UAB MEDICINE

Knowledge that will change your world

WHO 2022 Update on the Classifications of Urinary Tract Neoplasms

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WHO 2022 Update on the Classifications of Urinary Tract Neoplasms

I have the following financial relationships to disclose:

TERT Promoter Mutations in Urothelial Neoplasia
Patents: (US201660208340A1) (PCT/US2014/051808)

UroSEEK; **CancerSEEK; PapSEEK**

- Methods and Materials for Assessing and Treating Cancer
  Patents: (US16/250,703) (PCT/US2018/045669)
- Financial Interest in "**Thrive Early Detection Corp" and "Exact Sciences Inc"**

Genentech Advisory Pathology Board

I will not discuss off label use and/or investigational use in my presentation

WHO Classification of the Urinary and Male Genital Tumours

5th edition series

- WHO *5th edition series* **structural reorganization**
- Refinements of **terminology** and **classification**
- Precursor lesions **(Dysplasia, UPUMP)**
- **Grading / Staging/ Urine Cytology**
- **Intrinsic Molecular Subtypes** of UC

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WHO Classification of the Urinary and Male Genital Tumours
4th edition series

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 neoplasms	
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 carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Well-differentiated neuroendocrine tumour	8240/3
Paraganglioma	8693/1
Melanocytic tumours	
Malignant melanoma	8720/3
Naevus	8720/0
Melanosis	
Mesenchymal tumours	
Rhabdomyosarcoma	8900/3
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Inflammatory myofibroblastic tumour	8825/1
Perivascular epithelioid cell tumour	
Benign	8714/0
Malignant	8714/3
Solitary fibrous tumour	8815/1
Leiomyoma	8890/0
Haemangioma	9120/0
Granular cell tumour	9580/0
Neurofibroma	9540/0
Urothelial tract haematopoietic and lymphoid tumours	
Miscellaneous tumours	
Carcinoma of Skene, Cowper, and Littre glands	8140/3
Metastatic tumours and tumours extending from other organs	
Epithelial tumours of the upper urinary tract	
Tumours arising in a bladder diverticulum	
Urothelial tumours of the urethra	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [917A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification [756A], taking into account changes in our understanding of these lesions.

WHO Classification of the Urinary and Male Genital Tumours
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Urothelial papilloma
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Invasive urothelial carcinoma
Squamous cell neoplasms
Urothelial squamous cell papilloma
Verrucous carcinoma of the bladder
Pure urothelial squamous cell carcinoma
Glandular neoplasms
Adenomas
Villous adenoma
Adenocarcinomas
Adenocarcinoma NOS
Urachal and diverticular neoplasms
Urachal carcinoma
Diverticular carcinoma
Urethral neoplasms
Urethral accessory gland carcinomas
Littre gland carcinoma of the urethra
Skene gland carcinoma of the urethra
Cowper gland carcinoma of the urethra
Tumours of Mullerian type
Clear cell adenocarcinoma
Endometrioid carcinoma

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Terminology scheme across the WHO 5th edition:

- *The term **"subtype"** to replace **"variant"** for a distinct clinical or morphologic category within a **tumour type***
- *The term **"variant"** is reserved for **genomic rather than morphologic** alterations*

Subtypes of Urothelial Carcinoma are **morphologically distinct and have prognostic significance** (management implications)

WHO URO 4

Urothelial tumours

Infiltrating Urothelial Carcinoma

Histologic Variants

Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid/signet ring cell/diffuse
Sarcomatoid
Giant cell
Poorly differentiated
Lipid rich
Clear cell

WHO URO 5

Urothelial tumours

Invasive Urothelial Carcinoma

Histologic Subtypes of Urothelial Carcinoma

Nested
Large Nested
Tubular and Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid
Sarcomatoid
Giant cell
Poorly differentiated
Lipid rich
Clear cell (Glycogen Rich)

Urothelial Carcinoma with Divergent Differentiation

UC with Squamous Differentiation
UC with Glandular Differentiation
UC with Trophoblatic Differentiation
UC with Mullerian Differentiation (Clear Cell Adenocarcinoma)

WHO Classification of the Urinary and Male Genital Tumours
5th edition series

- A single Urothelial Carcinoma lesion can display admixture of conventional urothelial, **histologic subtypes**, and areas of **divergent differentiation**

- A listing and attempt to **quantify** the various components is required

Histologic Subtypes of Invasive Urothelial Carcinoma

Nested

Tubular and Microcystic

Large Nested

Histologic Subtypes of Invasive Urothelial Carcinoma
Nested

“Cancer Resembling Von Brunn Nests”

- *Talbert ML, Young RH. Am J Surg Pathol 1989;13:374*
  Carcinomas of the urinary bladder with deceptively benign-appearing foci: a report of three cases.

- *Murphy WM, Deana DG. Mod Pathol 1992;5:240-3*
  The nested variant of transitional cell carcinoma: a neoplasm resembling proliferation of Brunn’s nests.

Histologic Subtypes of Invasive Urothelial Carcinoma
Nested

- **RARE** less than 1% of invasive bladder carcinomas

Location

- Anywhere in the bladder
- **Rare in upper tract**

Cystoscopy

- Widely variable appearance: flat tumor, papillary tumor, submucosal **“bump”**
- Tumor size: 1-8 cm.

UC Nested Subtype
Prognosis

- Clinical course generally aggressive

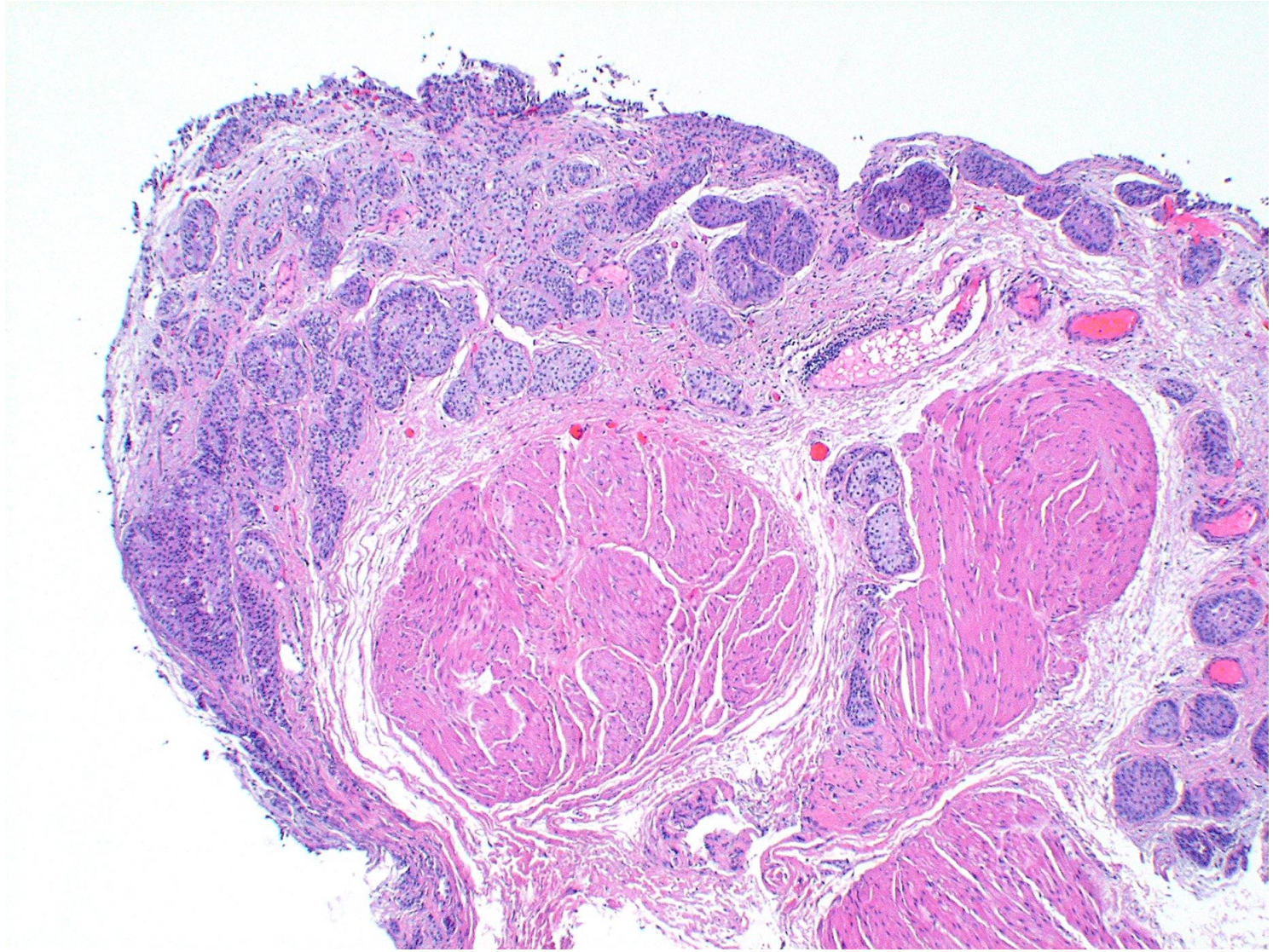
***Drew et al. Mod Pathol 1996*:**
- Review of 24 cases, 60% show aggressive behavior, **mortality rates similar to high grade UrCa**

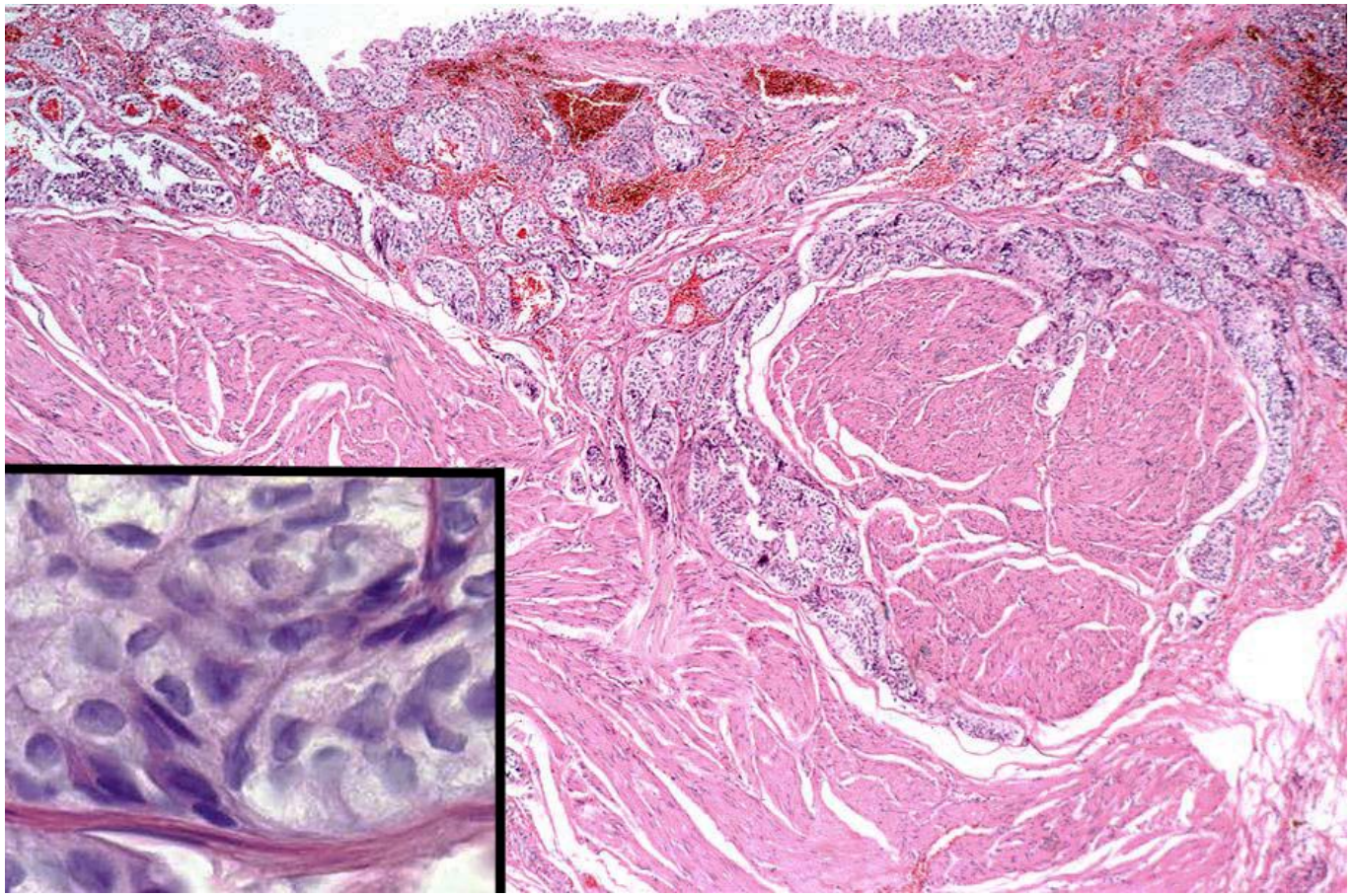
- Only 3/12 **(25%)** nested variant alive without disease (DFS) at 16 months follow-up

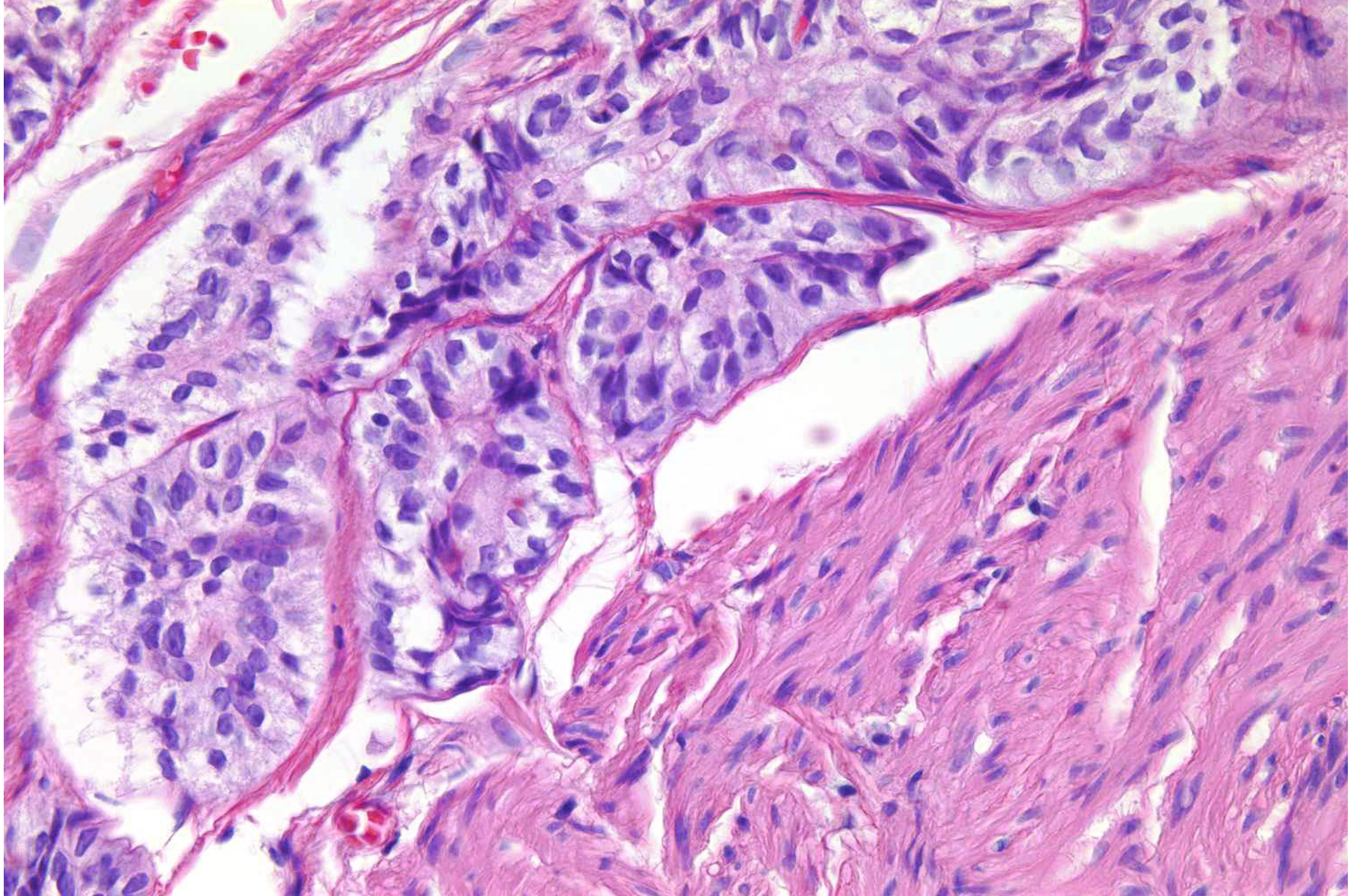
UC Nested Subtype

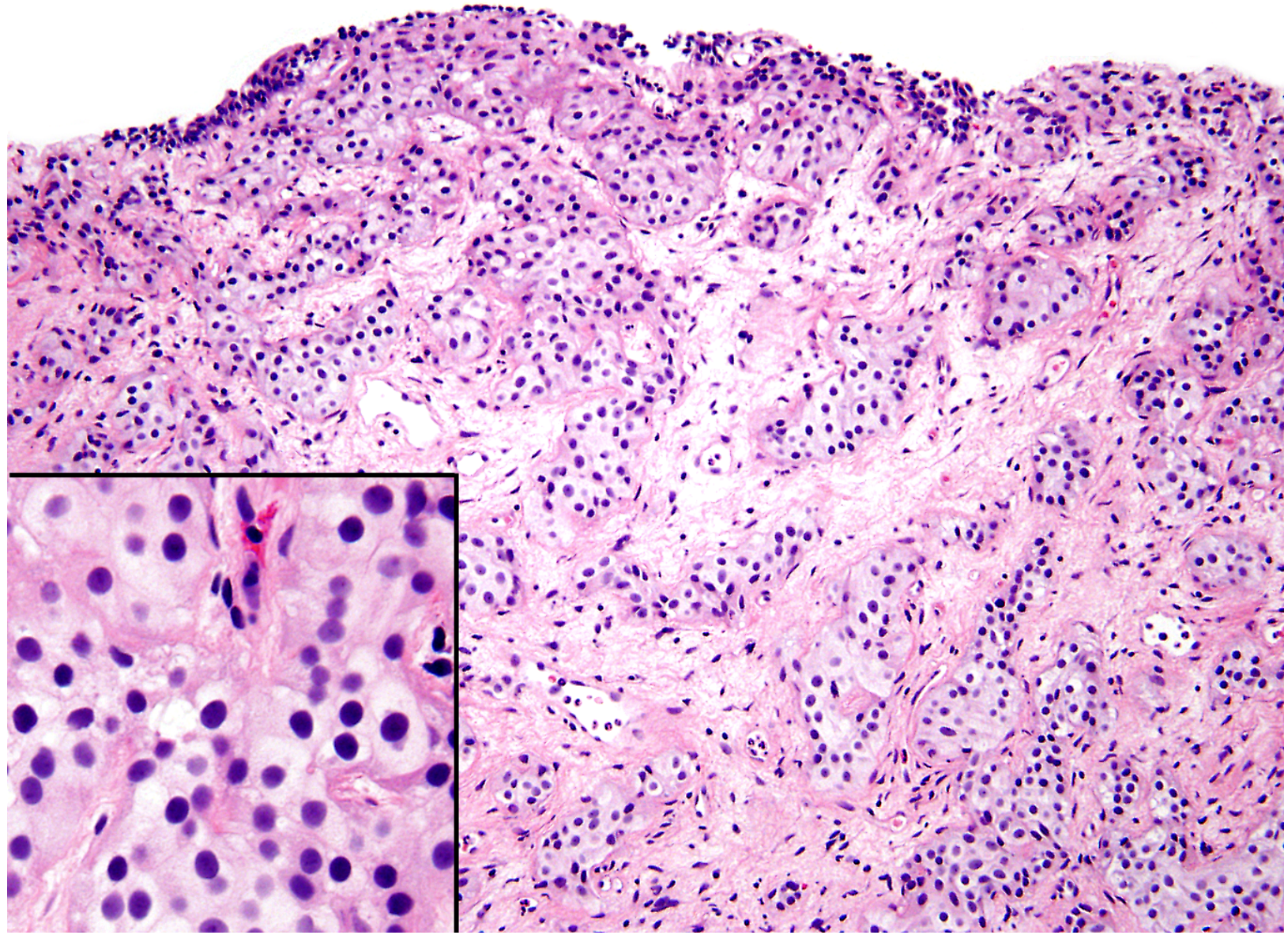
- **Small closely packed nests** of epithelial cells **irregularly infiltrating** lamina propria, at times anastomosing confluent nests
- Can be mixed with microcystic, tubular, and trabecular structures

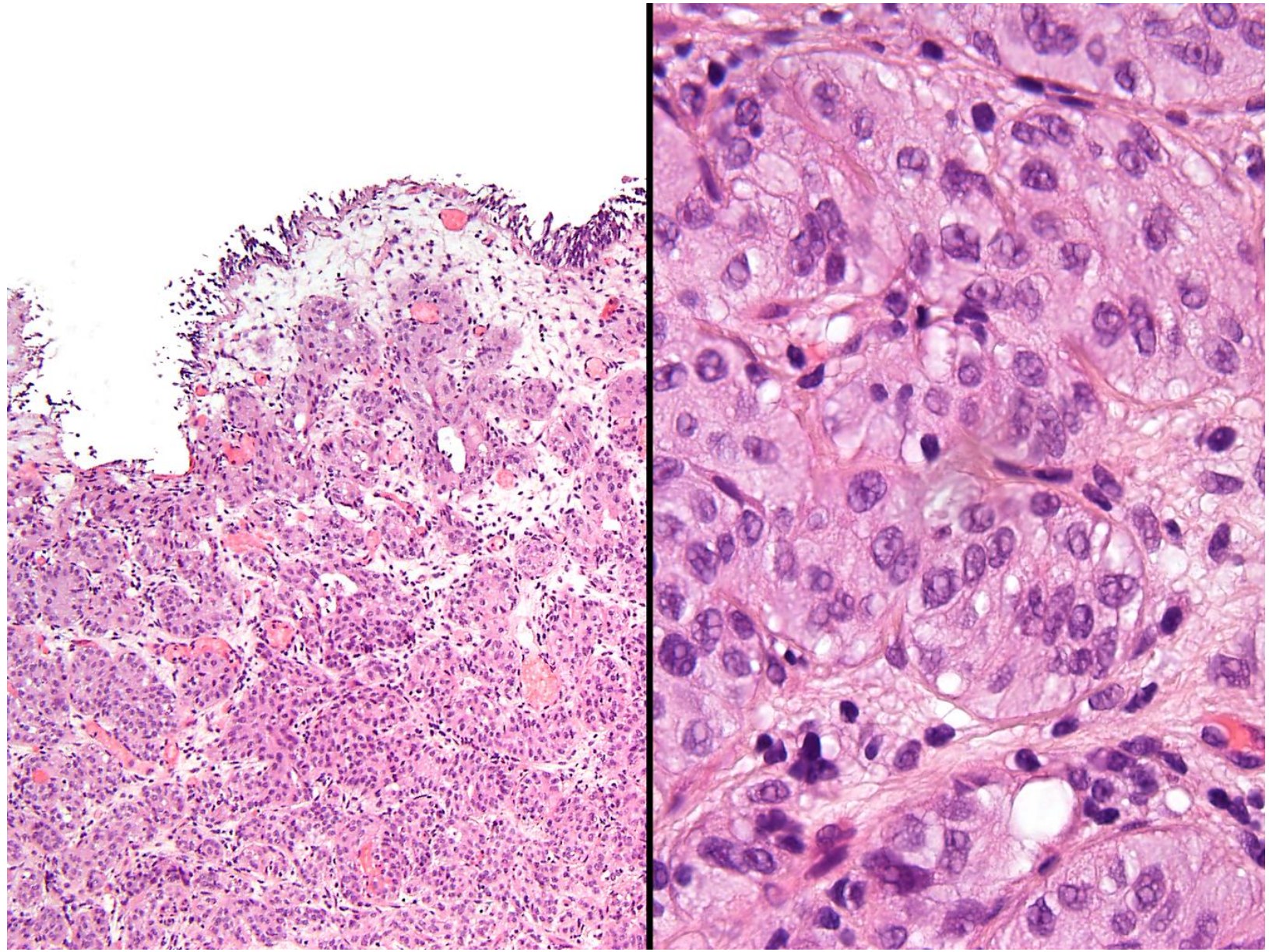
- **Histologically Difficult to Diagnose**
  - Very bland cells with only focal moderate atypia
  - Overlying urothelium may be normal
  - **Deep irregular infiltrative** pattern
  - **Identify muscularis propria invasion**

