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The Paris System
for Reporting
Urinary Cytology

Eva M. Wojcik
Daniel F.I. Kurtycz
Dorothy L. Rosenthal
Editors

Second Edition

Springer

Updates in Urine Cytology:
Paris 2.0

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Disclosures:

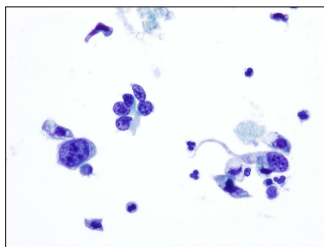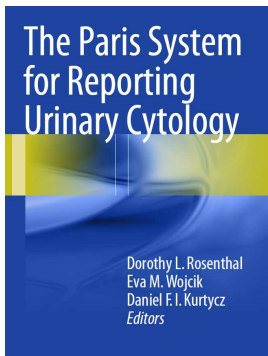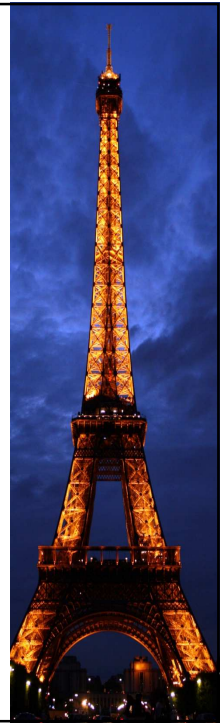- Book royalties from Springer

Outlines

- What is the goal of urine cytology?
- Why to standardize?
- The urine story – creation of the Paris System (TPS)
- Review of the Paris System – what worked and what needed to be improved
- What's new or different in TPS2.0?

The main purpose of urine cytology

To detect bladder cancer

What led to Paris?

- "I hate urines"
- Rate of atypia – range from 2% to >50%
- Wide interobserver variability
- No reproducibility
- Dwindling credibility
- Simultaneous publications on atypia
- 18th International Congress of Cytology, Paris, May, 2013

The Paris System for Reporting Urinary Cytology

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- New paradigm – Detection of High Grade Urothelial Carcinoma based on:
  - N/C ratio (>0.7)
  - Hyperchromasia
  - Irregularity of nuclear membrane (chromatic rim)
  - Coarseness of chromatin

I.	Pathogenesis of Urothelial Carcinoma
II.	Adequacy
III.	Negative for High Grade Urothelial Carcinoma
IV.	Atypical Urothelial Cells
V.	Suspicious for High Grade Urothelial Carcinoma
VI.	High Grade Urothelial Carcinoma
VII.	Low Grade Urothelial Neoplasm
VIII.	Other malignancies, both primary and secondary
IX.	Ancillary Studies
X.	Clinical management
XI.	Preparatory techniques relative to Urinary Tract samples

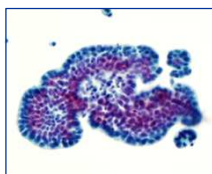# Goal – decrease the atypia rate

- Define what is NOT atypia
- Establish diagnostic criteria for atypia
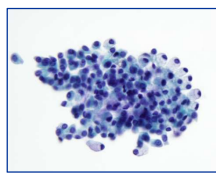
Spectrum of "normal"
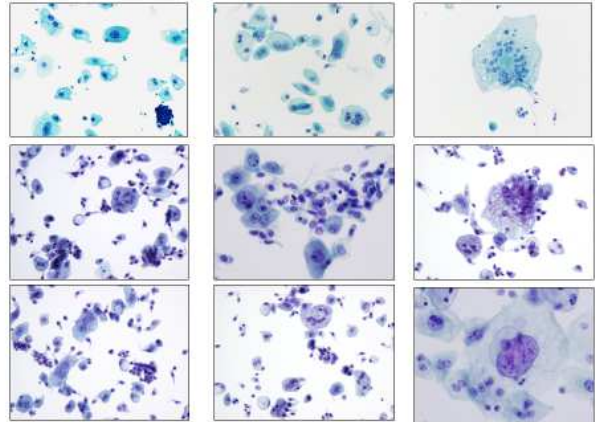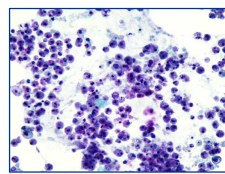

Negative (NHGUC), NOT atypia

Wojcik EM: What should not be reported as atypia in urine cytology: JASC 2015;4;3;30-36
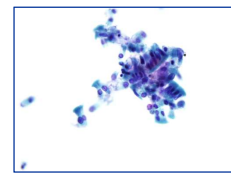
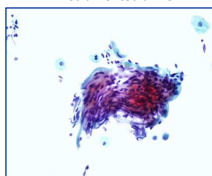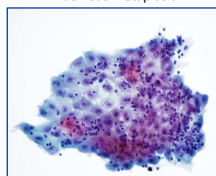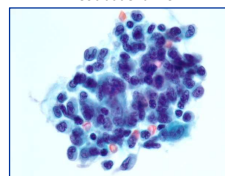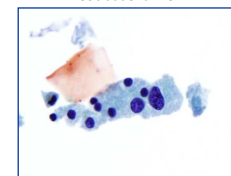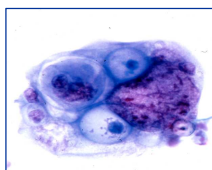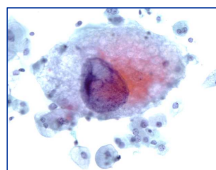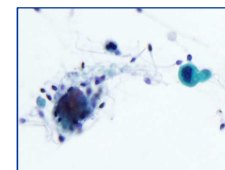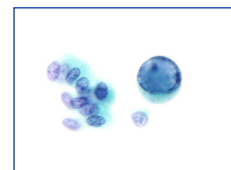|			
Instrumented urine	Mucinous metaplasia	Neobladder urine	Neobladder urine
S/P TURBT – Cautery artifact	Acute cystitis	S/P BCG immunotherapy - granuloma	Renal tubular cells
S/P Brachytherapy	S/P XRT	Seminal vesicle cells	Polyoma virus

What is Atypia ?

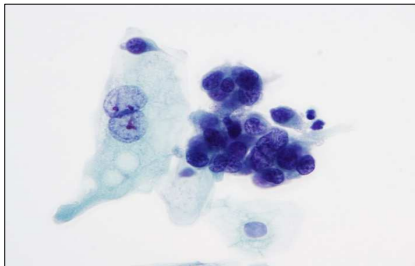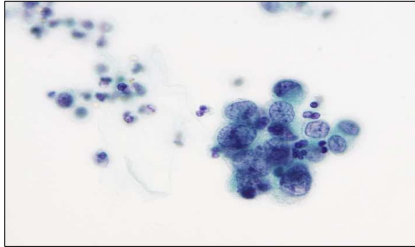Positive   Suspicious   Atypical   Negative
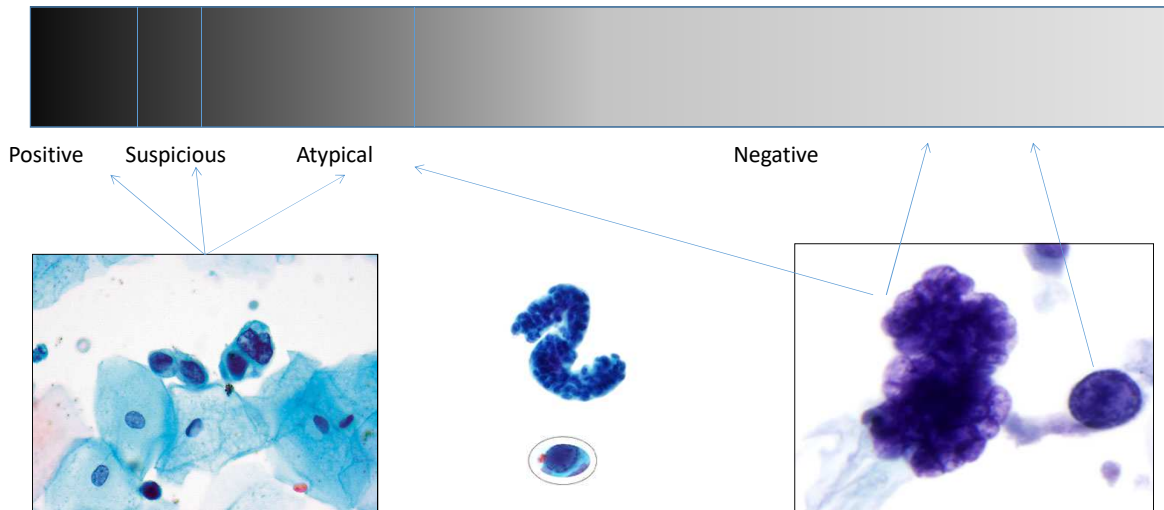
Findings in literature

