Az urotheliális daganatok „legújabb” nomenklatúrája, nemzetközi visszhangja

Székely Eszter
S.E. II. Patológiai Intézet

WHO 1973

- Grade 1 "Tumors with the least degree of cellular anaplasia compatible with a diagnosis of malignancy"
- Grade 2 carcinoma Histologic features between grades 1 and 3
- Grade 3 carcinoma "Tumors with the most severe degrees of cellular anaplasia"

WHO 1998/ISUP

Papilloma Discrete papillary growth with a central fibrovascular core lined by urothelium of normal thickness and

cytology; no need for counting number of cell layers

Papillary urothelial neoplasm Papillae delicate, generally discrete

of low malignant potential Umbrella cells present

(PUNLMP) Polarity normal, any thickness; cells uniform, cohesive, may be enlarged

Nuclei elongated or round to oval with fine chromatin, absent or inconspicuous nucleoli; mitosis rare and

basal in location

Low-grade carcinoma Papillae often fused and branching

Umbrella cells usually present

Generally orderly but with focal crowding, cells cohesive

Nuclei enlarged with slight variation in size and shape; chromatin variable, and nucleoli usually inconspicuous;

mitosis occasional and at any level

High-grade carcinoma Papillae fused and branching

Umbrella cells may be absent

Predominantly disorderly with marked loss of polarity, often dyscohesive

Nuclei enlarged with marked pleomorphism; chromatin coarse and variable; nucleoli multiple and prominent;

mitosis frequent and at any level

- **WHO 1973**
- Grade 1 "Tumors with the least degree of cellular anaplasia compatible with a diagnosis of malignancy"
- Grade 2 carcinoma Histologic features between grades 1 and 3
- Grade 3 carcinoma "Tumors with the most severe degrees of cellular anaplasia"

WHO 1998/ISUP

Papilloma Discrete papillary growth with a central fibrovascular core lined by urothelium of normal thickness and

cytology; no need for counting number of cell layers

Papillary urothelial neoplasm Papillae delicate, generally discrete

of low malignant potential Umbrella cells present

(PUNLMP) Polarity normal, any thickness; cells uniform, cohesive, may be enlarged

Nuclei elongated or round to oval with fine chromatin, absent or inconspicuous nucleoli; mitosis rare and

basal in location

Low-grade carcinoma Papillae often fused and branching

Umbrella cells usually present

Generally orderly but with focal crowding, cells cohesive

Nuclei enlarged with slight variation in size and shape; chromatin variable, and nucleoli usually inconspicuous;