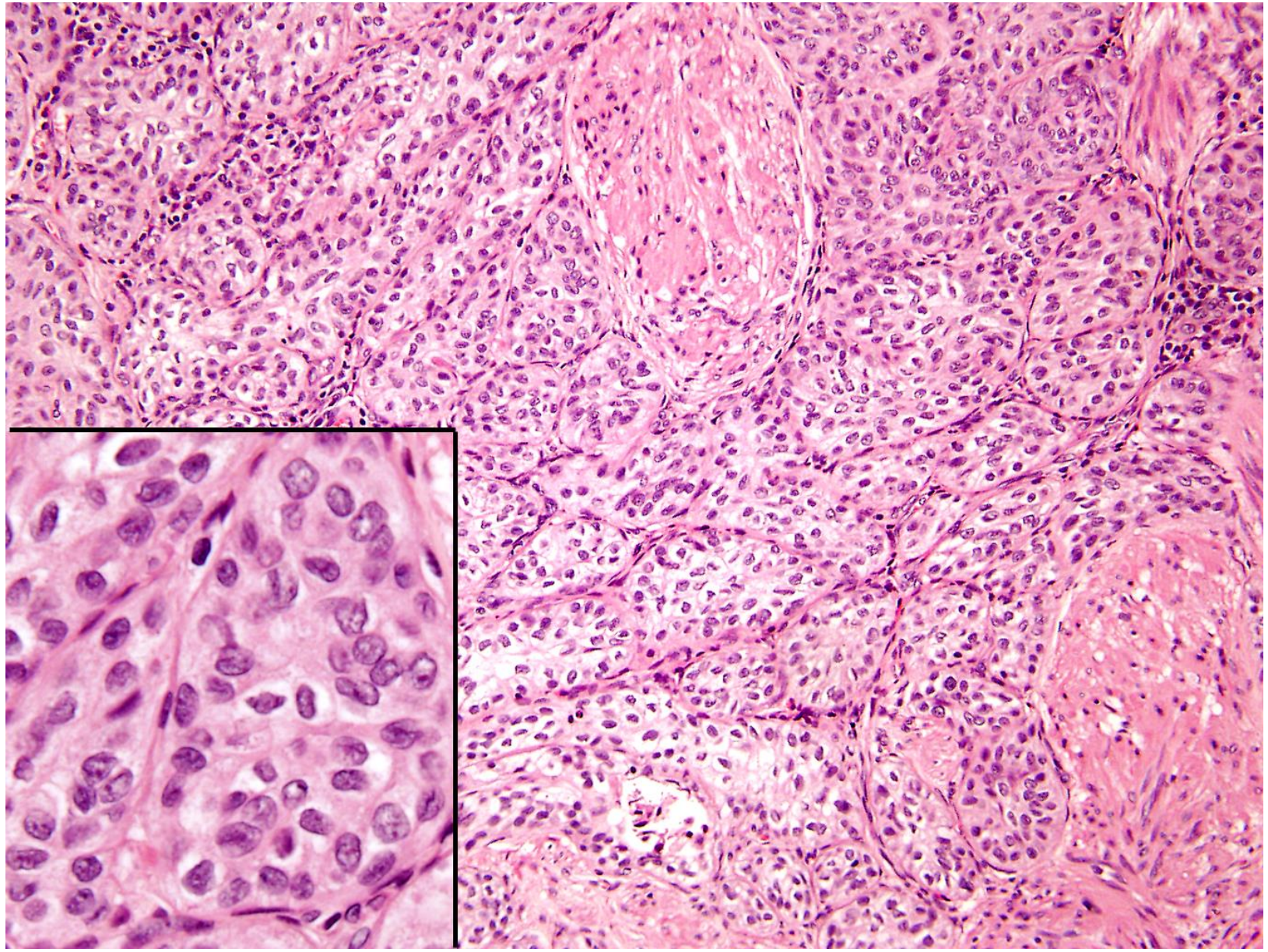


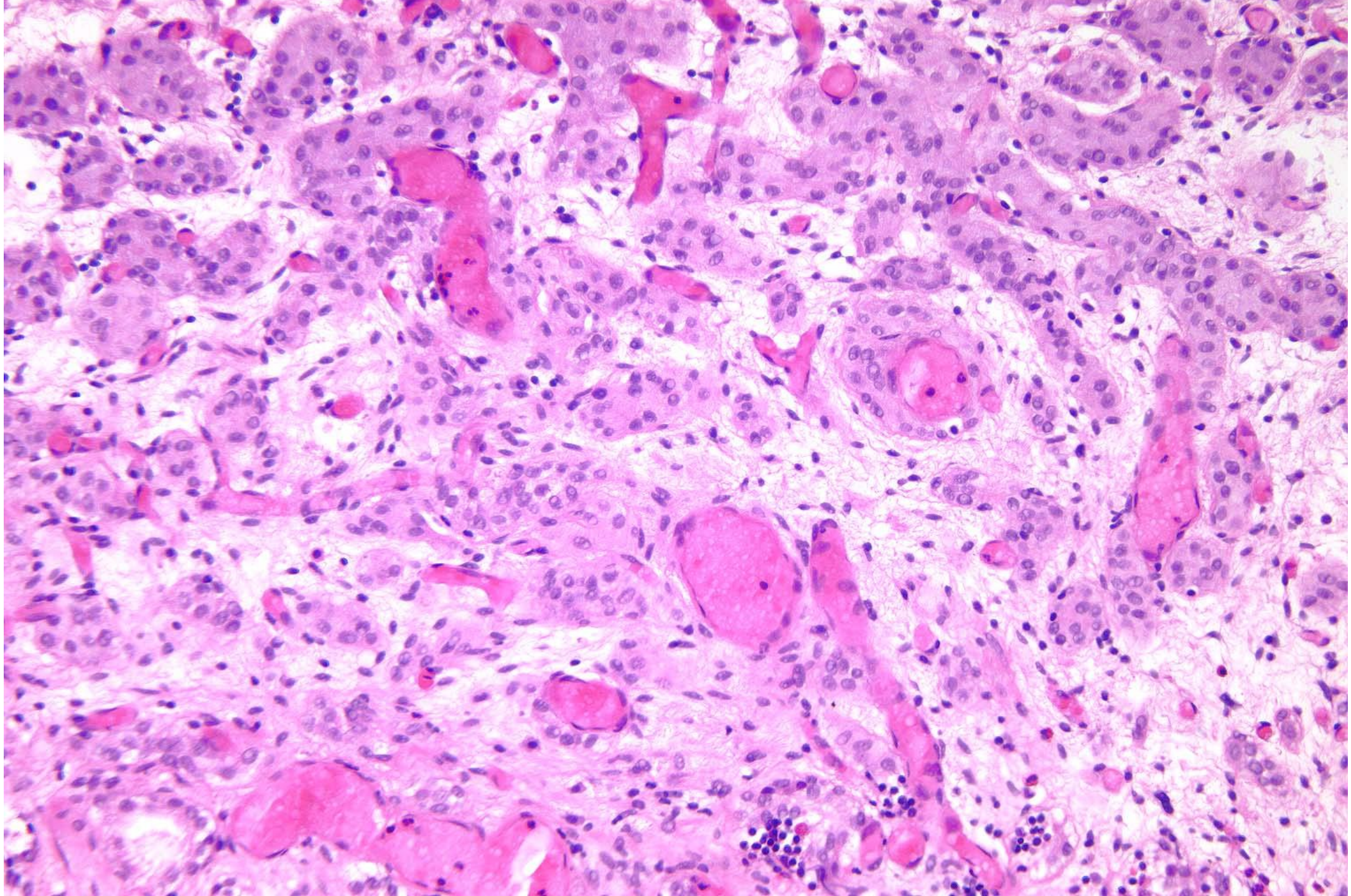




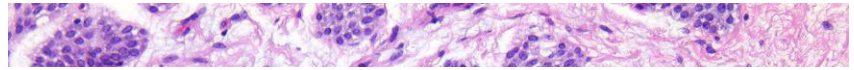


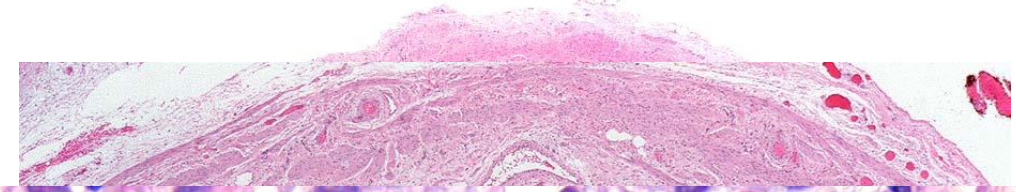


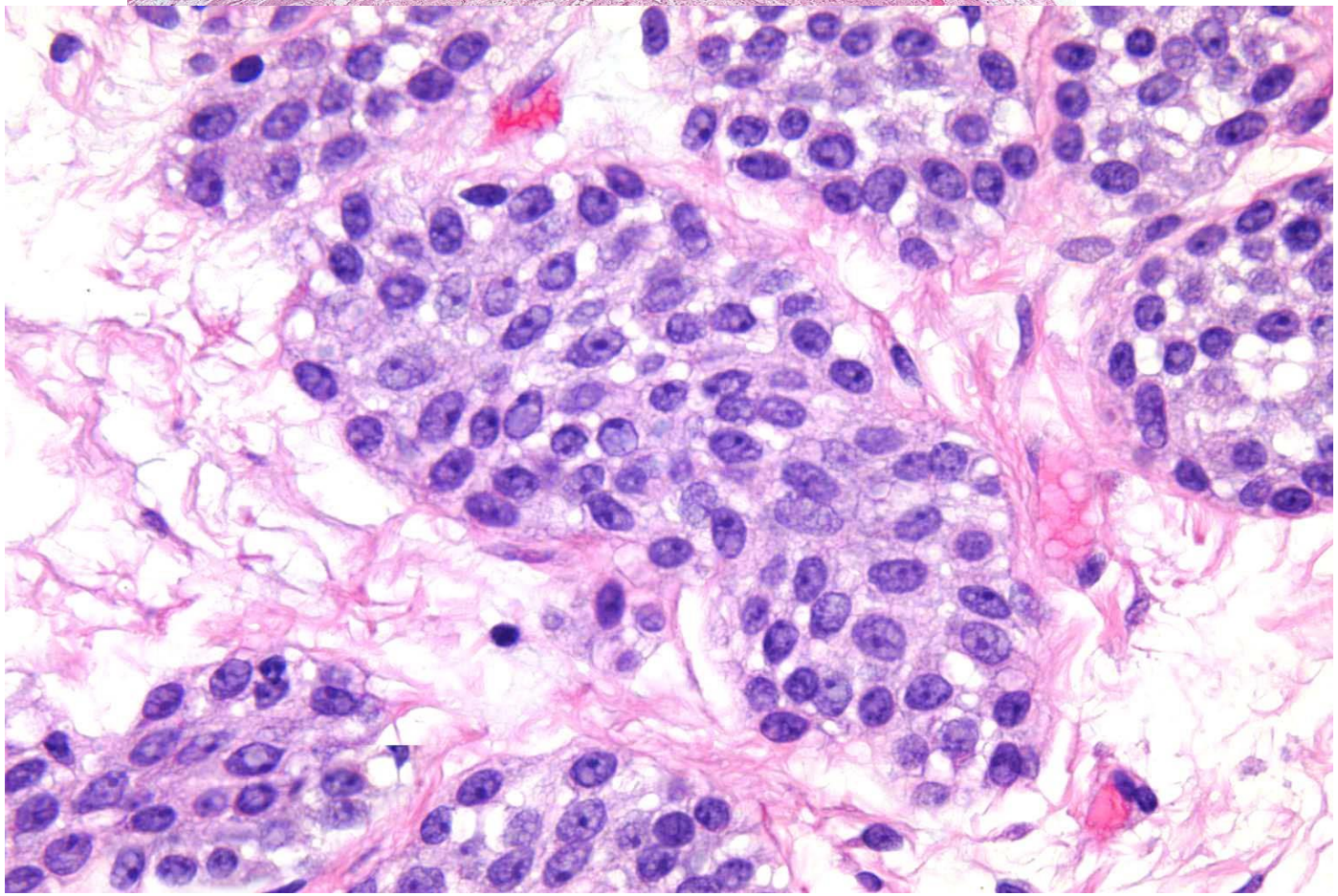




Urothelial Nested Architecture
DDX







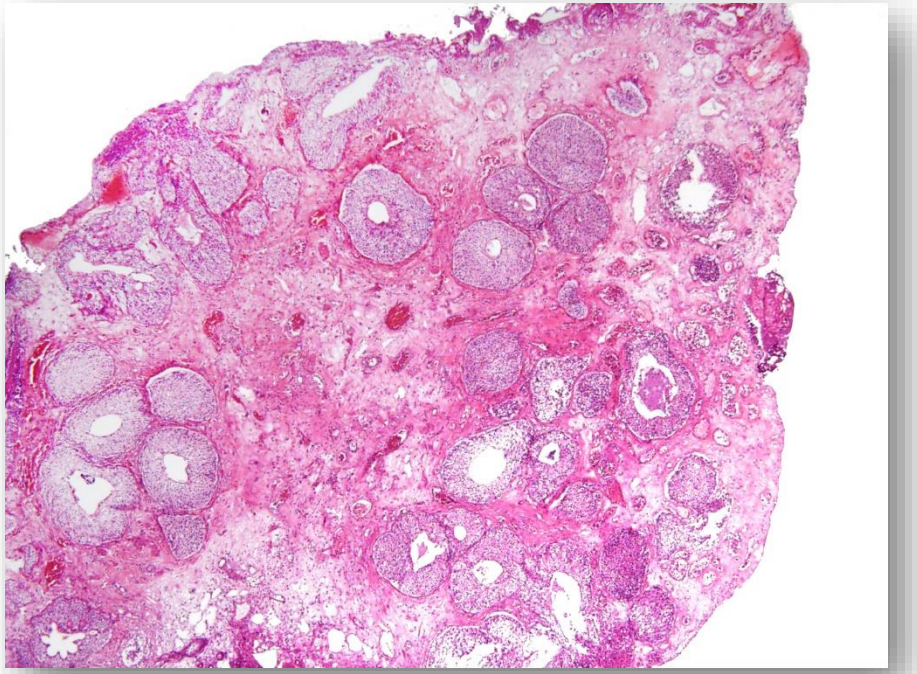
UC Nested Subtype

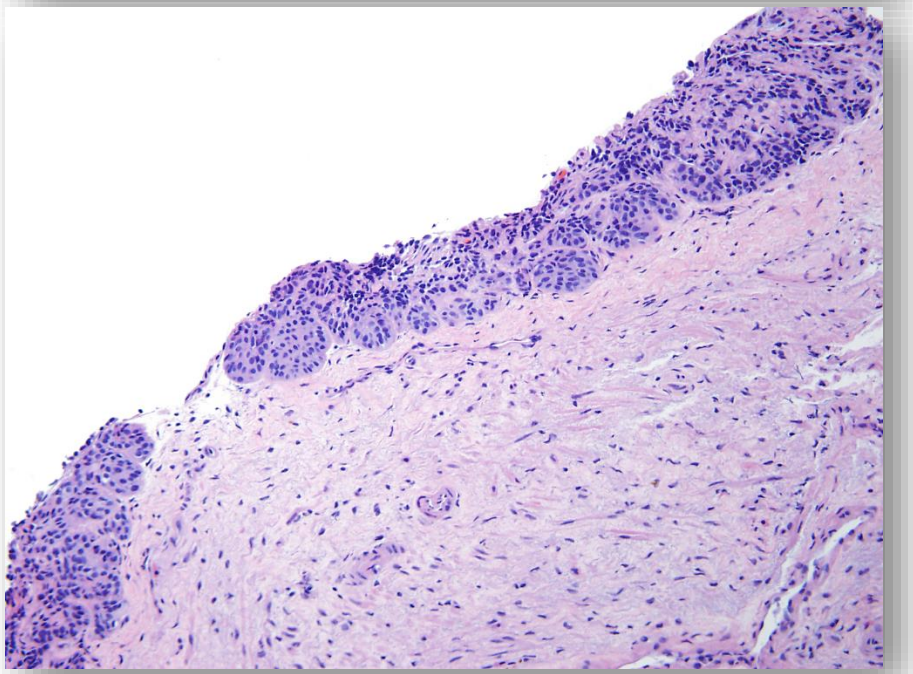
DDx

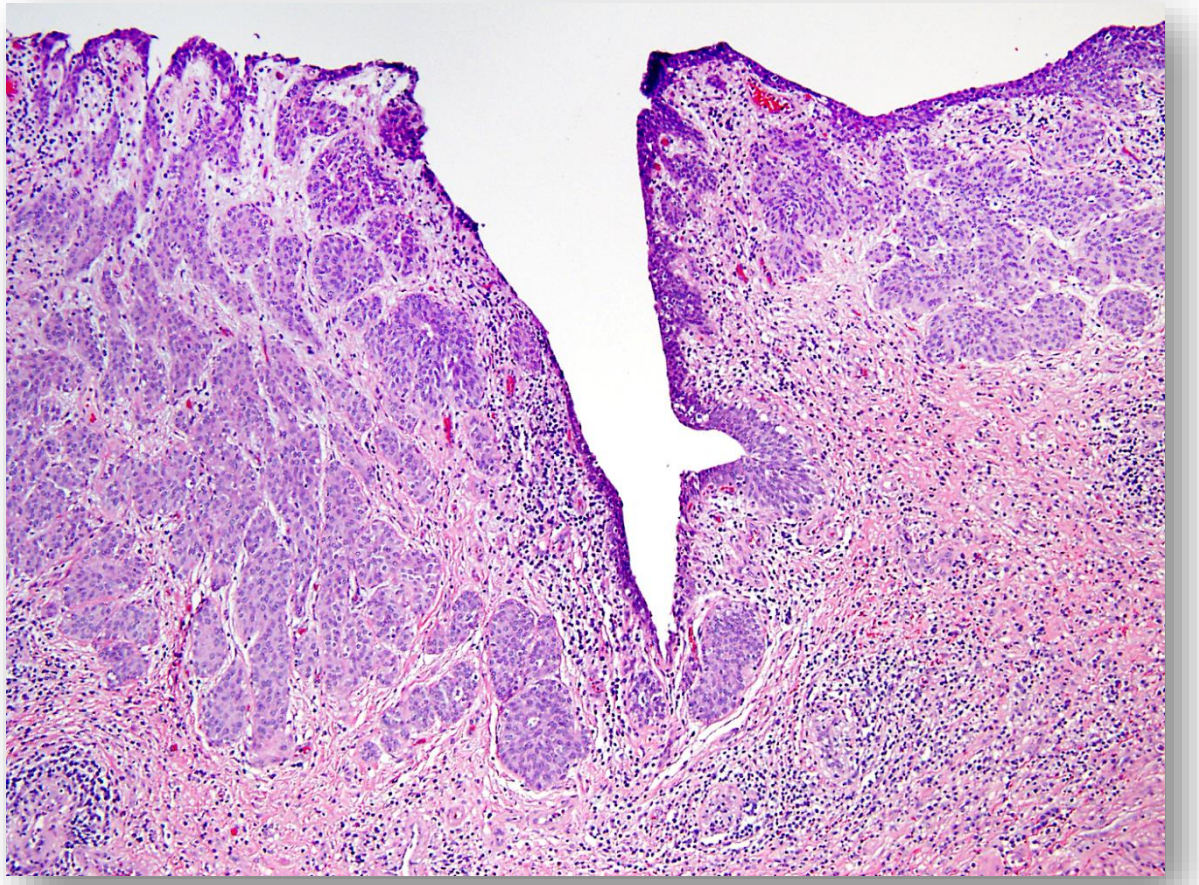
Proliferation of Von Brunn Nests

- Deep irregular infiltrative pattern
- Identify muscularis propria invasion

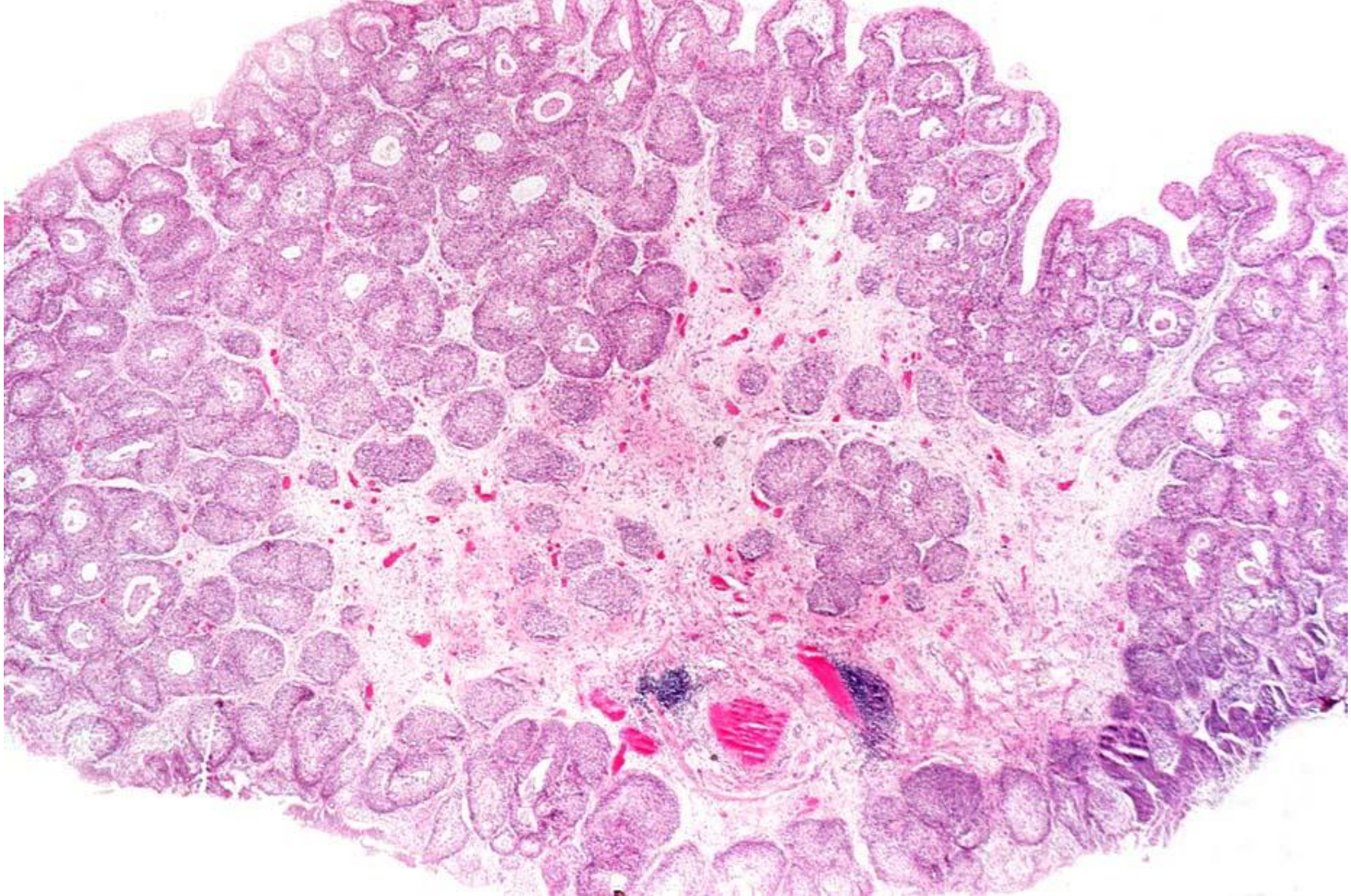
- *TERT* promoter mutation







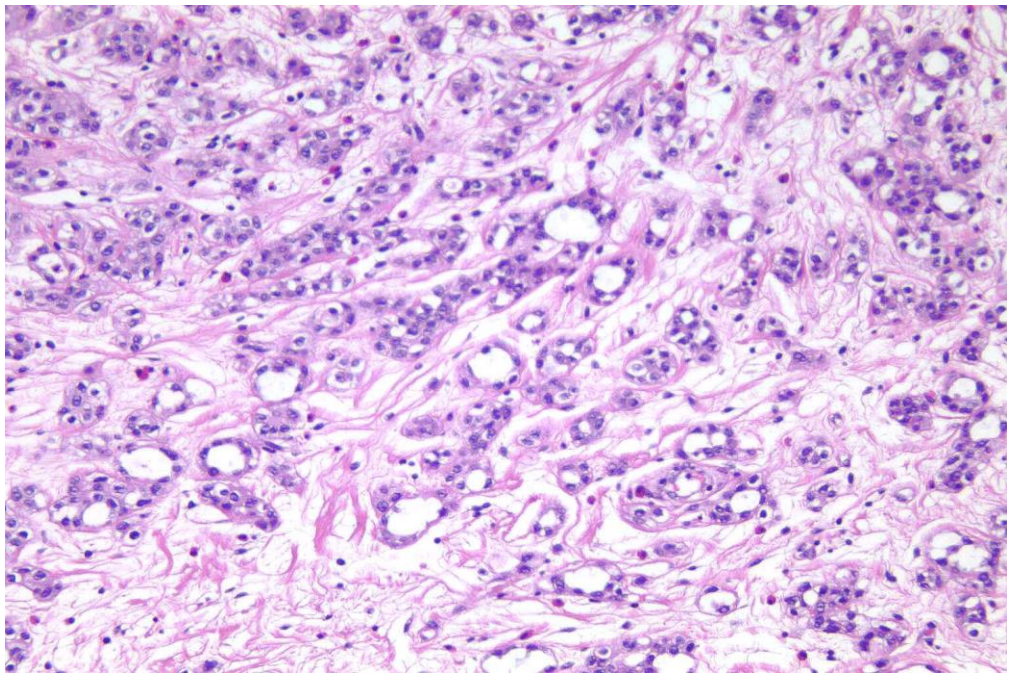
Urinary Bladder
Florid Proliferation of Von Brunn Nests



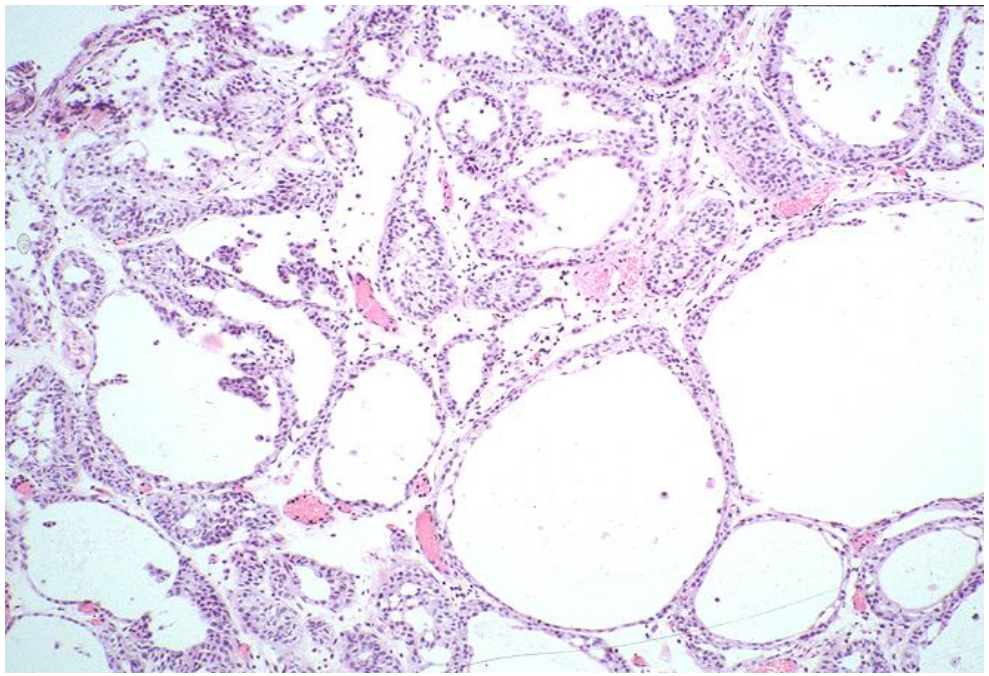
Urothelial Carcinoma
Tubular and Microcystic Subtypes

- **Closely related** to their nested counterpart
- **Bland cells** line small tubular or microcystic structures
- **DDx Cystitis Cystica**
  Like nested subtype, **deep irregular infiltration** & involvement of **muscularis propria** are clues
- Urothelial markers typically positive (GATA3 or p63)

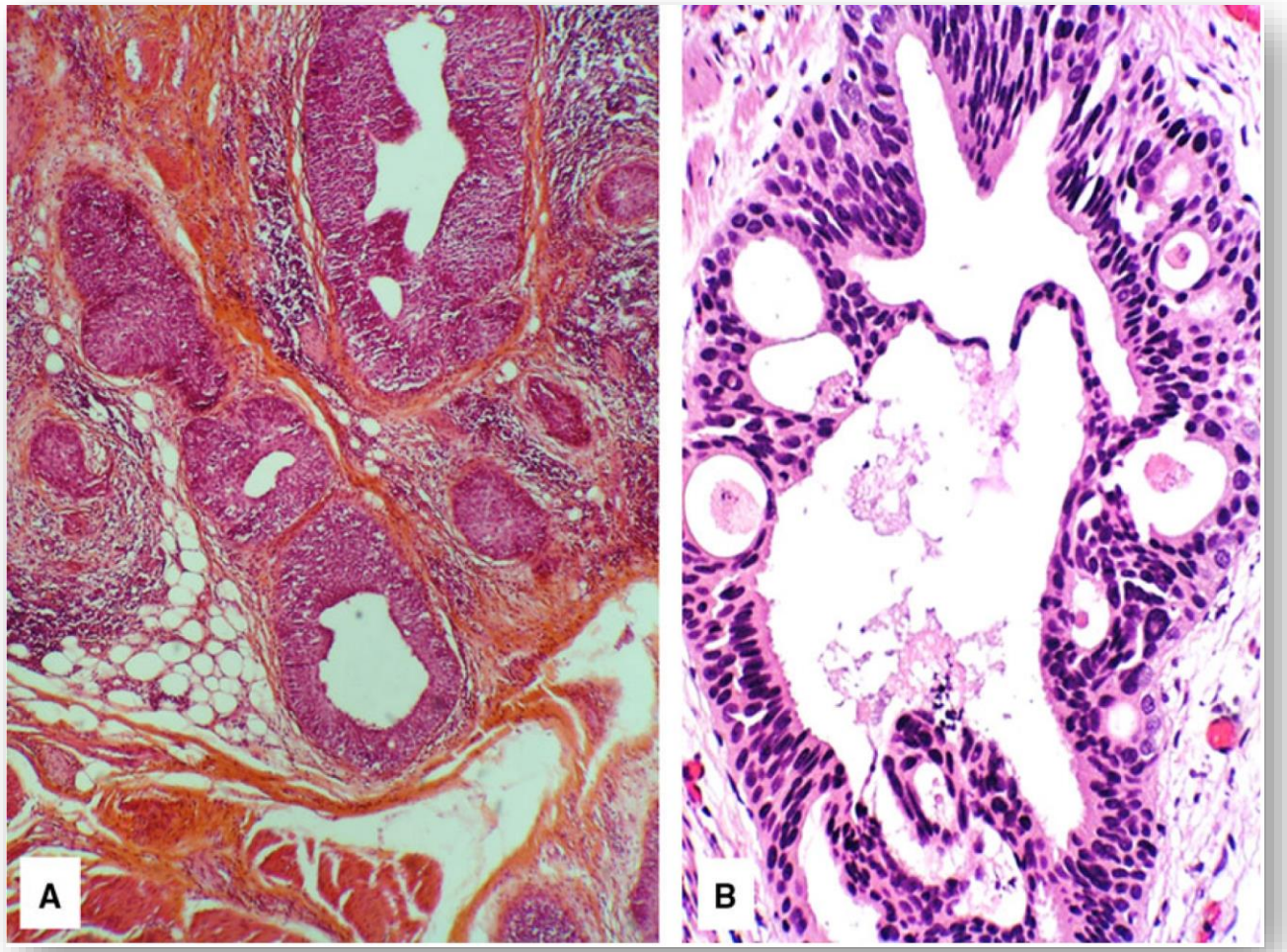
Paner GP…Amin MB: Hum Pathol 2014
Mai KT et al: Pathology International 2014
Lopez Beltran et al.: Histopathology. 2019



Tubular Subtype



Microcystic Subtype



Microcystic Subtype

Lopez Beltran et al.: Histopathology. 2019

Large Nested Variant of Urothelial Carcinoma: 23 Cases Mimicking von Brunn Nests and Inverted Growth Pattern of Noninvasive Papillary Urothelial Carcinoma

Roni Cox, MD and Jonathan I. Epstein, MD*† ‡* Am J Surg Pathol 2011

Histopathology

Histopathology 2017, 71, 703–710. DOI: 10.1111/his.13280

Large nested variant of urothelial carcinoma: a clinicopathological study of 36 cases

Eva Compérat,[1] Jesse K McKenney,[2] Arndt Hartmann,[3] Ondrej Hes,[4] Simone Bertz,[3] Justine Varinot[1] & Fadi Brimo[5]

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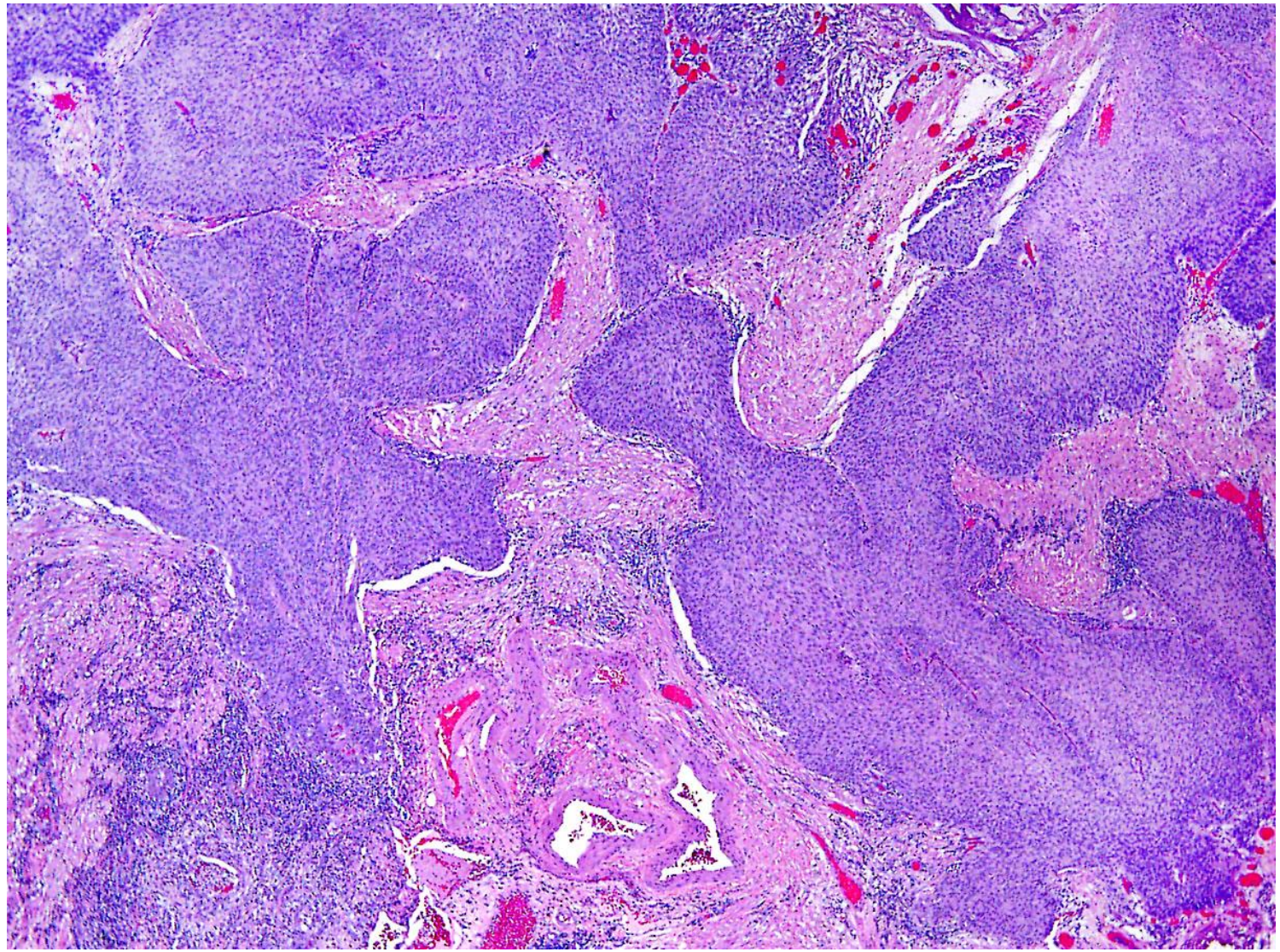
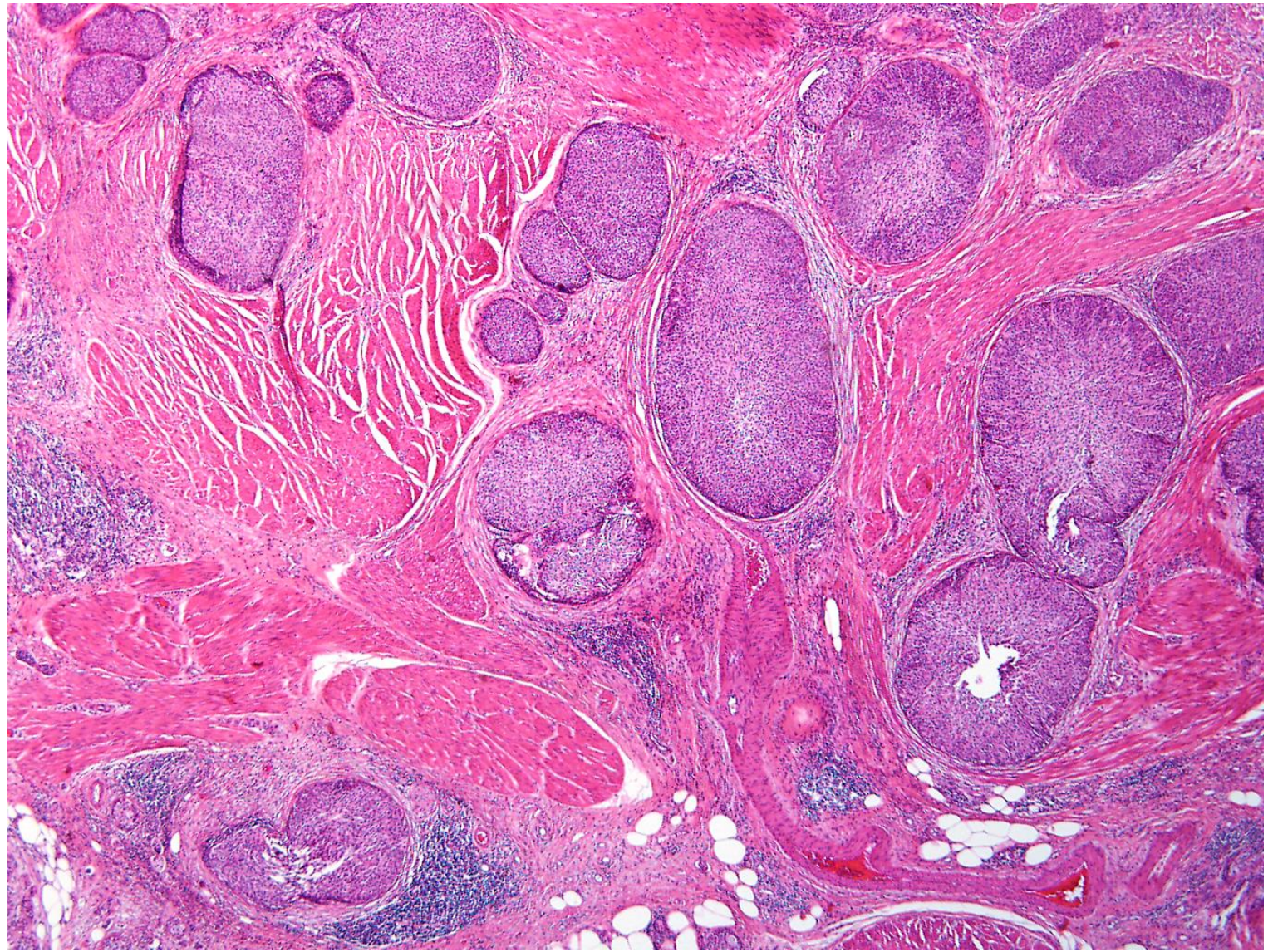
- **Bland** cytological appearance
- **Deceptive pattern of invasion (DDX Inverted)**

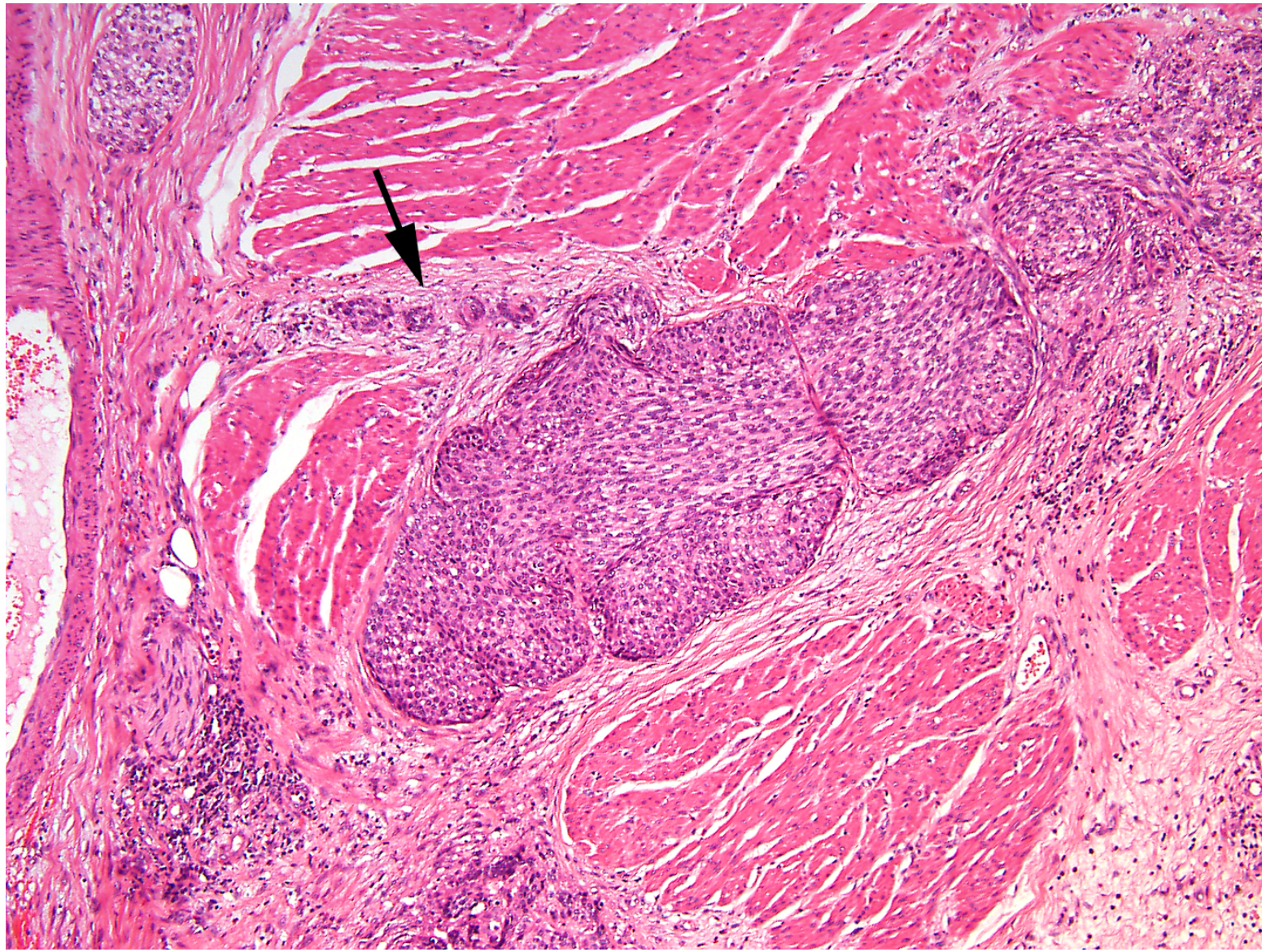
- **58%** extravesical disease (≥pT3 and/or ≥pN1); Mixed more advanced compared to pure large nested?

