III ЕЖЕГОДНЫЙ КОНГРЕСС
РОССИЙСКОГО ОБЩЕСТВА ОНКОПАТОЛОГОВ

20–21 апреля 2018 года

13.00–14.00	**ПЕРЕРЫВ НА ОБЕД**
14.00–15.40	**Сессия – Онкоурология** (председатель – Ковылина М.В.)
14.00–14.25	**Antonio Lopez-Beltran** (Испания) CIS/Dysplasia of the urothelium
14.25–14.50	**Antonio Lopez-Beltran** (Испания) Pathologic assessment of invasion in TUR specimens
14.50–15.10	**Antonio Lopez-Beltran** (Испания) Urothelial tumors with inverted growth
15.10–15.30	**Antonio Lopez-Beltran** (Испания) Variants of urothelial carcinoma
15.30–15.40	**Дискуссия – все участники**

Variants of Urothelial Carcinoma

A. Lopez-Beltran

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journal homepage: www.europeanurology.com

European Association of Urology

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

Antonio Lopez-Beltran[a,*], *Liang Cheng*[b], *Maria R. Raspollini*[c], *Rita Canas-Marques*[d], *Marina Scarpelli*[e], *Alessia Cimadamore*[e], *Silvia Gasparrini*[e], *Rodolfo Montironi*[e]

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

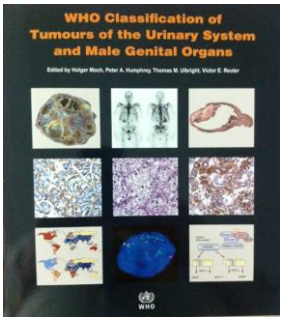
Urothelial carcinoma with divergent differentiation
-With squamous cell differentiation
-With glandular differentiation
-With trophoblastic differentiation
-Other
Nested urothelial carcinoma (including large nested)
Microcystic urothelial carcinoma
Micropapillary urothelial carcinoma
Lymphoepithelioma-like urothelial carcinoma
Plasmacytoid/signet ring cell/diffuse urothelial carcinoma
Sarcomatoid urothelial carcinoma
Giant cell urothelial carcinoma
Lipid-rich urothelial carcinoma
Clear cell (glycogen-rich) urothelial carcinoma
Poorly differentiated urothelial tumors

Table 3 – Histologic variations and variants of urothelial carcinoma not included in the current World Health Organization classification of tumors of the urinary tract [1]

Urothelial carcinoma, inverted growth (inverted papilloma-like)
Urothelial carcinoma in augmentation cystoplastia
Urothelial carcinoma with unusual stromal reactions
-Pseudosarcomatous stroma
-Stromal osseous metaplasia
-Stromal cartilaginous metaplasia
-Osteoclast-type giant cells
-Prominent lymphoid infiltrate
Pseudoangiosarcomatous (pseudoangiosarcoma-like) urothelial carcinoma
Urothelial carcinoma with myxoid stroma
Undifferentiated carcinoma
-Undifferentiated carcinoma with rhabdoid features
-Undifferentiated carcinoma NOS
-Osteoclast-rich undifferentiated carcinoma

NOS = not otherwise significant.

Classification of Bladder and Urinary Tract Cancer
WHO 2016



WHO classification of tumours of the urothelial tract

Urothelial tumours
Infiltrating urothelial carcinoma 8120/3
Nested, including large nested
Microcystic
Micropapillary 8131/3
Lymphoepithelioma-like 8082/3
Plasmacytoid / signet ring cell / diffuse
Sarcomatoid 8122/3
Giant cell 8031/3
Poorly differentiated 8020/3
Lipid-rich
Clear cell

Non-invasive urothelial lesions
Urothelial carcinoma in situ 8120/2
Non-invasive papillary urothelial carcinoma, low-grade 8130/2
Non-invasive papillary urothelial carcinoma, high-grade 8130/2
Papillary urothelial neoplasm of low malignant potential 8130/1
Urothelial papilloma 8120/0
Inverted urothelial papilloma 8121/0
Urothelial proliferation of uncertain malignant potential
Urothelial dysplasia

Squamous cell neoplasms
Pure squamous cell carcinoma 8070/3
Verrucous carcinoma 8051/3
Squamous cell papilloma 8052/0

Glandular neoplasms
Adenocarcinoma, NOS 8140/3
Enteric 8144/3
Mucinous 8480/3
Mixed 8140/3
Villous adenoma 8261/0

Urachal carcinoma 8010/3

Tumours of Müllerian type
Clear cell carcinoma 8310/3
Endometrioid carcinoma 8380/3

Neuroendocrine tumours
Small cell neuroendocrine carcin
Large cell neuroendocrine carcin
Well-differentiated neuroendocrin
Paraganglioma

Melanocytic tumours
Malignant melanoma
Naevus
Melanosis

Mesenchymal tumours
Rhabdomyosarcoma
Leiomyosarcoma
Angiosarcoma
Inflammatory myofibroblastic tu
Perivascular epithelioid cell tumo
Benign
Malignant
Solitary fibrous tumour
Leiomyoma
Haemangioma
Granular cell tumour
Neurofibroma

Urothelial tract haematopoietic lymphoid tumours

Miscellaneous tumours
Carcinoma of Skene, Cowper, ar
Metastatic tumours and tumours from other organs
Epithelial tumours of the upper u
Tumours arising in a bladder div
Urothelial tumours of the urethra

The morphology codes are from the Intern for Oncology (ICD-O) (917A). Behaviour is /1 for unspecified, borderline, or uncertain situ and grade III intraepithelial neoplasia. The classification is modified from the pre taking into account changes in our unders

- Histologic variants of bladder cancer :
- Histologic patterns that differ from conventional urothelial carcinoma.

- WHO 2016
- Morphologic variants of invasive urothelial carcinoma
  - Changes in terminology
  - Better definition criteria
  - New entries

Table 1. Histologic variants of infiltrating urothelial carcinoma according to WHO classification of tumors of the urinary tract [1]. 2016

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- Poorly differentiated urothelial tumors

Table 3. Histologic variations and variants of urothelial carcinoma not included in the current WHO classification of tumors of the urinary tract [1].

