** Decision tree for the clinical management of variant histology NMIBC. *Ensure adequate clinical staging with high level of suspicion for understaging in patients with squamous/glandular differentiation, nested, and other variants. For microcystic, papillary, and mixed variants initial treatment with intravesical therapy is not recommended except for select cases and extensive patient counseling regarding substantial risk.*

Porten-Kamat 2014
Infiltrating Urothelial Carcinoma with Divergent Differentiation

- Squamous Differentiation defined by presence of intercellular bridges or keratinization
- Glandular Differentiation
- Trophoblastic Differentiation
- Others
- Uncertain significance:
  - Poor prognosis in Pts radical cystectomy
  - Poor response to X-Ray ther.
  - Poor response to systemic therapy
  - High recurrence in PUca
Effect of Nonurothelial Histologic Variants on the Outcomes of Radical Cystectomy for Nonmetastatic Muscle-invasive Urinary Bladder Cancer.

**CONCLUSION:**

- Pure squamous cell and neuroendocrine carcinoma histologic types were associated with worse OS relative to PUC.
- However, no difference was found between adenocarcinoma and PUC.
- All histologic variants were associated with higher tumor stage at surgery compared with PUC.
Morphological Variants of BCA

Nested Variant

- Aggressive, 80 cases,
- Male predominance.
- 70% pts died 4-40 months after diagnosis.
- Deceptively benign appearance resembling Brunn nests.
- Some have small tubular lumens
- Nuclei generally little/no atypia
- Foci of anaplastic cells are invariable present in deeper aspects.
- High p53 and ki67
- Low p27
Inverted urothelial carcinoma: a series of 12 cases with a wide morphologic spectrum overlapping with the large nested variant.

Abstract

The current series presents 12 cases of invasive urothelial carcinoma (UC) with inverted growth pattern that fulfill the architectural criteria of the recently described "large nested" variant of UC, but which display a wider spectrum of morphologic and cytologic changes. All cases had an associated component of usual invasive UC, and 10 had an associated surface papillary component. Although many areas within the tumors were indistinguishable from a noninvasive endophytic growth pattern, at least some had an irregular ragged contour, and all showed haphazard arrangement with variable amount of intervening stroma at least focally. Inflammatory stromal reaction was noted in 11 cases, and desmoplasia and retraction artifact were present in 8 cases each. Although major areas showed mild atypia, many tumors showed marked hyperchromasia, prominent nucleoli, marked irregular nuclear membranes, and brisk mitotic activity. Final pathological stage on cystectomy specimens was T2 in 4 cases, T3 in 2 cases, and T4 in 3 cases. In 3 cases, lymph node metastases were documented histologically. Review of the literature shows that the "large nested," "inverted," "endophytic," and "inverted papilloma-like" variants of invasive UC are interrelated entities and should probably be considered as one variant with a wide spectrum of cytoarchitectural features. They should also be separated from the "nested" variant with which they rarely coexist and which shows different characteristics at the morphologic level.
Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder

- 56 cases
- Desmoplastic stroma was focally present in 16 cases
- Urothelial carcinoma component (mixed cases, 32). Carcinoma in situ was present in 29 cases

- Linder BJ et al.
- High rate of adverse pathological features since 36 patients (69%) had pT3-T4 disease and 10 (19%) had nodal invasion.
- No significant differences were noted in 10-year local RFS (83% vs 80%, p = 0.46) or 10-year CSS (41% vs 46%, p = 0.75).
- The nested variant of urothelial carcinoma is associated with a high rate of locally advanced disease at radical cystectomy.

Morphological Variants of BCA: Microcystic Variant

- Occasionally UCa>>striking cystic pattern with
- cysts ranging from microscopic up to 1-2 mm
- in diameter.
- Cysts round/oval/elongated
- Necrotic material or pale pink secretions are common.
- Cysts lining may be absent, flattened or urothelial and may show differentiation towards mucinous cells.
- DD:
  - Primary adenocarcinoma
  - Cystitis cystica
  - Cystitis glandularis
  - Nephrogenic metaplasia

Lopez Beltran, Montironi, Cheng et al 2015 Histopathology
Morphological Variants of BCA  Micropapillary Variant

- Resembles papillary serous Ca of the ovary, 70 cases,
- Male predominance, mean 66 y, hematuria.
- Always associated with conventional Uca or adenocarcinoma.
- Surface: delicate fine papillary processes with central vascular core.
- Invasive portion: tiny nests of cells or slender papillae within tissue retraction spaces that simulate lymphatic spaces
- Vascular/lymphatic invasion is always present
- Nuclei with prominent nucleoli, abundant cytoplasm and mitosis
- IHC: EMA (MUC-1), Ck7, Ck20, Leu M1, CEA(60%), CA -125 (30%).
Lopez-Beltran, Montironi, Cheng 2011
Micropapillary Bladder Cancer
A Review of the University of Texas M. D. Anderson Cancer Center Experience With 100 Consecutive Patients

- Kamat et al 2007; 100 cases
- 5y/10y OS<<51% and 24%
- Micropapillary bladder cancer is associated with a poor prognosis.
- Intravesical therapy appears to be ineffective in this disease and patients with surgically resectable disease should be offered early radical cystectomy
Noninvasive micropapillary urothelial carcinoma: a clinicopathologic study of 18 cases.