mitosis occasional and at any level

High-grade carcinoma Papillae fused and branching

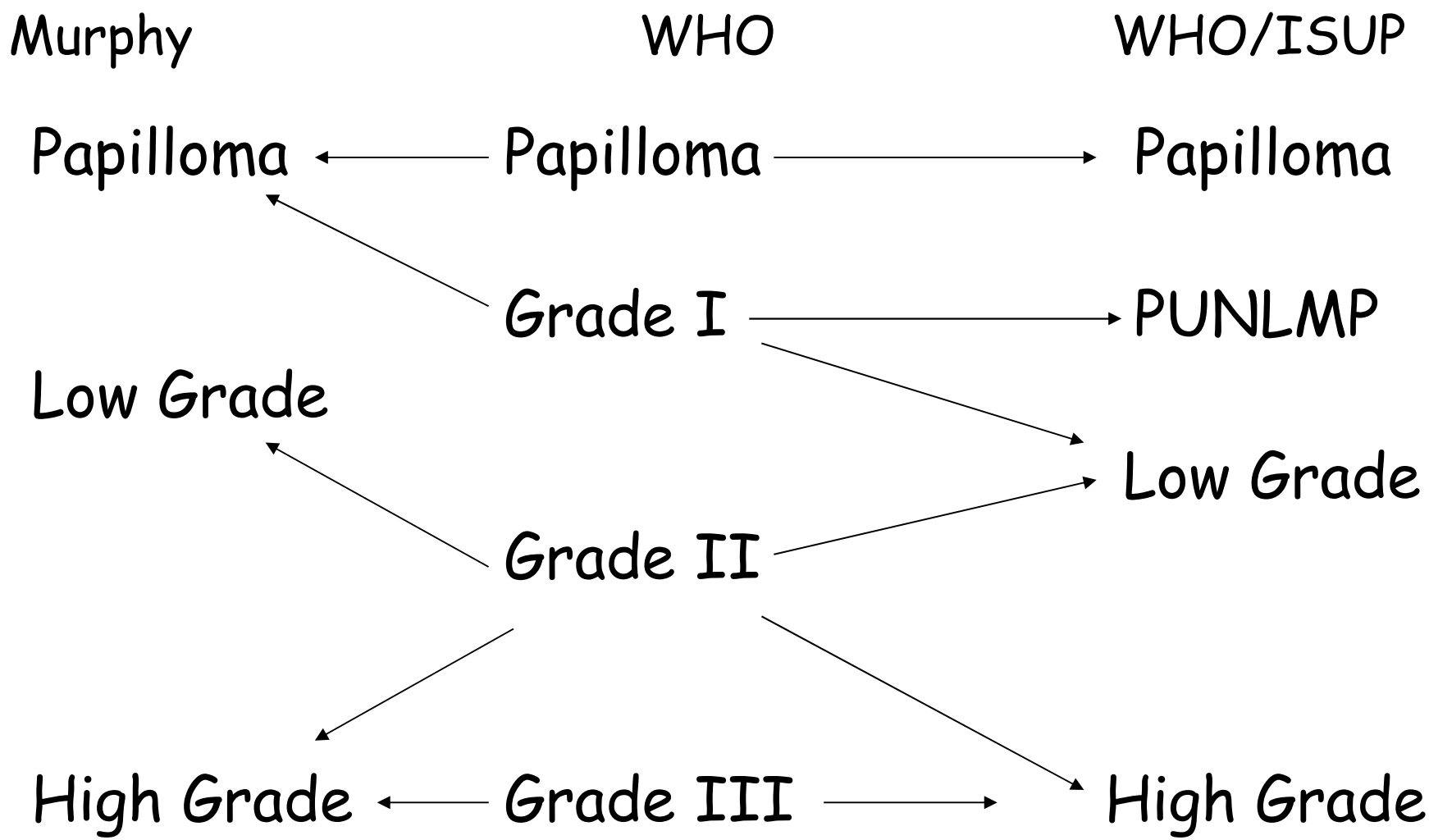
Umbrella cells may be absent

Predominantly disorderly with marked loss of polarity, often dyscohesive

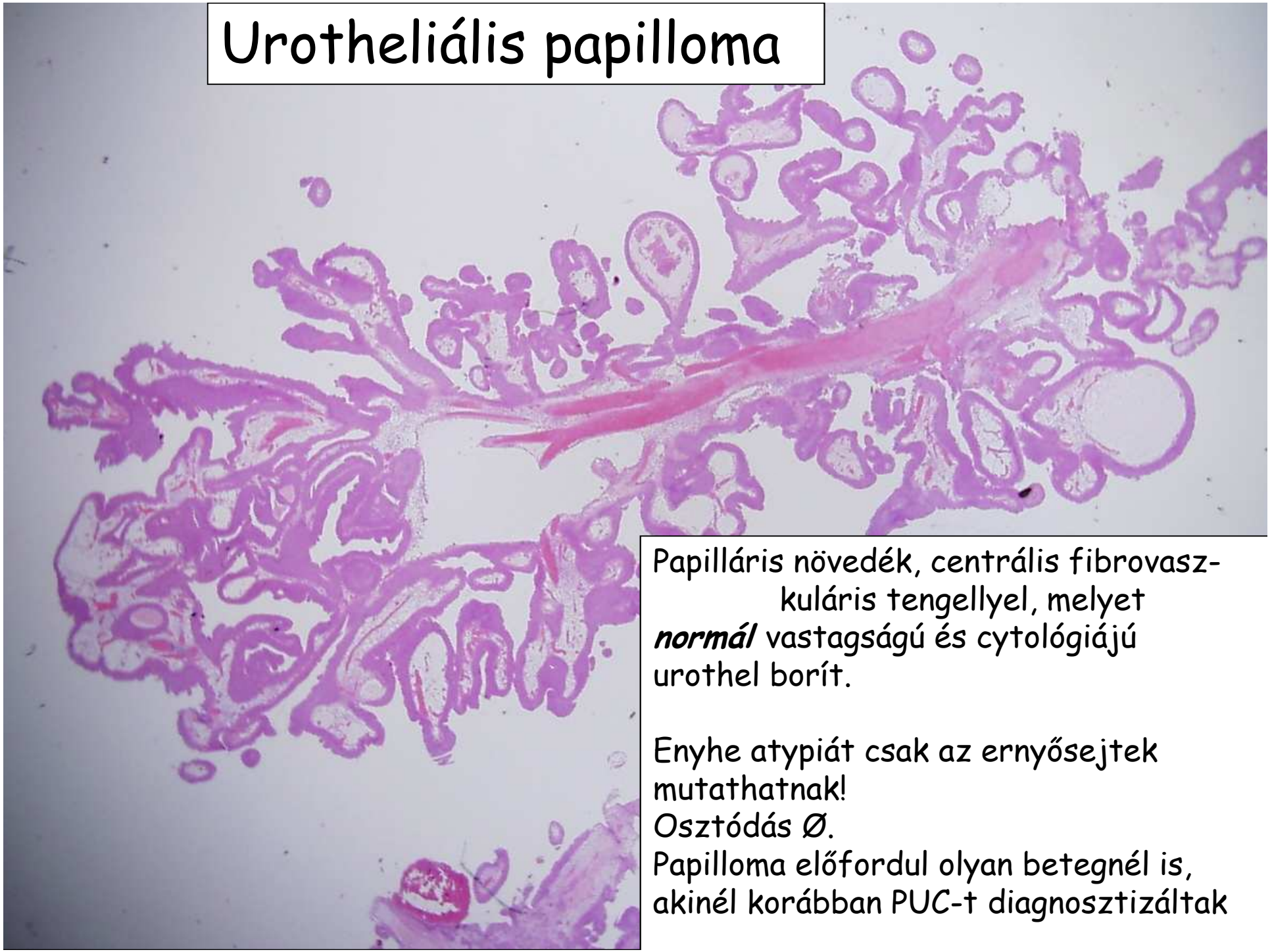
Nuclei enlarged with marked pleomorphism; chromatin coarse and variable; nucleoli multiple and prominent;