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- Undifferentiated carcinoma
  - -Undifferentiated carcinoma with rhabdoid features
  - -Undifferentiated carcinoma NOS
  - -Osteoclast-rich undifferentiated carcinoma

Lopez-Beltran, Montironi, Cheng et al 2017

The impact of variant histology on the outcome of bladder cancer treated with curative intent☆☆

Peter C. Black, M.D., Gordon A. Brown, D.O., Colin P.N. Dinney, M.D.*
Department of Urology, The University of Texas, M.D. Anderson Cancer Center, Houston, TX 77030, USA
Received 18 April 2007; received in revised form 27 June 2007; accepted 2 July 2007

- 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.

Front Oncol. 2016 Mar 15;6:43. doi: 10.3389/fonc.2016.00043. eCollection 2016.
The Response of Variant Histology Bladder Cancer to Intravesical Immunotherapy Compared to Conventional Cancer.
Gofrit ON[1],

- **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.

J Natl Compr Canc Netw. 2017 Oct;15(10):1268-1274. doi: 10.6004/jnccn.2017.7027.
Clinical Significance of Histologic Variants of Bladder Cancer.
Warrick JI[1].

- **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 is usually managed conservatively, 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
- Urol Oncol. 2015 Jan;33(1):18.e15-20. **Contemporary bladder cancer: variant histology may be a significant driver of disease.**
- 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.
- Clin Genitourin Cancer. 2016 Dec 14. pii: S1558-7673(16)30352-4. **Pure but Not Mixed Histologic Variants Are Associated With Poor Survival at Radical Cystectomy in Bladder Cancer Patients.**
- 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
- Clin Genitourin Cancer. 2016 Feb;14(1):e59-65. **Predictors of Complete Pathologic Response (pT0) to Neoadjuvant Chemotherapy in Muscle-invasive Bladder Carcinoma.**
- The presence of pure UC favored a pT0 response to NAC compared with those with variant histologic features or mixed tumors.

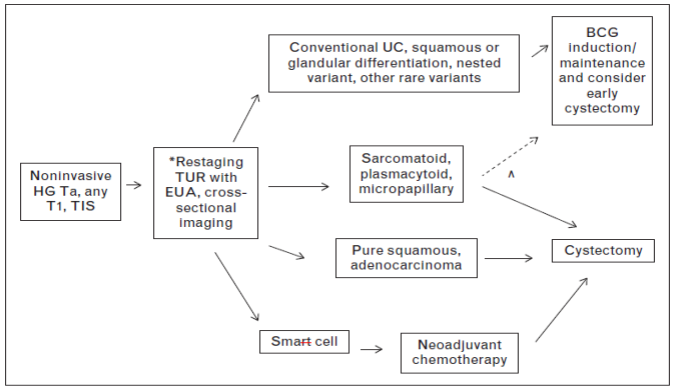
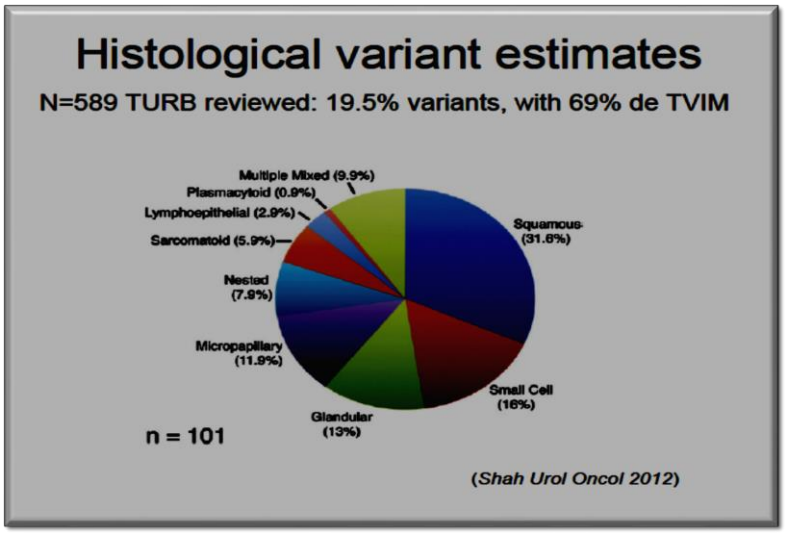


FIGURE 1. Decision tree for the clinical management of variant histology NIMBC. *Ensure adequate clinical staging with high level of suspicion for understaging in patients with squamous/glandular differentiation, nested, and other variants. ^For micropapillary, sarcomatoid, and plasmacytoid variants 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 Differentaition
- Others
- Uncertain significance:
  - Poor prognosis in Pts radical cystectomy
  - Poor response to X-Ray ther.
  - Poor response to systemic therapy
  - High recurrence in PUca

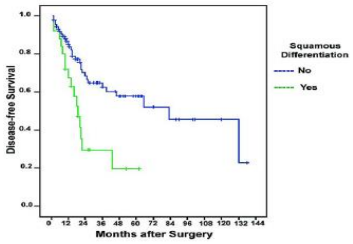


Figure 2 – Disease-free survival among patients with and without squamous differentiation (log-rank test; p = 0.

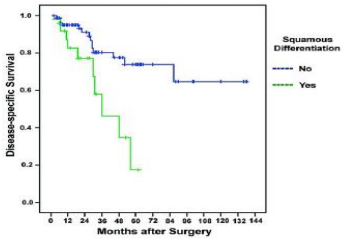


Figure 3 – Cancer-specific survival among patients with and without squamous differentiation (log-rank test; p = 0.001).

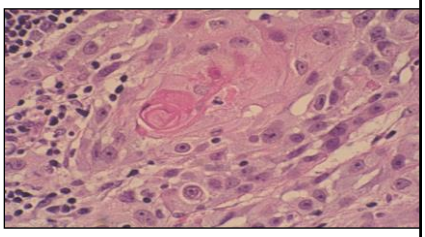


Table 4 – Multivariate Cox regression analysis for cancer-specific survival.

