WHO Classification of Tumours: Tumours of the Urothelial Tract

an update on the forthcoming 4th edition

Victor E. Reuter, M.D.
Memorial Sloan Kettering Cancer Center

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WHO Classification of Tumours: Tumours of the Urothelial Tract

an update on the forthcoming 4th edition

V. Reuter (ed)
J. McKenney
M. Amin
S.S. Shen
L. Cheng
J. Cheville
K. Trpkov
P. Humphrey
D. Grignon
G. Netto
E. Compérat
R. Knüchel
J.Y. Ro
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WHO Classification of Tumours:
Tumours of the Urothelial Tract
Differences between the 3rd and 4th editions

Third edition: urothelial tumours	Fourth edition: urothelial tumours*
Infiltrating urothelial carcinoma	Infiltrating urothelial carcinoma
with squamous differentiation	with divergent differentiation
with glandular differentiation	
with trophoblastic differentiation	
Nested	Nested, including large nested
Microcystic	Microcystic
Micropapillary	Micropapillary
Lymphoepithelioma-like	Lymphoepithelioma-like
Lymphoma-like	Plasmacytoid/signet ring cell/diffuse
Plasmacytoid	Sarcomatoid
Sarcomatoid	Giant cell
Giant cell	Poorly differentiated
Undifferentiated	Lipid rich
	Clear cell

WHO Classification of Tumours:
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Third edition: urothelial tumours

Non-invasive urothelial neoplasias

- Urothelial carcinoma in situ
- Papillary urothelial carcinoma, low grade
- Papillary urothelial carcinoma, high grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma

Fourth edition: urothelial tumours*

Non-invasive urothelial neoplasias

- Urothelial carcinoma in situ
- Papillary urothelial carcinoma, low grade
- Papillary urothelial carcinoma, high grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma
- Urothelial proliferation of uncertain malignant potential (hyperplasia)
- Urothelial dysplasia/atypia

WHO Classification of Tumours:
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<u>Fourth edition:</u>

Urachal Carcinoma

Tumours of Müllerian-type

- Clear cell carcinoma
- Endometrioid carcinoma

Neuroendocrine tumours

- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Well differentiated neuroendocrine carcinoma
- Paraganglioma

<u>Fourth edition:</u>

Mesenchymal tumours

- Inflammatory myofibroblastic tumour
- Perivascular epitheloid cell tumour
- Solitary fibrous tumour
- Granular cell tumour

Miscellaneous tumours

- Tumours of the upper urinary tract
- Tumors arising in a diverticulum
- Urothelial tumours of the urethra

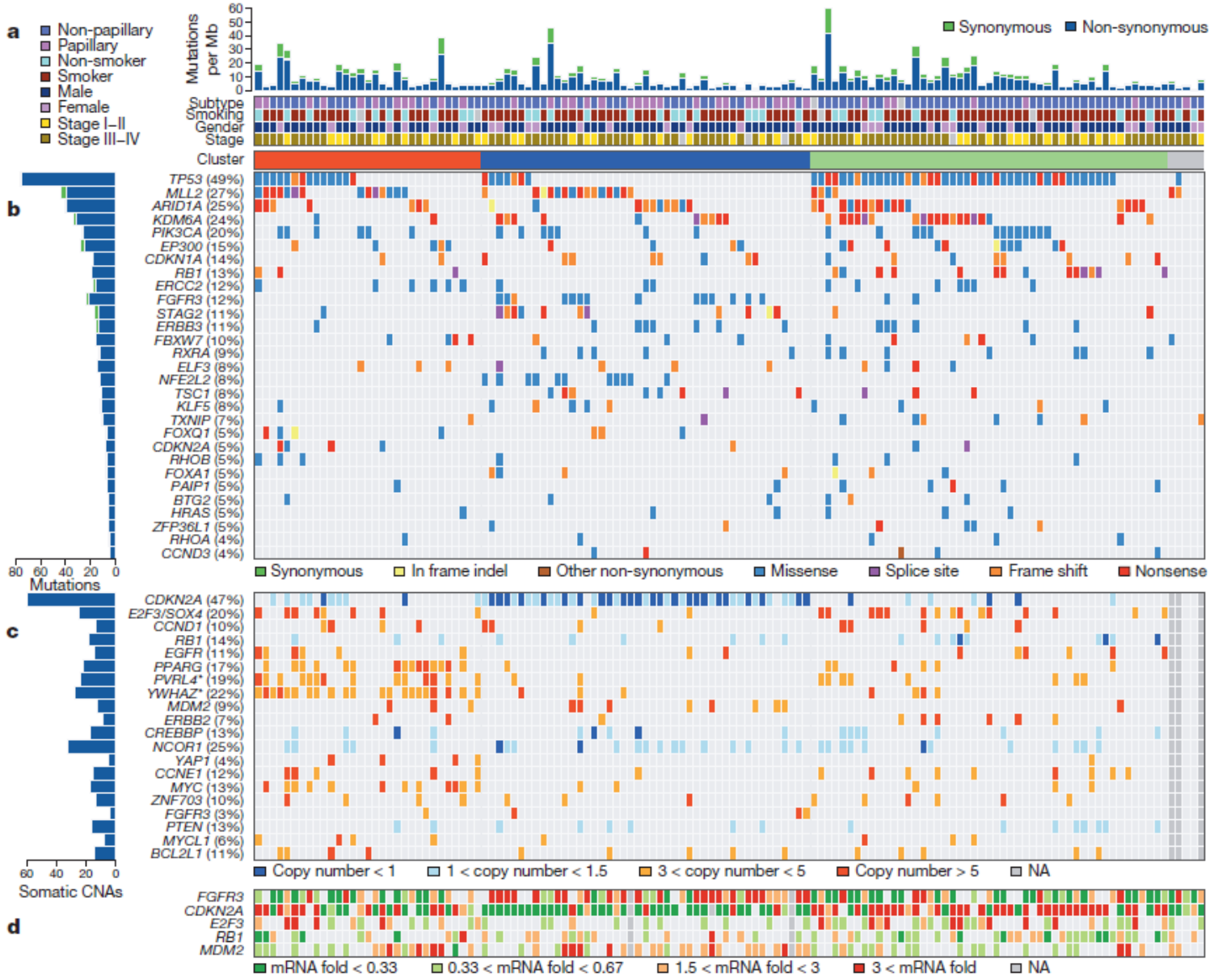
WHO Classification of Tumours: Tumours of the Urothelial Tract an update on the forthcoming 4th edition

Outline

- Molecular taxonomy of urothelial neoplasia
  - Classification
  - Therapeutics
- Divergent differentiation in urothelial neoplasia
- Tumours of Müllerian type
- Grading of papillary urothelial tumors
- Substaging tumours invading the lamina propria

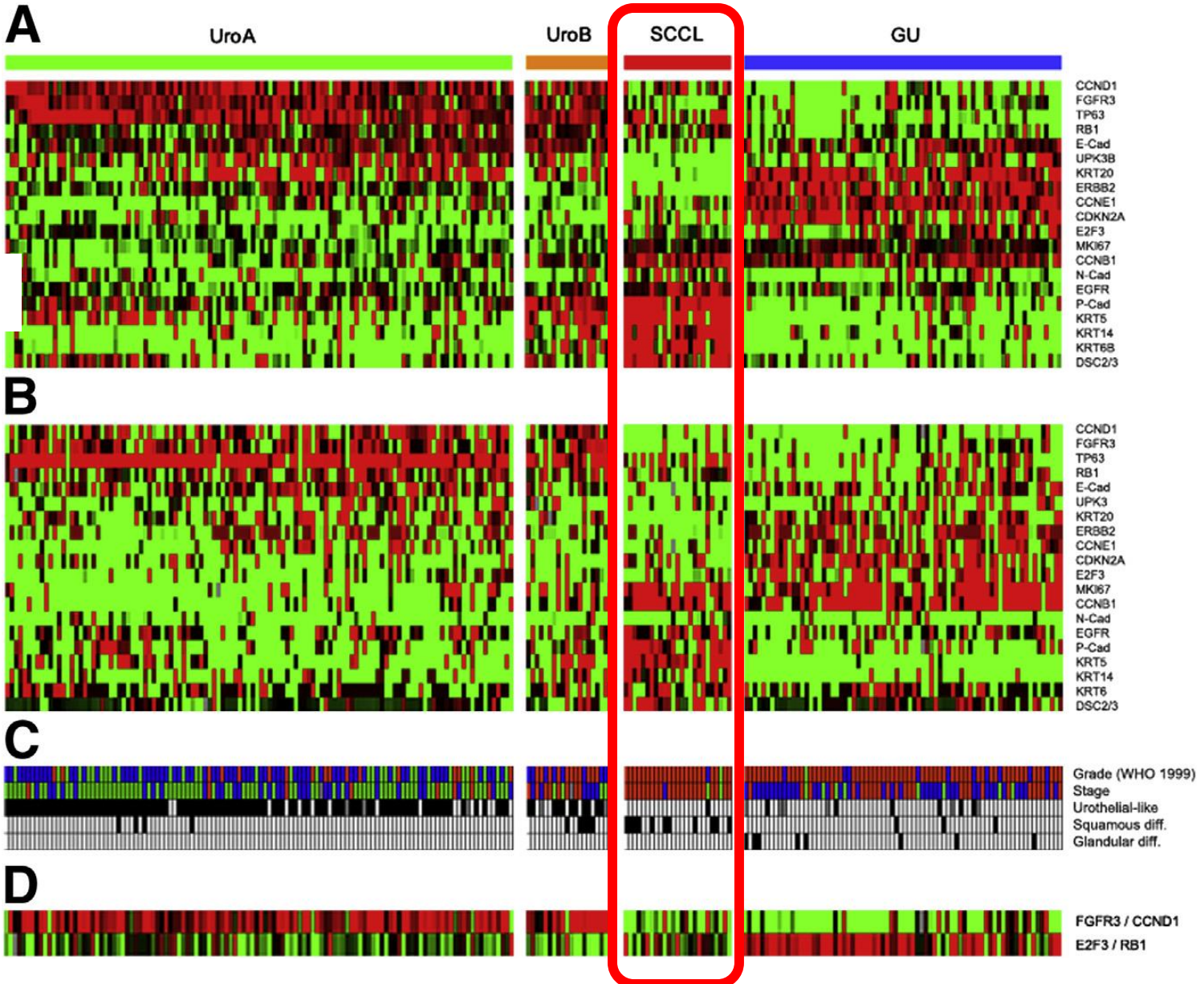
Comprehensive molecular characterization of urothelial carcinoma of the bladder

The Cancer Genome Atlas Research Network (n = 131)



Toward a Molecular Pathologic Classification of Urothelial Carcinoma

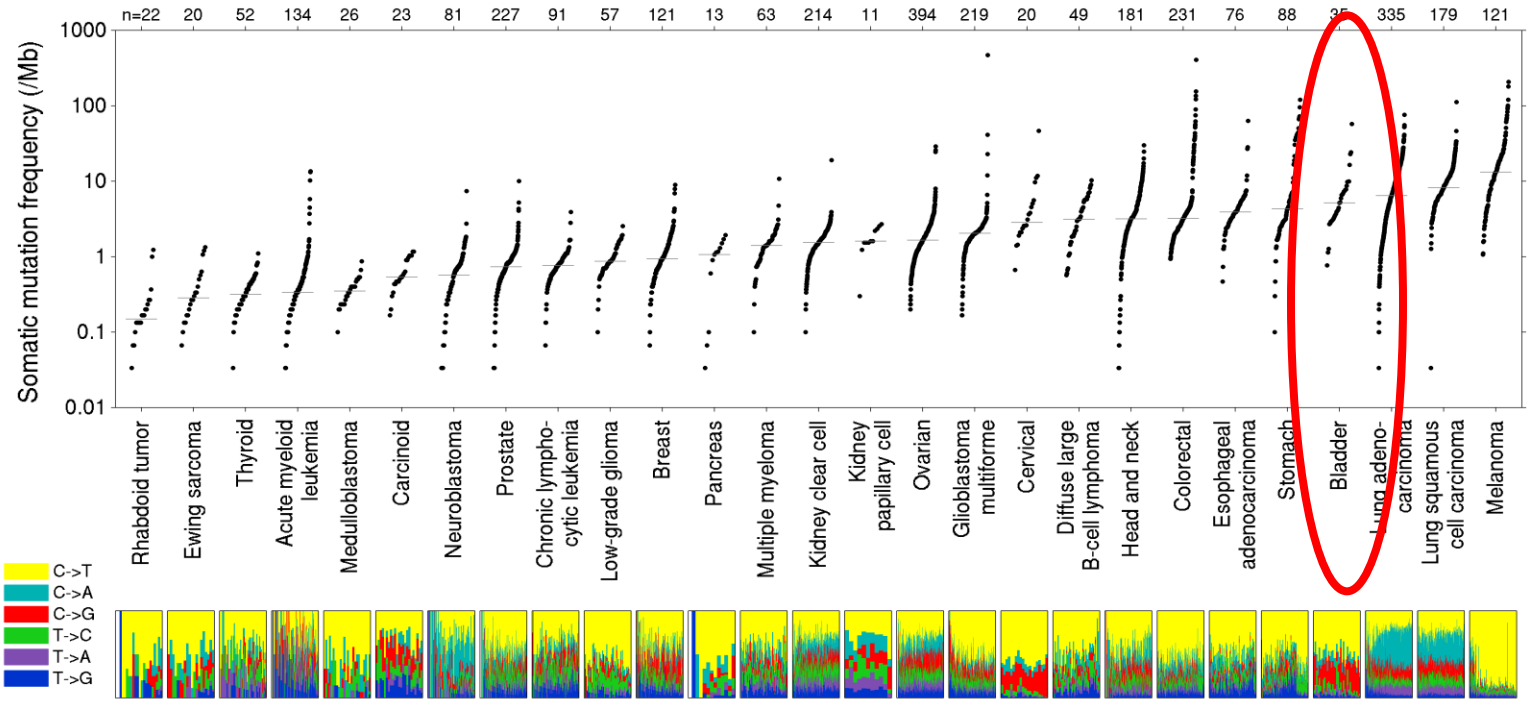
Sjödahl et al. *Am J Pathol* 2013



mRNA

IHC

High rate of somatic mutations in bladder cancer

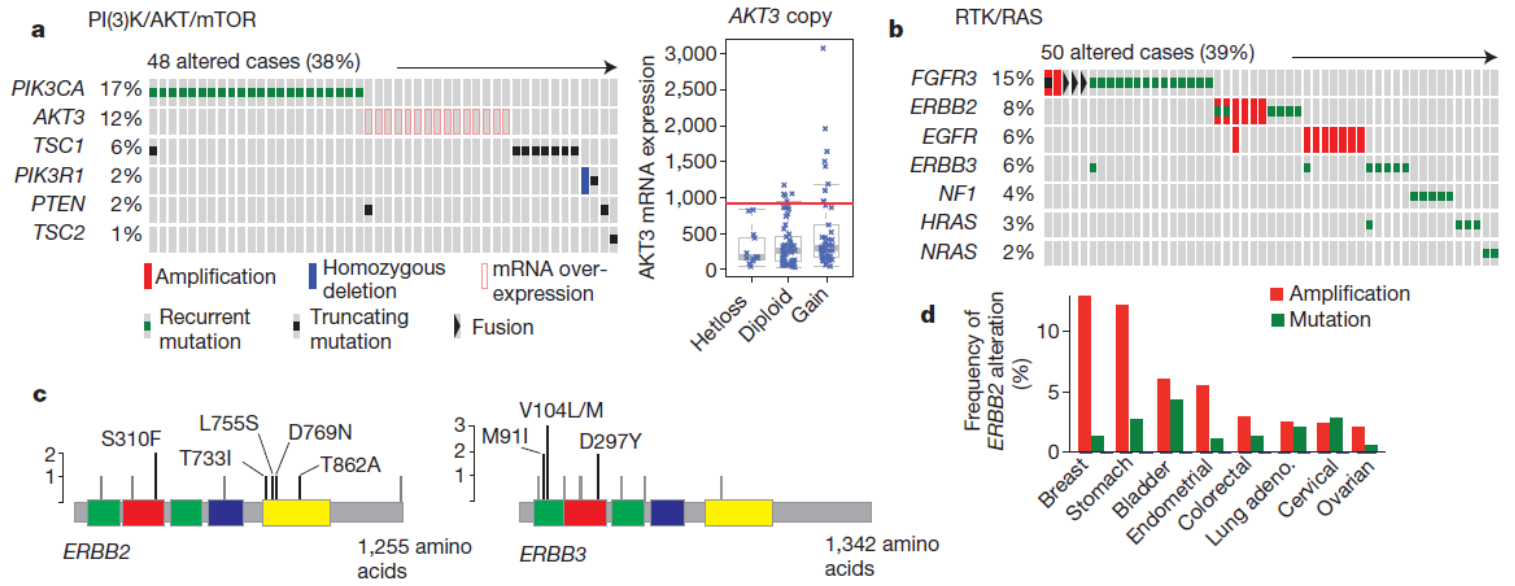


Frequency of somatic mutations in 27 tumor types (*Lawrence M. Nature 2013)*

Comprehensive molecular characterization of urothelial bladder carcinoma

Nature 2014

The Cancer Genome Atlas Research Network*



Targetable aberrations..

Neratinib study - any solid tumor with *HER2* mutations

Anti-Her2 immunotherapy (DN24-02)

RTOG 0524 trial (Her2)

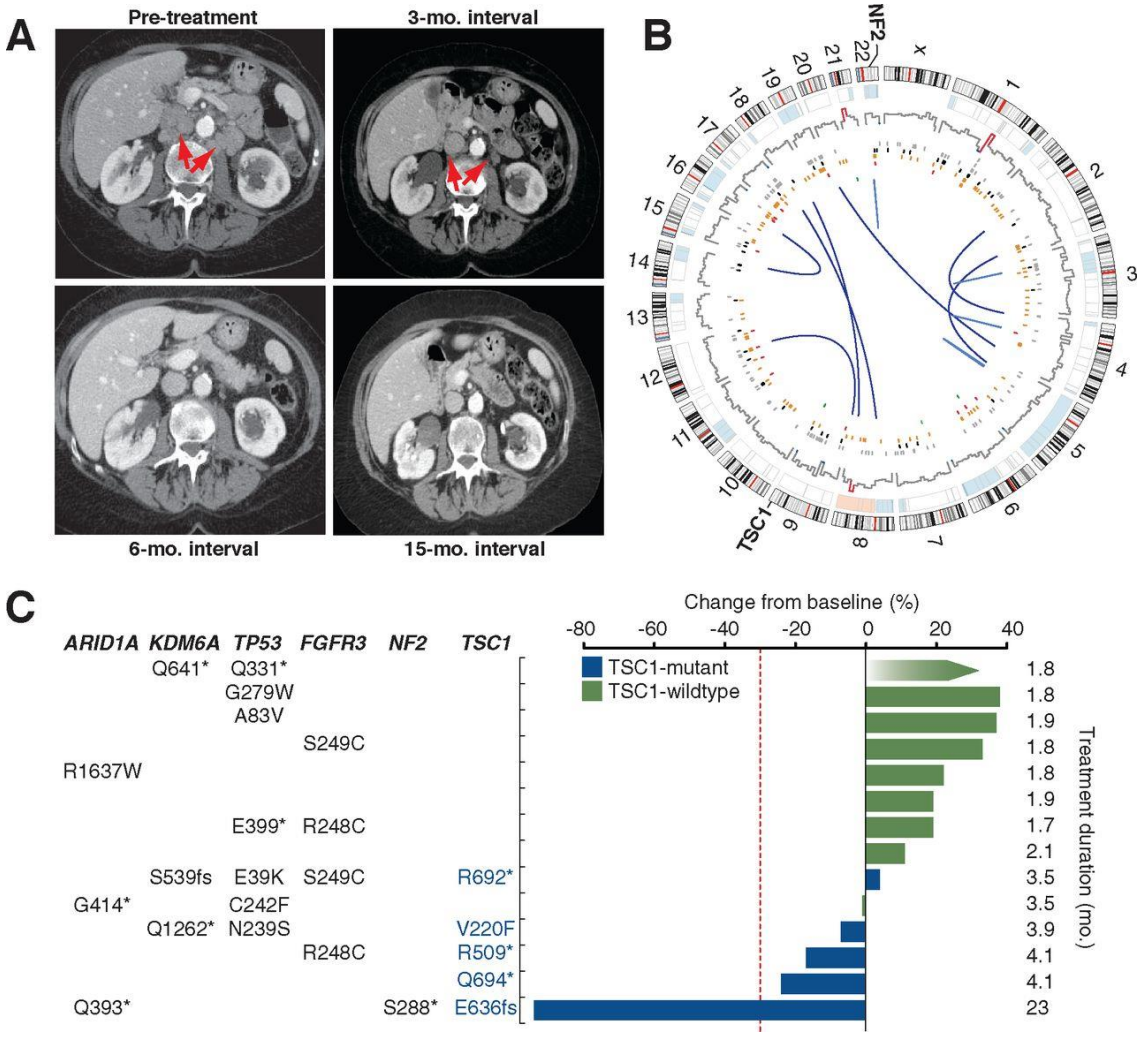
BKM10 trial for bladder cancer patients with alterations within the PI3K/Akt/mTOR pathway

Mocetinostat (histone deacetylase [HDAC] inhibitor) for UC with *CREBBP and/or EP300 alterations*

Other potential targets: *FGFR3*, *EGFR*, *ERBB3*, etc..