1. High nuclear cytoplasmic ratio (>0.7)
2. Nuclear hyperchromasia
3. Coarse, clumped chromatin
4. Irregular nuclear membranes

Atypia ⟶ **Suspicious** ⟶ **Positive**
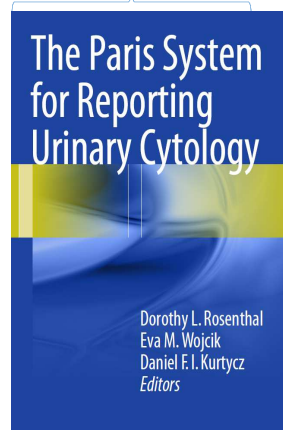
Atypical Urothelial Cells

- Non-superficial and non-degenerated urothelial cells with an **high N/C ratio > 0.5** (required)

  and one of the following:

- **Hyperchromasia** (compared to the umbrella cells or the intermediate squamous cell nucleus)
- **Irregular clumpy chromatin**
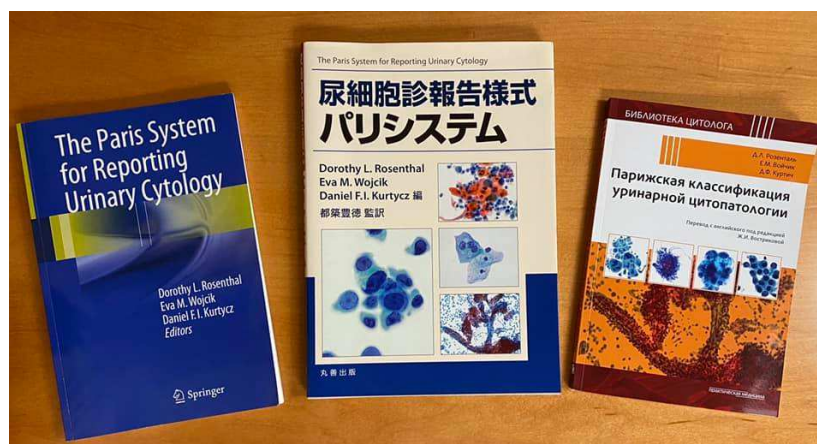- **Irregular nuclear contours**
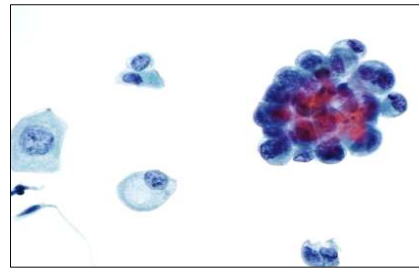
Author	Year	Study location	Pre-TPS % (n) Atypia	Post-TPS % (n) AUC
Vosoughi et al.	2021	USA (Miami)	16 (249)	9 (56)
Compton et al.	2021	USA (Nashville)	N/A	12.5 (199)
Stanzione et al.	2020	USA (Los Angeles)	59.8 (52)	41.5 (122)
Anbardar et al.	2020	Iran	26	1.2 (22)
Rai et al.	2019	India	16.7 (15)	11.1 (10)
Bakkar et al.	2019	USA (Los Angeles)	44 (44)	23 (23)
Vallamreddy et al.	2019	India	21.6 (16)	9.5 (7)
Wang et al.	2018	Canada	18.6 (442)	14.4 (345)
Meilleroux et al.	2018	France	6.1 (100)	5.2 (94)
VandenBussche et al.	2018	USA (Baltimore)	23.9 (568)	23.0 (589)
Xing et al.	2018	USA (Pittsburgh)	34 (52)	24 (37)
Rohilla et al.	2018	India	54.3 (73)	8.5 (114)
Zare et al.	2018	USA (San Diego)	24.2 (47)	11.9 (23)
Torous et al.	2017	USA (Boston)	29.5 (328)	21.8 (302)
Roy et al.	2017	India	41.2 (40)	11.3 (11)
Granados et al.	2017	Spain	4.7(7)	20.1 (30)
Suh et al	2017	Korea	25.4 (36)	14.8 (21)
Hassan et al.	2016	Canada	38.7 (48)	25.8 (32)

From TPS2.0, AUC Chapter by Barkan et al.

Positive | Suspicious | Atypical | Negative

The Paris System for Reporting Urinary Cytology

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Atypia

TPS – didn't eliminate the GRAY ZONE – it DEFINED it!

Great success story!

TPS is Great!
But not perfect

Challenges and Shortcomings

- N/C Ratio
  - Overestimated
  - Underestimated
  - High interobserver variability
- Degeneration
- Fibrovascular cores
- Squamous dysplastic cells
- Variants of HGUC

The Paris 2.0 preparatory survey

- 43 questions, July – December 2020
- 86% (451/523) of individuals who accessed the survey proved to be part of the cytology profession
- 54 countries, 50 US states
- 82% of survey participants use TPS
- Atypia rate before TPS was 22% and after TPS was 16%

Kurtycz DFI, Wojcik EM, Rosenthal DL: Perceptions of Paris: An international survey in preparation for The Paris System for Reporting Urinary Cytology 2.0 (TPS 2.0). JASC, 2023 Jan-Feb;12(1):66-74

Challenges - N/C Ratio

- Overestimated
- Underestimated
- High interobserver variability
- Strict numbers ($\geq$0.5 and $\geq$0.7)

Why $\geq$0.5
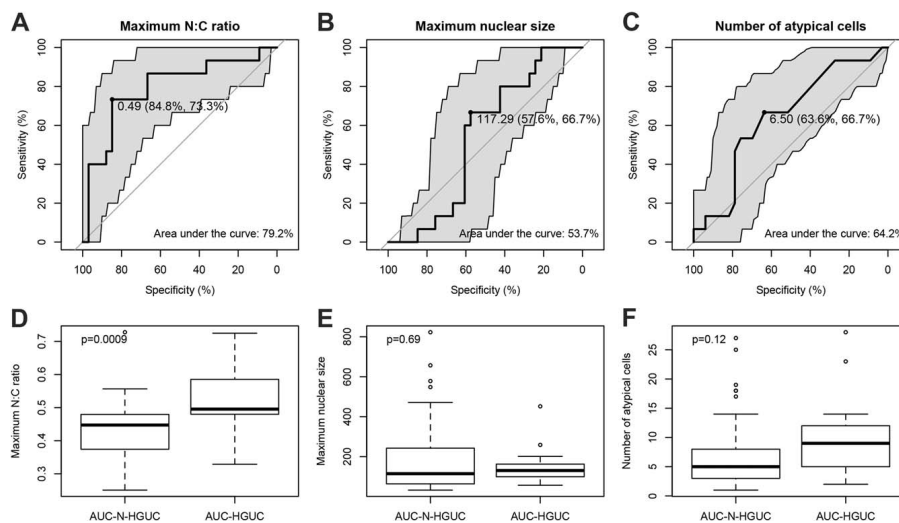
Digital Image Analysis Supports a Nuclear-To-Cytoplasmic Ratio Cutoff Value of 0.5 for Atypical Urothelial Cells
Jen-Fan Hang, MD; Vivek Charu, PhD; M. Lisa Zhang, MD; and Christopher J. VandenBussche, MD, PhD
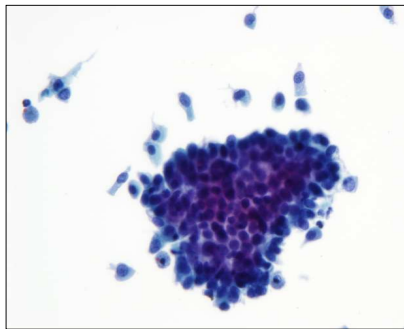Cancer Cytopathol 2017;125:710-6.

