

Urinary Cytology

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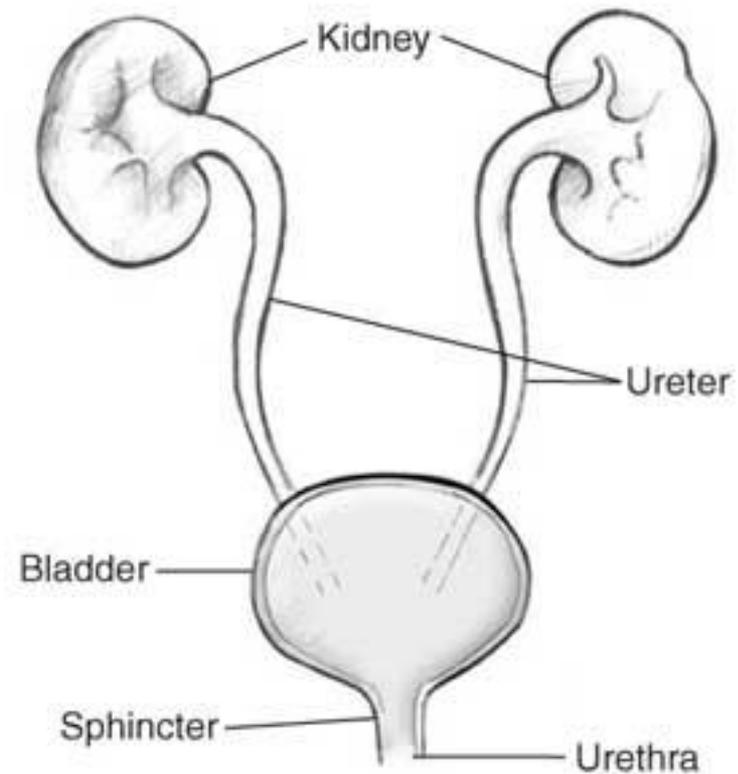
Pathology, University Hospital Basel, Switzerland

Outline

- Pre-analytics
- The Paris System (TPS):
 - Background
 - Diagnostic categories
 - Morphologic criteria for each category
- Ancillary FISH testing
- Examples

Urinary Specimens: Collection, preservation and processing

- Urine
 - Randomly voided
 - Forced diuresis
 - Catheter
 - Ileum conduit
- Washings
 - Bladder, UUT
- 50-100ml

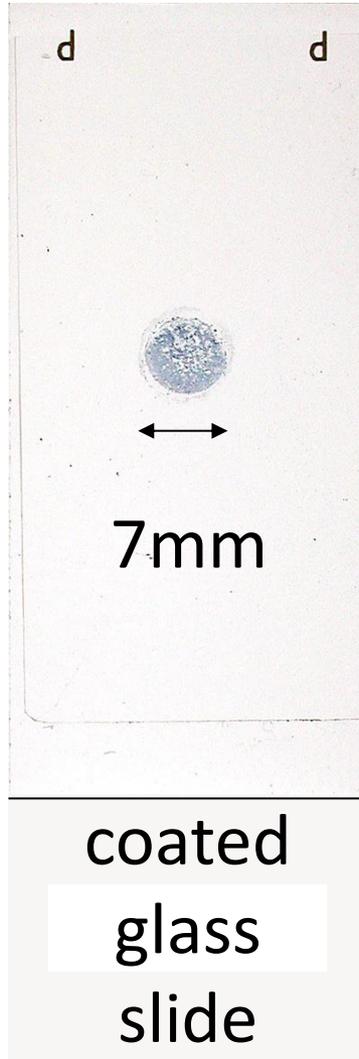


- Time to processing:
 - at RT: **4h**
 - at 4° C: **24h**
 - with preservation
(≠ fixation)
50% ethanol 1:1: **48h**

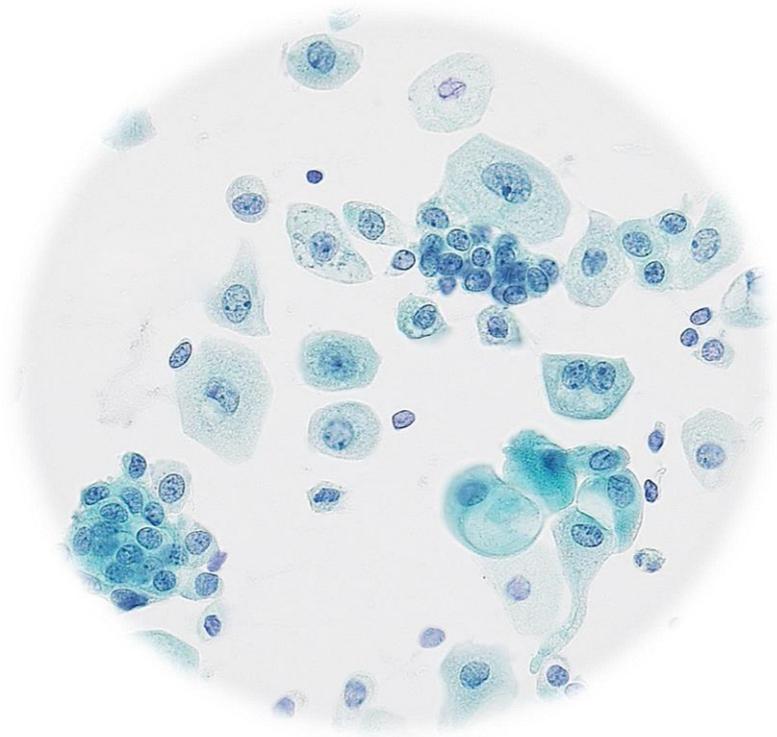


- native
- 50% ethanol 1:1

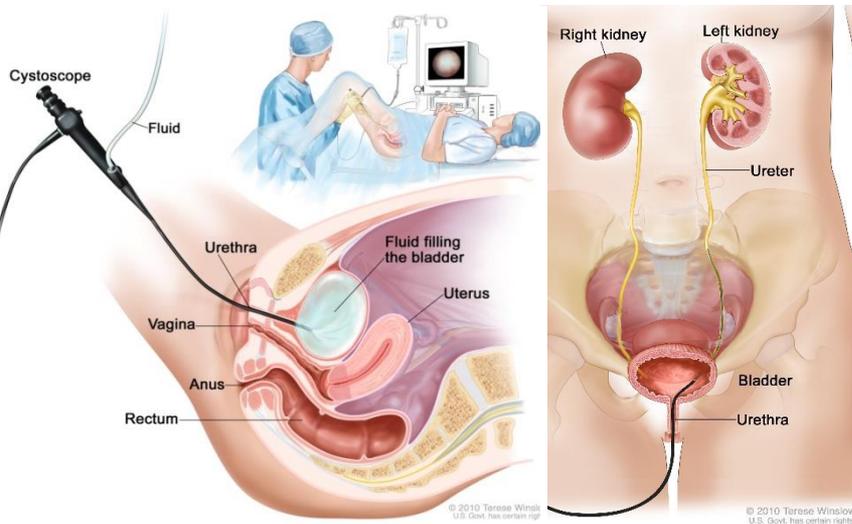
Cytospin



PAP



Cystoscopy



false neg. in -30%
invasive
long-term surveillance:
expensive

Urinary Cytology



cheap
high spec. for high-grade UC
non-visible high-grade UC
no universal classification system
equivocal atypia
low sens. for low-grade UC