mitosis frequent and at any level

Papilláris tumorok- GRADING, Nomenclatura

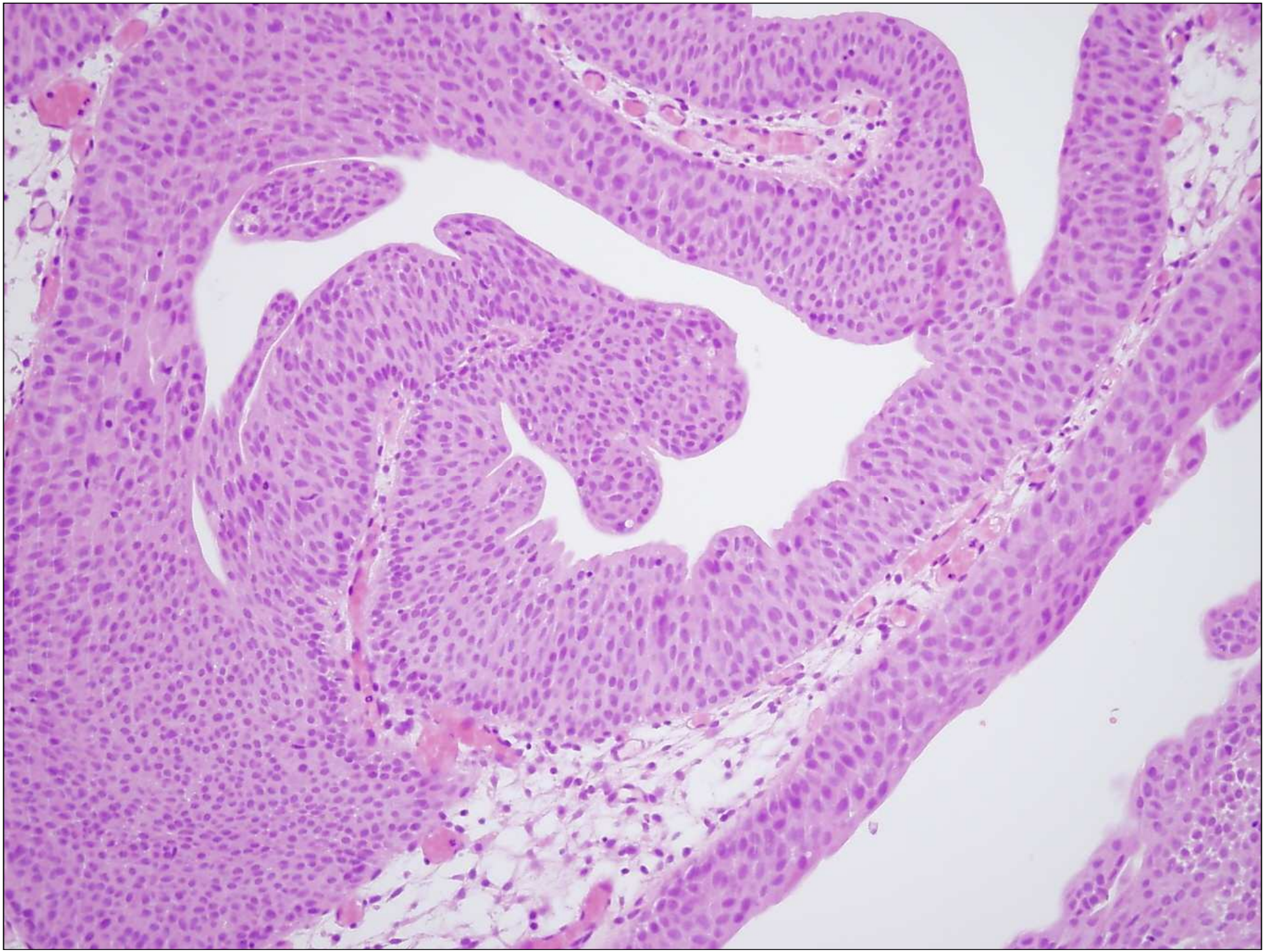


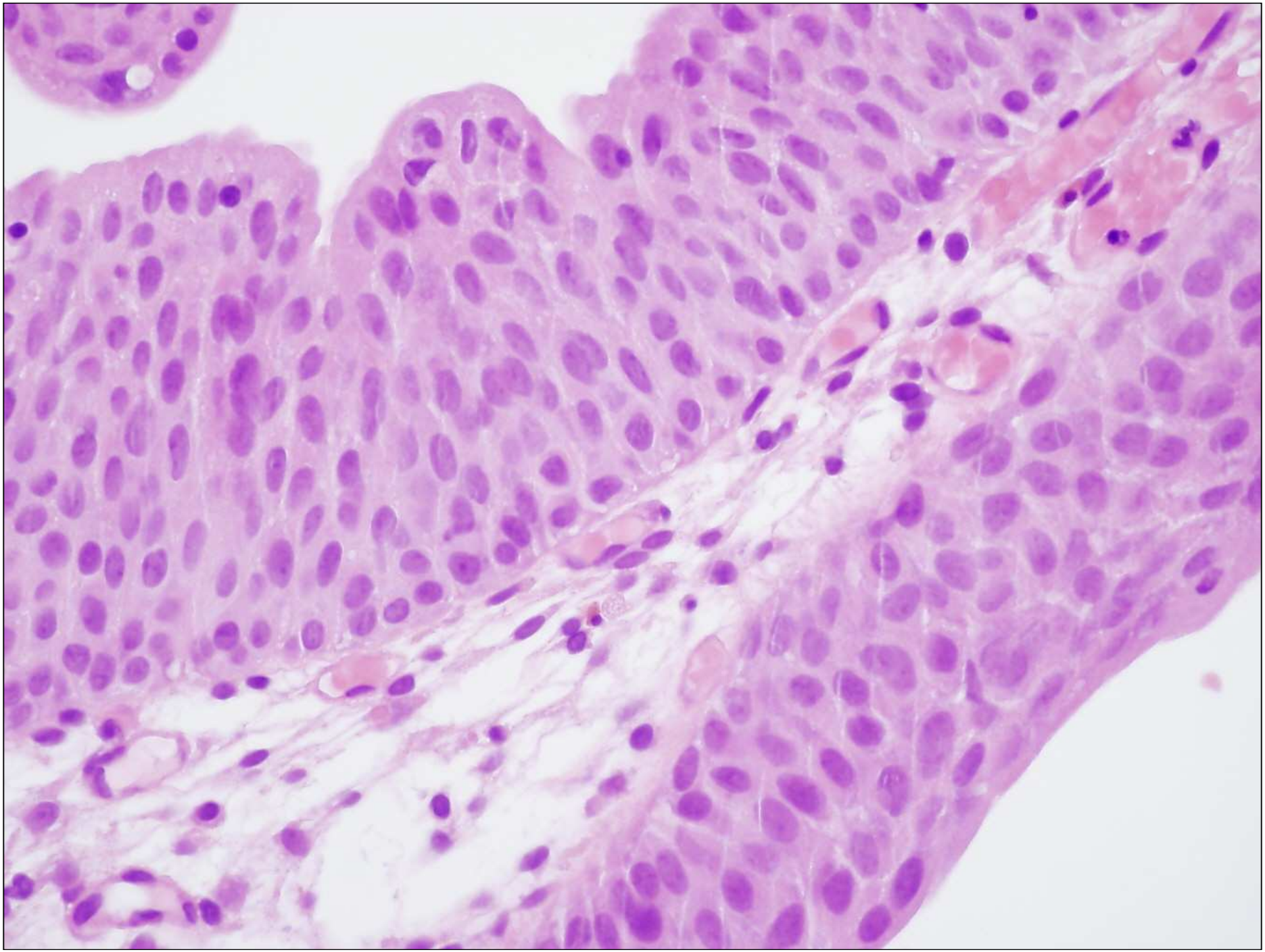
Urotheliális papilloma

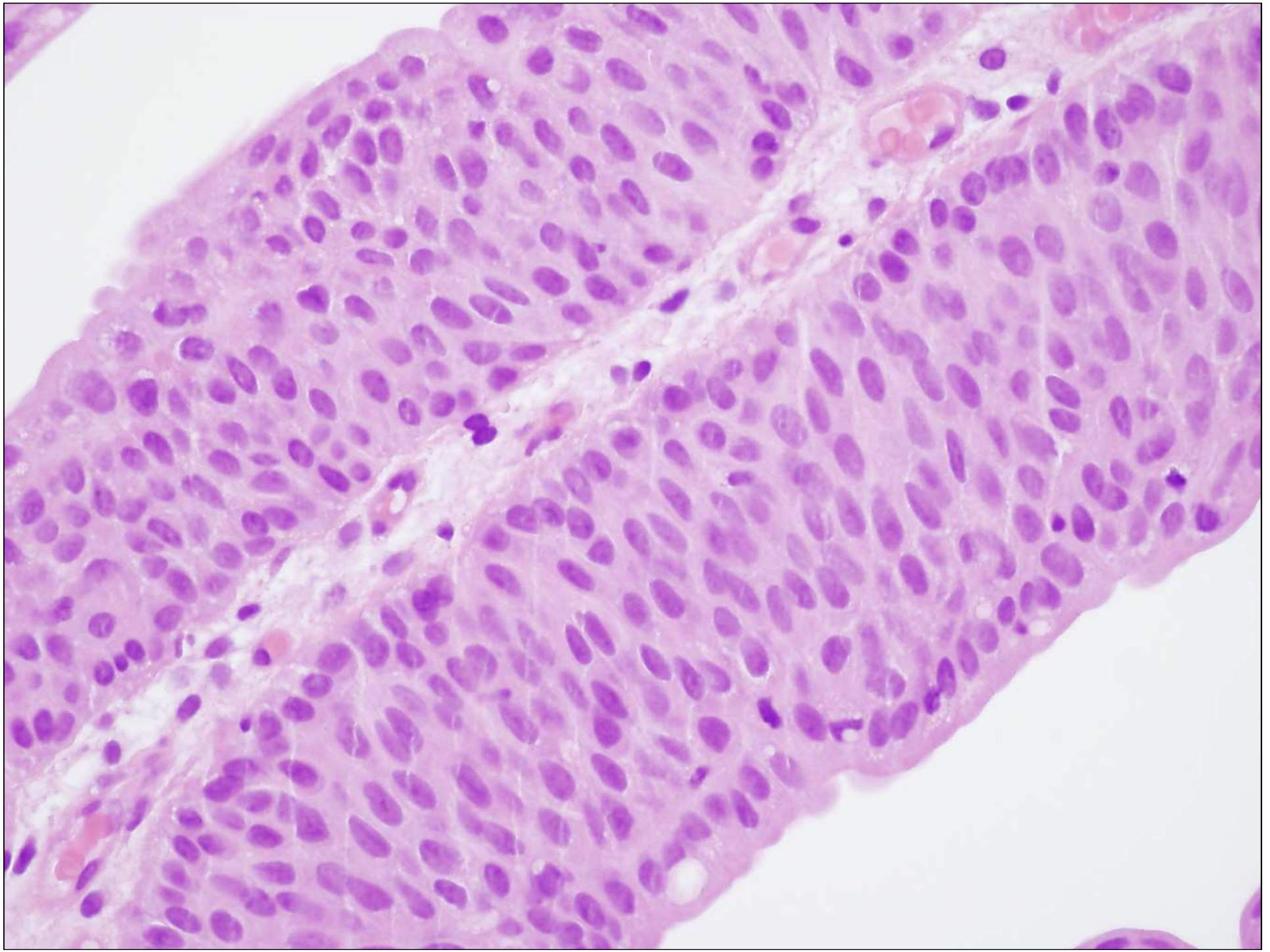


Papilláris növedék, centrális fibrovaszkuláris tengellyel, melyet ***normál*** vastagságú és cytológiájú urothel borít.

Enyhe atypiát csak az ernyősejtek mutathatnak!
Osztódás Ø.
Papilloma előfordul olyan betegnél is, akinél korábban PUC-t diagnosztizáltak