N:C threshold 0.486
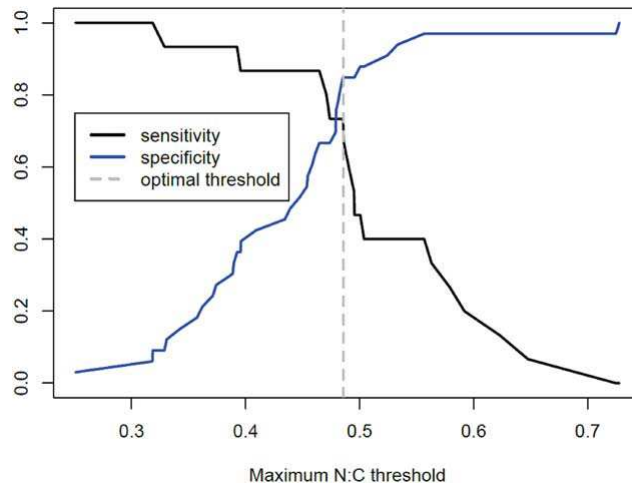
Digital Image Analysis Supports a Nuclear-To-Cytoplasmic Ratio Cutoff Value of 0.5 for Atypical Urothelial Cells
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Cancer Cytopathol 2017;125:710-6.
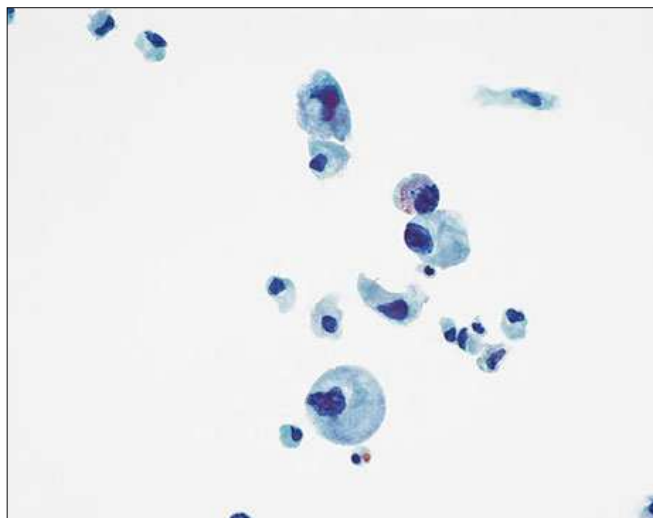
Challenges – N/C ratio
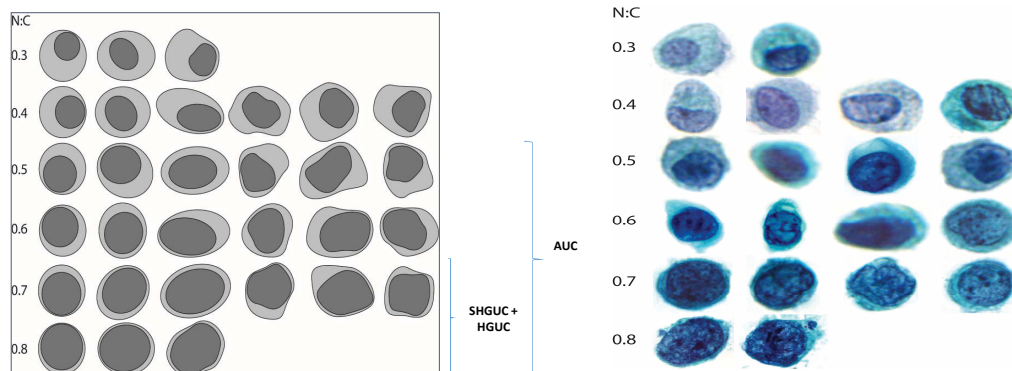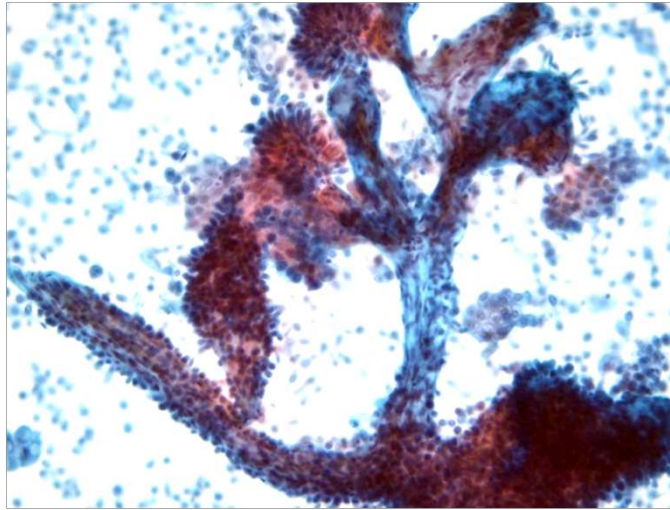

Zhang ML et al. Cancer Cytopathol 2016;124(9):669-677
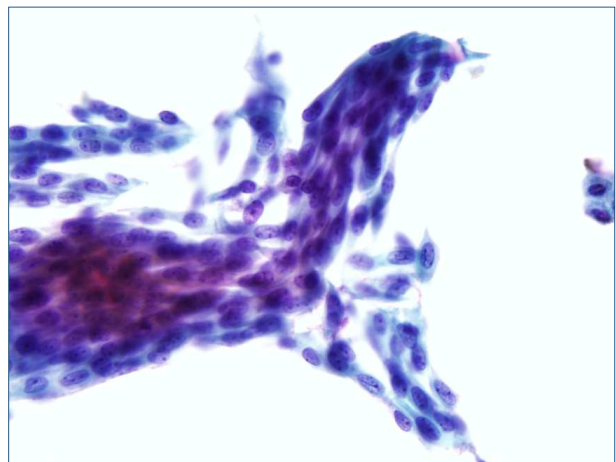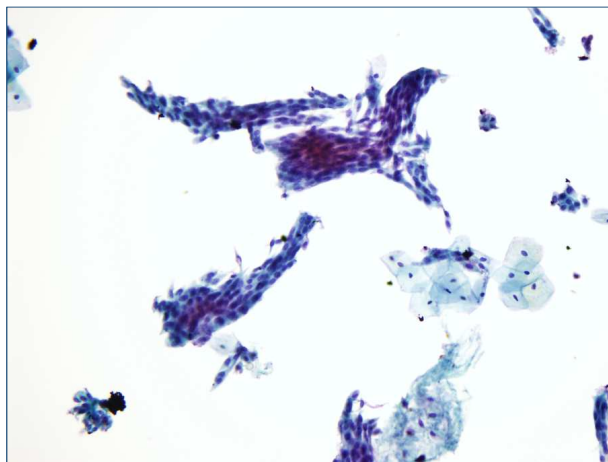
Basal cells – False high N/C ratio