Low grade Lesions

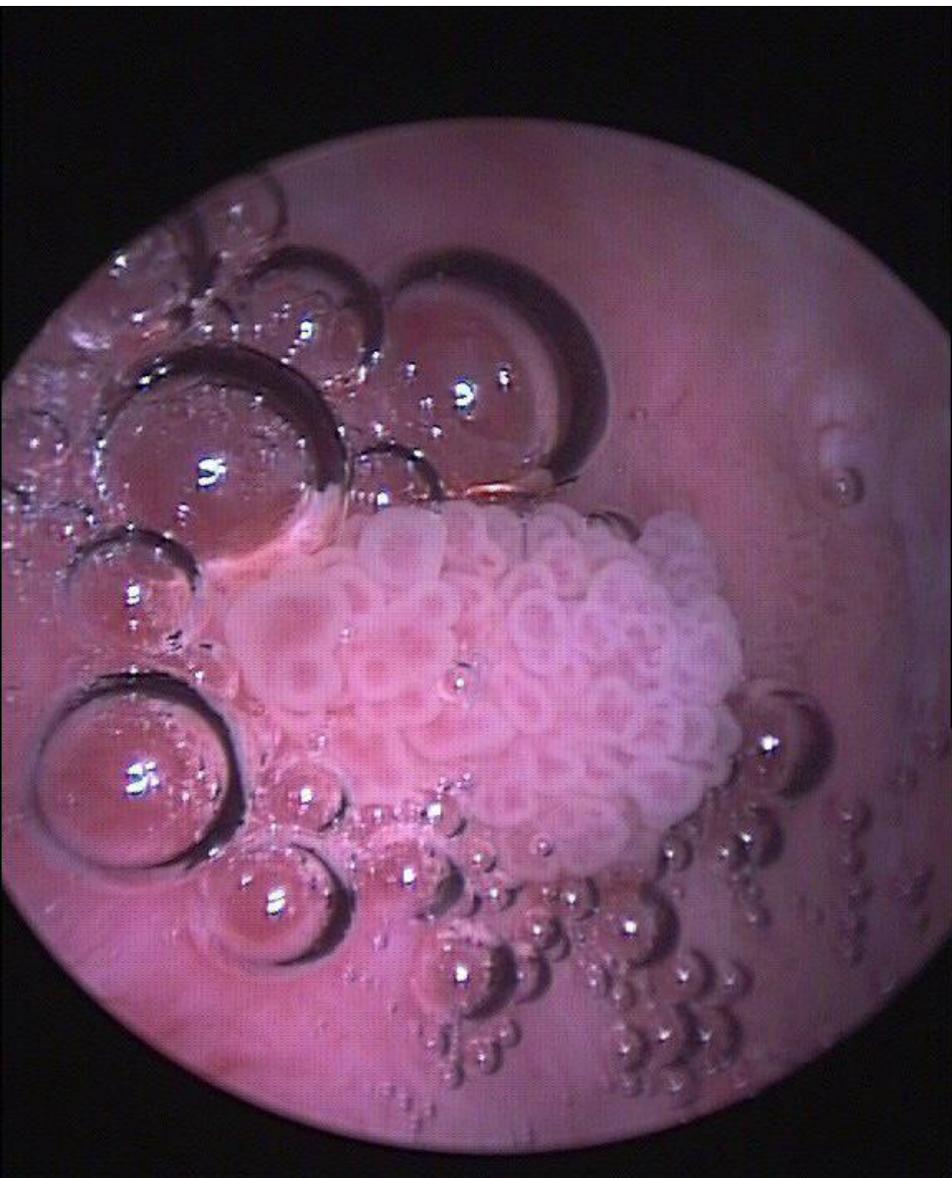


- Cells look benign
- Rarely shed
- Rarely invade
- Rarely kill

High grade Lesions

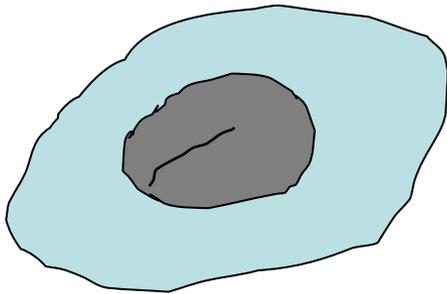


- Cells are UGLY
- Cells shed singly
- Often invade
- Often lethal

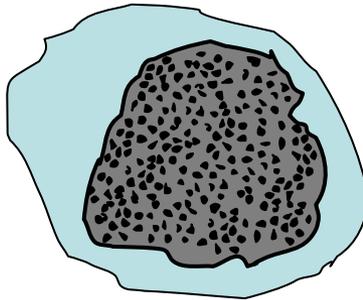


nuclear / cytologic atypia

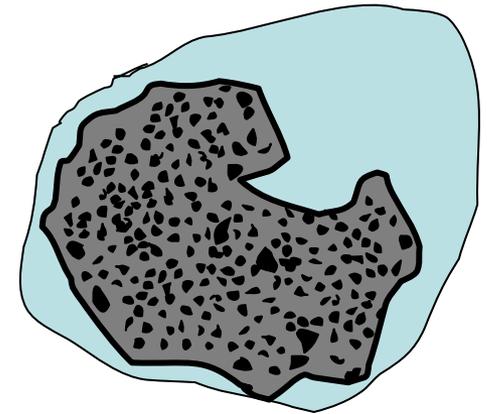
mild

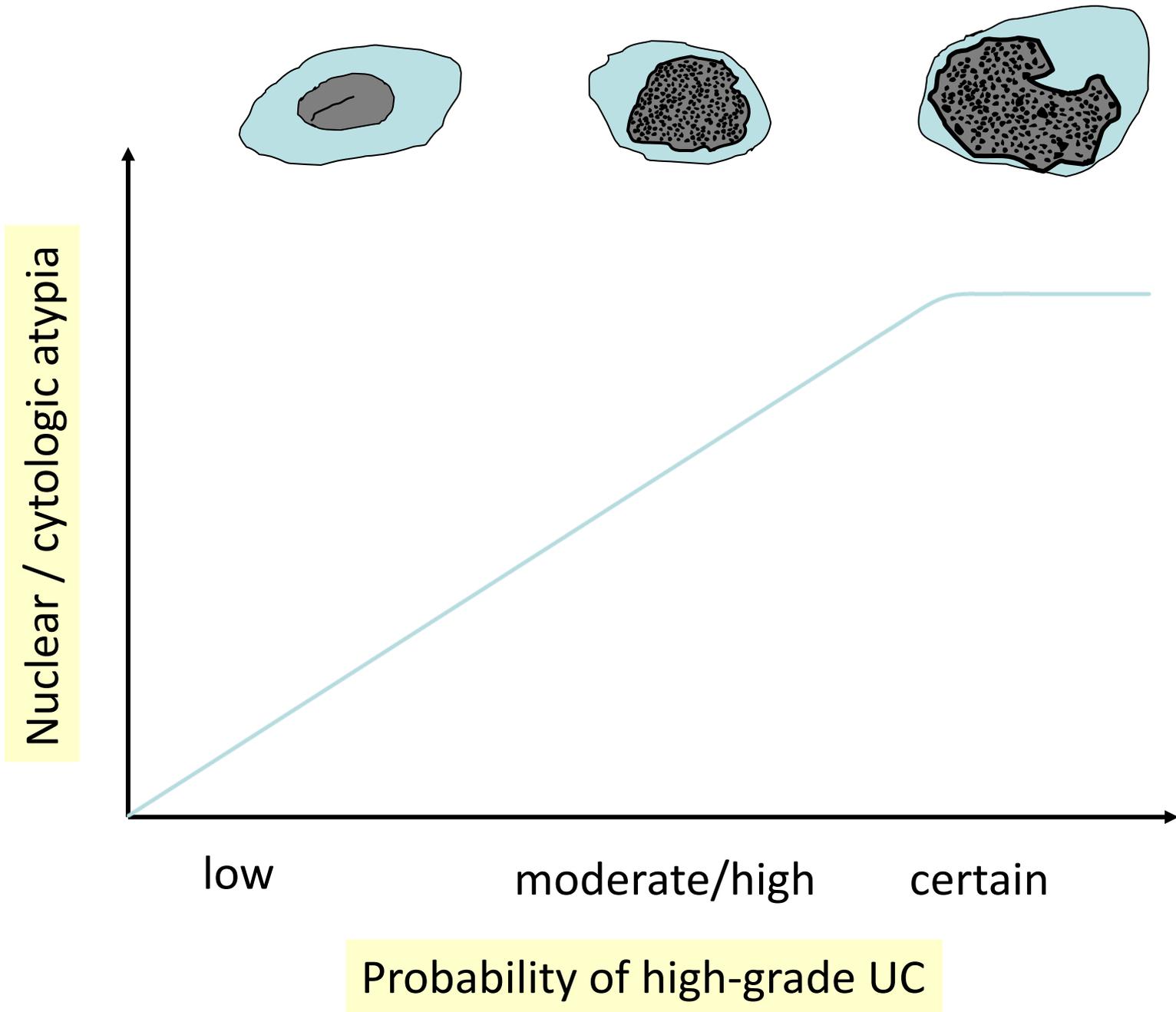


moderate

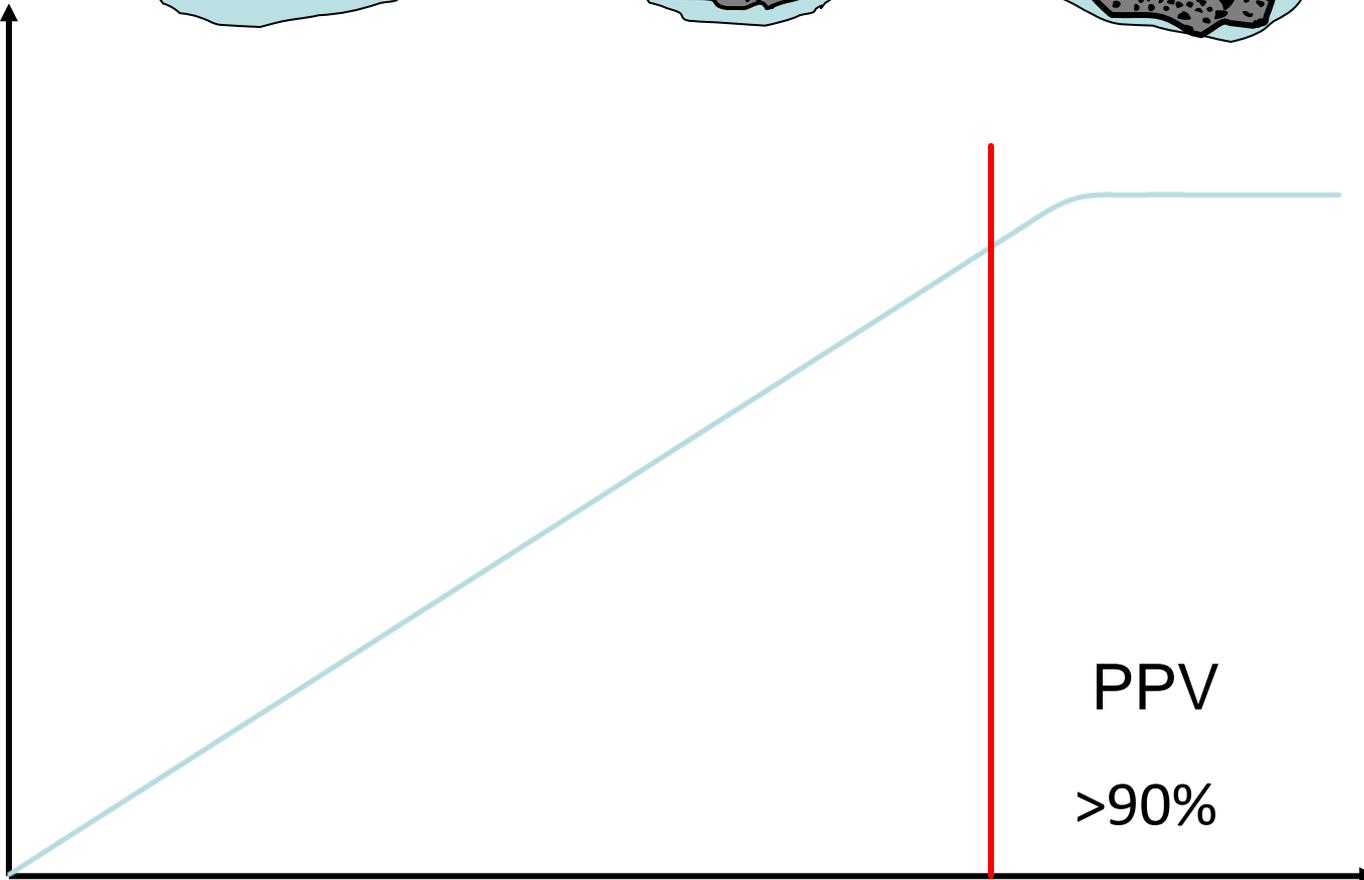
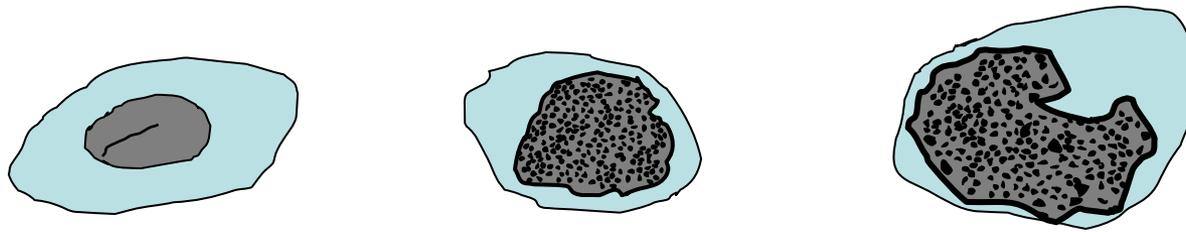


severe (G3)





