

UAB MEDICINE

Knowledge that will change your world

**The WHO 5th Edition Blue Book:
Urinary Tract Neoplasms Updates**

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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 | |
| <i>Infiltrating urothelial carcinoma</i> | 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 | |
| <i>Non-invasive urothelial neoplasms</i> | |
| Urothelial carcinoma in situ | 8120/2 |
| Non-invasive papillary urothelial carcinoma, low-grade | 8130/2 |
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| 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 |
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| 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 |

WHO Classification of the Urinary and Male Genital Tumours

5th edition series

- *WHO 5th edition series structural reorganization*
- Refinements of **terminology** and **classification**
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WHO Classification of the Urinary and Male Genital Tumours
5th edition series

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 Trophoblastic 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

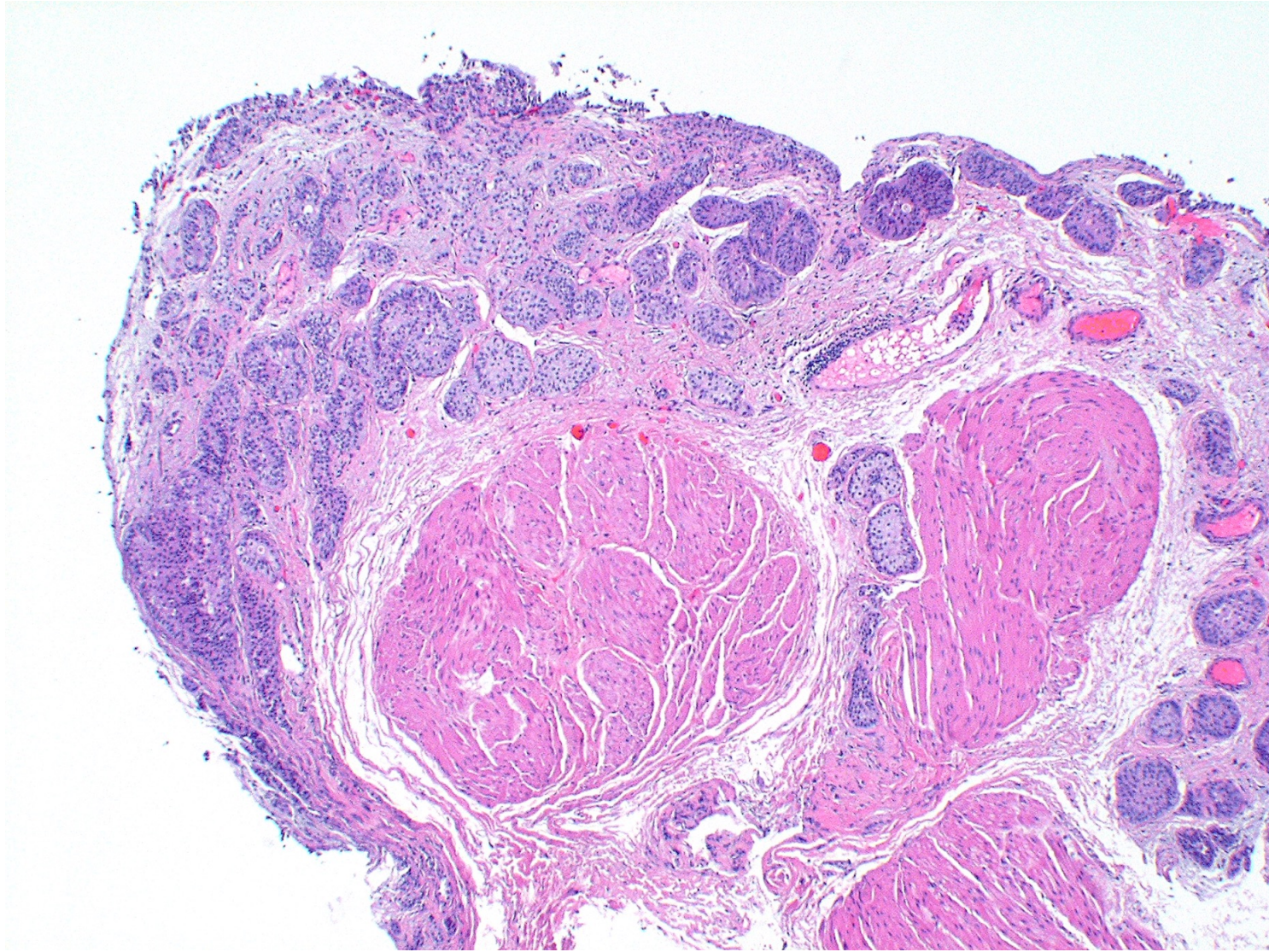
- Widely variable appearance: flat tumor, papillary tumor, submucosal “**bump**”
- Tumor size: 1-8 cm.

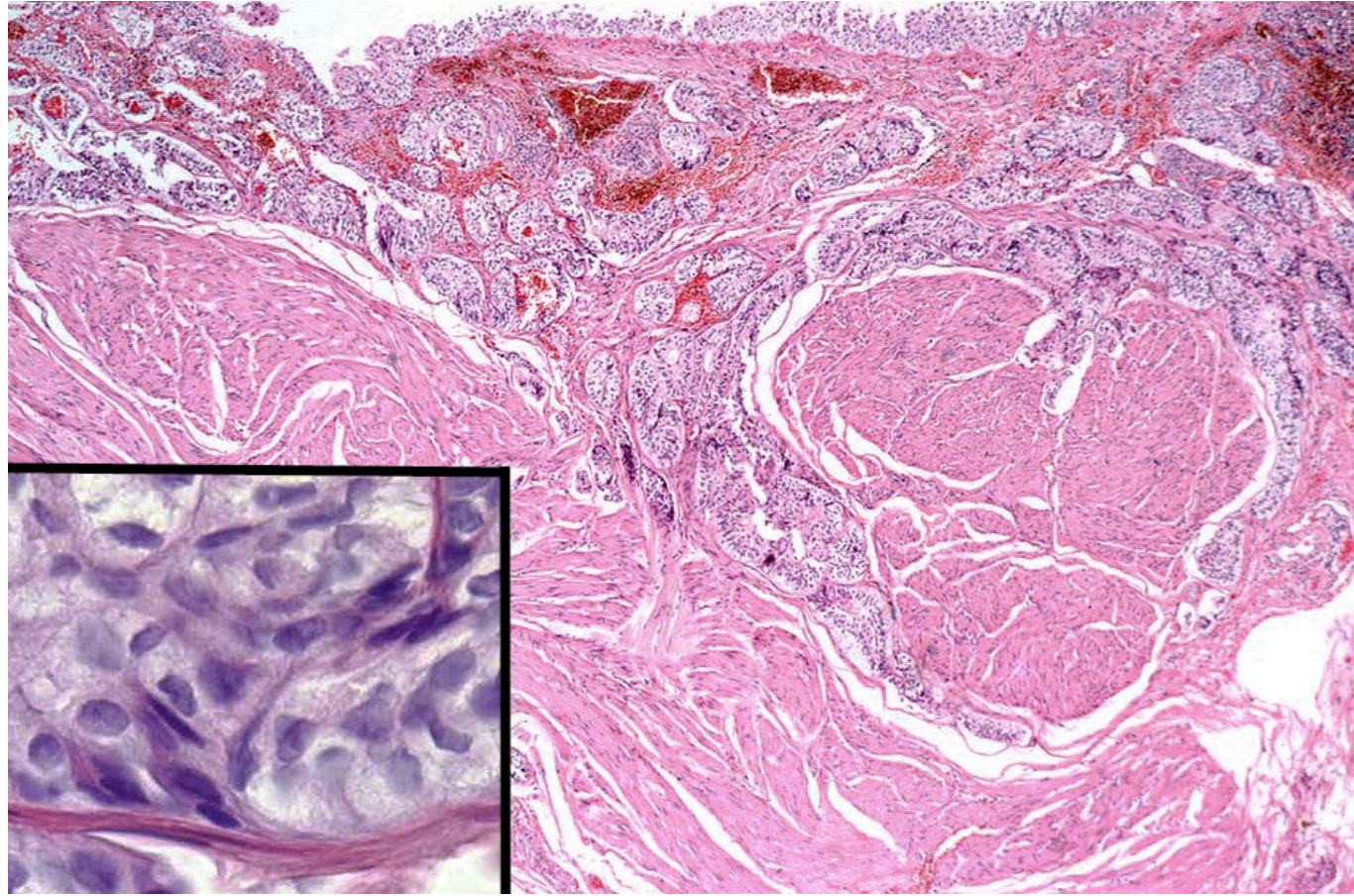
UC Nested Subtype Prognosis

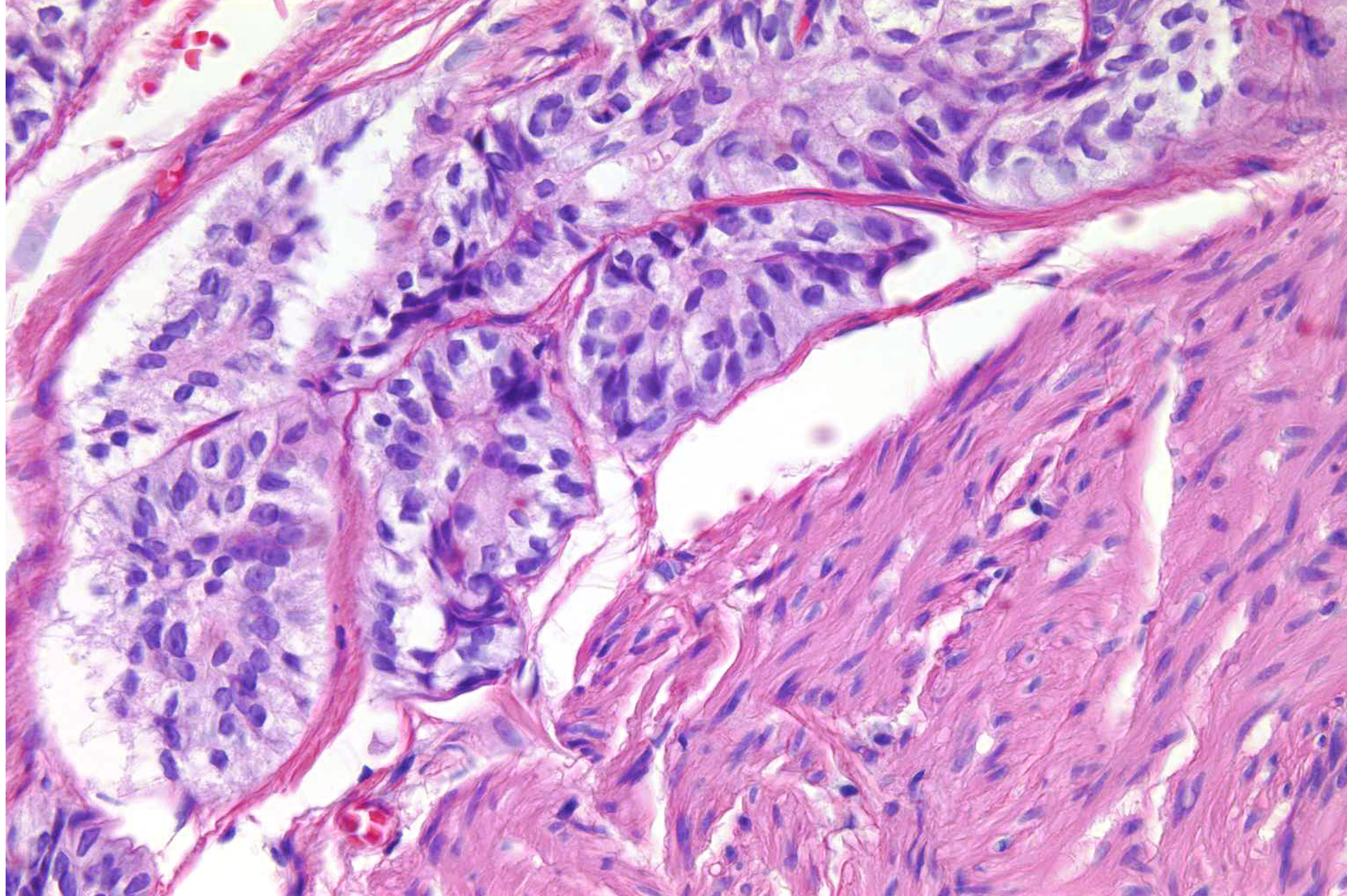
- Clinical course generally aggressive

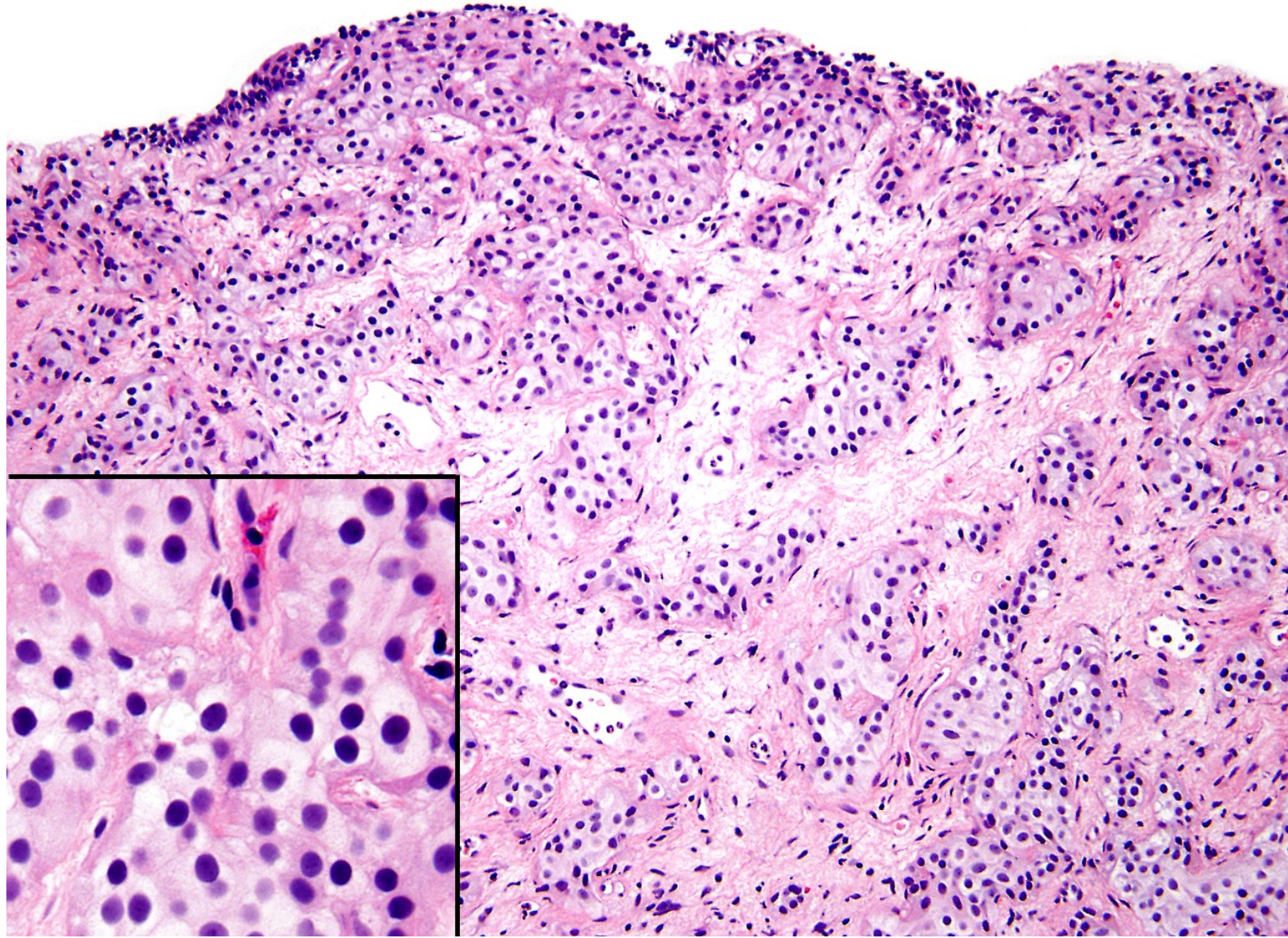
Drew et al. Mod Pathol 1996:

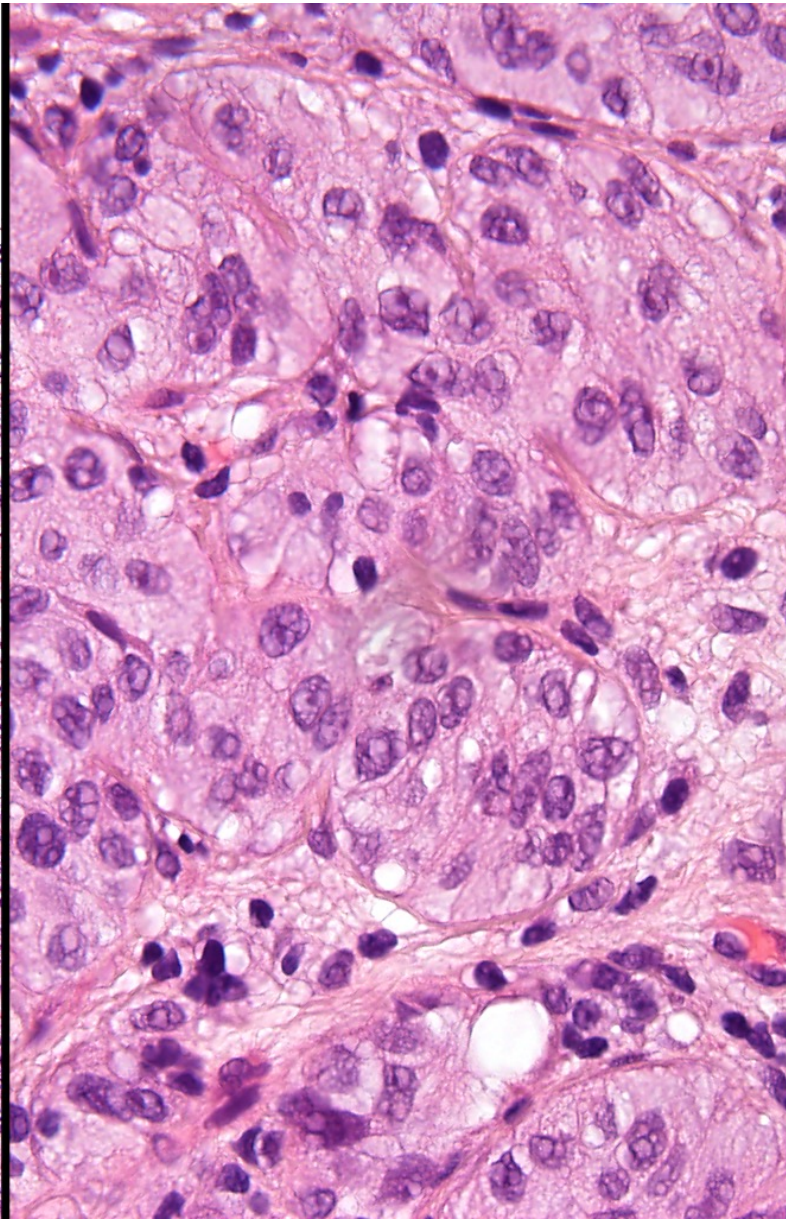
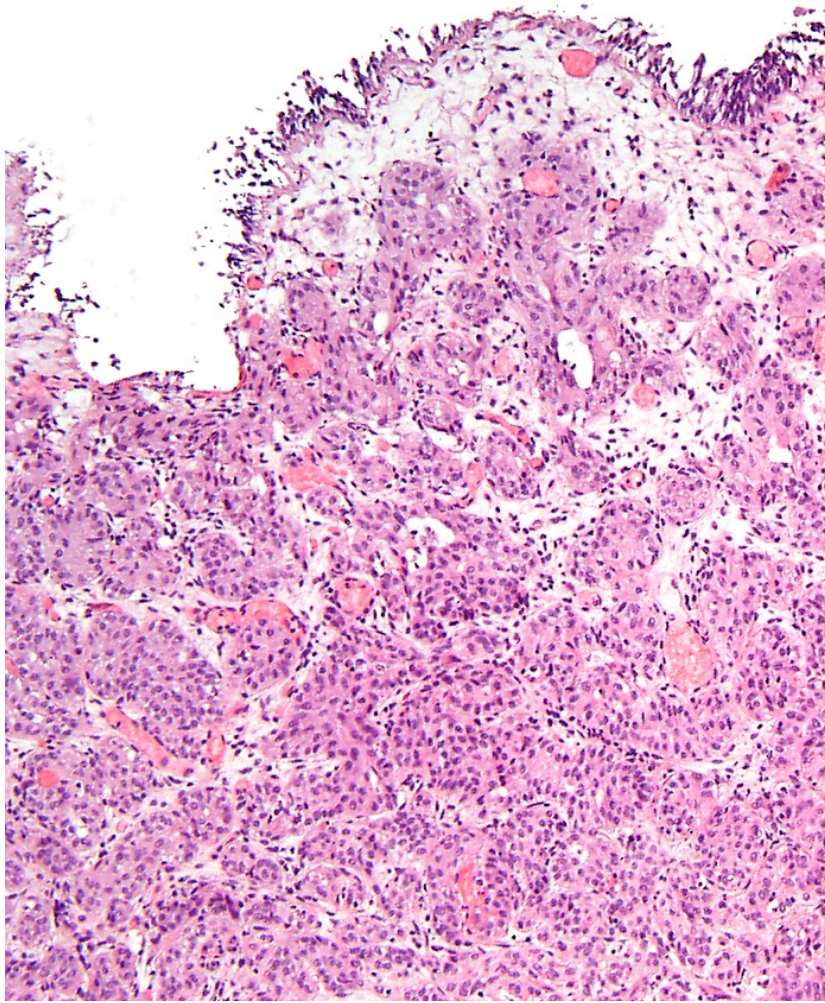
- Review of 24 cases, 60% show aggressive behavior, **mortality rates similar to high grade UrCa**
- Only 3/12 (**25%**) nested variant alive without disease (DFS) at 16 months follow-up