Shortcoming – Degeneration – False low N/C ratio
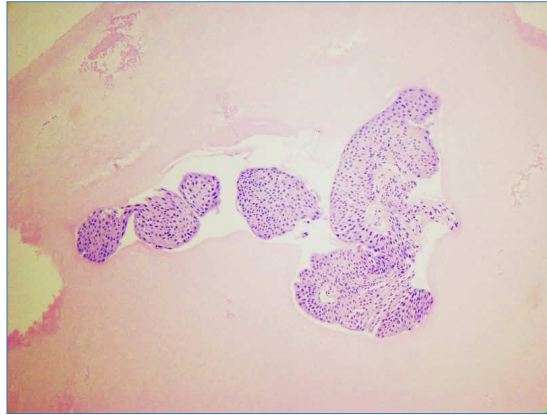
Challenges - Fibrovascular cores

Bladder barbotage from 68 year-old male with a history of low grade urothelial carcinoma (T1) three years ago that was treated by local excision. As part of routine follow-up, cystoscopy was performed and did reveal a papillary lesion

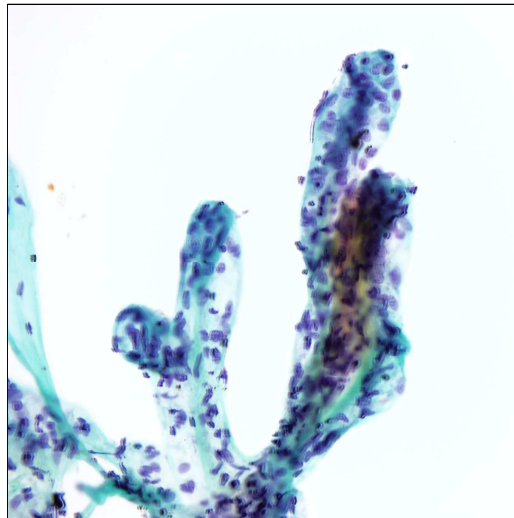Diagnosis – Negative for High Grade Urothelial Carcinoma

Cell block

Diagnosis - Negative for High Grade Urothelial Carcinoma
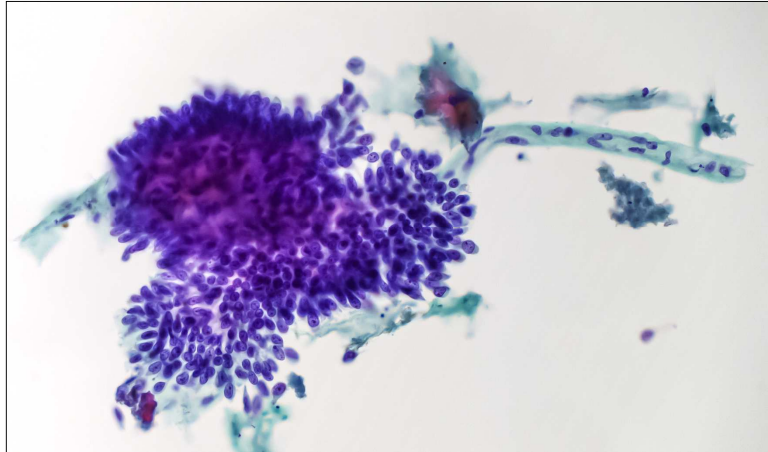Low Grade Urothelial Neoplasm (LGUN)

TPS2.0 - LGUN – no longer a primary diagnosis. It belongs to NHGUC category

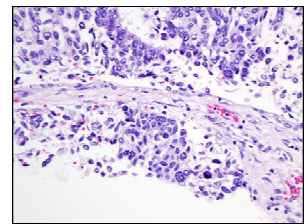# Challenges – Fibrovascular cores

Is this LGUN?

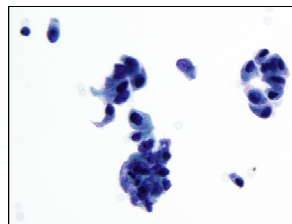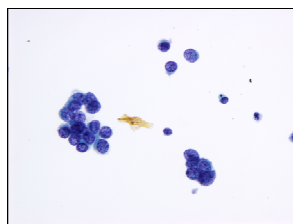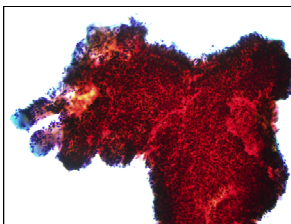# Is this LGUN?

Single cells in the background (not shown) fit criteria for HGUC. Subsequent TURP – High grade papillary UC

TPS2.0 - LGUN – no longer a primary diagnosis. It belongs to NHGUC category

Diagnosis is based on cells and not solely on the presence of F/V cores

Papillary High Grade Urothelial Carcinoma

F/V cores in HGUC
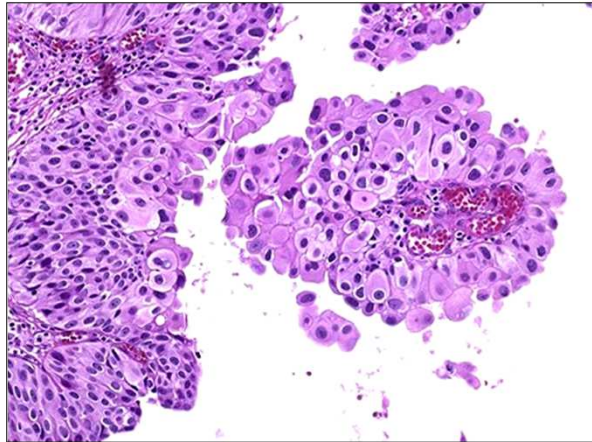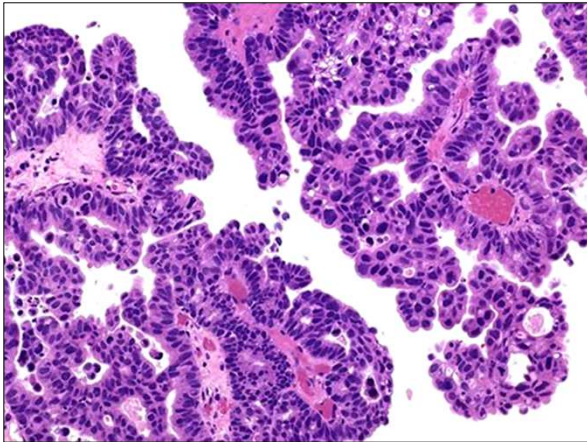
Challenges – N/C ratio – Many faces of HGUC
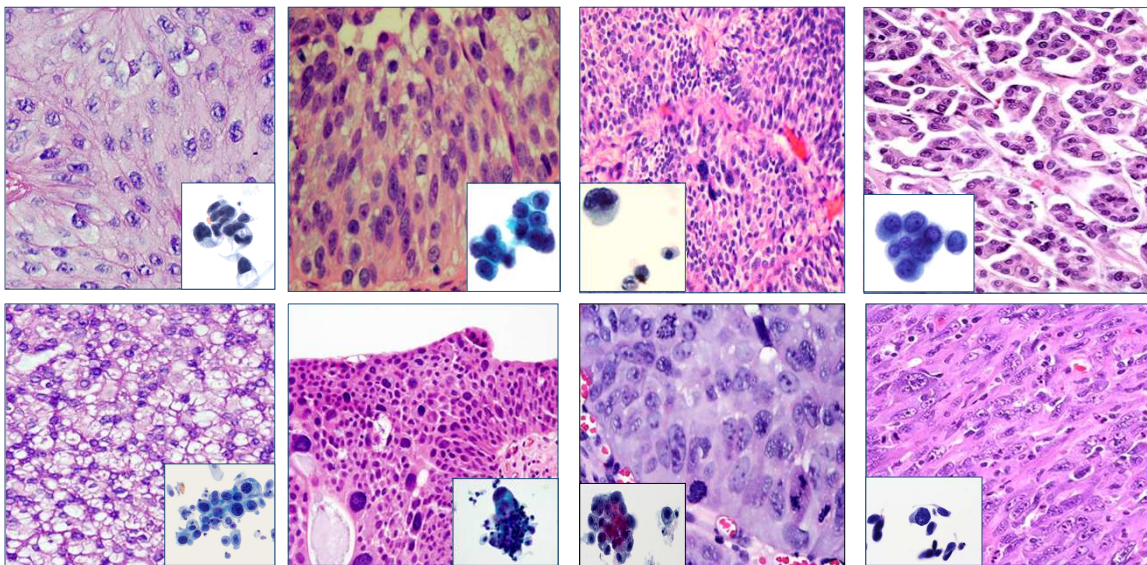
HGUC - is N:C $\geq$ 0.7 too high?