Nuclear / cytologic atypia



low

moderate/high

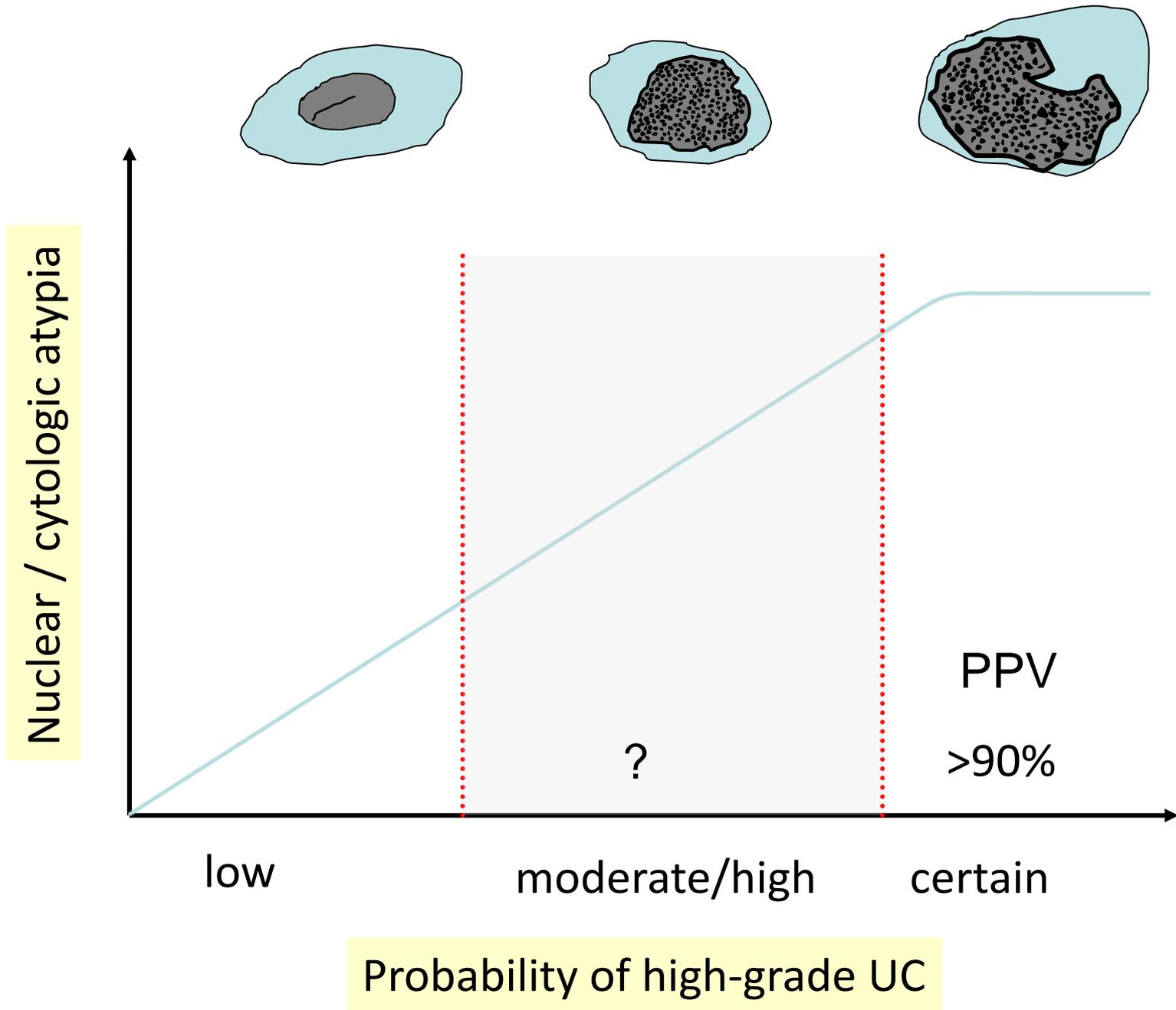
certain

Probability of high-grade UC

PPV
>90%

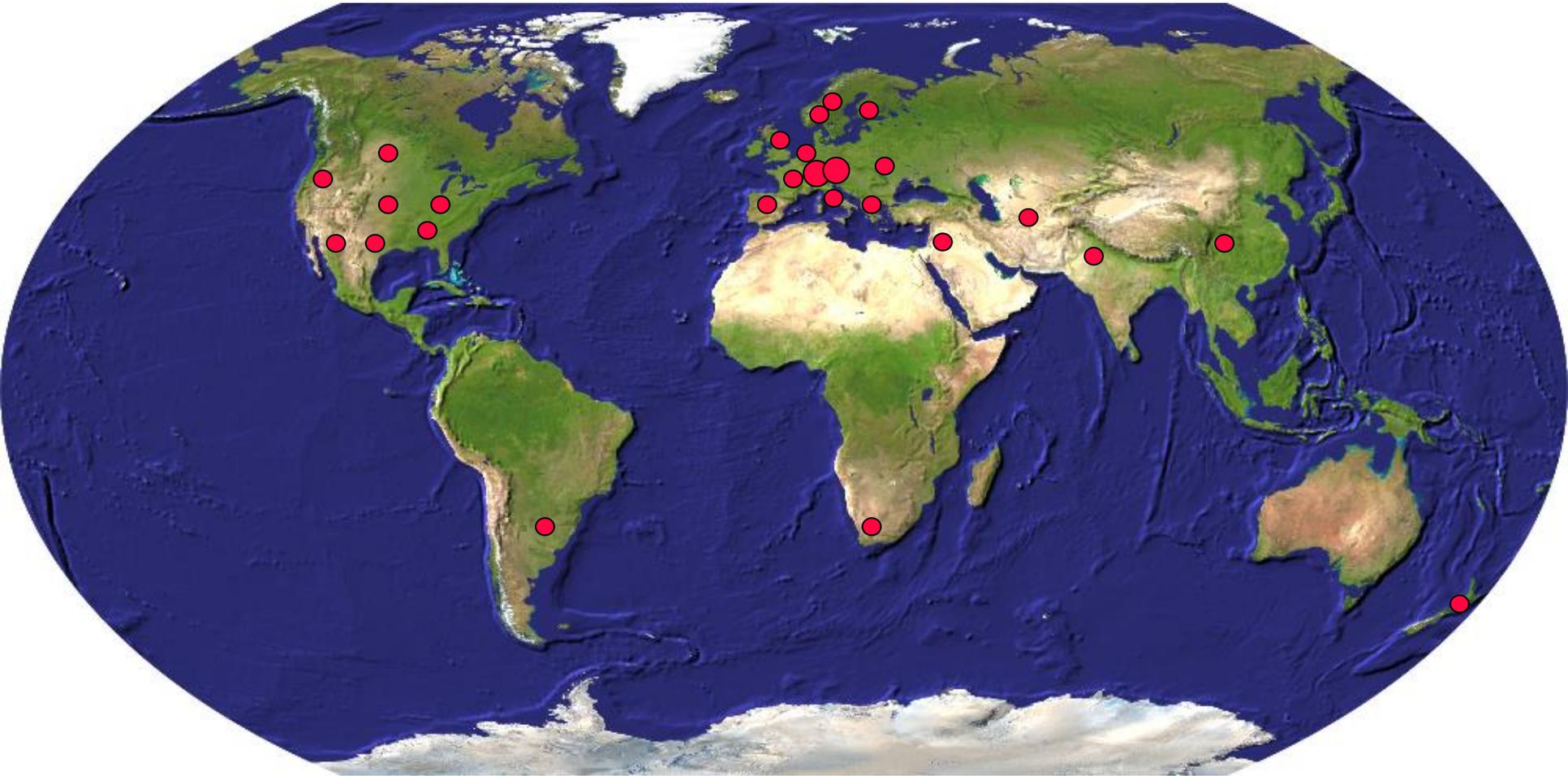
Distribution of diagnostic categories utilized in The Paris System survey (unpublished data)

Total range	Academic	Private Practice
Positive	1.0 – 6.3%	1.2 – 4.9%
Suspicious	0.7 – 5.4%	0.2 – 2.7%
Atypical	1.8 – 23.7%	3.1 – 21.4%
Negative	75.4 – 94.8%	71.4 – 96.1%
Washing	1.0 – 74%	1.0 – 22.2%
Number/year	841 – 9210	81 - 4932



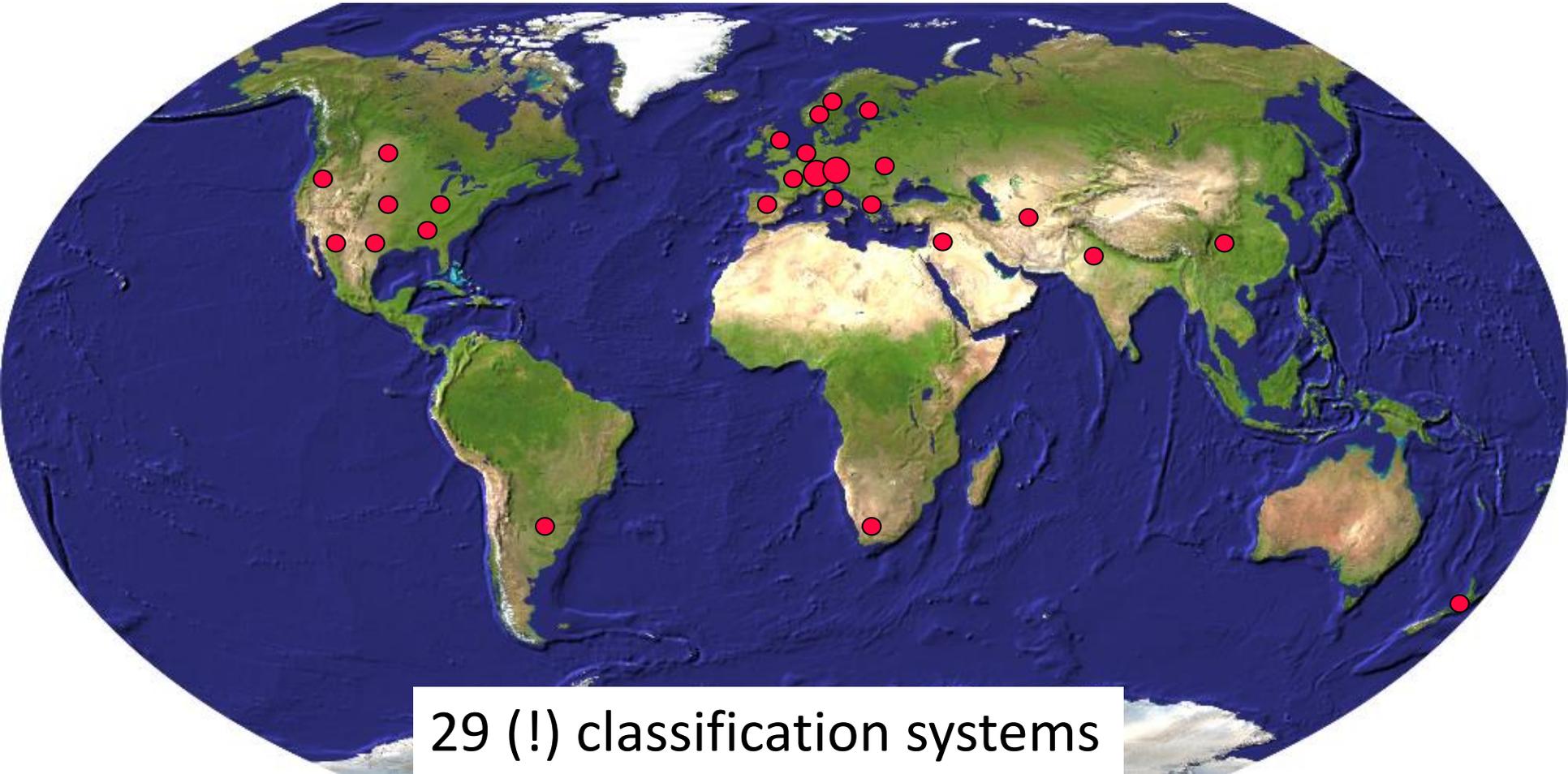
International online Quiz on Urinary cytology

246 participants; 52 cases, mostly difficult



International online Quiz on Urinary cytology

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Case 17

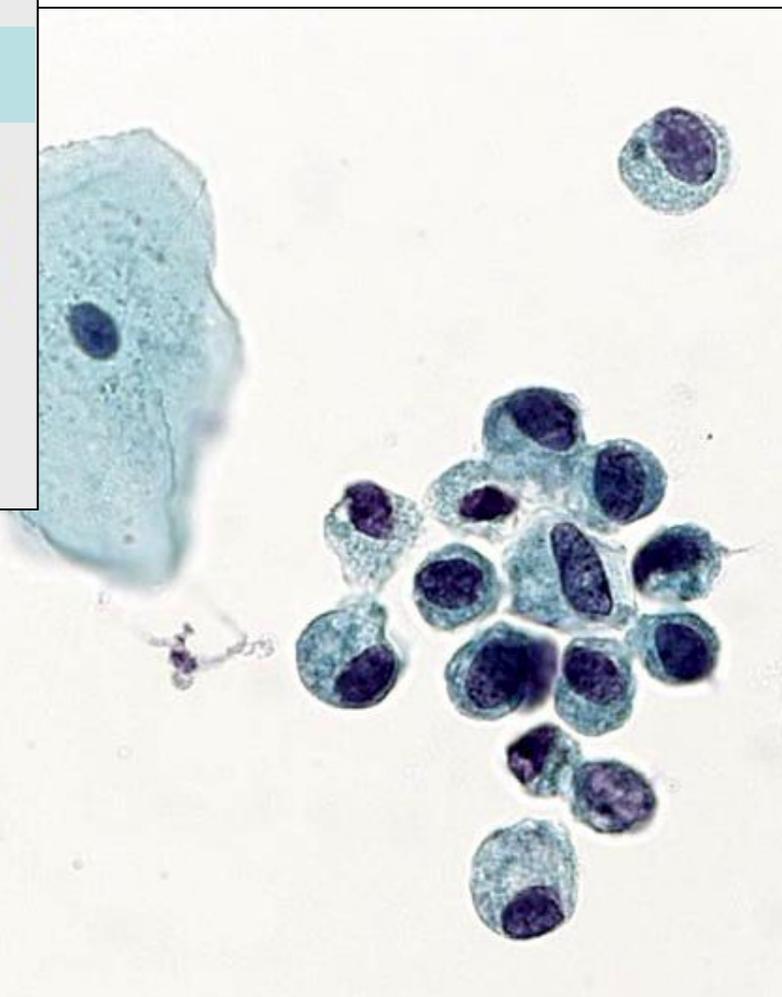
Bladder wash. History of hematuria. 58 year-old man.



What is your diagnosis for case 17 (required)

FISH neg; Cystoscopy inconspicuous

- 1 Negative, benign — 3.3%
- 2 Reactive changes — 17.1%
- 3 Mild atypia, cannot exclude low grade neoplasia — 30.9%
- 4 Moderate atypia, suspicious — 37.8%
- 5 Severe atypia, positive — 11.0%



58 year-old male with hematuria

Case 17

58 jg. Mann mit Hämaturie

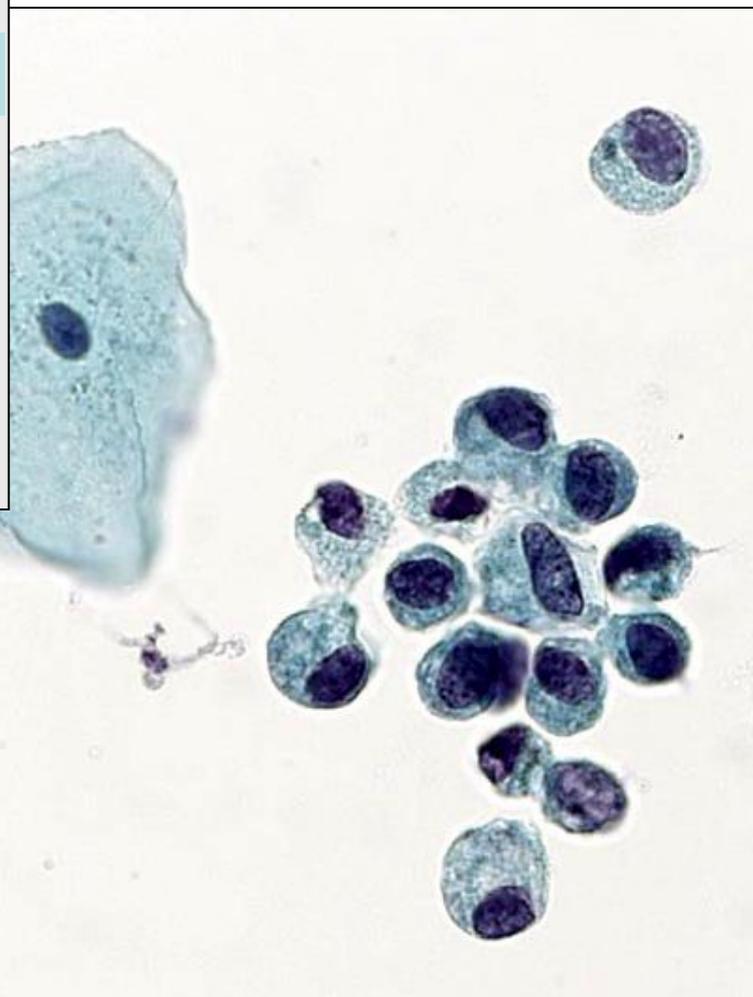


What is your diagnosis for case 17 (required)

FISH neg; Zystoskopie unauffällig

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- 5 Severe atypia, positive — 11.0%