	Hazards Ratio	95% CI	p Value
Tumor size ≥ 3 cm / < 3 cm	5.49	[1.74 - 17.31]	0.004
Squamous differentiation Yes / No	5.21	[1.87 - 14.54]	0.002

Antunes et al 2010

Clin Genitourin Cancer. 2017 Aug 24. pii: S1558-7673(17)30248-3. doi: 10.1016/j.clgc.2017.08.007. [Epub ahead of print]

Effect of Nonurothelial Histologic Variants on the Outcomes of Radical Cystectomy for Nonmetastatic Muscle-invasive Urinary Bladder Cancer.

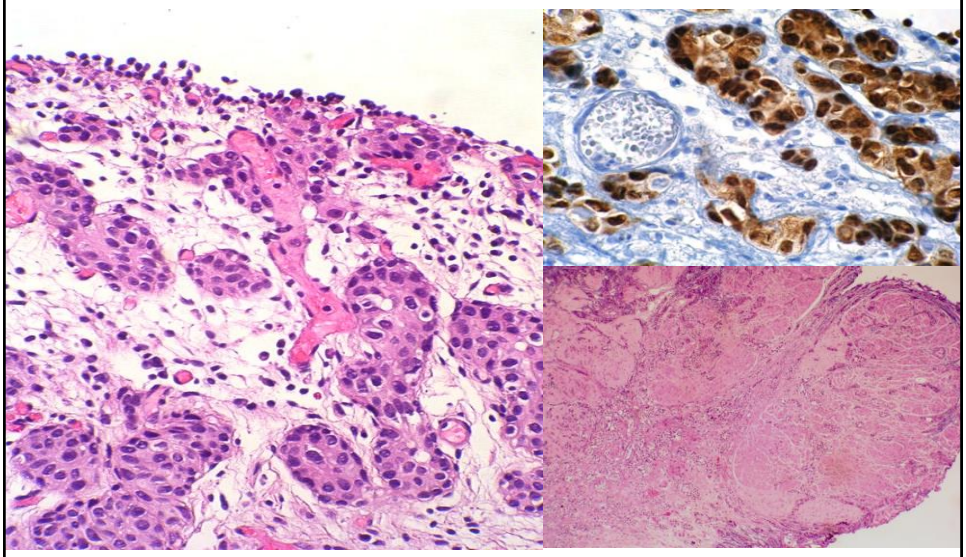
Vetterlein MW[1], Seisen T[2], Leow JJ[3], Preston MA[4], Sun M[4], Friedlander DF[4], Meyer CP[1], Chun FK[5], Lipsitz SR[4], Menon M[6], Kibel AS[4], Bellmunt J[7], Choueiri TK[7], Trinh QD[8].

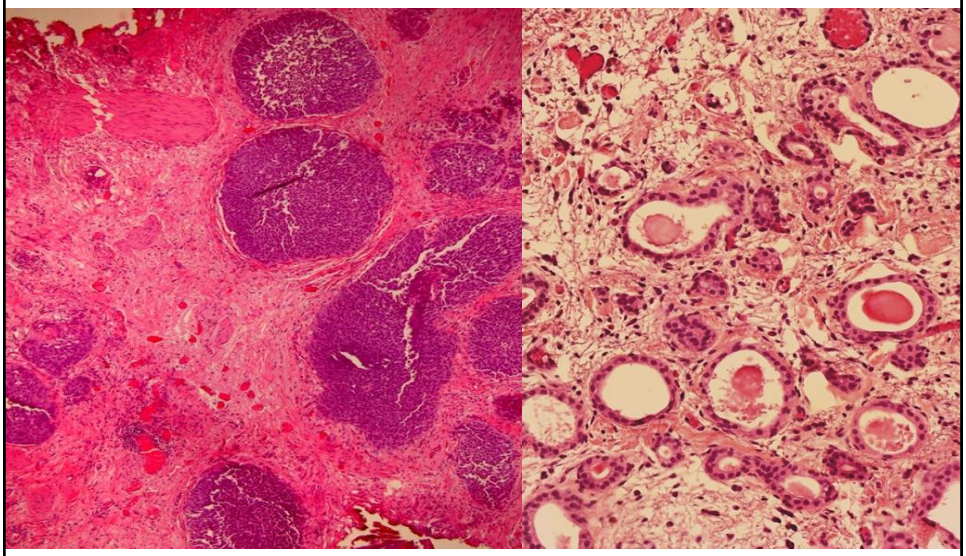
- **CONCLUSION:**
- Pure squamous cell and neuroendocrine carcinoma histologic types were associated with worse OS relative to PUC.
- However, no difference was found between adenocarcinoma and PUC.
- All histologic variants were associated with higher tumor stage at surgery compared with PUC.

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





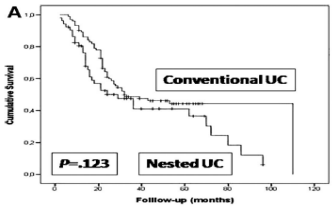
Human Pathol 2015 Oct;46(10):1506-13.

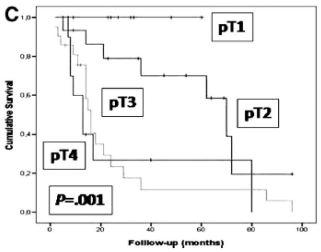
Inverted urothelial carcinoma: a series of 12 cases with a wide morphologic spectrum overlapping with the large nested variant. Brimo F. et al

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





- Lopez Beltran et al Virchows Arch (2015) 465:199–205
- 56 cases
- Desmoplastic stroma was focally present in 16 cases
- Urothelial carcinoma component (mixed cases, 32). Carcinoma in situ was present in 29 cases

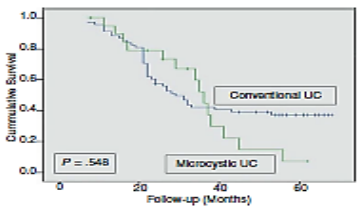
- Linder BJ et al.
- J Urol. 2013 May;189(5):1670-5 **Outcomes following radical cystectomy for nested variant of urothelial carcinoma: a matched cohort analysis.**
- High rate of adverse pathological features since 36 patients (69%) had pT3-T4 disease and 10 (19%) had nodal invasion.
- No significant 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.