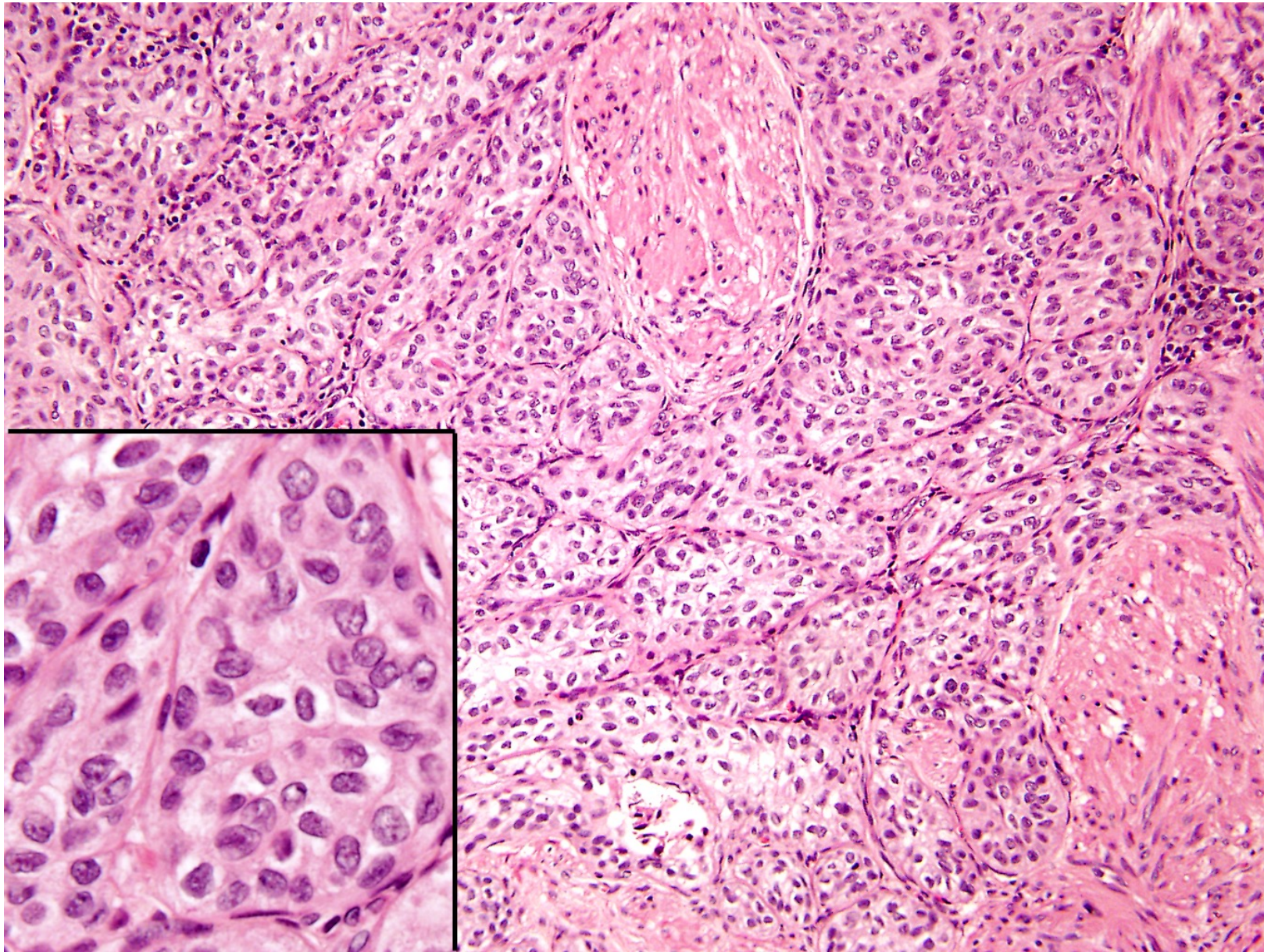


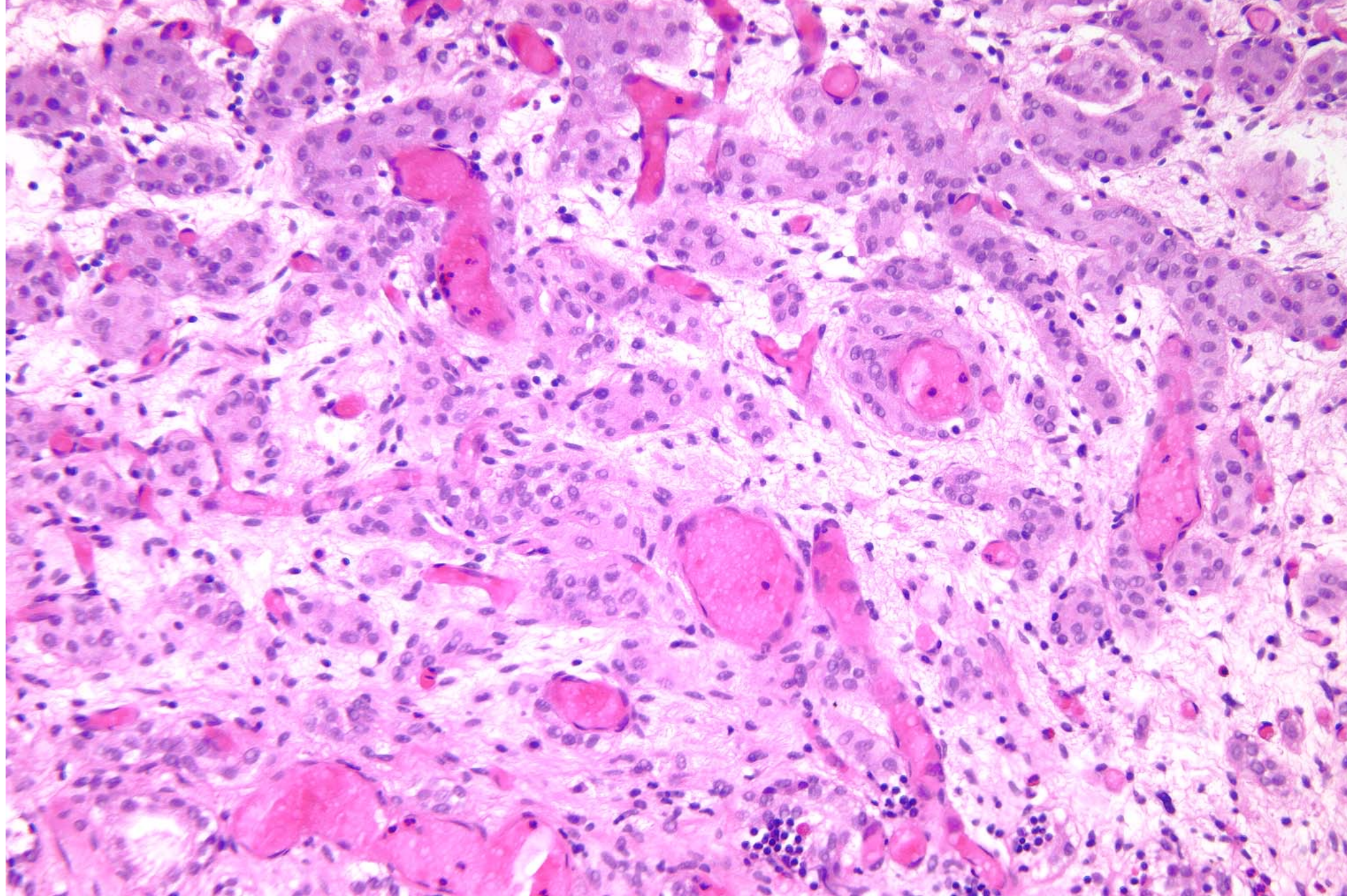




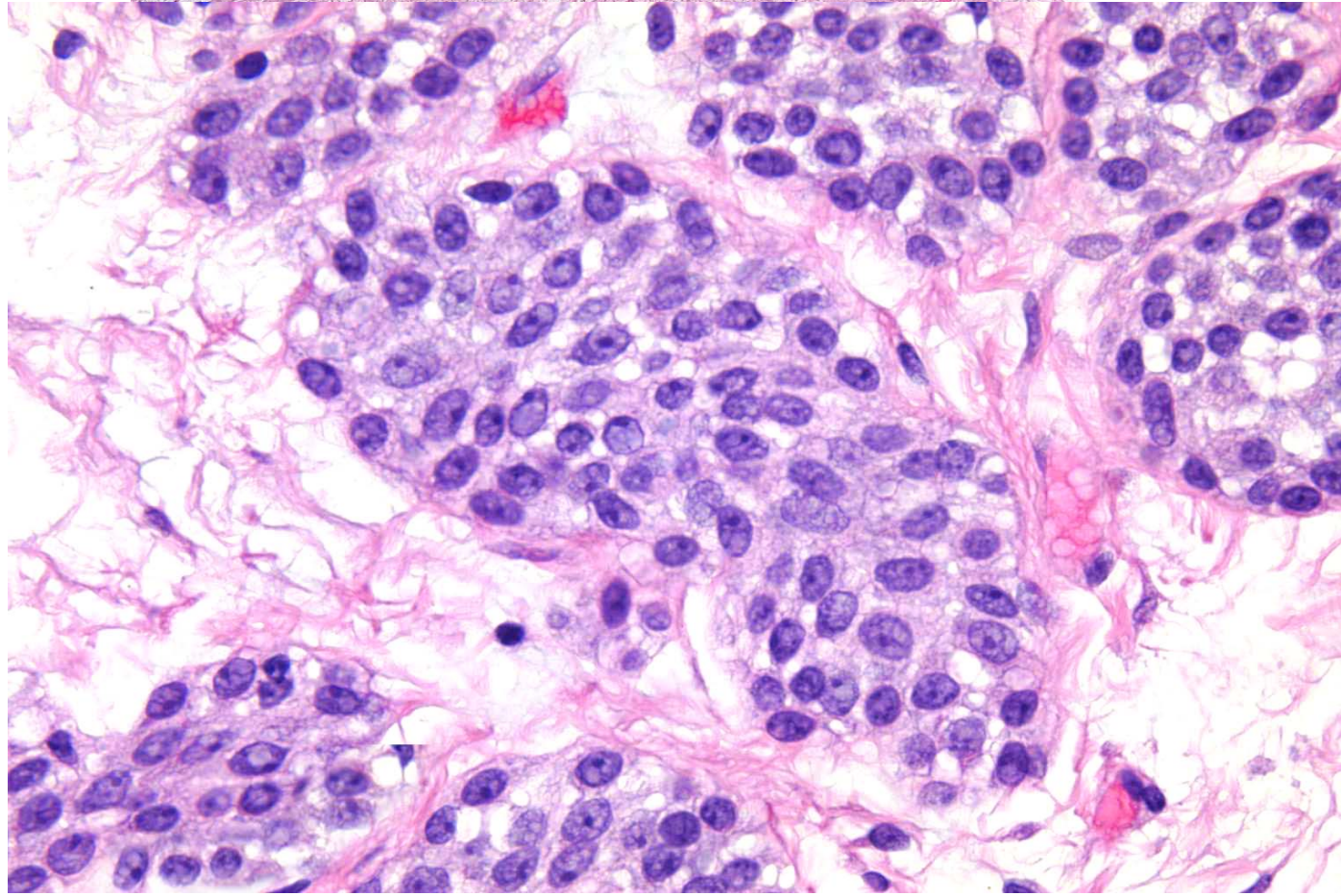
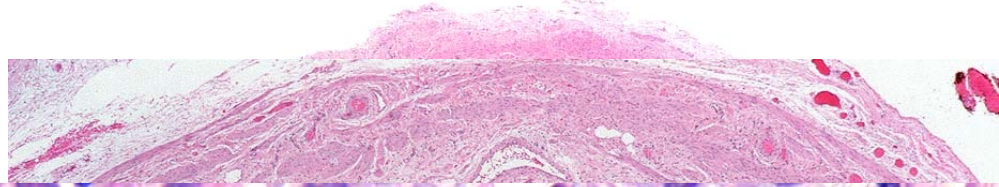
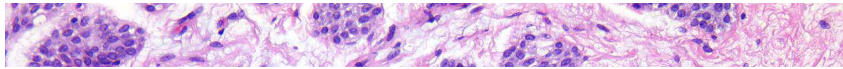








**Urothelial Nested Architecture
DDX**



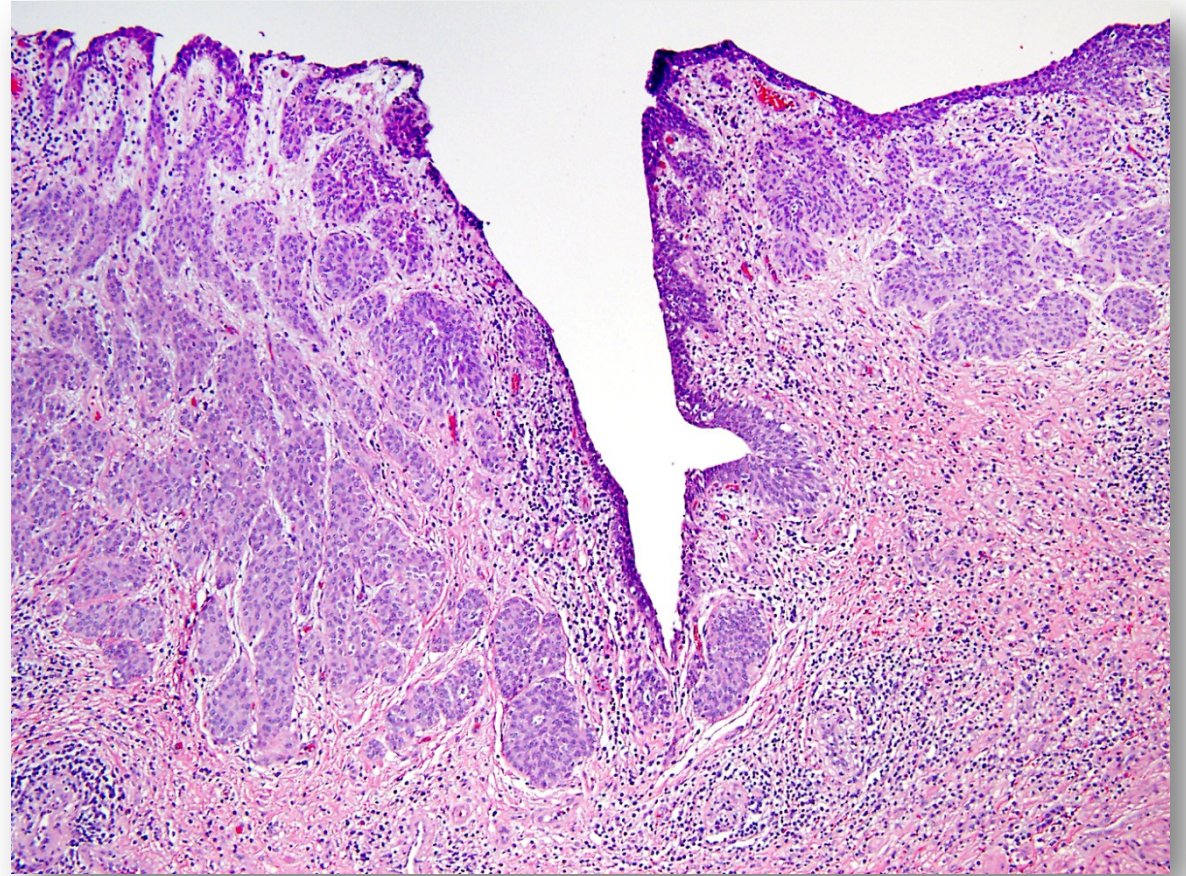
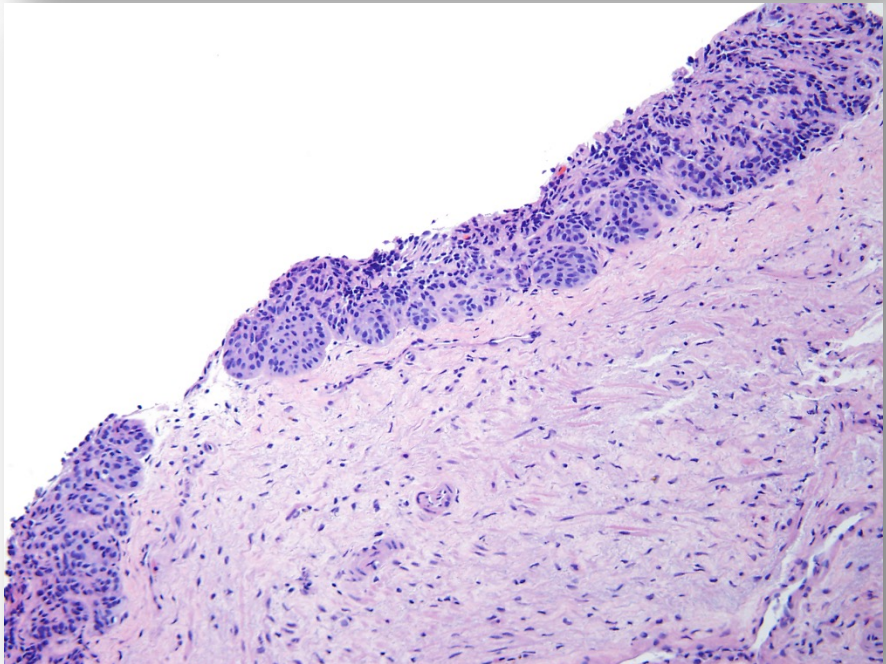
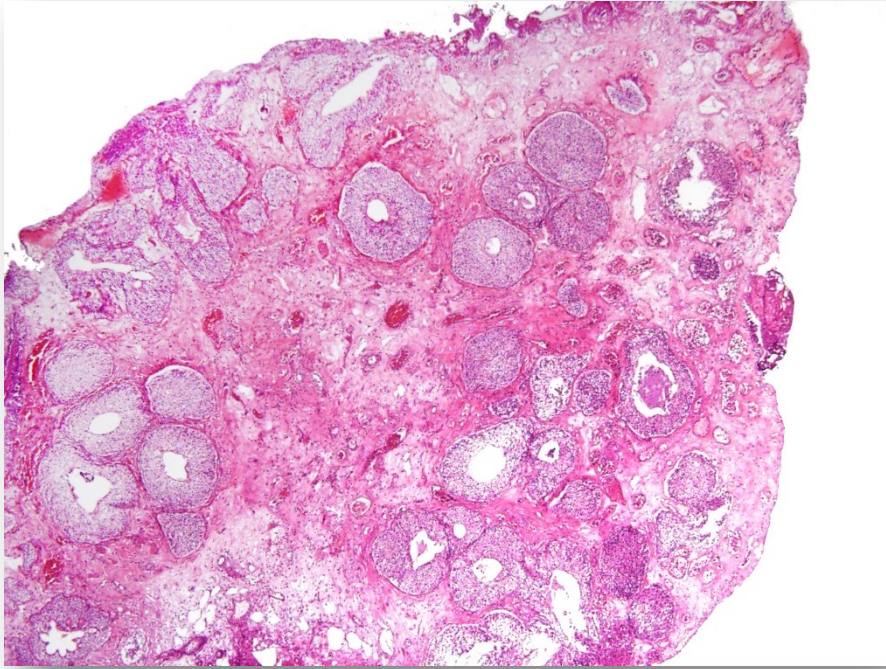
UC Nested Subtype

DDx

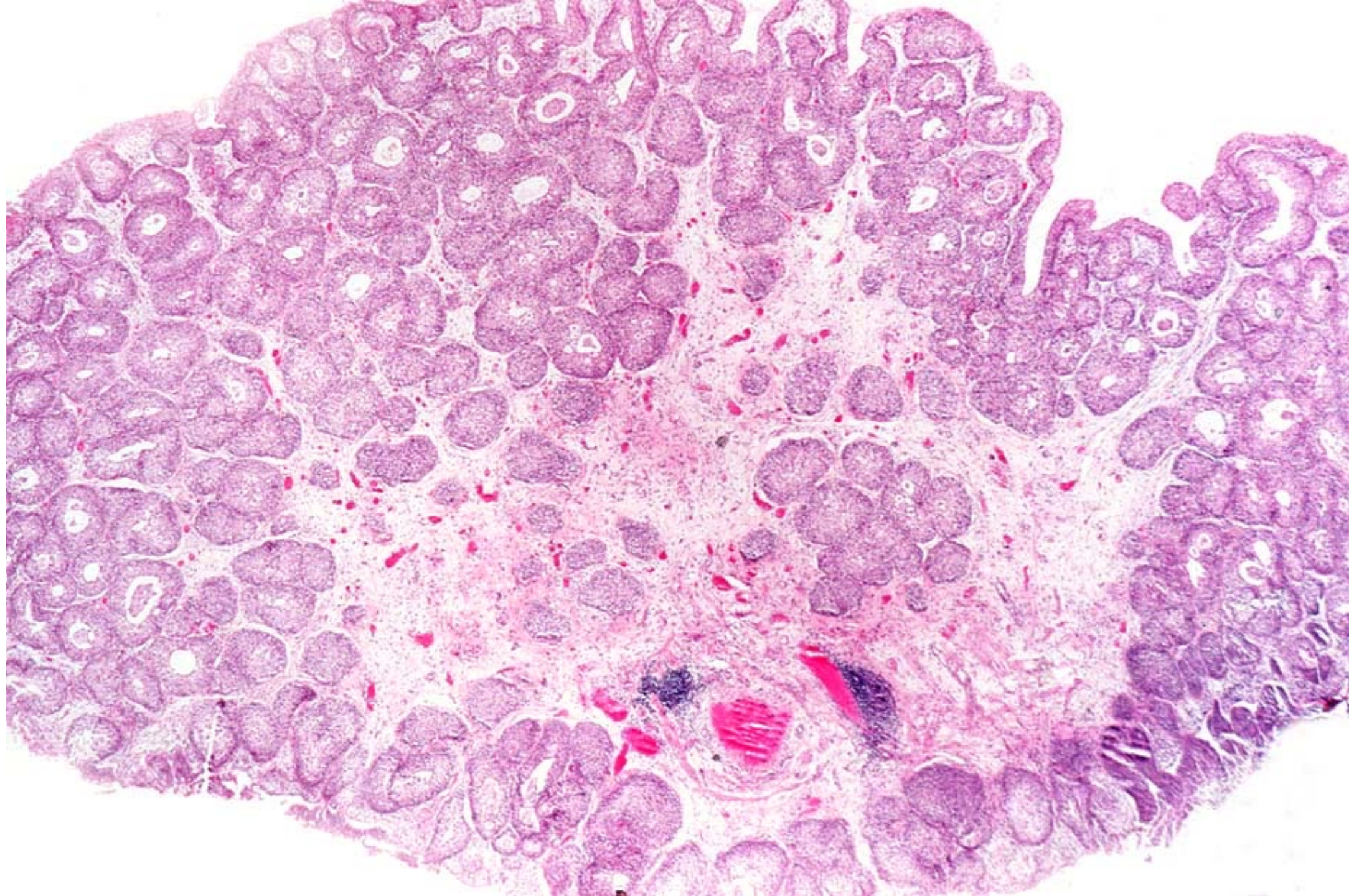
Proliferation of Von Brunn Nests

- Deep irregular infiltrative pattern
- Identify muscularis propria invasion

- *TERT* promoter mutation



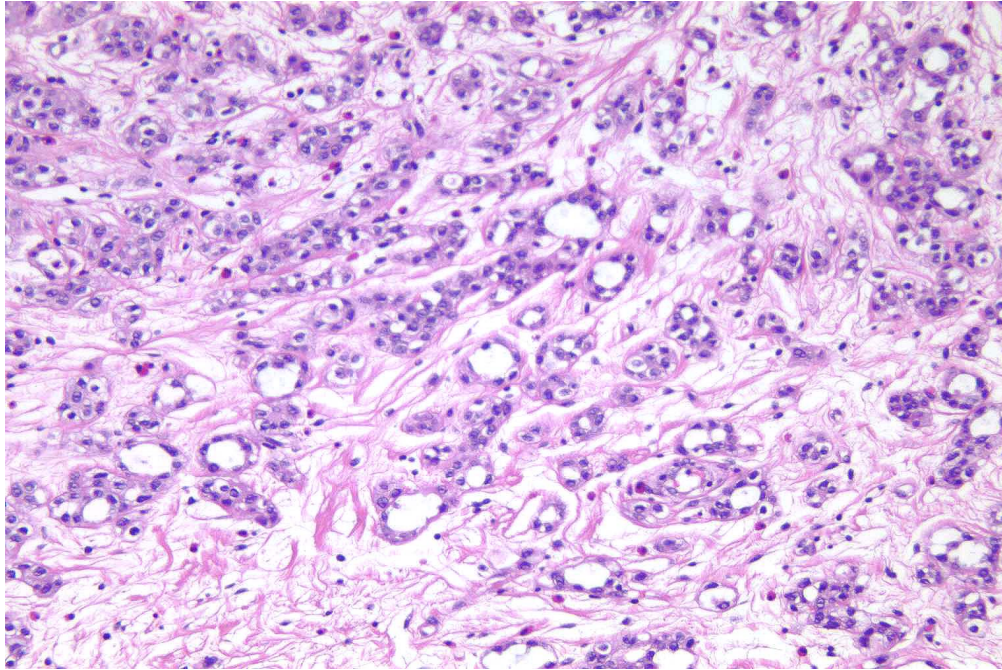
Urinary Bladder
Florid Proliferation of Von Brunn Nests