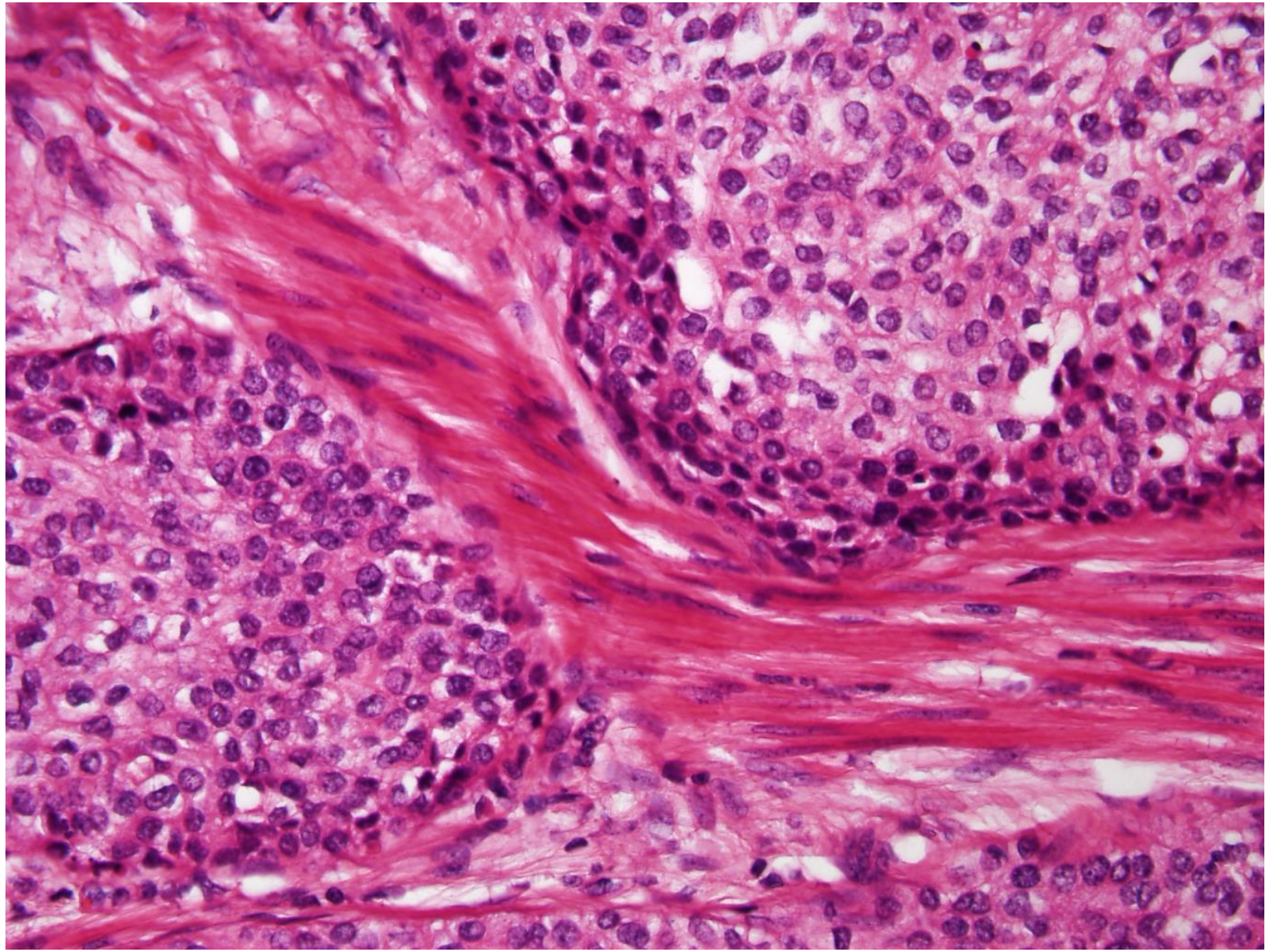
- **21%** recurrence/metastasis
- **24%** died of disease (mean 21.7 months)

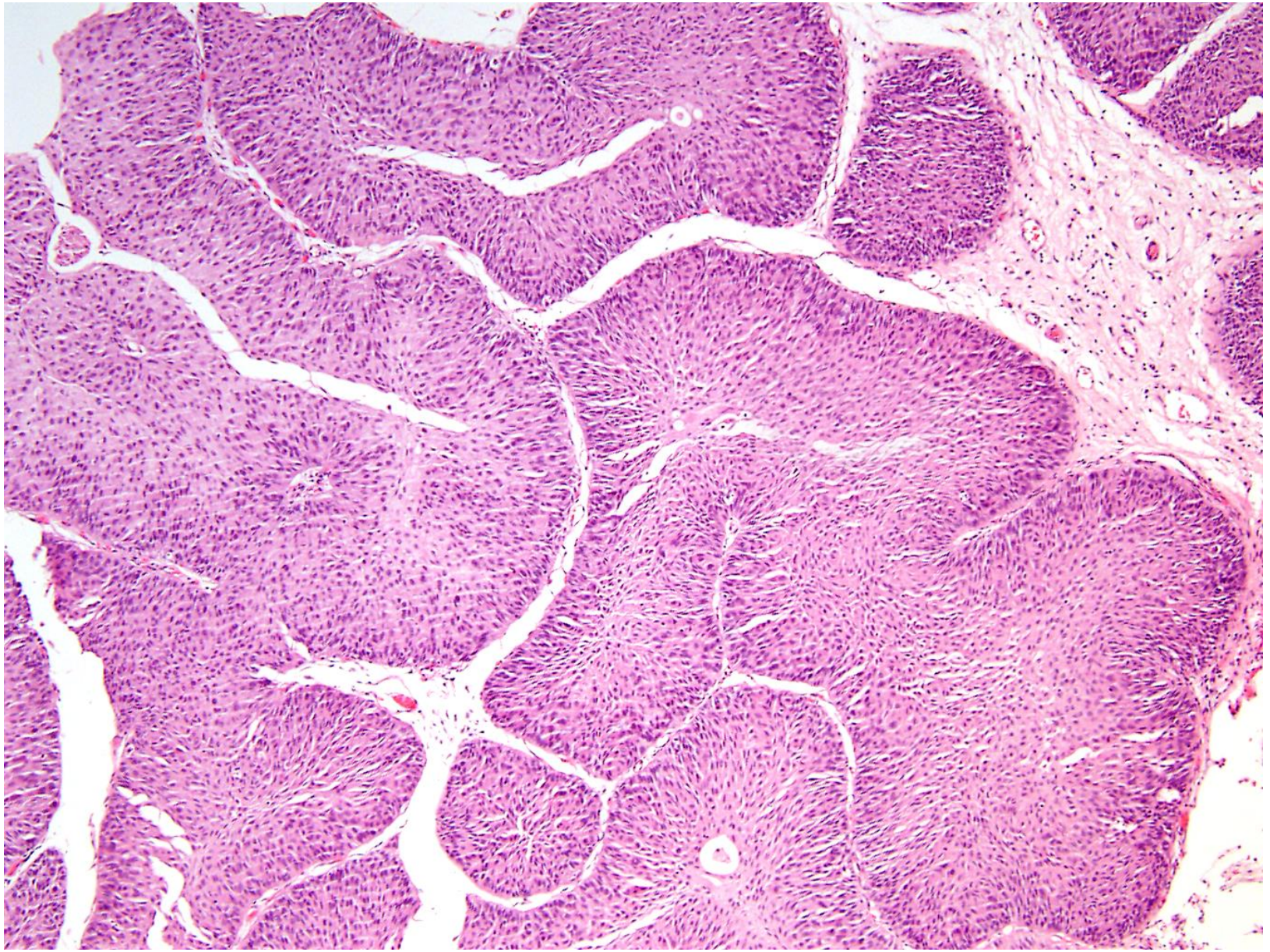
- IHC same as conventional & nested UrCa











Non-invasive LG papillary urothelial carcinoma with **inverted pattern**

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- **Grading / Staging/ Urine Cytology**
- Advances in **molecular pathways** (targets of therapy)

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Urothelial dysplasia	

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Urothelial carcinoma in situ
Invasive Urothelial Neoplasia
Invasive urothelial carcinoma

“Flat” Precursor Lesions

Urothelial Dysplasia

Should “Urothelial Dysplasia” remain an entity ?

- Term is greatly debated
- **Definition** of dysplasia in urinary tract is **not a synonym of intraepithelial neoplasia** in other organs (**SIL**/**PeIN** etc)

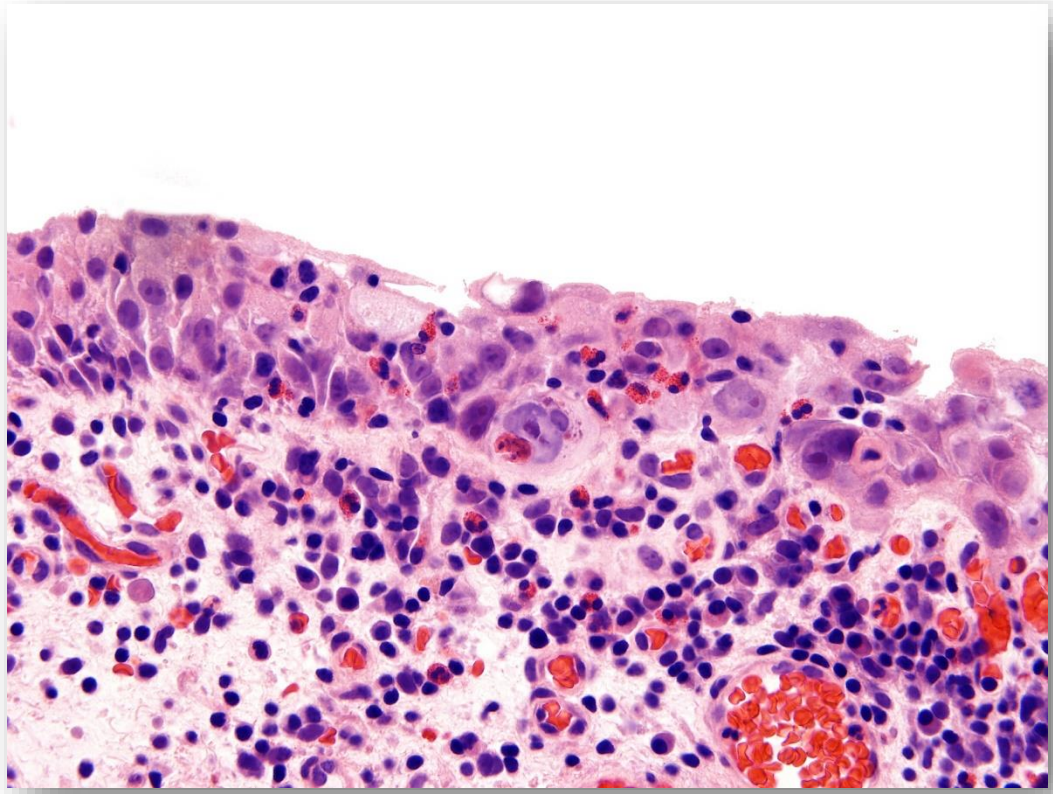
  “*Lesion that encompasses changes that are thought to be pre-neoplastic in nature, but cytologically fall short of the diagnosis of carcinoma in situ*”

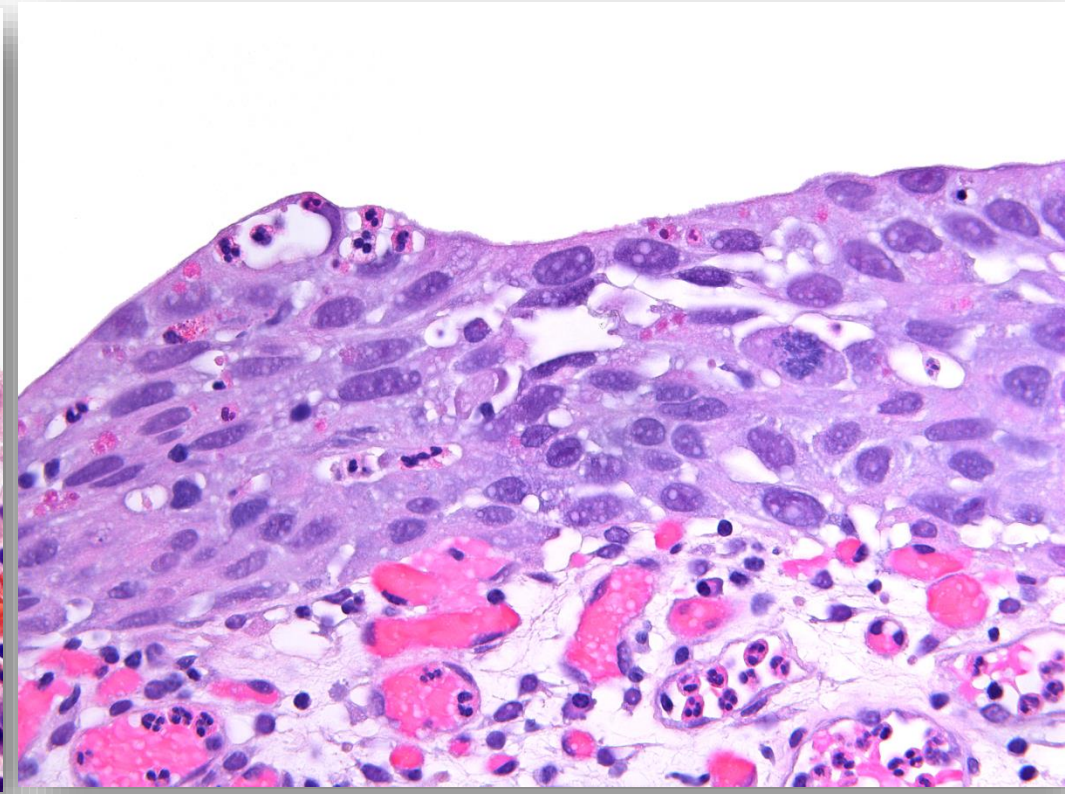
Urothelial CIS

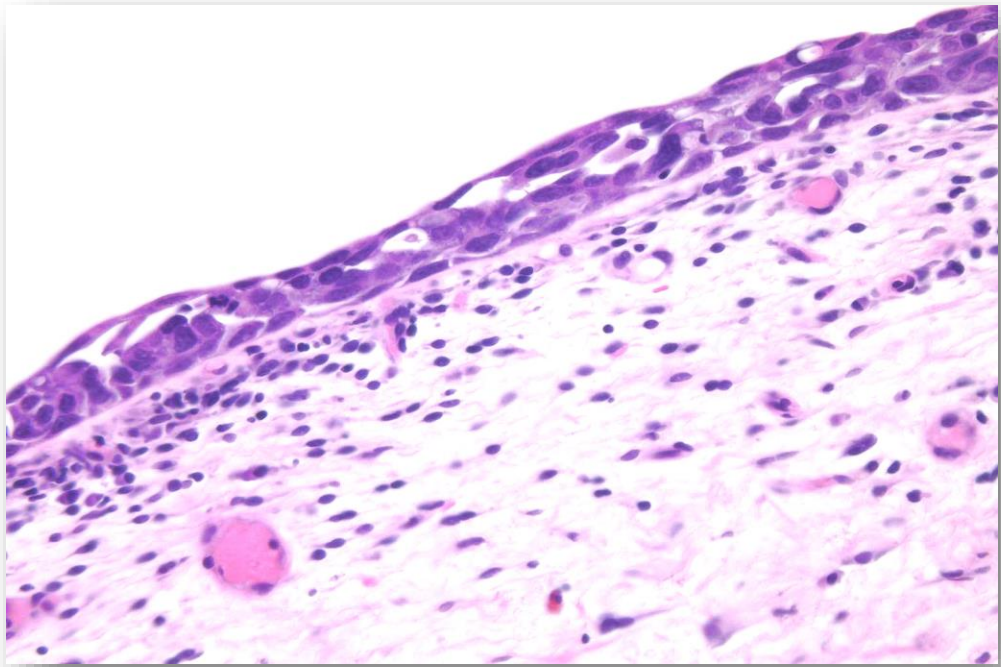
- Presence of cytologically malignant cells **regardless of quantity**
  - No need to be full **thickness**
  - **Pagetoid** cells
  - **Spectrum** of atypia and cell size
  - **Umbrella** cell layer may still be present

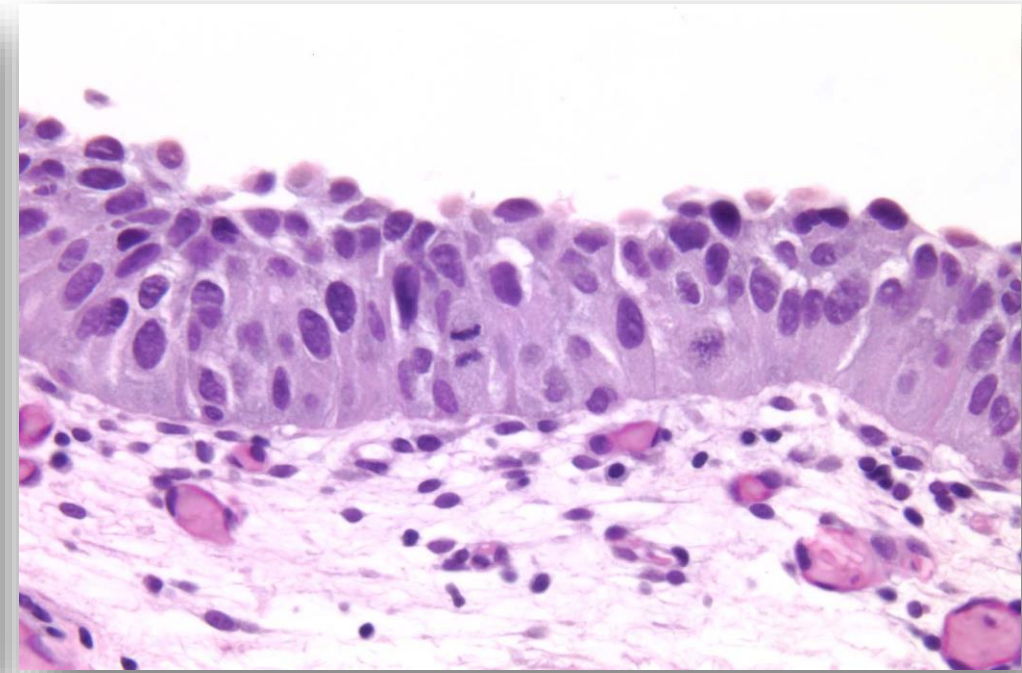
- CIS cells **5x size** of stromal lymphocytes, compared to normal cells which are 2x size of lymphocytes
- Enlarged & hyperchromatic **ON 10X OBJECTIVE**

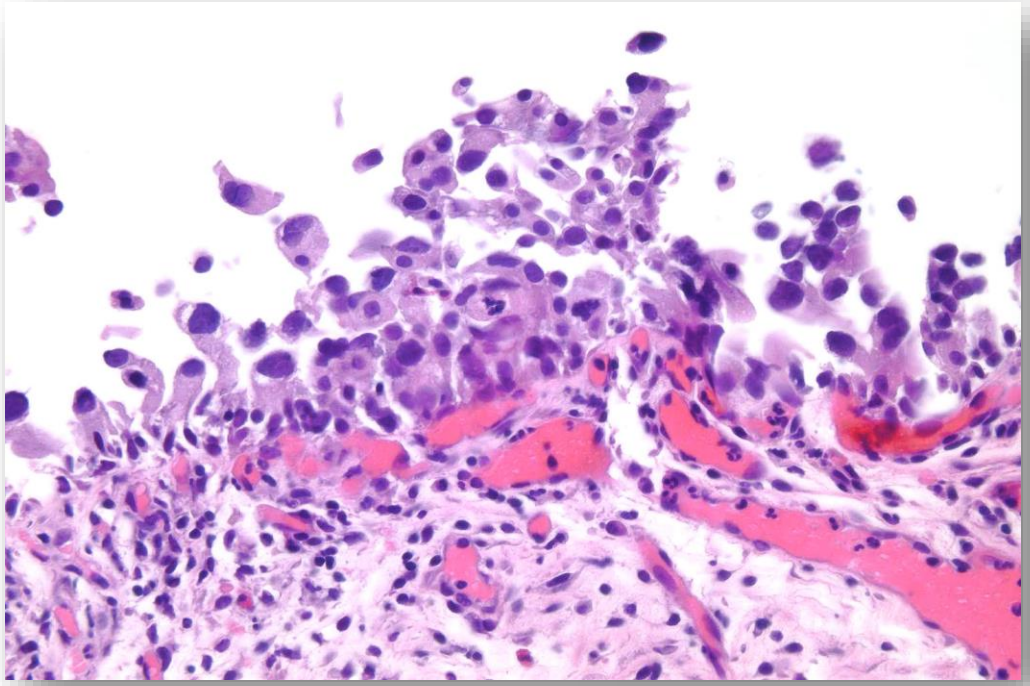
- Dyscohesive : **“denuding cystitis”**

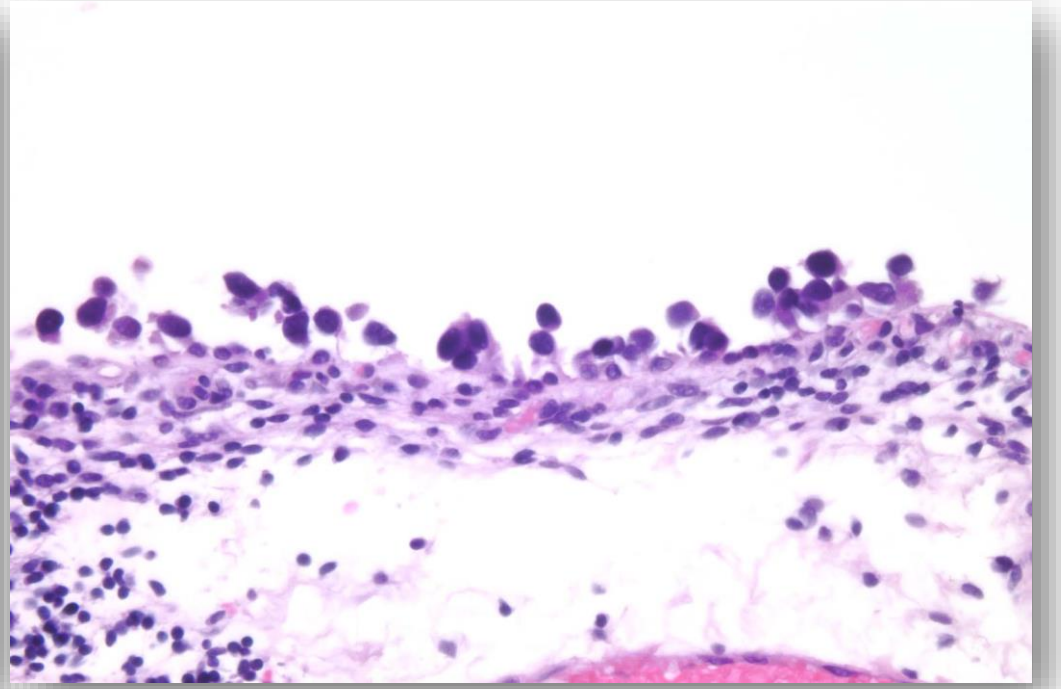


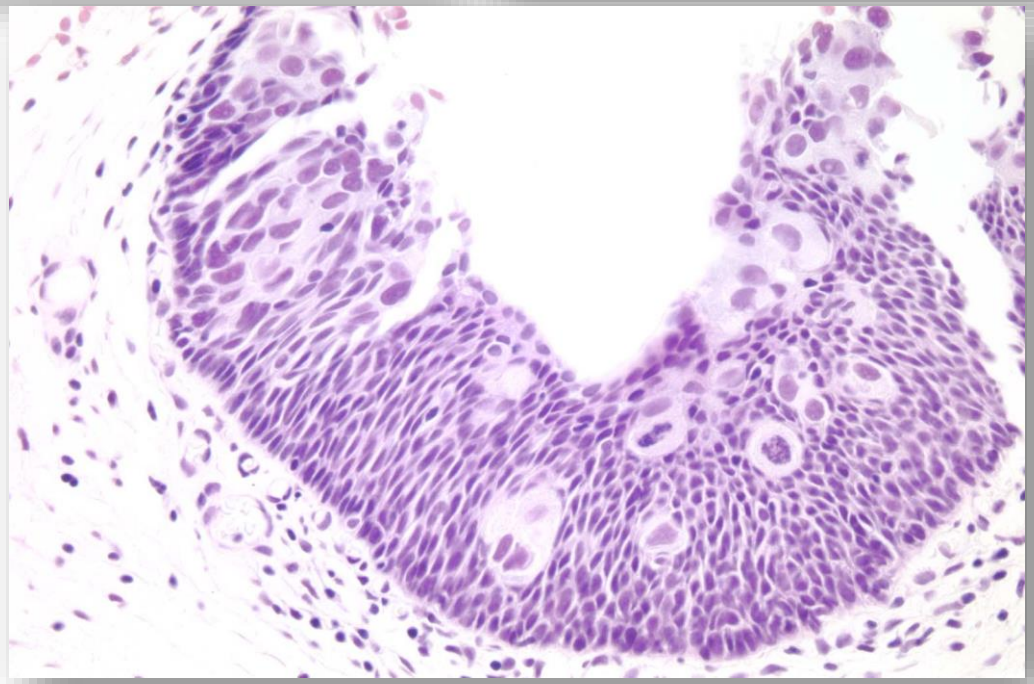










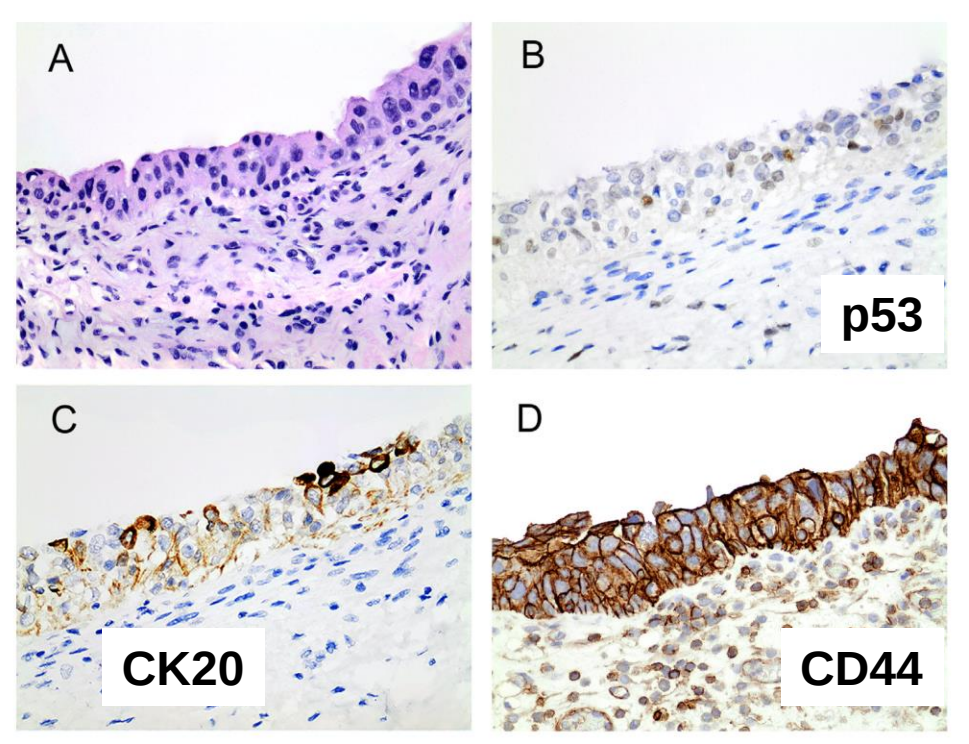


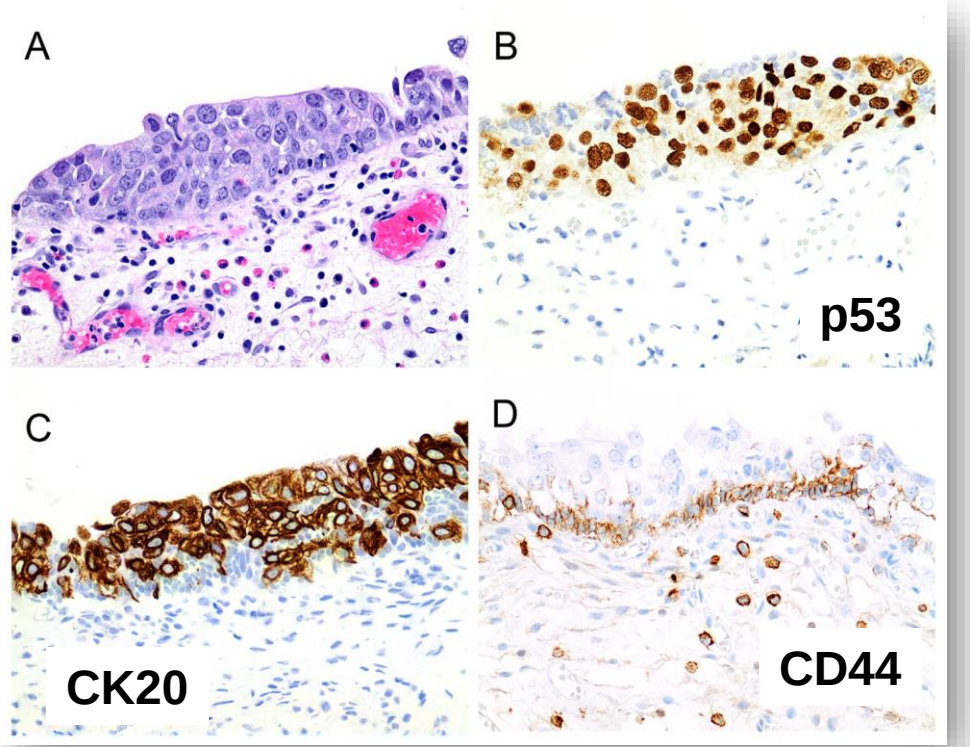
Immunohistochemistry in the workup of bladder biopsies: Frequency, variation and utility of use at an academic center

Patrick McIntire*, Reema Khan, Irem Kilic, Eva M. Wojcik, Stefan E. Pambuccian, Güliz A. Barkan

Loyola University Medical Center, Department of Pathology and Laboratory Medicine, Maywood, IL, United States

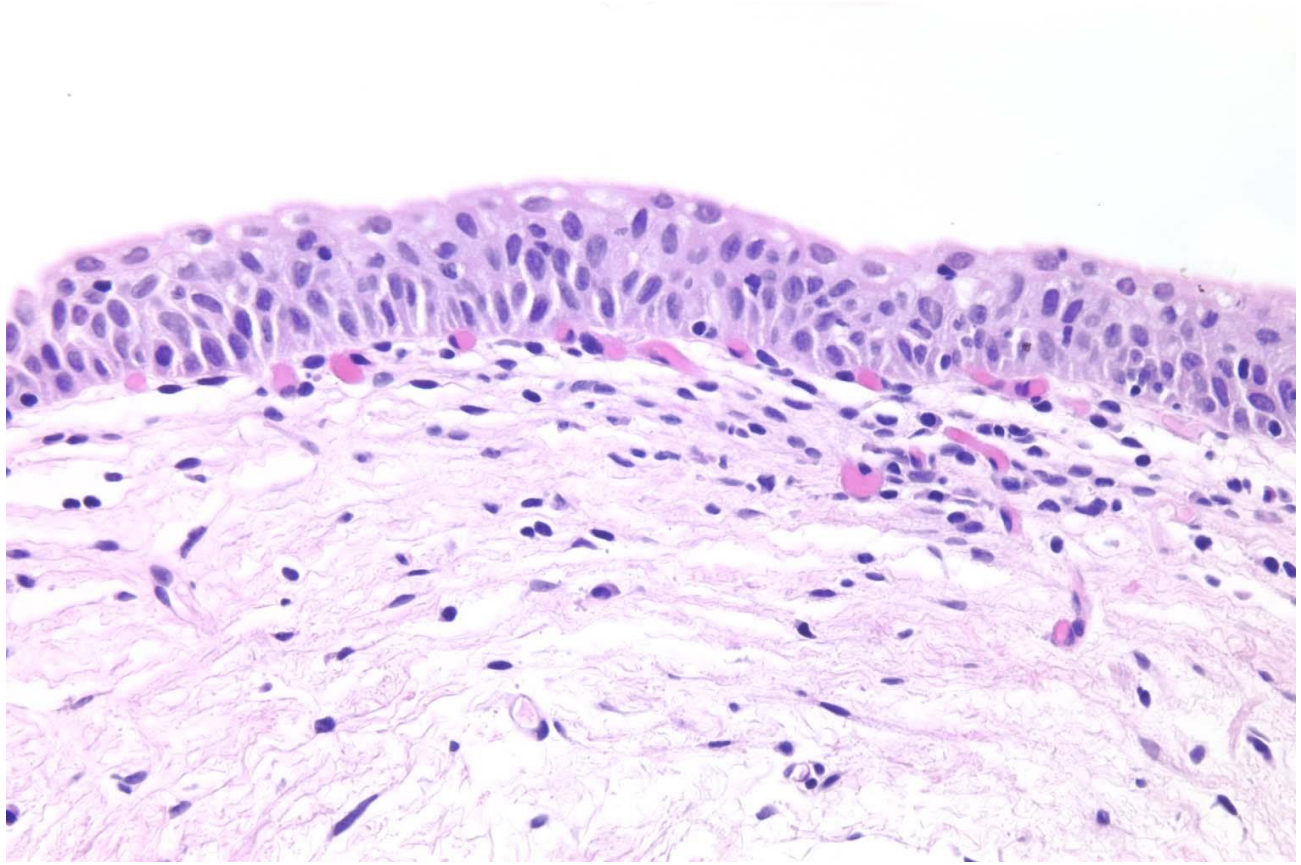
Annals of Diagnostic Pathology 41 (2019) 124–128