- Great pleomorphism
- Squamous differentiation
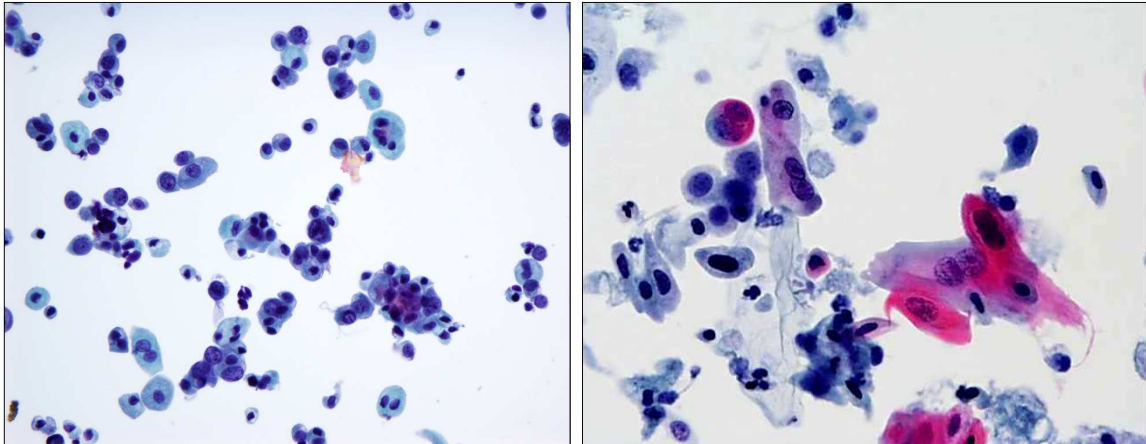
- Not all cells of HGUC will have N/C ratio $\geq$ 0.7. As long as >5 cells are identified, the diagnosis of HGUC can securely be made

Atypical Squamous Cells (ASC)
Not AUC
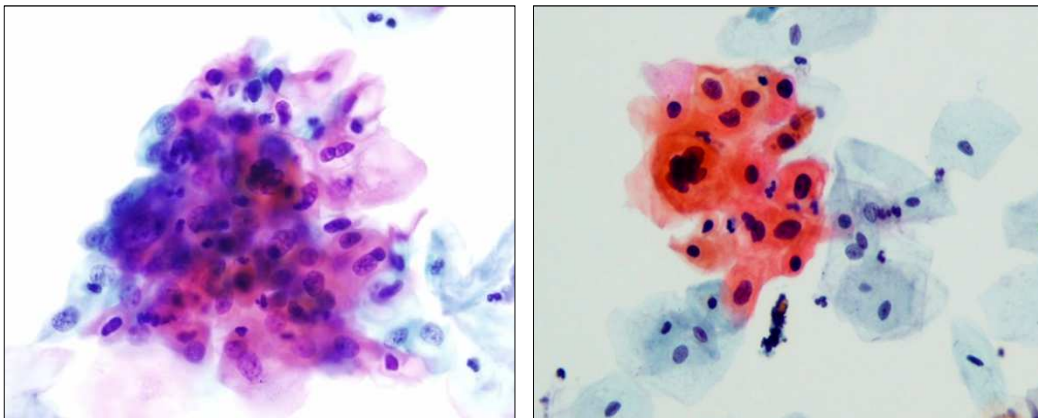
Bladder barbotage from an 81 year-old male who presented with persistent hematuria. The cystoscopy revealed a bladder mass
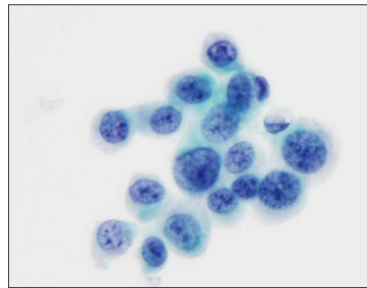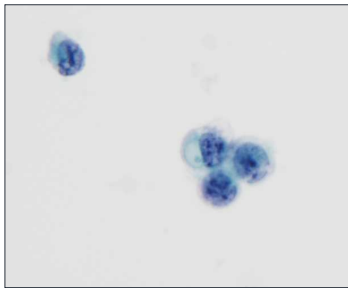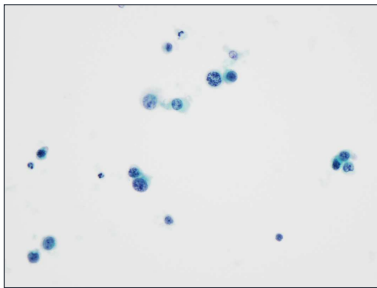
HGUC (hypochromatic)

Not all variants of HGUC fulfil all diagnostic criteria as seen in this rare variant of hypochromatic high grade urothelial carcinoma. Other exceptions are micropapillary and plasmacytoid variants
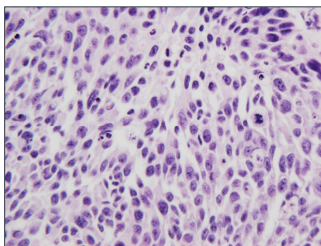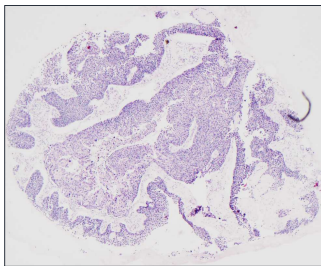
F/U Bx
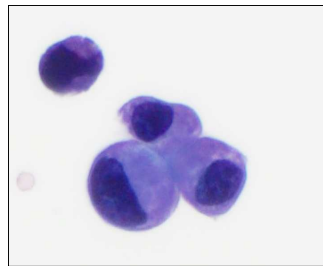
Plasmacytoid
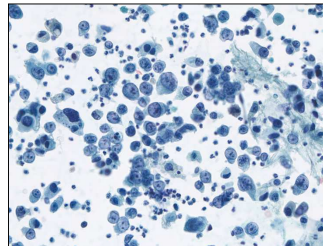
Hypochromatic

Defined number of cells

- TPS 1.0 - Positive vs. Suspicious for HGUC
  - ≥10 - HGUC
  - ≤5 – SHGUC
  - 5 – 10 cells – gray zone, based on experience, history, individual threshold, etc
- TPS2.0 – Deemphasize strict numbers
  - "Many" cells (≥10)
  - "Few" cells (≤5)
  - "High" N/C ratio (≥0.7)
  - "Increased" N/C ratio (≥0.5)

- "The number of atypical urothelial cells is an important criterion to classify urine cytology specimens into the 'positive' or the 'suspicious' categories. A cut-off number of >10 cells to render a definitive diagnosis of HGUCA seems valid from the clinical standpoint ."