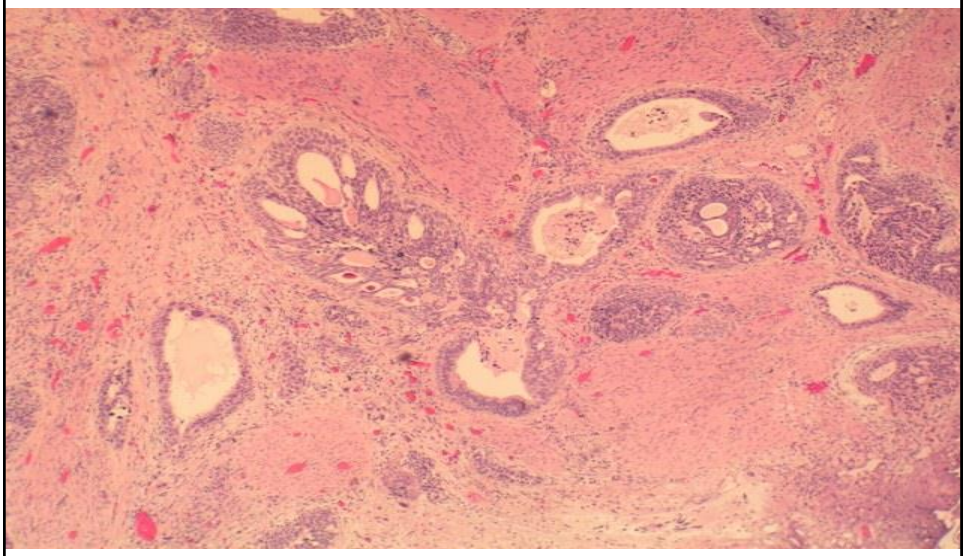
Morphological Variants of BCA :Microcystic Variant

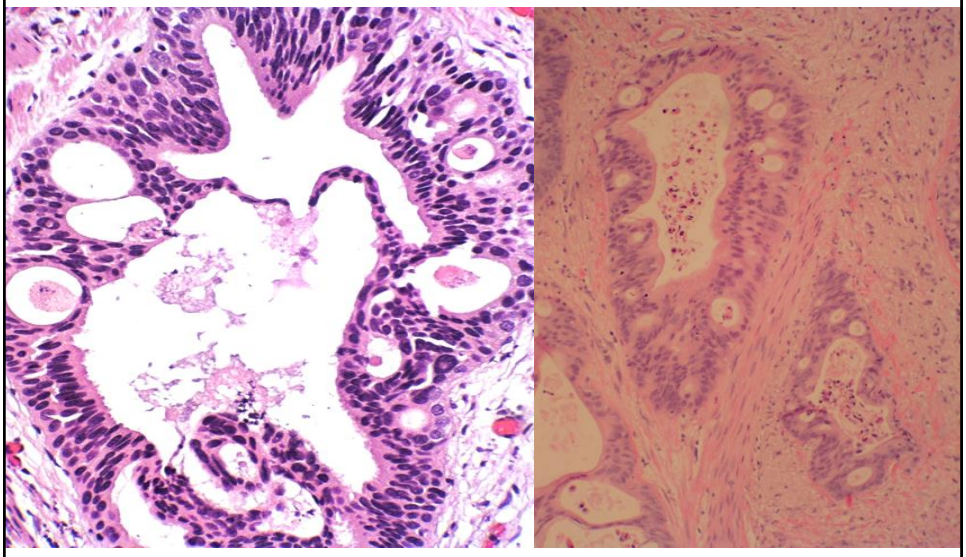
Urothelial tumours
Infiltrating urothelial carcinomas with divergent differentiation
Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Diffuse/ Plasmacytoid/ Signet ring cell
Sarcomatoid
Giant cell
Undifferentiated
Lipid rich
Clear cell