Genome sequencing identifies a basis for everolimus sensitivity

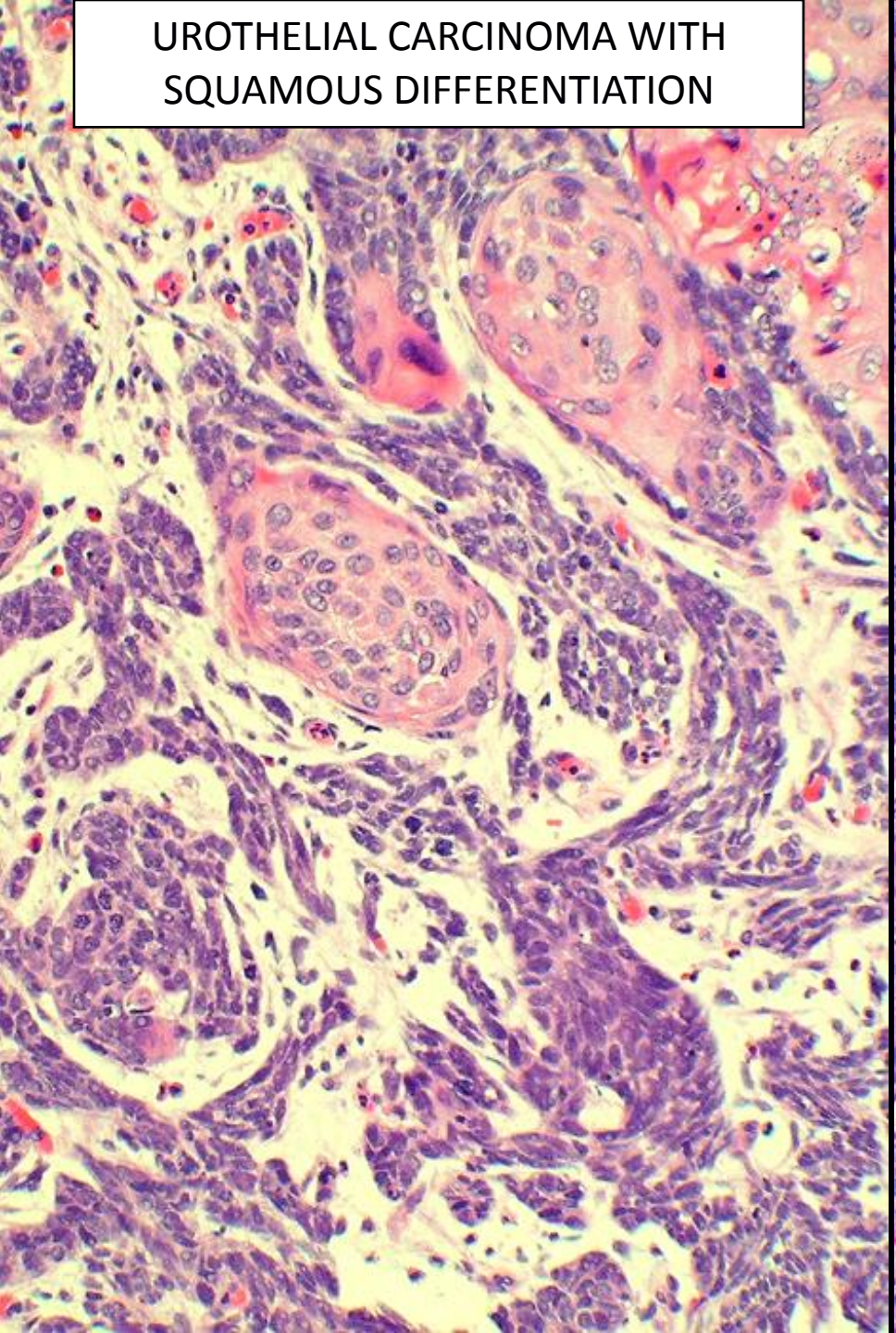
Fig. 1 (A) Computed tomography images of the index patient demonstrating complete resolution of metastatic disease (arrows).



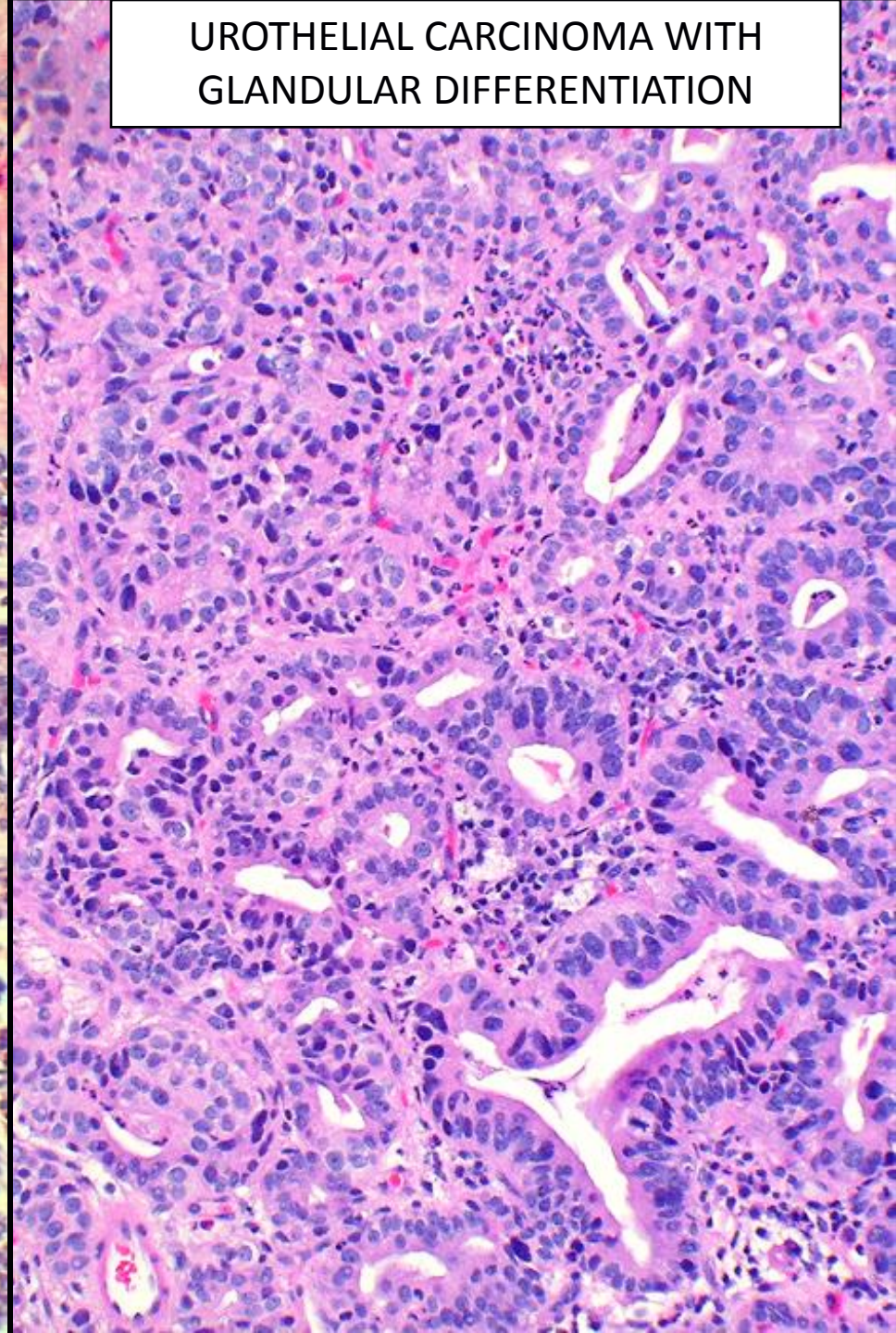
Published by AAAS

G Iyer et al. Science 2012;338:221

UROTHELIAL CARCINOMA WITH SQUAMOUS DIFFERENTIATION



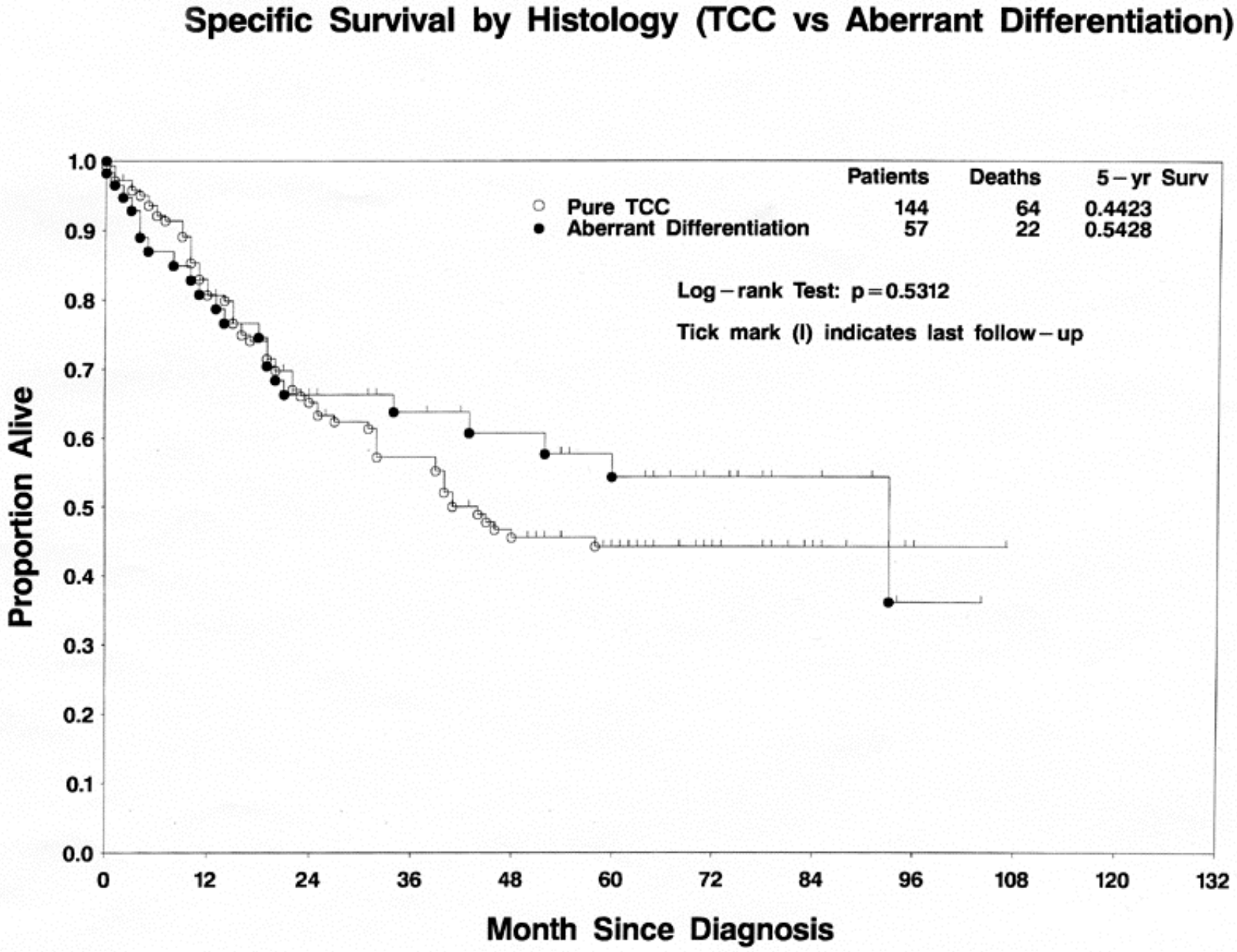
UROTHELIAL CARCINOMA WITH GLANDULAR DIFFERENTIATION



CYSTECTOMY FOR BLADDER CARCINOMA
300 consecutive cases

Residual MP invasive disease	212
• Conventional UC	154 (73%)
• UC with DD	58 (27%)
– Squamous	37
– Glandular	14
– SMCL/NE	3
–Squamous, glandular	3
–SMCL/NE, squamous	1

Dalbagni et al, J Urol 2001;165:1111-1116



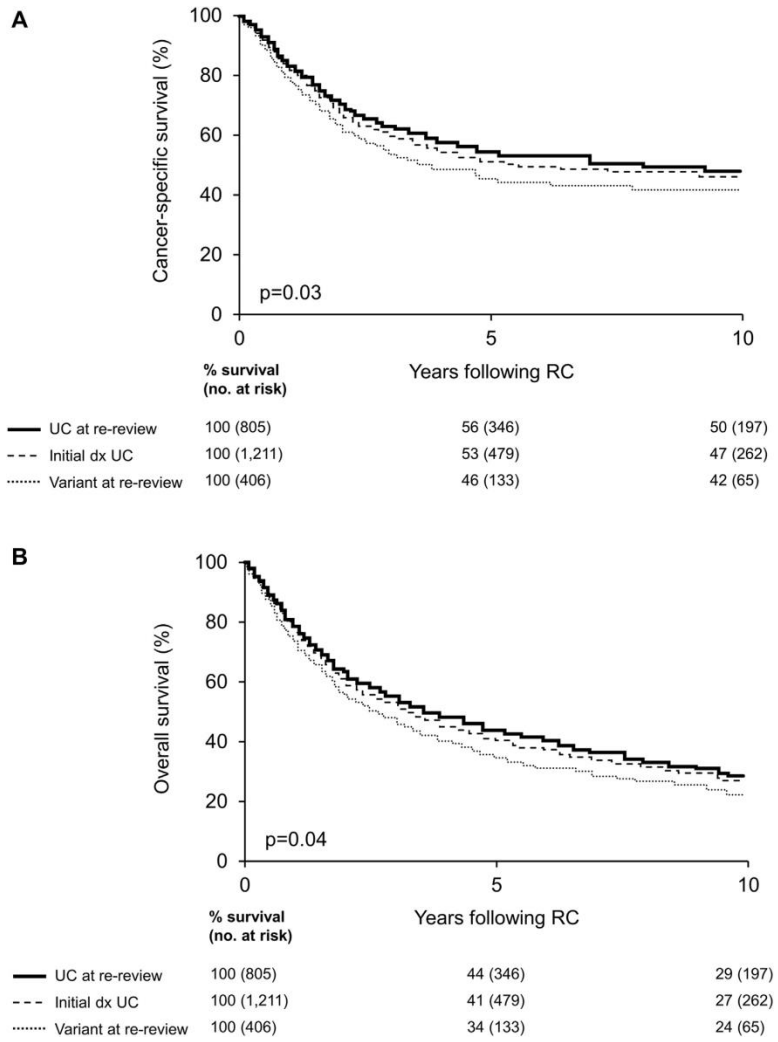
Dalbagni et al, J Urol 2001;165:1111-1116

Reclassification after pathology re-review - radical cystectomy (n=1,211)

Mayo Clinic experience (Linder et al. *J Urol* 2013)

Histological UC subtypes identified at pathological re-review in 406 patients **(33% of entire cohort)**

	No. Variant UC (%)
Squamous differentiation	122 (30)
Micropapillary	62 (15)
Nested variant	51 (13)
Pure squamous Ca	39 (10)
Small cell Ca	36 (9)
Glandular differentiation	33 (8)
Adenoca	30 (7)
Sarcomatoid	14 (3)
Mixed differentiation	11 (3)
Inverted growth pattern	4 (1)
Plasmacytoid	1 (0.2)



THE IMPACT OF OF SQUAMOUS AND GLANDULAR DIFFERENTIATION ON SURVIVAL AFTER RADICAL CYSTECTOMY FOR UROTHELIAL CARCINOMA

Kim SP et al, J Urol 2012;188:405-409

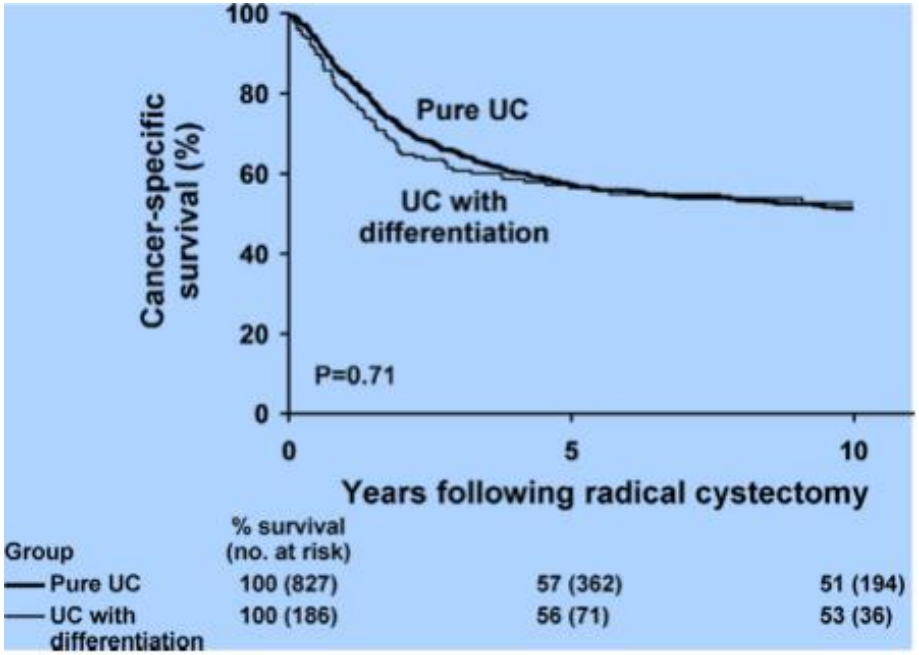


Figure 1. CSS after RC, stratified by pure UC in 827 patients vs UC with squamous and/or glandular differentiation in 186 in RC specimen.

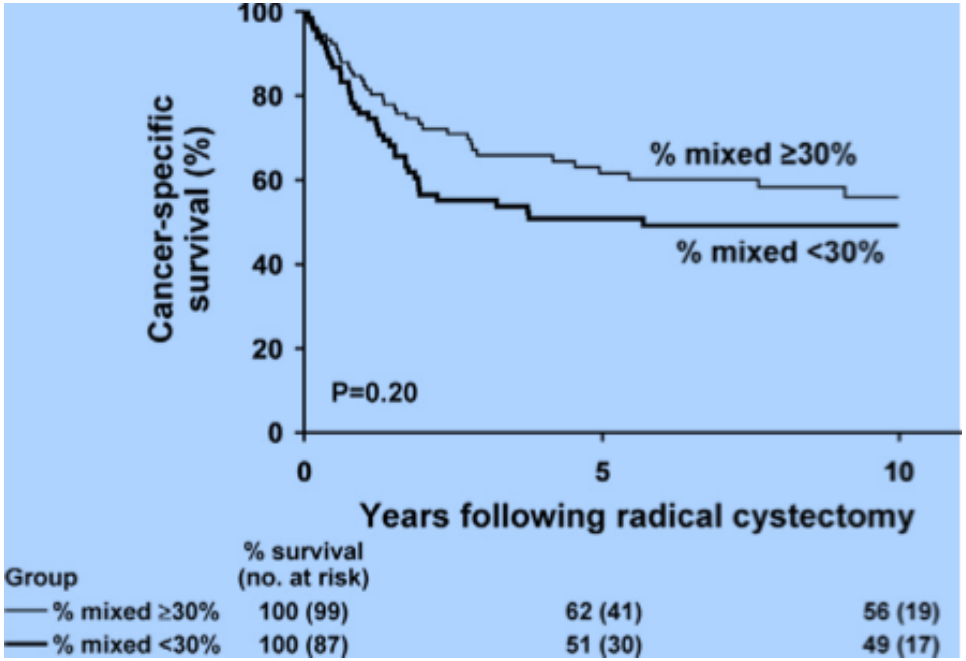


Figure 2. CSS in 186 patients with squamous and/or glandular differentiation at RC, stratified by degree of histological differentiation in specimen. Median differentiation in this cohort was 30% (IQR 10, 60).