ORIGINAL ARTICLE

Urine cytology: does the number of atypical urothelial cells matter? A qualitative and quantitative study of 112 cases

Fadi Brimo, MD[a,*], Bin Xu, MD[a], Wassim Kassouf, MD[b],
Babak Ahmadi-Kaliji, MD[a], Michele Charbonneau, CT[a],
Ayoub Nahal, MD[a], Yonca Kanber, MD[a], Derin Caglar, MD[a],
Manon Auger, MD[a]

JASC 2015;4(4)232 238

Bladder barbotage from a 78 year-old male with a history of low grade urothelial carcinoma. Currently, patient presented with hematuria. During cystoscopy there was no evidence of papillary lesions; however, there was a small area that appeared velvety and reddish
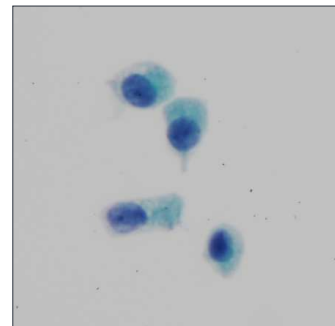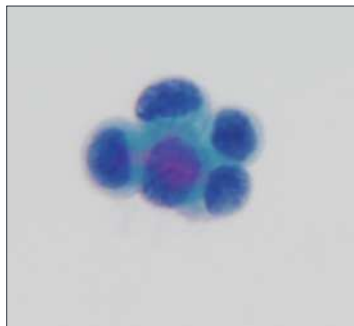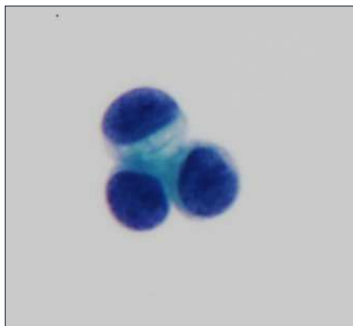
Diagnosis – Atypical Urothelial Cells (AUC)
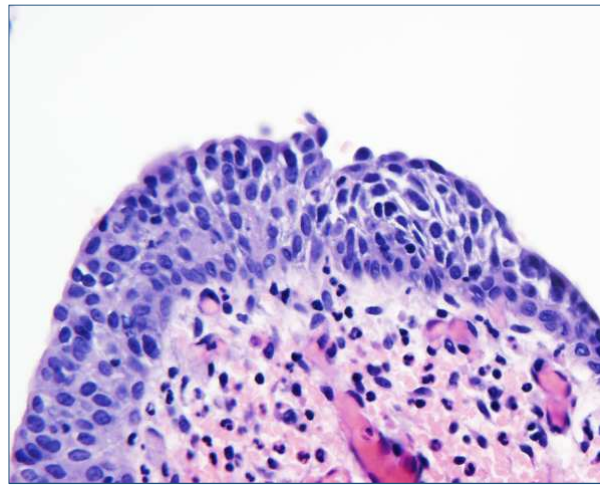
Follow up biopsy – Severe dysplasia/Carcinoma in situ

- **The risk of high grade malignancy (ROHM) for AUC ranges from 24% to 53%**

Diagnostic category	Diagnostic criteria	Example	Frequency	ROHM
Unsatisfactory	Voided urine – volume (>30ml) Instrumented urine - cellularity		0% - 5%	0% - 16%
Negative for High Grade Urothelial Carcinoma (NHGUC)	Benign urothelial, glandular, squamous cells, benign tissue fragments, changes due to instrumentation, lithiasis, polyoma virus, therapy. Low Grade Urothelial Neoplasm (LGUN)		70% - 90%	8% - 24%
Atypical Urothelial Cells (AUC)	Required – increased N/C ratio ($\geq$ 0.5) and one of: Hyperchromasia, Irregular clumpy chromatin or Irregular nuclear contours		5% - 15%	24% - 53%
Suspicious for High Grade Urothelial Carcinoma (SHGUC)	Required – Few cells (< 5-10) with high N/C ratio (> 0.7) and at least two of: Hyperchromasia, Irregular clumpy chromatin, Irregular nuclear contours		0.5% - 3%	59% - 94%
Positive for High Grade Urothelial Carcinoma (HGUC)	Required – Many cells (>10) with high N/C ratio ($\geq$ 0.7) and at least two of: Hyperchromasia, Irregular clumpy chromatin, Irregular nuclear contours		0.1% - 3%	76% -100%

ROHM – Risk of High Grade Malignancy

Bladder barbotage from 75 year-old male with history of high grade urothelial carcinoma treated by transurethral resection and follow-up intravesical BCG therapy. Patient presented with urinary tract infection symptoms, such as dysuria, urinary urgency and frequency
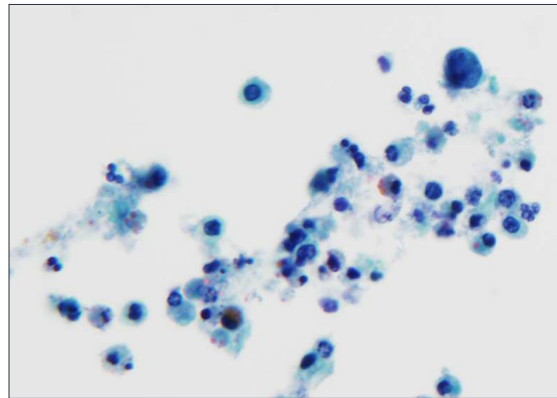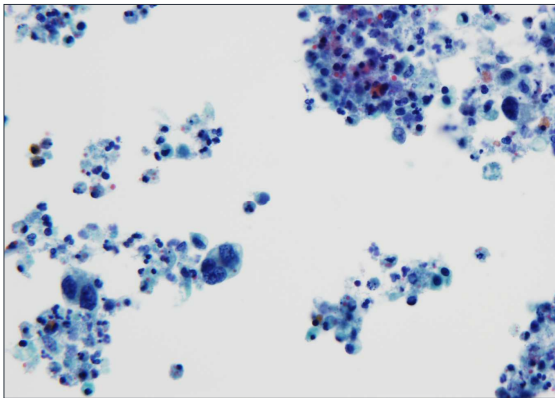
- 5-10 cells fulfilling the criteria for HGUC (N/C ≥ 0.7, hyperchromasia, irregular nuclear membrane, clumped/irregular chromatin) is required to make this diagnosis

Diagnostic category	Diagnostic criteria	Example	Frequency	ROHM
Unsatisfactory	Voided urine – volume (>30ml) Instrumented urine - cellularity		0% - 5%	0% - 16%
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Positive for High Grade Urothelial Carcinoma (HGUC)	Required – Many cells (>10) with high N/C ratio (≥ 0.7) and at least two of: Hyperchromasia, Irregular clumpy chromatin, Irregular nuclear contours		0.1% - 3%	76% -100%