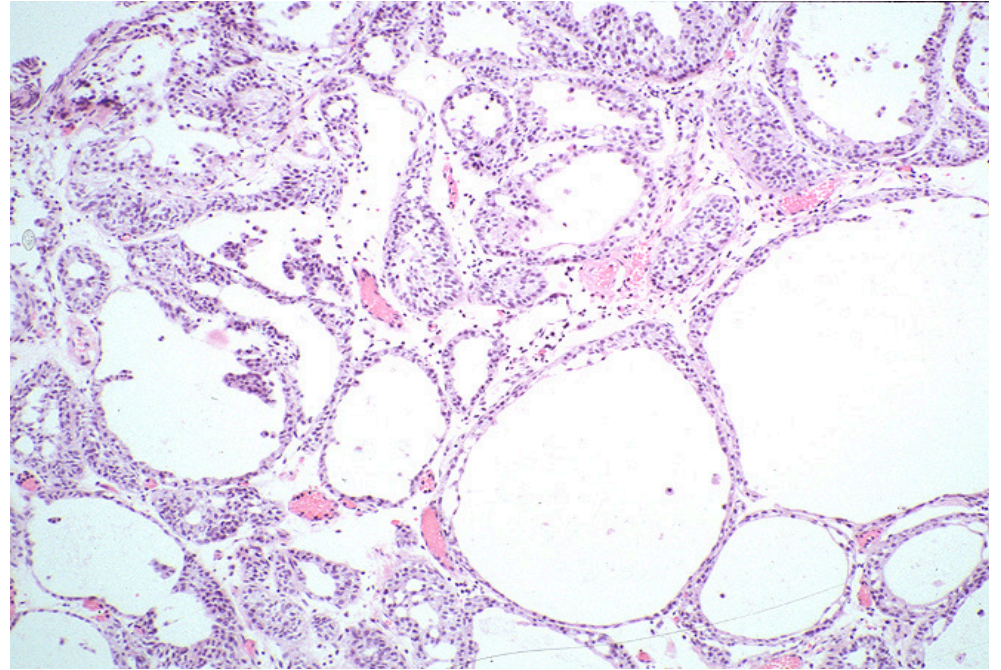
Urothelial Carcinoma

Tubular and Microcystic Subtypes

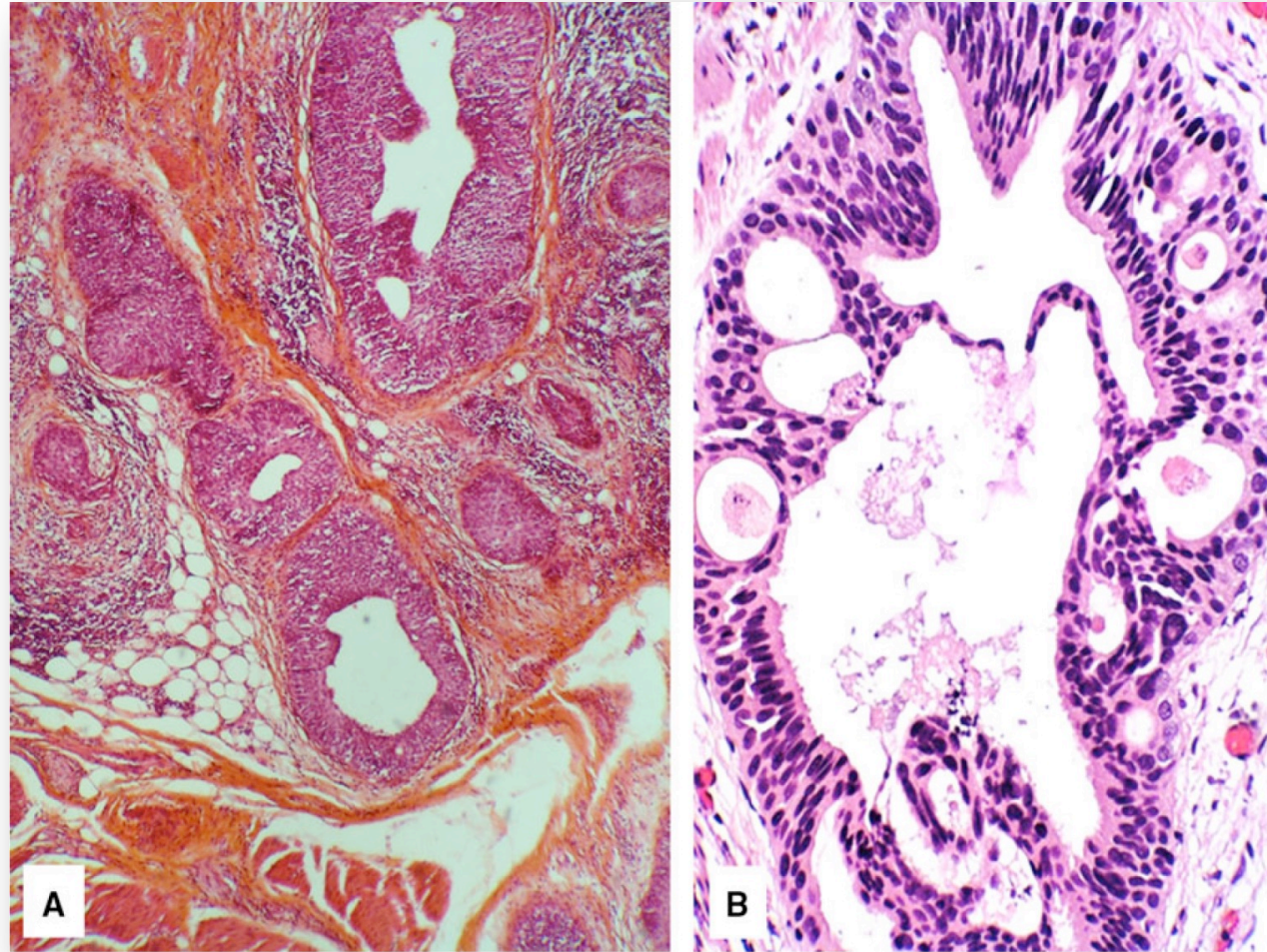
- **Closely related** to their nested counterpart
- **Bland cells** line small tubular or microcystic structures
- **DDx Cystitis Cystica**
Like nested subtype, **deep irregular infiltration** & involvement of **muscularis propria** are clues
- Urothelial markers typically positive (GATA3 or p63)



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

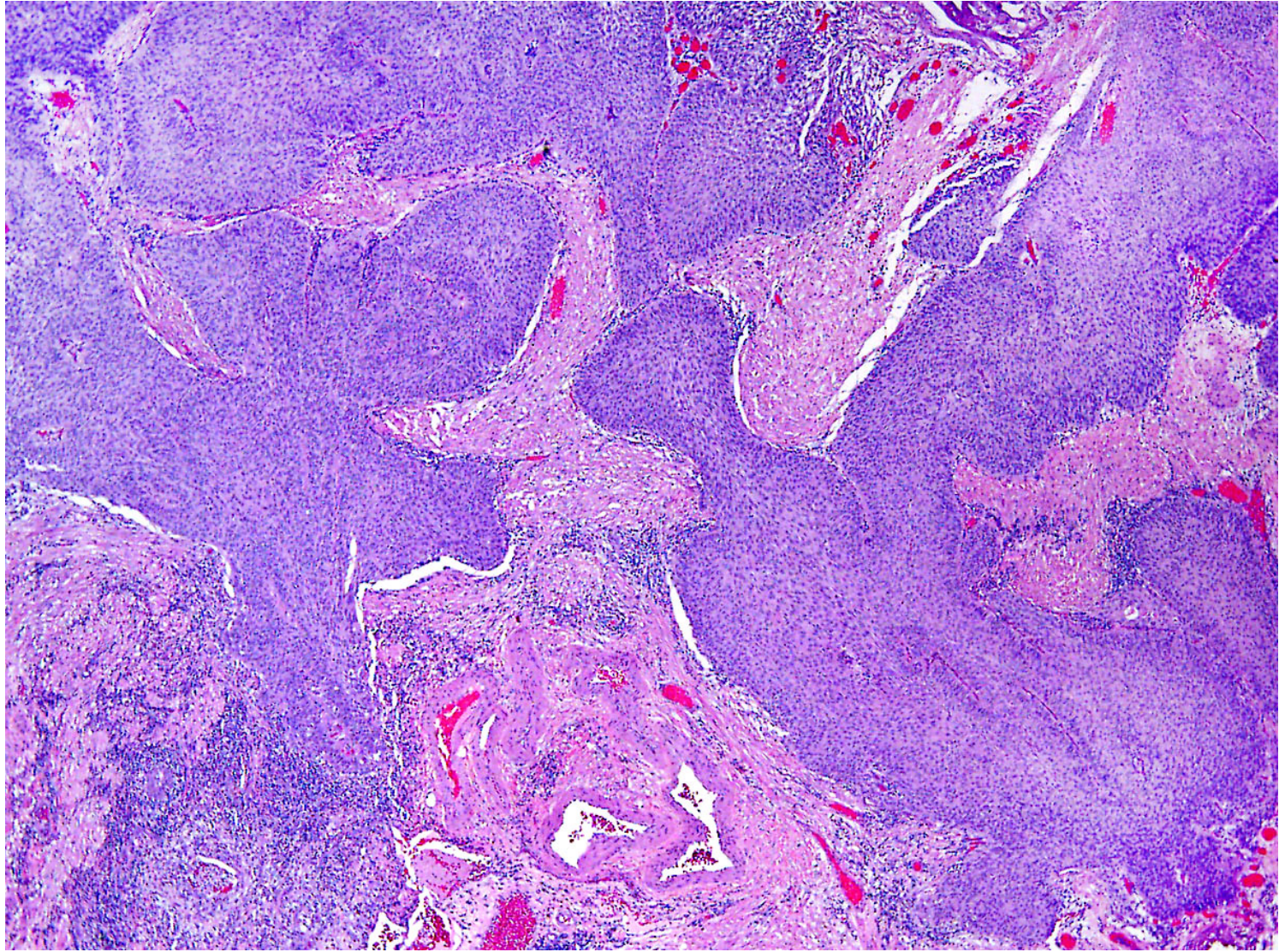
Large nested variant of urothelial carcinoma: a clinicopathological study of 36 cases

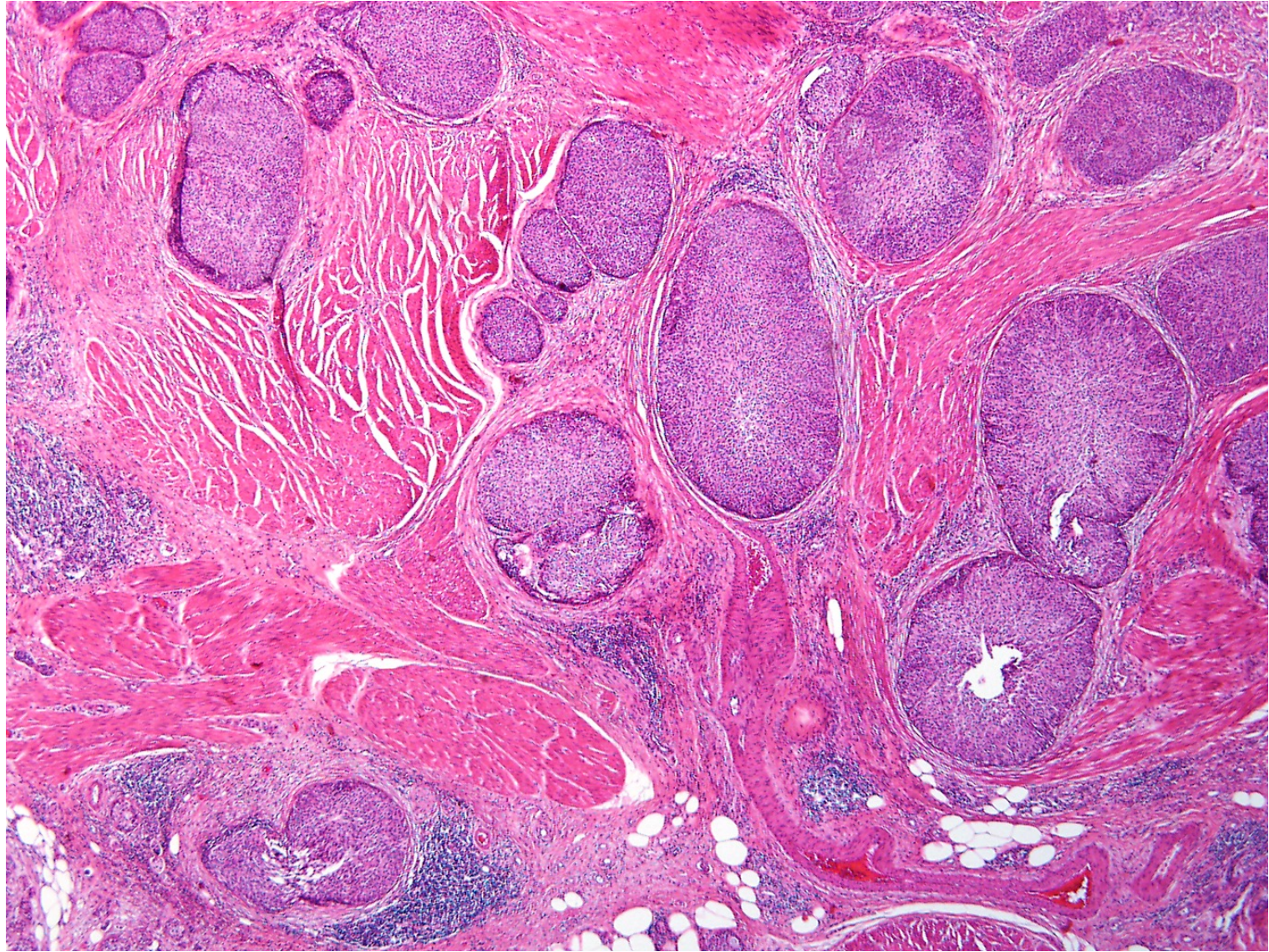
Eva Compérat,¹ Jesse K McKenney,²  Arndt Hartmann,³ Ondrej Hes,⁴  Simone Bertz,³
Justine Varinot¹  & Fadi Brimo⁵