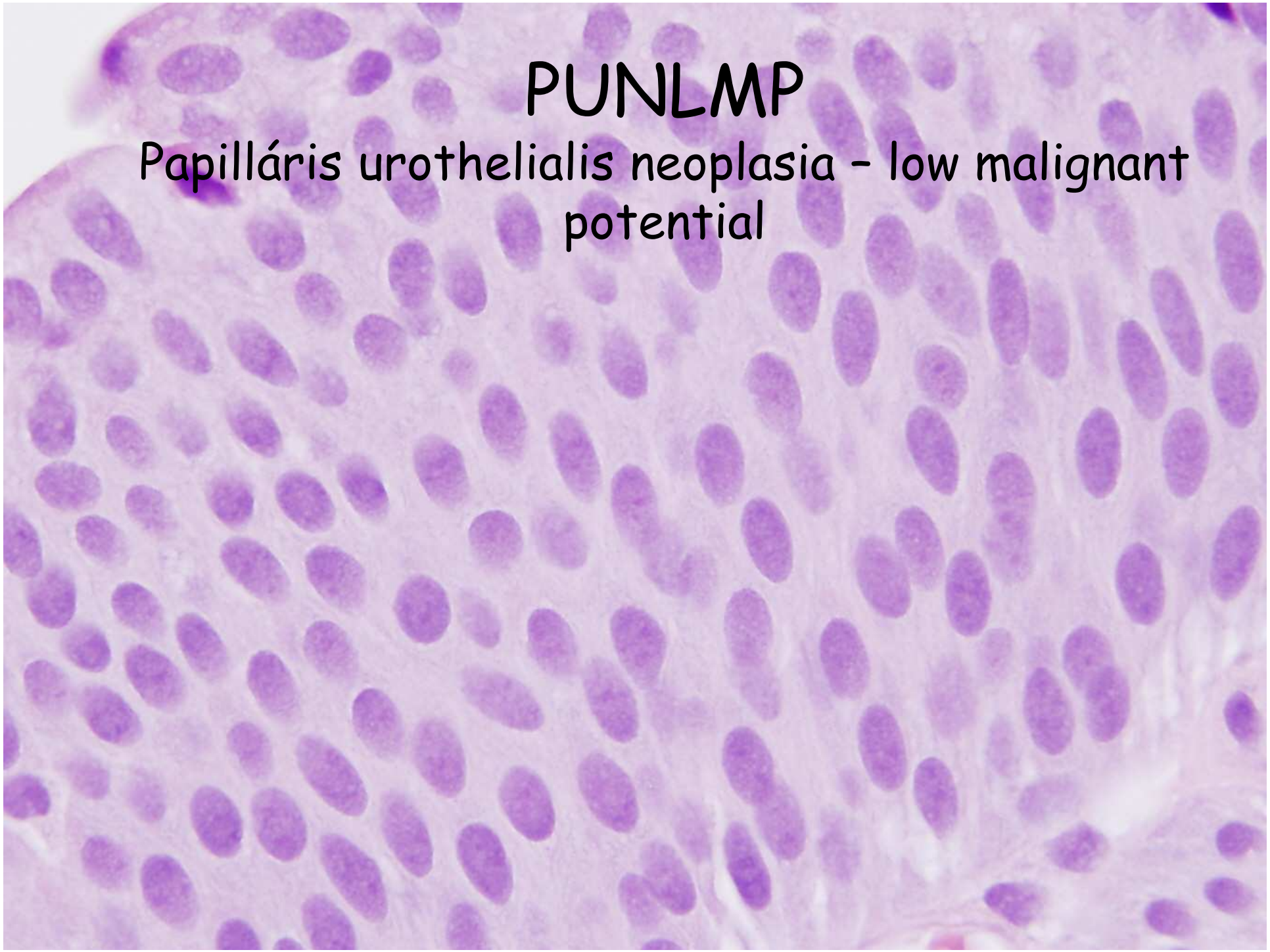




PUNLMP

Papilláris urothelialis neoplasia – low malignant potential

- Papilláris növedék,
- Minimális strukturális atypia
- Minimális cytológiai atypia
  (inkább monoton atypia,
  de a sejtmagok nagyobbak a normál méretnél)
- +/- vaskos sejtréteg a kötőszövetes tengelyeken – de a sejtsorok száma nem számlálandó!
- Mitózisok előfordulnak, de ritkák, és a bázison látni


PUNLMP
Papilláris urothelialis neoplasia – low malignant potential

PUNLMP

Papilláris urothelialis neoplasia – low malignant potential

Használatának indoka:

- Pszichoszociális – nincs megbélyegzés – „rákos"
- Financiális (biztosító) (!!!)
- Egyes szerzők szerint

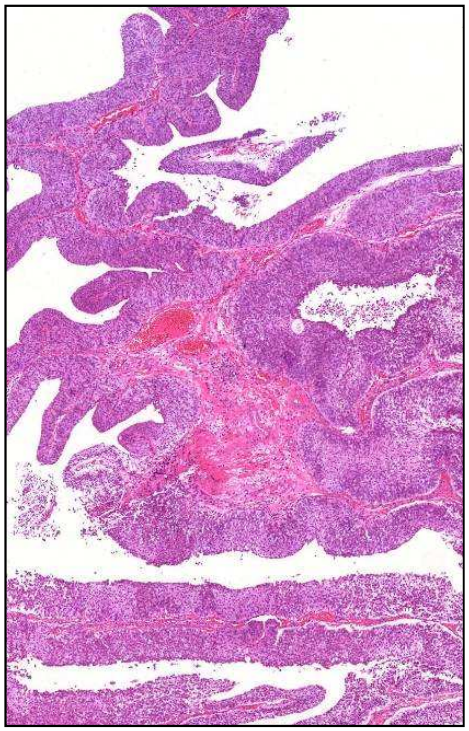
  prognosztikai jelentősége van (alacsonyabb recidiva arány), mások szerint nincs

Papilláris urothelialis carcinoma – G2 Low grade

- Viszonylag rendezett összkép,

DE

Kis nagyítással is jól érzékelhető



Cytológiai

(magpolymorphiznus, magnagyobbodás, chromatineloszlási zavar)

Strukturális

(polaritási zavar)

atypia

- Osztódások nem gyakoriak, általában a bázison vannak, de előfordulhatnak bármely rétegben