THE CLINICAL RELEVANCE OF VARIANT HISTOLOGY IN UROTHELIAL CARCINOMA AFTER RADICAL CYSTECTOMY

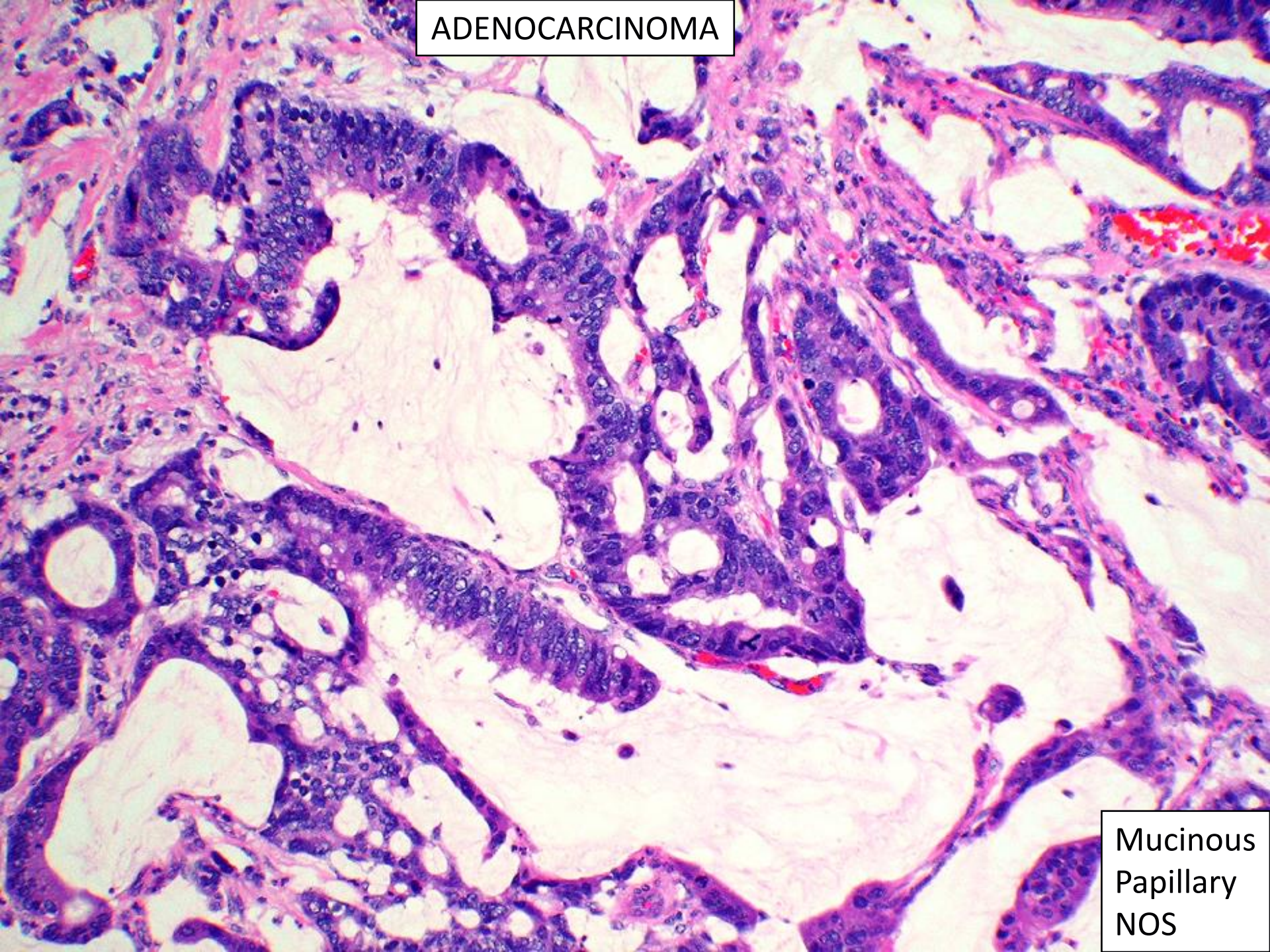
Soave A et al, Urol Oncol 2015;33:ePub

Non-squamous variant histology is associated with inferior survival but are not independent predictors of survival

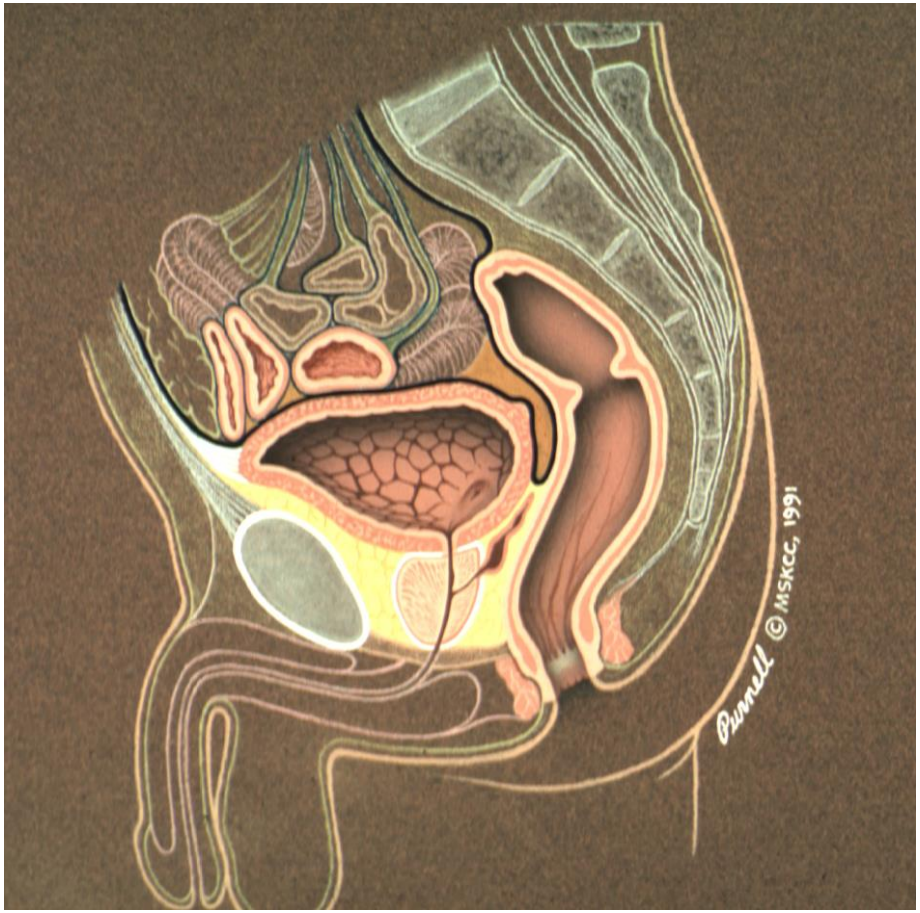
Variant histology is associated with established predictors of aggressive tumor biology

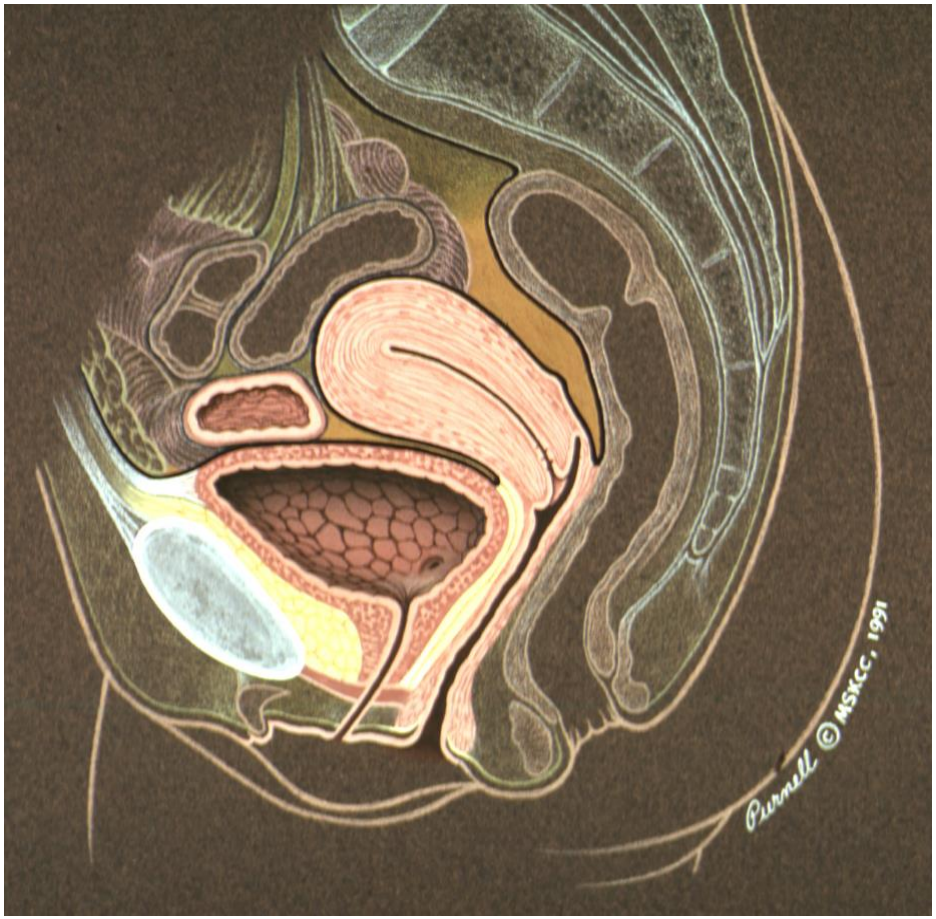
Xylinas A et al, Eur J Cancer 2013;49:1889-1897

While variant UCB histology was associated with worse outcomes on univariate analysis, this effect did not remain significant on multivariable analyses


ADENOCARCINOMA
Mucinous
Papillary
NOS

"I would accept as primary at this site if direct extension or a metastasis from another organ has been ruled out clinically"

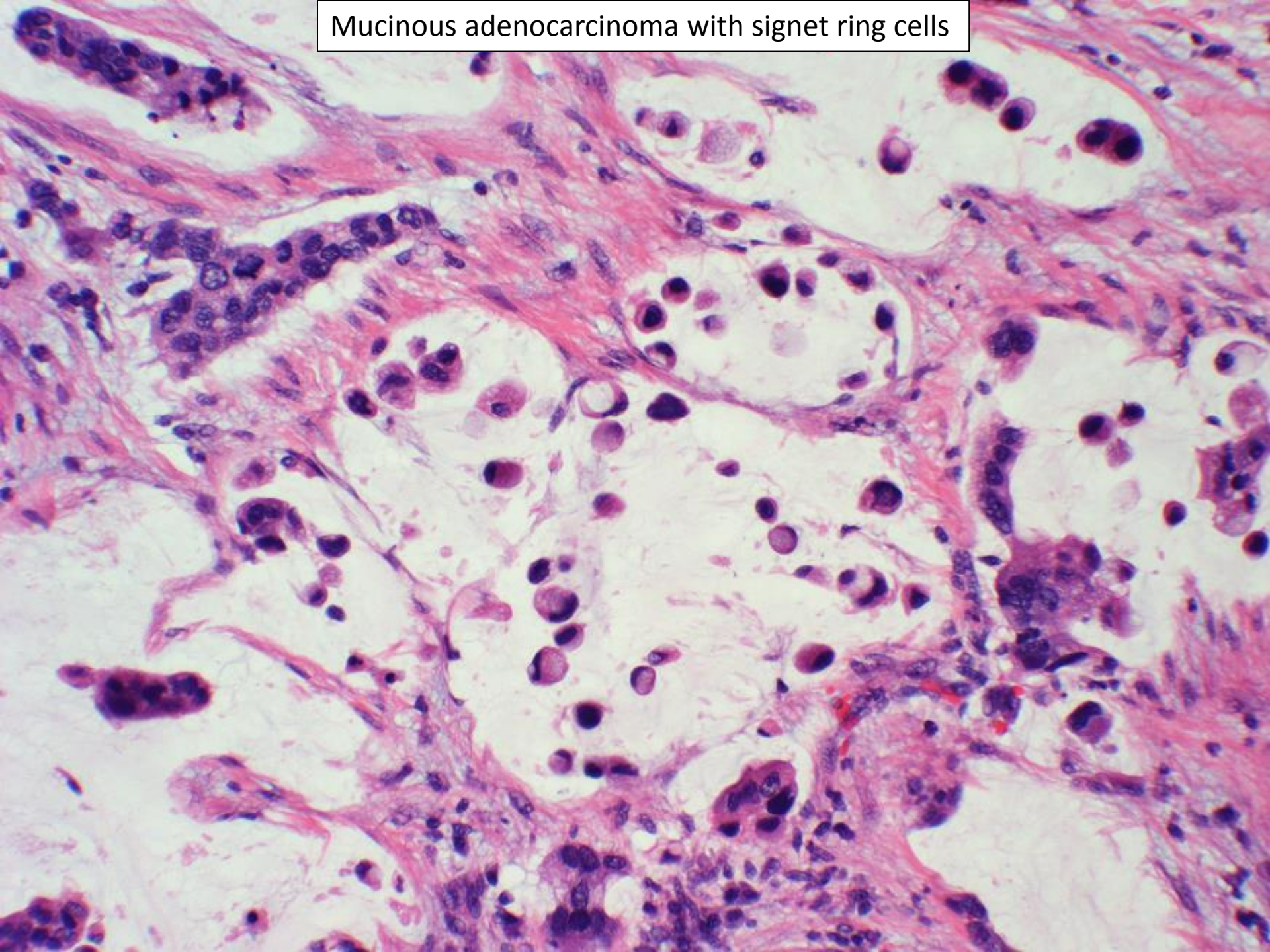




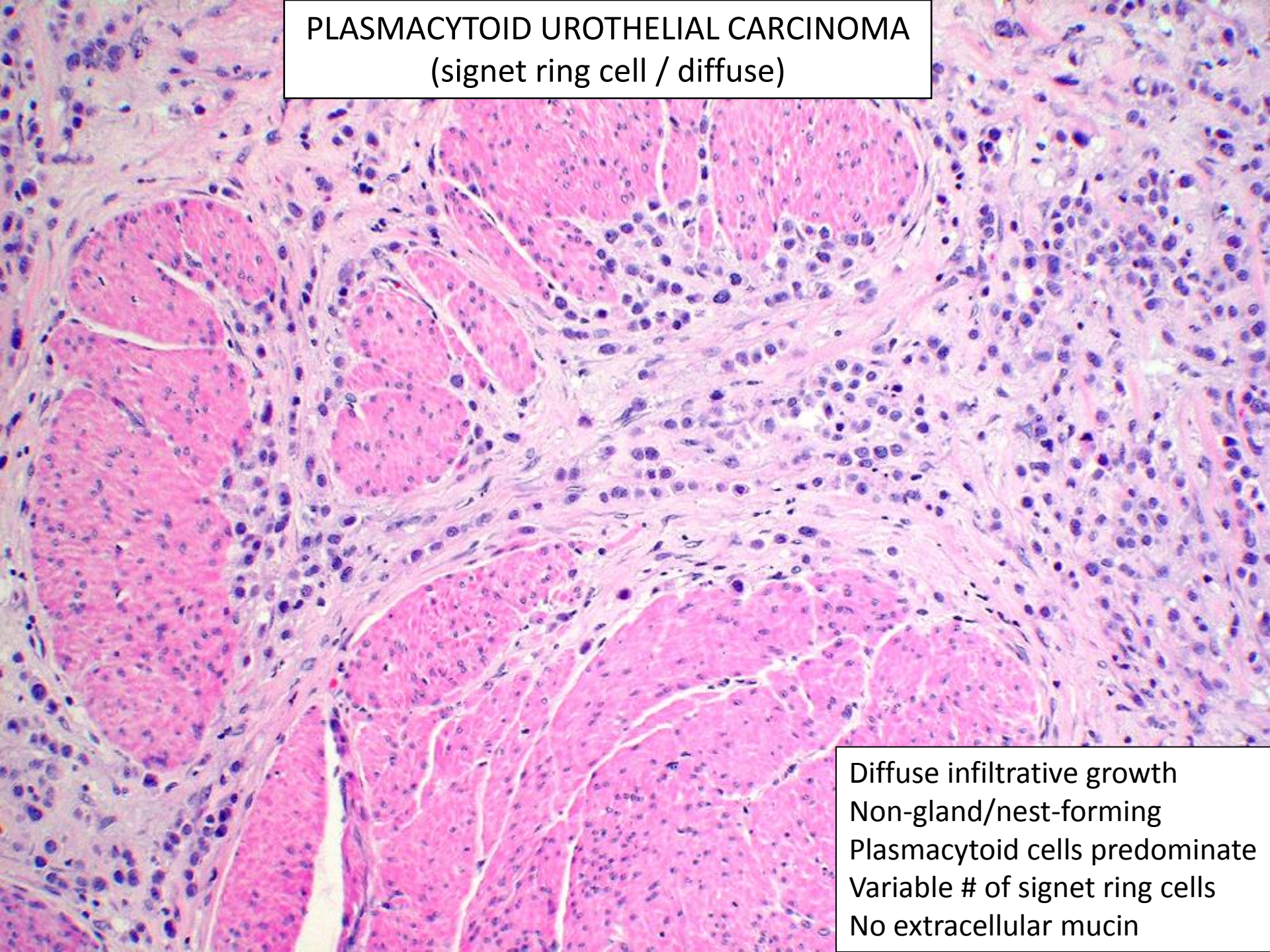
ADENOCARCINOMA OF THE URINARY BLADDER
Grignon et al

Stage at Presentation	Cases(%)	Survival(%)
pT1	2 (4)	100
pT2-pT3a	11 (20)	76
pT3b	12 (23)	28
pT4	24 (45)	20

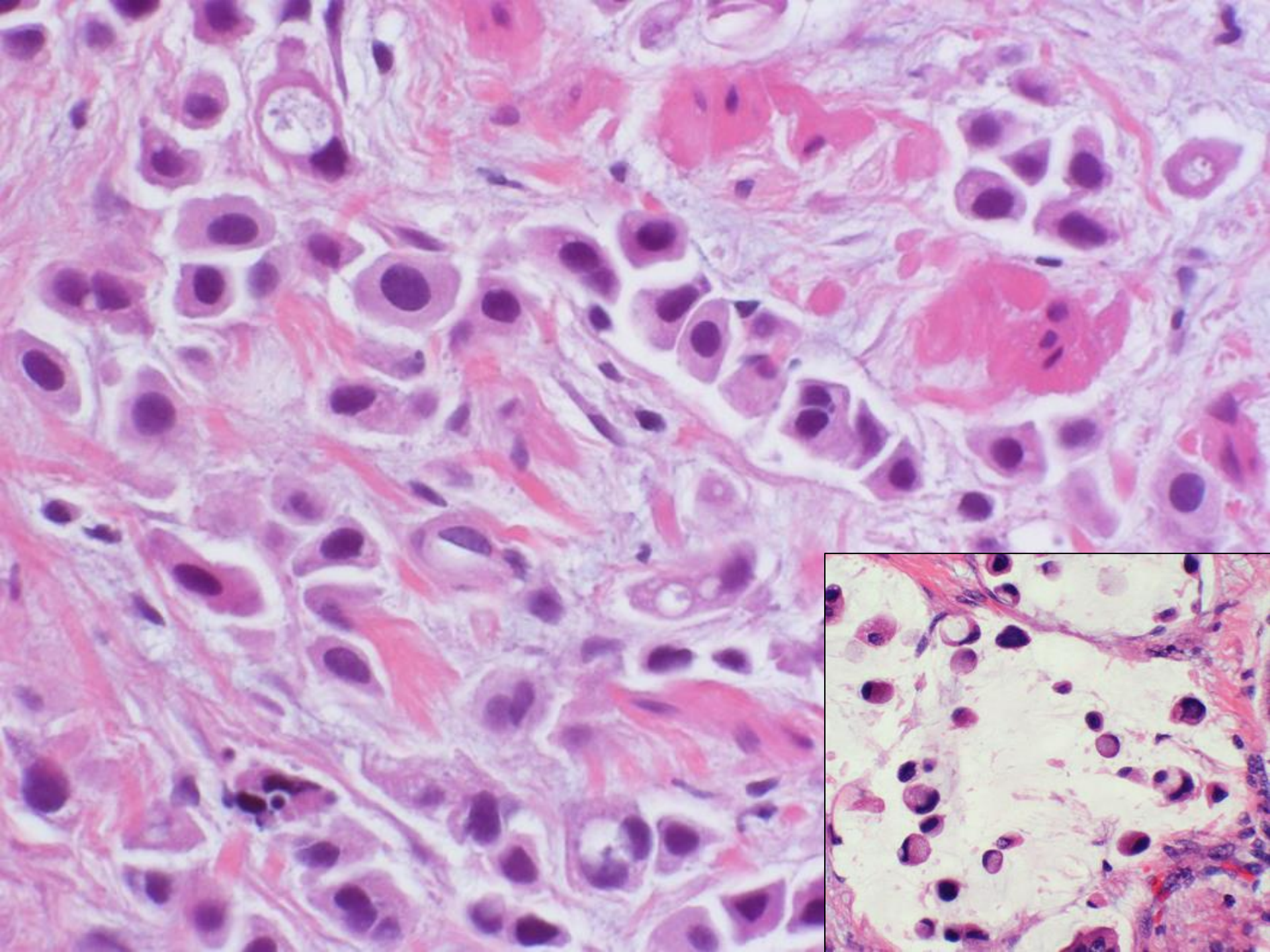
Cancer 1991;67:2165-2172


Mucinous adenocarcinoma with signet ring cells

PLASMACYTOID UROTHELIAL CARCINOMA
(signet ring cell / diffuse)