48.8%
false positive





ICC Paris, May 2013



ASC 2013



ASC 2014



USCAP 2014



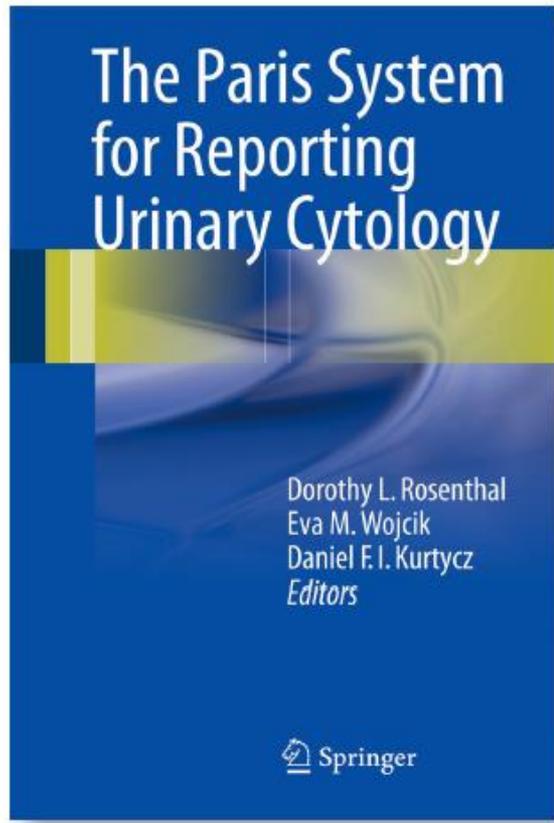
ECC, Geneva, 2014

The Paris System for Reporting Urinary Cytology

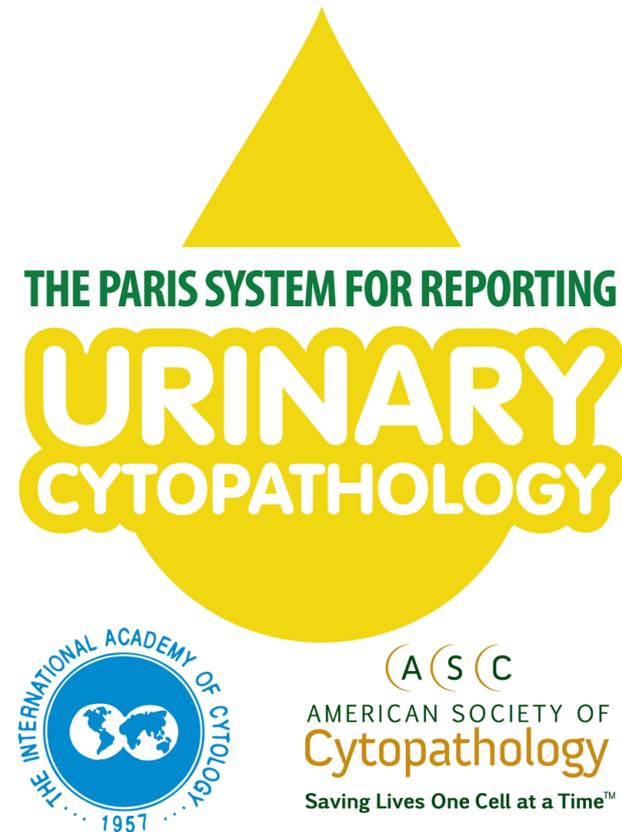
- **2013** - IAC International Congress of Cytology in Paris
- ASC and IAC agreed to support TPS Working Group by establishing Websites to invite comments from members
- **2014** - Website Statements went live in Spring, translated into Japanese, Chinese and Korean
- **2016** - Springer Publishers to produce “The Paris System for Reporting Urinary Cytology” in the same format as The Bethesda System

Goal of The Paris System:

FIND THE HIGH-GRADE CANCERS



1st ed. 2016, XV, 220 p.
101 illus., 97 illus. in color



Diagnostic Categories of TPS

- Negative for HGUC: negative
- Atypical Urothelial Cells: AUC
- Suspicious for HGUC: SHGUC
- High Grade Urothelial Carcinoma: HGUC
- Low Grade Urothelial **Neoplasia**: LGUN
- Other malignancies – Primary/secondary

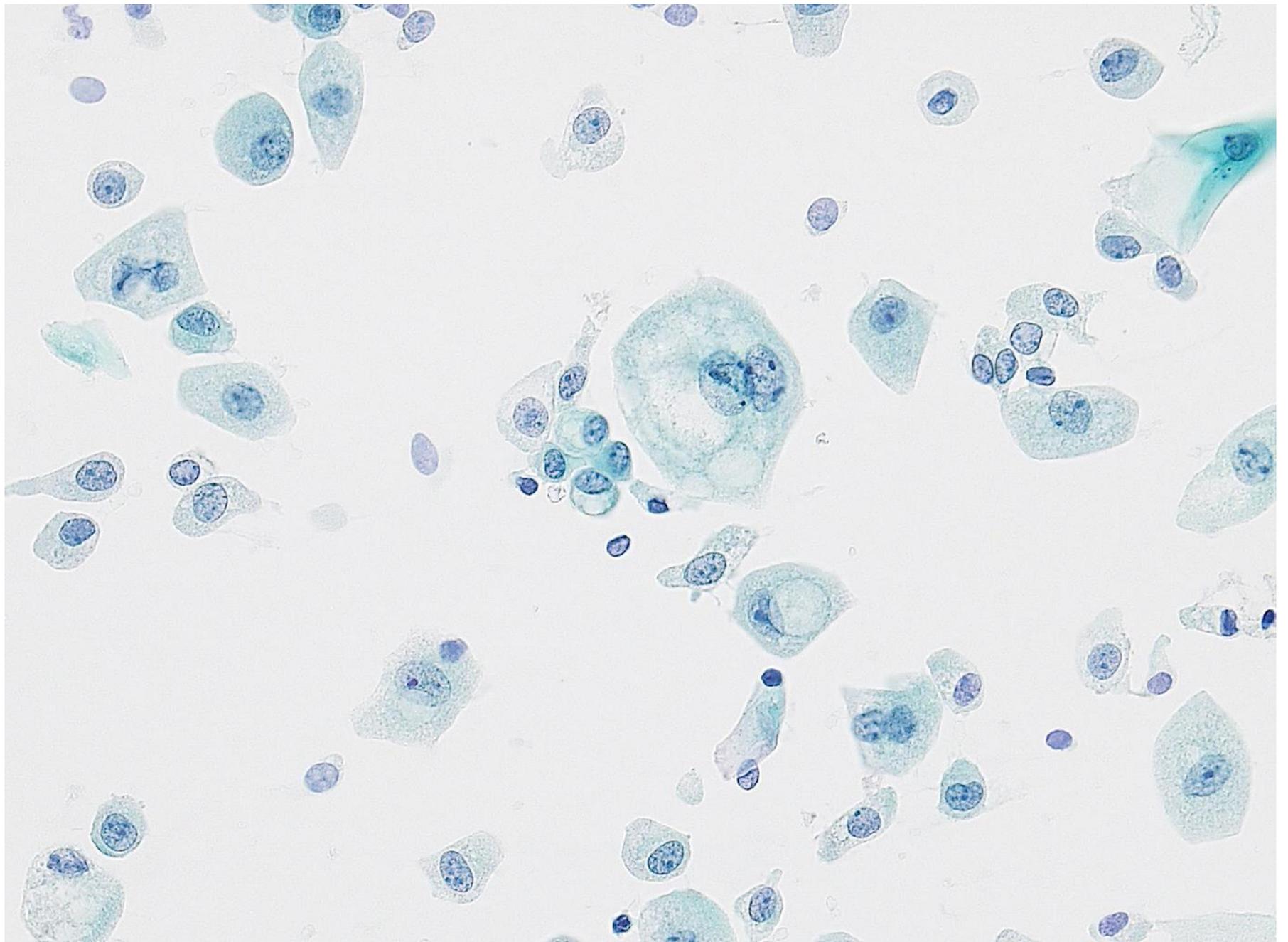
Relative Risk of the Diagnostic Categories Outlined in the Paris System, Based on Studies to Date:

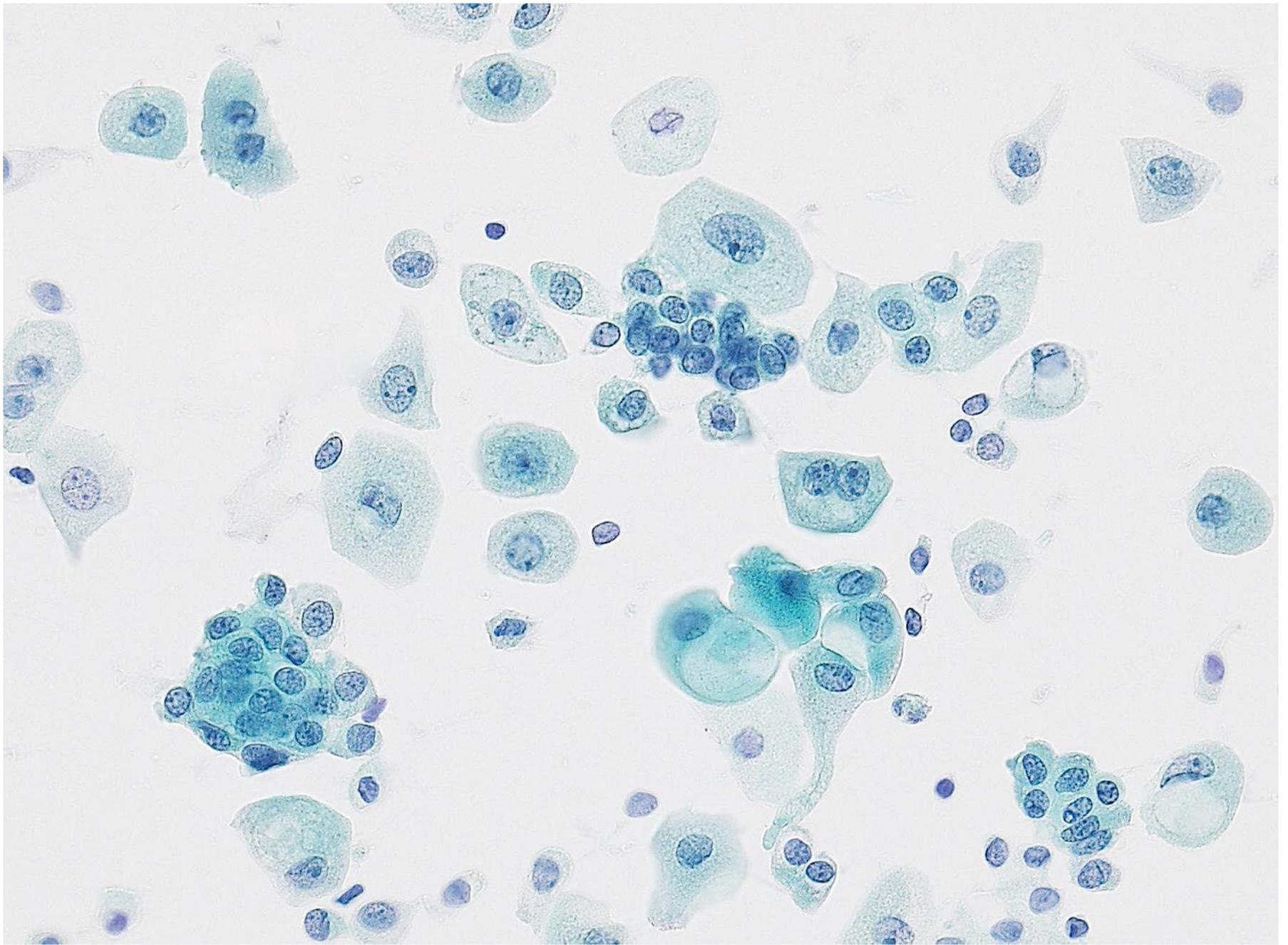
TABLE 4. Relative Risk of the Diagnostic Categories Outlined in the Paris System, Based on Studies to Date

Category	Risk of Malignancy (%)	Management
Unsatisfactory/nondiagnostic	< 5-10	Repeat cytology, cystoscopy in 3 mo if increased clinical suspicion
Negative for high-grade urothelial carcinoma	0-10	Clinical follow-up as needed
Atypical urothelial cells	8-35	Clinical follow-up as needed Potential use of ancillary testing
Suspicious for high-grade urothelial carcinoma	50-90	More aggressive follow-up, cystoscopy, biopsy
Low-grade urothelial neoplasm	~ 10	Need cystoscopy and biopsy to further evaluate grade and stage
High-grade urothelial carcinoma	> 90	More aggressive follow-up, cystoscopy, biopsy, staging
Other malignancy	> 90	More aggressive follow-up, cystoscopy, biopsy, staging