- A szöveti kép változatos, a *legsúlyosabb* eltérés értékelendő,

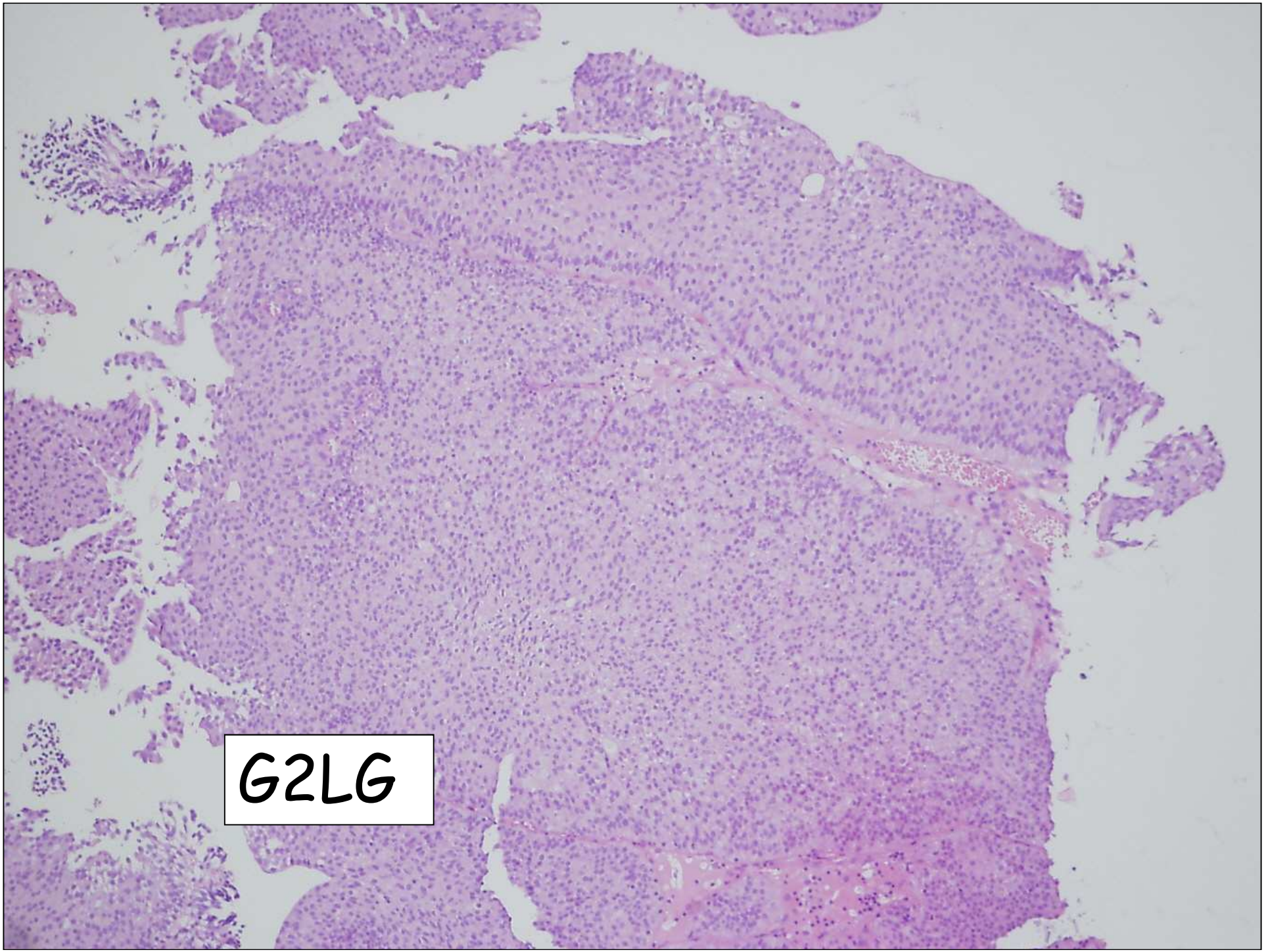
DE

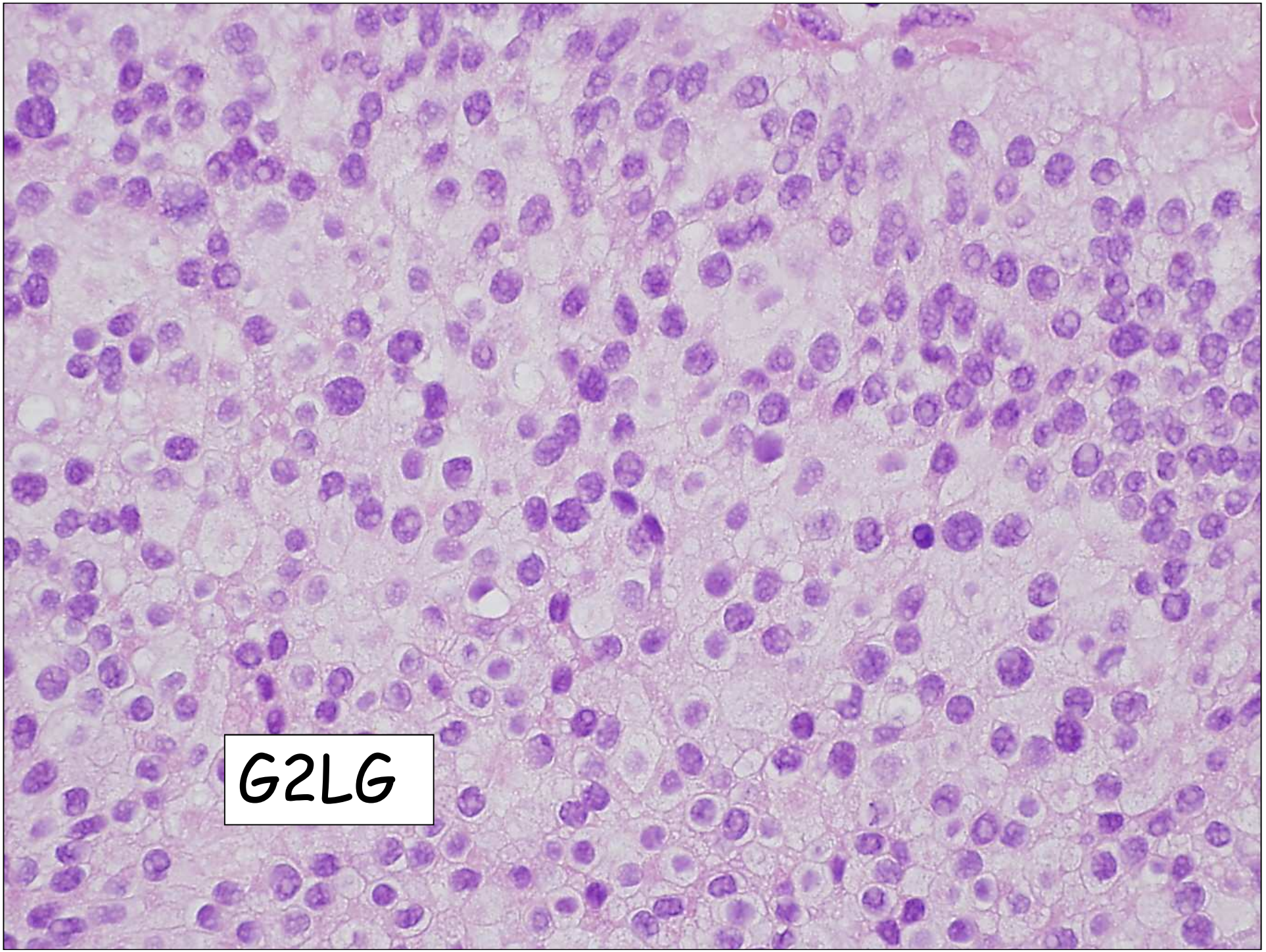
UCC- Low grade

- ha a durvább eltérés 5 %-nál kisebb területen, fokálisan mutatkozik, nem kell figyelembe venni.