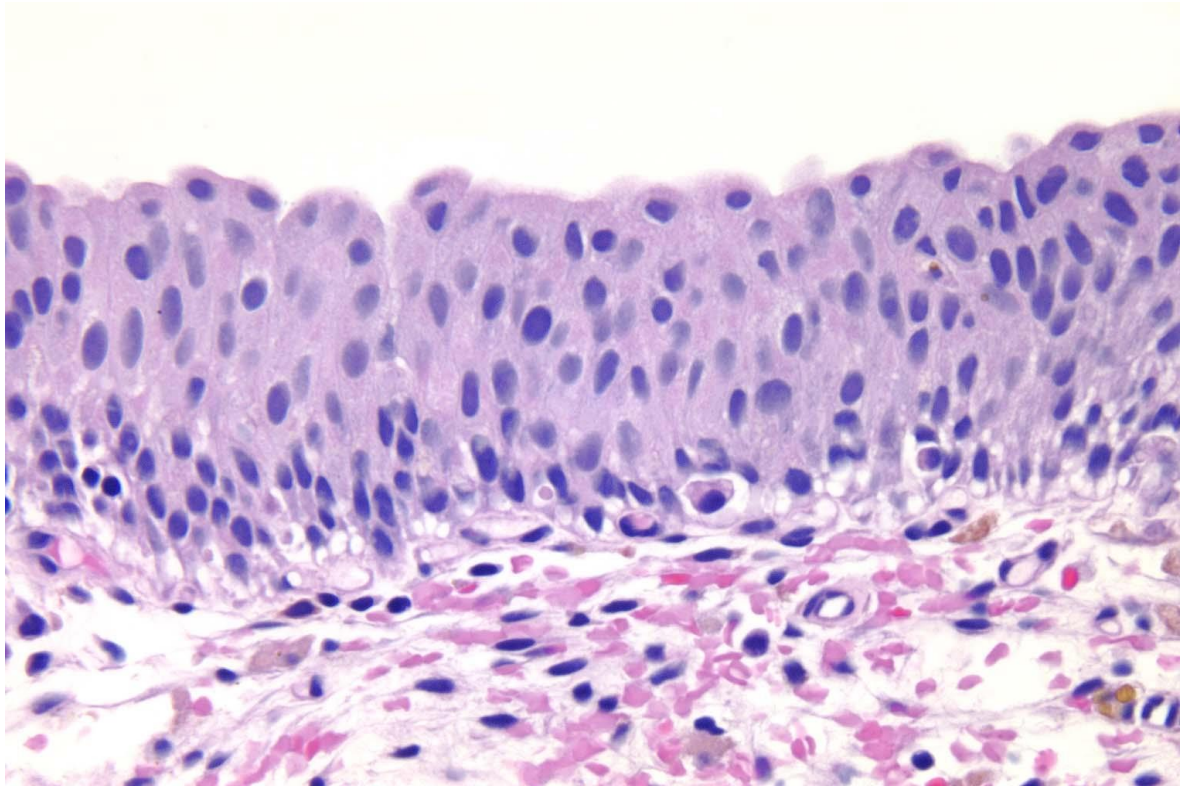




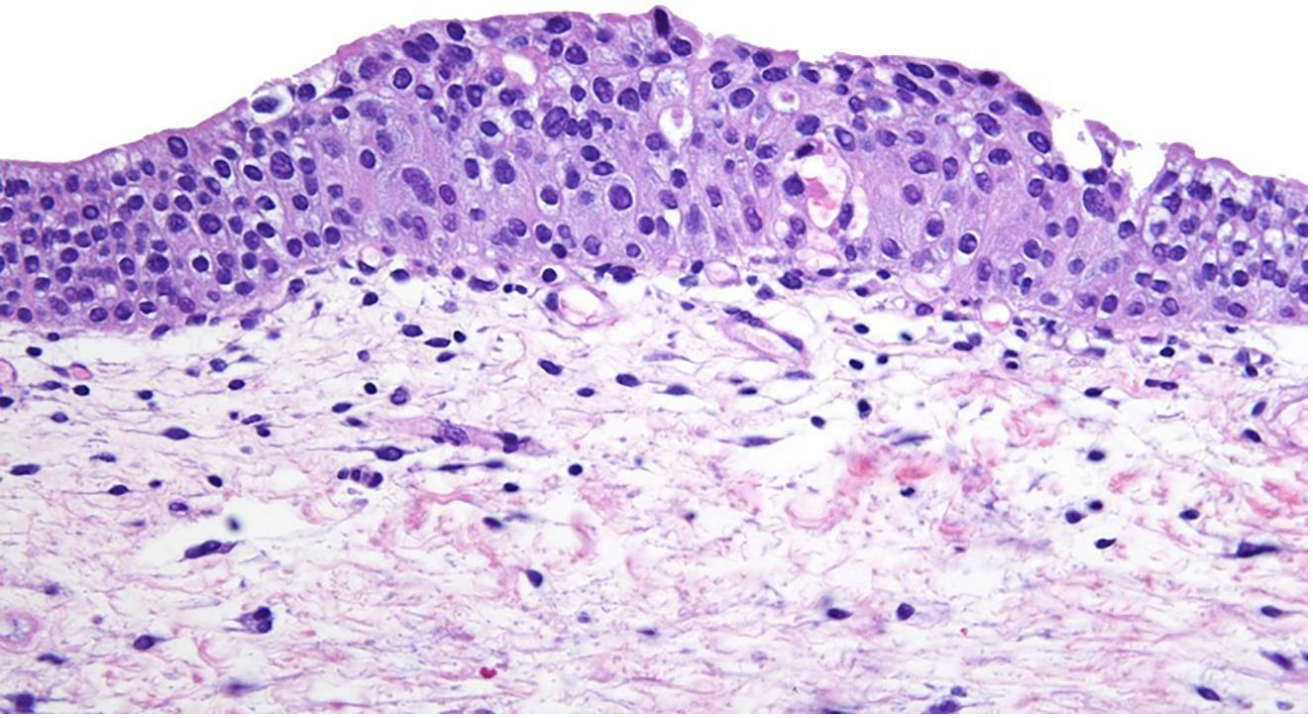
"our institution was an early adopter of IHC but it quickly fell out of favor to a total of only 5 cases in 2017"

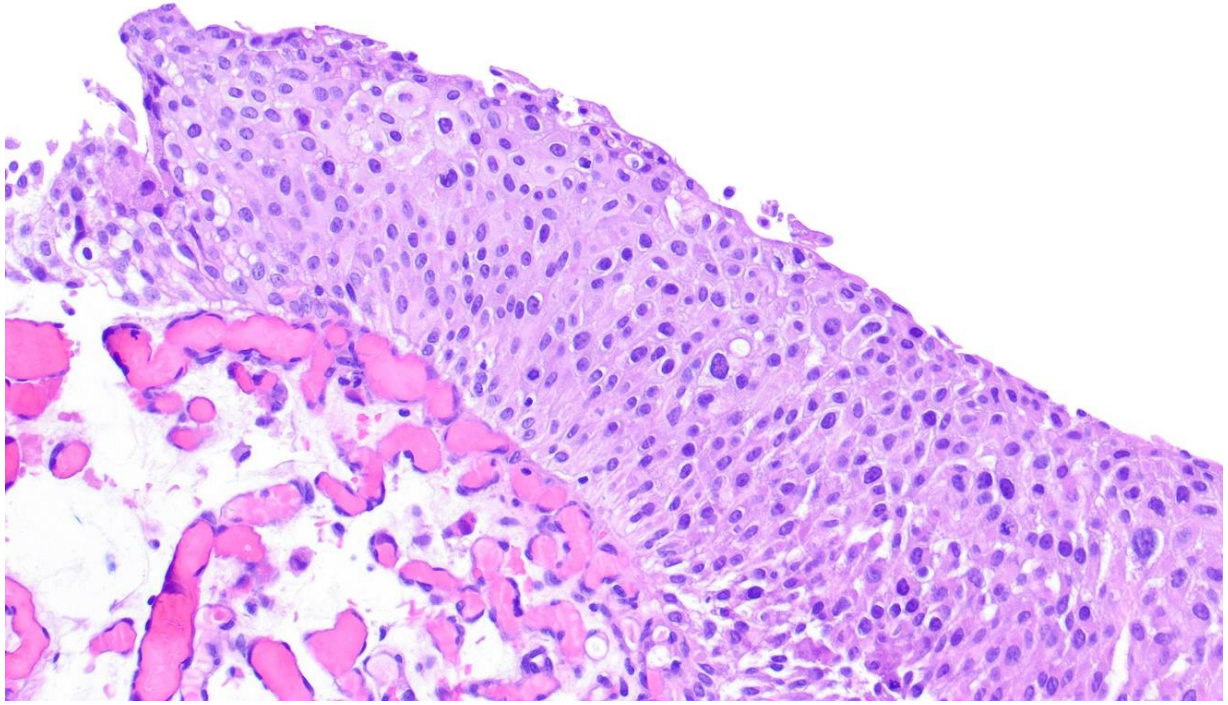
Urothelial Dysplasia





Urothelial Dysplasia





Urothelial Dysplasia

“Flat” Precursor Lesions
Urothelial Dysplasia

Should “Urothelial Dysplasia” remains an entity ?

- Term is greatly debated
- Definition of dysplasia in urinary tract is not a synonym of intraepithelial neoplasia in other organs (SIL/PeIN etc)

“Lesion that encompasses changes that are thought to be pre-neoplastic in nature, but cytologically fall short of the diagnosis of carcinoma in situ”

- Lack of agreement on concrete morphologic criteria ➡ **poor diagnostic reproducibility**
- **IHC is of no help** differentiating from CIS

- **Biologic significance**, difficult to assess:
  - Reproducibility in diagnosis
  - Compounding aspects of multifocality
  - Need for long FU

WHO 5th edition Consensus: While term is preserved, entity **does not merit** an independent section. **Mentioned under urothelial CIS** for potential use when lesions fall short of CIS

Urothelial Dysplasia

My current approach

Diagnosis: Marked urothelial atypia, see comment.
Comment: can not R/O CIS

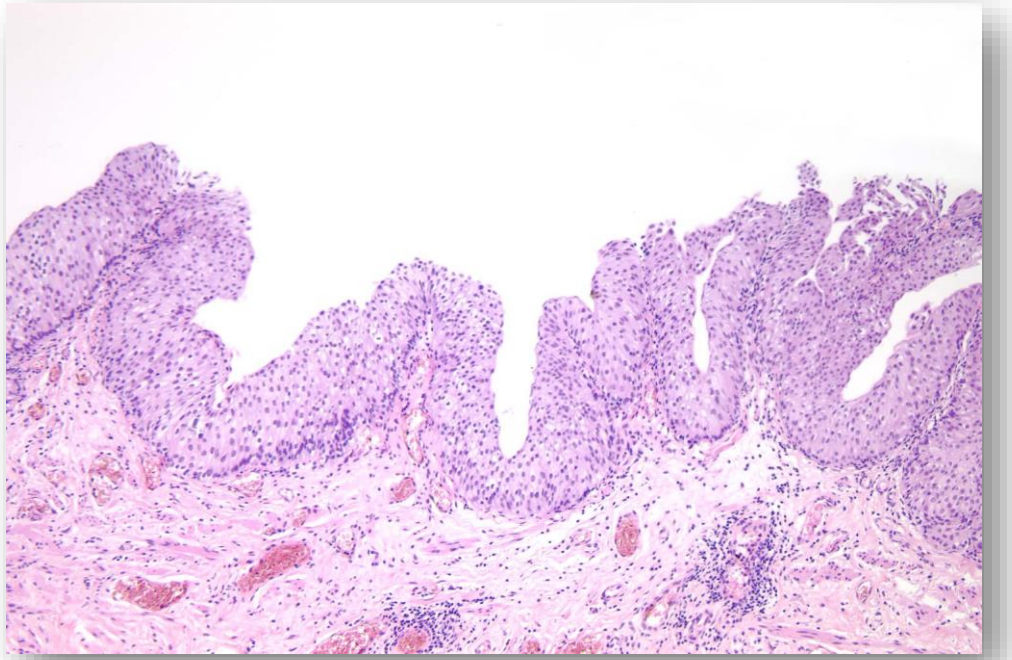
“Flat” Precursor Lesions
UPUMP

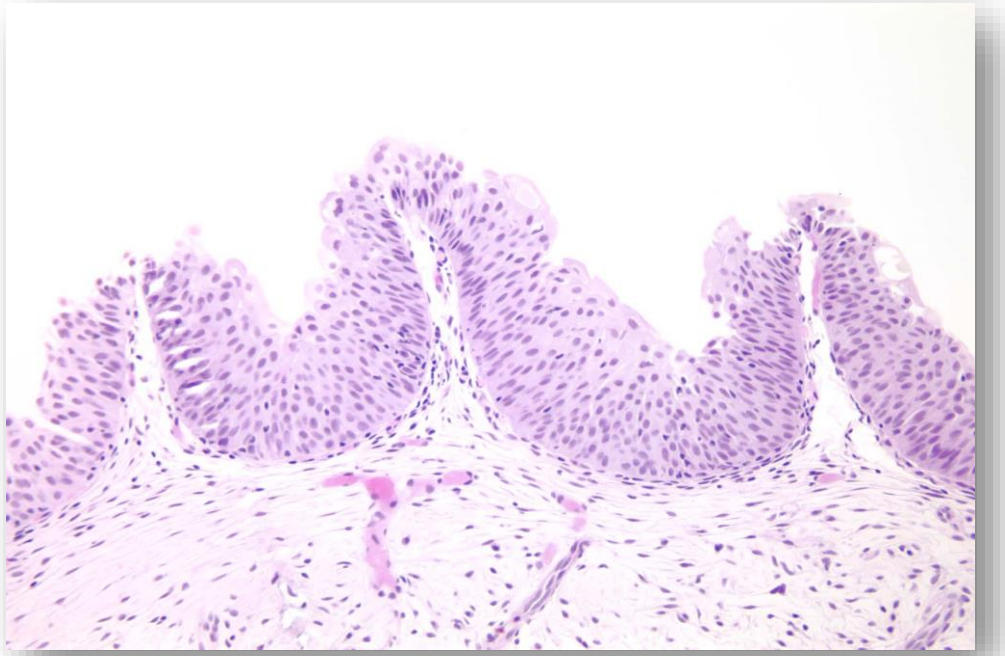
Should “Urothelial Proliferation of Undetermined Malignant Potential” remain an entity ?

UPUMP

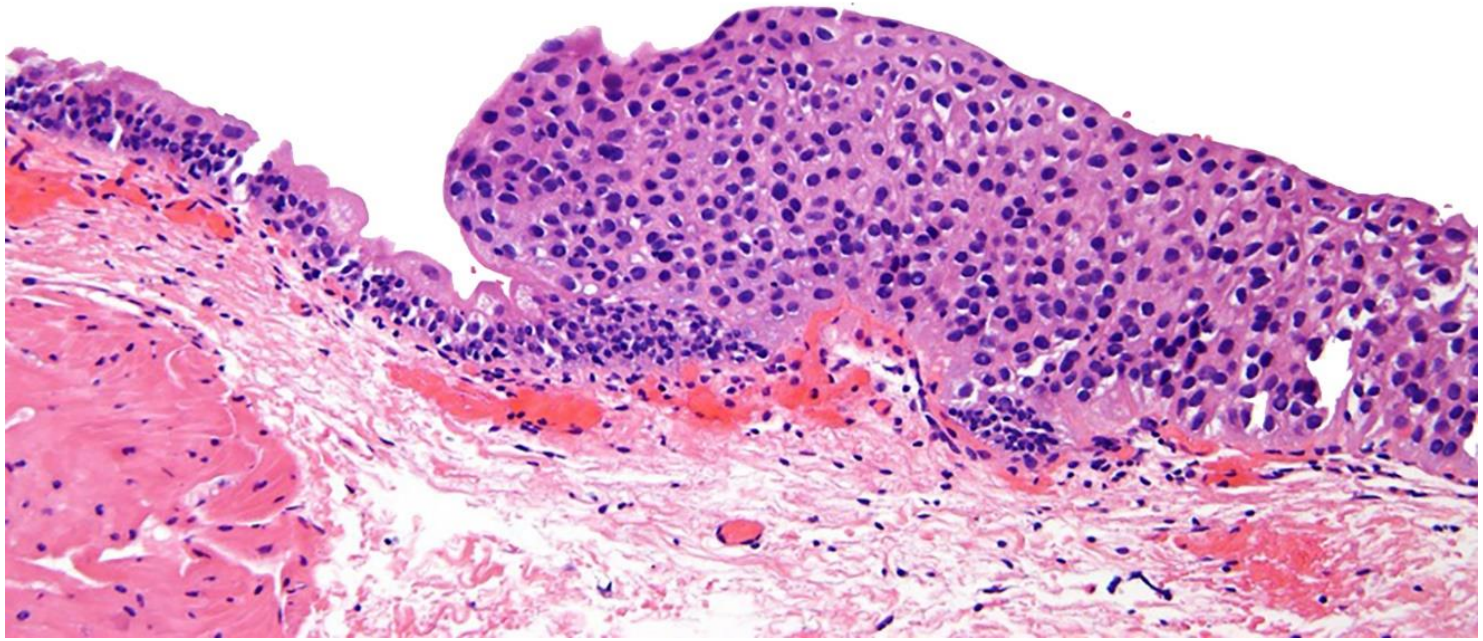
- Term **introduced in WHO 4th** edition
- **Encompass** lesions previously designated as
  “papillary urothelial hyperplasia”
  “Flat hyperplasia with atypia?”
- **Tented** architectural appearance with **short non branching papillae** covered by **mildly atypical** urothelium
- Thought to be **precursors of non-invasive low grade** papillary carcinoma

WHO 5th edition Consensus: UPUMP is **no longer recognized as an entity**
(considered early non-invasive low grade papillary carcinoma or shoulder extension of such tumors)





UMPUM



UMPUM

WHO Classification of the Urinary and Male Genital Tumours

5th edition series

- WHO *5th edition series* **structural reorganization**
- Refinements of **terminology** and **classification**
- Precursor lesions **(HGPIN; IDC-P; IAP)**
- **Grading / Staging / Urine Cytology**
- Advances in **molecular pathways** (targets of therapy)

Grading

WHO Classification of the Urinary and Male Genital Tumours
5th edition series

- First proposed in 1998
- Promulgated by the **WHO in the third (2004) and fourth (2016)**
- Based on **architectural and cytological** disorder
- Closely reflects the **two major molecular pathogenesis** pathways
- Clinically relevant

Urothelial Tumours
Non-Invasive Urothelial Neoplasia
Urothelial papilloma
Inverted urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non-invasive papillary urothelial carcinoma, low-grade
Non-invasive papillary urothelial carcinoma, high-grade
Urothelial carcinoma in situ
Invasive Urothelial Neoplasia
Invasive urothelial carcinoma

Platinum Opinion

Grading Noninvasive Bladder Cancer: World Health Organisation 1973 or 2004 May Be the Wrong Question

Murali Varma [a,*], *Brett Delahunt* [b], *Theodorus van der Kwast* [c]

EUROPEAN UROLOGY 76 (2019) 413–415

Reply re: Murali Varma, Brett Delahunt, Theodorus van der Kwast. Grading Noninvasive Bladder Cancer: World Health Organisation 1973 or 2004 May Be the Wrong Question. Eur Urol 2019;76:413–5

Two Decades of World Health Organisation/International Society of Urological Pathology Bladder Cancer Grading: Time to Reflect on Accomplishments and Plan Refinement in the Molecular Era, Not Regress to Readoption of a 45-year-old Classification

Eva Compérat [a,*], *Mahul Amin* [b], *Victor Reuter* [c,d]

European Association of Urology (EAU) Prognostic Factor Risk Groups for Non–muscle-invasive Bladder Cancer (NMIBC) Incorporating the WHO 2004/2016 and WHO 1973 Classification Systems for Grade: An Update from the EAU NMIBC Guidelines Panel

Richard J. Sylvester[a,], Oscar Rodríguez[b], Virginia Hernández[a,c], Diana Turturica[d], Lenka Bauerová[e], Harman Max Bruins[a,f], Johannes Bründl[g], Theo H. van der Kwast[h], Antonin Brisuda[i], José Rubio-Briones[j], Maximilian Seles[k], Anouk E. Hentschel[l,m], Venkata R.M. Kusuma[n], Nicolai Huebner[o], Juliette Cotte[p], Laura S. Mertens[m], Dimitrios Volanis[q], Olivier Cussenot[q], Jose D. Subiela Henríquez[b], Enrique de la Peña[c], Francesca Pisano[b,d], Michael Pešl[s], Antoine G. van der Heijden[f], Sonja Herdegen[g], Alexandre R. Zlotta[t], Jaromir Hacek[u], Ana Calatrava[v], Sebastian Mannweiler[w], Judith Bosschieter[l], David Ashabere[n], Andrea Haitel[x], Jean-François Côté[y], Soha El Sheikh[z], Luca Lunelli[r], Ferran Algaba[aa], Isabel Alemany[bb], Francesco Soria[d], Willemien Runneboom[cc], Johannes Breyer[g], Jakko A. Nieuwenhuijzen[l], Carlos Llorente[c], Luca Molinaro[dd], Christina A. Hulsbergen-van de Kaa[cc], Matthias Evert[ee], Lambertus A.L.M. Kiemeney[ff], James N'Dow[gg], Karin Plass[gg], Otakar Čapoun[a,s], Viktor Soukup[a,s], Jose L. Dominguez-Escrig[a,j], Daniel Cohen[a,q], Joan Palou[a,b], Paolo Gontero[a,d], Maximilian Burger[a,g], Richard Zigeuner[a,k], Amir Hugh Mostafid[a,n], Shahrokh F. Shariat[a,i,o], Morgan Rouprêt[a,p], Eva M. Compérat[a,hh], Marko Babjuk[a,i,o], Bas W.G. van Rhijn[a,t]*

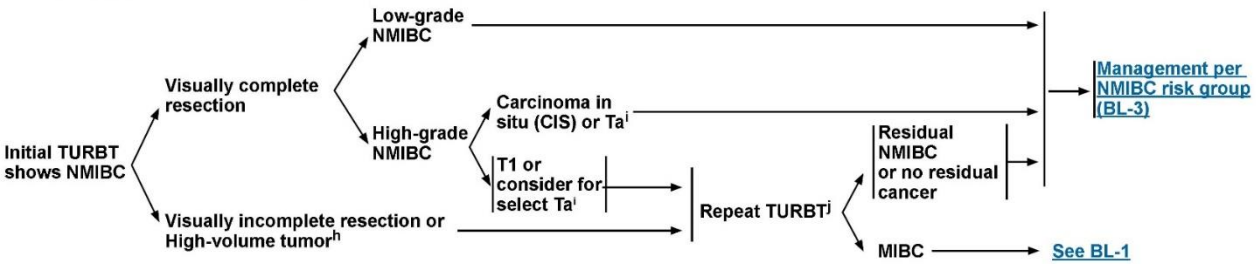
EUROPEAN UROLOGY 79 (2021) 480–488

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
Non-Muscle Invasive Bladder Cancer

NCCN Guidelines Index
Table of Contents
Discussion

RISK STRATIFICATION OF NMIBC



AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• Low grade urothelial carcinoma ▸ T1 or ▸ >3 cm or ▸ Multifocal or ▸ Recurrence within 1 year • High grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• High grade urothelial carcinoma ▸ CIS or ▸ T1 or ▸ >3 cm or ▸ Multifocal • Very high risk features (any): ▸ BCG unresponsive[k] ▸ Variant histologies[l] ▸ Lymphovascular invasion ▸ Prostatic urethral invasion

Reproduced with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021.
*Within each of these risk strata an individual patient may have more or less concerning features that can influence care.

Grading

WHO Classification of the Urinary and Male Genital Tumours
5th edition series

- First proposed in 1998
- Promulgated by the WHO in the third (2004) and fourth (2016)
- Based on architectural and cytological disorder
- Closely reflects the **two major molecular pathogenesis** pathways
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Urothelial Tumours
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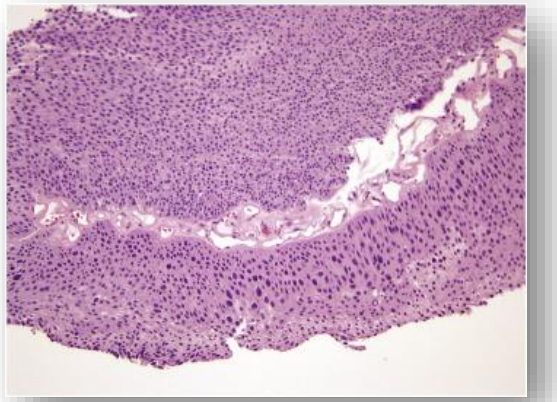
Urothelial carcinoma in situ
Invasive Urothelial Neoplasia
Invasive urothelial carcinoma

Three tiered classification (two tier grading) is **maintained**

Grading Heterogeneity

WHO Classification of the Urinary and Male Genital Tumours
5th edition series



- **Heterogeneity in grade** occurs in up to **one third** of non-Invasive papillary urothelial Carcinoma
- Influence outcome?

WHO 5th edition proposition

- Report as **high grade** if high grade component represents **≥ 5%**
- Tumors with **<5% high grade** component should be reported as **low grade with less than 5% high grade**

- **Pragmatic approach**
  - Promote **consistency** in grading heterogeneous tumors
  - Allow for **further data** in large appropriately powered and prospectively designed studies

Reis LO et al. Hum Path 2016
Gofrit ON et al. J Urol 2014
Schubert T et al. World J Urol 2015

Computational and Digital Pathology

Urothelial Carcinoma Grading & Urine Cytology

The American Journal of Pathology, Vol. 190, No. 7, July 2020

ELSEVIER

The American Journal of PATHOLOGY
ajp.amjpathol.org

MACHINE LEARNING, COMPUTATIONAL PATHOLOGY, AND BIOPHYSICAL IMAGING

Automated Detection and Grading of Non—Muscle-Invasive Urothelial Cell Carcinoma of the Bladder

Check for updates

Ilaria Jansen,*† Marit Lucas,* Judith Bosschieter,‡ Onno J. de Boer,§ Sybren L. Meijer,§ Ton G. van Leeuwen,* Henk A. Marquering,*¶ Jakko A. Nieuwenhuijzen,‡ Daniel M. de Bruin,*† and C. Dilara Savci-Heijink§

Colling *et al. BMC Cancer* (2021) 21:995
https://doi.org/10.1186/s12885-021-08698-4

BMC Cancer

RESEARCH ARTICLE Open Access

Validation of grading of non-invasive urothelial carcinoma by digital pathology for routine diagnosis

Check for updates

Richard Colling[1,2*], Hayleigh Colling[1], Lisa Browning[2,3] and Clare Verrill[1,2,3]

BJU Int 2021 doi:10.1111/bju.15382

Original Article

BJUI
BJU International

Artificial intelligence to improve cytology performances in bladder carcinoma detection: results of the VisioCyt test

Thierry Lebret[1,2], Geraldine Pignot[3], Marc Colombel[4,5], Laurent Guy[6], Xavier Rebillard[7], Laurent Savareux[8], Mathieu Roumigue[9], Sebastien Nivet[10], Monique Coutade Saidi[11], Eric Piaton[12] and Camelia Radulescu[13]

Grading of Invasive Urothelial Carcinoma

WHO Classification of the Urinary and Male Genital Tumours
5th edition series

- **Overwhelming majority** of invasive urothelial carcinoma are high grade
- **Rare low-grade** invasive urothelial carcinoma **lacking significant nuclear atypia** are recognized
  - No standardized criteria
  - Favorable outcome?

WHO 5th edition
*"Required to **grade every invasive** urothelial carcinoma"*
*"Histologic **subtypes** of urothelial carcinoma and those with **divergent** differentiation are **all considered high grade"***

Staging

WHO Classification of the Urinary and Male Genital Tumours
5th edition series

pT1 subcategorization

- **Extent of lamina propria invasion** carries PGx value
  - **Micrometric** measurements (microscopic vs extensive invasion)
  - **Histo-anatomic** landmarks (*MM* and vascular plexus)
  - Micrometric ? more feasible and better predictor

- Higher subcategories correlate with **recurrence and stage progression**

System	Technique	Measure of Invasion	Landmark or Cutoff	Approximate Microscope Objective Cutoff
T1a/T1b	Histoanatomic	Depth (level)	MM/VP	—
T1a/T1b/ T1c	Histoanatomic	Depth (level)	MM/VP	—
T1m/T1e	Micrometric	Depth* or diameter†	0.5 mm	×40
ROL1/ ROL2	Micrometric	Diameter†	1 mm	×20
ALLICA	Micrometric	Diameter†	2.3 mm‡	×10

WHO 5th Edition
Well designed prospective head-to-head comparisons **NEEDED**
"Pathologists are strongly encouraged to convey the extent of lamina propria invasion using any of the proposed approaches"

Compérat E … Reuter V. Adv Anat Pathol. 2021
Raspollini MR et al. Virchows Arch 2020
Fransen Van de Putte EE et al. Urol Oncology 2018
Paner GP, Montironi R, Amin MB. Adv Anat Pathol. 2017

Staging

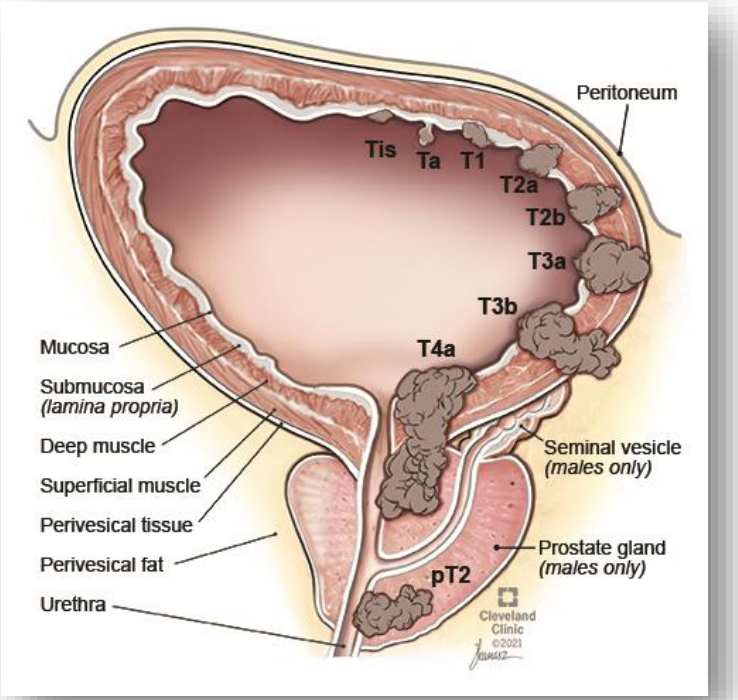
WHO Classification of the Urinary and Male Genital Tumours
5th edition series

Staging urothelial carcinoma invading prostate stroma

- Contiguous **direct invasion** from transmural bladder primary **(pT4a)**
- Originated in urethra **(pT2)**

- Differences of pT4a by **gender-specific organ** involvement have conflicting results

"maintaining a single category appears to be the optimal approach at present"



Courtesy of Drs. Oleksandr Kryvenko and Sean Williamson

Paner GP… Amin MB. Eur Urol. 2018
May M et al. Urol Oncol 2013
Grajales V et al. Urology 2021

Urine Cytology

WHO Classification of the Urinary and Male Genital Tumours
5th edition series

The Paris System for Reporting Cytology (TPS)

- **Accuracy** significantly improved
- **Acknowledges inability** to reliably detect low grade urothelial neoplasms
- Low grade urothelial neoplasm (**LGUN**) encompasses papilloma, PUNLMP and LGUC
- Prioritize identification of High Grade Urothelial Ca (**HGUC**)

WHO 5th edition
Recommends adoption of **The Paris System for Reporting Cytology (TPS)**

Rosenthal DL, Wojcik EM, Kurtycz DFI, editors. The Paris System for reporting urinary cytology.
Cham (Switzerland): Springer International Publishing; 2016

The Paris System TPS

Diagnostic category	Diagnostic criteria	ROHM
Negative for High Grade Urothelial Ca **(NHGUC)**	Benign urothelial, glandular, squamous cells, changes due to instrumentation, lithiasis, polyoma, therapy	8% - 24%
Atypical Urothelial Cells **(AUC)**	**Required** N/C ratio ≥ 0.5 and one of: Hyperchromasia Irregular clumpy chromatin Irregular nuclear contours	24% - 53%
Suspicious for High Grade Urothelial Ca **(SHGUC)**	**Required** N/C ratio > 0.7 and hyperchromasia, and one of: Irregular clumpy chromatin Irregular nuclear contours	59% - 94%
Positive for High Grade Urothelial Ca **(HGUC)**	**Required** cellularity (> 5-10 cells) and N/C ratio > 0.7 - Hyperchromasia - Irregular clumpy chromatin - Irregular nuclear contours	76% - 100%
Low Grade Urothelial Neoplasm **(LGUN)**	**Required** fibrovascular cores and absence of nuclear atypia	0% - 44%

WHO Classification of the Urinary and Male Genital Tumours

5th edition series

- WHO *5th edition series* **structural reorganization**
- Refinements of **terminology** and **classification**
- Precursor lesions **(HGPIN; IDC-P; IAP)**
- **Grading / computational pathology (AI)**
- Advances in **molecular pathways** (targets of therapy)

Overview

Advances in Urothelial Carcinoma

Genomic Advances in Urothelial Carcinoma

- Bladder Cancer TCGA Studies: Genomic Taxonomy
- Immuno-oncology (I/O)
- Molecular insights into Variants Histology
- UTUC Genomics

Liquid Biopsy

- Early Detection
- Prognostics and Rx Prediction

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Liquid Biopsy

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Comprehensive molecular characterization of urothelial bladder carcinoma