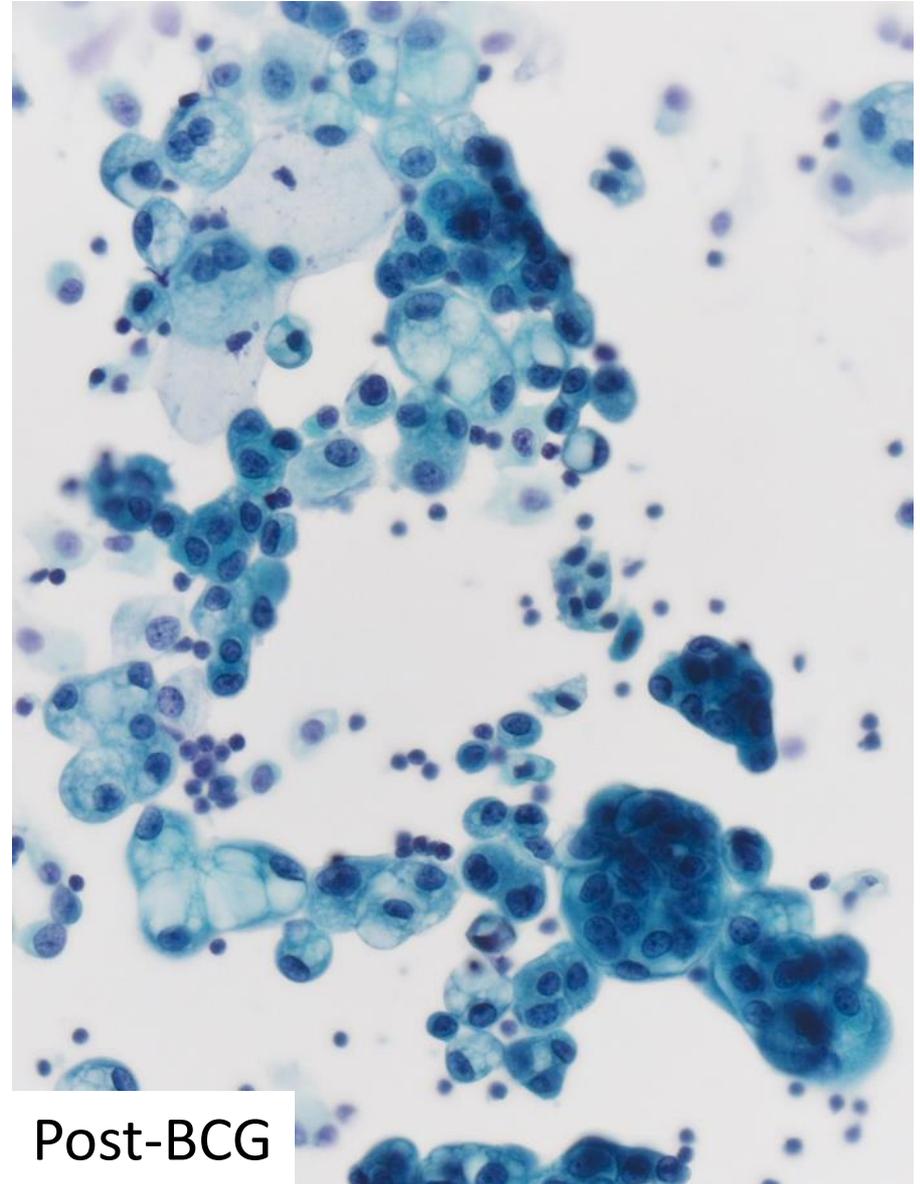
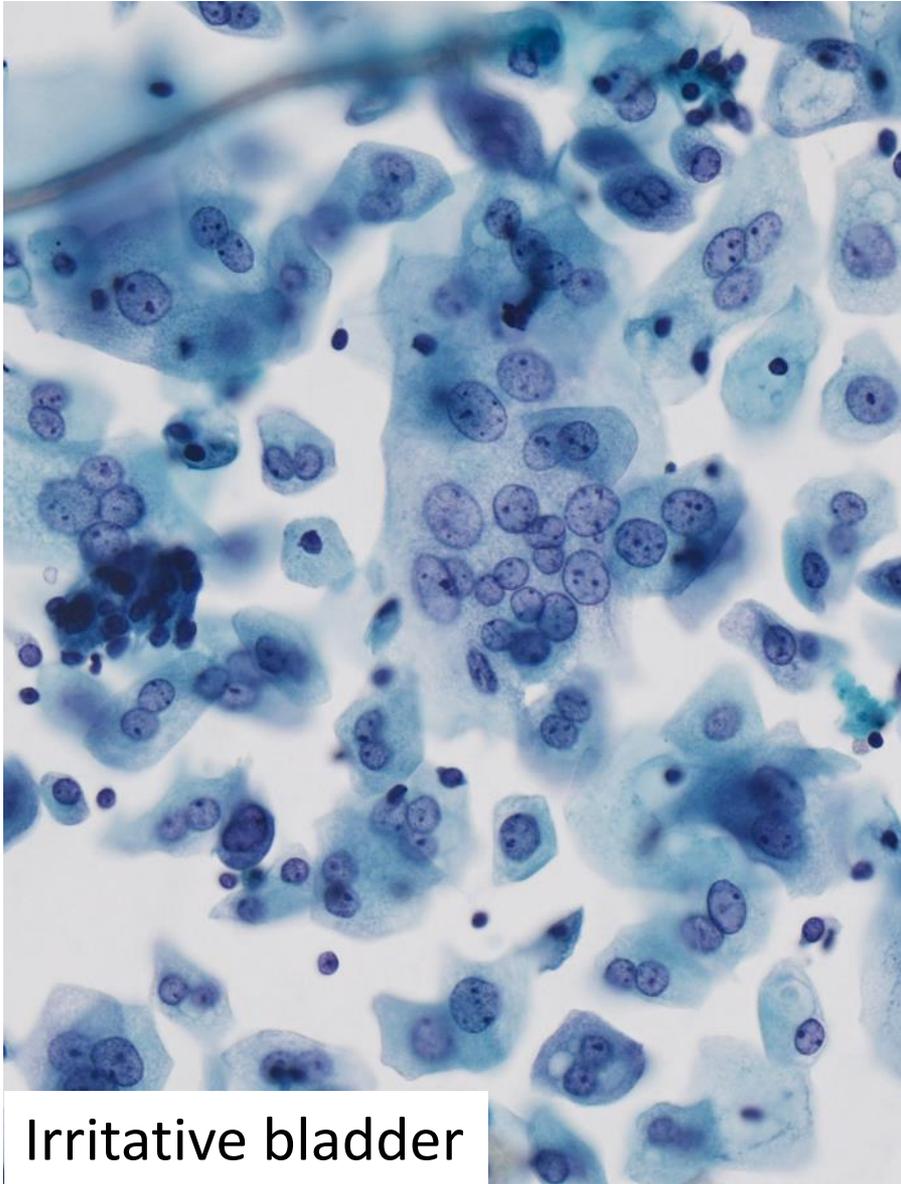
Negative for HGUC (Negative)

- Benign/reactive urothelial & other epithelial cells
- Benign urothelial fragments and sheets or clusters
- Changes associated with lithiasis
- Viral cytopathic effects (e.g. Decoy cells)
- Post-therapy effect (BCG, chemoth., Rx)





Reactive changes

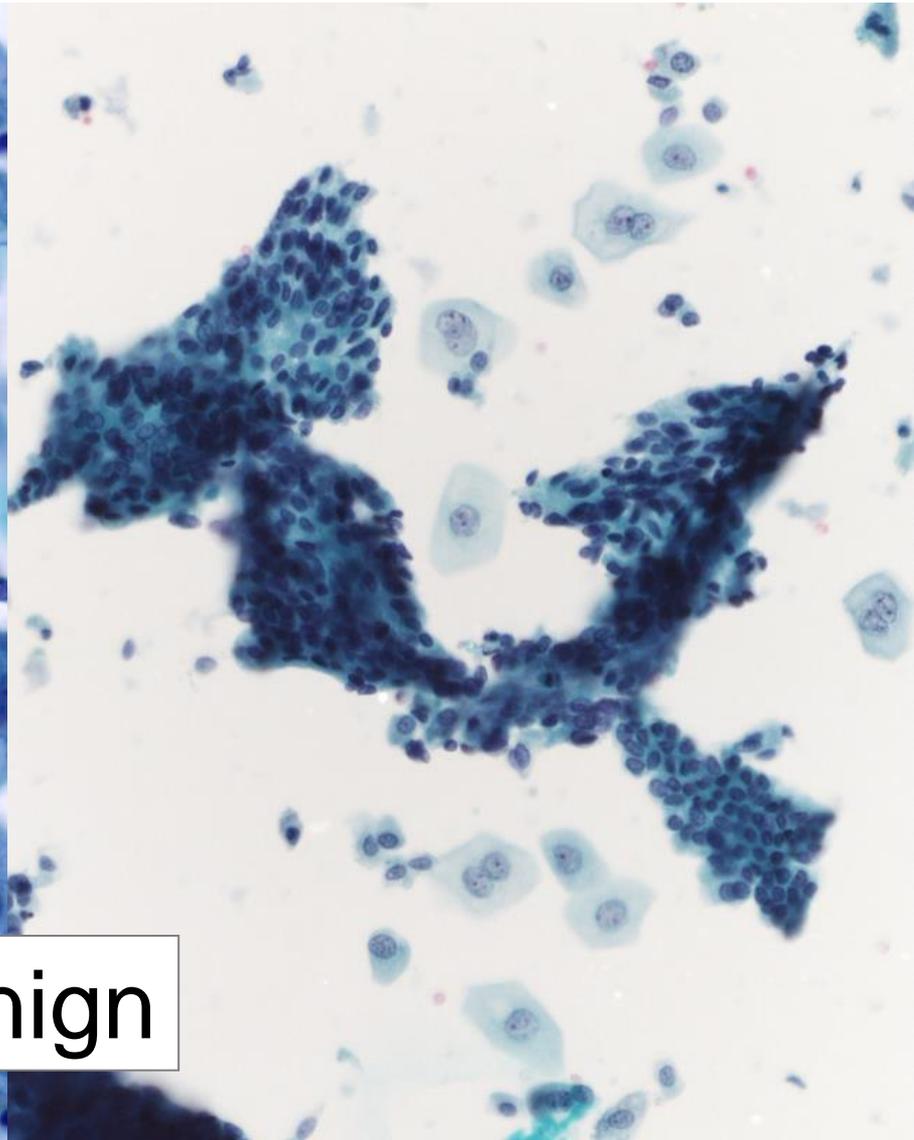
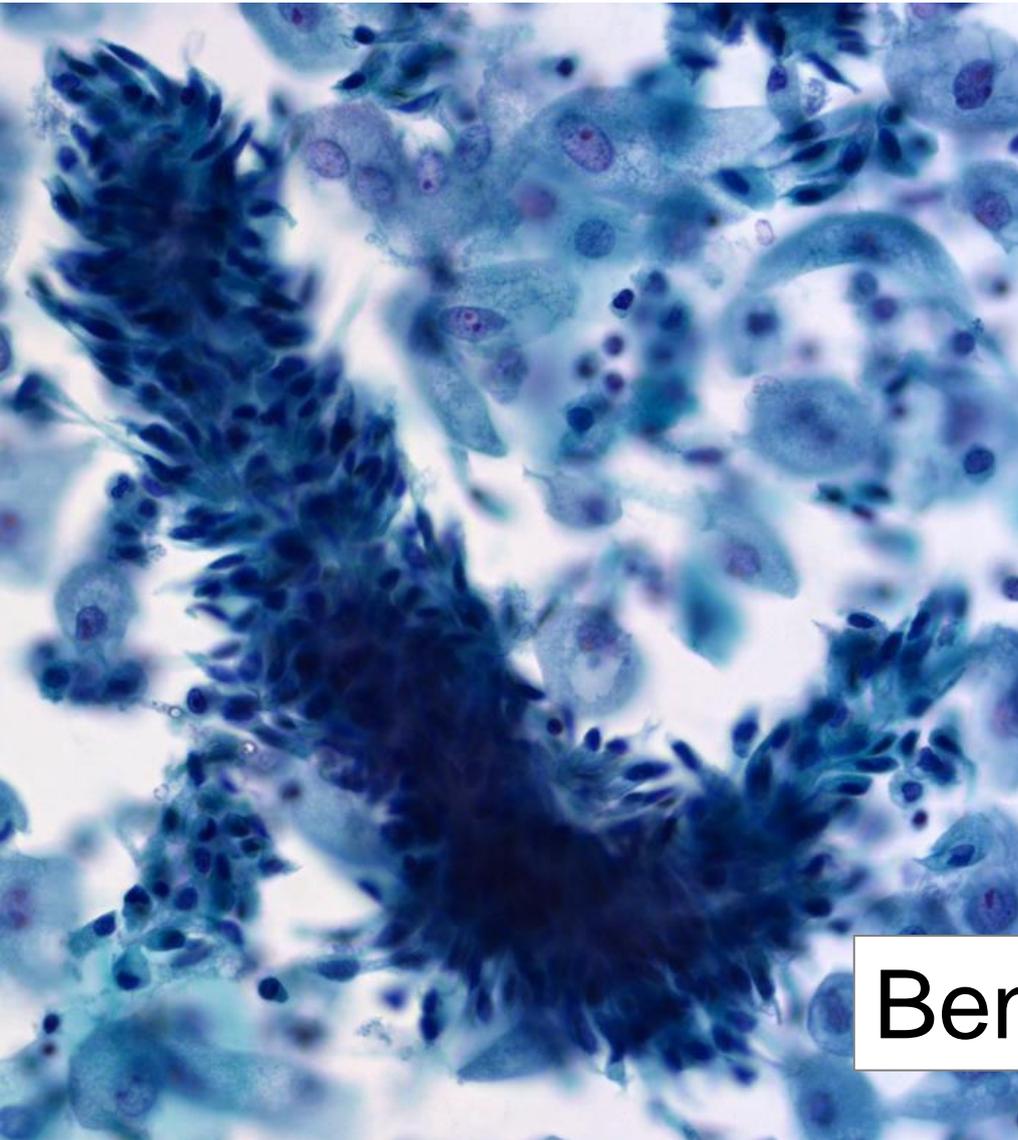


Reactive changes



Mitomycin effect

Urothelial Fragments: Papillary-like cell clusters (washings and voided urine)



Benign

High Grade Urothelial Carcinoma

- Histopathologic definition:
 - Non-invasive papillary urothelial carcinoma
 - Moderate to marked architectural and cytologic atypia
 - Urothelial carcinoma in situ
 - Flat lesion with cytologically malignant cells
 - Invasive urothelial carcinoma
 - Invasion beyond the basement membrane

HGUC (1-6%; gross hematuria: 20%)