(???)

- OK: egyenlőre nem világos, biztosan rontja-e a prognózist


G2LG


G2LG

Papilláris urothelialis carcinoma – G2 / HG

- Viszonylag rendezett összkép,

  DE

- Kis nagyítással is jól érzékelhető
  kifejezett

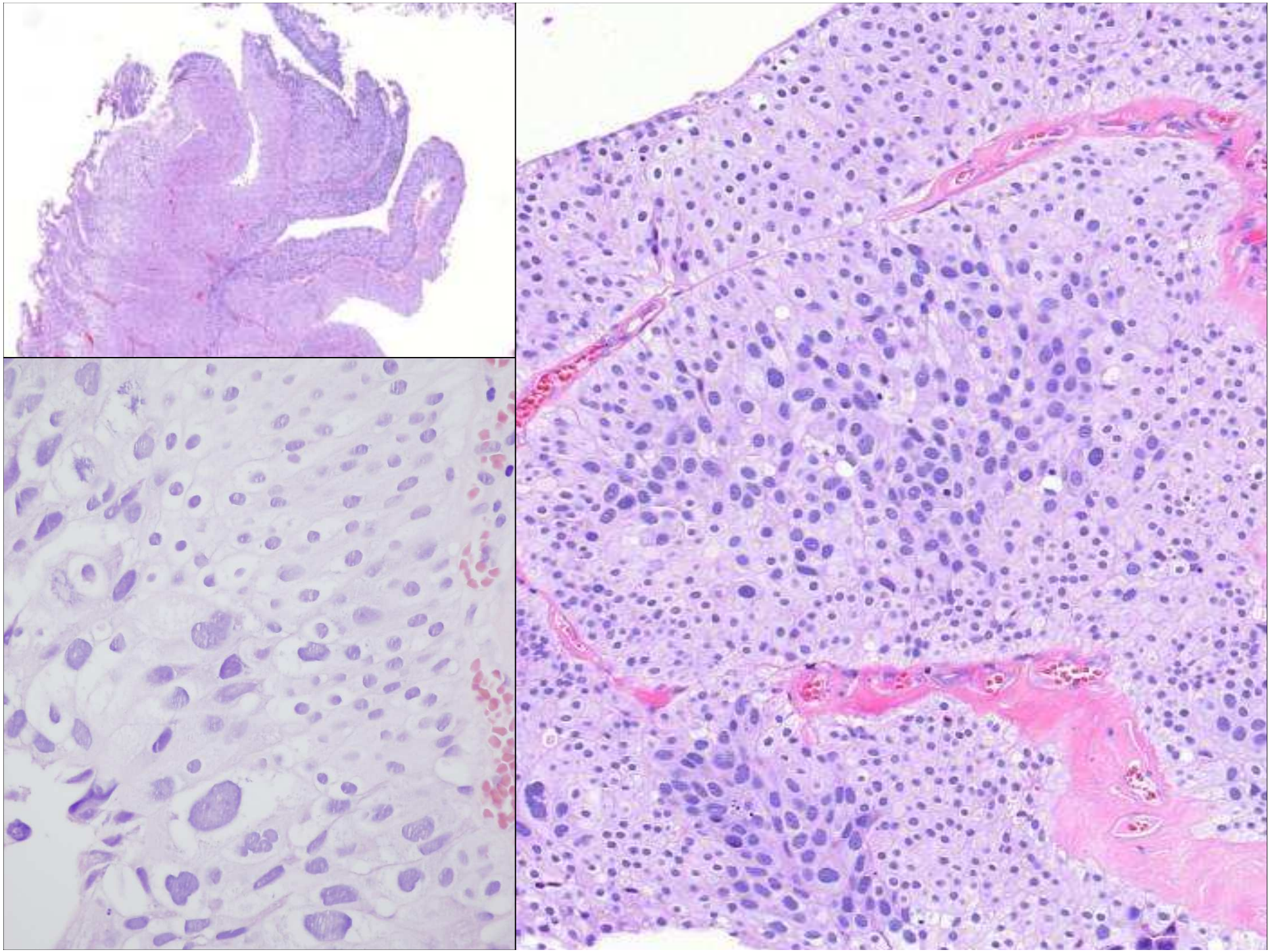