Noninvasive micropapillary urothelial carcinoma consists of slender tufts of urothelial carcinoma lacking fibrovascular cores analogous to ovarian papillary serous tumors of borderline malignancy.

18 pts, noninvasive micropapillary urothelial carcinoma
12 pts initially treated with surveillance, Bacillus-Calmette Guérin, or intravesical chemotherapy:
4 did not recur and were without evidence of disease on follow up
4 pts experienced recurrences with 3 of them without evidence of disease and fourth recurred at 84 months.
1 pts is alive at 11 months with disease
1 died of other causes at 1 month
2 pts progressed to pT2 and pT3 disease at 5 and 21 months
Some cases of noninvasive micropapillary urothelial carcinoma are not necessarily associated with an adverse outcome.


Conclusion: outcomes of radical cystectomy for patients with MUC are similar to those with UC


Conclusions: NAC utilization and early cystectomy did not show a survival benefit in patients with MPBC.
HER2 gene amplification occurs frequently in the micropapillary variant of urothelial carcinoma: analysis by dual color in situ hybridisation

• 19 pts
• HER2neu gene amplification 42% (FISH)
• 53% of samples had aneusomy of chromosome 17 (HER2 is at 17q11-21)

Outcome of patients with micropapillary urothelial carcinoma following radical cystectomy; ERBB2 (HER2) amplification identifies patients with poor outcome.

• 61 pts, 15% with HER2 neu amplifications (FISH) and 9% conventional UC
• HER2neu amplification associated 3-fold increased risk of death by cancer
• Potential role as Target for therapy
HER2 gene amplification occurs frequently in the micropapillary variant of urothelial carcinoma: analysis by dual color in situ hybridisation

Ching CB et al. Mod Pathol 2011;24

- 68% of 19 cases of micropap. U Ca had 2+ or 3+ IHC for HER2 protein.
- Gene amplification was present in 42% of 19 cases with 100% correlation with 2+ or 3+ protein expression.
- 53% of samples had aneusomy of chromosome 17 (HER2 is at 17q11-21)

- Previous investigations on conventional urothelial carcinoma found an inconsistent and often low frequency of HER2 gene amplification with no strong correlation between protein expression and gene amplification.
Morphological Variants of BCA
Diffuse/Plasmocytoid Variant

- Resembles malignant plasmacytoma, <50 cases.
- Single malignant cells in a loose or myxoid stroma.
- Clear/eosinophilic cytoplasm
- Eccentrically placed, enlarged hyperchromatic nuclei with small nucleoli
- Associated high grade Uca.
- Some cases diagnosed because metastases
- IHC: CkAE1/AE3, Ck 7, CD138+
- 70% pts died shortly after diagnosis

RESULTS:
- MOST PUCS LACKED IMMUNOREACTIVITY FOR:
  - THE RETINOBLASTOMA (RB) GENE PROTEIN (12/32)
  - E-CADHERIN (8/30) (26%) >> DISTINCT DISCOHESIVE HISTOLOGIC APPEARANCE
- FOLLOW-UP:
  - 25 DIED OF PUC AT A MEAN OF 23 MONTHS
  - 19 PATIENTS WERE ALIVE AT A MEAN OF 22 MONTHS.

Plasmacytoid Urothelial Carcinoma of the Urinary Bladder: A Clinicopathologic and Immunohistochemical Analysis of 49 Cases.
Fox MD1, Xiao L1, Zhang M1, Kamat AM2, Siefker-Radtke A1, Zhang L1, Dinney CP2, Czerniak B1, Guo CC1.
RESULTS:

-IHC-HER2 expression score was 3+ in 4 cases, 2+ in one case, and negative in one case.