The Cancer Genome Atlas Research Network*

Nature 2014

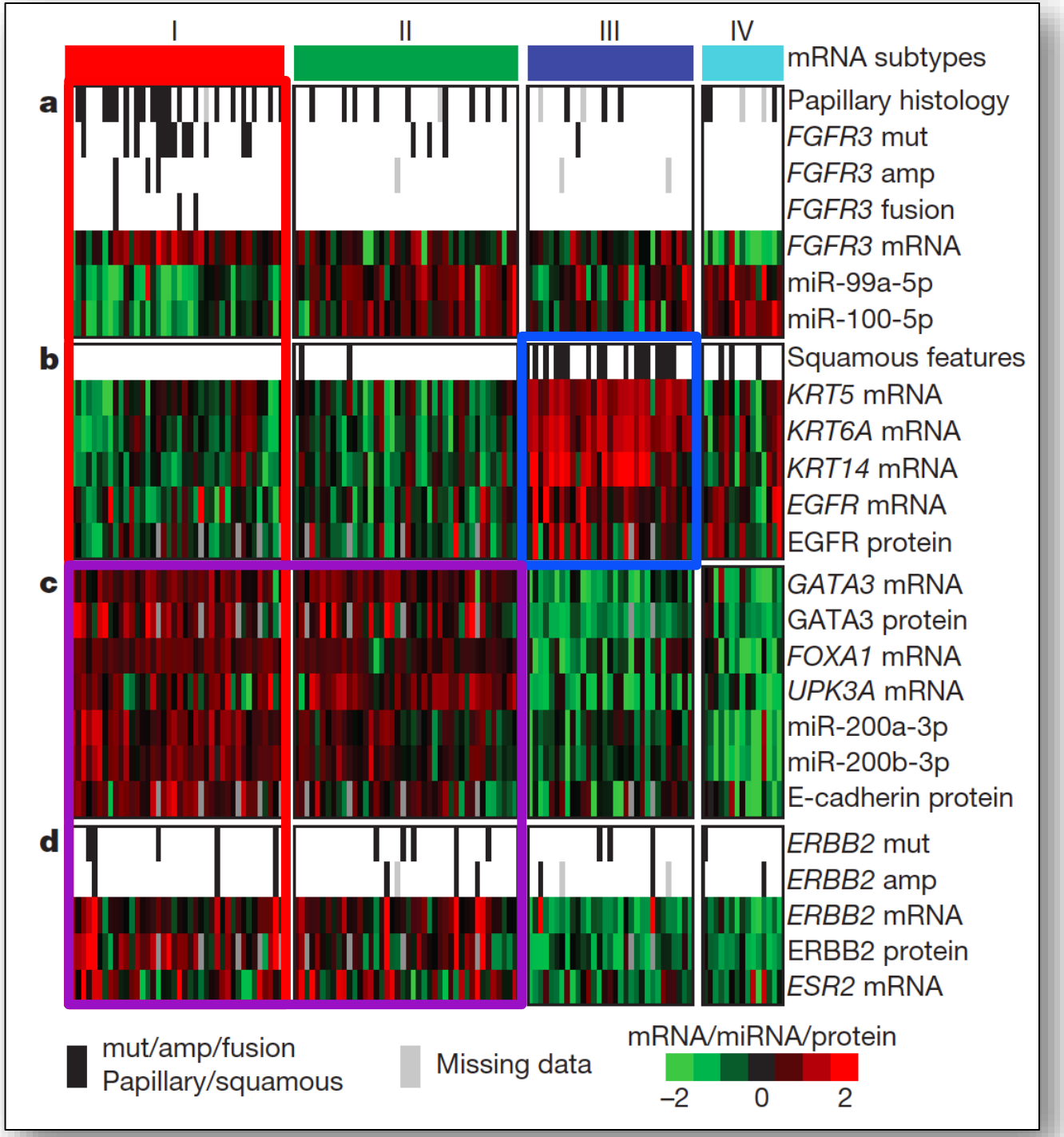
Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

A. Gordon Robertson[1,25], Jaegil Kim[2,25], Hikmat Al-Ahmadie[3], Joaquim Bellmunt[4], Guangwu Guo[5], Andrew D. Cherniack[2], Toshinori Hinoue[6], Peter W. Laird[6], Katherine A. Hoadley[7], Rehan Akbani[8], Mauro A.A. Castro[9], Ewan A. Gibb[1], Rupa S. Kanchi[8], Dmitry A. Gordenin[10], Sachet A. Shukla[5], Francisco Sanchez-Vega[11], Donna E. Hansel[12], Bogdan A. Czerniak[13], Victor E. Reuter[3], Xiaoping Su[8], Benilton de Sa Carvalho[14], Vinicius S. Chagas[9], Karen L. Mungall[1], Sara Sadeghi[1], Chandra Sekhar Pedamallu[2], Yiling Lu[15], Leszek J. Klimczak[16], Jiexin Zhang[8], Caleb Choo[1], Akinyemi I. Ojesina[17], Susan Bullman[2], Kristen M. Leraas[18], Tara M. Lichtenberg[18], Catherine J. Wu[19], Nicholaus Schultz[11], Gad Getz[2], Matthew Meyerson[20], Gordon B. Mills[15], David J. McConkey[21], TCGA Research Network, John N. Weinstein[8,22,26], David J. Kwiatkowski[23,26], and Seth P. Lerner[24,26]

Cell 2017

TCGA 2014
mRNA/miRNA/Protein clusters

Cluster I	**PAPILLARY-LIKE**
Clusters III	**BASAL SQUAMOUS-LIKE**
Clusters I/II	**LUMINAL BREAST-LIKE**

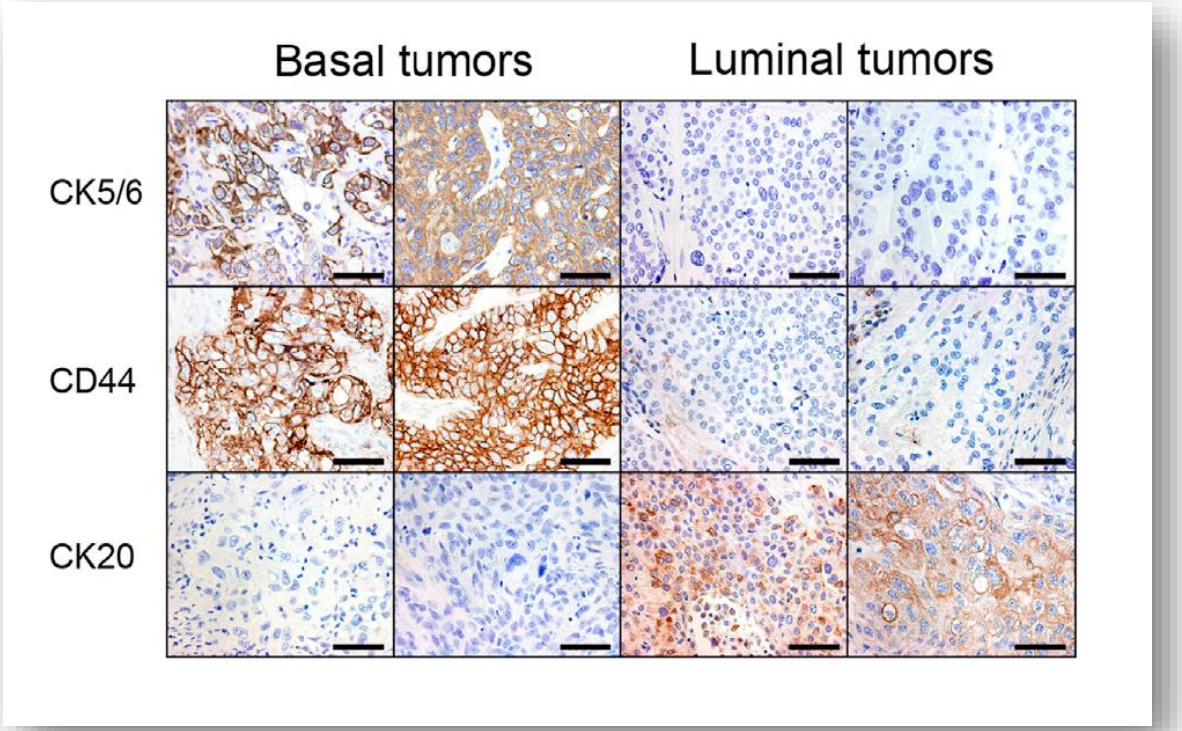


Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy

Choi W et al, Cancer Cell 2014

Three molecular subtypes of MIBC

Basal/Luminal/p53-like



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TCGA

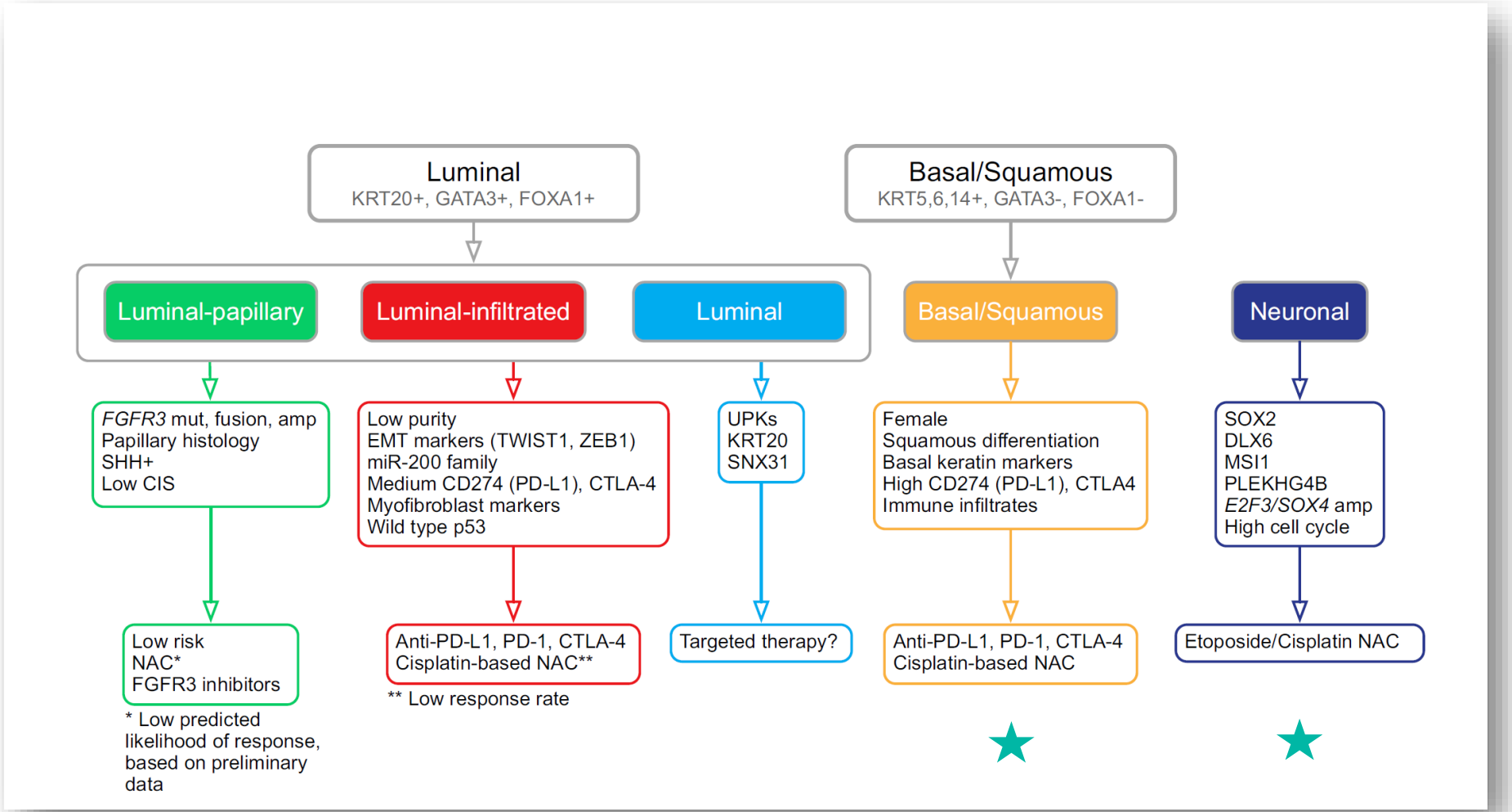
Cell 2017

TCGA
Cell 2017

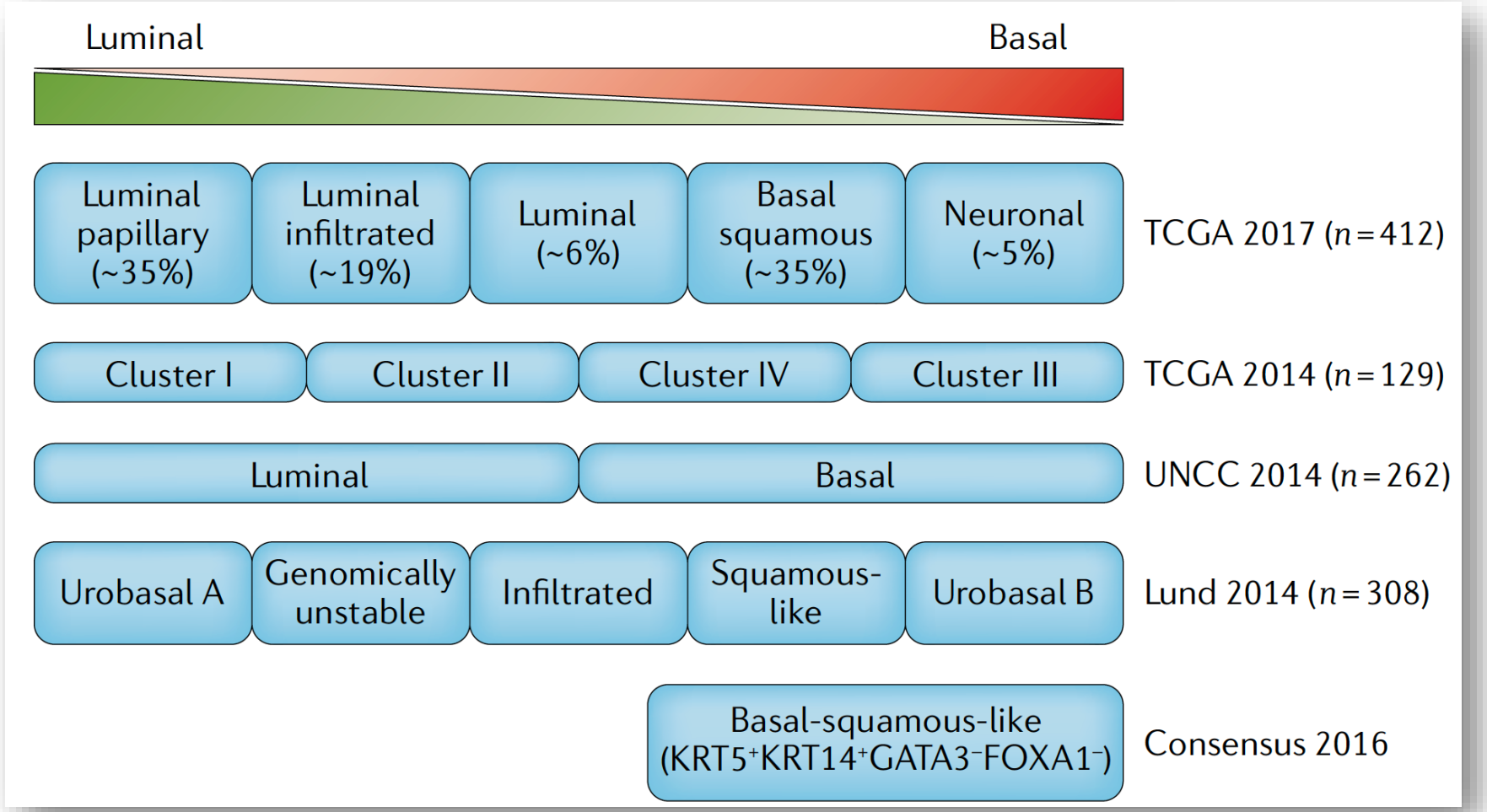
1- Luminal Pap
2- Luminal Infiltrated
3- Luminal
4- Basal-Squamous
5- Neuronal

Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

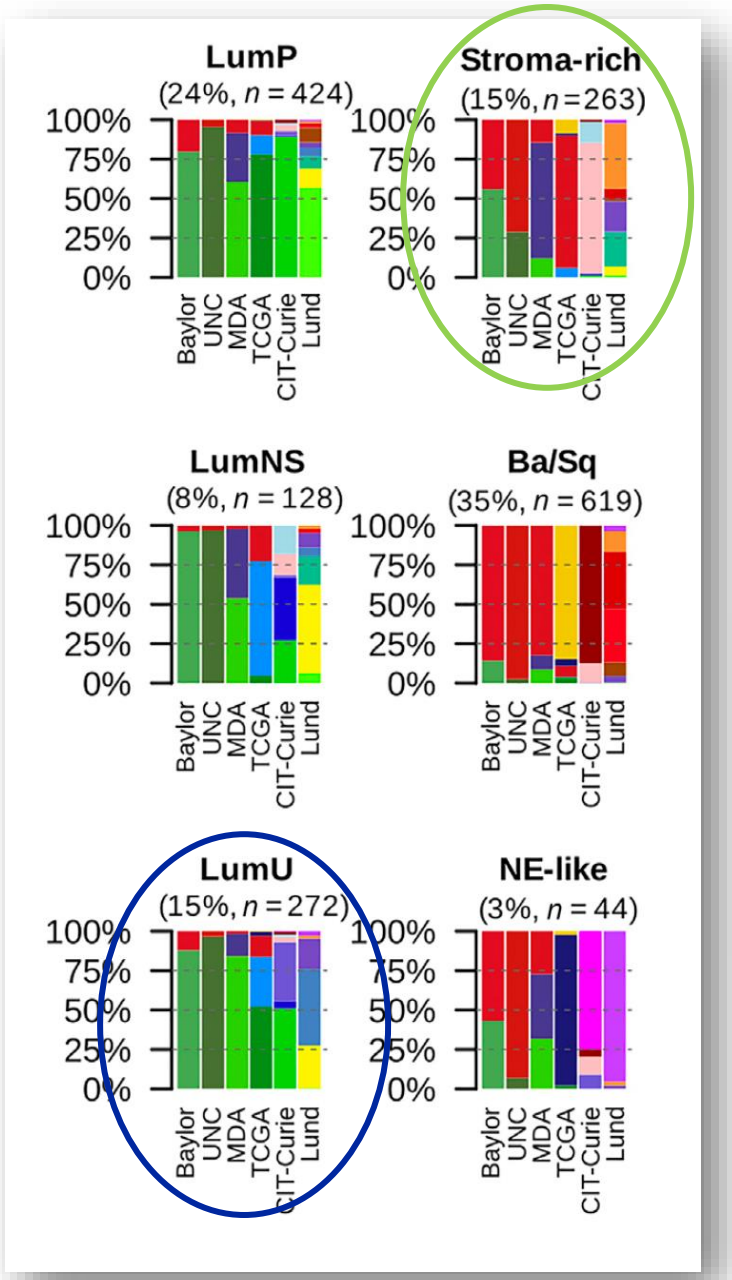
Cell 2017

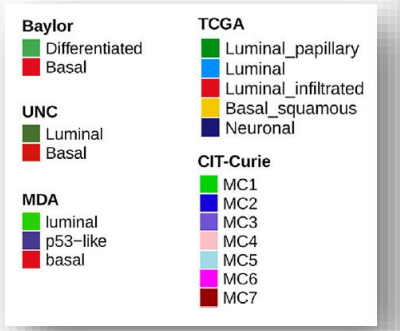


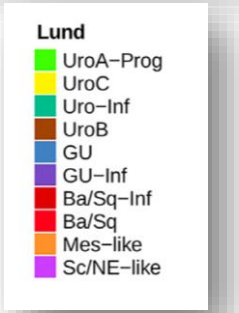
Molecular and histopathology directed therapy for advanced bladder cancer



Alifrangis C. et al Nature Rev. Urology 2019



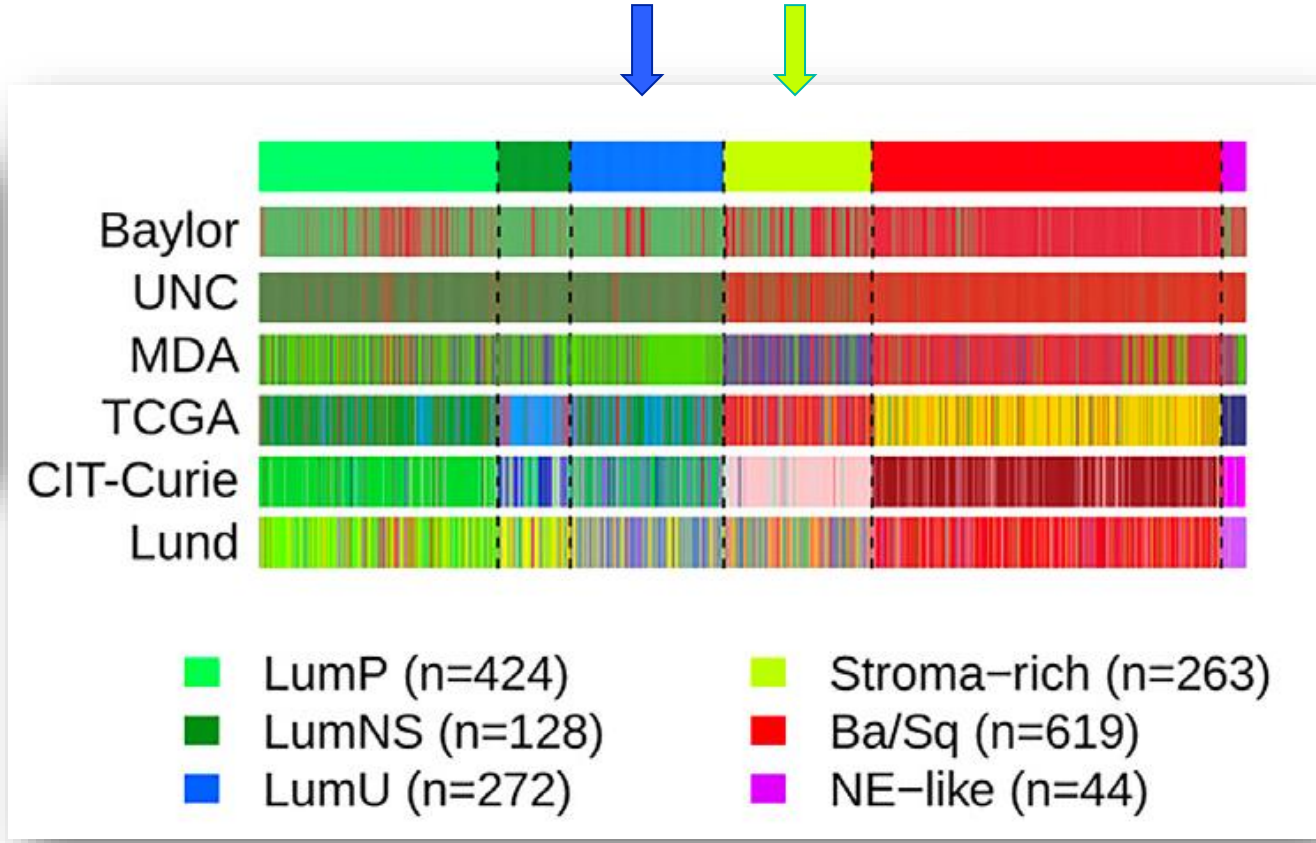




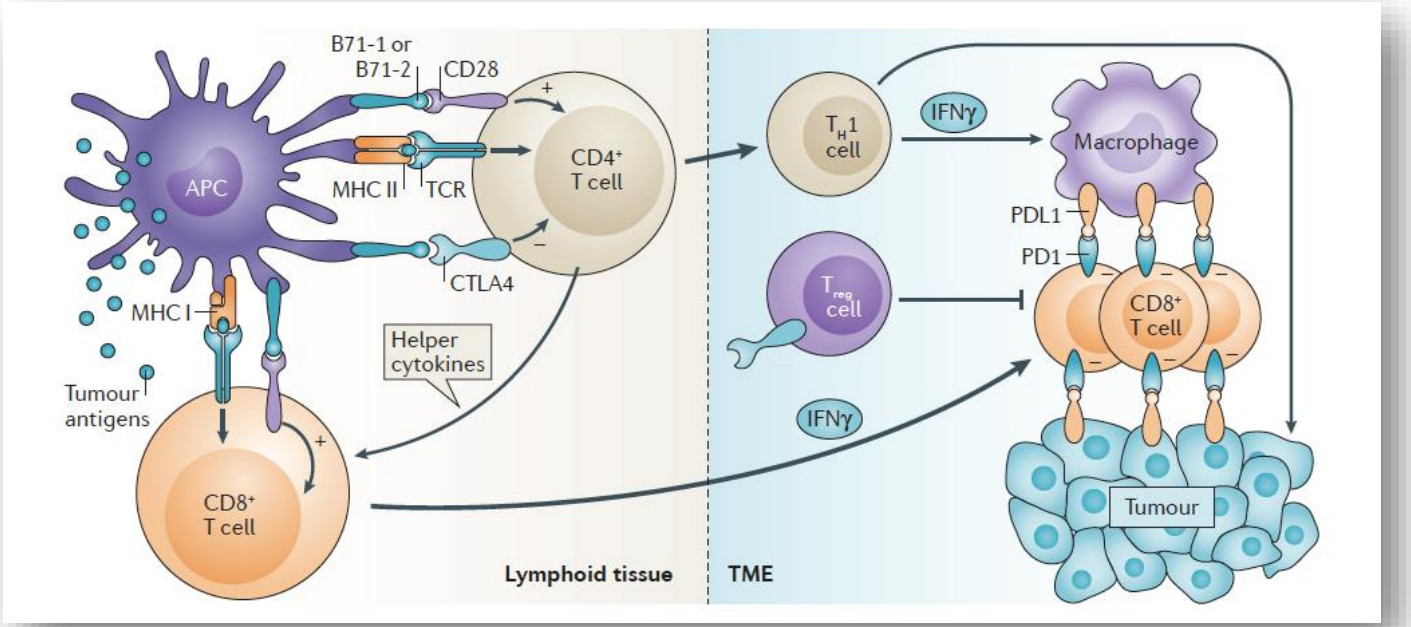
A Consensus Molecular Classification of Muscle-invasive Bladder Cancer

Aurélie Kamoun [a,], Aurélien de Reyniès [a,†], Yves Allory [b,c,†], Gottfrid Sjödahl [d,†], A. Gordon Robertson [e,†], Roland Seiler [f], Katherine A. Hoadley [g], Clarice S. Groeneveld [a,c,h], Hikmat Al-Ahmadie [i], Woonyoung Choi [j], Mauro A.A. Castro [h], Jacqueline Fontugne [b,c], Pontus Eriksson [k], Qianxing Mo [l], Jordan Kardos [g], Alexandre Zlotta [m], Arndt Hartmann [n], Colin P. Dinney [o,p], Joaquim Bellmunt [q], Thomas Powles [r], Núria Malats [s], Keith S. Chan [t], William Y. Kim [u,v], David J. McConkey [j], Peter C. Black [w], Lars Dyrskjøt [x], Mattias Höglund [k], Seth P. Lerner [y], Francisco X. Real [z], François Radvanyi [c], the Bladder Cancer Molecular Taxonomy Group [‡]*

Eur Urology 2019

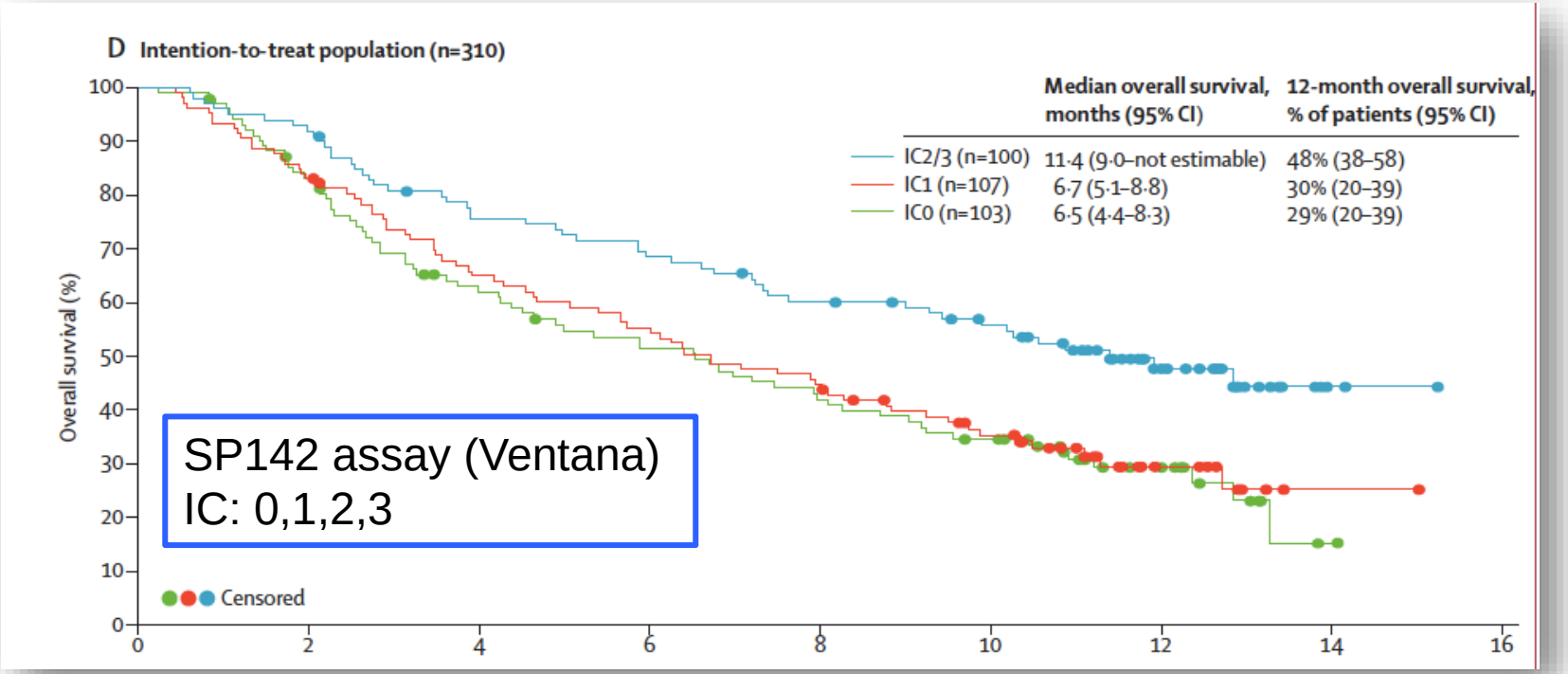


Immune Checkpoint Inhibitors in Bladder Cancer



Nature Reviews CANCER 2016

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial



Rosenberg J et al Lancet 2016

Immune Check inhibitors Trials in Advanced BC

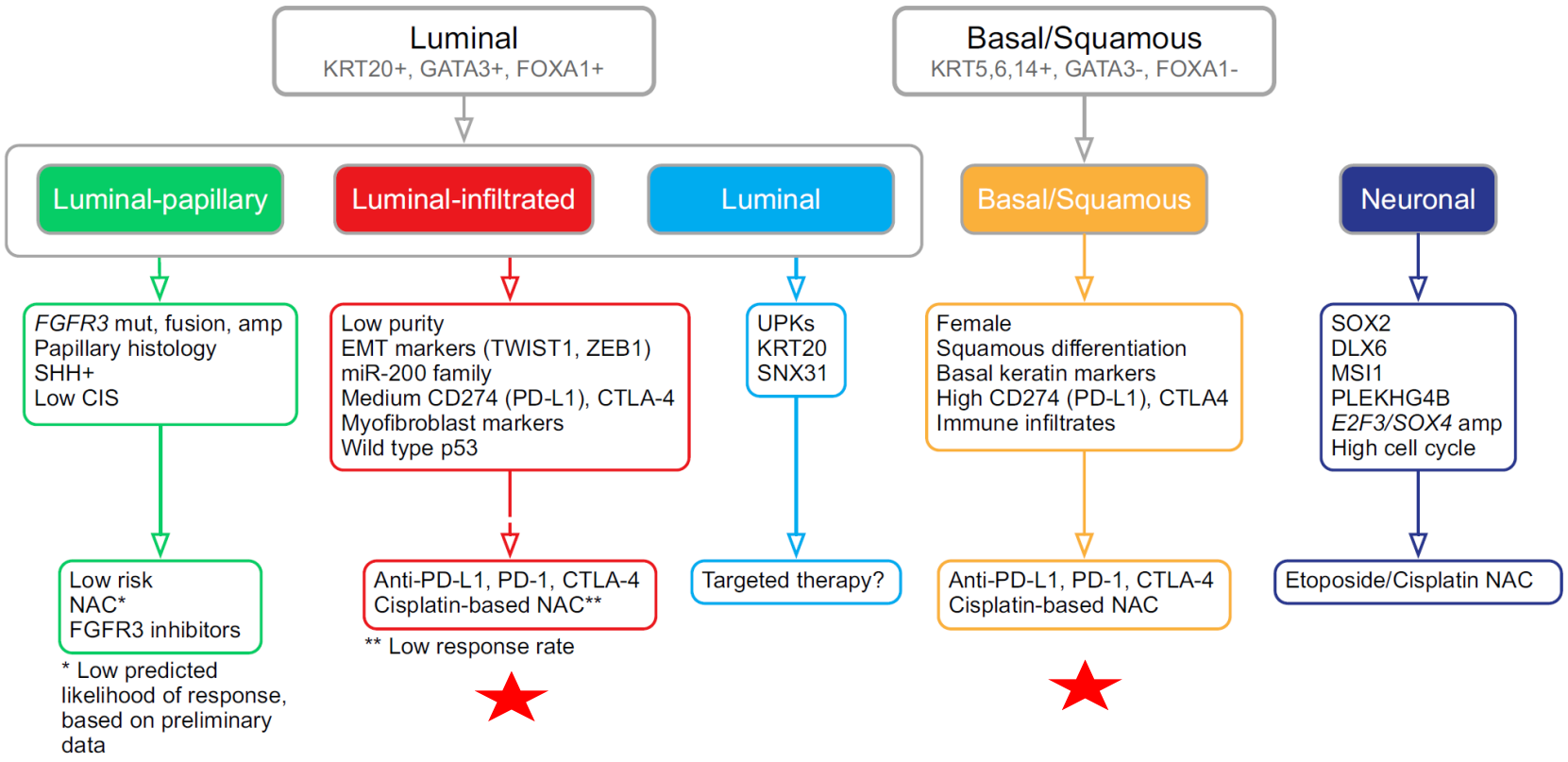
Study details	Treatment	End points	Patient selection	ORR (%)	RR by PD-L1 expression (%)	Survival (months)	Grade 3–4 toxicity (%)	IHC mAb and comments
KEYNOTE-012 (REF.[64]); phase Ib	Pembrolizumab	Safety, tolerability, ORR	aUC, post-PLT setting; $n = 33$ (27 evaluable)	26	PD-L1$^+$: 38	• mPFS: 2 • mOS: 13	15	• Dako 22C3 mAb
KEYNOTE-045 (REF.[51]); phase III	Pembrolizumab or physician's choice of chemotherapy (vinflunine, paclitaxel or docetaxel)	Co-primary: OS and PFS	aUC, second-line setting; $n = 542$	21.1 versus 11.4	CPS ≥10%: 21.6 versus 6.7	• OS: 10.3 versus 7.4 (HR 0.73; $P = 0.002$) • PFS: 2.1 versus 3.3 (HR 0.98, $P = 0.42$) • mOS for CPS ≥10%: 8 versus 5.2 (HR 0.57; $P = 0.005$)	15.0 versus 49.4	• Dako 22C3 mAb • Benefit of pembrolizumab in all subgroups, including the PD-L1 <1% group and patients with liver metastasis
KEYNOTE-052 (REF.[52]); phase II	Pembrolizumab	ORR	aUC, PLT-ineligible setting; $n = 374$ (370 treated)	24	• CPS validation cohort ($n = 270$) • CPS ≥10%: 39 • CPS 1% to <10%: 20 • CPS <1%: 11	mPFS: 2 (6-month OS: 67%)	15	• Dako 22C3 mAb • PD-L1 centrally reviewed • Durable response rate
CheckMate 032 (REF.[53]); phase I/II	Nivolumab	ORR	aUC, post-PLT setting; $n = 86$ (78 treated)	24.4	• ≥1% on TCs: 24.0 • <1% on TCs: 26.2	• mPFS: 2.8 • mOS: 9.7 • mDR: 9.4	22	• Dako 28-8 mAb • Unselected on PD-L1
CheckMate 275 (REF.[54]); phase II	Nivolumab	ORR	aUC, post-PLT setting; $n = 270$ (265 evaluable)	19.6	• ≥5% on TCs: 28.4 • 1–4% on TCs: 23.8 • <1% on TCs: 16.1	• mPFS: 2 • mOS: 8.7	18	• Dako 28-8 mAb • Unselected on PD-L1 • 25-gene IFNγ response signature
PCD4989g[171]; phase I	Atezolizumab	Safety, tolerability, ORR	mUBC, any line; 72% ≥2 lines; $n = 68$ (67 evaluable)	26.2	• PD-L1 IHC 0–1: 11 • PD-L1 IHC 2–3: 43	Not reported	4	• Ventana SP142 • Initially only PD-L1$^+$ patients and then expanded to all patients
PCD4989g (updated)[172]; phase I	Atezolizumab	Safety, tolerability, ORR	mUBC, any line; 72% ≥2 lines; $n = 95$	10.1	• ≥5% on ICs: 40 • <5% on ICs: 11	• mPFS: 2.7 • mOS: 10.1 • mDR: 22.1 • mPFS for PD-L1 ≥5% on ICs: 5.5 • mOS for PD-L1 ≥5% on ICs: 14.6	9	• Ventana SP142 • Similar OS in patients aged ≥65 years and patients aged <65 years
IMvigor210 (cohort 1)[74]; phase II	Atezolizumab	ORR	aUC, PLT-ineligible setting; $n = 123$ (119 evaluable)	23	• <1% on ICs: 21 • 1% to <5% on ICs: 21 • ≥5% on ICs: 28	• mPFS: 2.7 • mOS: 15.9	7	• Ventana SP263 mAb • High ORR in UTUC • TMB predicts ORR
IMvigor210 (cohort 2)[56]; phase II	Atezolizumab	ORR	aUC, post-PLT setting; $n = 315$ (310 treated)	15	• <1% on ICs: 8 • 1% to <5% on ICs: 10 • ≥5% on ICs: 26	• mPFS: 2.1 • mOS: 11.4 • mDR: 13.7 (not reached)	16	• Ventana SP263 mAb • TCGA-T and TMB predictive of ORR
IMvigor211 (REF.[58]); phase III	Atezolizumab versus physician's choice of chemotherapy (vinflunine, paclitaxel or docetaxel)	ORR in PD-L1$^+$ patients (≥5% PD-L1 expression of immune cells)	aUC; $n = 931$	13 versus 13	≥5% on ICs: 23 versus 22	• OS for PD-L1 ≥5% on ICs: 11.1 versus 10.6 (HR 0.87; $P = 0.41$) • OS for PD-L1 ITT population: 8.6 versus 8.0 (HR 0.85; NS)	20 versus 43	• Ventana SP142 mAb • PD-L1 expression not predictive