Diagnostic work-up



Tis



Ta



T1



≥ pT2



TUR + intravesical Treatment



Cystectomy

Lifelong follow-up

Morphologic criteria: High Grade Urothelial Carcinoma

- Non-superficial and non-degenerated urothelial cells with \uparrow N/C ratio of ≥ 0.7
- Nuclear hyperchromasia, moderate – severe
- Marked irregular nuclear membranes: shape and thickness
- Irregular, coarse, clumped chromatin
- Minimum of $\geq 5-10$ viable malignant cells

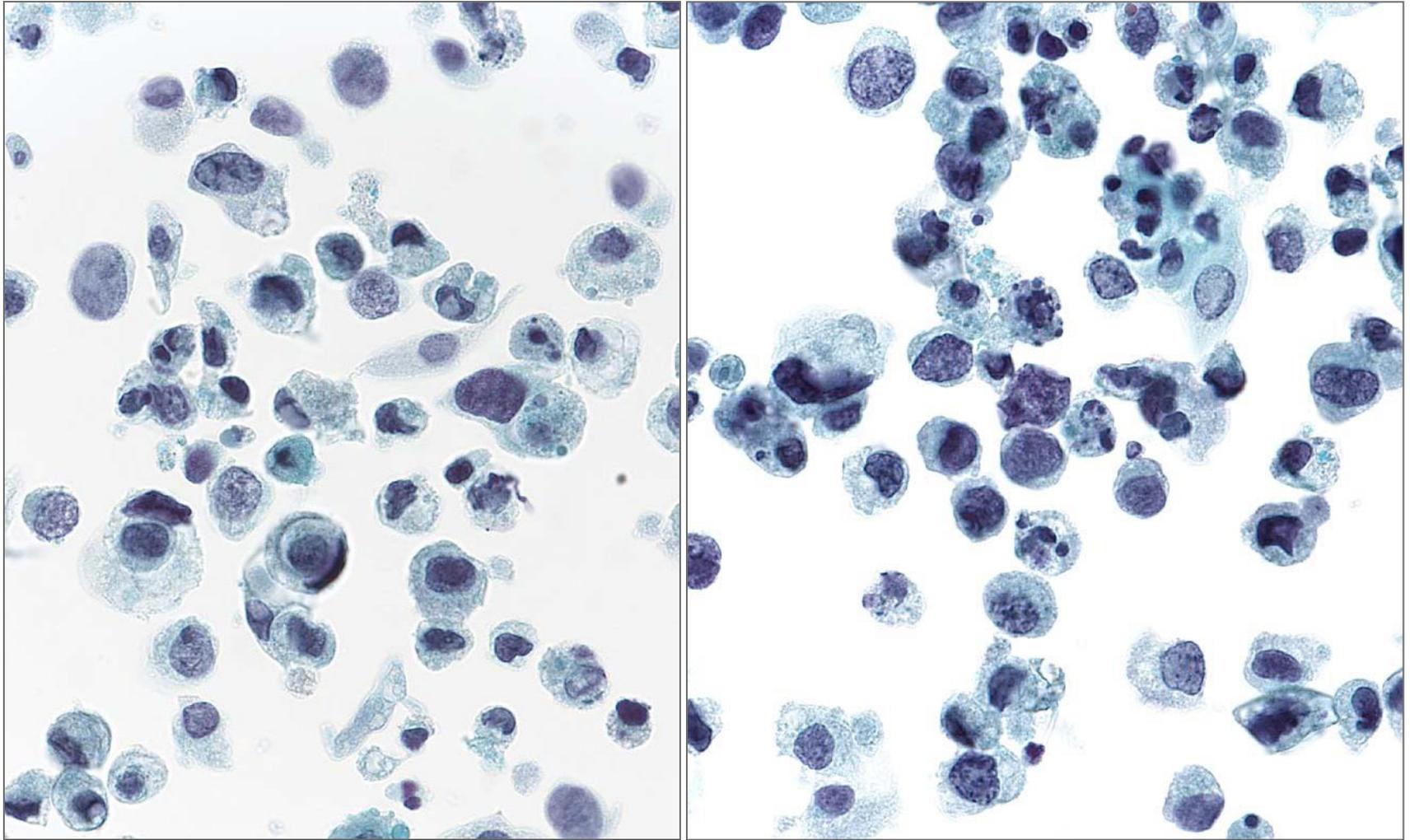
Other features: High Grade Urothelial Carcinoma

- Cellular pleomorphism: Look for the BIG cells
- Marked variation in cellular size and shapes
- Malignant cells may be oval, rounded, elongated, or plasmacytoid (Comet cells)
- Scant, pale or dense cytoplasm
- Prominent nucleoli
- Mitoses
- Necrotic debris
- Inflammation

5-seconds rule

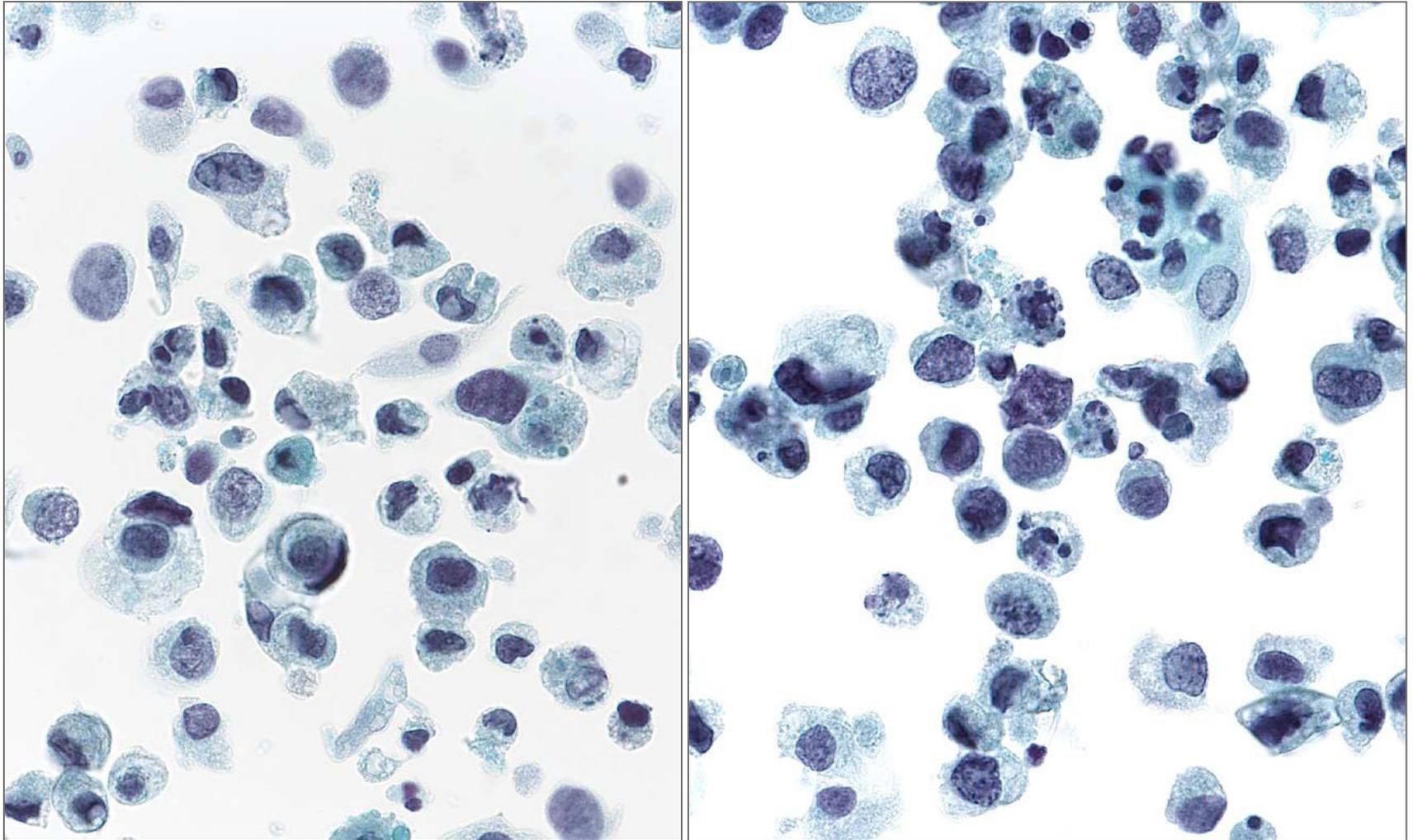


HGUC



G3

HGUC



Carcinoma in situ

WHO 1973

G1



G2



G3



WHO 2004/15



Low grade



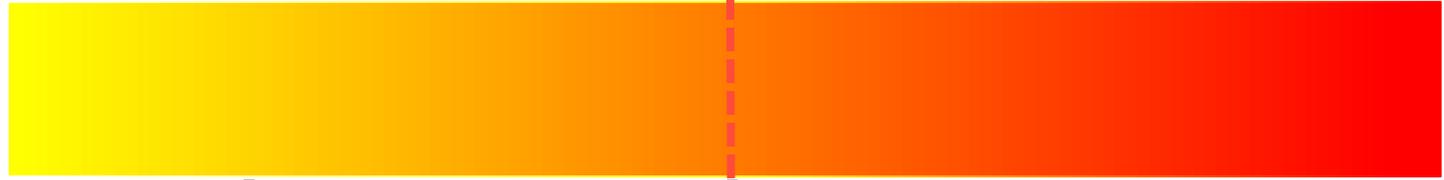
High grade

WHO 1973

G1

G2

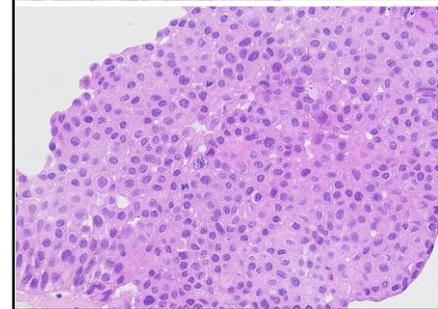
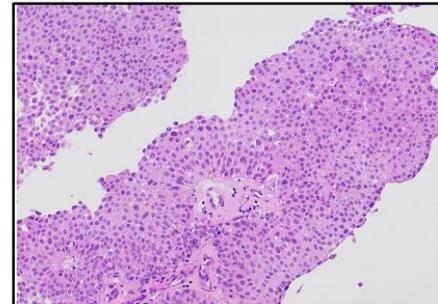
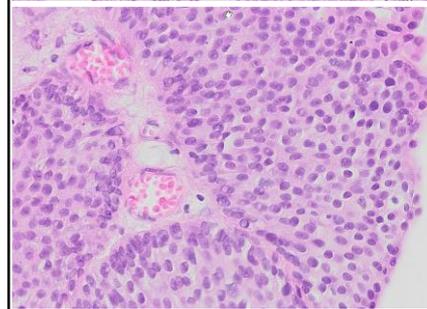
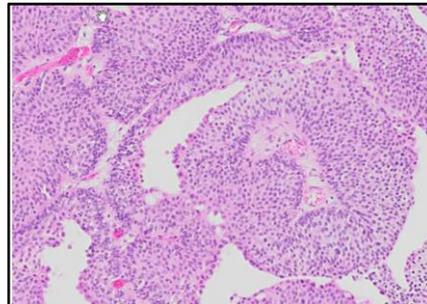
G3



WHO 2004/15

Low grade

High grade



Diagnostic Categories of TPS

- Negative for HGUC: negative
- Atypical Urothelial Cells: AUC
- Suspicious for HGUC: SHGUC
- High Grade Urothelial Carcinoma: HGUC
- Low Grade Urothelial Neoplasia: LGUN
- Other malignancies – Primary/secondary