- 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

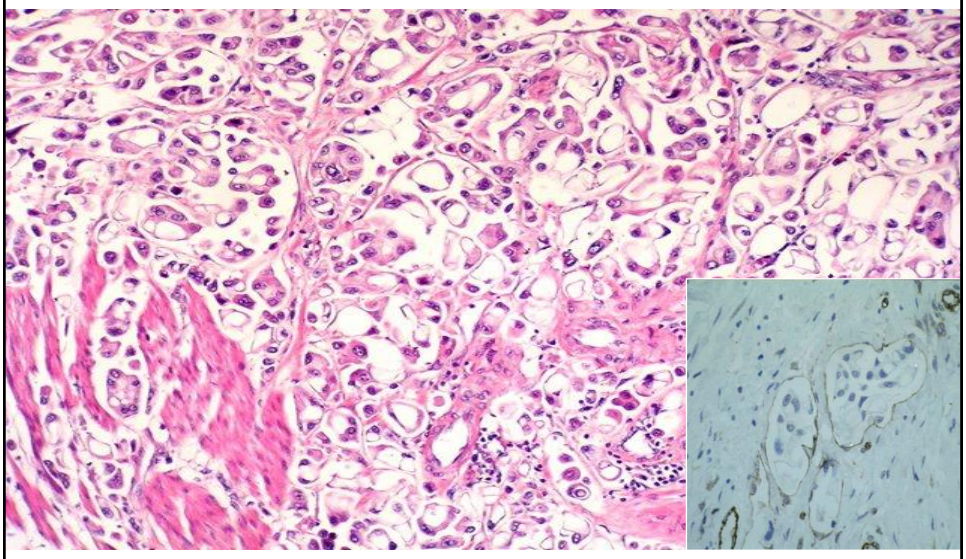


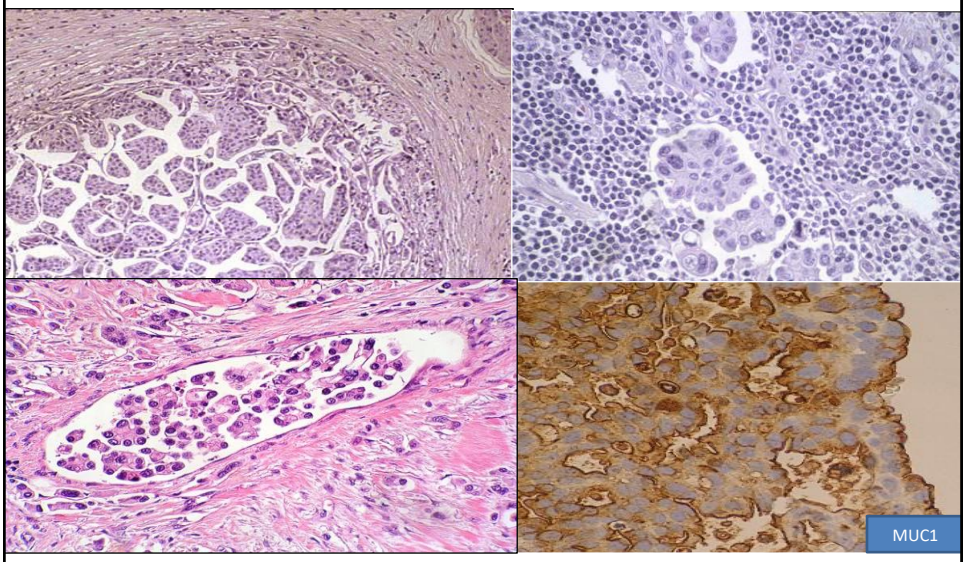


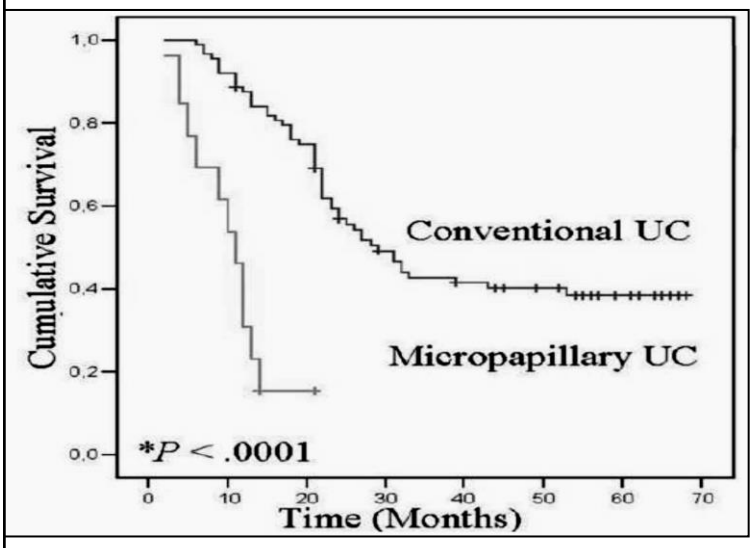


Morphological Variants of BCA — Micropapillary Variant

- 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%).

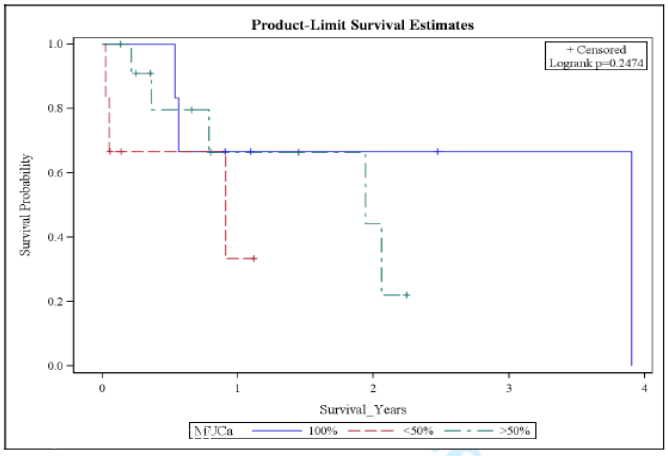






Lopez-Beltran, Montironi, Cheng 2011

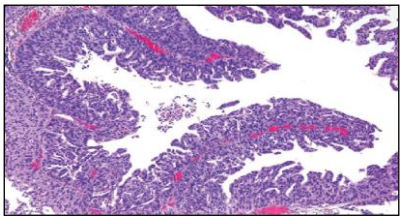
% MPC <<Prognosis?

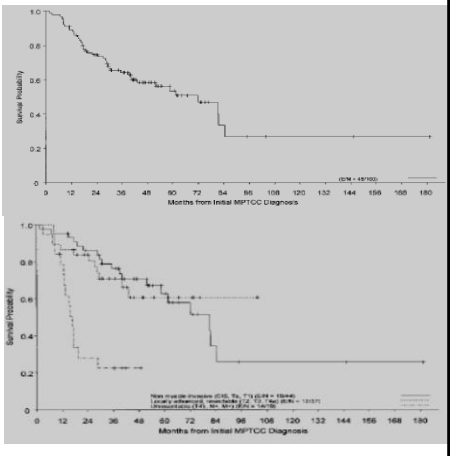


Micropapillary Bladder Cancer

A Review of the University of Texas M. D. Anderson Cancer Center Experience With 100 Consecutive Patients

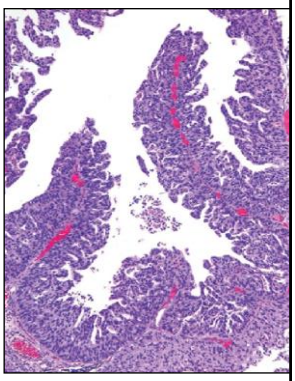
- Kamat et al 2007; 100 cases
- 5y/10y OS<<51% and 24%
- Micropapillary bladder cancer is associated with a poor prognosis.
- Intravesical therapy appears to be ineffective in this disease and patients with surgically resectable disease should be offered early radical cystectomy





- Amin A[1], Epstein JI. Hum Pathol. 2012 Dec;43(12):2124-8. **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.

WHO 2016:
Not to diagnose in NMIBC



- Fairey AS **et al.** Urol Oncol. 2014 Feb;32(2):110-6. **Impact of micropapillary urothelial carcinoma variant histology on survival after radical cystectomy.**
- Conclusion: outcomes of radical cystectomy for patients with MUC are similar to those with UC

- Sui W et al. Bladder Cancer. 2016 Oct 27;2(4):415-423. **Micropapillary Bladder Cancer: Insights from the National Cancer Database.**
- **Conclusions:** NAC utilization and early cystectomy did not show a survival benefit in patients with MPBC.