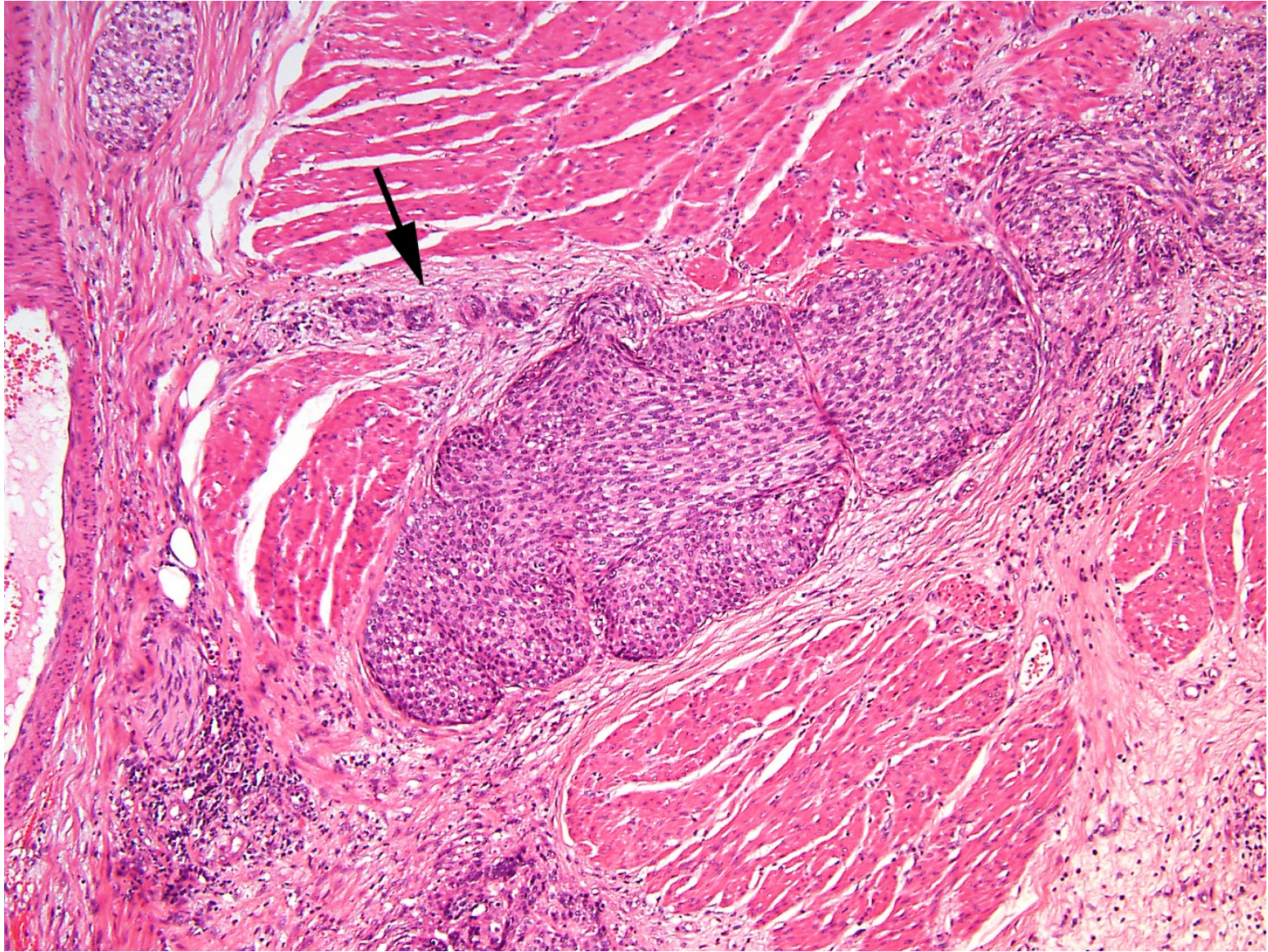
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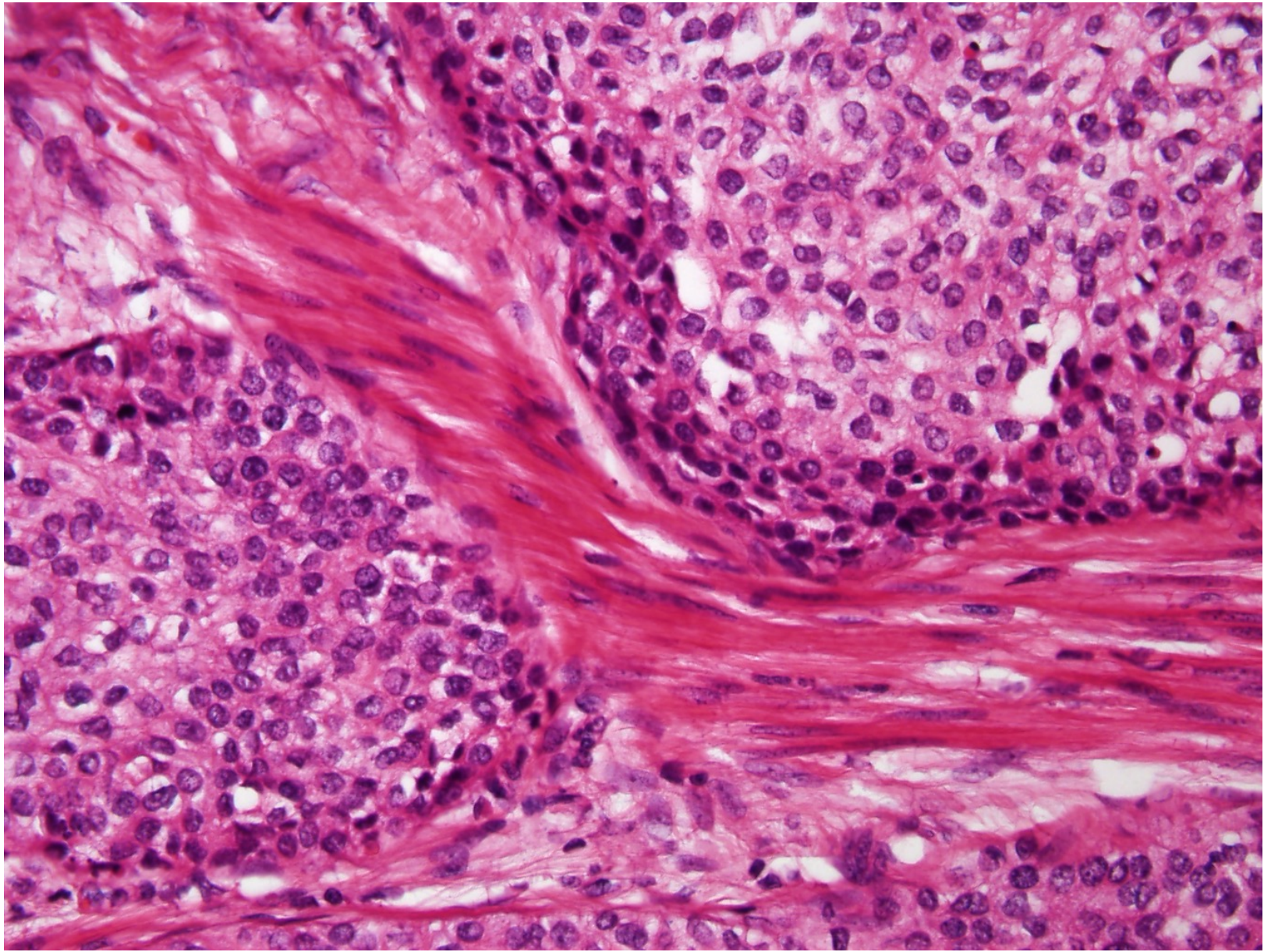
Eva Comp erat,¹ Jesse K McKenney,²  Arndt Hartmann,³ Ondrej Hes,⁴  Simone Bertz,³
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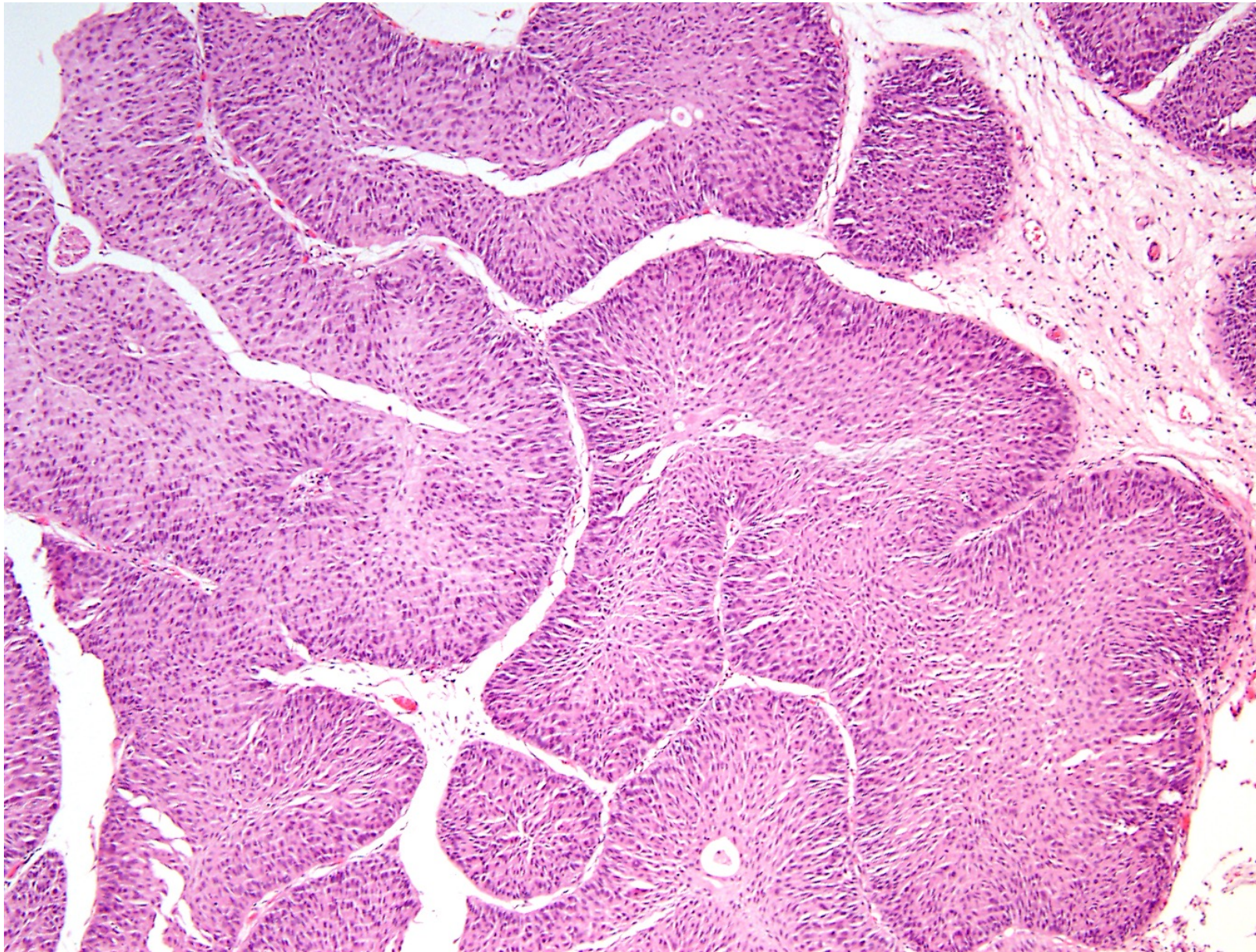
- **Bland** cytological appearance
- **Deceptive pattern of invasion (DDX Inverted)**
- **58%** extravesical disease (\geq pT3 and/or \geq pN1); Mixed more advanced compared to pure large nested?
- **21%** recurrence/metastasis
- **24%** died of disease (mean 21.7 months)
- IHC same as conventional & nested UrCa











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

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

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

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| → Urothelial proliferation of uncertain malignant potential | |
| → Urothelial dysplasia | |