Suspicious for High Grade Urothelial Carcinoma

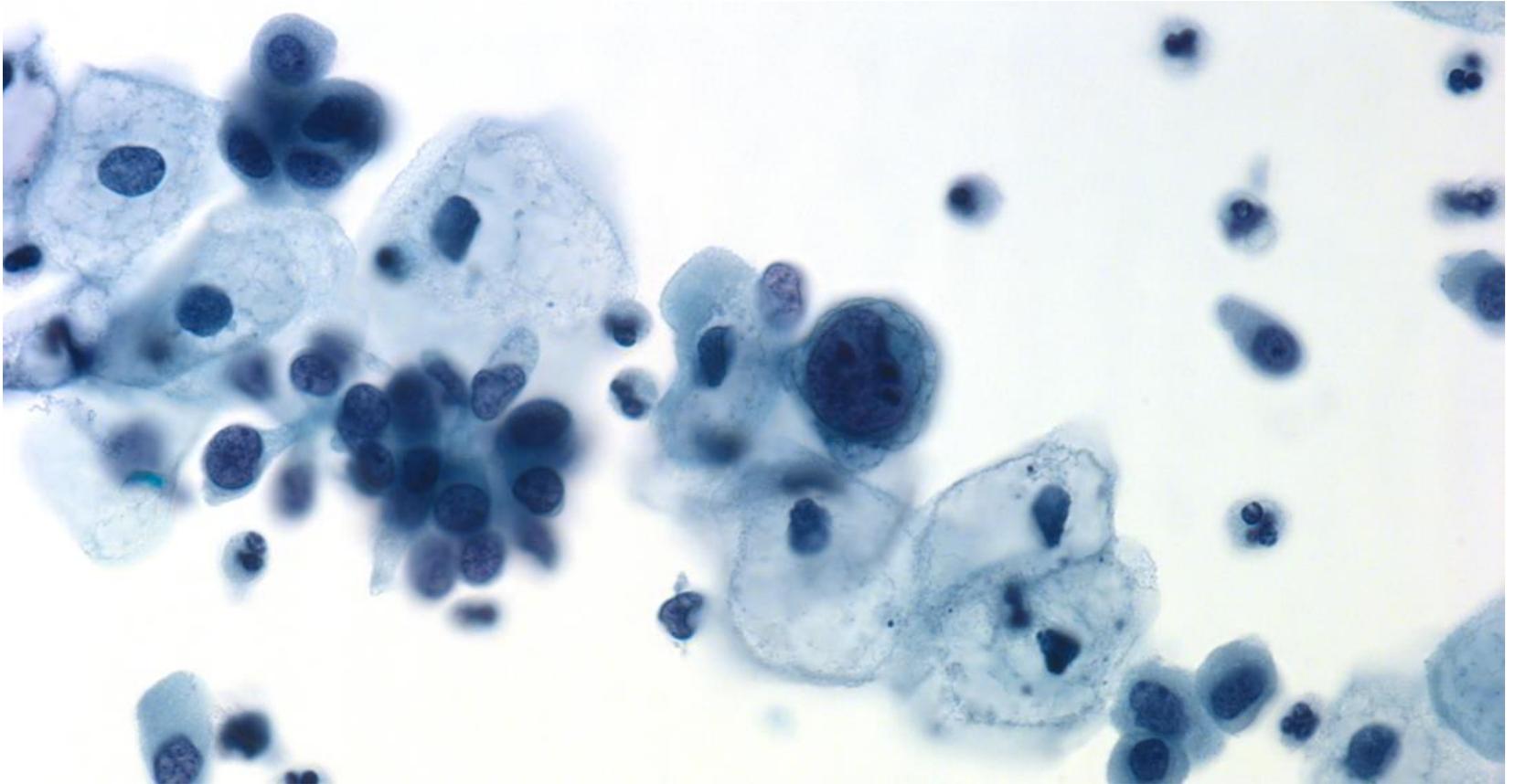
- Definition:

Urothelial cells with severe atypia that quantitatively fall short of a diagnosis of HGUC and are beyond atypia of the AUC category

Morphologic criteria: Suspicious for High Grade Urothelial Carcinoma

- Major criterion (required)
 - Non-superficial and non-degenerated urothelial cells with \uparrow N/C ratio of $\geq 0.5 - 0.7$
 - Nuclear hyperchromasia, moderate - severe
- Minor criterion (at least one required)
 - Marked irregular nuclear membranes: shape and thickness
 - Irregular, coarse, clumped chromatin
- Cells of HGUC but only < 5 (-10)

Suspicious for HGUC



Biopsy: CIS

Atypical Urothelial Cells

“The Goal for the AUC category is to capture the cases worrisome for HGUC that fall short of the suspicious for HGUC category”

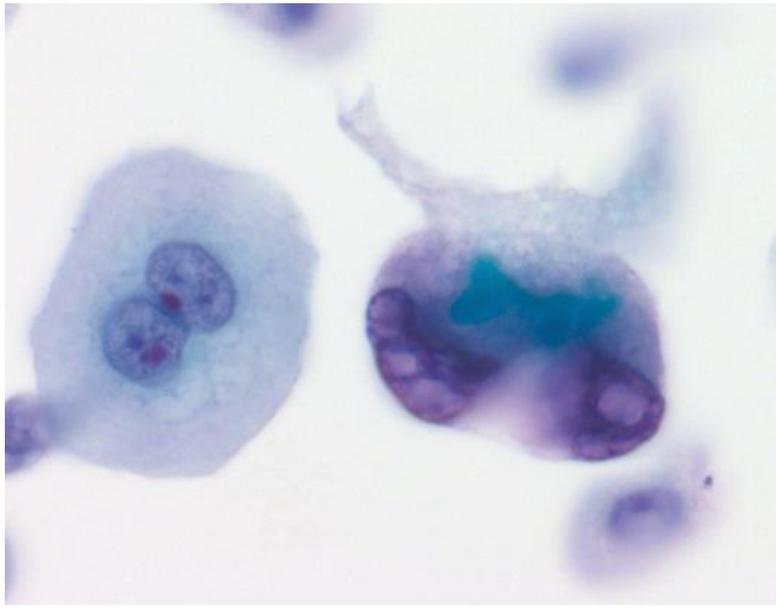
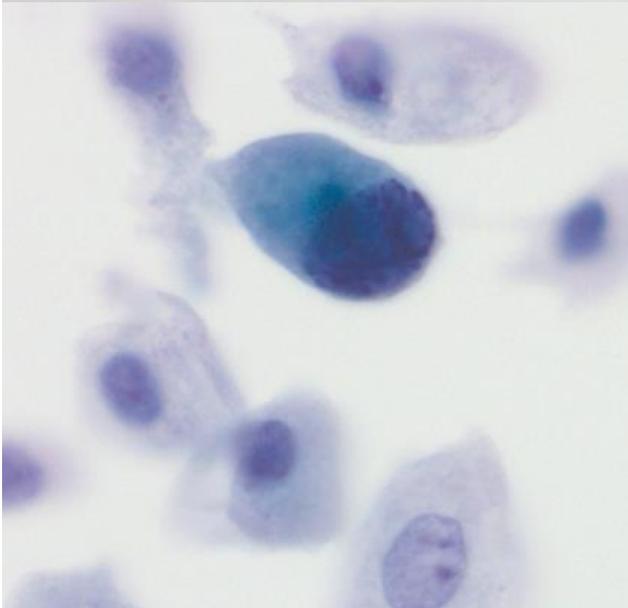
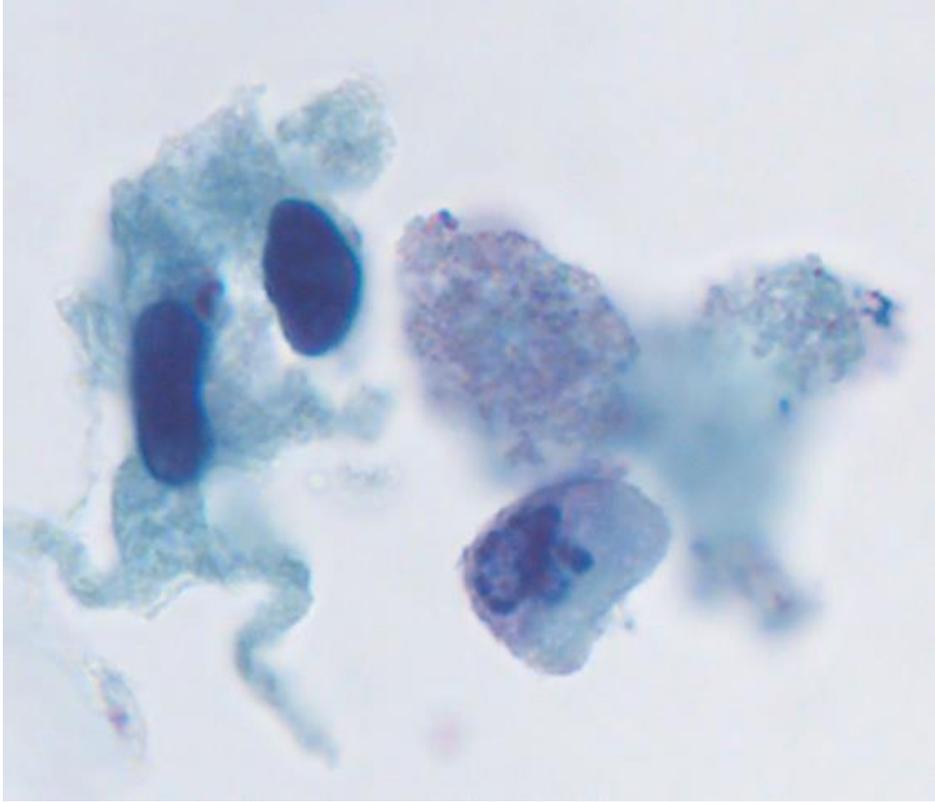
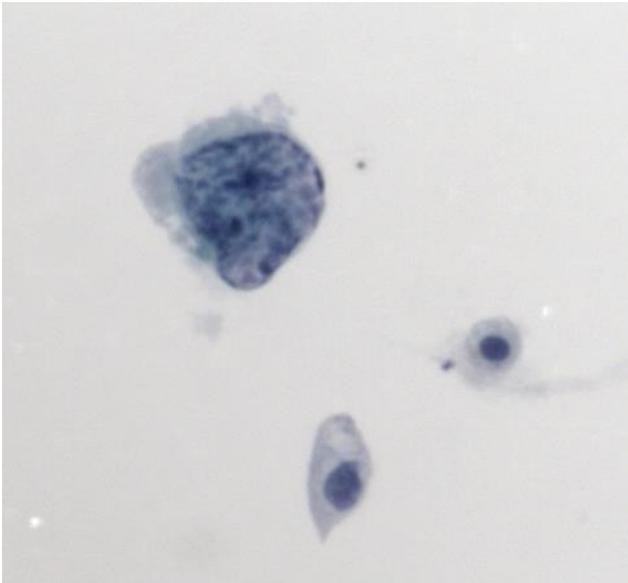
Atypical Urothelial Cells

- Urothelial cells with mild to moderate cytological (not architectural) atypia
- Degenerated cells of uncertain atypia
- Requires exclusion of changes in which the reason for atypia is evident:
 - reactive urothelial cells, urothelial clusters (tissue fragments), post-therapy effects, decoy cells

Morphologic criteria: Atypical Urothelial Cells

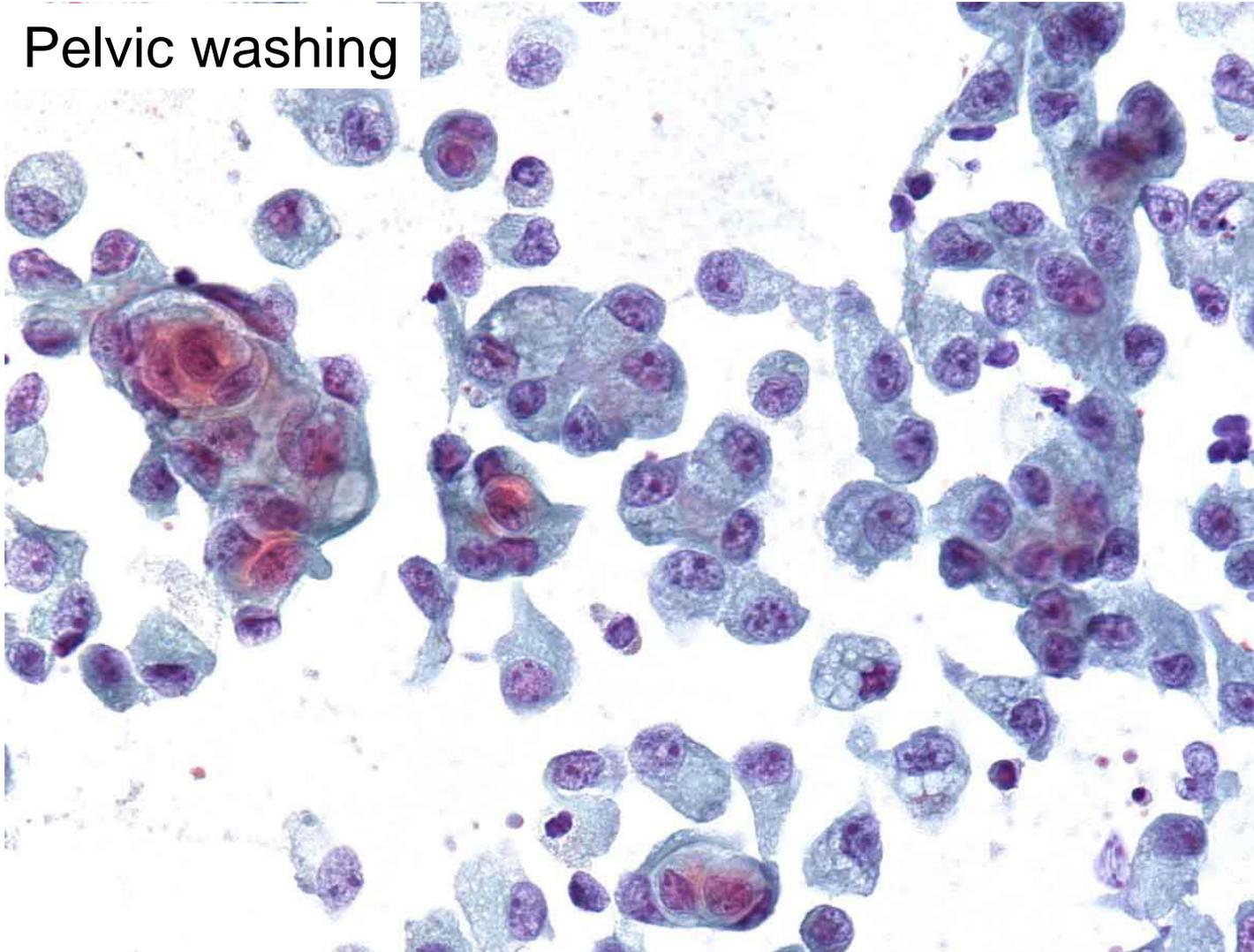
- Major criterion (required)
 - Non-superficial urothelial cells with \uparrow N/C ratio of >0.5
- Minor criterion (one required)
 - Nuclear hyperchromasia, mild - moderate
 - Irregular nuclear membranes: shape and thickness
 - Irregular, coarse, clumped chromatin

Degenerative atypia



AUC

Pelvic washing



Vacuolar changes of the cytoplams: in favor of benign

What about LGUC?