Study details	Treatment	End points	Patient selection	ORR (%)	RR by PD-L1 expression (%)	Survival (months)	Grade 3–4 toxicity (%)	IHC mAb and comments
Massard et al. 2016 (REF.[59]); phase I/II	Durvalumab	Safety, ORR	mUBC, any line; 31.1% ≥3 lines; $n = 61$ (42 evaluable)	31	• ≥25% on TCs and ICs: 46.4 • <25% on TCs and ICs: 0	Not reported	G3: 4.9	• SP263 mAb • Median FU 4.3 months
Powles et al. 2017 (REF.[60]); phase I/II	Durvalumab	Safety, ORR	aUBC, any line; 95.3% post-PLT setting; $n = 191$	17.8	• ≥25% on TCs and ICs: 27.6 • <25% on TCs and ICs: 5.1	• mPFS: 1.5 • mOS: 18.2 (median FU only 4.3 months)	6.8	• SP263 mAb • High ORR in LN only disease
JAVELIN[61]; phase I	Avelumab	Safety, tolerability, ORR	mUC, post-PLT setting; $n = 44$	18.2	• ≥5% on TCs: 50 • <5% on TCs: 4.3	• mPFS: 2.9 • mOS: 13.7	6.8	• Dako 73-10 mAb • 5 CRs
JAVELIN (updated)[62]; phase I	Avelumab	Safety, tolerability, ORR	aUC, post-PLT setting or PLT-ineligible setting; $n = 249$ (161 second line)	16	• ≥5% on TCs: 24 • <5% on TCs: 13	• mPFS: 1.6 • mOS: 6.5	8	• Dako 73-10 mAb • Pooled analysis of 2 cohorts

Alifrangis C. et al Nature Rev. Urology 2019

Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

Cell 2017



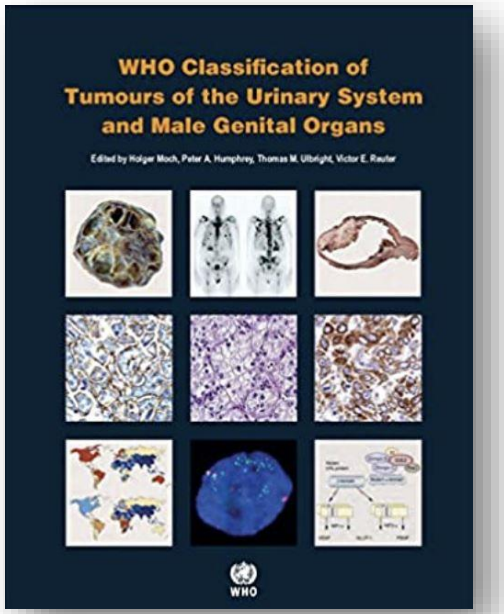
Take home points

- Urothelial Dysplasia is on the way out ☺
- UPUMP no more
- Invasive urothelilal carcinoma subtypes and divergent differentiation should be recognized and stated
- The many flavors of Nested subtype
- Grading: WHO 04 survives
- pT1 substaging should be attempted

Take home points

- Integrated genomic and transcriptomic analysis has improved the identification of clinically relevant **intrinsic molecular subtypes** of MIBC and UrCa Subtypes
- Molecular subtyping can help predict response to **NAC**
- **ICI** lead to durable response in subsets of MIBC that could be refined by molecular subtyping (prospective trials)

THANK YOU !



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 neoplasms	
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 carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Well-differentiated neuroendocrine tumour	8240/3
Paraganglioma	8693/1
Melanocytic tumours	
Malignant melanoma	8720/3
Naevus	8720/0
Melanosis	
Mesenchymal tumours	
Rhabdomyosarcoma	8900/3
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Inflammatory myofibroblastic tumour	8825/1
Perivascular epithelioid cell tumour	
Benign	8714/0
Malignant	8714/3
Solitary fibrous tumour	8815/1
Leiomyoma	8890/0
Haemangioma	9120/0
Granular cell tumour	9580/0
Neurofibroma	9540/0
Urothelial tract haematopoietic and lymphoid tumours	
Miscellaneous tumours	
Carcinoma of Skene, Cowper, and Littre glands	8140/3
Metastatic tumours and tumours extending from other organs	
Epithelial tumours of the upper urinary tract	
Tumours arising in a bladder diverticulum	
Urothelial tumours of the urethra	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [917A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification [756A], taking into account changes in our understanding of these lesions.

WHO Classification of the Urinary and Male Genital Tumours
5th edition series

Urothelial Tumours
Non-Invasive Urothelial Neoplasia
Urothelial papilloma
Inverted urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Non-invasive papillary urothelial carcinoma, low-grade
Non-invasive papillary urothelial carcinoma, high-grade
Urothelial carcinoma in situ
Invasive Urothelial Neoplasia
Invasive urothelial carcinoma
Squamous cell neoplasms
Urothelial squamous cell papilloma
Verrucous carcinoma of the bladder
Pure urothelial squamous cell carcinoma
Glandular neoplasms
Adenomas
Villous adenoma
Adenocarcinomas
Adenocarcinoma NOS
Urachal and diverticular neoplasms
Urachal carcinoma
Diverticular carcinoma
Urethral neoplasms
Urethral accessory gland carcinomas
Littre gland carcinoma of the urethra
Skene gland carcinoma of the urethra
Cowper gland carcinoma of the urethra
Tumours of Mullerian type
Clear cell adenocarcinoma
Endometrioid carcinoma

Bladder Cancer (MIBC)
TCGA 2014

- Integrated genomic analysis of **131 MIBC**

- Average Genetic Alterations per tumor:
  - 302 mutations
  - 204 segmental CNA
  - 22 rearrangements

- Recurrent mutations in **32 genes**:
  - Cell-cycle regulation
  - Chromatin regulation
  - RTK signaling pathways
  - Nine genes not frequently mutated in cancers (MLL2,ERCC2,ELF3,KLF5,RXRA, CDKN1A)

- **Rx Targets in 69%** of MIBC

NEW GENOMIC TAXONOMY ?

TCGA 2014

INTEGARTED GENE EXPRESSION SUBTYPES

PAPILLARY-LIKE

BASAL / SQUAMOUS-LIKE

LUMINAL / BREAST-LIKE

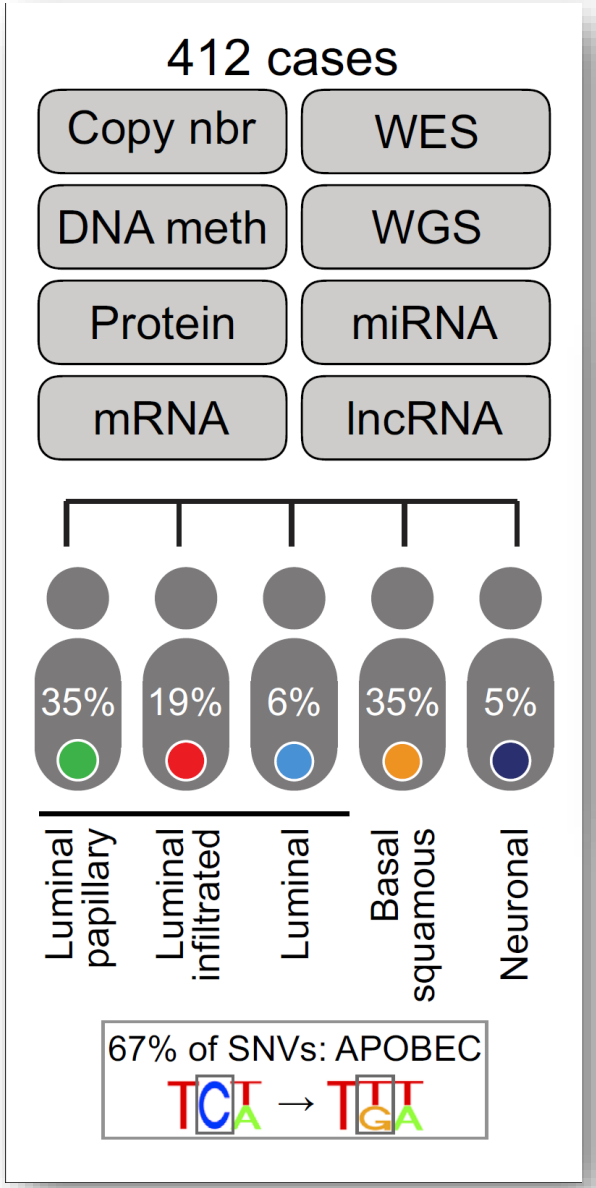
TCGA

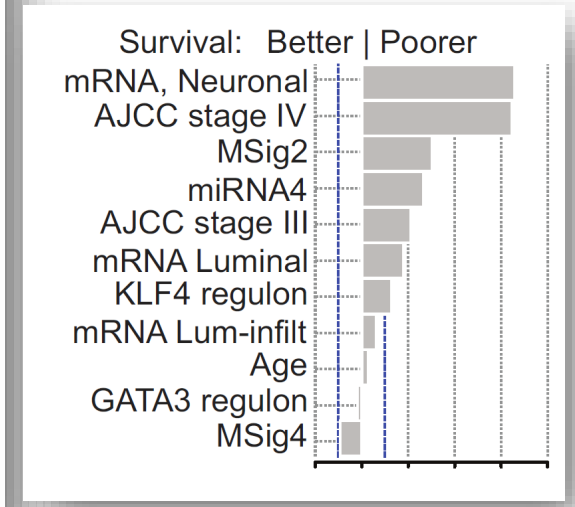
Cell 2017

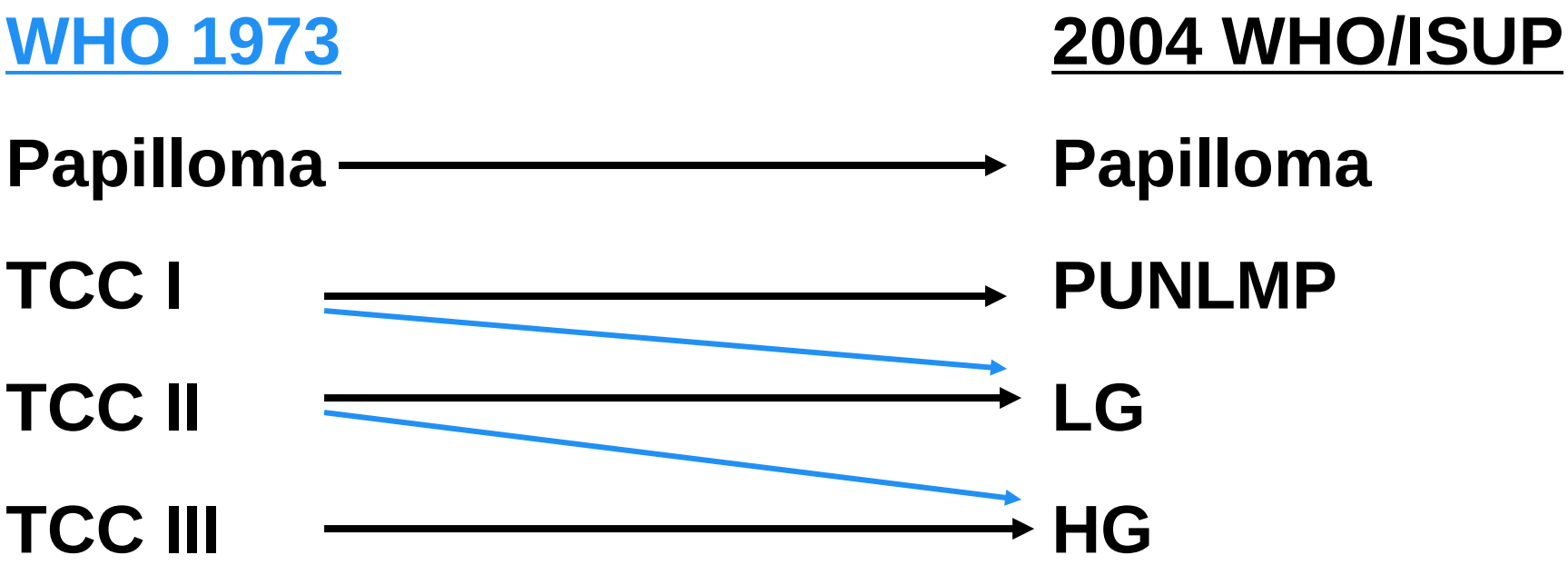
- 412 MIBC
- Integrated molecular platforms

- High mutation rates *(mean 8.2/MB)*
  - ✓ **58** frequently mutated genes
  - ✓ **5** mutagenesis signatures ***(APOBEC)***
  - ✓ **4** mutation signature clusters ***(MSig1-4)***

- **5** Expression molecular subtypes

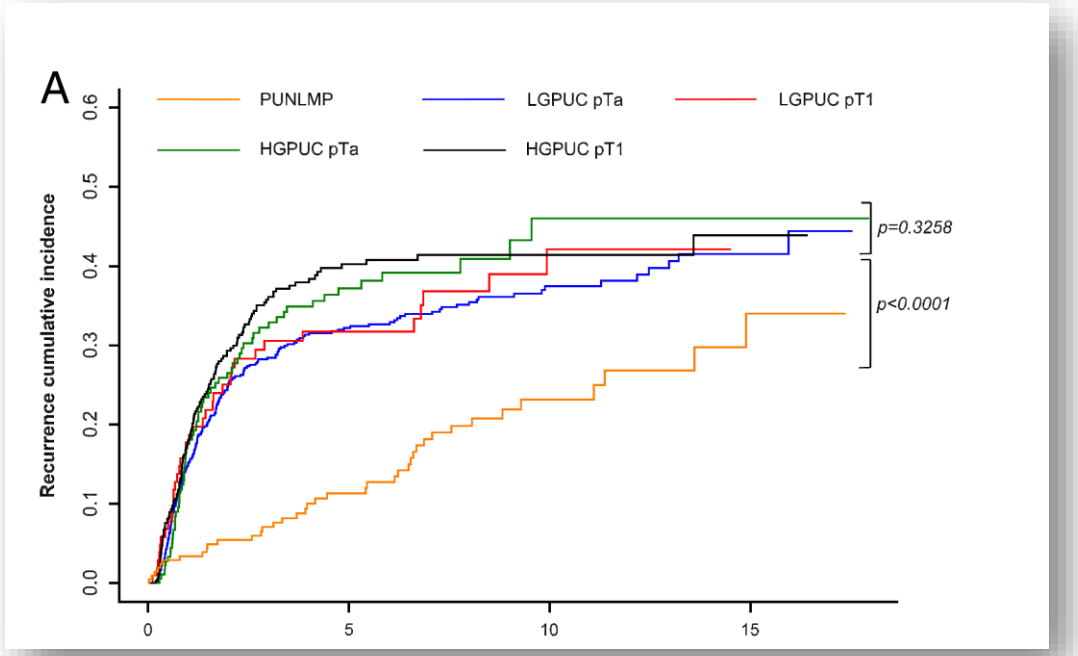





WHO 1973
2004 WHO/ISUP
Papilloma
Papilloma
TCC I
PUNLMP
TCC II
LG
TCC III
HG

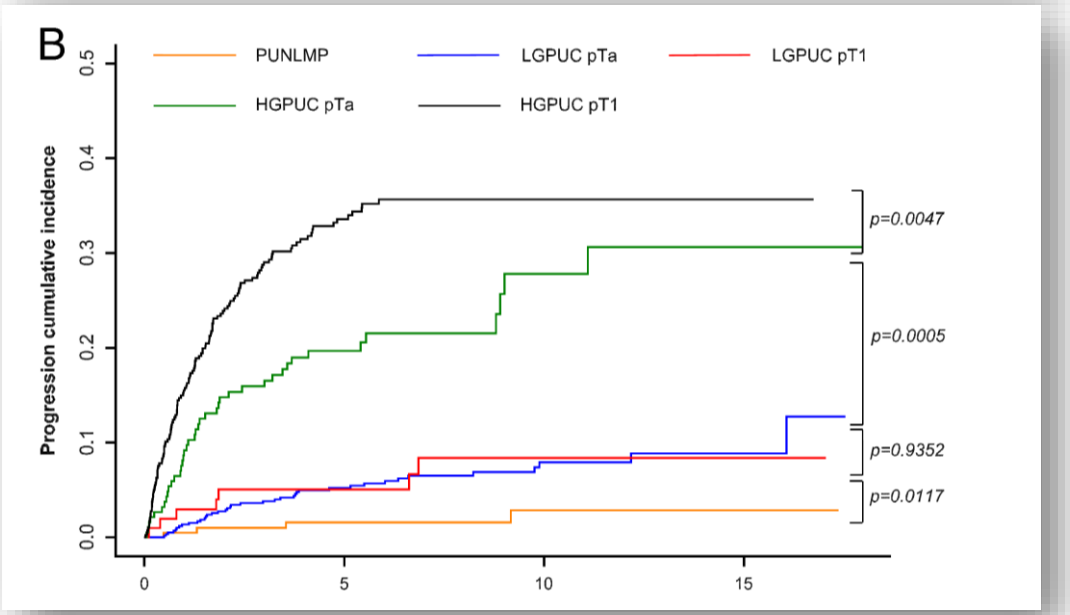
HISTOLOGIC FEATURES OF PAPILLARY UROTHELIAL LESIONS

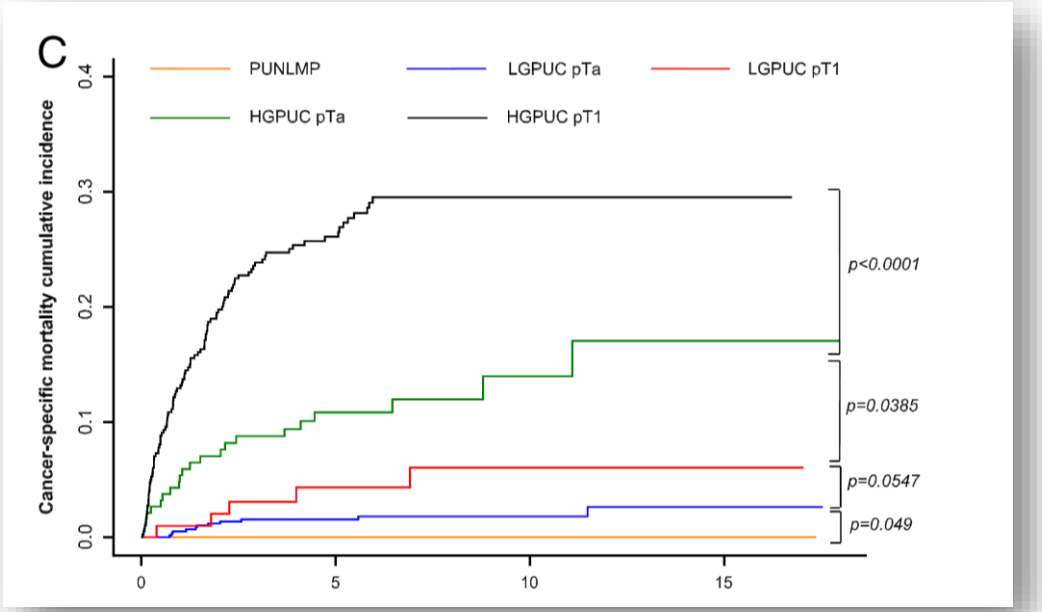
	Papilloma	**Papillary neoplasm of low malignant potential**	**Low-grade papillary carcinoma**	**High-grade papillary carcinoma**
Architecture				
Papillae	Delicate.	Delicate. Occasionally fused.	Fused, branching, and delicate.	Fused, branching and delicate.
Organization of cells	Identical to normal.	Polarity identical to normal. Any thickness. Cohesive.	Predominantly ordered, yet minimal crowding and minimal loss of polarity. Any thickness. Cohesive.	Predominantly disordered with frequent loss of polarity. Any thickness. Often dyscohesive.
Cytology				
Nuclear size	Identical to normal.	May be uniformly enlarged.	Enlarged with variation in size.	Enlarged with variation in size.
Nuclear shape	Identical to normal.	Elongated, round-oval, uniform.	Round-oval. Slight variation in shape and contour.	Moderate-marked pleomorphism.
Nuclear chromatin	Fine.	Fine.	Mild variation within and between cells.	Moderate-marked variation both within and between cells with hyperchromasia.
Nucleoli	Absent.	Absent to inconspicuous.	Usually inconspicuous.	Multiple prominent nucleoli may be present.
Mitoses	Absent	Rare, basal.	Occasional, at any level.	Usually frequent, at any level. May be atypical
Umbrella cells	Uniformly present.	Present.	Usually present.	May be absent.



The Genitourinary Pathology Society Update on Classification and Grading of Flat and Papillary Urothelial Neoplasia With New Reporting Recommendations and Approach to Lesions With Mixed and Early Patterns of Neoplasia

Adv Anat Pathol • Volume 28, Number 4, July 2021





Pan CC et al. AJCP 2010

Histopathology 2019, **75**, 865–875. DOI: 10.1111/his.13958

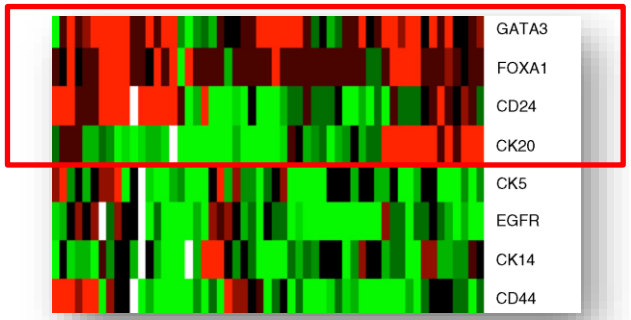
Distinct genetic alterations and luminal molecular subtype in nested variant of urothelial carcinoma

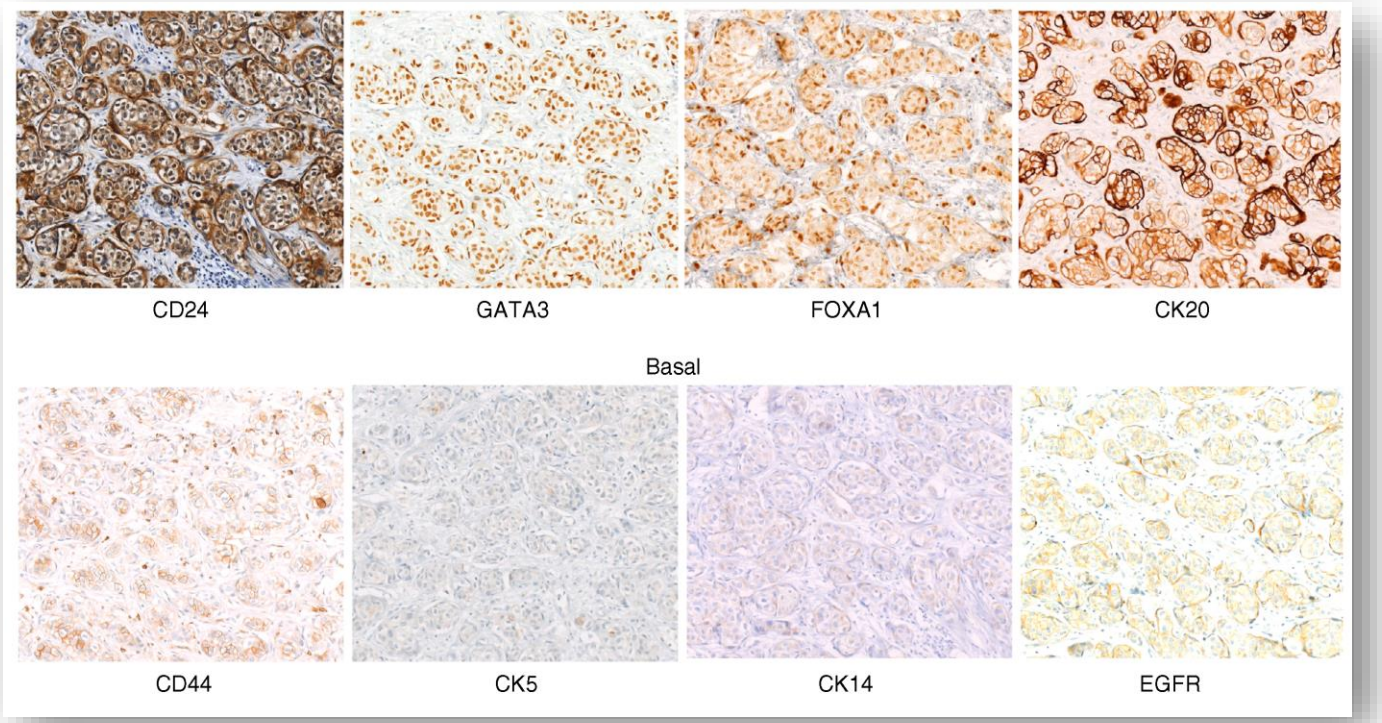
Veronika Weyerer,[1,*] Rebecca Weisser,[1,*] Evgeny A Moskalev,[1] Florian Haller,[1] Robert Stoehr,[1] Markus Eckstein,[1] Ulrike Zinnall,[1,2] Nadine T Gaisa,[3] Eva Compérat,[4] Aurel Perren,[5] Bastian Keck,[6,7] Yves Allory,[8] Glen Kristiansen,[9] Bernd Wullich,[6] Abbas Agaimy,[1] Arndt Hartmann[1] & Simone Bertz[1]

- 60 Nested UrCa
- **TERT** promoter mutation and **NGS panel of 48 genes** (in 26 cases)

- 62.5% TERT promoter mutations
- **TP53, JAK3 & CTNNB1** most frequently mutated

- All expressed **luminal markers**





Take home points

- Integrated genomic and transcriptomic analysis has improved the identification of clinically relevant **intrinsic molecular subtypes** of MIBC and UrCa Subtypes
- Molecular subtyping can help predict response to **NAC**
- **ICI** lead to durable response in subsets of MIBC that could be refined by molecular subtyping (prospective trials)
- **Targeted Rx** is promising (FGR3 and VEGF-R inhibitors)

Reproducibility and Prognostic Value of WHO1973 and WHO2004 Grading Systems in TaT1 Urothelial Carcinoma of the Urinary Bladder

Mangrud et al PLOS 2013

Inter-observer Reproducibility

	Overall agreement (95% CI)	Kappa (95% CI)
WHO73	66% (59–73%)	0.68 (0.57–0.78)*
WHO73 (1&2 vs. 3)	89% (83–93%)	0.68 (0.56–0.80)
WHO04	87% (81–91%)	0.70 (0.59–0.81)

*: Quadratic weighted kappa.
CI: Confidence interval.
doi:10.1371/journal.pone.0083192.t002

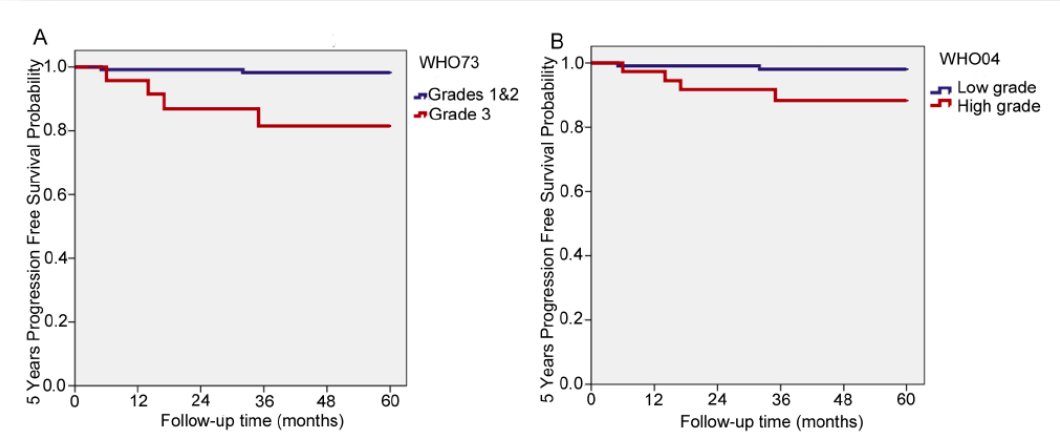
Intra-observer Reproducibility

	Pathologist 1		Pathologist 2	
	Overall agreement (95% CI)	**Estimated kappa (95% CI)**	**Overall agreement (95% CI)**	**Estimated kappa (95% CI)**
WHO73	68% (61–74%)	0.69 (0.59–0.79)*	63% (56–70%)	0.61 (0.48–0.74)*
WHO73 (1&2 vs. 3)	88% (82–92%)	0.66 (0.54–0.79)	89% (83–93%)	0.68 (0.55–0.80)
WHO04	Not performed	Not performed	93% (88–96%)	0.83 (0.74–0.92)

