UNDERSTANDING SUBTYPES AND VARIANTS OF UROTHELIAL CARCINOMA

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Worldwide standard
WHO 2016 TYPING OF INFILTRATING UROTHELIAL CARCINOMA

- With divergent squamous differentiation
- With divergent glandular differentiation
- With divergent trophoblastic differentiation
- Nested
- Microcystic
- Micropapillary
- Lymphoepithelioma-like
- Plasmacytoid/signet ring cell like/diffuse
- Sarcomatoid
- Giant cell
- Poorly differentiated
- Lipid rich
- Clear cell
WHO 2016 TYPING OF NON-UROTHELIAL CARCINOMAS IN THE BLADDER

- Squamous neoplasms
- Glandular neoplasms
- Urachal carcinoma
- Tumors of Mullerian type
- Neuroendocrine tumors
“Urothelial carcinoma plus squamous, adenocarcinoma, micropapillary, nested, plasmacytoid, and sarcomatoid should be identified because of the potential to have a more aggressive natural history.

These are usually treated in a similar manner to pure urothelial carcinoma of the bladder.

Micropapillary, plasmacytoid, and sarcomatoid histologies are generally at higher risk for progression to muscle-invasive disease and a more aggressive approach should be considered.”
INFILTRATING UROTHELIAL CARCINOMA WITH SQUAMOUS DIFFERENTIATION

- 20 to 40% of urothelial carcinomas
- Increases with grade and stage
- Presents with higher stage compared to pure urothelial carcinoma
- Uncertain responsiveness to radiation and chemotherapy
- Basal/squamous-like subtype (TCGA) may be linked to response
UROTHELIAL CARCINOMA WITH GLANDULAR DIFFERENTIATION

- Present in about 6 to 18% of urothelial carcinomas
- Usually: luminal spaces and enteric appearance
- Distinguish vs. pure adenocarcinoma
- Present at higher-stage but stage-matched outcome not different vs. pure urothelial carcinoma
IMPACT OF SQUAMOUS AND GLANDULAR DIFFERENTIATION ON OUTCOME

Figure 1. CSS after RC, stratified by pure UC in 827 patients vs UC with squamous and/or glandular differentiation in 186 in RC specimen.
NESTED VARIANT OF UROTHELIAL CARCINOMA

- Crowded, small nests and tubules infiltrating lamina propria; some extend into muscularis propria
- Little nuclear atypia – more apparent at base
- Can be mixed with usual urothelial carcinoma
- Aggressive: 82% with pT3/pT4 and 57% with lymph node metastasis (in largest series of 30 patients; Hum Pathol 41:163-171, 2010) but no difference in stage-matched outcome (Virchows Arch 485; 199-205, 2014)
MICROPAPILLARY VARIANT OF UROTHELIAL CARCINOMA

- A rare to uncommon variant: incidence of 1% or less to 5.6%
- High-grade and high-stage, with vascular invasion common
- Commonly admixed with usual urothelial carcinoma. Unclear if percentage influences outcome but any amount likely significant.
MICROPAPILLARY CARCINOMA

- Associated with locally advanced disease at radical cystectomy but outcome comparable to pure urothelial carcinoma after controlling for clinicopathologic parameters.

- Optimal treatment of T1 patients?

- Strong association with HER2 gene amplification and protein overexpression.

Lymphatic invasion
PLASMACYTOID VARIANT OF UROTHELIAL CARCINOMA

- Rare; resembles plasmacytoma
- Mixed with high-grade urothelial carcinoma in 50%
- CK, CK7, CK20, p63, GATA3, CD79a immunostains needed
- Discohesive and single cell growth due to loss E-cadherin expression secondary to CDH1 mutations
- Aggressive, high-grade and high-stage disease, with high risk for peritoneal carcinomatosis and positive surgical margins
SARCOMATOID VARIANT OF UROTHELIAL CARCINOMA

- 0.6% of bladder tumors
- Radiation and cyclophosphamide: risk factors
- With or without heterologous elements
- Epithelial immunostains can be helpful; GATA3 positive in 73%; epithelial-mesenchymal markers overexpressed
- 5 year survival: 20%; pathologic stage most predictive of outcome

HETEROLOGOUS, WITH CHONDROSARCOMA
SARCOMATOID CARCINOMA

- **Grossly** often polypoid but also deeply invasive into muscularis propria
- **Microscopically** : epithelial component usually urothelial, but can be squamous, glandular, or small cell. Amount of epithelioid area can vary
- Sarcomatoid element typically high-grade. Most common : undifferentiated spindle cell population. Most common heterologous component : osteosarcoma, followed by chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, angiosarcoma
SARCOMATOID CARCINOMA, HOMOLOGOUS PATTERN

Squamous epithelioid element
NEUROENDOCRINE TUMORS OF THE URINARY BLADDER

- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Well-differentiated neuroendocrine tumor
- Paraganglioma
SMALL CELL CARCINOMA OF THE URINARY BLADDER

- About 1% of bladder carcinomas
- Three-quarters present with surgically resectable disease (≤ cT4aN0M0)
- Paraneoplastic syndromes rare
- Grossly not distinguishable from urothelial carcinoma
SMALL CELL CARCINOMA OF URINARY BLADDER

- Often found mixed with urothelial carcinoma: 47%–70% of cases
- Can also be admixed with adenocarcinoma (8%) or squamous cell carcinoma (10%)
- In WHO 2016, small cell carcinoma, when mixed, must be most of the tumor to be categorized as small cell carcinoma

T1 (5% of cases; Eur Urol 2013)
MIXED SMALL CELL- UROTHELIAL CARCINOMA
URINARY BLADDER SMALL CELL CARCINOMA

- NCCN 2019:
  Neoadjuvant chemotherapy followed by cystectomy or radiation therapy for patients with localized disease regardless of stage

Muscularis propria invasion
SMALL CELL CARCINOMA OF BLADDER IN SMALL BIOPSY SAMPLE
IMMUNOPHENOTYPE OF SMALL CELL CARCINOMA OF URINARY BLADDER

- Chromogranin
- Synaptophysin
- Pan-cytokeratin
- Chromogranin
- Synaptophysin
SMALL CELL CARCINOMA OF THE BLADDER: OUTCOME

- Neoadjuvant chemotherapy improved pathologic downstaging and long-term outcomes (MD Anderson, 172 cases, 2013).

- Compared with pure urothelial carcinoma at similar stages, small cell had a worse prognosis when metastatic (MD Anderson, 81 cases, 2018).

- SEER database: 11 month median overall survival

- Survival related to age > 64 years, high TNM stage, and metastasis at presentation
PD-L1 TESTING: UROTHELIAL CARCINOMA AND VARIANTS

- Method: immunohistochemistry
- A number of different antibodies used
- Variants can be PD-L1 positive. Anecdotal reports of durable responses.

Scoring: Percentage of tumor cells and immune cells: Positive if combined proportion score is 10 or greater
FUTURE DIRECTIONS

- Utilization of tumor tissue, urine, and serum-based molecular markers in refinement of classification and as predictors of response to therapy