- Cells look benign
- Rarely shed
- Rarely invade
- Rarely kill

What about LGUC?



- Cells look benign
- Rarely shed
- Rarely invade
- Rarely kill

LG urothelial NEOPLASIA:

- Urothelial papilloma
- PUNLMP
- LGPUC

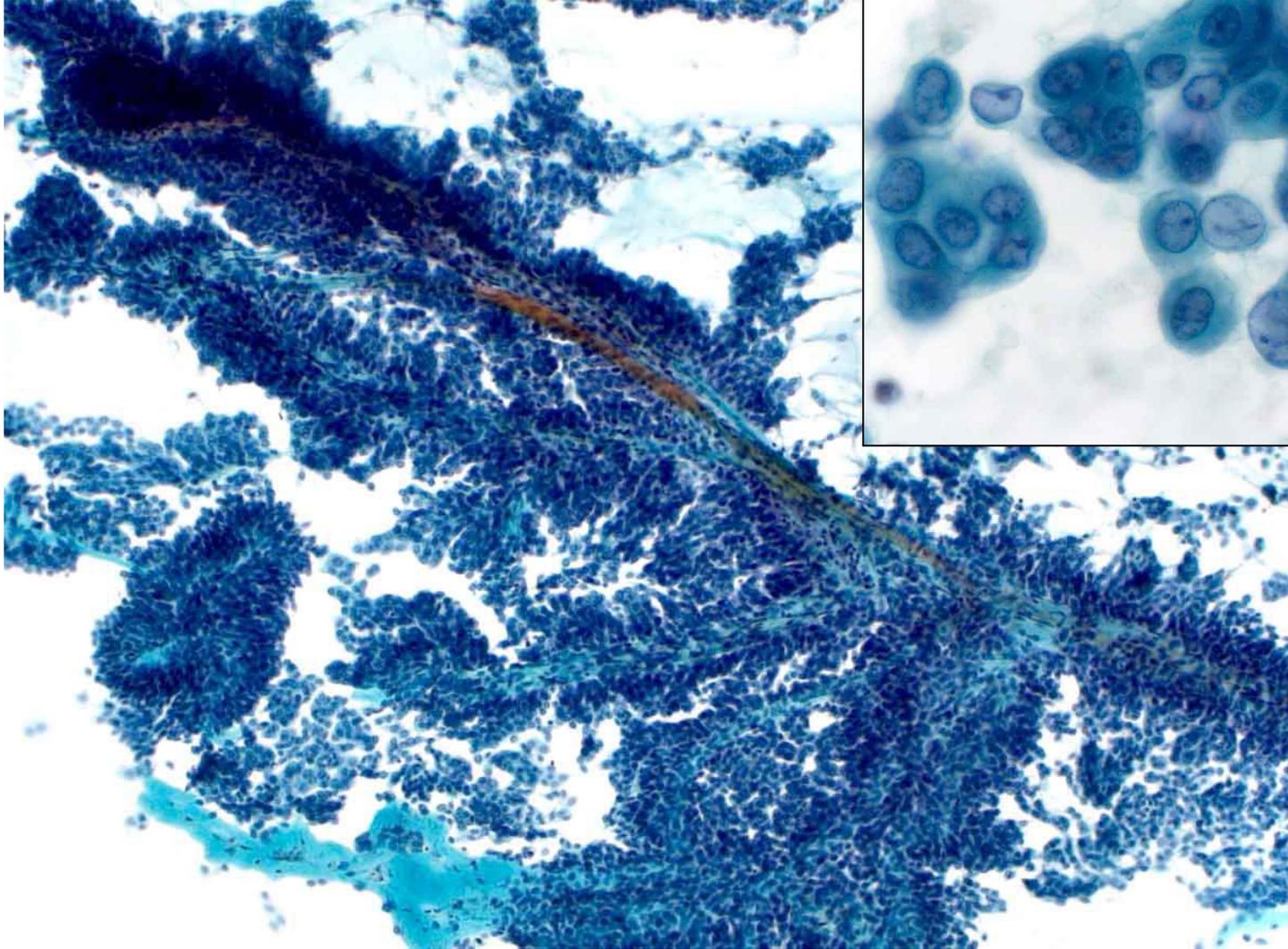
Morphologic criteria: Low-Grade Urothelial Neoplasia

- True papillae
 - Three-dimensional cellular papillary clusters with fibrovascular cores including capillaries
- definitive cytologic diagnosis of LGPUN

Morphologic criteria: Low-Grade Urothelial Neoplasia

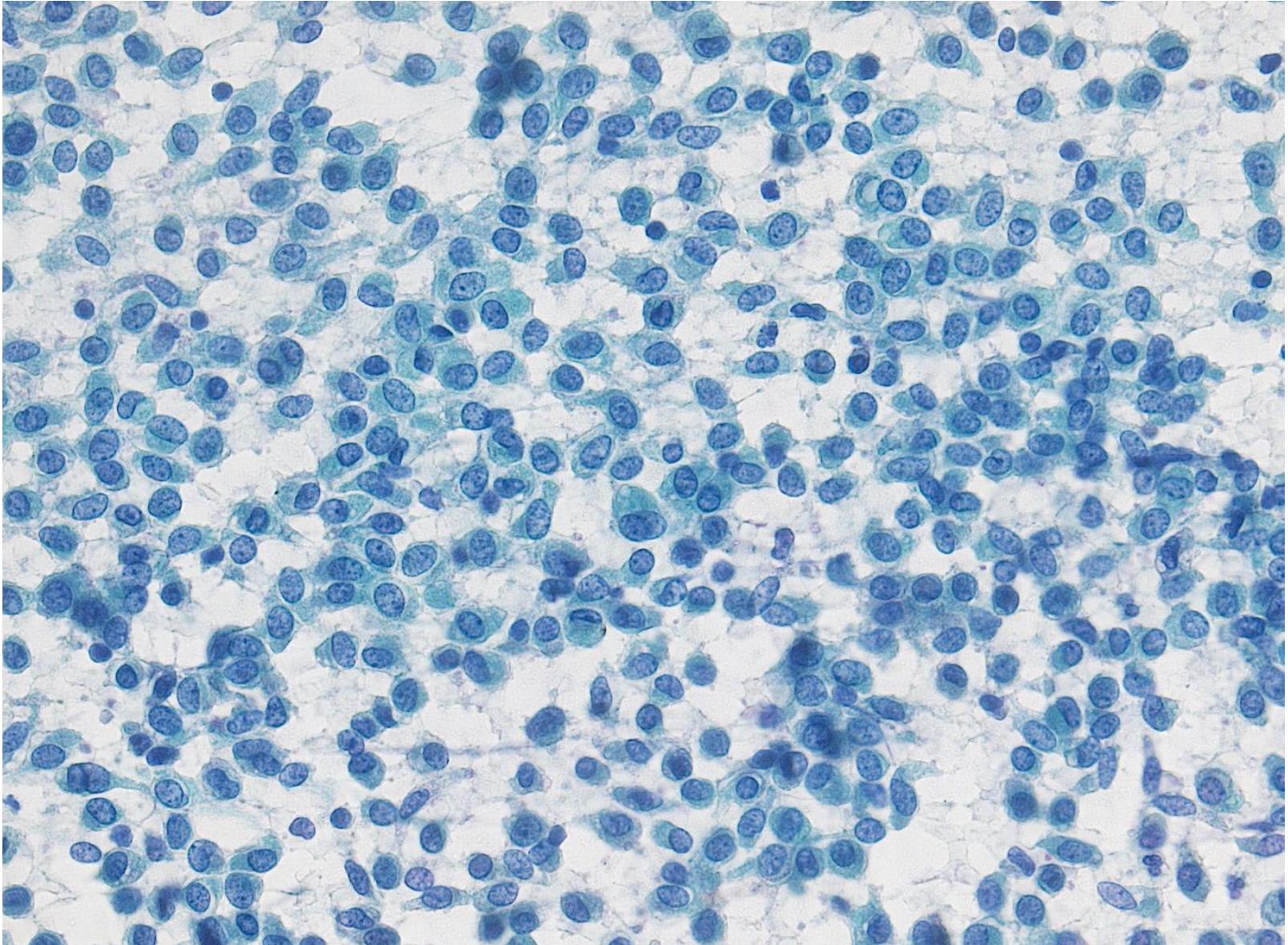
- Monotonous single (non-umbrella) cell pattern:
 - G1-G2: N/C ratio \uparrow , nuclear border irregularities, cytoplasmic homogeneity
 - DD LGUN
 - correlation with cystoscopy
 - categorized as "**Negative for HGUC**" with a note

LGUN

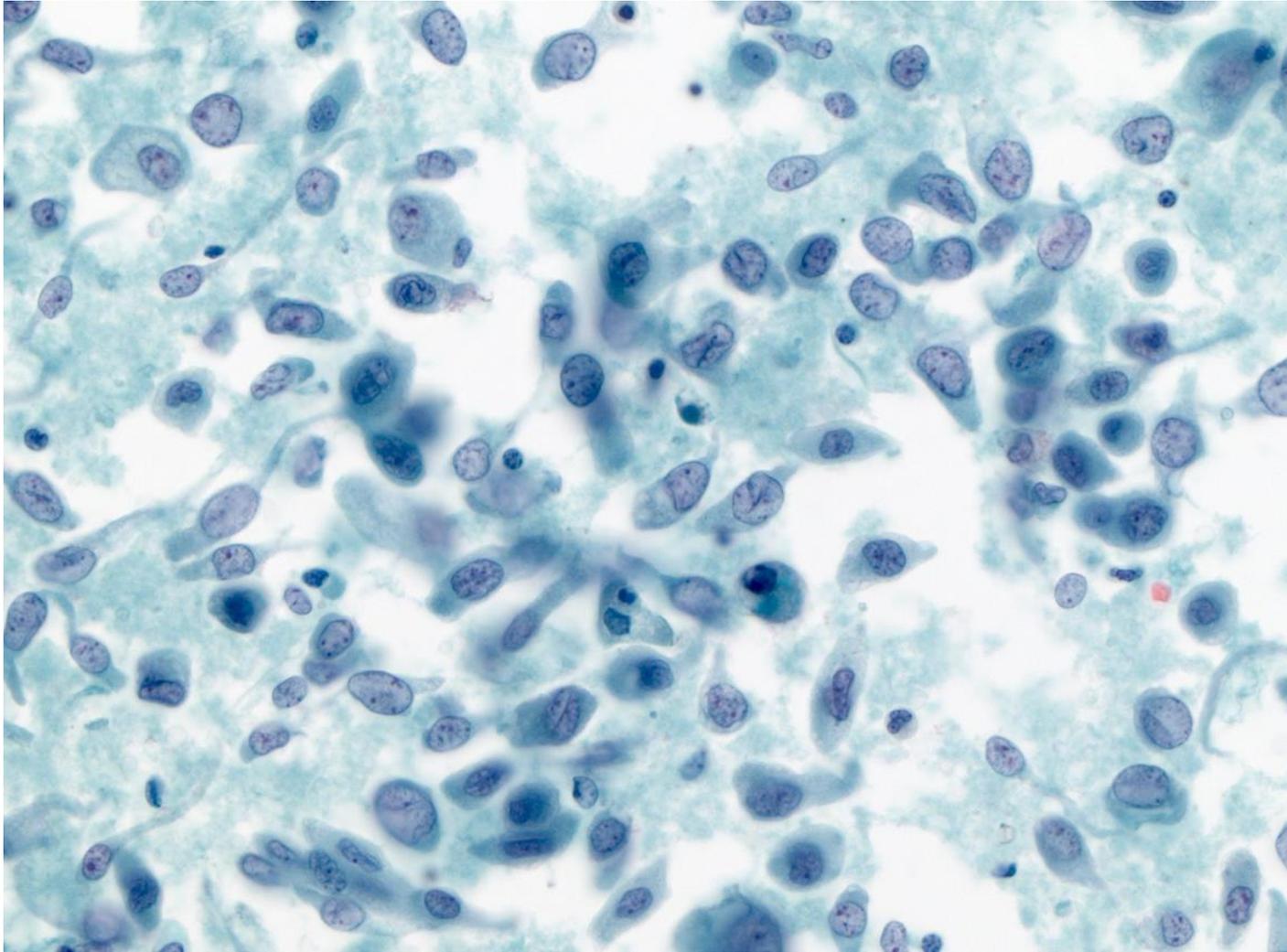


pTa, G2, low-grade

Negative for HGUC
Comment: Suggestive of LGUN



Negative for HGUC
Comment: Suggestive of LGUN



Morphological aspects not considered *for know*

- Monotony of the cell image
- Nucleoli
- Mitoses
- Excentric position of the nuclei
- Quality of the cytoplasm
 - Vacuolisation
 - Perinuclear clearing

Paris Reporting: Examples

Bladder washing:

Decoy cells (6/10 HPF).

Paris: NHGUC (negativ für high grade UC)

Voided urine:

Urothelial cells with not classifiable nuclear atypia.

Paris: AUC (atypical urothelial cells)

Bladder washing:

Numerous urothelial cells with severe nuclear atypia (G3).

Paris: HGUC (high grade Urothelkarzinom)