5 Year Recurrence Free Survival

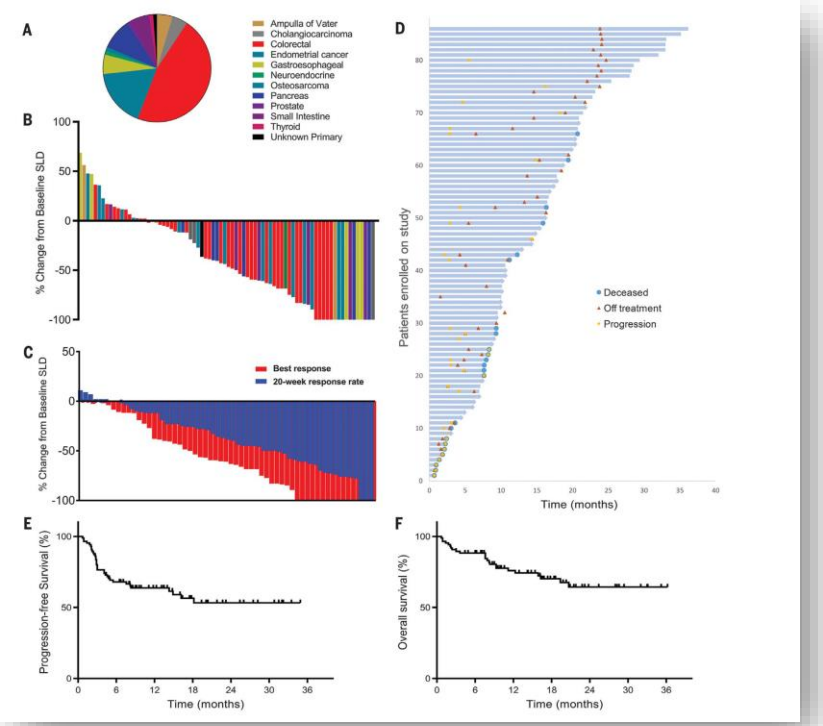
	Threshold	Recurrence/patients n (%)
WHO73	Grade 1	25/44 (57)
	Grade 2	45/98 (46)
	Grade 3	31/51 (61)
WHO73 (1&2 vs. 3)	Grades 1&2	70/142 (49)
	Grade 3	31/51 (61)
WHO04	Low grade	61/119 (51)
	High grade	40/74 (54)

5 Year Progression Free Survival (PFS)



Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

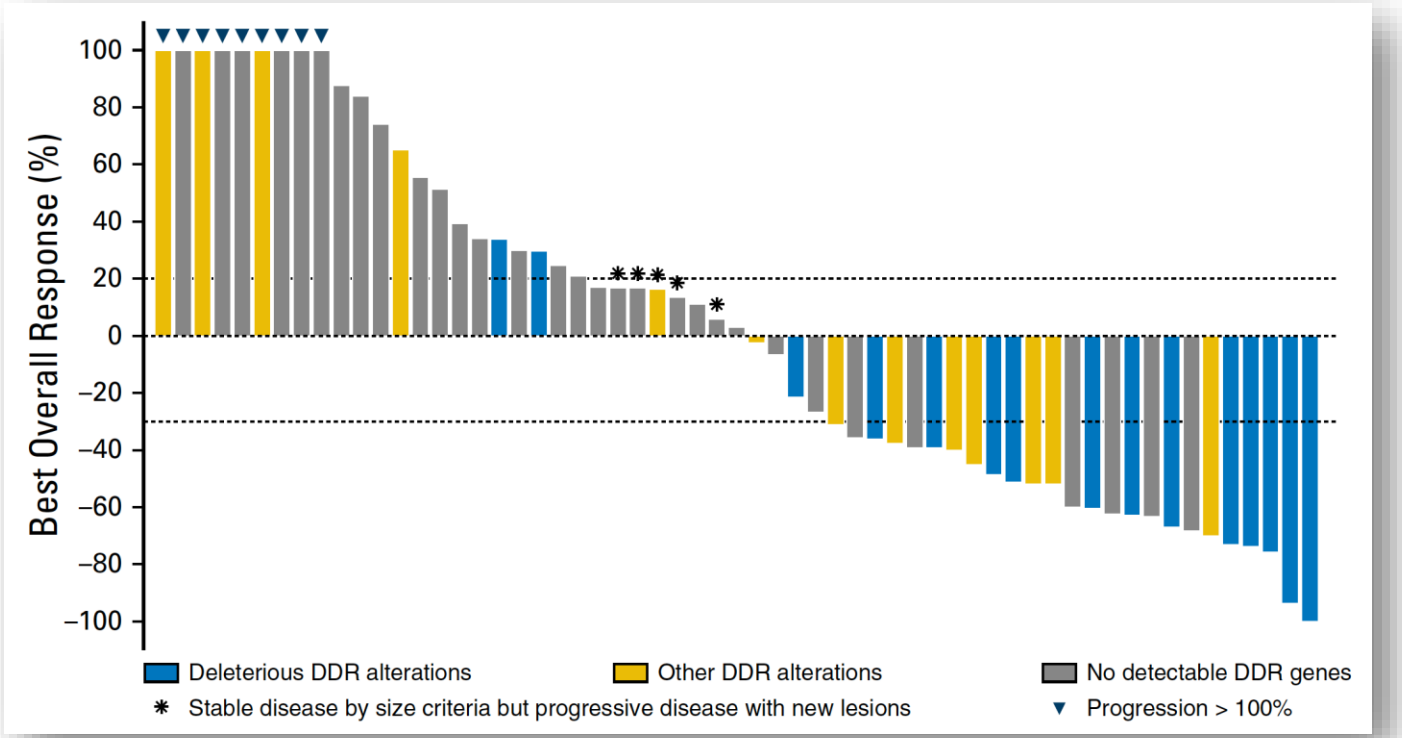
Dung T. Le,[1,2,3] Jennifer N. Durham,[1,2,3]* Kellie N. Smith,[1,3]* Hao Wang,[3]* Bjarne R. Bartlett,[2,4]* Laveet K. Aulakh,[2,4] Steve Lu,[2,4] Holly Kemberling,[3] Cara Wilt,[3] Brandon S. Luber,[3] Fay Wong,[2,4] Nilofer S. Azad,[1,3] Agnieszka A. Rucki,[1,3] Dan Laheru,[3] Ross Donehower,[3] Atif Zaheer,[5] George A. Fisher,[6] Todd S. Crocenzi,[7] James J. Lee,[8] Tim F. Greten,[9] Austin G. Duffy,[9] Kristen K. Ciombor,[10] Aleksandra D. Eyring,[11] Bao H. Lam,[11] Andrew Joe,[11] S. Peter Kang,[11] Matthias Holdhoff,[3] Ludmila Danilova,[1,3] Leslie Cope,[1,3] Christian Meyer,[3] Shibin Zhou,[1,3,4] Richard M. Goldberg,[12] Deborah K. Armstrong,[3] Katherine M. Bever,[3] Amanda N. Fader,[13] Janis Taube,[1,3] Franck Housseau,[1,3] David Spetzler,[14] Nianqing Xiao,[14] Drew M. Pardoll,[1,3] Nickolas Papadopoulos,[3,4] Kenneth W. Kinzler,[3,4] James R. Eshleman,[15] Bert Vogelstein,[1,3,4] Robert A. Anders,[1,3,15] Luis A. Diaz Jr.[1,2,3]†‡



Le et al., Science 2017

Alterations in DNA Damage Response and Repair Genes as Potential Marker of Clinical Benefit From PD-1/PD-L1 Blockade in Advanced Urothelial Cancers

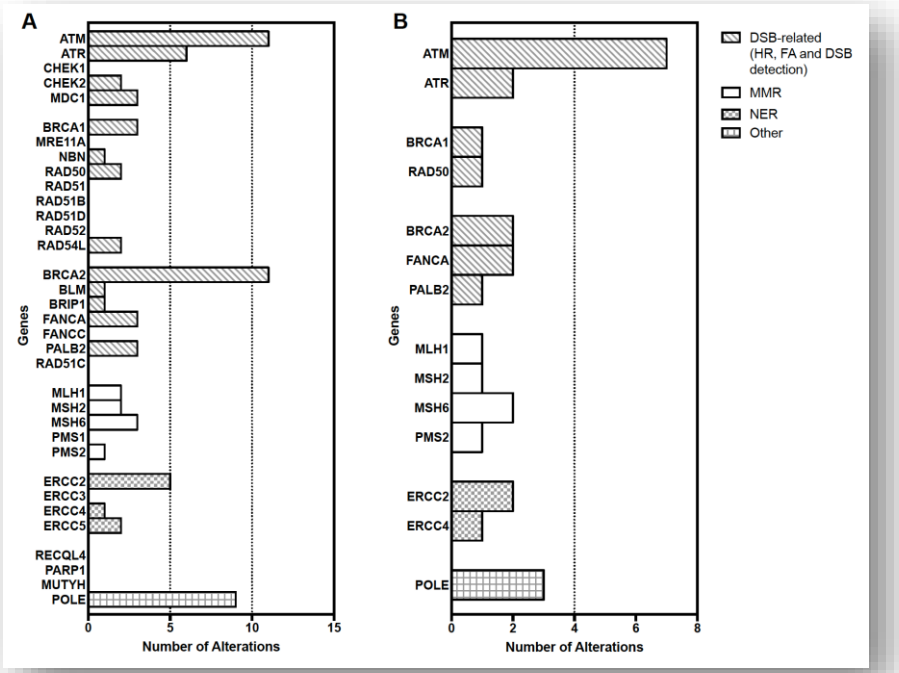
Min Yuen Teo, Kenneth Seier, Irina Ostrovnaya, Ashley M. Regazzi, Brooke E. Kania, Meredith M. Moran, Catharine K. Cipolla, Mark J. Bluth, Joshua Chaim, Hikmat Al-Ahmadie, Alexandra Snyder, Maria I. Carlo, David B. Solit, Michael F. Berger, Samuel Funt, Jedd D. Wolchok, Gopa Iyer, Dean F. Bajorin, Margaret K. Callahan, and Jonathan E. Rosenberg

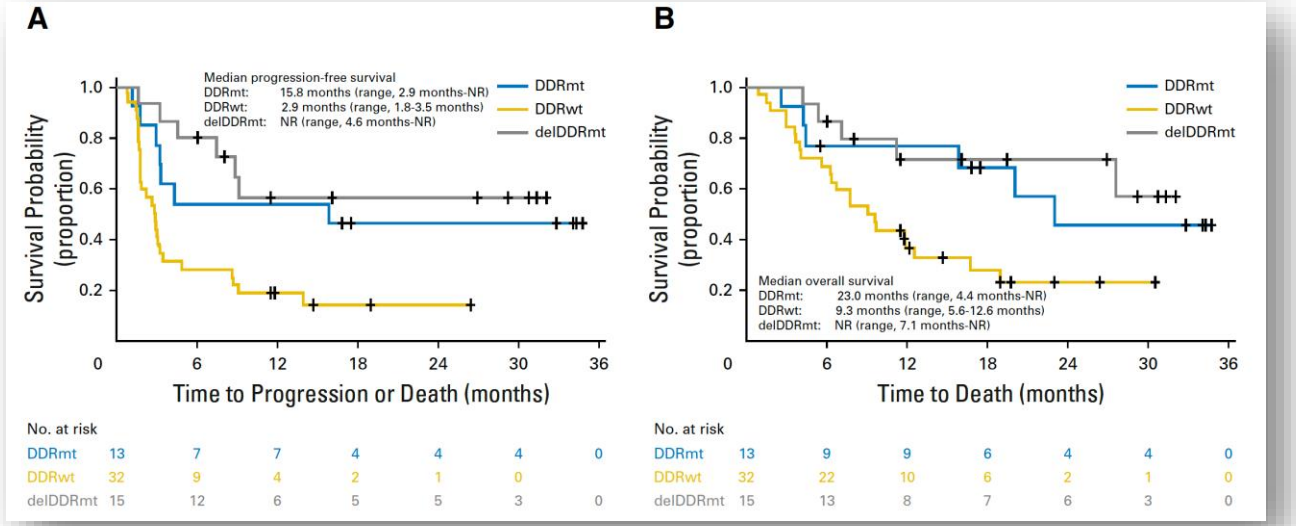


Teo MU et al., JCO 2018

Alterations in DNA Damage Response and Repair Genes as Potential Marker of Clinical Benefit From PD-1/PD-L1 Blockade in Advanced Urothelial Cancers

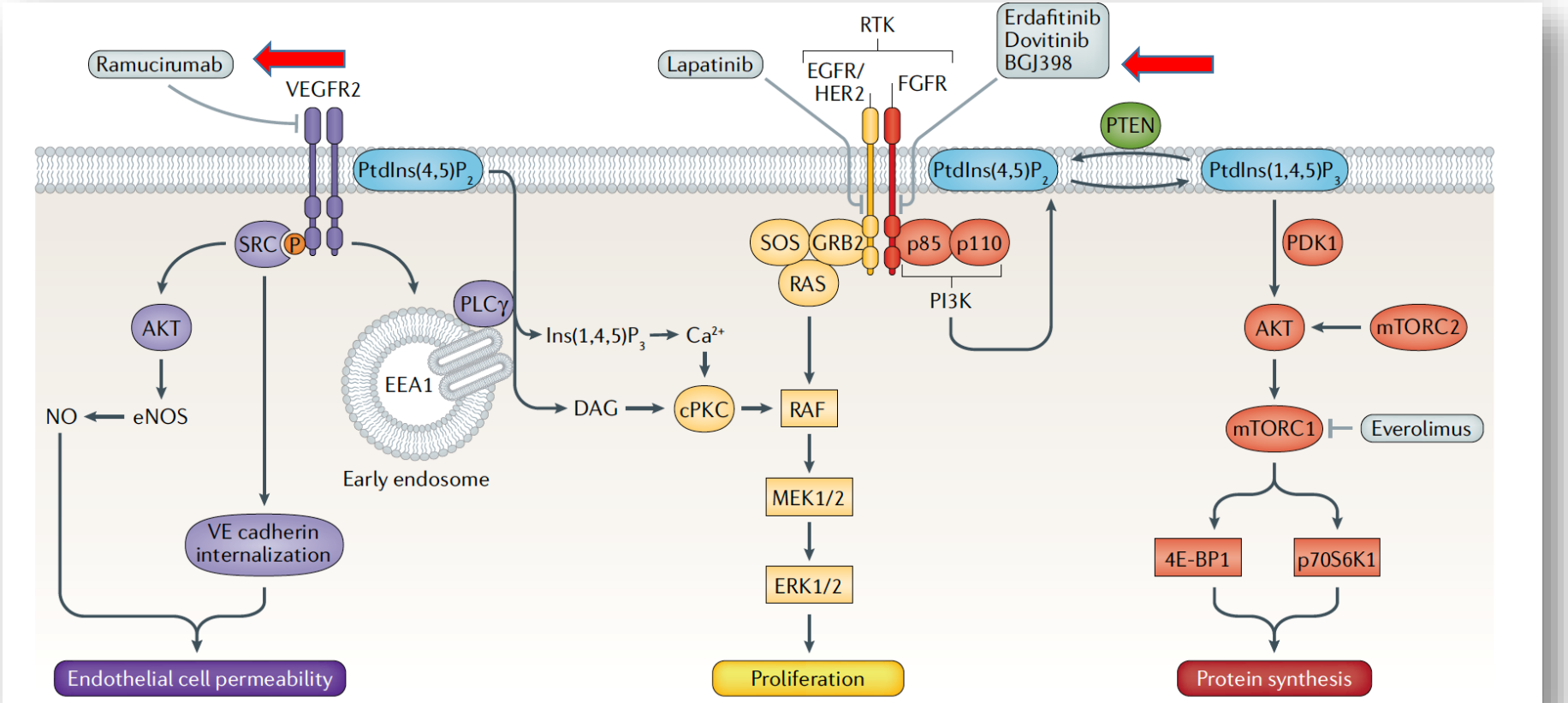
Min Yuen Teo, Kenneth Seier, Irina Ostrovnaya, Ashley M. Regazzi, Brooke E. Kania, Meredith M. Moran, Catharine K. Cipolla, Mark J. Bluth, Joshua Chaim, Hikmat Al-Ahmadie, Alexandra Snyder, Maria I. Carlo, David B. Solit, Michael F. Berger, Samuel Funt, Jedd D. Wolchok, Gopa Iyer, Dean F. Bajorin, Margaret K. Callahan, and Jonathan E. Rosenberg



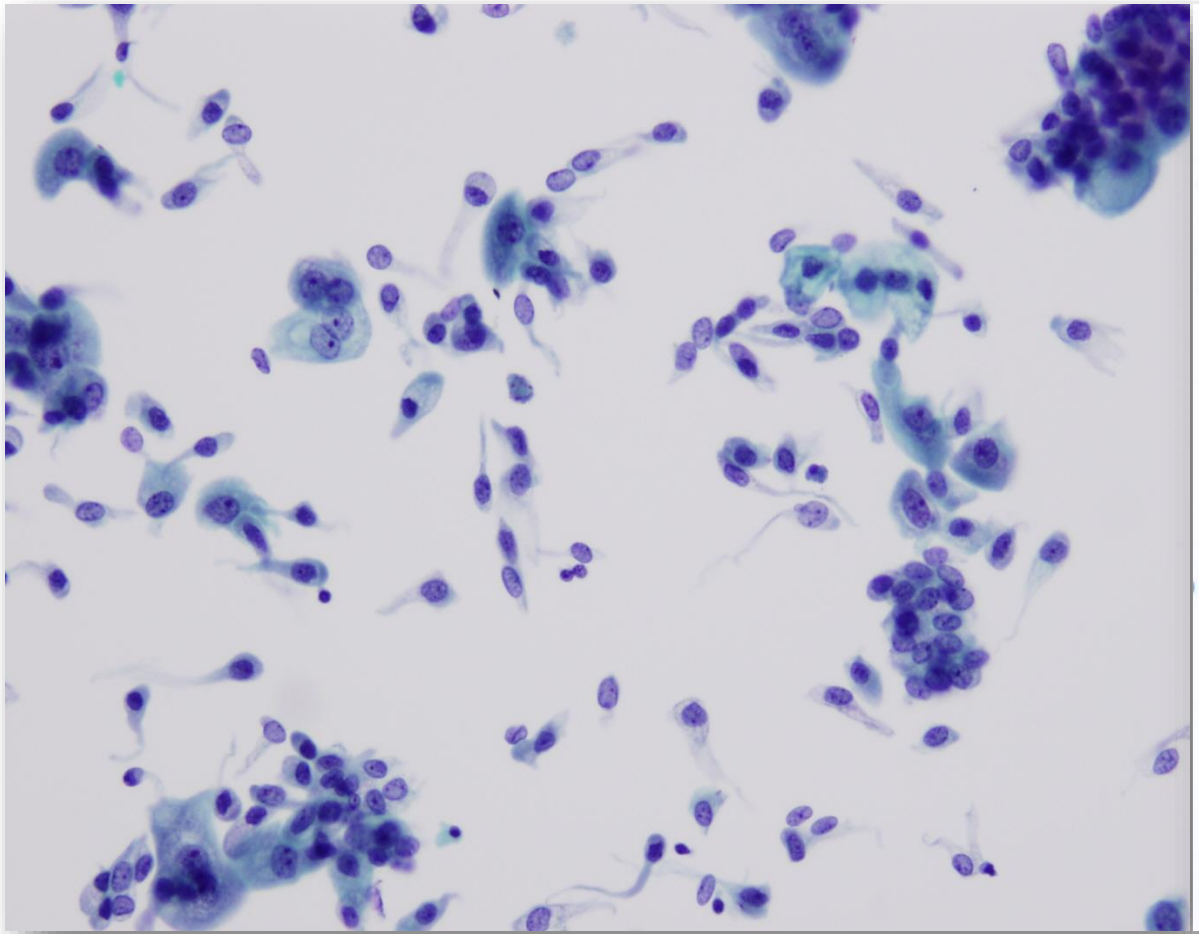


Teo MU et al., JCO 2018

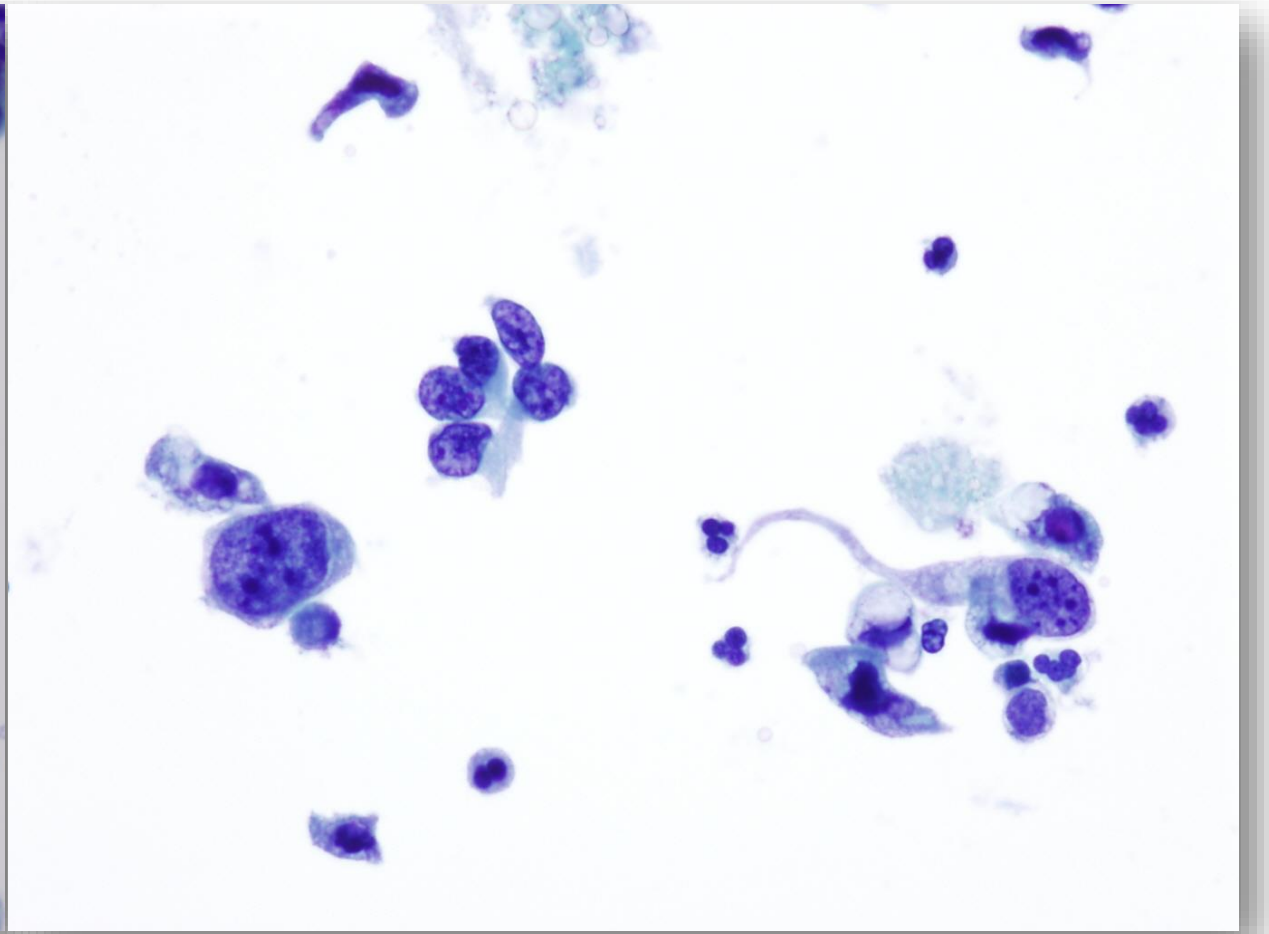
Targeted Signaling Pathways in Clinical Trials for Advanced BC



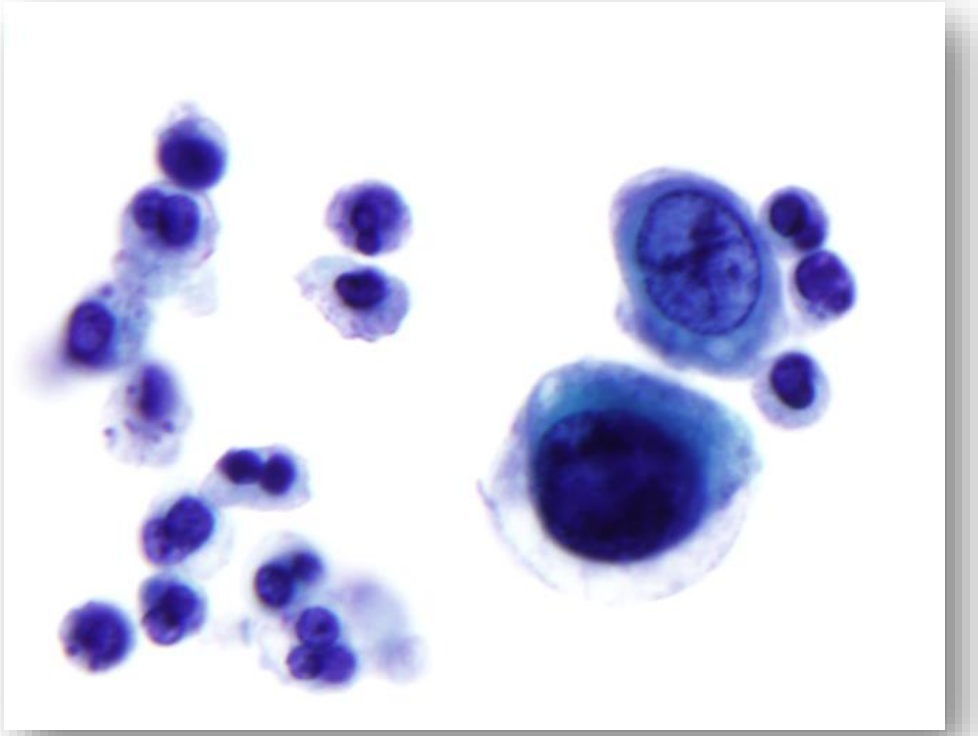
Alifrangis C. et al Nature Rev. Urology 2019



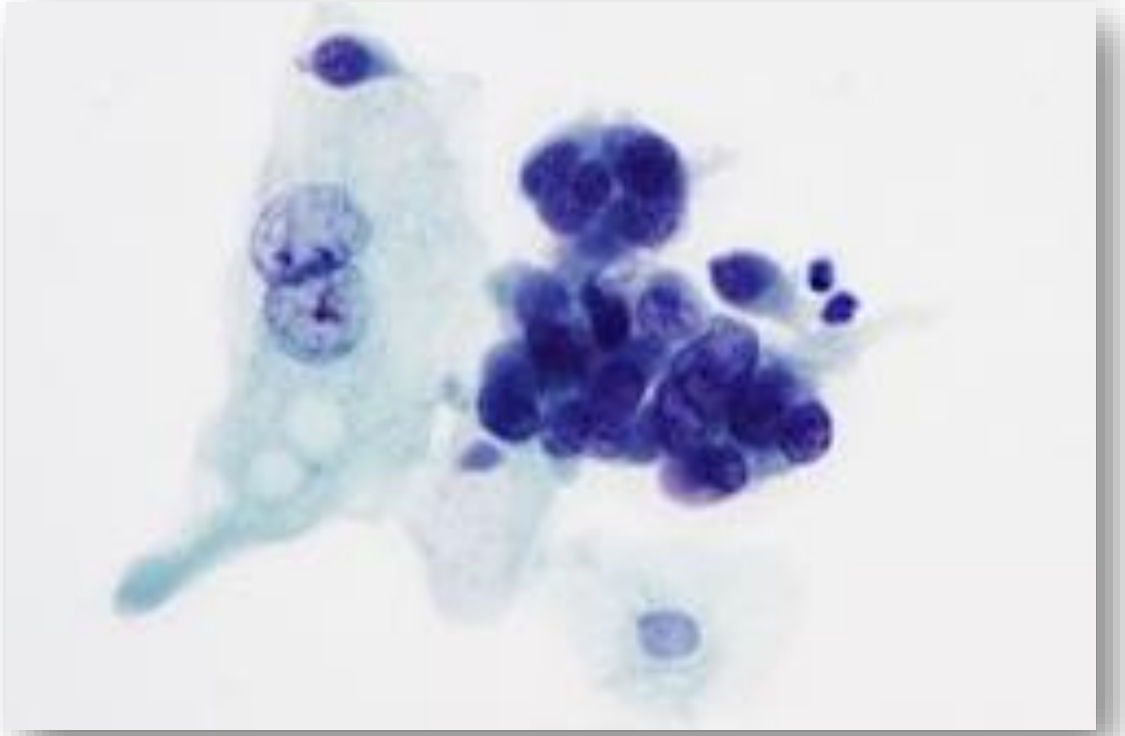
NHGUC



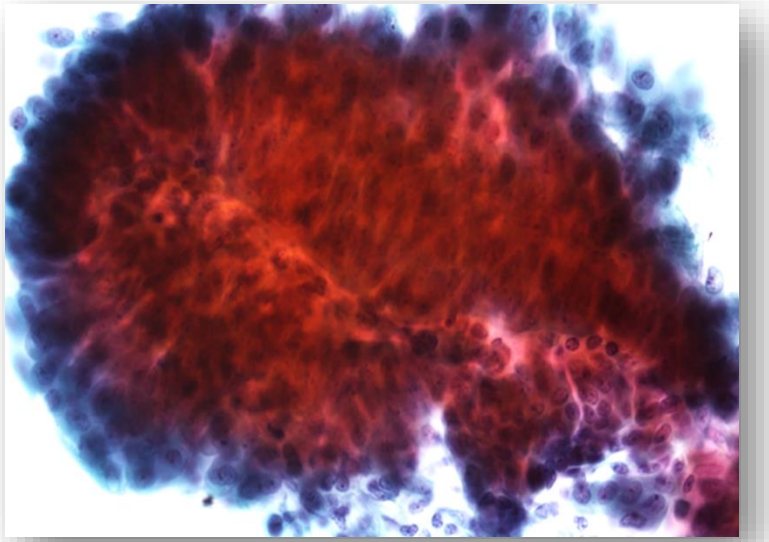
HGUC



AUC



SHGUC



LGUN

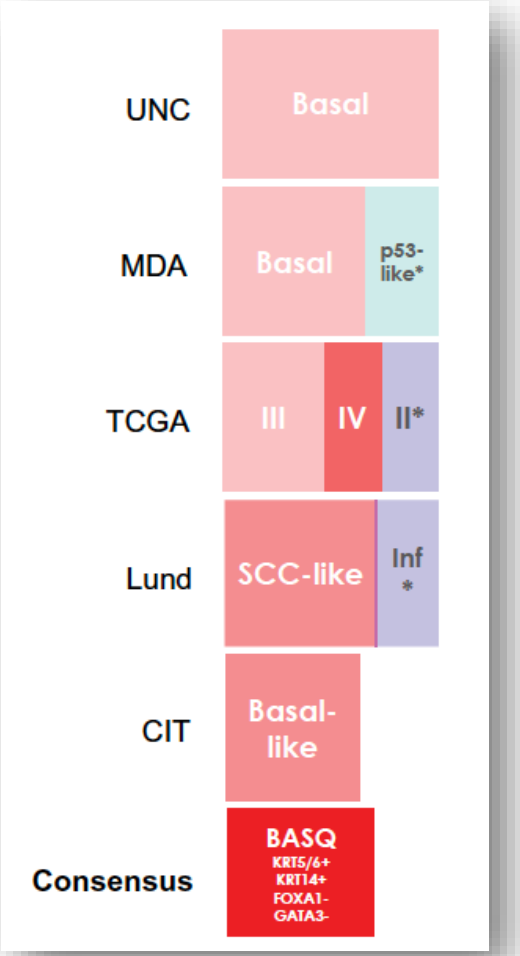
Bladder Cancer Molecular Taxonomy: Summary from a Consensus Meeting

Seth P. Lerner[a], David J. McConkey[b], Katherine A. Hoadley[c], Keith S. Chan[d], William Y. Kim[e], François Radvanyi[f], Mattias Höglund[g] and Francisco X. Real[h,*]

therefore, the group reached the consensus conclusion that a

"… subgroup of invasive bladder cancers can be identified as being **KRT5/6(+) KRT14(+)** FOXA1(−) GATA3(−)…"

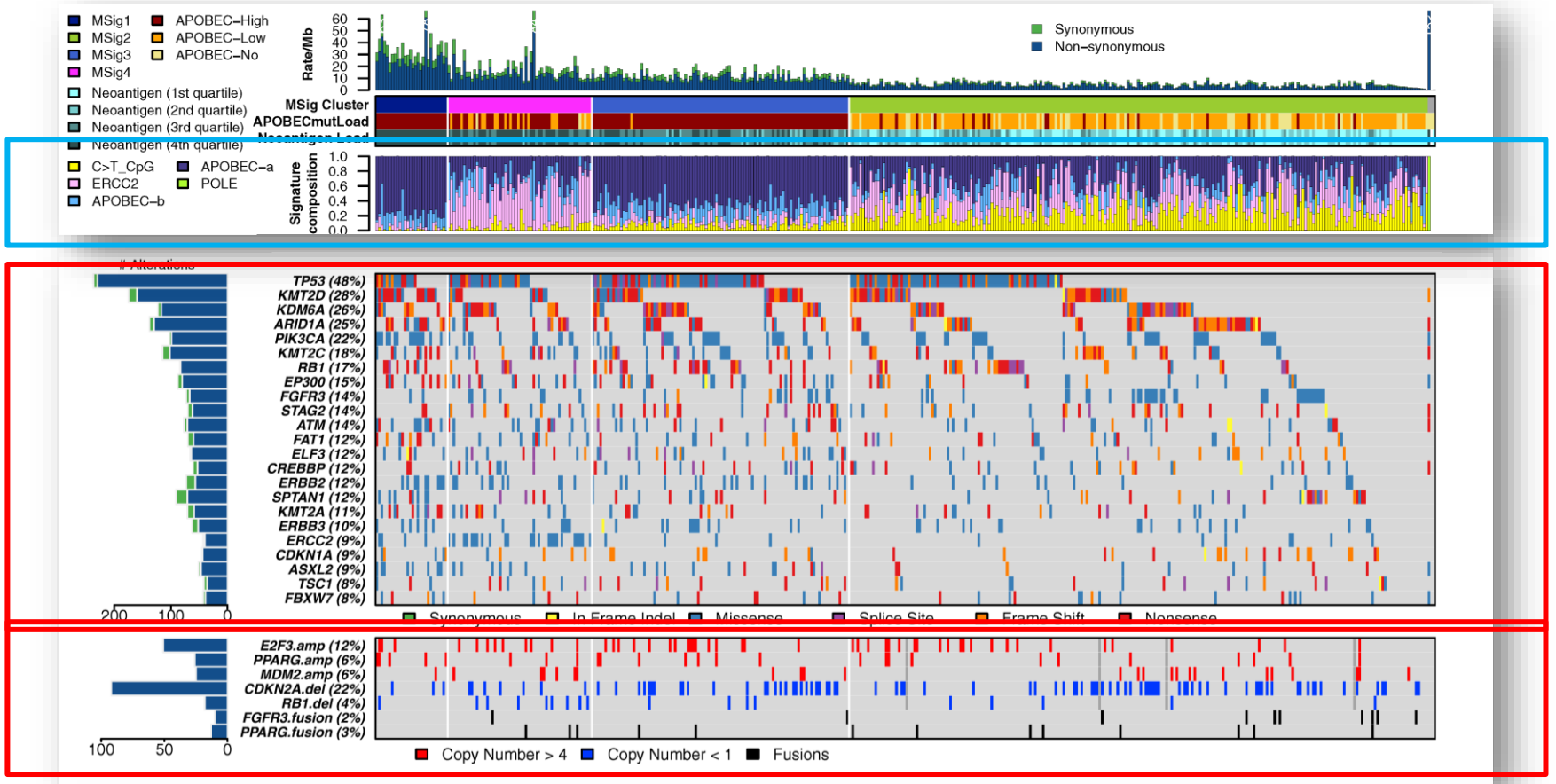
"… use **Basal/Squamous-like** (proposed acronym, **BASQ**) to designate these tumors…"