Diffuse infiltrative growth
Non-gland/nest-forming
Plasmacytoid cells predominate
Variable # of signet ring cells
No extracellular mucin



Plasmacytoid urothelial carcinoma

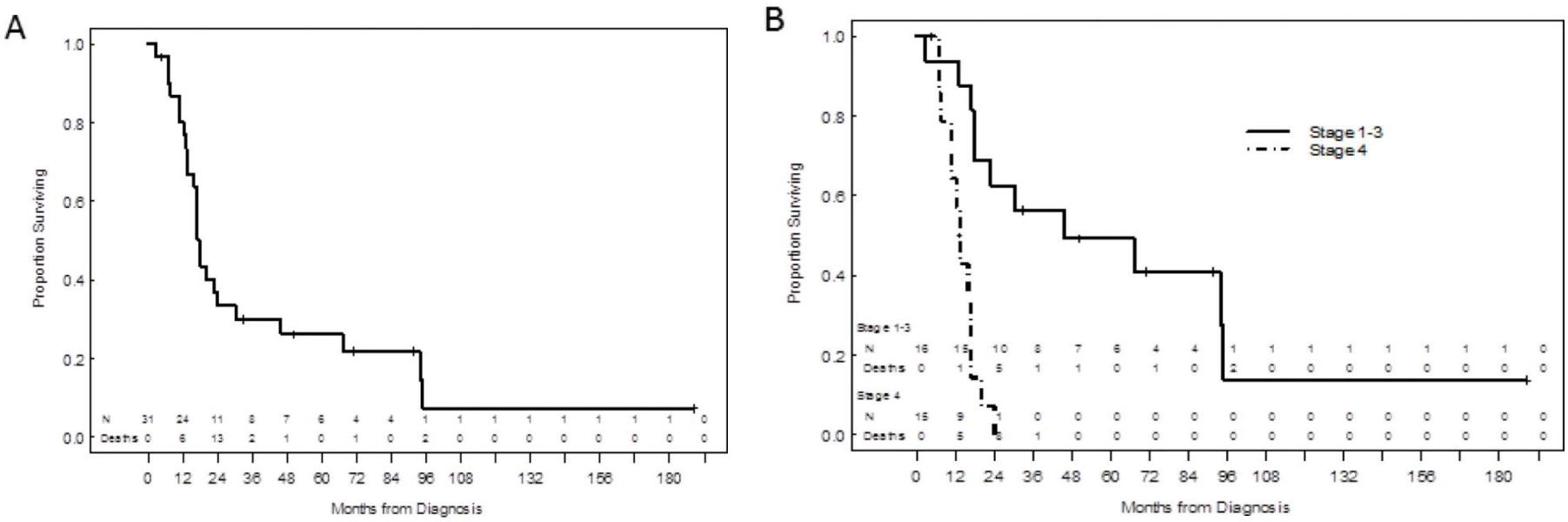


Figure 2.
(A) Overall survival (OS) for all patients (n=31) was 17.7 months. (B) OS by stage (I-III [45.8 months] vs. IV [13.4 months]; *P<0.001).*

Dayyeni F et al, J Urol. 2013 May ; 189(5): 1656–1661

Plasmacytoid variant of bladder cancer defines patients with poor prognosis if treated with cystectomy and adjuvant cisplatin-based chemotherapy

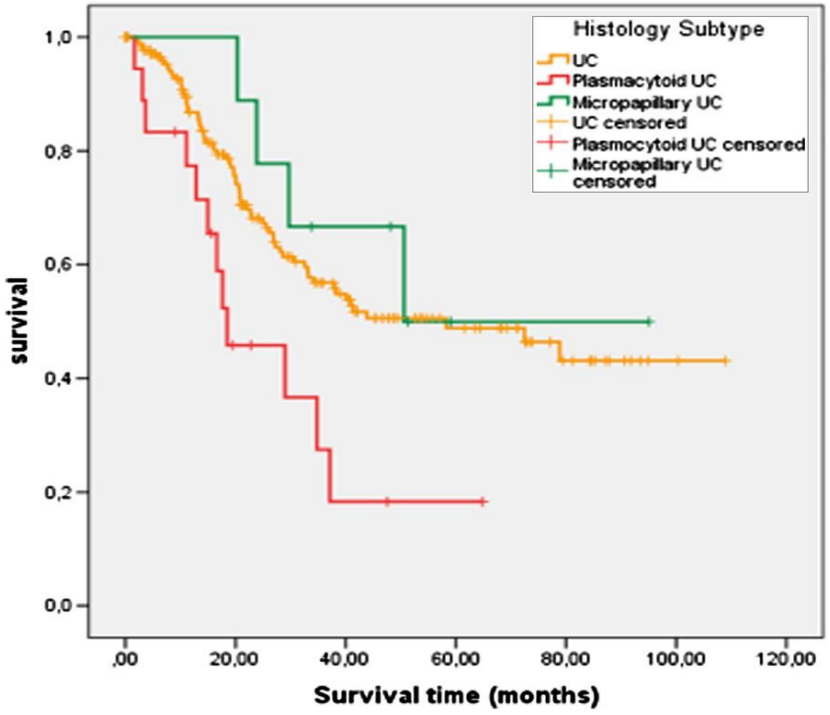


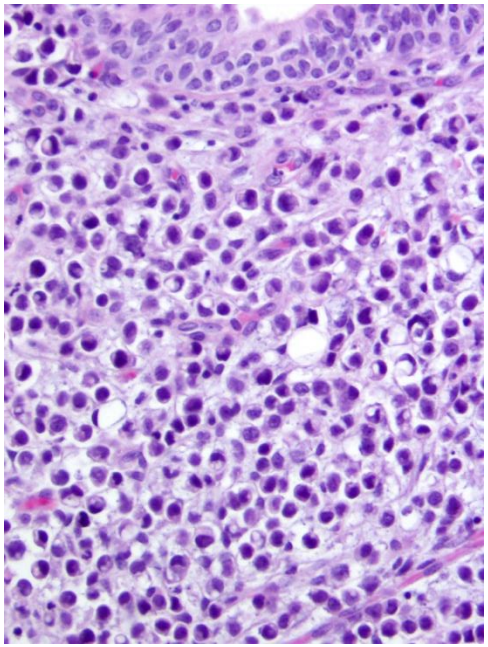
Figure 3 Kaplan-Meier analysis: Correlation of histology subtype with overall survival. Patients with a plasmacytoid urothelial cancer (lower curve, N=18) showed with 27.4 months (range: 16.8-37.9) the shortest overall survival, patients with a conventional UC (middle curve, N=178) survived in average 62.6 months (range: 54.8-70.4) whereas patients with a micropapillary urothelial cancer possessed the longest average survival with 64.2 months (range: 41.9-86.4; upper curve N=9). The mean survival was significantly different between patients with plasmacytoid urothelial cancer and those with micropapillary urothelial cancer (P=0.013; log rank test). Censoring of patients (marked with a cross) means mathematically removing a patient from the survival curve at the end of his/her follow-up time.

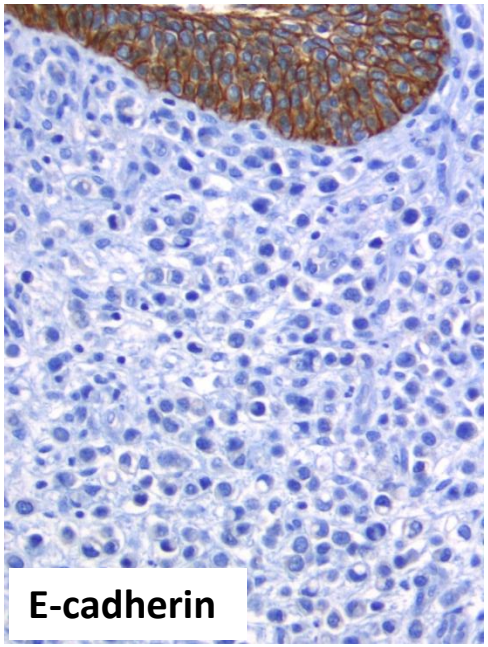
Keck et al. BMC Cancer 2013, 13:71

Plasmacytoid/Signet Ring Cell Carcinoma of the Bladder

Inactivation of *CDH1* and loss of E-cadherin expression by IHC

All cases had loss of e-cadherin except:
1 tumor with splice site mutation and 1 tumor with missense mutation





Nature Medicine, in press

E-cadherin

Müllerian-type tumours

- Arise from pre-existing Müllerian precursors within the bladder
  - Endometriosis, rarely Müllerianosis
- Tumour types*:
- Clear cell carcinoma (F:M, 2:1)
- Endometrioid carcinoma (only females)
- Histopathology – identical to those seen in the female genital tract

Clear cell carcinoma:

- Tubulocystic, papillary, diffuse
- Basophilic or eosinophilic secretions
- Tumour cells flat, cuboidal or columnar
- Hobnail cells common
- Nuclear enlargement and hyperchromasia
- Brisk mitotic activity

Immunohistochemistry

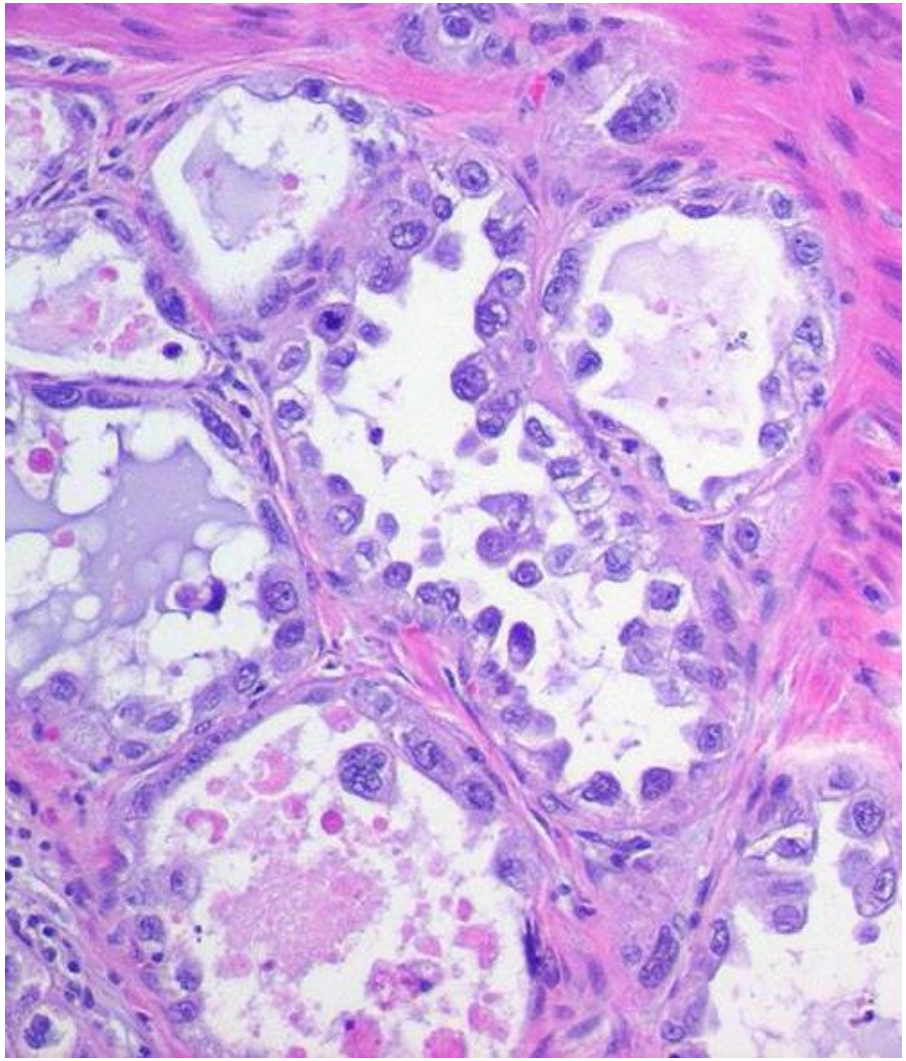
- PAX8, HNFß1, CA-125, p53 positive and high Ki-67
- Endometrioid carcinoma express ER and PR

*Similar morphologies may be seen in urothelium-derived tumours

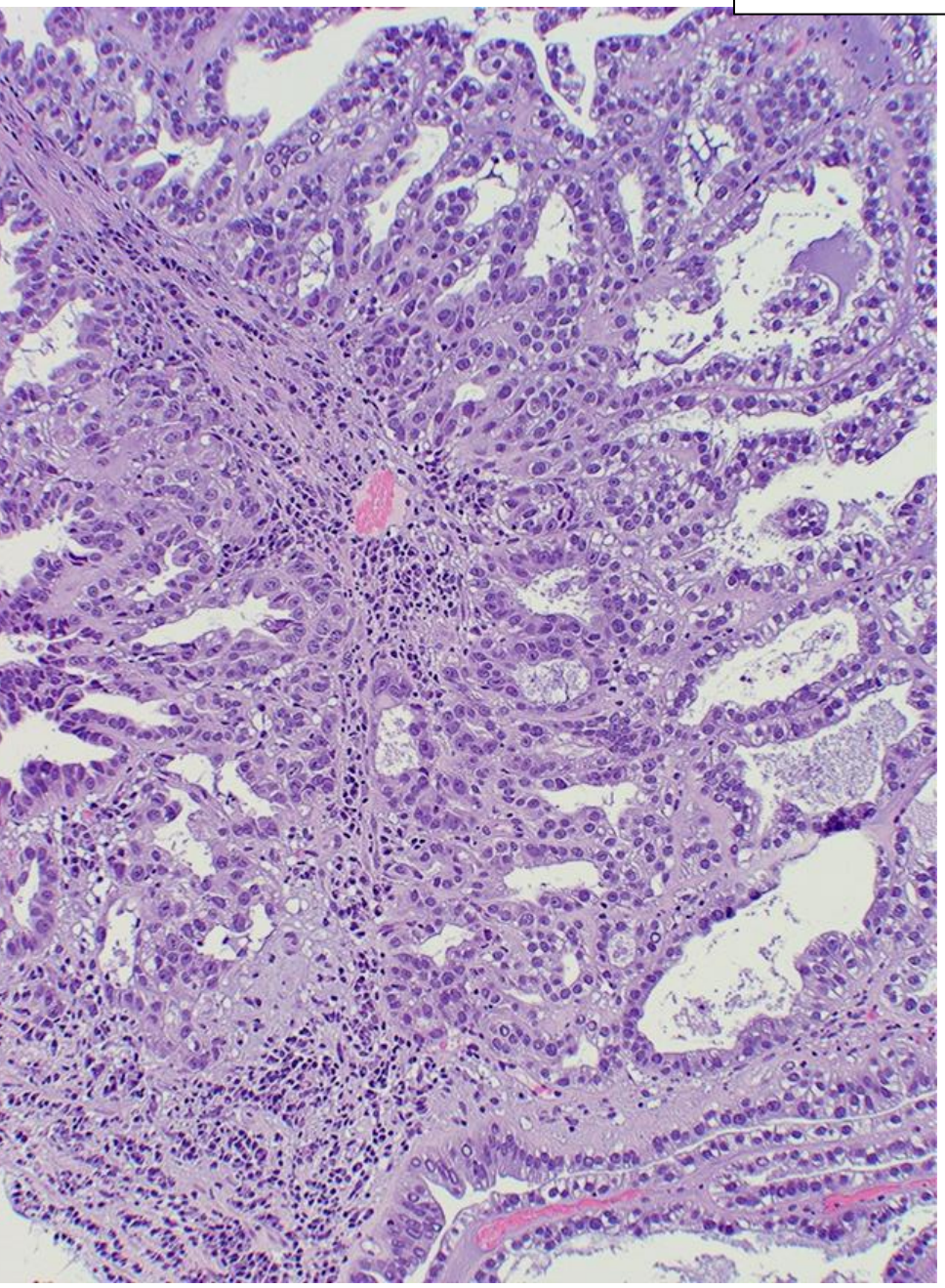
Clear Cell Carcinoma of the Urinary Bladder

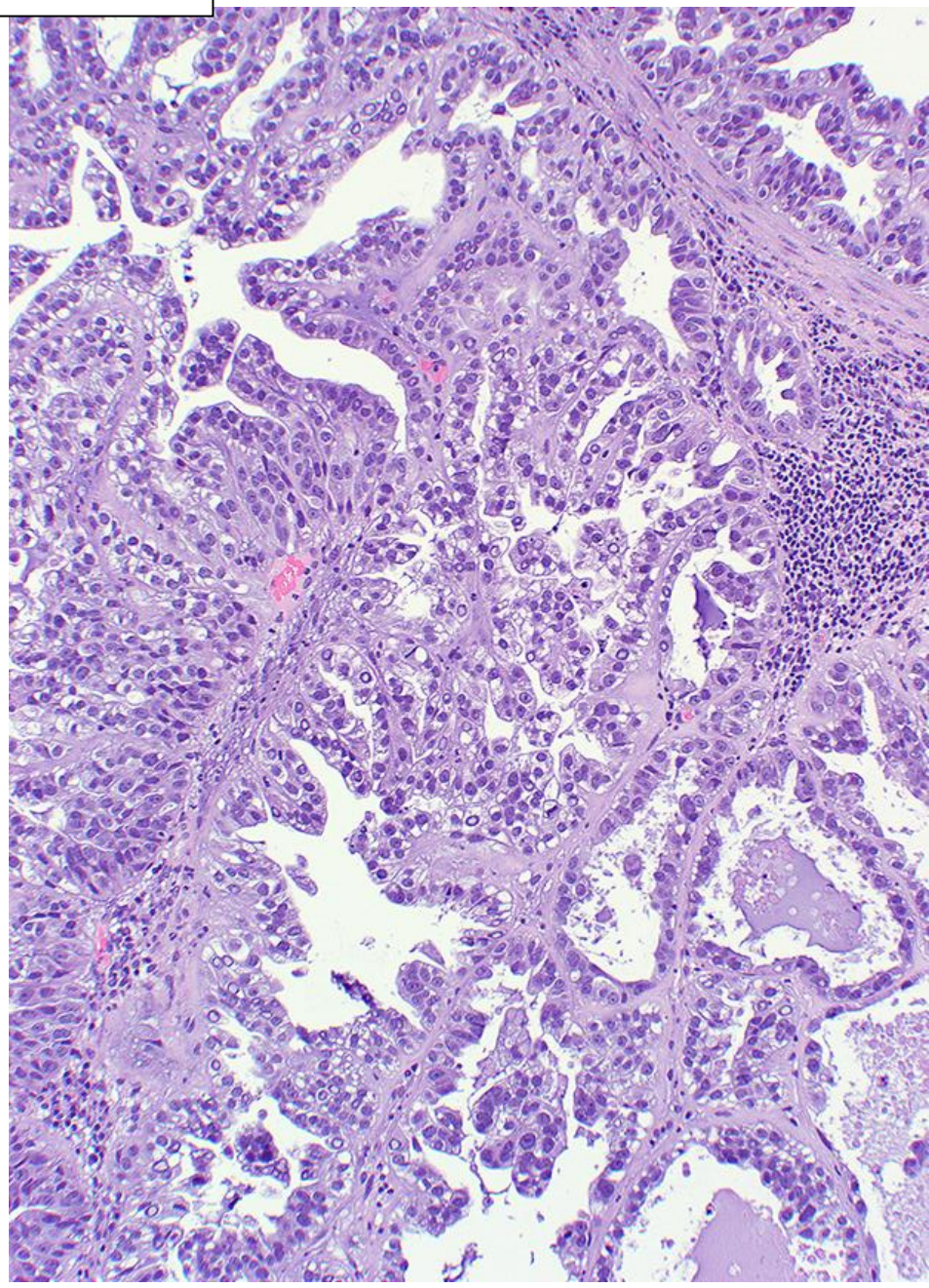
Cases	13
M:F	2:11
Age	22-83 (57)
Endometriosis	2
Mullerian-type cysts	2

Oliva et al. AJSP 26:190,2002.