Ching CB et al. Mod Pathol 2011;24 **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)

Schneider SA et al. Mod Pathol. 2014 May;27(5):758-64. **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 amplication associated 3-fold increased risk of deat by cancer
- Potential role as Target for therapy

European Association of Urology

Platinum Priority – Editorial and Reply from Authors

Referring to the article published on pp. x–y of this issue

Micropapillary Variant Bladder Cancer: A Bad Apple or a New Fruit?

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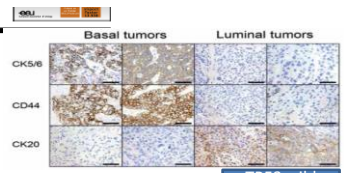
The outlook for aggressive bladder cancer remains poor, despite improvements in the treatment of many other malignancies [1]. One of the (many) reasons for a lack of improvement in outcomes has been our limited understanding of the biology of urothelial cell carcinoma (UCC). For example, until recently the presence and importance of histologic variants of UCC were not recognized. Many variants are refractory to standard treatments used in UCC, so this lack of recognition prevented advances in care. A common variant is micropapillary UCC (MPUC). MPUC appear as discrete nests of papillary tumors in otherwise empty urothelial space [2]. This pathologic subtype was first recognized in the mid-1990s and is characterized by an aggressive clinical phenotype with chemoresistance. This makes MPUC challenging to manage in both localized and advanced settings [3] and can double the all-cause mortality compared to other histologic UCC subtypes [4].

However, help may be coming soon. Technological advances in UCC are accelerating such that our understanding is catching up with that for other malignancies. For example, we now know that there are distinct molecular subclasses of invasive UCC and that these may have differing treatment sensitivities and prognoses [5,6]. Clinical trials that stratify care by subtype are eagerly awaited. We also know that UCC is one of the most stimulating tumors to the immune system [7], so new immunomodulating therapies appear extremely promising [8].

In this issue of *European Urology*, Guo et al [2] add to our knowledge with the first in-depth genetic analysis of MPUC. These authors, who have pioneered much of our understanding of MPUC and UCC, undertook global RNA expression profiling using microarrays on a largish MPUC cohort and matching nonvariant UCC. Their key finding is that MPUC appears to (mostly) belong to a subtype of UCC characterized by expression of luminal breast cancer markers (termed luminal UCC subtype) rather than being a discrete pathologic identity. This luminal subtype appears as a dominant trait, such that even UCC with small regions of micropapillary growth share this subtype. Luminal tumors may have wild-type p53 and can be resistant to chemotherapy, as seen within this cohort. In fact the authors suggest that MPUC may be subdivided (almost in half) into those with and without a wild-type p53 phenotype. The former prove especially resistant to treatment. In breast cancer, luminal-B tumors have poor prognosis despite the use of multimodal treatment regimens (including systemic anti-estrogens and chemotherapy). Current hopes are that inhibitors targeted against mTOR, PI3K, or IGFR-1 may work in these cancers.

The authors were also able to identify two individual hallmarks of MPUC that potentially characterize the disease: downregulation of miR-296 and activation of chromatin-remodeling complex RUVBL1 [1]. The former was detected through the upregulation of many miR-296 target mRNAs and has been implicated in chemotherapy and radiotherapy resistance [4]. The latter is a common oncogene in cancer that facilitates various downstream carcinogenic traits, such as metastases and cell growth [9]. These genetic hallmarks are important as they offer both a therapeutic axis with which to attack MPUC and an ability to improve the detection of MPUC using genetic screens. Critically,



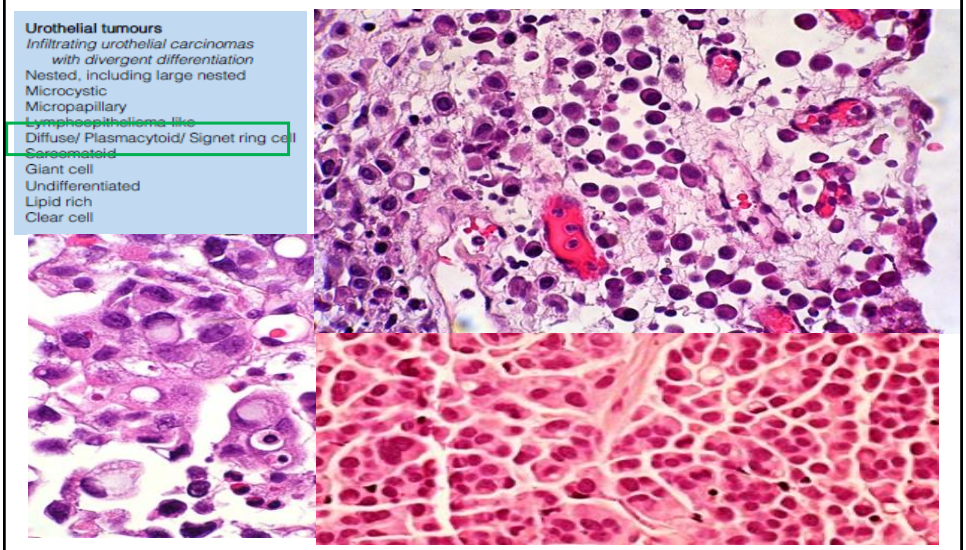
TP53 wild
Non-mutated

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 nuceoli
- Associated high grade Uca.
- Some cases diagnosed because metastases
- IHC: CkAE1/AE3, Ck 7, **CD138+**
- 70% pts died shortly after diagnosis

nature genetics

Frequent somatic *CDH1* loss-of-function mutations in plasmacytoid variant bladder cancer

Hikmat A Al-Ahmadie[1,11], Gopa Iyer[2,3,11], Byron H Lee[4,11], Sasinya N Scott[1], Rohit Mehra[5], Aditya Bagrodia[4], Emmet J Jordan[3], Sizhi Paul Gao[6], Ricardo Ramirez[6,7], Eugene K Cha[4], Neil B Desai[8], Emily C Zabor[9], Irina Ostrovnaya[9], Anuradha Gopalan[1], Ying-Bei Chen[1], Samson W Fine[1], Satish K Tickoo[1], Anupama Gandhi[1], Joseph Hreiki[1,0], Agnès Viale[10], Maria E Arcila[1,10], Guido Dalbagni[2,4], Jonathan E Rosenberg[2,3], Bernard H Bochner[2,4], Dean F Bajorin[2,3], Michael F Berger[1,10], Victor E Reuter[1,2], Barry S Taylor[6,9,10] & David B Solit[2,3,6,10]