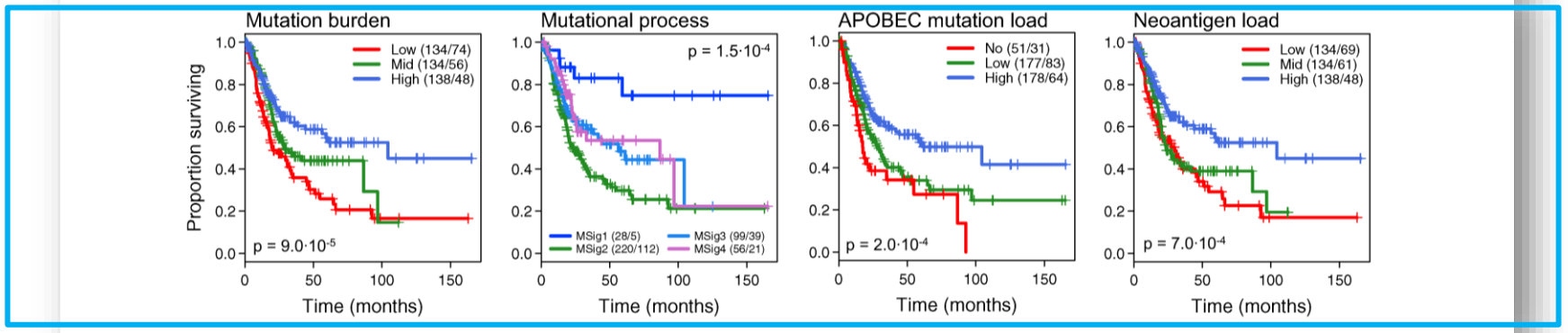


Bladder Cancer 2016

TCGA *2017*

MIBC Landscape of Mutational Signatures





Overview

Genomic Advances in Urothelial Carcinoma

- Bladder Cancer TCGA Studies: Genomic Taxonomy
- Immuno-oncology
- Molecular insights into Variants Histology
- UTUC Genomics

Liquid Biopsy

- Early Detection
- Prognostics and Rx Prediction

Computational Advances

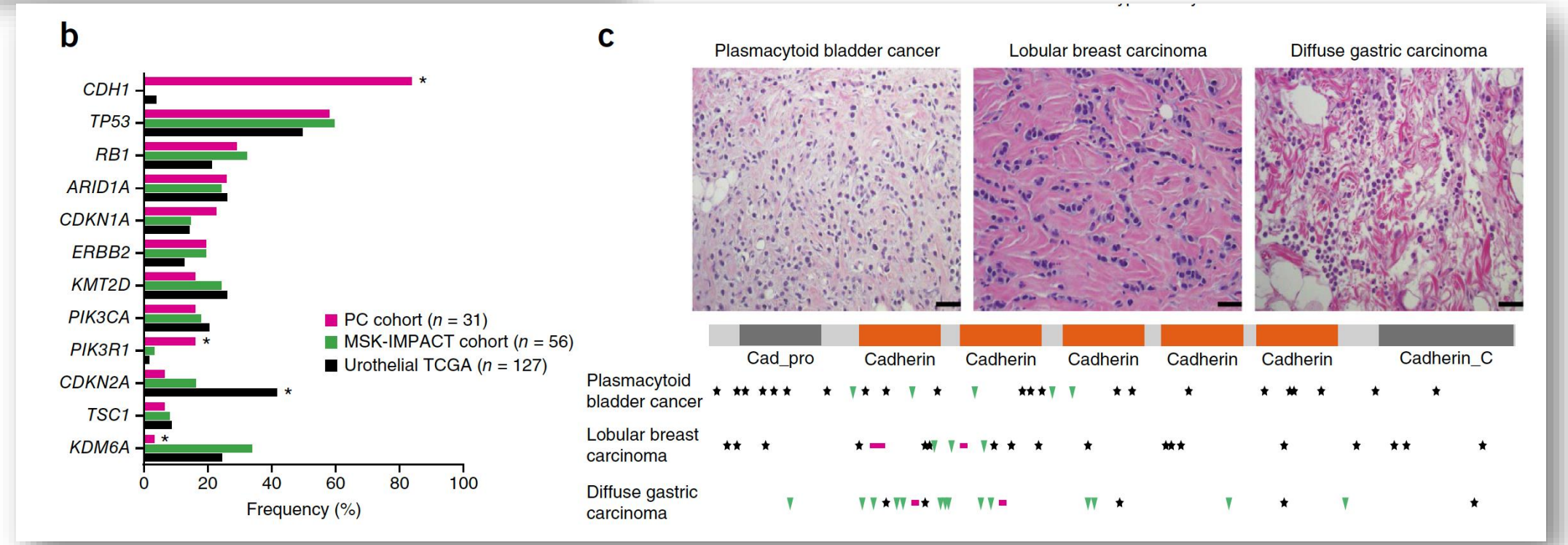
- Machine Learning/AI

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[10], 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]

Al-Ahmadie et al Nature Genetic 2016

- Whole-exome/MSK-IMPACT
- *CDH1* truncating **somatic** alterations
- 84% of plasmacytoid ca.

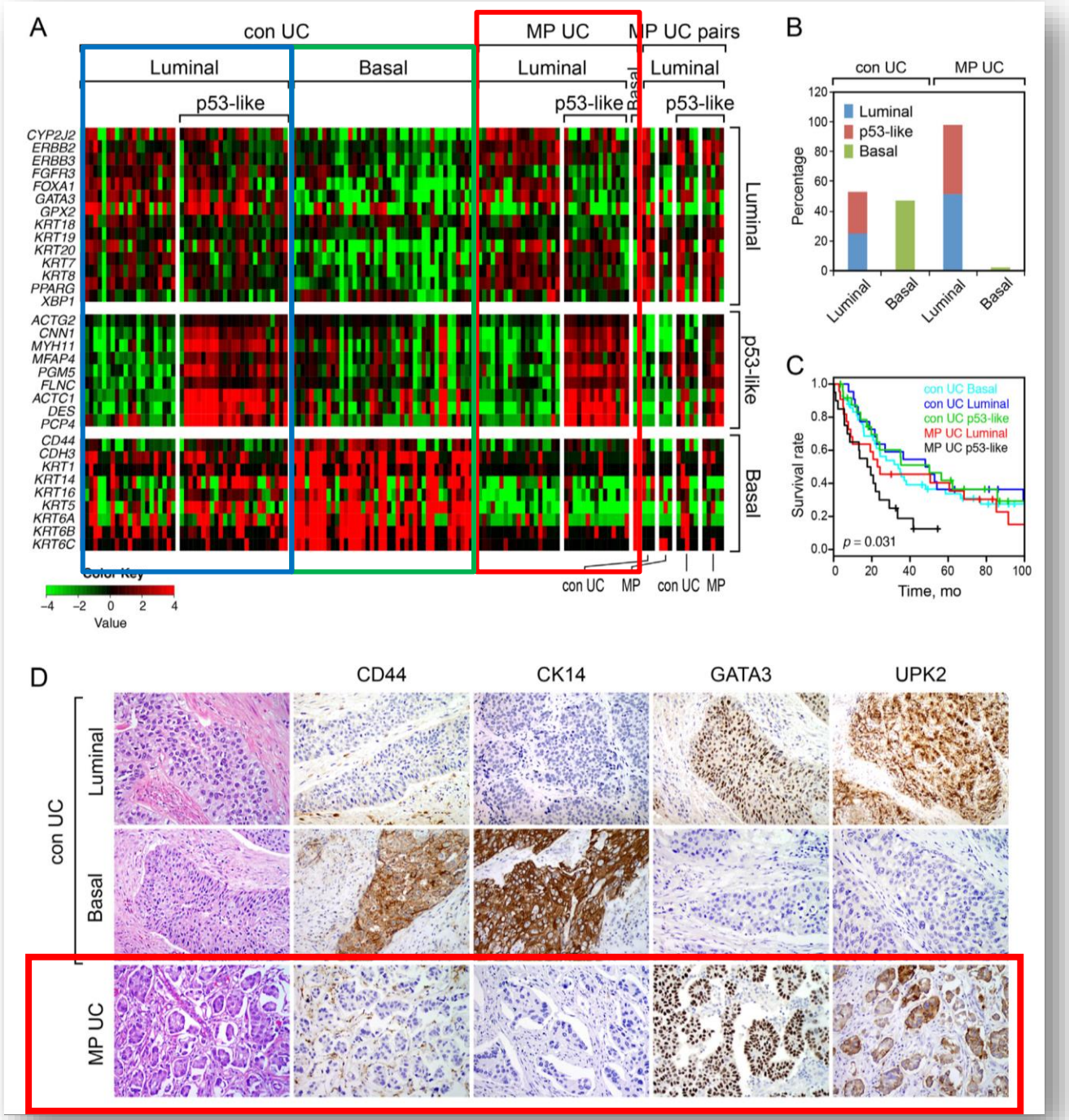


Gene Expression Profile of the Clinically Aggressive Micropapillary Variant of Bladder Cancer

Charles Chuanhai Guo [a,†], Vipulkumar Dadhania [a,†], Li Zhang [b,†], Tadeusz Majewski [a], Jolanta Bondaruk [a], Maciej Sykulski [c], Weronika Wronowska [d], Anna Gambin [c], Yan Wang [a], Shizhen Zhang [a], Enrique Fuentes-Mattei [a], Ashish Madhav Kamat [e], Colin Dinney [e], Arlene Siefker-Radtke [f], Woonyoung Choi [e], Keith A. Baggerly [b], David McConkey [e], John N. Weinstein [b], Bogdan Czerniak [a,]*

Guo et al 2016 European Urology

- 43 MP-UC; WES
- MP-UC almost exclusively **luminal**
- Enrichment of **PPARG** and suppression of p63 target genes
- Similar to luminal UrCa; a subset exhibits activation of wild-type p53 downstream genes (**p53-Like**)
- **P53-Like most aggressive** molecular subtype of MP-UC

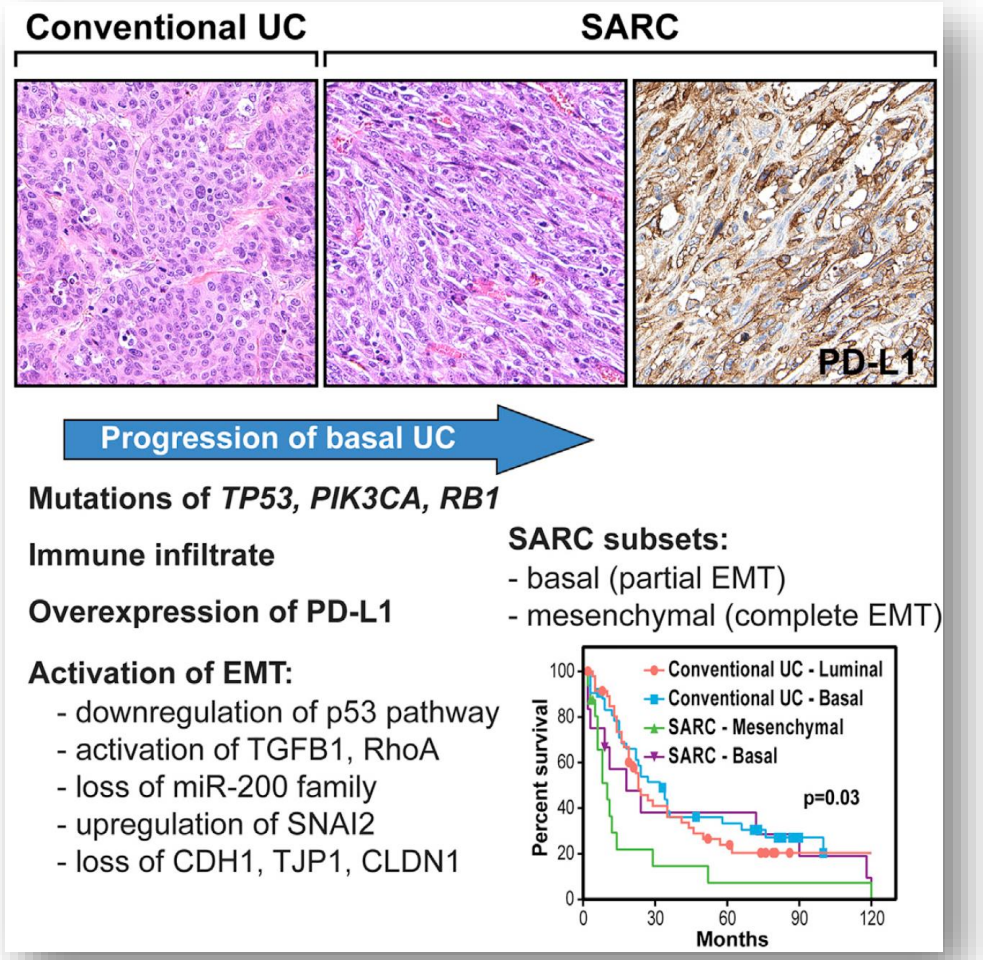


Dysregulation of EMT Drives the Progression to Clinically Aggressive Sarcomatoid Bladder Cancer

Charles C. Guo,[1,8] Tadeusz Majewski,[1,8] Li Zhang,[2,8] Hui Yao,[3] Jolanta Bondaruk,[1] Yan Wang,[1] Shizhen Zhang,[1] Ziqiao Wang,[4] June Goo Lee,[1] Sangkyou Lee,[1] David Cogdell,[1] Miao Zhang,[1] Peng Wei,[4] H. Barton Grossman,[5] Ashish Kamat,[5] Jonathan James Duplisea,[5] James Edward Ferguson III,[5] He Huang,[1] Vipulkumar Dadhania,[1] Jianjun Gao,[6] Colin Dinney,[5] John N. Weinstein,[3] Keith Baggerly,[3] David McConkey,[7] and Bogdan Czerniak[1,9,*]

Guo CC et al., Cell Reports 2019

- 28 Sarcomatoid Ca.
- **Progression from basal UrCa**
- Two subsets: **Basal** and **mesenchymal** (most aggressive) subsets **(p63)**
- **Drivers:** Dysregulation of **cell cycle** and **EMT networks**
- Infiltrated immune phenotype and upregulation of **PD-L1**

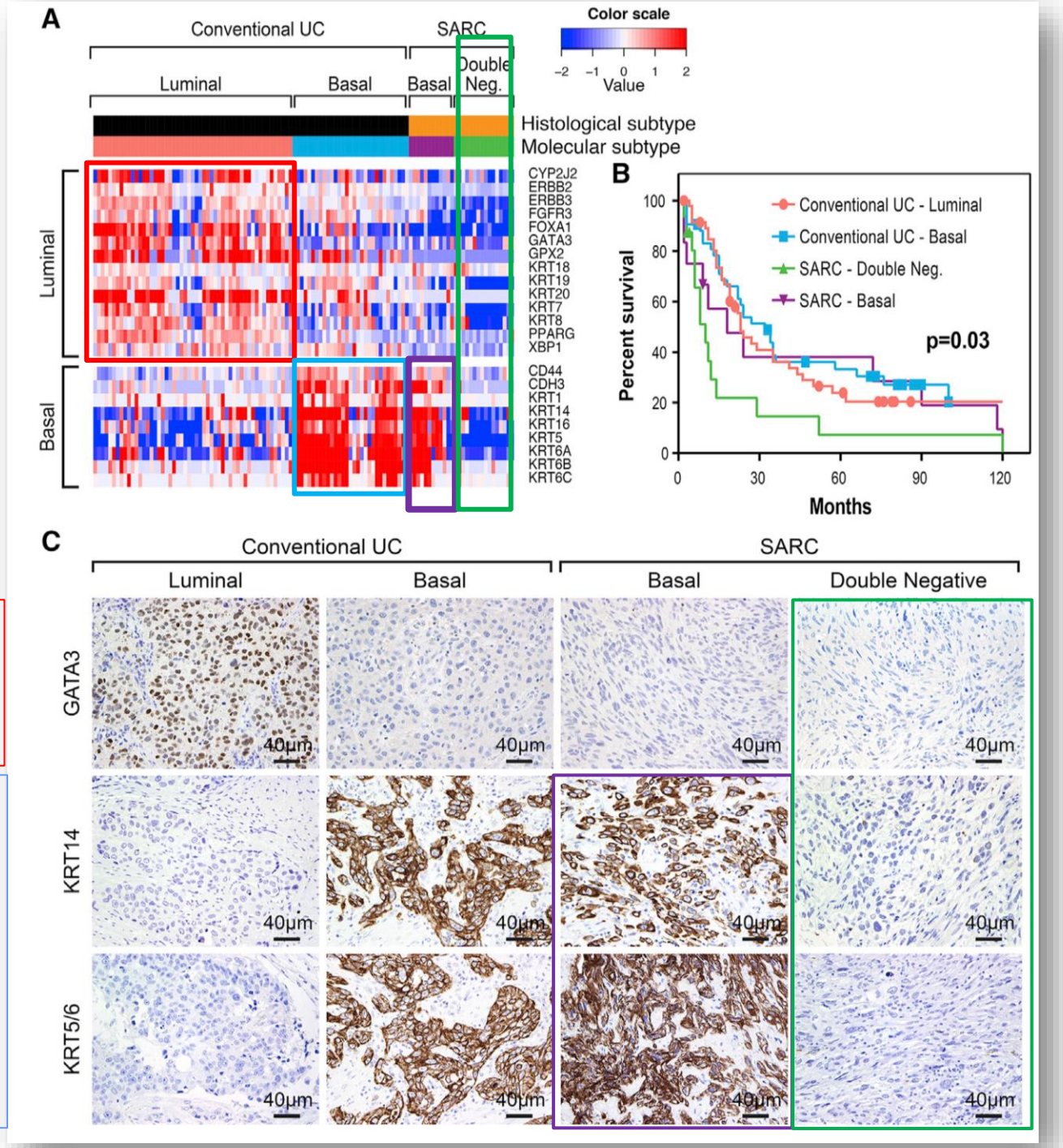


Dysregulation of EMT Drives the Progression to Clinically Aggressive Sarcomatoid Bladder Cancer

Guo CC et al., Cell Reports 2019

LUM IHC

BASAL IHC



Histopathology 2019, **75**, 865–875. DOI: 10.1111/his.13958

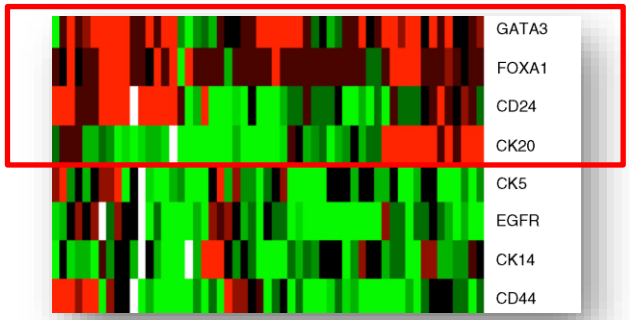
Distinct genetic alterations and luminal molecular subtype in nested variant of urothelial carcinoma

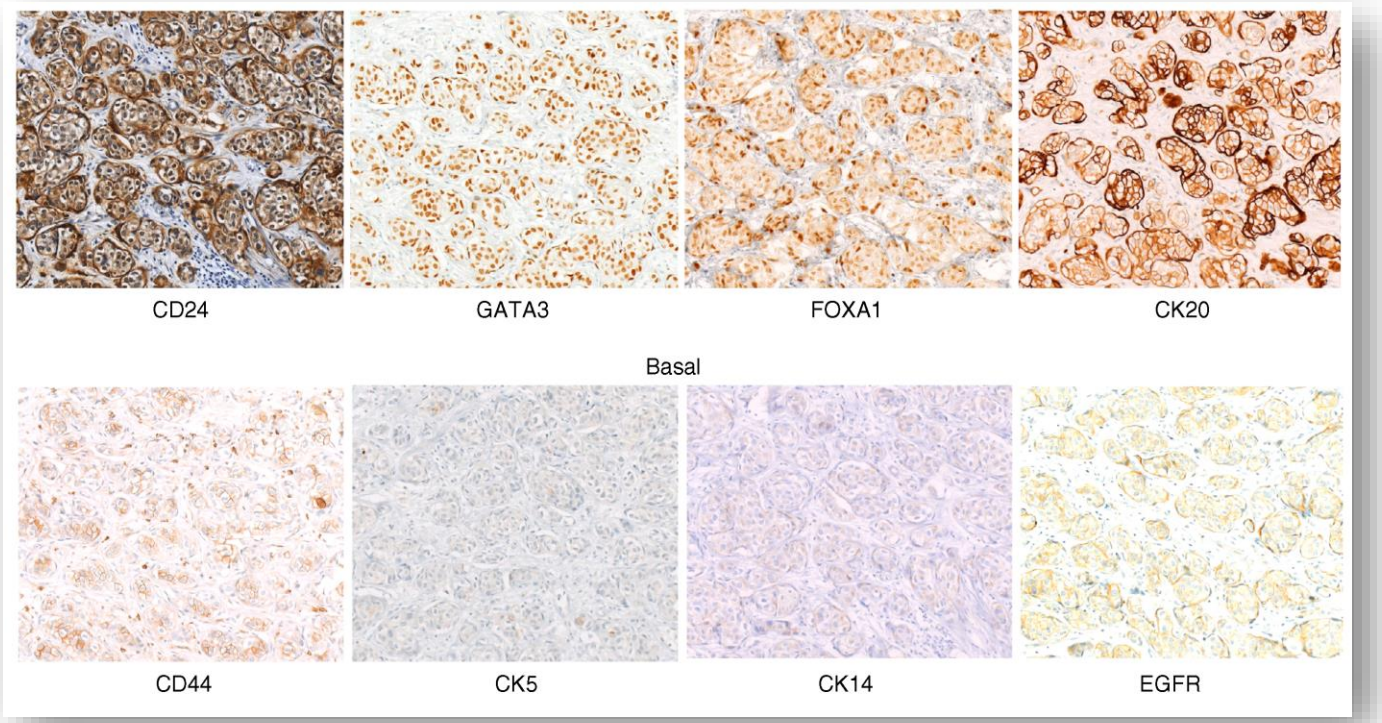
Veronika Weyerer,[1,*] Rebecca Weisser,[1,*] Evgeny A Moskalev,[1] Florian Haller,[1] Robert Stoehr,[1] Markus Eckstein,[1] Ulrike Zinnall,[1,2] Nadine T Gaisa,[3] Eva Compérat,[4] Aurel Perren,[5] Bastian Keck,[6,7] Yves Allory,[8] Glen Kristiansen,[9] Bernd Wullich,[6] Abbas Agaimy,[1] Arndt Hartmann[1] & Simone Bertz[1]

- 60 Nested UrCa
- **TERT** promoter mutation and **NGS panel of 48 genes** (in 26 cases)

- 62.5% TERT promoter mutations
- **TP53, JAK3 & CTNNB1** most frequently mutated

- All expressed **luminal markers**



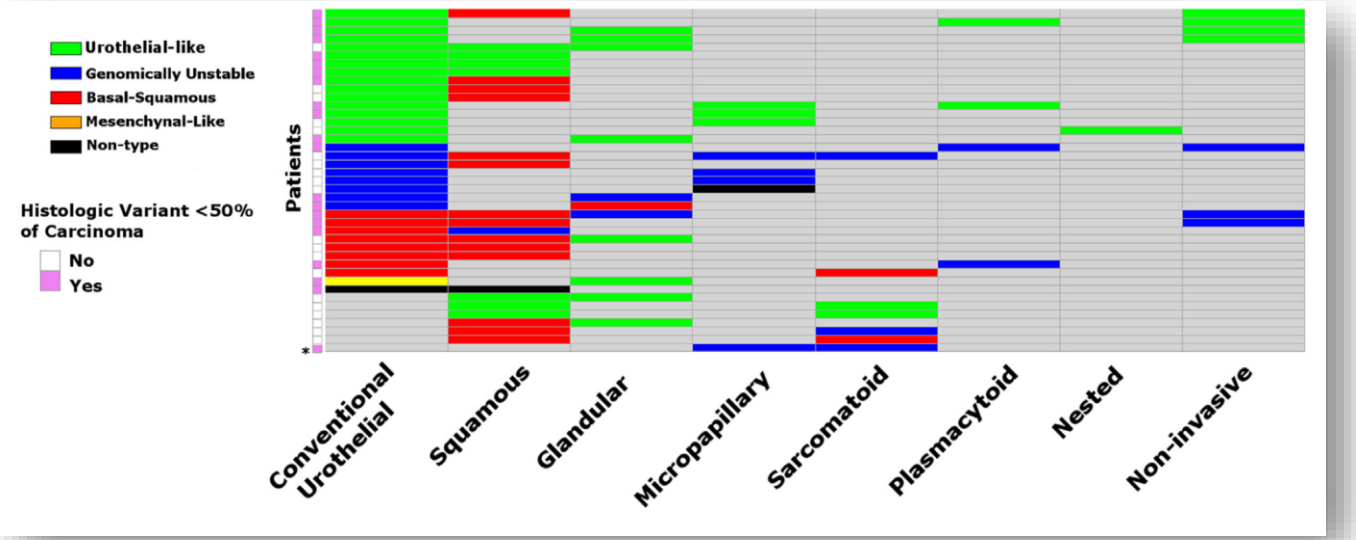


Intratumoral Heterogeneity of Bladder Cancer by Molecular Subtypes and Histologic Variants

Joshua I. Warrick [a,b,], Gottfrid Sjödahl [c], Matthew Kaag [b], Jay D. Raman [b], Suzanne Merrill [b], Lauren Shuman [a], Guoli Chen [a], Vonn Walter [d], David J. DeGraff [a,b]*

Warrick JI et al, 2018 European Urology

- Molecular heterogeneity is frequent in BC particularly in **basal-squamous subtype**
- Concerns for **sampling representation** when guiding Rx



JAMA | Review

Bladder Cancer
A Review

Andrew T. Lenis, MD, MS; Patrick M. Lec, MD; Karim Chamie; MD, MSHS

American Urological Association risk group		
Low	**Intermediate**	**High**
Definitions		
Low-grade solitary Ta ≤3 cm PUNLMP	Recurrence within 1 y, low-grade Ta Solitary low-grade Ta >3 cm Low-grade Ta, multifocal High-grade Ta ≤3 cm Low-grade T1	High-grade T1 Any recurrent high-grade Ta High-grade Ta >3 cm or multifocal Any CIS Any BCG failure in patient with high-grade disease Any variant histology Any LVI Any high-grade prostatic urethral involvement
Outcomes[43]		
5-y relapse-free survival: 43%	5-y relapse-free survival: 33%	5-y relapse-free survival: 23%
5-y progression-free survival: 93%	5-y progression-free survival: 74%	5-y progression-free survival: 54%

JAMA. 2020;324(19):1980-1991.

WHO/ISUP System: Potential Advantages

- **Detailed definition of the various grades ⟹ greater interobserver reproducibility**
- **Acceptance by a broad spectrum of urological pathologists**
- **Patients with PUNLMP avoid a diagnosis of carcinoma**

NCCN Guidelines Version 5.2021
Non-Muscle Invasive Bladder Cancer

NCCN Guidelines Index
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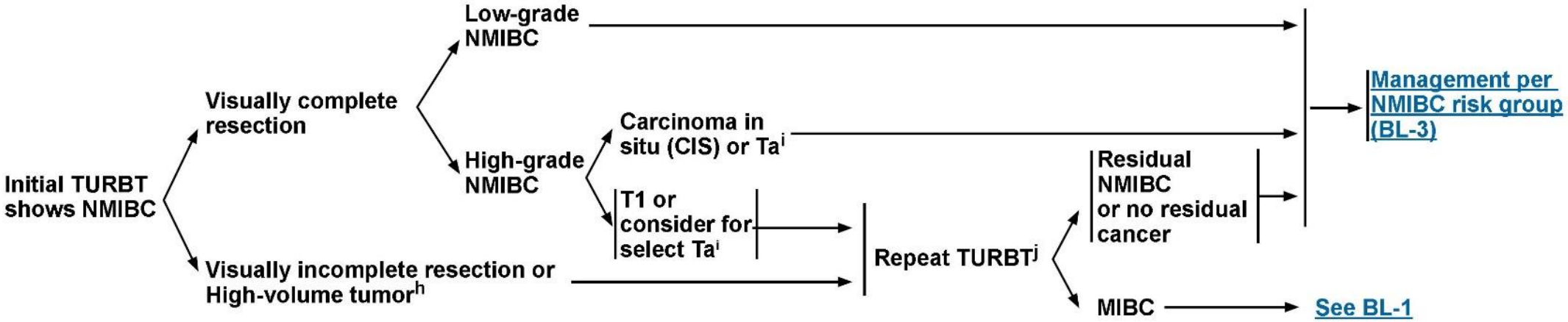
Discussion

RISK STRATIFICATION OF NMIBC



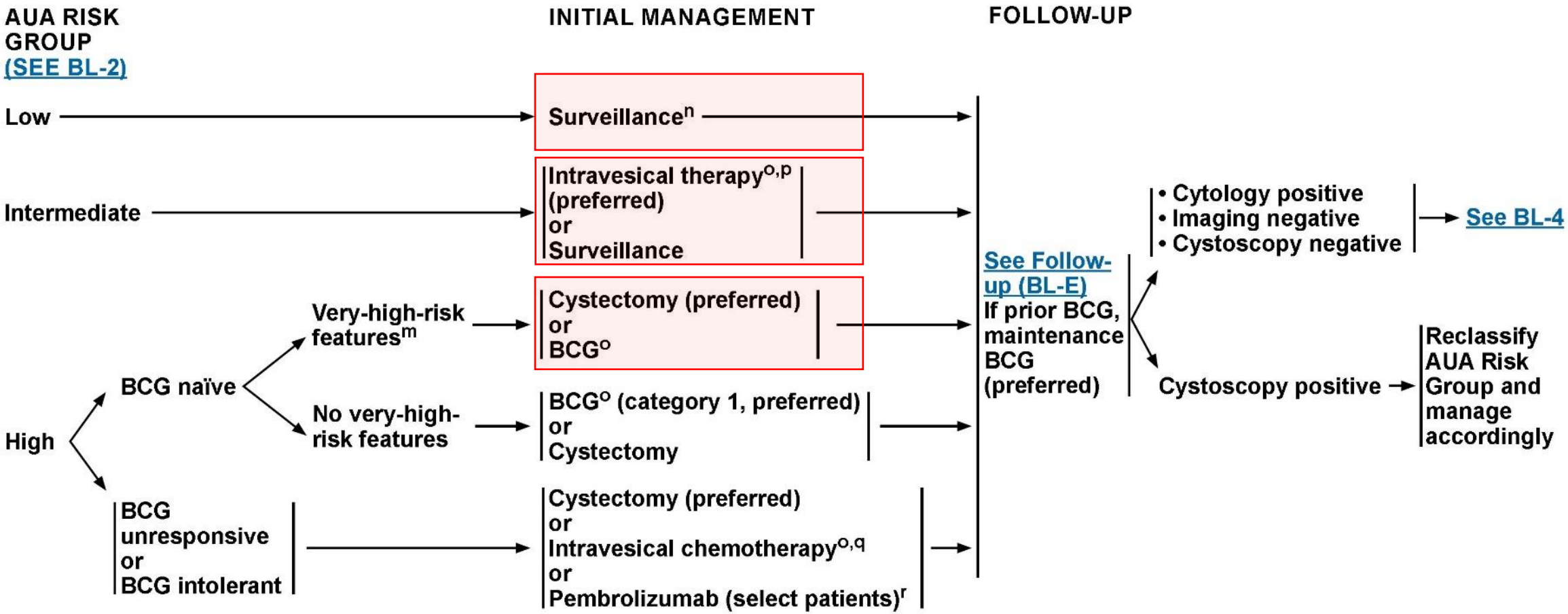
AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• Low grade urothelial carcinoma ▸ T1 or ▸ >3 cm or ▸ Multifocal or ▸ Recurrence within 1 year • High grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• High grade urothelial carcinoma ▸ CIS or ▸ T1 or ▸ >3 cm or ▸ Multifocal • Very high risk features (any): ▸ BCG unresponsive[k] ▸ Variant histologies[l] ▸ Lymphovascular invasion ▸ Prostatic urethral invasion

Reproduced with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021.
*Within each of these risk strata an individual patient may have more or less concerning features that can influence care.

NCCN Guidelines Version 5.2021
Non-Muscle Invasive Bladder Cancer

MANAGEMENT PER NMIBC RISK GROUP



Imaging

Computed tomography (CT) may be used to assess for extraluminal tumour spread and lymph node staging. Detection of upper urinary tract cancer with CT urography is superior to excretory urography {21512076}. To assess for muscle invasion, multiparametric (mp)-MRI, including diffusion weighted image (DWI) and dynamic contrast enhanced image (DCEI) in addition to T2 weighted image (T2WI) are preferred, as they enable differentiation of submucosal (or lamina propria) tissue from the muscularis propria. The vesical imaging of reporting and data system (VI-RADS) using mp-MRI proposes a five-point scale for staging, which suggests the likelihood of detrusor muscle and extravesical invasion of bladder cancer. T2 WI is defined as first pass images and DWI and DCEI as dominant images {29755006}. This system was tested positively by systematic review and meta-analysis {32199915; 33076505}. Using this system, select patients could avoid unnecessary secondary tumour resection