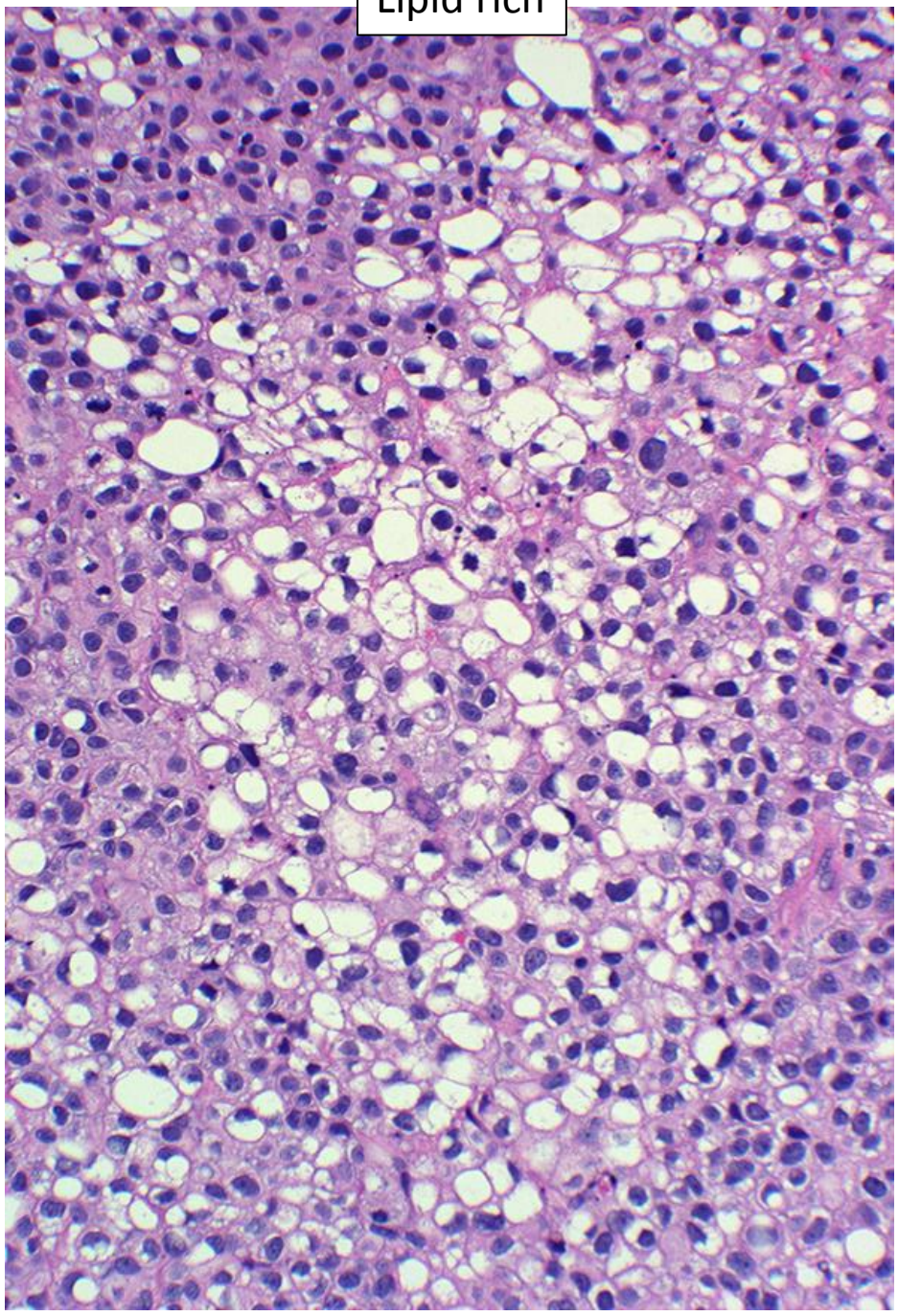


Clear cell carcinoma

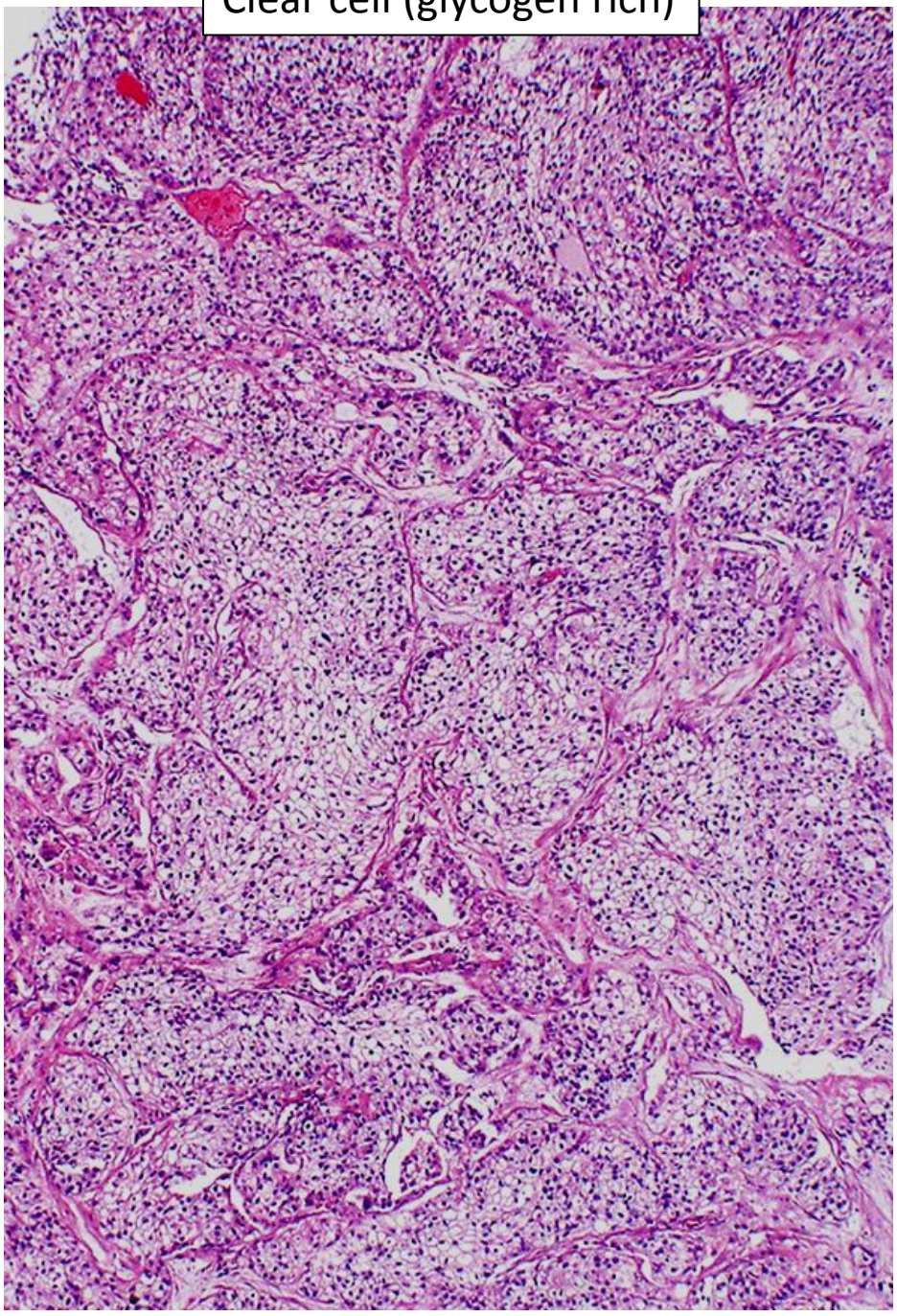




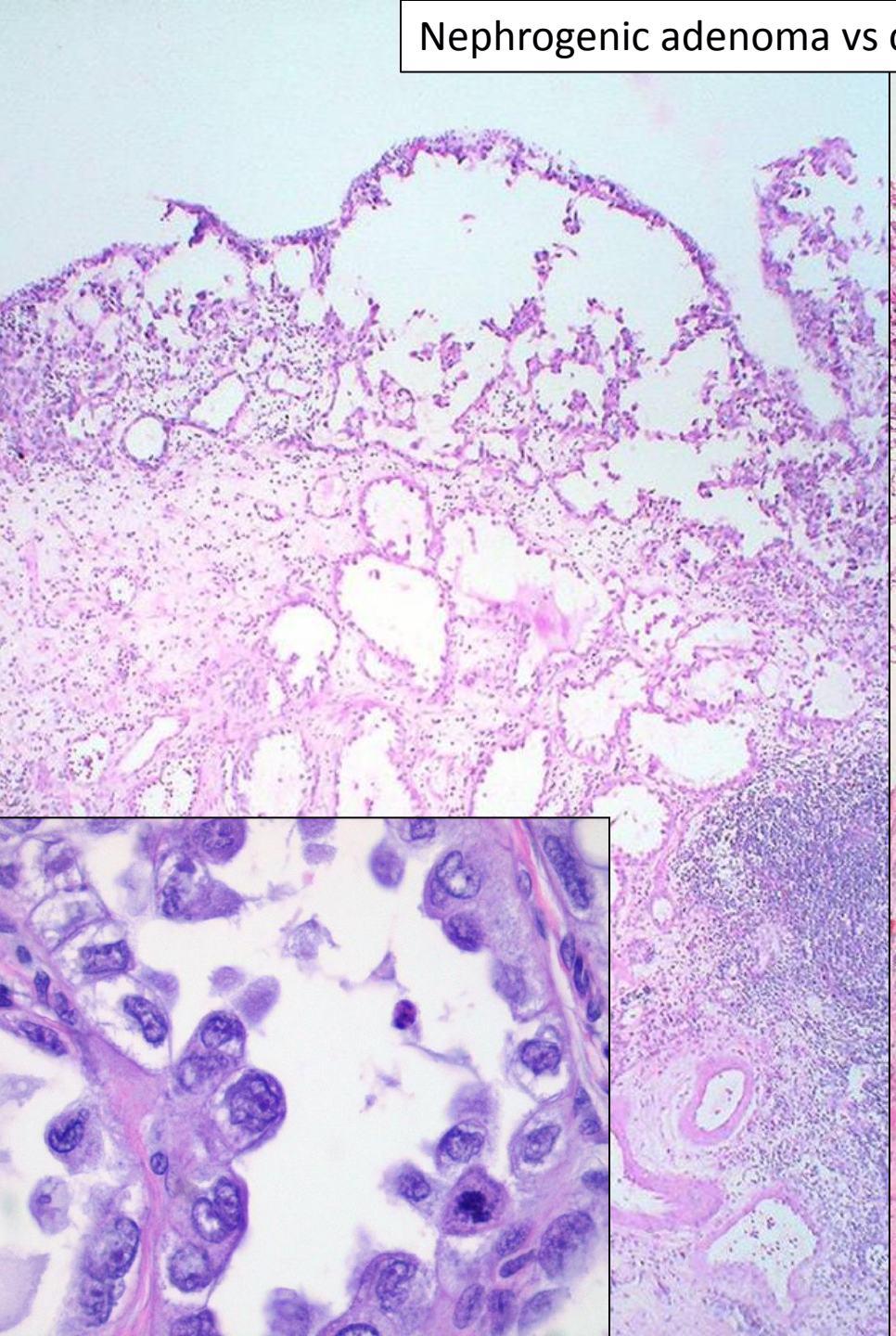
Lipid rich

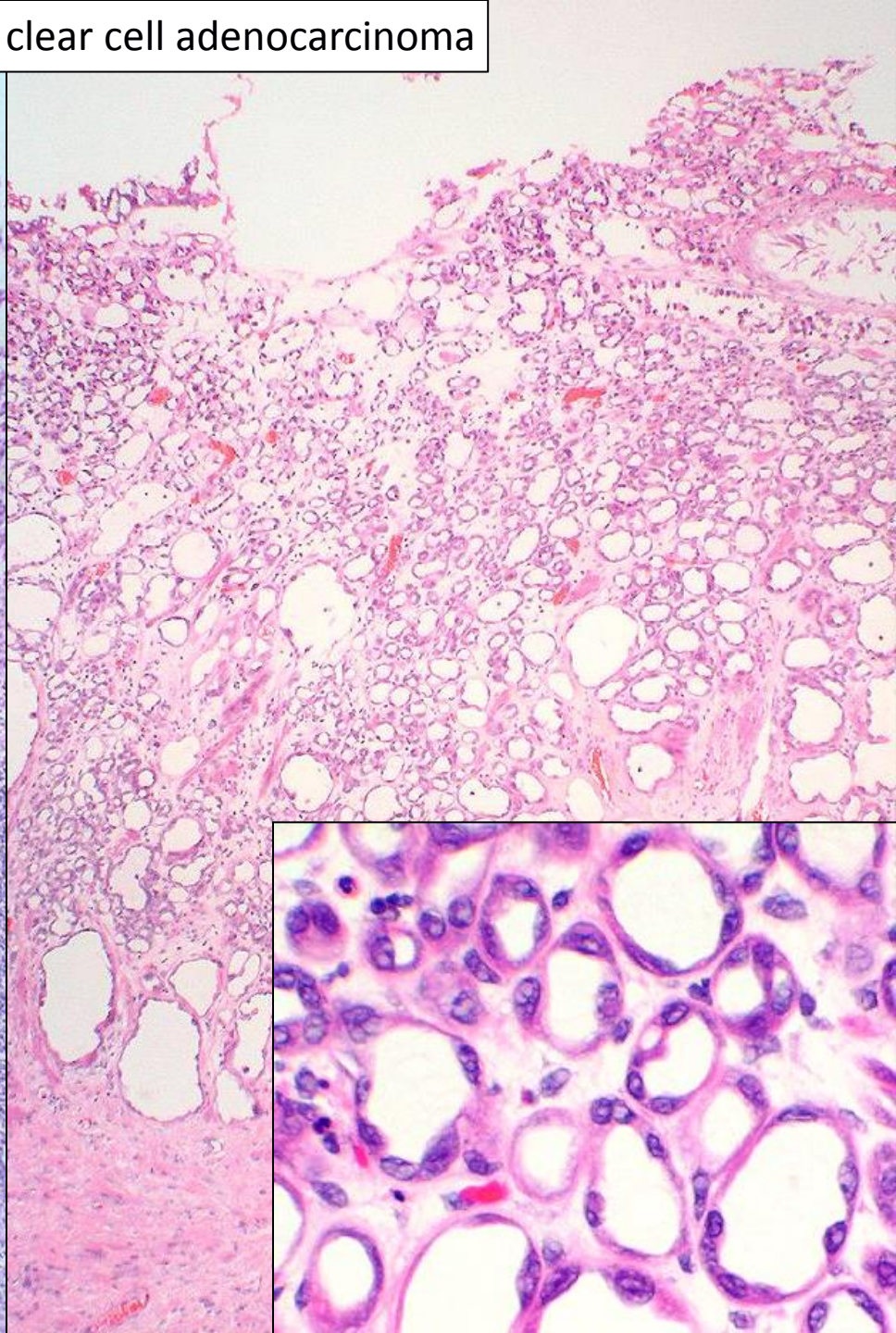


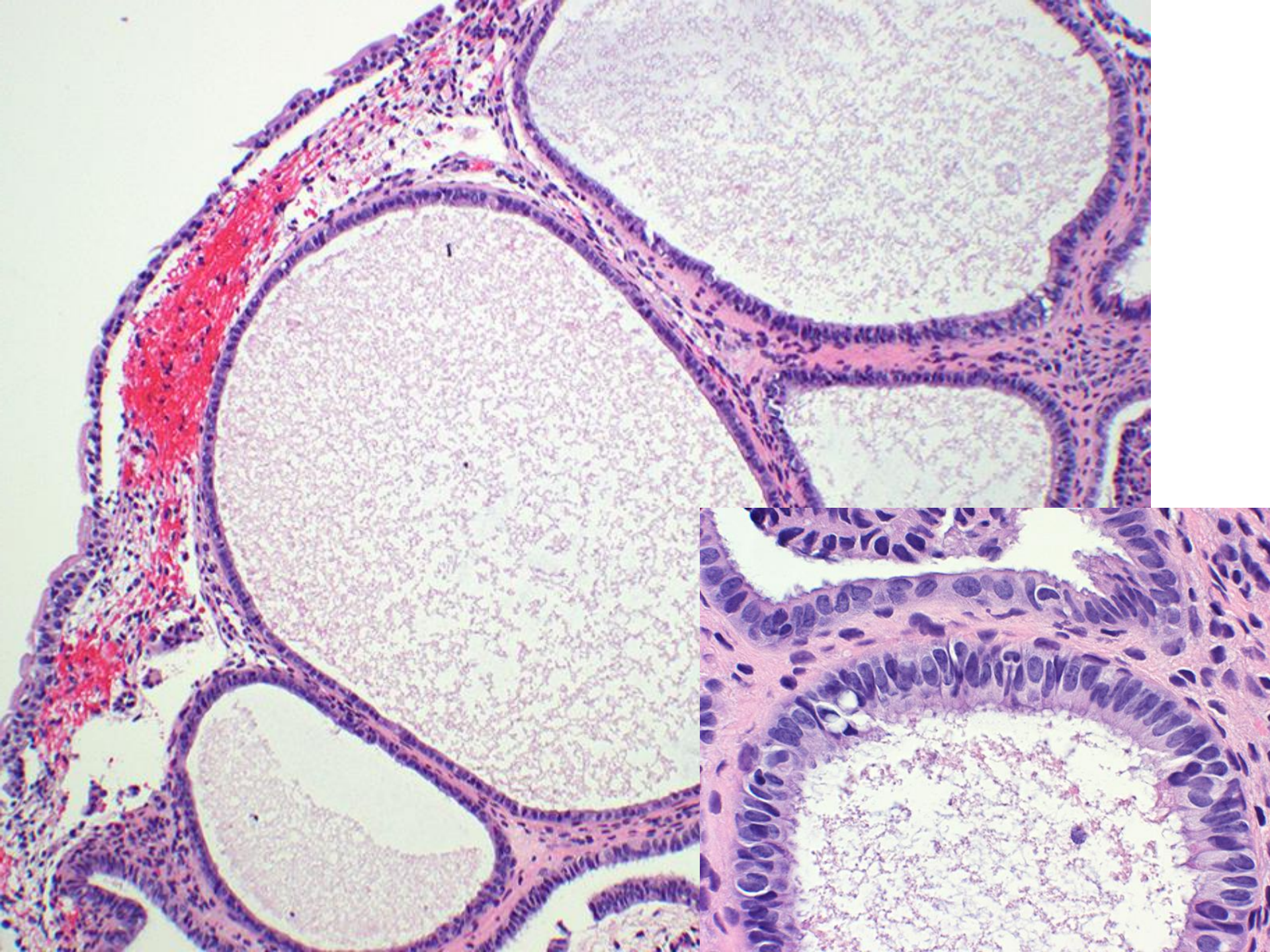
Clear cell (glycogen rich)