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

“Flat” Precursor Lesions Urothelial Dysplasia

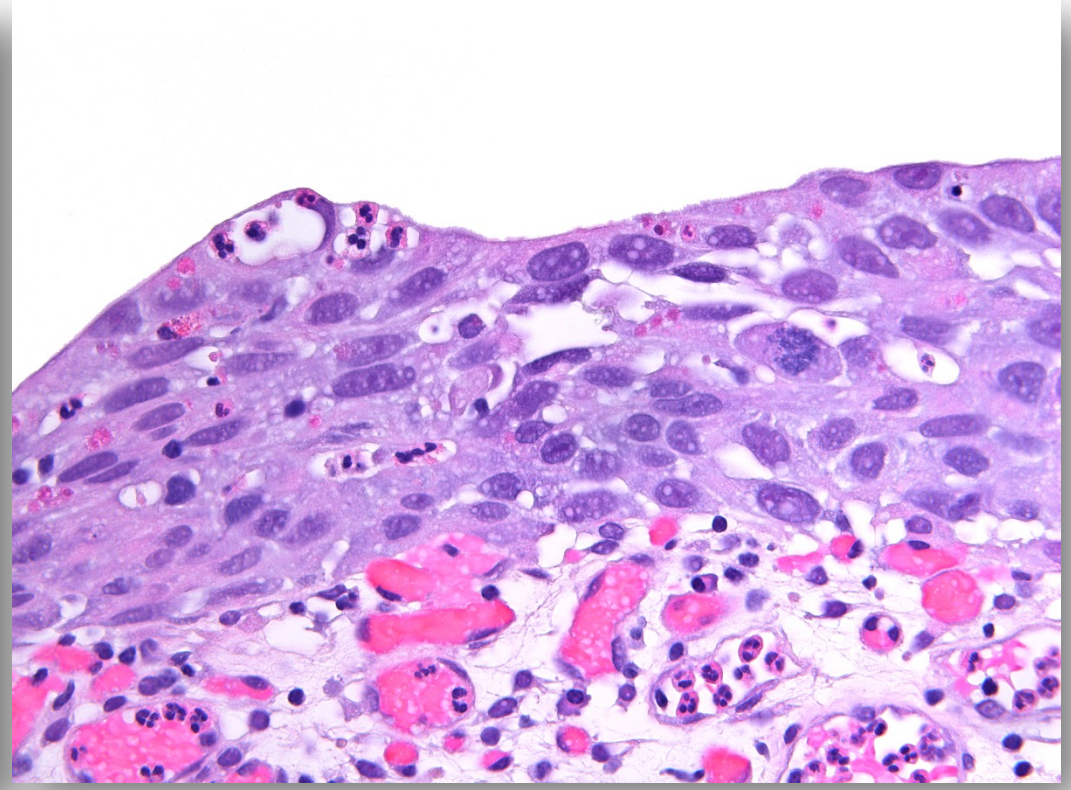
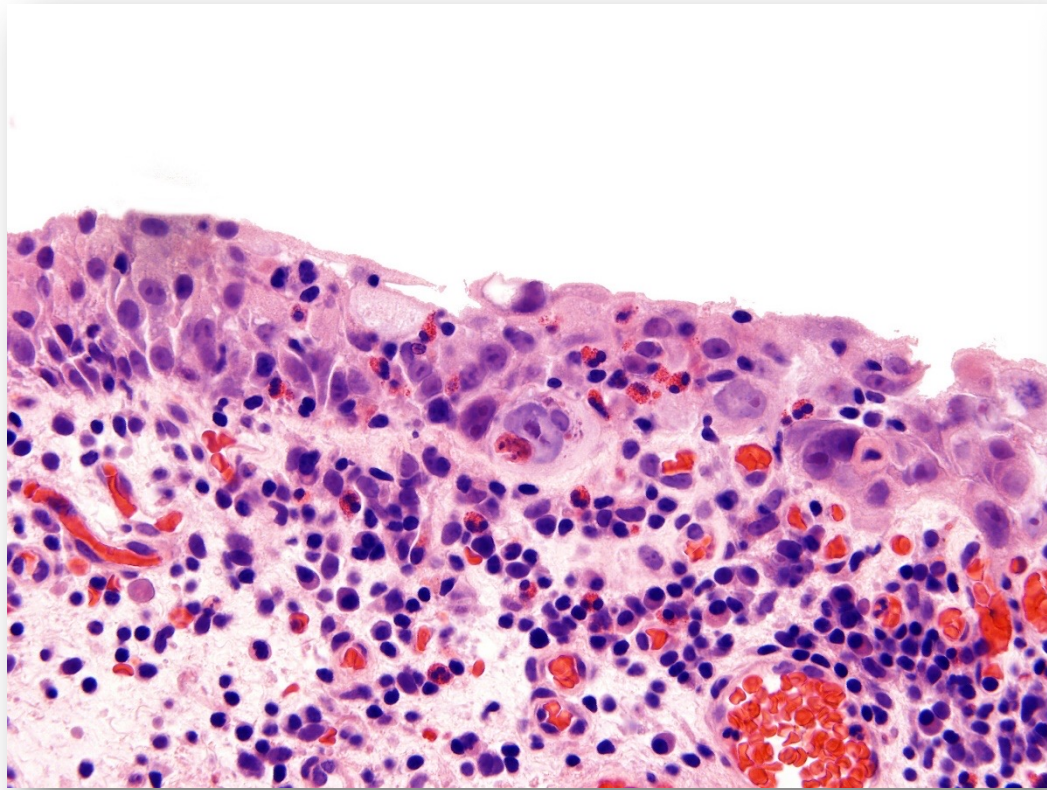
Should “Urothelial Dysplasia” remain an entity ?

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

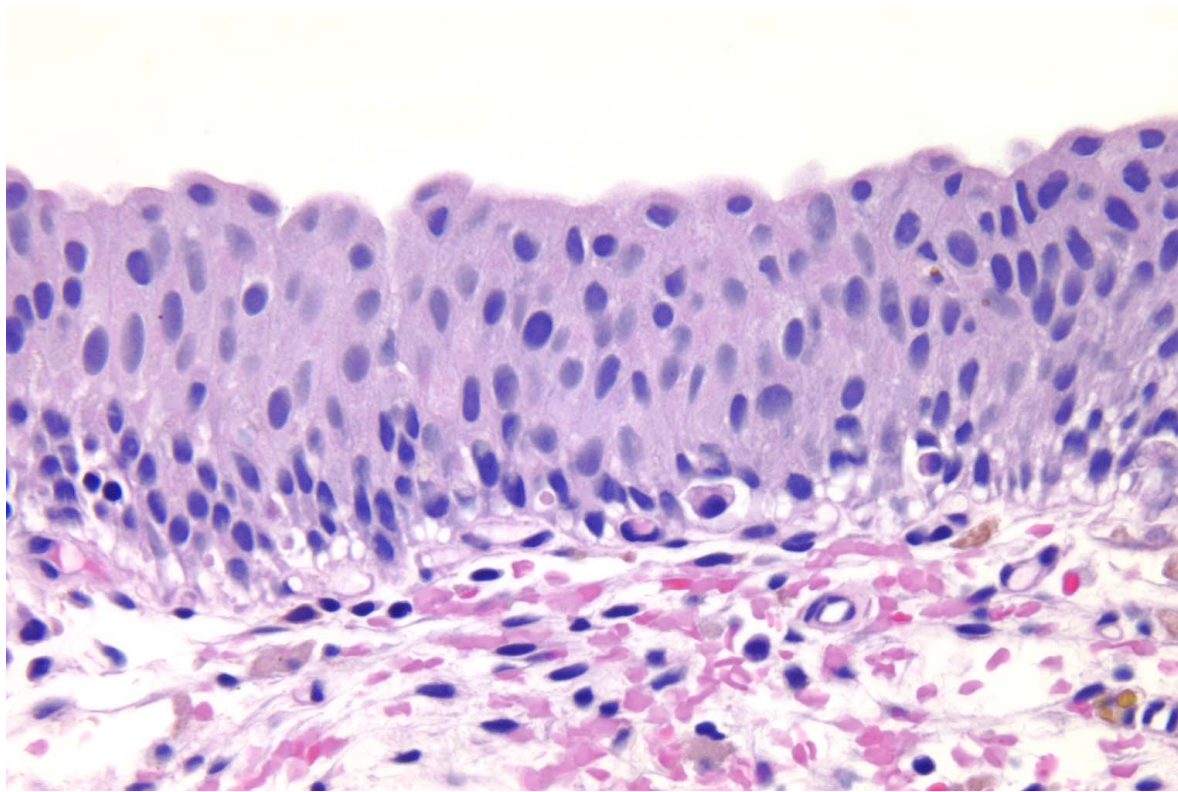
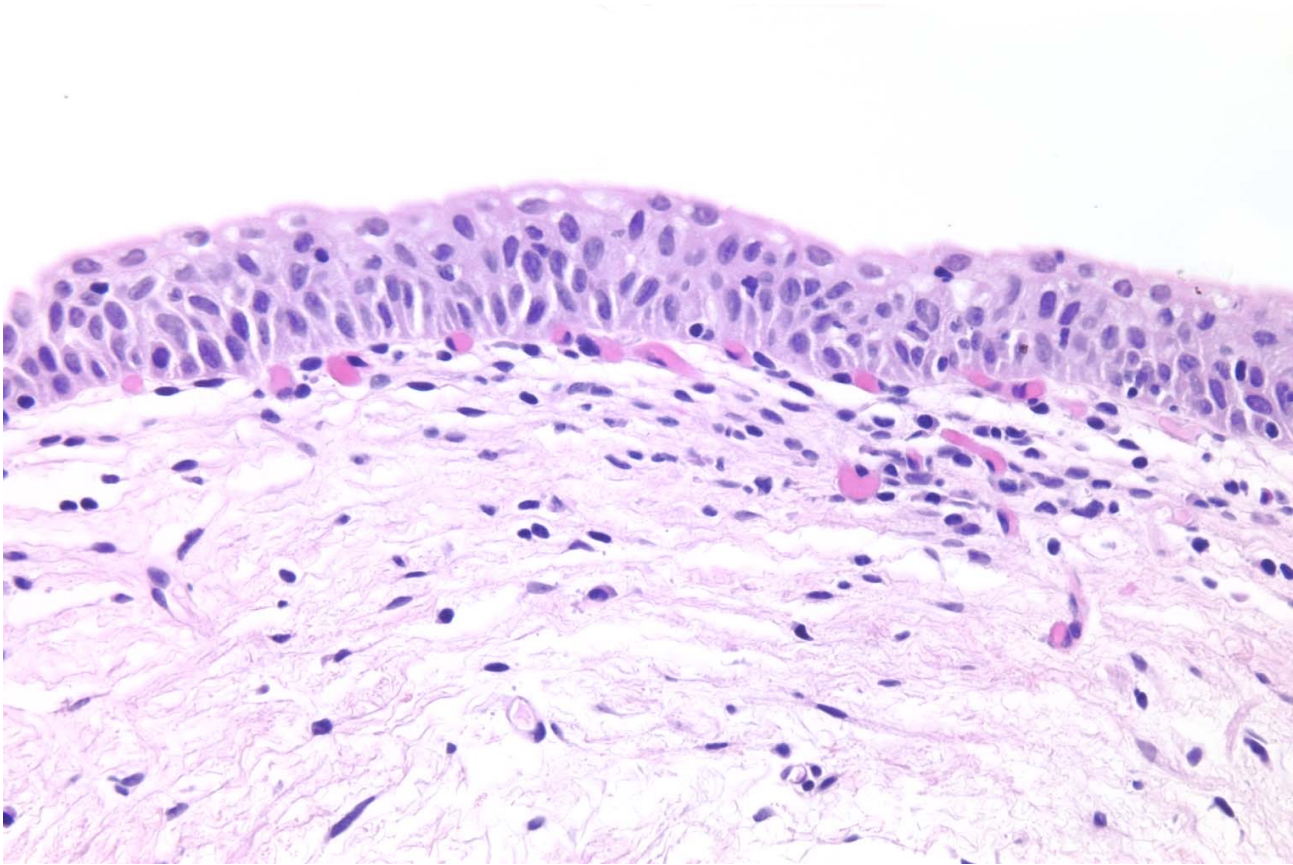
“Lesion that encompasses changes that are thought to be pre-neoplastic in nature, but cytologically fall short of the diagnosis of carcinoma in situ”

Urothelial CIS

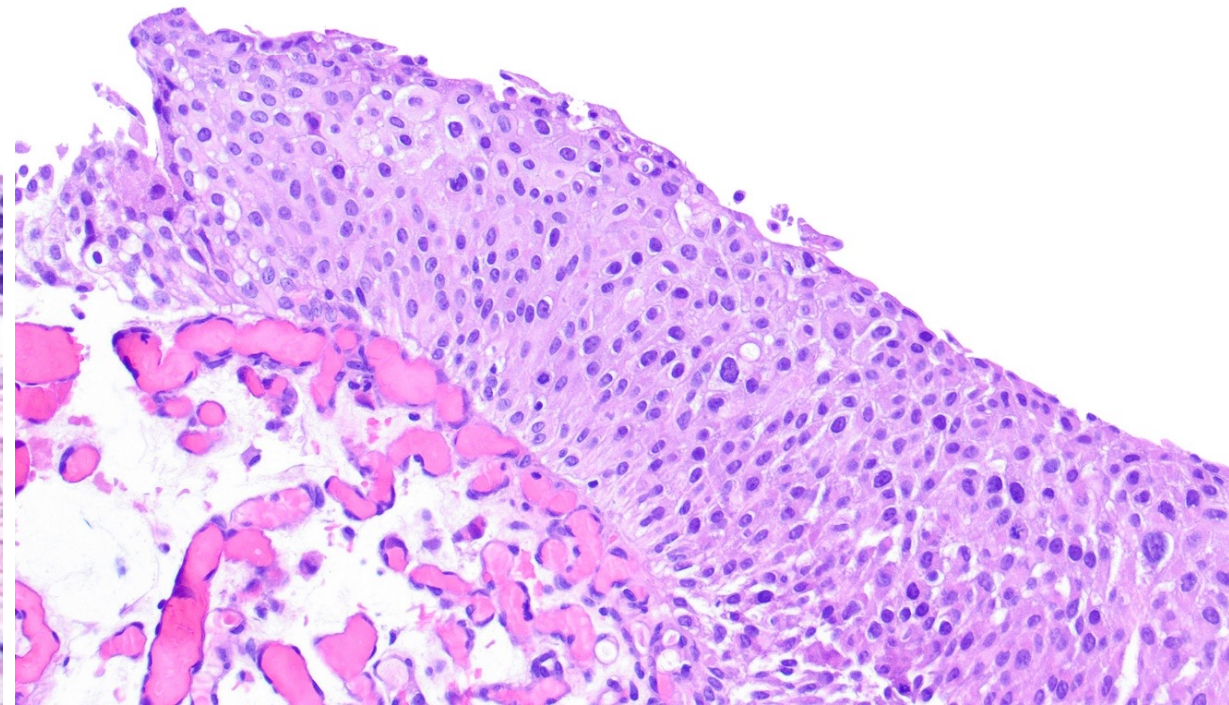
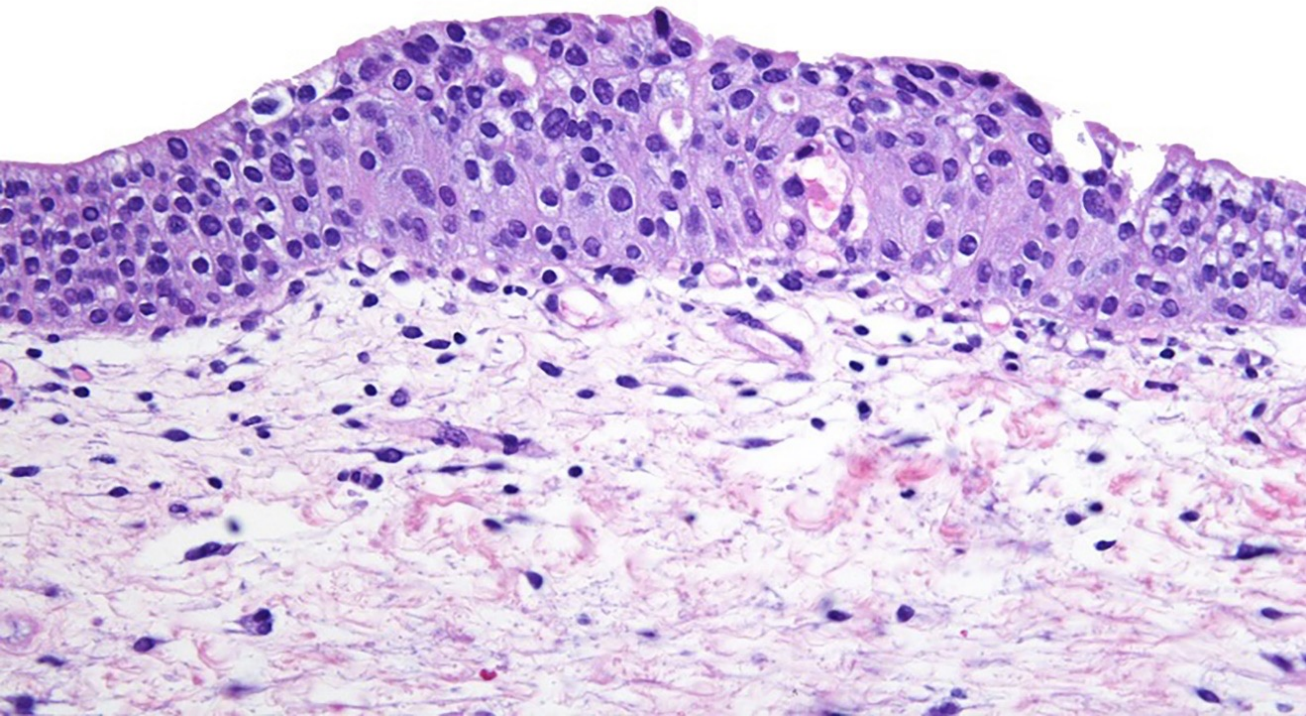
- Presence of cytologically malignant cells **regardless of quantity**
 - No need to be full **thickness**
 - **Pagetoid** cells
 - **Spectrum** of atypia and cell size
 - **Umbrella** cell layer may still be present
- CIS cells **5x size** of stromal lymphocytes, compared to normal cells which are 2x size of lymphocytes
- Enlarged & hyperchromatic **ON 10X OBJECTIVE**
- Dyscohesive : “**denuding cystitis**”