-FISH HER2 gene amplification was positive in 3 cases, of which 2 cases showed a 3+ her2 IHC score but one case was negative for HER2 IHC, another 2 cases showed equivocal her2 fish results, and one remaining case was negative for HER2 FISH.
Morphological Variants of BCA

Lipid Cell Variant

- Defined as Uca which exhibits transition to a cell type resembling signet-ring lipoblasts
- < 50 reported cases
- Mean age 74 y
- Males.
- Cell react with CK
- StageTa-T4
- 59% died, mean 33 m
- Conventional Uca always present
- Clonally related to the urothelial carcinoma

Clear Cell Glycogenic Variant

- <25 cases reported
- 22-83 y, Male/female
- Ca125 variably +; Ck20+ focal to diffuse in some cases;
- CK7+ diffuse, GATA3+,p63+

Lopez-Beltran, Montironi, Cheng, AJSP, 2010

Clear cell carcinoma of the urinary bladder: a report and comparison of four tumors of mullerian origin and nine of probable urothelial origin with discussion of histogenesis and diagnostic problems.
Oliva E, Amin MB, Jimenez R, Young RH.
### Pathologic Scenario

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>Molecular Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial carcinoma with divergent differentiation</td>
<td>Most unrelated to HPV</td>
</tr>
<tr>
<td>With squamous cell differentiation</td>
<td>Unknown</td>
</tr>
<tr>
<td>With glandular differentiation</td>
<td>Choriocarcinoma &gt;&gt; high copy number of isochromosome 12p</td>
</tr>
<tr>
<td>With trophoblastic differentiation</td>
<td></td>
</tr>
<tr>
<td>Urothelial carcinoma with deceptively benign features</td>
<td>TERT Promoter Mutation</td>
</tr>
<tr>
<td>Nested urothelial carcinoma (including large nested and small tubules)</td>
<td></td>
</tr>
<tr>
<td>Microcystic urothelial carcinoma</td>
<td></td>
</tr>
<tr>
<td>Differential diagnosis with metastases to the bladder</td>
<td></td>
</tr>
<tr>
<td>Diffuse/plasmacytoid/signet ring cell urothelial carcinoma</td>
<td>CDH1 loss (mutation or methylation) in &gt;80% of cases, E-Cadherin loss in &gt;70% of cases, HER2 gene amplification, PI3K and TSC1 genes altered.</td>
</tr>
<tr>
<td>Sarcomatoid urothelial carcinoma (carcinosarcoma)</td>
<td>TERT Promoter Mutation</td>
</tr>
<tr>
<td>Giant cell urothelial carcinoma</td>
<td></td>
</tr>
<tr>
<td>Clear cell (glycogen-rich) urothelial carcinoma</td>
<td></td>
</tr>
<tr>
<td>Urothelial carcinoma, lipid-cell variant</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated tumors (undifferentiated NOS/Oc-rich)</td>
<td></td>
</tr>
<tr>
<td>Marked immune cell response</td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelioma-like urothelial carcinoma</td>
<td>Unrelated to Epstein-Barr virus</td>
</tr>
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</table>

### Molecular Taxonomy

**UB-MIBC (TCGA)**

- **Luminal MIBCs**
- Cluster I (luminal, differentiated) with FGFR3 aberrations and CDKN2A deletions
- Cluster II (luminal, less differentiated, p53-like)
- Cluster III (squamous)
- **Basal MIBCs**
- Poorly differentiated tumors (undifferentiated NOS/Oc-rich)
- Cluster IV (EMT and immune infiltrated)
<table>
<thead>
<tr>
<th>VARIANT TYPE</th>
<th>MOLECULAR SUBTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>With squamous cell differentiation</td>
<td>Basal</td>
</tr>
<tr>
<td>With glandular differentiation</td>
<td>Luminal</td>
</tr>
<tr>
<td>With trophoblastic differentiation</td>
<td>Unknown</td>
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<td>Nested urothelial carcinoma (including large nested and small tubules)</td>
<td>Luminal</td>
</tr>
<tr>
<td>Microcystic urothelial carcinoma</td>
<td>Luminal</td>
</tr>
<tr>
<td>Micropapillary urothelial carcinoma</td>
<td>Luminal (30-50% of cases)</td>
</tr>
<tr>
<td>Diffuse/ plasmacytoid/signet ring cell urothelial carcinoma</td>
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</tr>
<tr>
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<td>Lymphospathelioma-like urothelial carcinoma</td>
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Lopez-Beltran, Montironi et al 2017, Eur Urol Suppl 16:210-222
Take-home messages

• WHO 2016 mostly refines previous concepts in morphologic variants of invasive urothelial carcinoma with some new entries
• Current diagnosis of variant histology in urothelial carcinoma substantially informs patient care and provides a novel framework to stratify patients according to potential response to a given therapy.
• Molecular alterations, in particular new molecular classifiers, which characterize some of the variants of urothelial carcinoma, might become targets for novel drugs to improve the overall response of these patients.
¡THANKS!