ROHM – Risk of High Grade Malignancy

43 year old female with a large soft renal pelvis mass. Left renal brushing
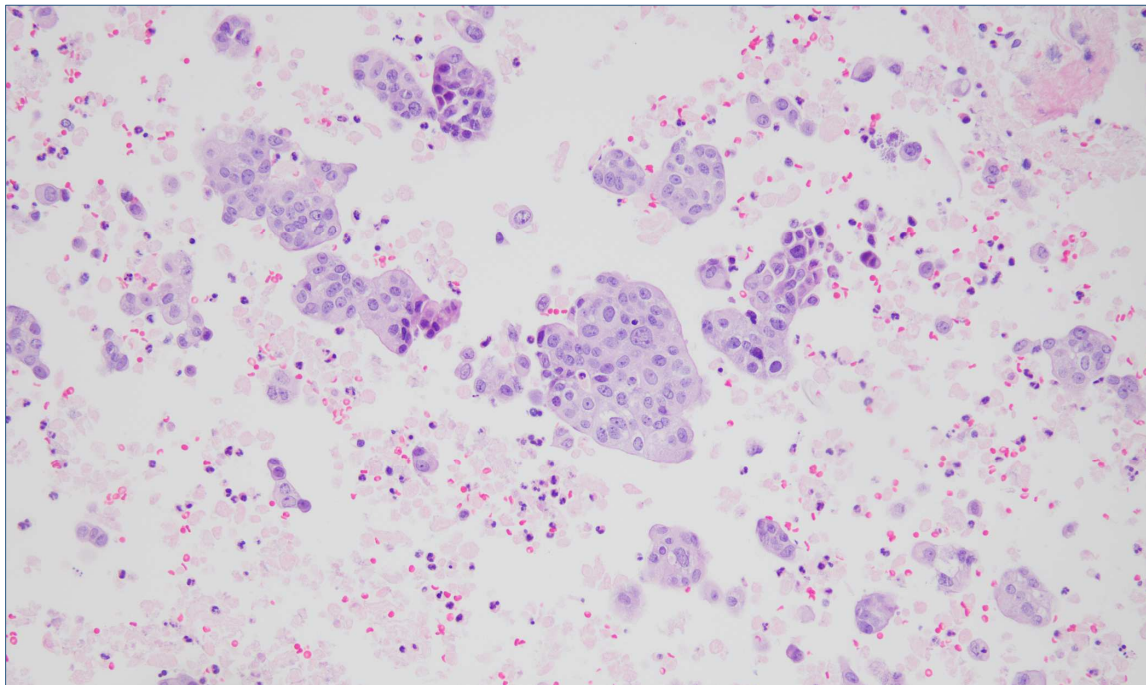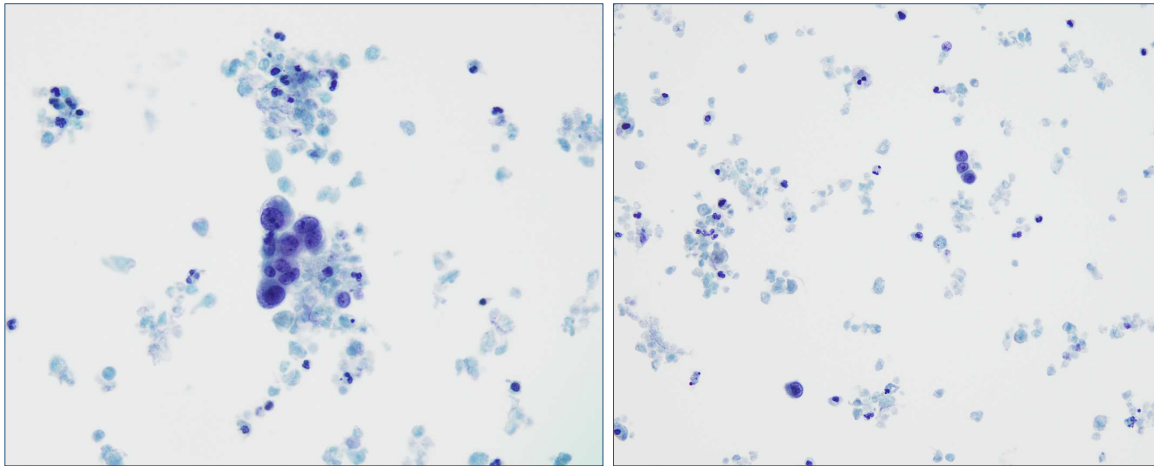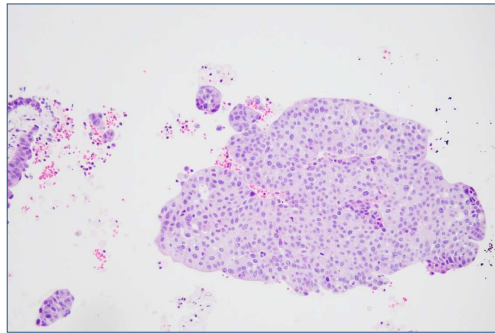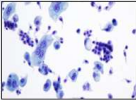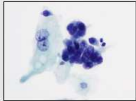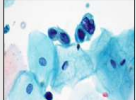
Cell blocks
- Architecture
- Material for adjuvant studies

GATA3

p63

The Paris System Approach to Diagnosis in Urinary Cytology (TPS2.0)

The Paris System for Reporting Urinary Cytology
Eva M. Wojcik
Daniel F.I. Kurtycz
Dorothy L. Rosenthal
Editors
Second Edition
Springer

Is there increased **N/C ratio (≥0.5)?** (i.e., not intermediate and basal urothelial cells)

No → Is there a **reason** for the "atypia"?
- Polyomavirus?
- Granuloma?
- Ileal conduit?
- Urolithiasis?
- Reactive changes?
→ **NEGATIVE FOR HGUC**

Yes → Are any one of the following features present in the atypical cells?
1. Hyperchromasia
2. Coarse Chromatin
3. Irregular chromatinic rim

At least 2 features present

At least 1 feature present → **ATYPICAL**

How many cells with these features?