Urothelial Dysplasia



Urothelial Dysplasia



Urothelial Dysplasia

“Flat” Precursor Lesions Urothelial Dysplasia

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“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

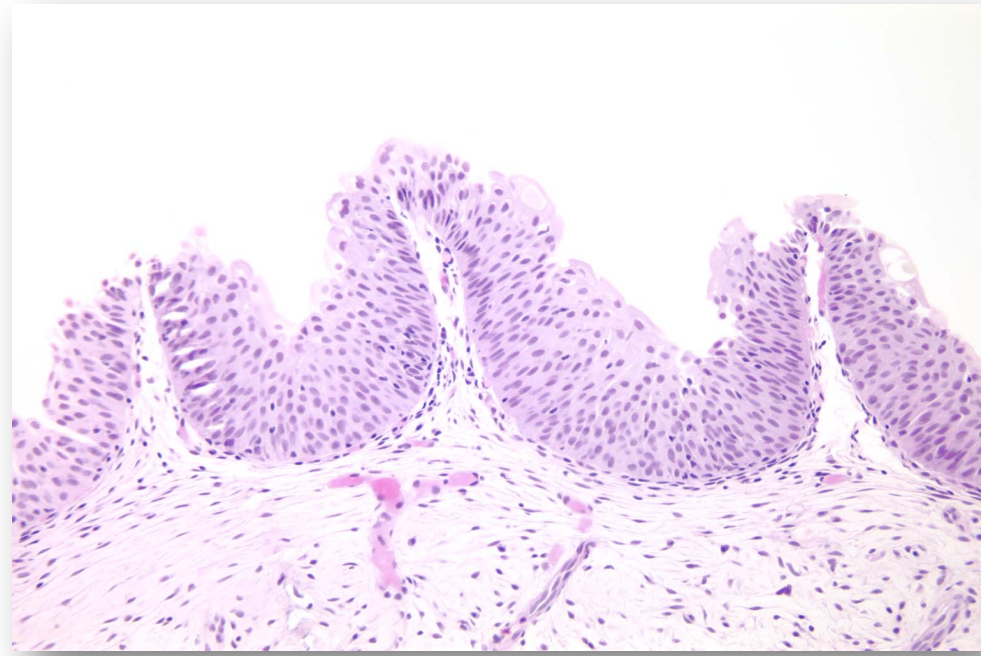
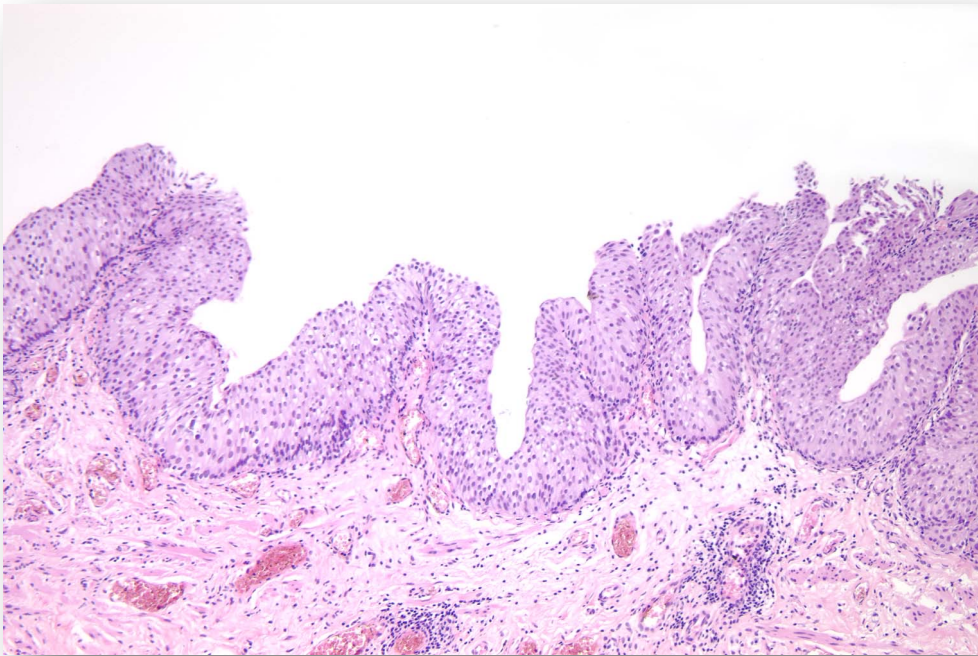
Should “Urothelial Proliferation of Undetermined Malignant Potential” remain an entity ?

UPUMP

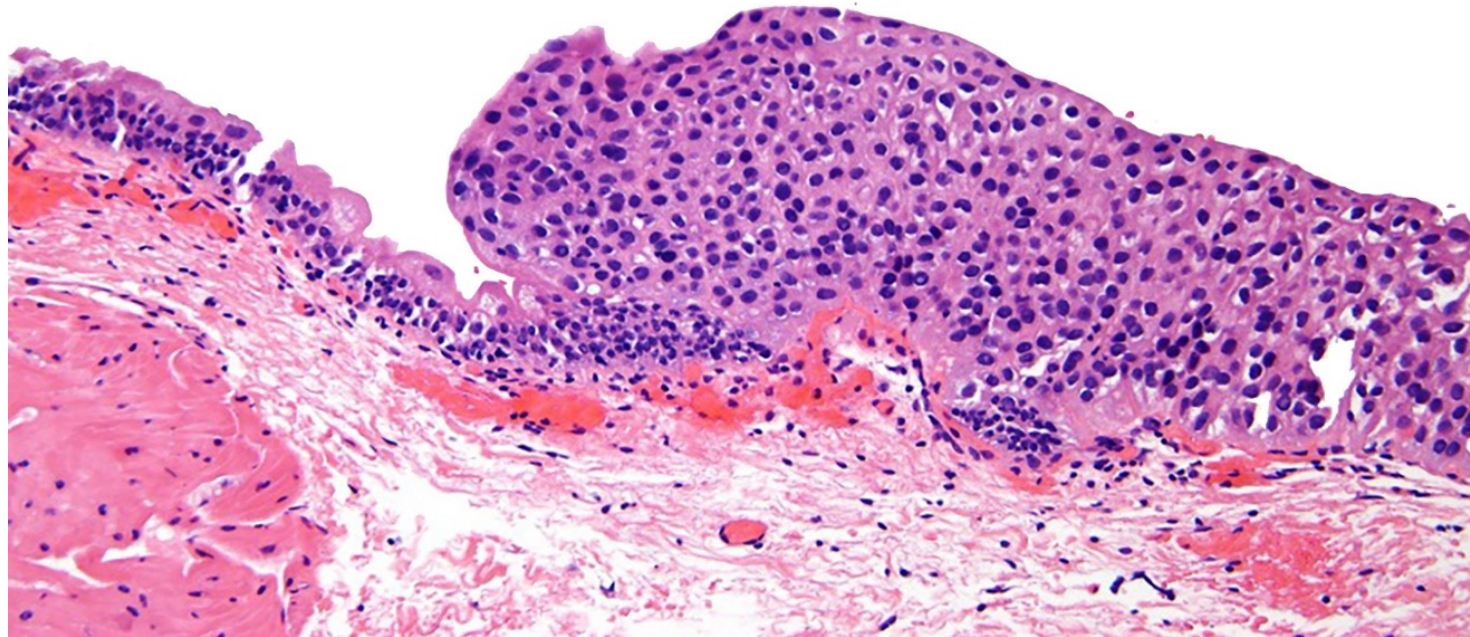
- Term **introduced in WHO 4th** edition
- **Encompass** lesions previously designated as
“**papillary urothelial hyperplasia**”
“**Flat hyperplasia with atypia?**”
- **Tented** architectural appearance with **short non branching papillae** covered by **mildly atypical** urothelium
- Thought to be **precursors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

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- **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

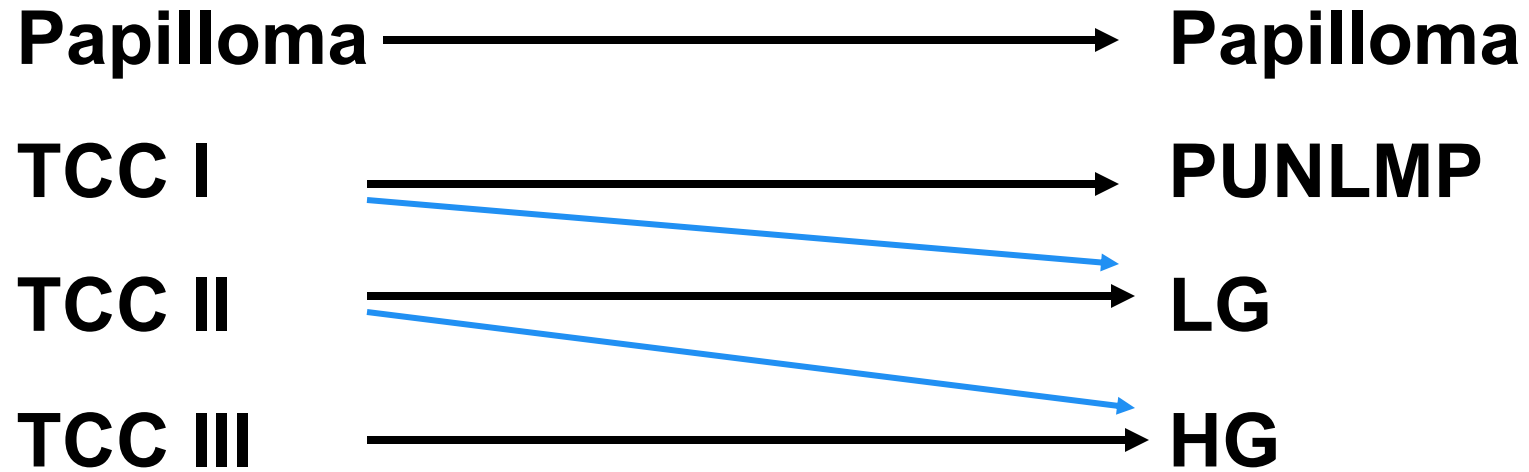
Urothelial carcinoma in situ

Invasive Urothelial Neoplasia

Invasive urothelial carcinoma

WHO 1973

2004 WHO/ISUP



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. |

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 Brisudaⁱ, José Rubio-Briones^j, Maximilian Seles^k, Anouk E. Hentschel^{l,m}, Venkata R.M. Kusumaⁿ, 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 Ashabereⁿ, 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. Kiemeny^{ff}, James N'Dow^{gg}, Karin Plass^{gg}, Otakar Capoun^{a,s}, Viktor Soukup^{a,s}, Jose L. Dominguez-Escrig^{aj}, Daniel Cohen^{aa,q}, Joan Palou^{ab}, Paolo Gontero^{aa,d}, Maximilian Burger^{aa,g}, Richard Zigeuner^{aa,k}, Amir Hugh Mostafid^{aa,n}, Shahrokh F. Shariat^{aa,i,o}, Morgan Rouprêt^{aa,p}, Eva M. Compérat^{aa,hh}, Marko Babjuk^{aa,i,o}, Bas W.G. van Rhijn^{aa,t}

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
Non-Muscle Invasive Bladder Cancer

[NCCN Guidelines Index](#)
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[Discussion](#)

RISK STRATIFICATION OF NMIBC

Initial TURBT shows NMIBC

Visually complete resection

Visually incomplete resection or High-volume tumor^h

Low-grade NMIBC

High-grade NMIBC

Carcinoma in situ (CIS) or Taⁱ

T1 or consider for select Taⁱ

Repeat TURBT^j

Residual NMIBC or no residual cancer

MIBC

Management per NMIBC risk group (BL-3)

See BL-1

AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

| Low Risk | Intermediate Risk | High Risk |
|---|---|--|
| <ul style="list-style-type: none"> • Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma <ul style="list-style-type: none"> ▶ Ta and ▶ ≤3 cm and ▶ Solitary | <ul style="list-style-type: none"> • Low grade urothelial carcinoma <ul style="list-style-type: none"> ▶ T1 or ▶ >3 cm or ▶ Multifocal or ▶ Recurrence within 1 year • High grade urothelial carcinoma <ul style="list-style-type: none"> ▶ Ta and ▶ ≤3 cm and ▶ Solitary | <ul style="list-style-type: none"> • High grade urothelial carcinoma <ul style="list-style-type: none"> ▶ CIS or ▶ T1 or ▶ >3 cm or ▶ Multifocal • Very high risk features (any): <ul style="list-style-type: none"> ▶ 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
- 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

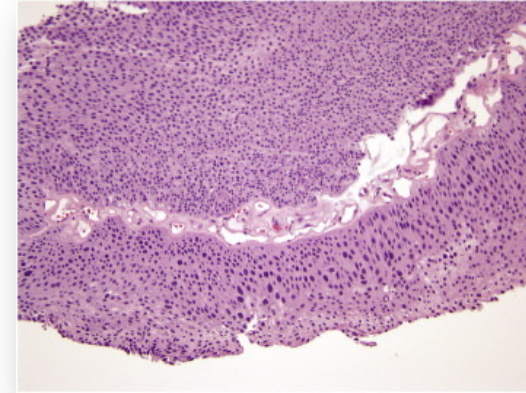
Invasive urothelial carcinoma

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 $\geq 5\%$
 - 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



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

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




Richard Colling^{1,2*} , Hayleigh Colling¹, 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 Pignot³, Marc Colombel^{4,5}, Laurent Guy⁶, Xavier Rebillard⁷, Laurent Savareux⁸,
Mathieu Roumigue⁹, Sebastien Nivet¹⁰, Monique Coutade Saidi¹¹, Eric Piaton¹² and Camelia Radulescu¹³

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

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

Overview

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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