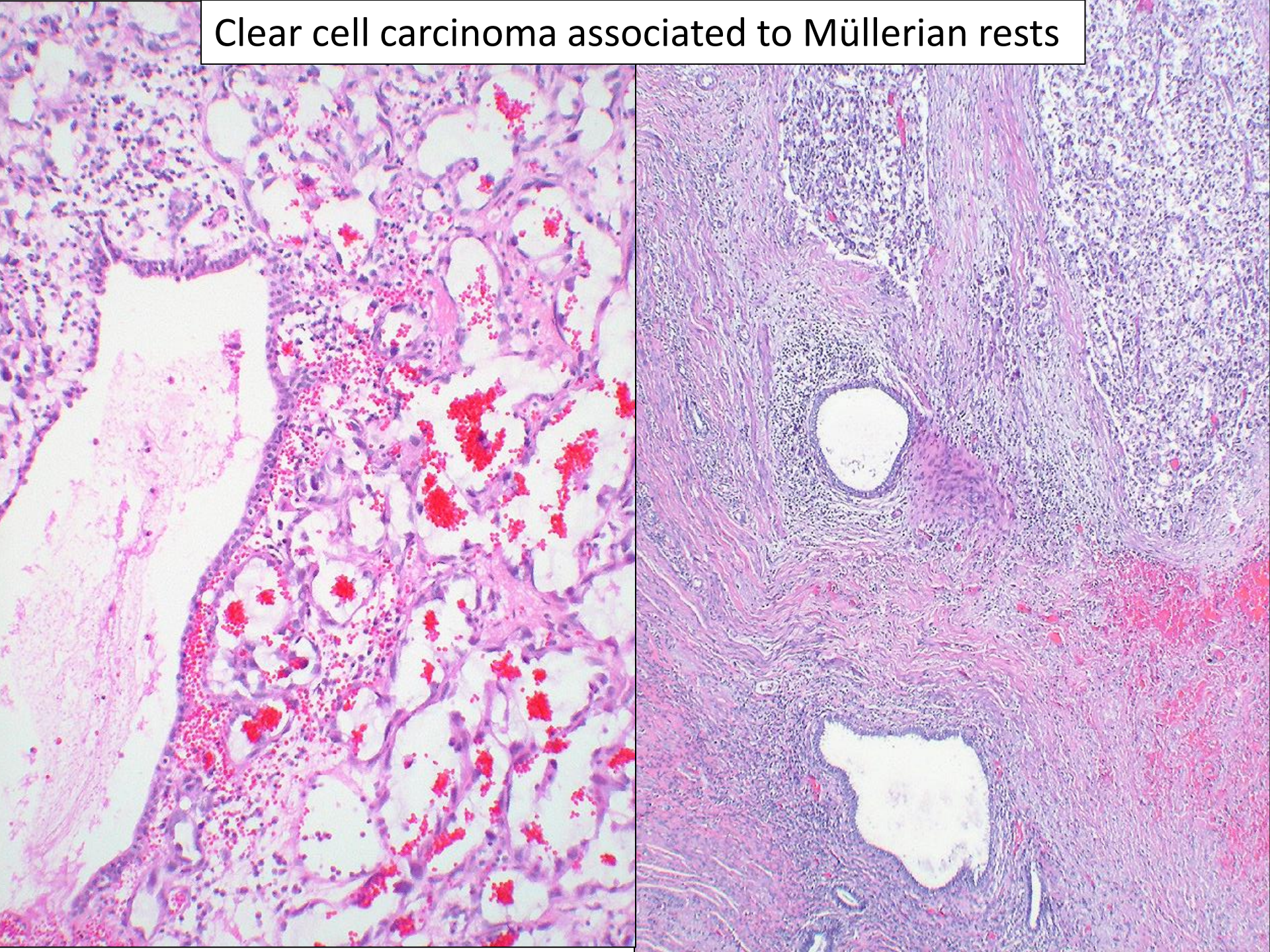
Nephrogenic adenoma vs clear cell adenocarcinoma



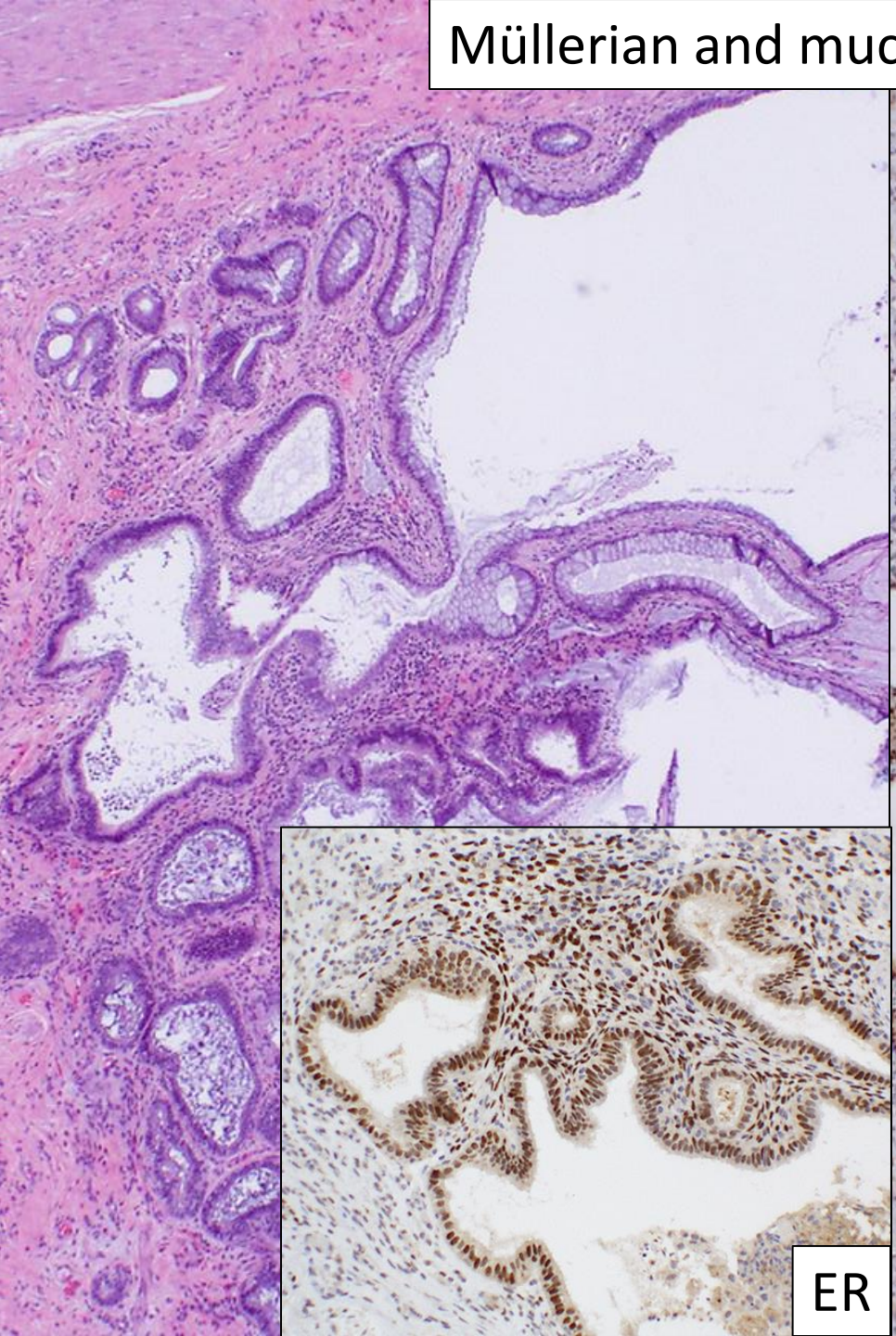


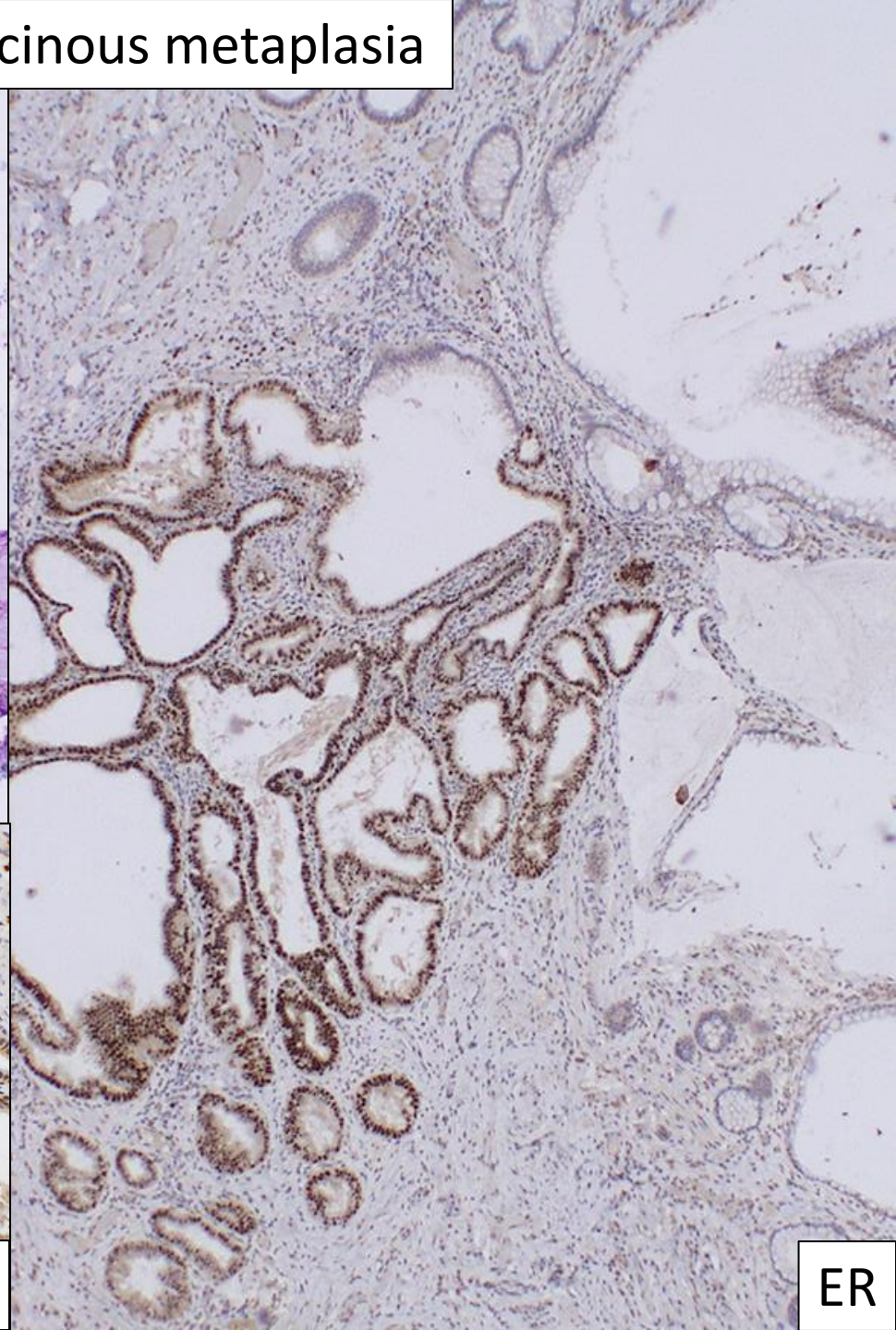


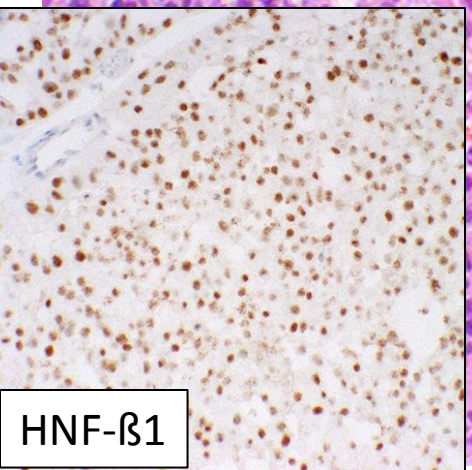
Clear cell carcinoma associated to Müllerian rests

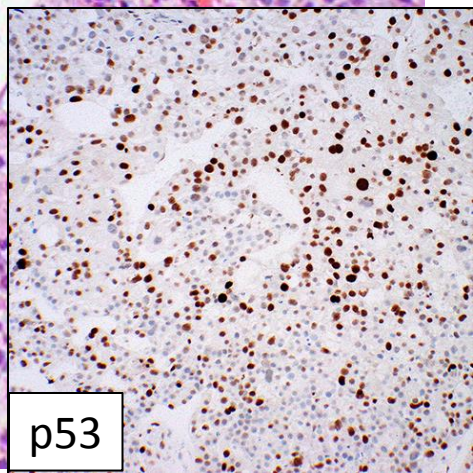


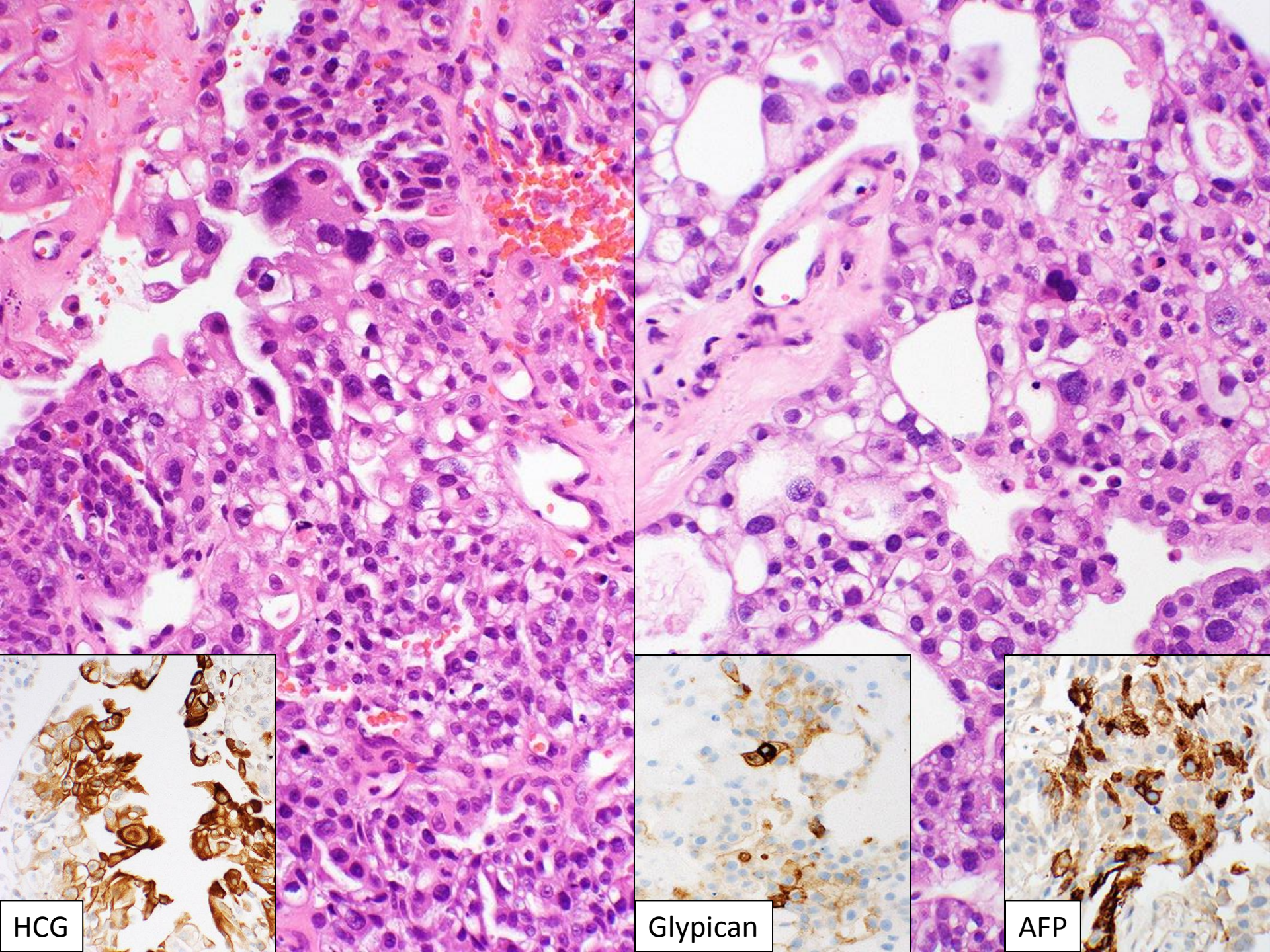
Müllerian and mucinous metaplasia






HNF-ß1


p53


HCG
Glypican
AFP

Clinical and Pathologic Factors Predicting Recurrence and High Risk in Superficial Bladder Cancer

Definition of High Risk:

- High grade Ta disease
- Diffuse carcinoma in situ
- Lamina propria invasion (T1) HG
- Multifocal recurrent superficial disease

Natural History of Superficial Bladder Cancer

176 cases (Ta and T_1) without adjuvant therapy followed for a least 20 years

- 80% experience recurrence
- 22% died of disease
  - 11% Ta
  - 30% T_1

Death from disease was related to:

Grade

# of tumors

# of recurrences

Holmang et al , J Urol, 153: 1995.

WHO/ISUP CLASSIFICATION OF UROTHELIAL TUMORS (2004 and 2010)

PAPILLARY NEOPLASMS

- Papilloma
- Inverted papilloma
- Papillary urothelial neoplasm of low malignant potential
- Papillary urothelial carcinoma, low grade
- Papillary urothelial carcinoma, high grade

Why should we commit to the ISUP/WHO classification?

Adoption of uniform terminology and definitions, based on cytological and architectural disorder

Establishment of detailed criteria for various preneoplastic conditions and tumor grades (AJSP 1998;22:1435-1448)

Elimination of the ambiguity in diagnostic categories in the WHO 1973 system (for example, carcinoma, grade I-II or carcinoma, grade II-III).

Synchronizing terminology with cytology, facilitating cysto-histologic correlation

Creation of a category of papillary neoplasm (PUNLMP) that has a negligible risk of progression although the potential for recurrence requires some level of clinical follow-up.

Defining a group of lesions (high grade) with a high risk of progression and which may be candidates for adjuvant therapy

Recommended by ISUP, WHO, ICCR

ASSESSMENT OF PAPILLARY UROTHELIAL NEOPLASMS

At medium magnification, the tumour pattern gives a predominant impression of:

ORDER
Of architectural and cytological features?

DISORDER
Of architectural and cytological features?

PUNLMP or Papillary Urothelial carcinoma, low grade

VARIATION
Of architectural and cytological features **readily** seen?