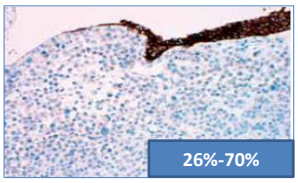
Plasmacytoid bladder cancer is an aggressive histologic variant with a high risk of disease-specific mortality. Using whole-exome and targeted sequencing, we find that truncating somatic alterations in the *CDH1* gene occur in 84% of plasmacytoid carcinomas and are specific to this histologic variant. Consistent with the aggressive clinical behavior of plasmacytoid carcinomas, which frequently recur locally, CRISPR/Cas9-mediated knockout of *CDH1* in bladder cancer cells enhanced cell migration.

Am J Clin Pathol. 2017 May 1;147(5):500-506. doi: 10.1093/ajcp/aqx029.

Plasmacytoid Urothelial Carcinoma of the Urinary Bladder: A Clinicopathologic and Immunohistochemical Analysis of 49 Cases.

Fox MD[1], Xiao L[1], Zhang M[1], Kamat AM[2], Siefker-Radtke A[3], Zhang L[4], Dinney CP[2], Czerniak B[1], Guo CC[1].

-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.



Dis Markers. 2016;2016:8463731. doi: 10.1155/2016/8463731. Epub 2016 Mar 10.

HER2 Protein Overexpression and Gene Amplification in Plasmacytoid Urothelial Carcinoma of the Urinary Bladder.

Kim B[1], Kim G[1], Song B[1], Lee C[1], Park JH[1], Moon KC[2].

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.

Plasmacytoid urothelial carcinoma, a chemosensitive cancer with poor prognosis, and peritoneal carcinomatosis.
Dayyani F, Czerniak BA, Sircar K, Munsell MF, Millikan RE, Dinney CP, Siefker-Radtke AO.
J Urol. 2013 May;189(5):1656-61.

- 31 patients, median age of 63.5 years, 83.3% were male.
- 20 TNM stage was cT3b-4aN0 or cT4b, N+ or M+ in 15.
- Median overall survival was 17.7 months.
- Despite pathological down staging in 80% of the patients who received neoadjuvant chemotherapy, relapses were common.
- There was no survival difference between patients treated with neoadjuvant chemotherapy or initial surgery.

CONCLUSIONS:

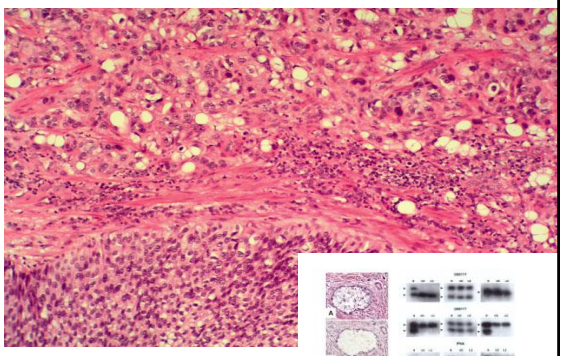
- Plasmacytoid urothelial carcinoma is an aggressive >>poor outcomes.
- Down staging >>neoadjuvant chemotherapy
- There are few long-term survivors.
- Strong predilection for recurrence along the peritoneal lining.

- HER2 Protein Overexpression and Gene Amplification in Plasmacytoid Urothelial Carcinoma of the Urinary Bladder.
- Kim B et al Dis Markers. 2016;2016:8463731.

- FISH HER2 gene amplification was positive in 3 cases,

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

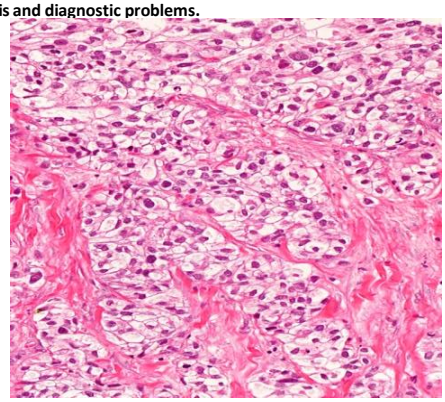


Lopez-Beltran, Montironi, Cheng, AJSP, 2010

Morphological Variants of BCA
Clear Cell Glycogenic Variant

Am J Surg Pathol. 2002 Feb;26(2):190-7.
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[1], Amin MB, Jimenez R, Young RH.

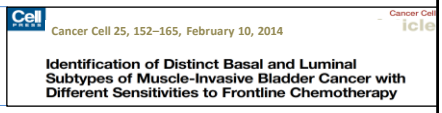
- <25 cases reported
- 22-83 y, Male/female
- Ca125 variably +; Ck20+ focal to diffuse in some cases;
- CK7+ diffuse, GATA3+,p63+