"Few" ~ ≤ 5-10 cells High (~≥0.7) N/C ratio → **SUSPICIOUS HGUC**

"Many" ~ >10 cells High (~≥0.7) N/C ratio → **HGUC**

From The Paris System 2022 by Wojcik, Kurtycz, Rosenthal

TPS 2.0 in a nutshell

The Paris System for Reporting Urinary Cytology
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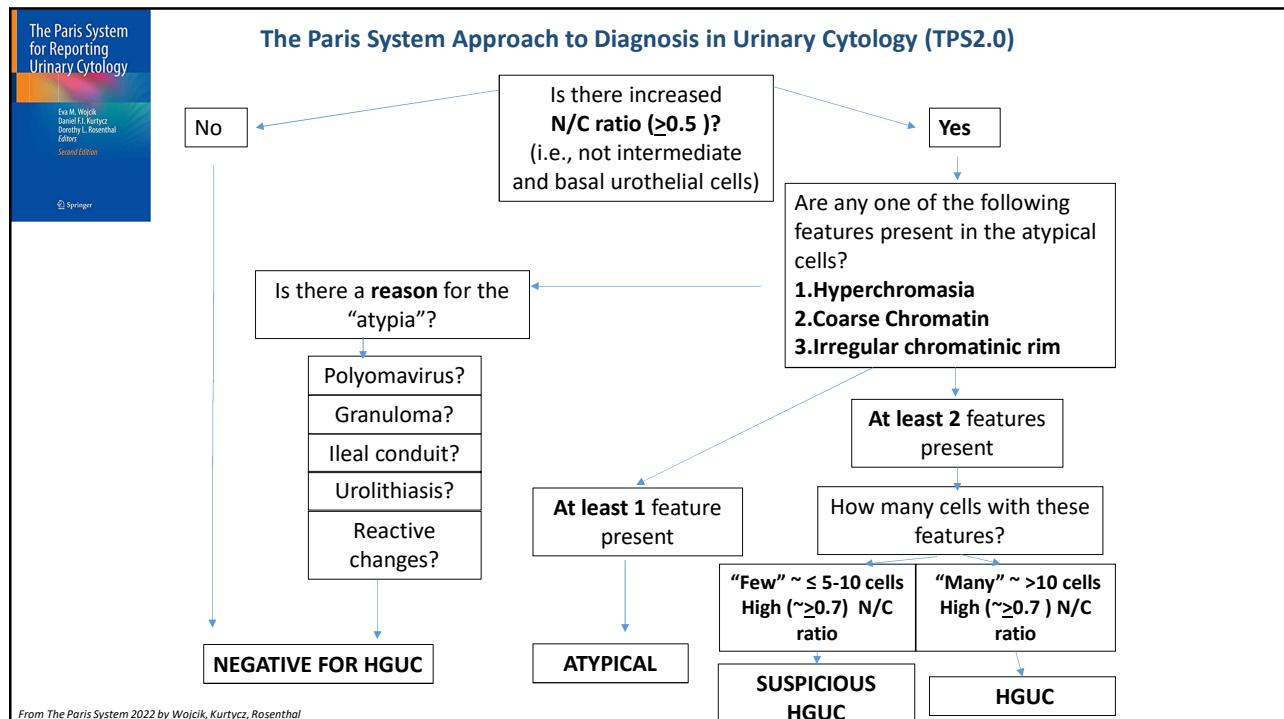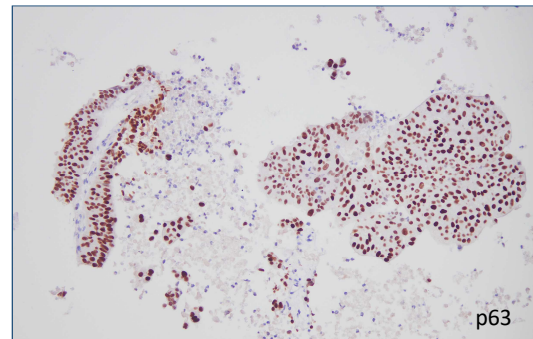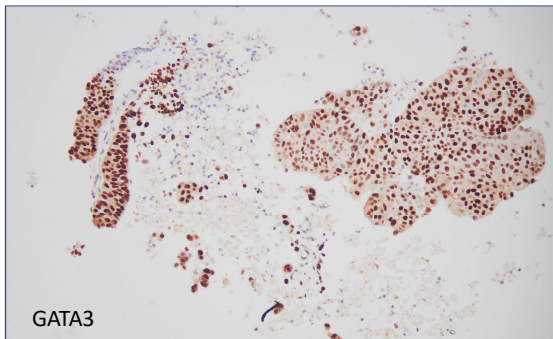| Diagnostic category	Diagnostic criteria	Example	Frequency	ROHM
Unsatisfactory	Voided urine – volume (>30ml) Instrumented urine - cellularity		0% - 5%	0% - 16%
Negative for High Grade Urothelial Carcinoma (NHGUC)	Benign urothelial, glandular, squamous cells, benign tissue fragments, changes due to instrumentation, lithiasis, polyoma virus, therapy. Low Grade Urothelial Neoplasm (LGUN)		70% - 90%	8% - 24%
Atypical Urothelial Cells (AUC)	Required – increased N/C ratio ($\geq$ 0.5) and one of: Hyperchromasia, Irregular clumpy chromatin or Irregular nuclear contours		5% - 15%	24% - 53%
Suspicious for High Grade Urothelial Carcinoma (SHGUC)	Required – Few cells (< 5-10) with high N/C ratio ($\geq$ 0.7) and at least two of: Hyperchromasia, Irregular clumpy chromatin, Irregular nuclear contours		0.5% - 3%	59% - 94%
Positive for High Grade Urothelial Carcinoma (HGUC)	Required – Many cells (>10) with high N/C ratio ($\geq$ 0.7) and at least two of: Hyperchromasia, Irregular clumpy chromatin, Irregular nuclear contours		0.1% - 3%	76% -100%

ROHM – Risk of High Grade Malignancy

From The Paris System 2022 by Wojcik, Kurtycz, Rosenthal


ROHM – Risk of High Grade Malignancy

Table 2. Pooled risk of high-grade malignancy (ROHM) associated with each of the Paris System categories.

Paris System Categories	No of Studies Pooled	ROHM (%)	95% CI	Tau^2	Q	I^2 (%)
Nondiagnostic	11	17.70	(0.0650; 0.3997)	1.8070	29.22	72.6
NHGUC	24	13.04	(0.0932; 0.1796)	0.6056	355.67	87.3
AUC	23	38.65	(0.3042; 0.4759)	0.5272	84.57	76.4
LGUN	10	12.45	(0.0431; 0.3101)	1.1790	4.89	55.4
SHGUC	26	76.89	(0.7063; 0.8216)	0.3291	53.12	66.1%
HGUC and other malignancies	25	91.79	(0.8722; 0.9482)	0.8732	92.36	82.6

Abbreviations: CI, confidence interval; NHGUC, negative for high-grade urothelial carcinoma; AUC, atypical urothelial cells; LGUC, low-grade urothelial neoplasm; SHGUC, suspicious for high-grade urothelial carcinoma; HGUC, high-grade urothelial carcinoma.

Nikas IP et al. The Paris System for Reporting Urinary Cytology: A Meta-Analysis. J Pers Med 2022, 12(2), 170

Is it perfect now?
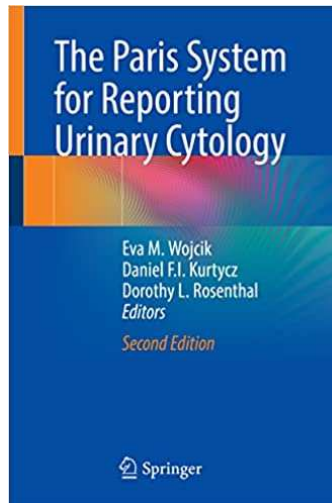
Opportunities

- Molecular studies to further define undetermined categories (AUC and SHGUC)
- Adequacy criteria for different (or standardized) collection and preparation methods
- AUC as a quality improvement metric (AUC/HGUC ratio)
- SHGUC and HGUC – one diagnostic category?
- Use of AI to refine diagnostic criteria (N/C ratio, # of cells)
- Risk of malignancy for NUM, especially for ASC
- Compare new metrics (likelihood ratios and pre-test probability) to ROHM
- Clinical trials integrating TPS with new diagnostic techniques and novel urine-based molecular markers
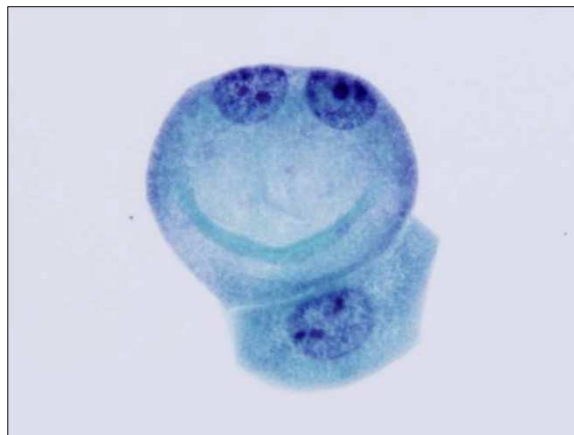- And more….
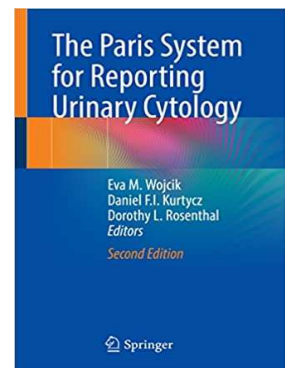
Future Clinical and Research Needs, pp.318-321

Objectives

- What is the goal of urine cytology?

- Why to standardize?

- The urine story – creation of the Paris System

- Review of the Paris System (TPS) – what worked what needed to be improved

- What's new in TPS2.0 – highlights

- Detect High Grade Urothelial Carcinoma

- Reproducibility

- Great Success!

- Overall criteria worked Improvements related to N/C ratio, F/V cores, degenerations, variants of HGUC

- More images, additional chapters, updated data (ROHM), summary at the beginning, examples of reports

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Thank you!

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