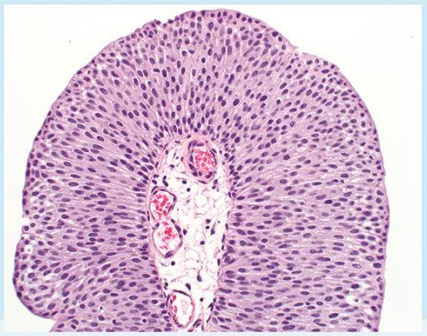
NO

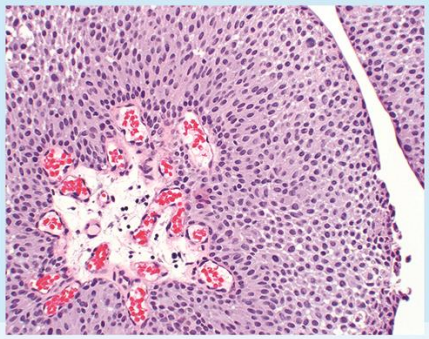
YES

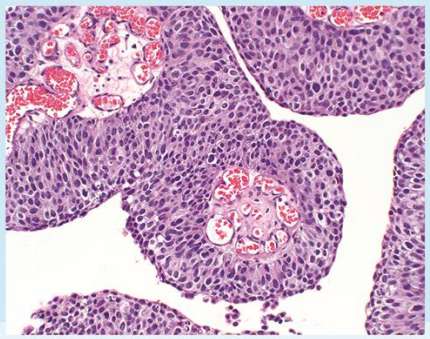
PUNLMP

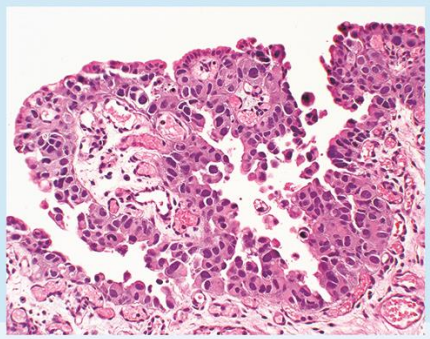
Urothelial carcinoma, low grade

Urothelial carcinoma,high grade









PUNLMP

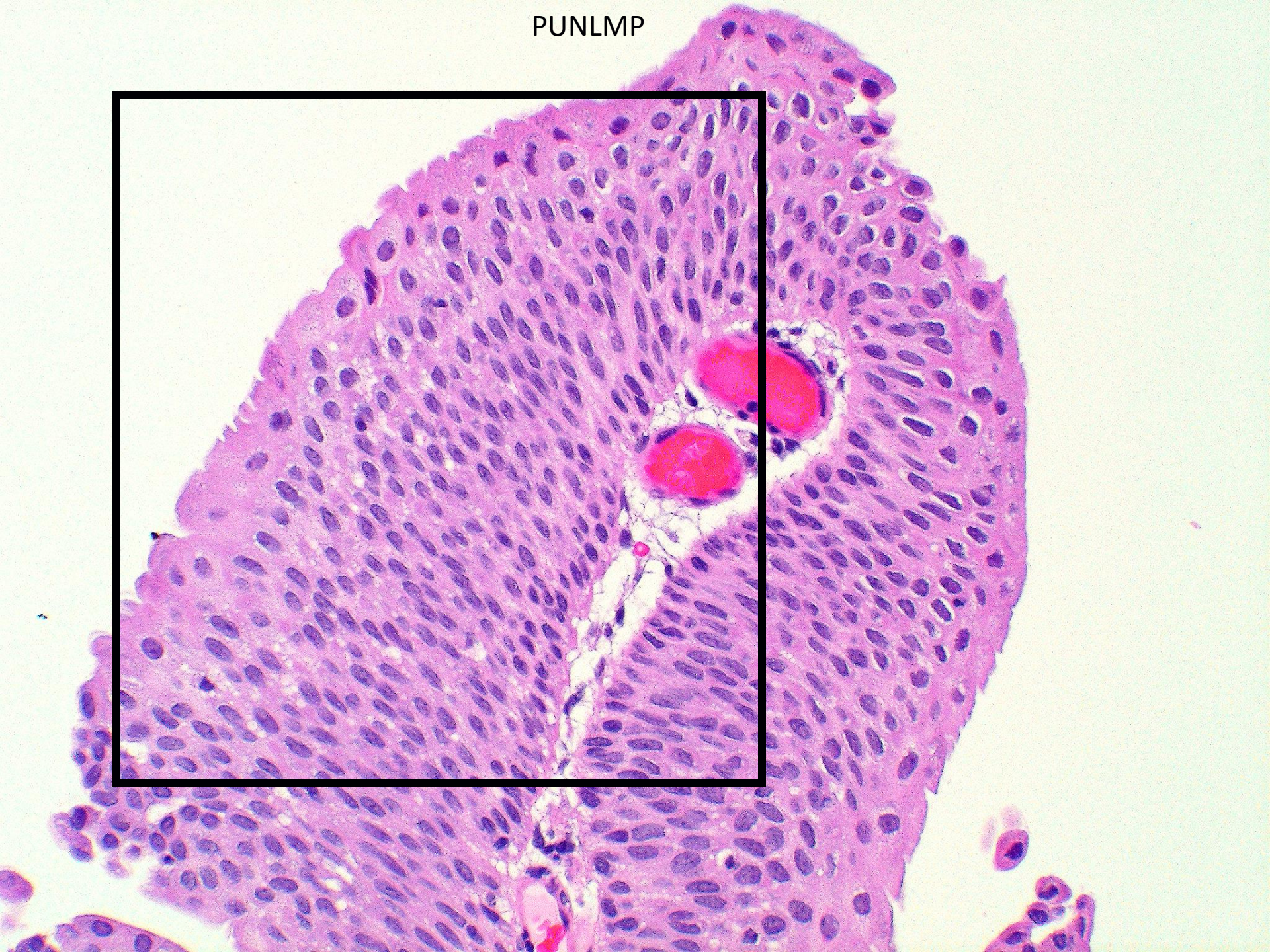


TABLE 5. *Clinical status at last followup*

	No. Papillary Neoplasms of Low Malignant Potential (%)	No. Low Grade Papillary Ca (%)	Total No. WHO I
Alive without bladder tumor*	75 (79)	91 (57)	166 (65)
Alive with bladder tumor†	3 (3)	16 (10)	19 (8)
Dead, no bladder tumor at last followup	14 (15)	31 (19)	45 (18)
Dead, with bladder tumor at last followup	1 (1)	10 (6)	11 (4)
Dead of bladder Ca‡	0	6 (4)	6 (2)
Dead, not examined after diagnosis	2 (2)	6 (4)	8 (3)
Totals	95	160	255

* Followup less than 48 months in 16 patients.
† Followup less than 48 months in 1 patient.
‡ One patient died of treatment complications.

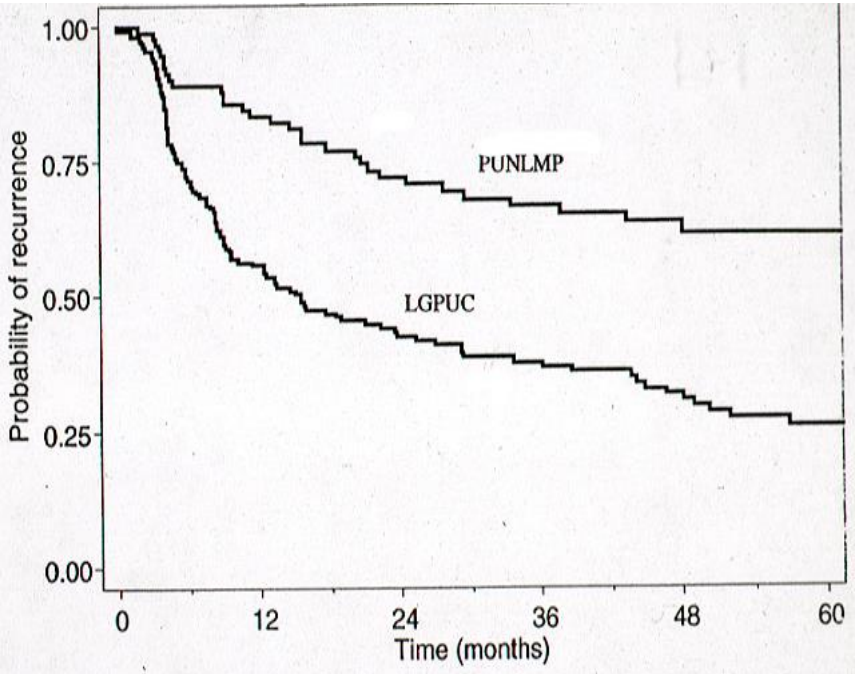
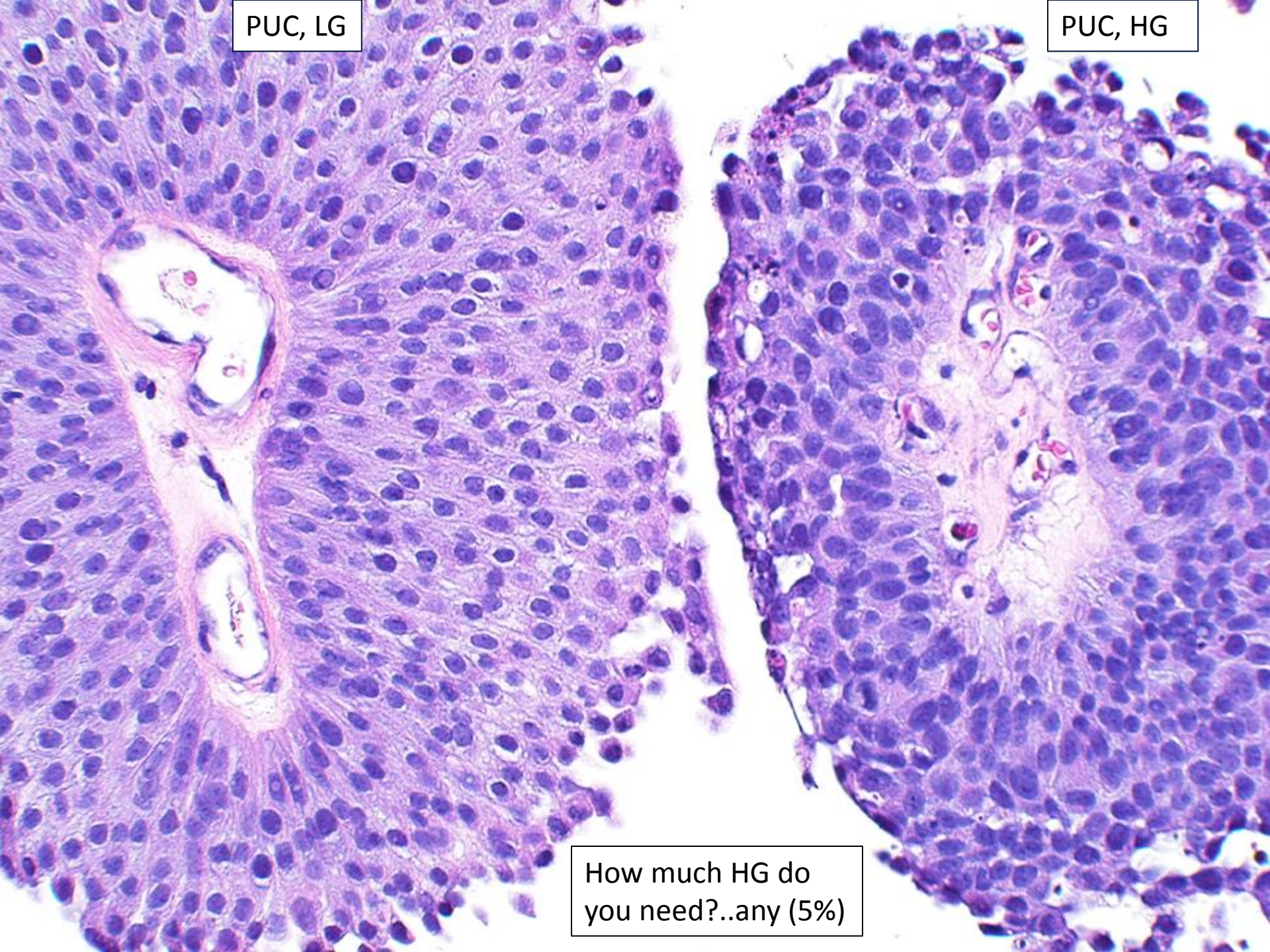
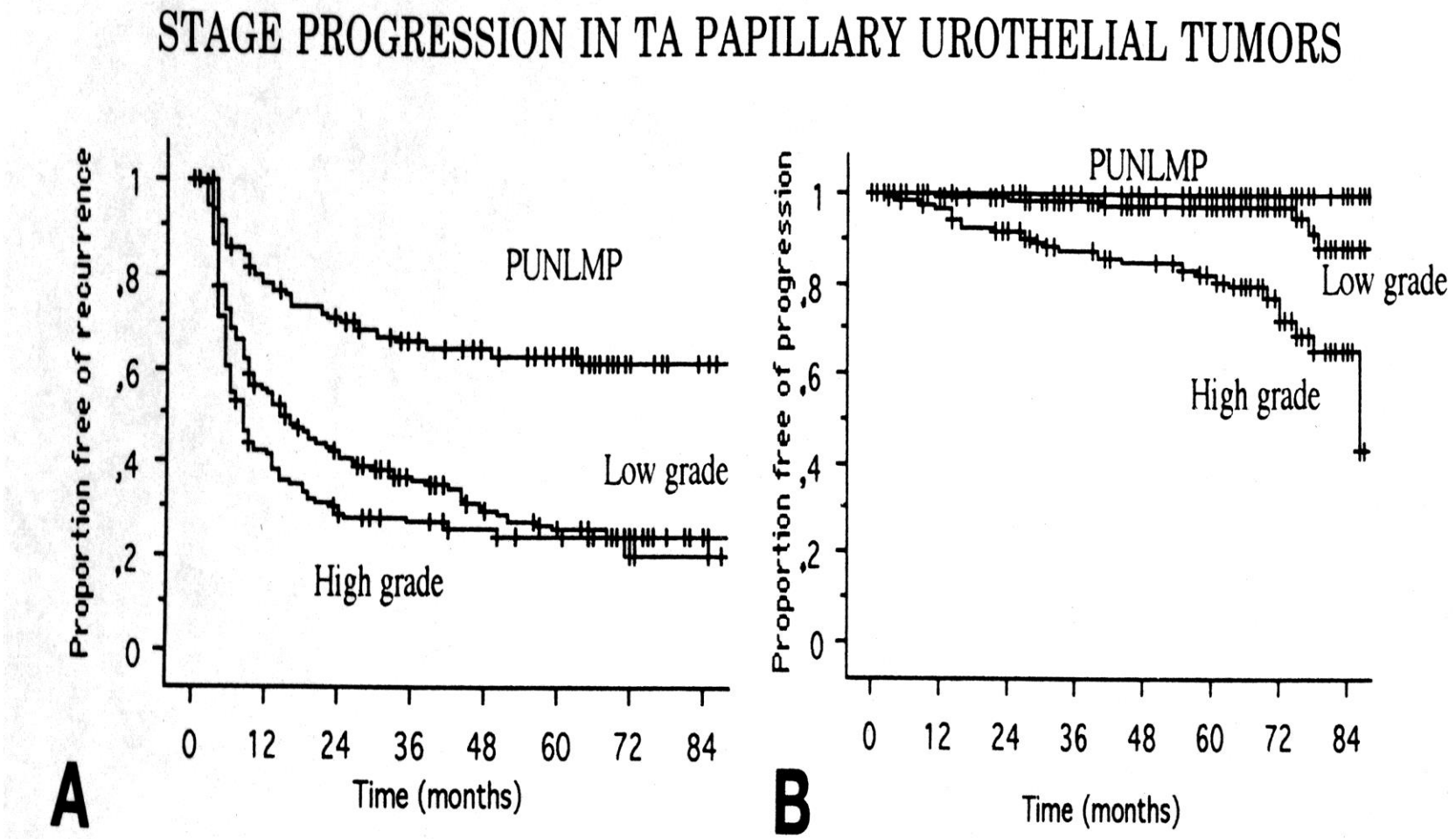


FIG. 3. Relationship between papillary neoplasm of low malignant potential (*PUNLMP*) and low grade papillary carcinoma (*LGPUC*), and interval to first recurrence.

Holmang et al. J Urol. 162:702,1999.


PUC, LG
PUC, HG
How much HG do you need?..any (5%)



A: interval to first recurrence B: interval to progression

Holmang et al. J Urol. 165:1124-1130,2001

EORTC Risk Tables For Stage Ta T1 Bladder Cancer

EORTC Risk Tables for Stage Ta T1 Bladder Cancer

Prior Reccurence Rate
- (•) Primary
- ( ) Recurrent <= 1 per year
- ( ) Recurrent > 1 per year

Number of Tumors
- (•) 1
- ( ) 2 to 7
- ( ) 8 or more

Tumor Diameter
- (•) < 3 cm
- ( ) >= 3 cm

T Category
- (•) Ta
- ( ) T1

Grade (WHO 1973)
- (•) G1
- ( ) G2
- ( ) G3

Concomitant CIS
- (•) No
- ( ) Yes

[Calculate Probabilities] [Clear] [Exit]

	1 Year	2 Years	3 Years	4 Years	5 Years
Probability of Recurrence	0.15	0.21	0.25	0.28	0.31
Probability of Progression	0.002	0.002	0.008	0.008	0.008

Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.

Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

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Grade (WHO 1973)
- ( ) G1
- (•) G2
- ( ) G3

Concomitant CIS
- (•) No
- ( ) Yes

[Calculate Probabilities] [Clear] [Exit]

	1 Year	2 Years	3 Years	4 Years	5 Years
Probability of Recurrence	0.24	0.34	0.40	0.43	0.46
Probability of Progression	0.002	0.002	0.008	0.008	0.008

Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.

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- ( ) G2
- (•) G3

Concomitant CIS
- (•) No
- ( ) Yes

[Calculate Probabilities] [Clear] [Exit]

	1 Year	2 Years	3 Years	4 Years	5 Years
Probability of Recurrence	0.24	0.34	0.40	0.43	0.46
Probability of Progression	0.01	0.03	0.04	0.05	0.06

Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.

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EORTC Risk Tables For Stage Ta T1 Bladder Cancer

EORTC Risk Tables for Stage Ta T1 Bladder Cancer

Prior Reccurence Rate
- ○ Primary
- ◉ Recurrent <= 1 per year
- ○ Recurrent > 1 per year

Number of Tumors
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- ◉ 2 to 7
- ○ 8 or more

Tumor Diameter
- ◉ < 3 cm
- ○ >= 3 cm

T Category
- ◉ Ta
- ○ T1

Grade (WHO 1973)
- ◉ G1
- ○ G2
- ○ G3

Concomitant CIS
- ◉ No
- ○ Yes

Calculate Probabilities | Clear | Exit

	1 Year	2 Years	3 Years	4 Years	5 Years
Probability of Recurrence	0.38	0.51	0.56	0.59	0.62
Probability of Progression	0.01	0.03	0.04	0.05	0.06

Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.

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Grade (WHO 1973)
○ G1
◉ G2
○ G3

Concomitant CIS
◉ No
○ Yes

Calculate Probabilities | Clear | Exit

	1 Year	2 Years	3 Years	4 Years	5 Years
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◉ Ta
○ T1

Grade (WHO 1973)
○ G1
○ G2
◉ G3

Concomitant CIS
◉ No
○ Yes

Calculate Probabilities | Clear | Exit

	1 Year	2 Years	3 Years	4 Years	5 Years
Probability of Recurrence	0.38	0.51	0.56	0.59	0.62
Probability of Progression	0.05	0.08	0.11	0.15	0.17

Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. European Urology 49: 466-477, 2006.

Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

GRADING OF PAPILLARY UROTHELIAL TUMORS

- Good interobserver concordance within a single institution ($\kappa = 0.5 – 0.65$)
- Fair to poor interobserver concordance globally
  - incidence of PUNLMP: 0-12%
  - PUNLMP vs LG
  - LG vs HG
- Absence of data* on the use of markers to grade lesions in a clinically significant manner

Table 1. Interobserver variability based on comparing 5 categories	Before biomarker evaluation	After biomarker evaluation
Free-marginal kappa	0.64	0.74
Complete agreement-6/6 pathologists	21/50 cases (42%)	25/45 cases (55%)
Majority agreement-4/6 pathologists	42/50 cases (84%)	42/45 cases (93%)

Mehra R et al, USCAP, 2012

Combining molecular and pathologic data to prognosticate non-muscle-invasive bladder cancer

Bas W.G. van Rhijn

Urologic Oncology: Seminars and Original Investigations, Volume 30, Issue 4, 2012, 518–523

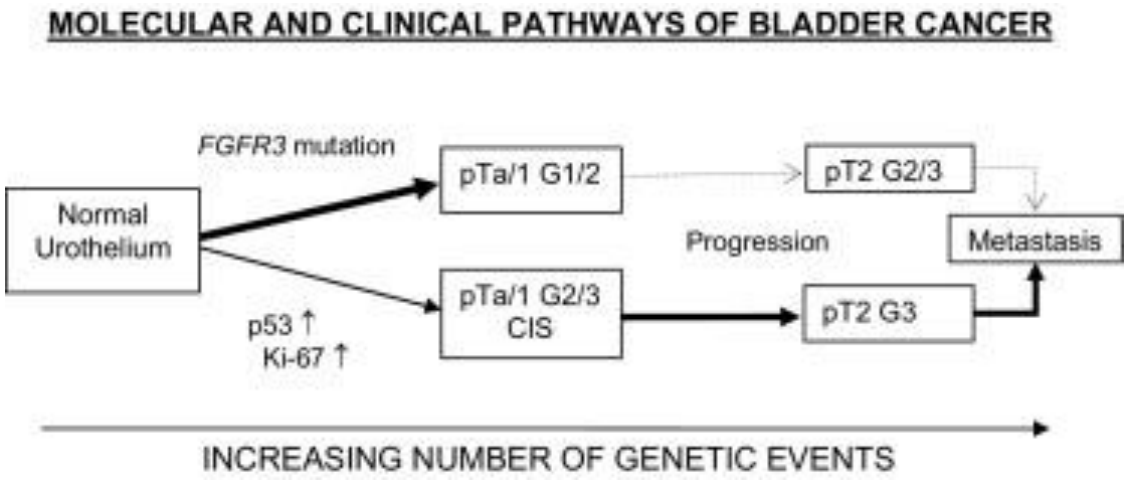
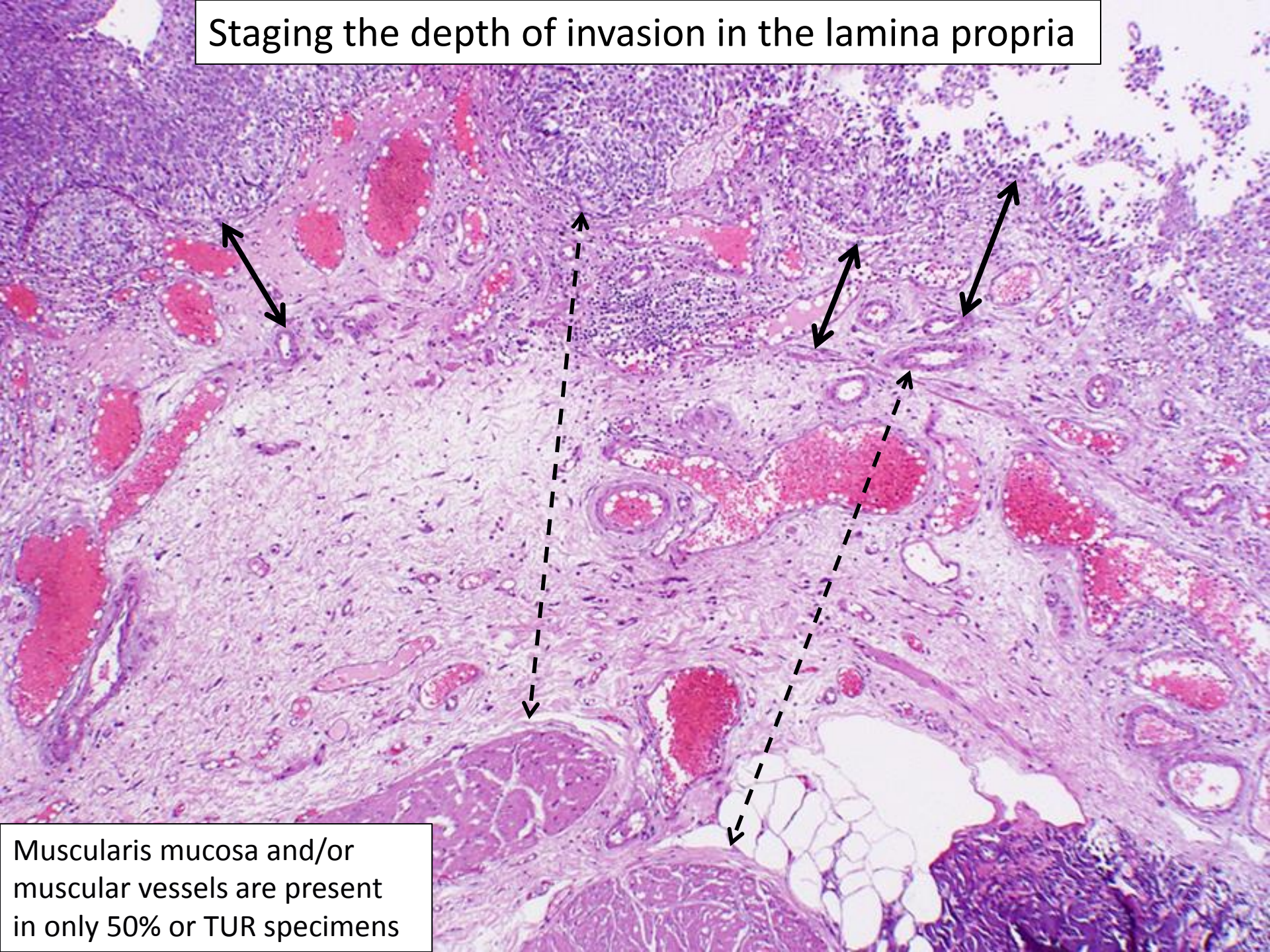


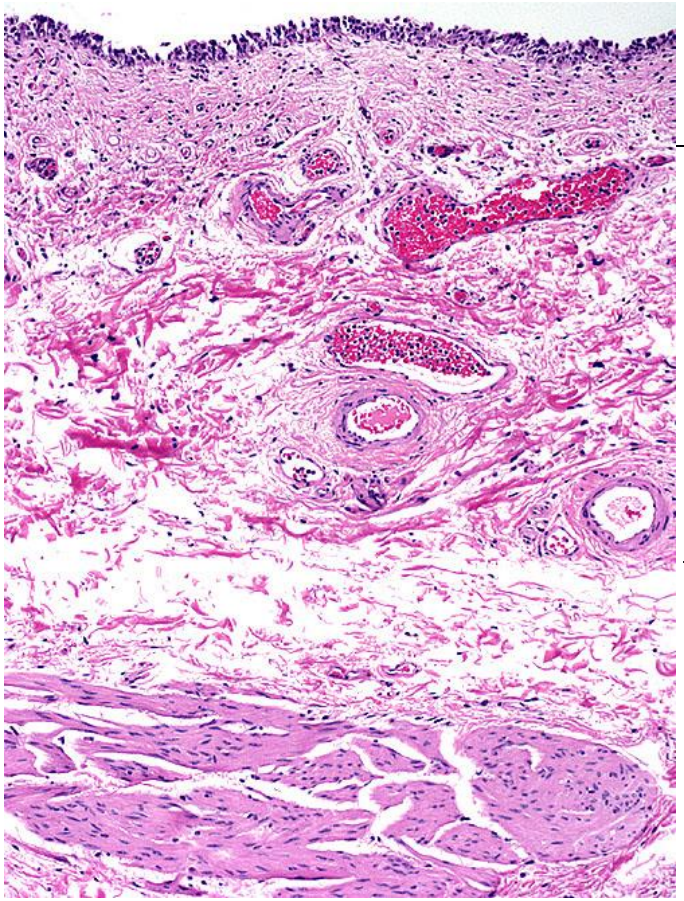
Figure 1: Simplified two-pathway model for disease pathogenesis of BC. This figure shows the combination of molecular and pathologic data in non-muscle-invasive BC. Arrow thickness is indicative for the percentage of tumors. The *FGFR3* mutation is largely responsible for the favorable molecular pathway in NMI-BC. Among many others, P53 and Ki-67 overexpression are examples of unfavorable NMI-BC. Molecular alterations, not included in the figure in the interest of clarity, are represented by the bottom arrow. *FGFR3* = fibroblast growth factor receptor 3 gene; mt = mutation; ↑ = elevated expression (Ki-67, p53); CIS = carcinoma in situ.

Staging the depth of invasion in the lamina propria



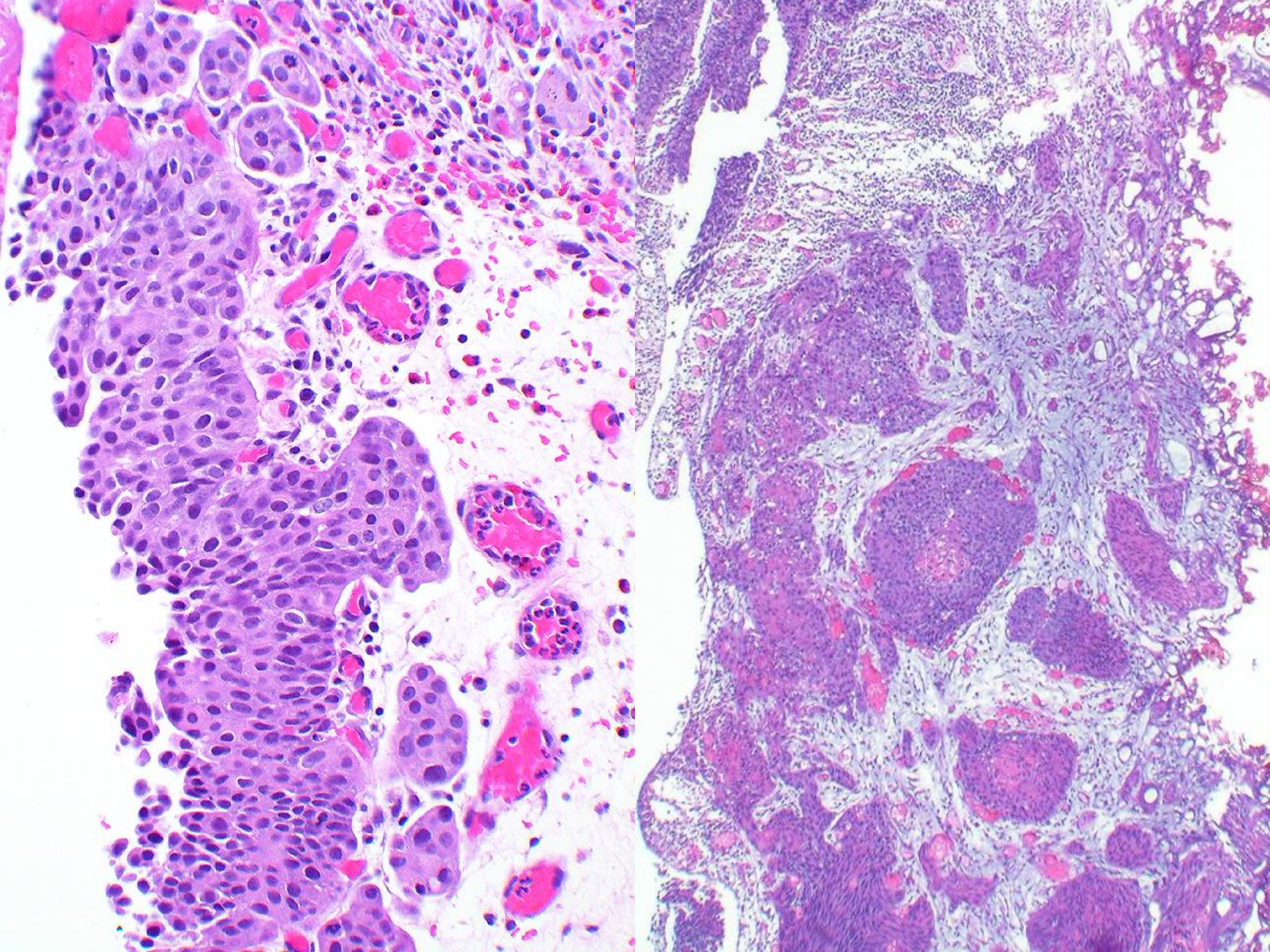
Muscularis mucosa and/or
muscular vessels are present
in only 50% or TUR specimens

Subclassification relative to MM – different schema with overlapping terminology

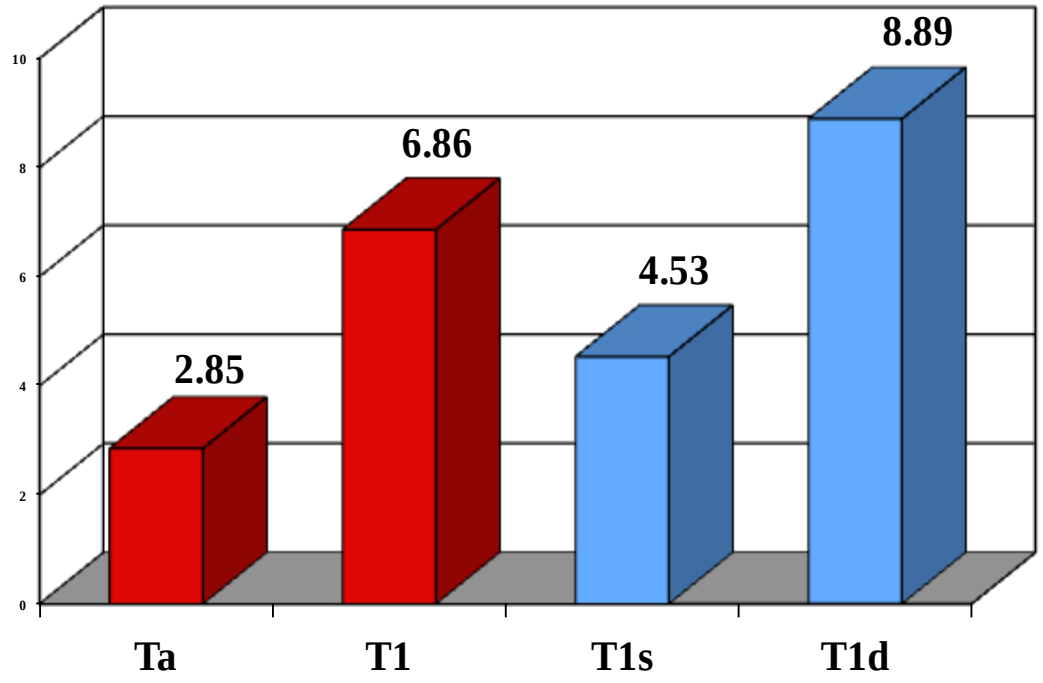


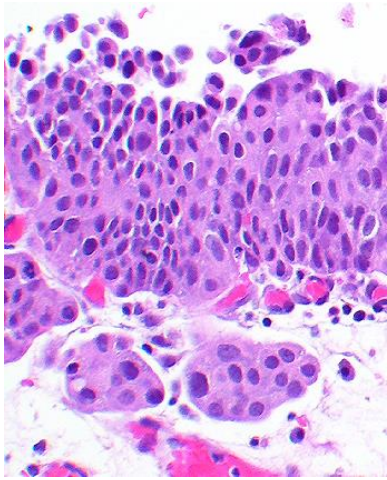
pT1a	pT1m		pT1a (Czech)	pT1
	pT1e	pT1a (French)		
pT1b (MM or VP)			pT1b	
pT1c		pT1b		

- Microinvasive (≤0.5 mm vs >0.5 mm; pT1e versus pT1m)
- Above, within and below the muscularis muscose (pT1a, pT1b, pT1c)
- Above and into the MM versus below (pT1a, pT1b)
- Actual depth of invasion using micrometer (basement membrane to deepest tumor)
- Greatest dimension of invasive focus
- # fragments with invasion (also unifocal versus multifocal)



CARCINOMA OF THE BLADDER
Tumor Stage vs Progression





Progression per 100 person/year

MEMORIAL SLOAN-KETTERING CANCER CENTER
ESTABLISHED 1884

Example of pT1e/pT1m

European Association of Urology

Bladder Cancer

A New and Highly Prognostic System to Discern T1 Bladder Cancer Substage

Bas W.G. van Rhijn [a,b,], Theo H. van der Kwast [c,d], Sultan S. Alkhateeb [a], Neil E. Fleshner [a], Geert J.L.H. van Leenders [d], Peter J. Bostrom [a], Madelon N.M. van der Aa [b], David M. Kakiashvili [a], Chris H. Bangma [b], Michael A.S. Jewett [a], Alexandre R. Zlotta [a,e]*

- ≤ 0.5 mm single focus (pT1m) versus
  > 0.5 mm or multifocal (pT1e)
- Doesn't need MM/VP landmark
- Showed pT1m/e significant for PFS and DSS but not the pT1a/b/c system

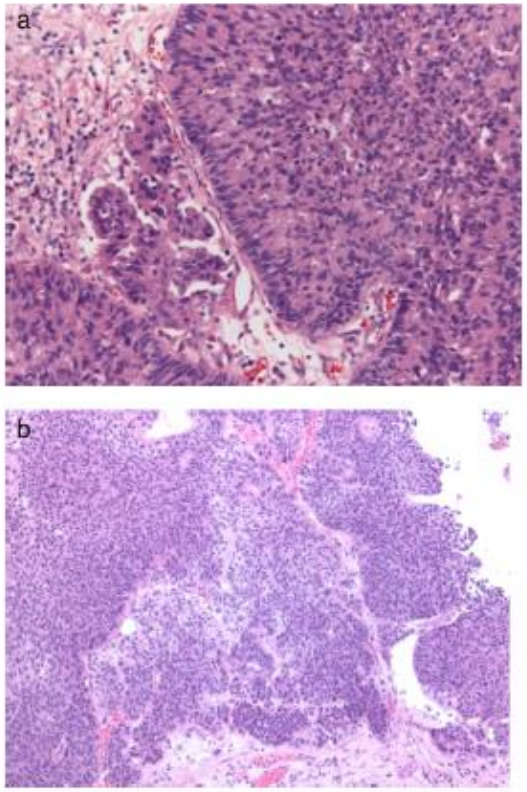


Fig. 1 – Examples of T1m and T1e substaging. (a) T1m: a single focus of lamina propria invasion ≤0.5 mm (within one high-power field, objective ×40); (b) T1e: specimens showing a >0.5-mm lamina propria invasion or multiple microinvasive areas. In this example, the lamina propria invasion is >0.5 mm.

Outcomes

Urological Oncology

Prognostic Significance of Substaging according to the Depth of Lamina Propria Invasion in Primary T1 Transitional Cell Carcinoma of the Bladder

Ji Yong Lee*, Hee Jae Joo[1]*, Dae Sung Cho[2], Sun Il Kim, Hyun Soo Ahn, Se Joong Kim

Departments of Urology and [1]Pathology, Ajou University School of Medicine, Suwon, [2]Department of Urology, Bundang Jesaeng Hospital, Seongnam, Korea

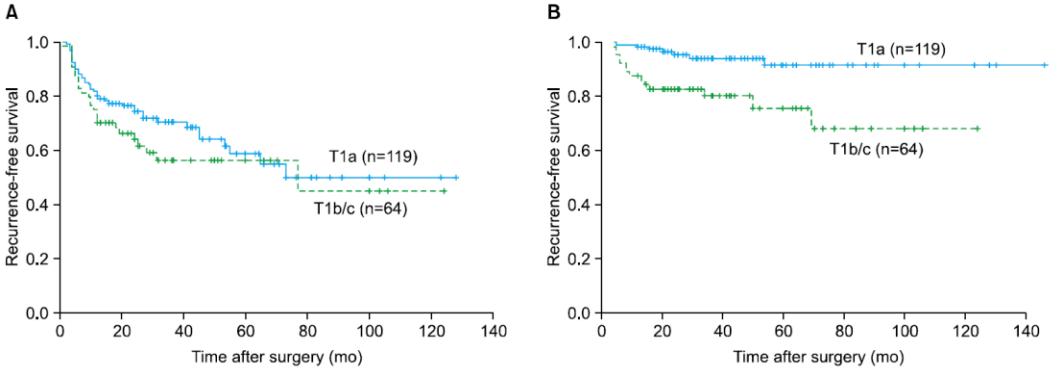


FIG. 2. Kaplan-Meier estimates of recurrence-free (A) and progression-free (B) survival according to the depth of lamina propria invasion in primary T1 transitional cell carcinoma (TCC) of the bladder. Whereas the recurrence-free interval was similar for both groups, the progression-free interval was significantly shorter in patients with T1b/c compared with T1a tumors.

Original contribution

Prognostic factors in T1 bladder urothelial carcinoma: the value of recording millimetric depth of invasion, diameter of invasive carcinoma, and muscularis mucosa invasion

Fadi Brimo MD[a,*], Chenbo Wu[a], Nebras Zeizafoun MD[b], Simon Tanguay MD[c], Armen Aprikian MD[c], Jose Joao Mansure PhD[c], Wassim Kassouf MD[c]

Table 3 Recorded pathologic variables in relation to WFS

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Maximum tumor depth (mm)	2.94	1.86-4.66	.0001	3.58	1.87-6.85	.0001
Maximum tumor diameter (mm)	1.38	1.16-1.64	.0001	1.41	1.07-1.87	.016
Muscularis mucosa invasion	21.2	4.61-97.46	.0001	18.79	3.14-112.35	.001
No. of chips containing invasion	1.11	1.03-1.20	.008	0.98	0.81-1.20	.896
Total diameter of invasive carcinoma (mm)	1.05	1.02-1.08	.0001	1.04	0.96-1.14	.28
Lymphovascular invasion	1.83	0.53-6.39	.341	0.51	0.07-3.77	.506
CIS	1.65	0.64-4.24	.30	1.27	0.43-3.77	.371
Adverse histologic subtype	11.57	3.03-44.12	.0001	3.97	0.53-29.47	.178

Abbreviation: CI, confidence interval.

Recommendation
*8th ed AJCC and 4th ed WHO

- Try to substage the lamina propria
- Best system may be to substage pT1 as
  - above MM (would also include microinvasive disease)
  - involving MM and beyond
  - Is invasion multifocal?
  - Is invasion extensive?

Thank you!