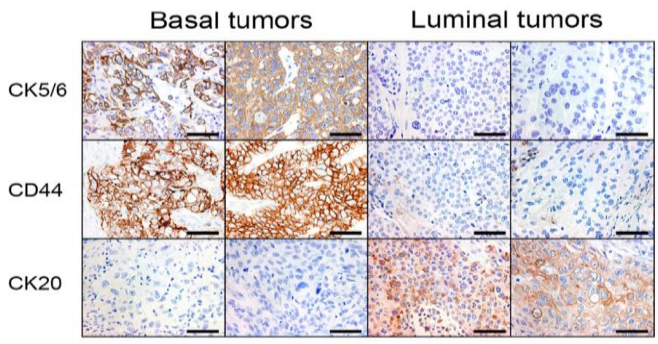
PATHOLOGIC SCENARIO	VARIANT TYPE	MOLECULAR ALTERATION
Urothelial carcinoma with divergent differentiation	With squamous cell differentiation	Most unrelated to HPV
	With glandular differentiation	Unknown
	With trophoblastic differentiation	Choriocarcinoma>> high copy number of isochromosome 12p
Urothelial carcinoma with deceptively benign features	Nested urothelial carcinoma (including large nested and small tubules)	TERT Promoter Mutation
	Microcystic urothelial carcinoma	TERT Promoter Mutation
Differential diagnosis with metastases to the bladder	Micropapillary urothelial carcinoma	Variable HER2-neu gene amplifications or mutations. TERT Promoter mutation.
	Diffuse/ plasmacytoid/signet ring cell urothelial carcinoma	CDH1 loss (mutation or methylation) in >80% of cases. E-Cadherin loss in >70% of cases. HER2 gene ampl/PI3K and TSC1 genes altered.
	Sarcomatoid urothelial carcinoma (carcinosarcoma)	Altered EMT protein expression by IHC-Loss Ecad-high N cad/TERTmut
	Giant cell urothelial carcinoma	Unknown
	Clear cell (glycogen-rich) urothelial carcinoma	Similar to conventional urothelial carcinoma
	Urothelial carcinoma, lipid-cell variant	Similar to conventional urothelial carcinoma
	Poorly differentiated tumors (undifferentiated NOS/ Oc-rich)	Unknown
Marked immune cell response	Lymphoepithelioma-like urothelial carcinoma	Unrelated to Epstein-Barr virus

Urothelial carcinoma variants and molecular subtypes

Molecular Taxonomy
UB-MIBC (TCGA)



- Luminal MIBCs
- Cluster I (luminal, differentiated) with *FGFR3* aberrations and *CDKN2A* deletions
- Cluster II (luminal, less differentiated, p53like)
- (Cluster II,p53like, luminal>>chemo-resistant)
- Basal MIBCs
- Cluster III (squamous)
- Cluster IV (EMT and immune infiltrated)



Luminal:
Foxa1
GATA3
Basal:
P63
HMWCK

Cancer Cell 25, 152–165, February 10, 2014

VARIANT TYPE	MOLECULAR SUBTYPE
With squamous cell differentiation	Basal
With glandular differentiation	Luminal
With trophoblastic differentiation	Unknown
Nested urothelial carcinoma (including large nested and small tubules)	Luminal
Microcystic urothelial carcinoma	Luminal
Micropapillary urothelial carcinoma	Luminal (30-50% of cases)
Diffuse/ plasmacytoid/signet ring cell urothelial carcinoma	Luminal
Sarcomatoid urothelial carcinoma (carcinosarcoma)	Basal
Giant cell urothelial carcinoma	Unknown
Clear cell (glycogen-rich) urothelial carcinoma	Luminal
Urothelial carcinoma, lipid-cell variant	Luminal
Poorly differentiated tumors (undifferentiated NOS/ Oc-rich)	Unknown
Lymphoepithelioma-like urothelial carcinoma	Luminal

Lopez-Beltran, Montironi et al 2017, Eur Urol Suppl 16:210-222

Table 2 – Variants of urothelial carcinoma and their potential clinical significance

Pathologic category	Variant type	Clinical scenario and differential diagnosis	Molecular alteration
Urothelial carcinoma with divergent differentiation	With squamous cell differentiation	Primary or secondary squamous cell carcinoma	Common basal molecular classification; most unrelated to HPV
	With glandular differentiation	Primary or secondary adenocarcinoma	Unknown
	With trophoblastic differentiation	Trophoblastic cells present in urothelial carcinoma. Choriocarcinoma either primary or secondary. β-HCG (serum/tissue) in 30% of high stage urothelial carcinoma	True choriocarcinoma either primary or secondary shows high copy number of isochromosome 12p
Urothelial carcinoma with deceptively benign features	Nested urothelial carcinoma (including large nested)	Von Brunn's hyperplasia, nephrogenic adenoma	TERT promoter mutation
	Microcystic urothelial carcinoma	Cystitis cystica, cystitis glandularis, adenocarcinoma	TERT promoter mutation
Differential diagnosis with metastases to the bladder	Micropapillary urothelial carcinoma	Serous carcinoma of the ovary; micropapillary carcinomas from other sites; micropapillary morphology in carcinoma in situ or in NMIBC carcinoma seems less aggressive than invasive micropapillary carcinoma	Variable HER2-neu (*ERBB2*) gene amplifications or mutations. Basal molecular classification in 50% of cases. TERT promoter mutation. Luminal genotype.
	Plasmacytoid/signet ring cell/ diffuse urothelial carcinoma	Plasmacytoma; lymphoma; metastases from adenocarcinoma of stomach (poorly cohesive/diffuse); plasmacytoid morphology in carcinoma in situ or in NMIBC carcinoma seems less aggressive than invasive plasmacytoid carcinoma	CDH1 loss (mutation or methylation) in >80% of cases. E-cadherin loss in >70% of cases. Some with *HER2* gene amplification and alterations in genes such as *PI3K* and *TSC1*.
	Sarcomatoid urothelial carcinoma (carcinosarcoma)	Inflammatory myofibroblastic tumor (inflammatory pseudotumor); metastatic sarcomatoid carcinoma; sarcoma either primary or metastatic	Altered EMT protein expression by immunohistochemistry
	Giant cell urothelial carcinoma	Highly bizarre pleomorphic tumor giant cells similar to giant cell carcinoma of lung	Unknown
	Clear cell (glycogen-rich) urothelial carcinoma	Clear cell carcinomas from kidney or gynecologic organs; other	Similar to conventional urothelial carcinoma
	Urothelial carcinoma, lipid-cell variant	Liposarcoma; carcinosarcoma (heterologous sarcomatoid carcinoma)	Similar to conventional urothelial carcinoma
	Poorly differentiated tumors (undifferentiated carcinoma NOS, osteoclast-rich undifferentiated carcinoma, other)	Large cell carcinoma of lung; giant cell tumor of bone	Unknown
Marked immune cell response	Lymphoepithelioma-like urothelial carcinoma	Metastases from other sites; may be missed in small biopsies due to marked inflammatory background	Mostly unrelated to Epstein-Barr virus

b-HCG = beta-human chorionic gonadotropin; HPV = human papilloma virus; NMIBC = Nonmuscle invasive bladder cancer; NOS = not otherwise significant.

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 !