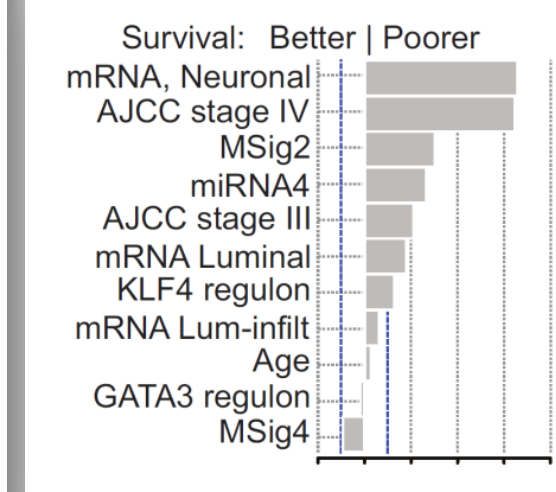
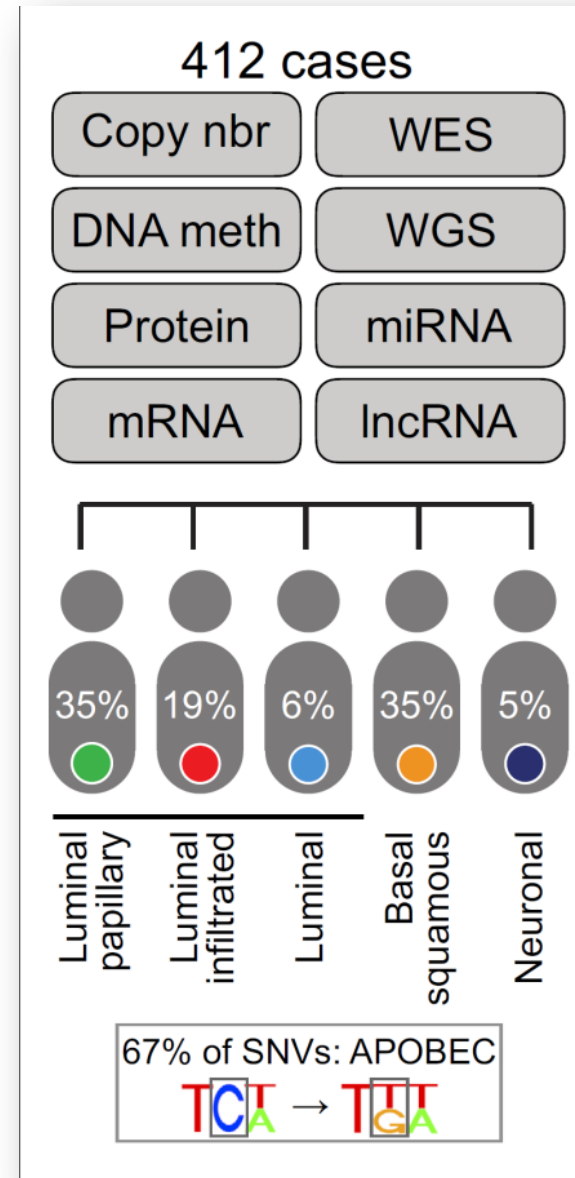
A. Gordon Robertson^{1,25}, Jaegil Kim^{2,25}, Hikmat Al-Ahmadie³, Joaquim Bellmunt⁴, Guangwu Guo⁵, Andrew D. Cherniack², Toshinori Hinoue⁶, Peter W. Laird⁶, Katherine A. Hoadley⁷, Rehan Akbani⁸, Mauro A.A. Castro⁹, Ewan A. Gibb¹, Rupa S. Kanchi⁸, Dmitry A. Gordenin¹⁰, Sachet A. Shukla⁵, Francisco Sanchez-Vega¹¹, Donna E. Hansel¹², Bogdan A. Czerniak¹³, Victor E. Reuter³, Xiaoping Su⁸, Benilton de Sa Carvalho¹⁴, Vinicius S. Chagas⁹, Karen L. Mungall¹, Sara Sadeghi¹, Chandra Sekhar Pdamallu², Yiling Lu¹⁵, Leszek J. Klimczak¹⁶, Jiexin Zhang⁸, Caleb Choo¹, Akinyemi I. Ojesina¹⁷, Susan Bullman², Kristen M. Leraas¹⁸, Tara M. Lichtenberg¹⁸, Catherine J. Wu¹⁹, Nicholas Schultz¹¹, Gad Getz², Matthew Meyerson²⁰, Gordon B. Mills¹⁵, David J. McConkey²¹, TCGA Research Network, John N. Weinstein^{8,22,26}, David J. Kwiatkowski^{23,26}, and Seth P. Lerner^{24,26}

Cell 2017

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



TCGA
Cell 2017

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

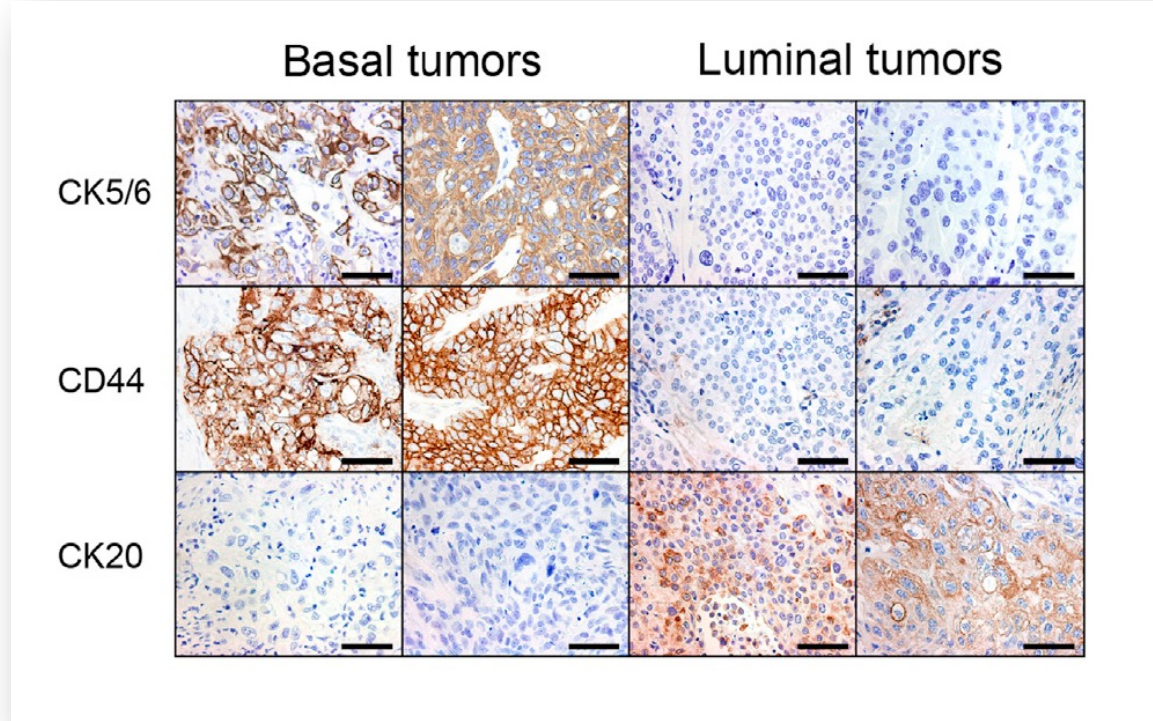


Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy

Choi W et al, Cancer Cell 2014

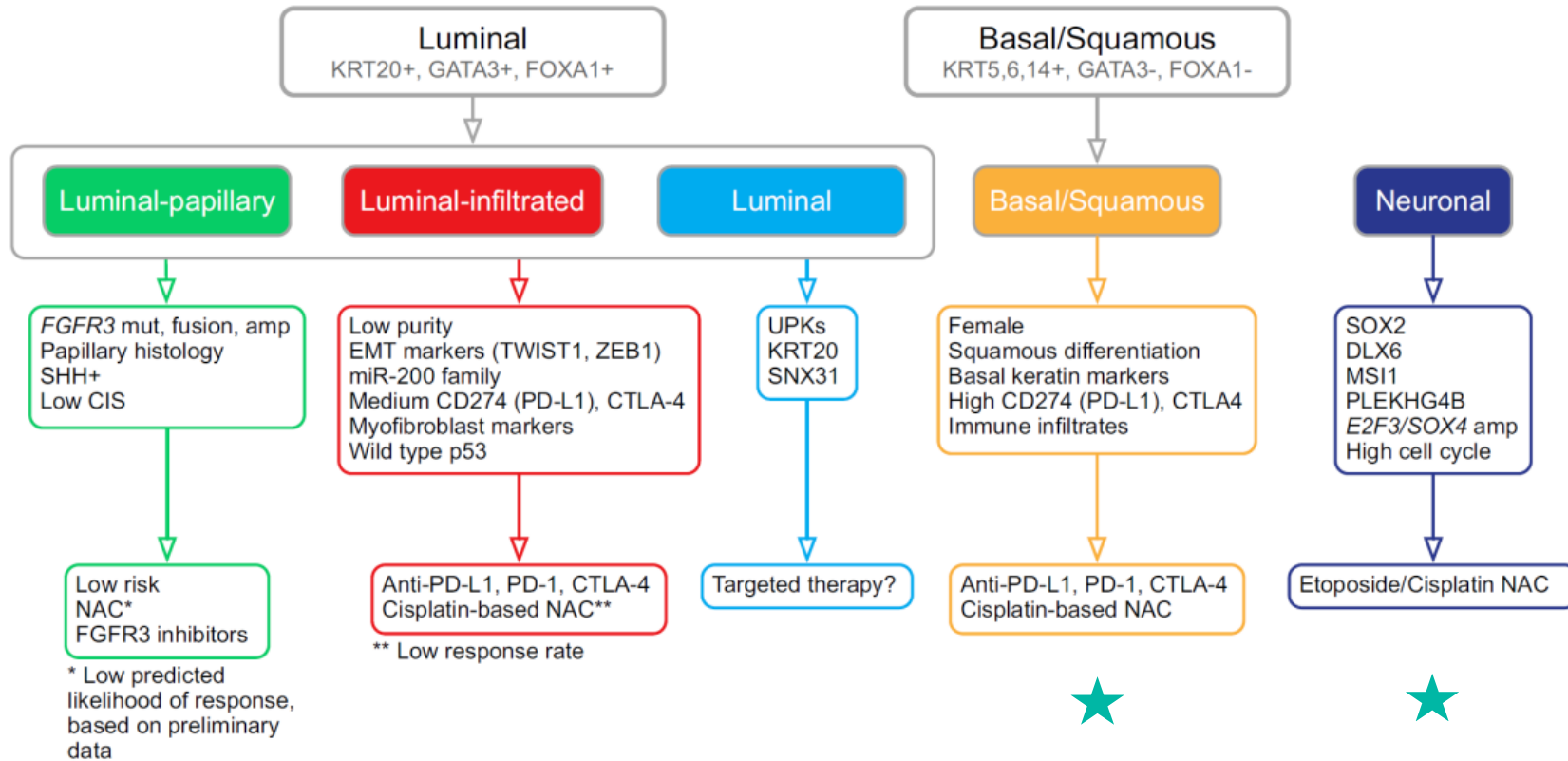
Three molecular subtypes of MIBC

Basal/Luminal/p53-like



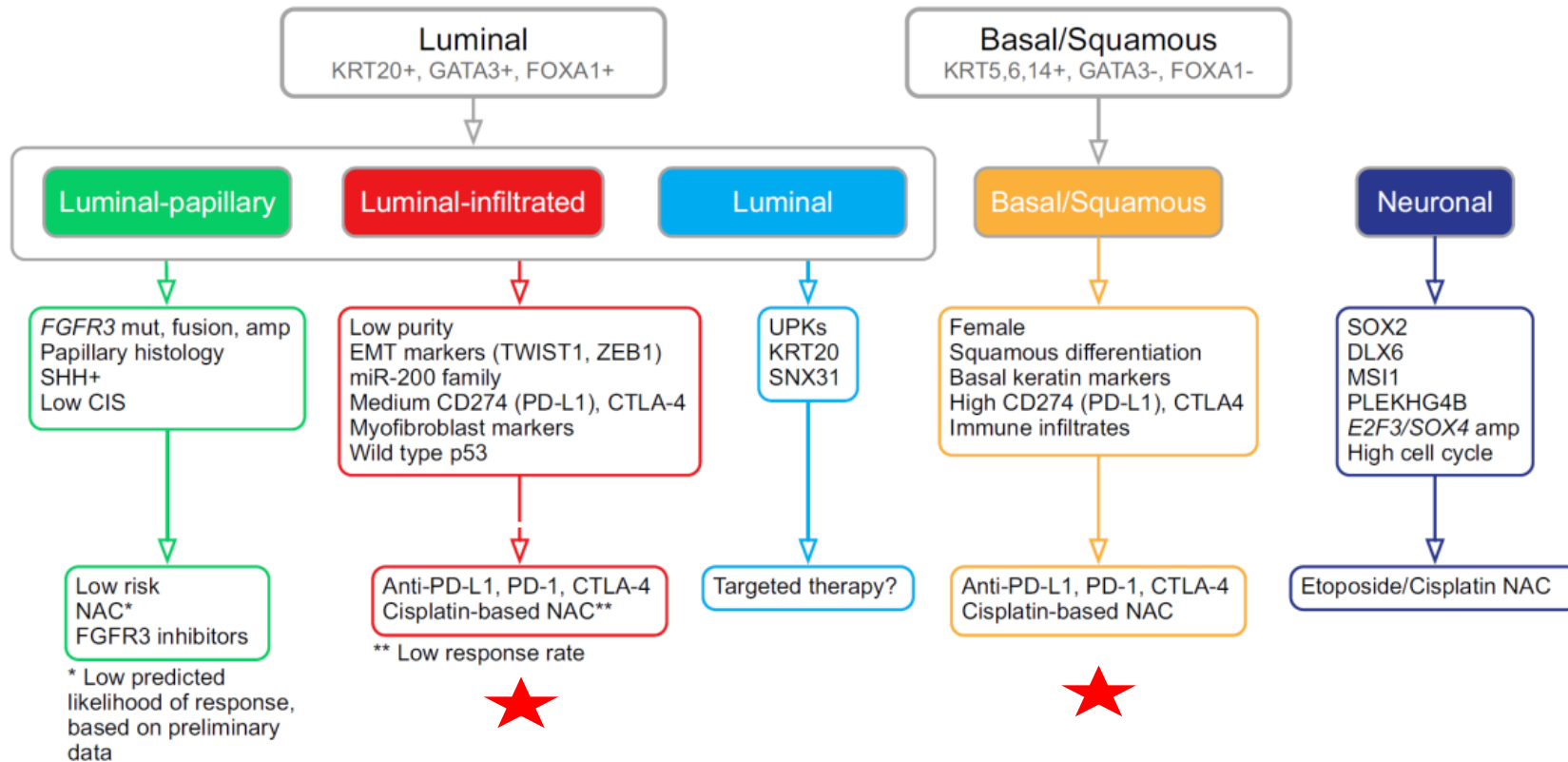
Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

Cell 2017



Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

Cell 2017



Take home points

- Urothelial Dysplasia is on the way out 😊
- UPUMP no more
- Invasive urothelial 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 !