  - Cytológiai

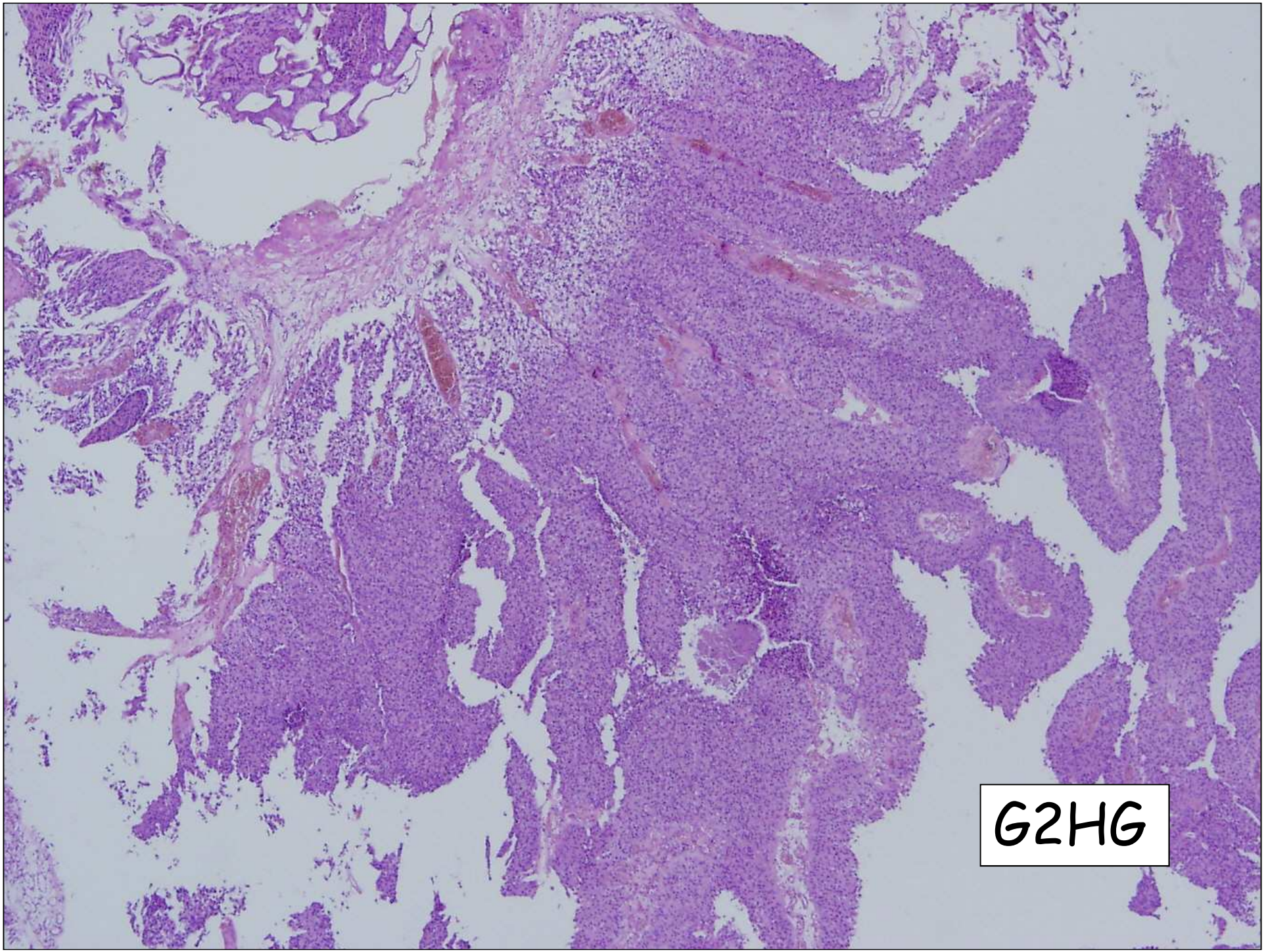
    (magpolymorphiznus, magnagyobbodás, chromatineloszlás)

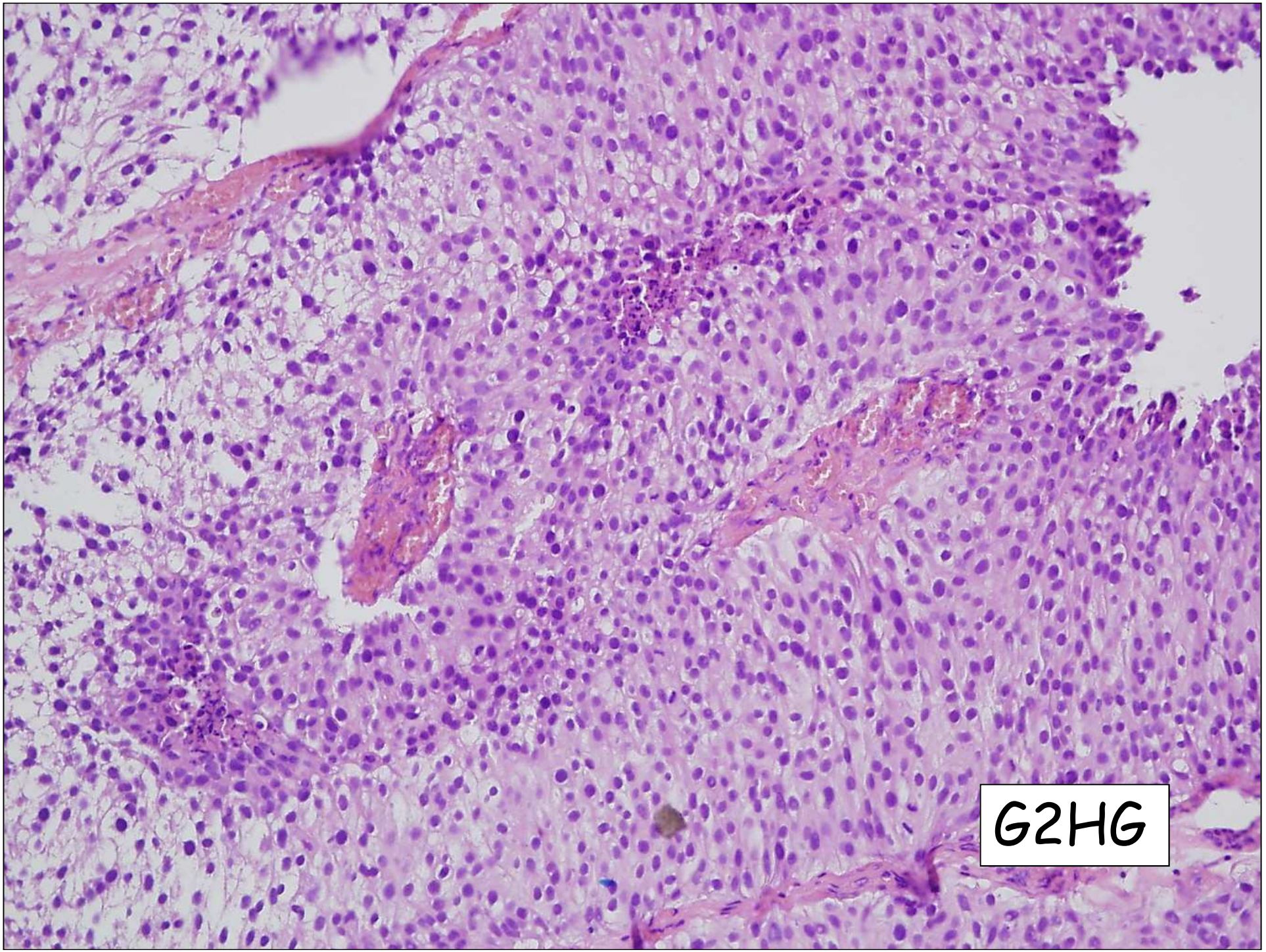
  - Strukturális atypia
    - (polaritási zavar)
    - papilla fúzió

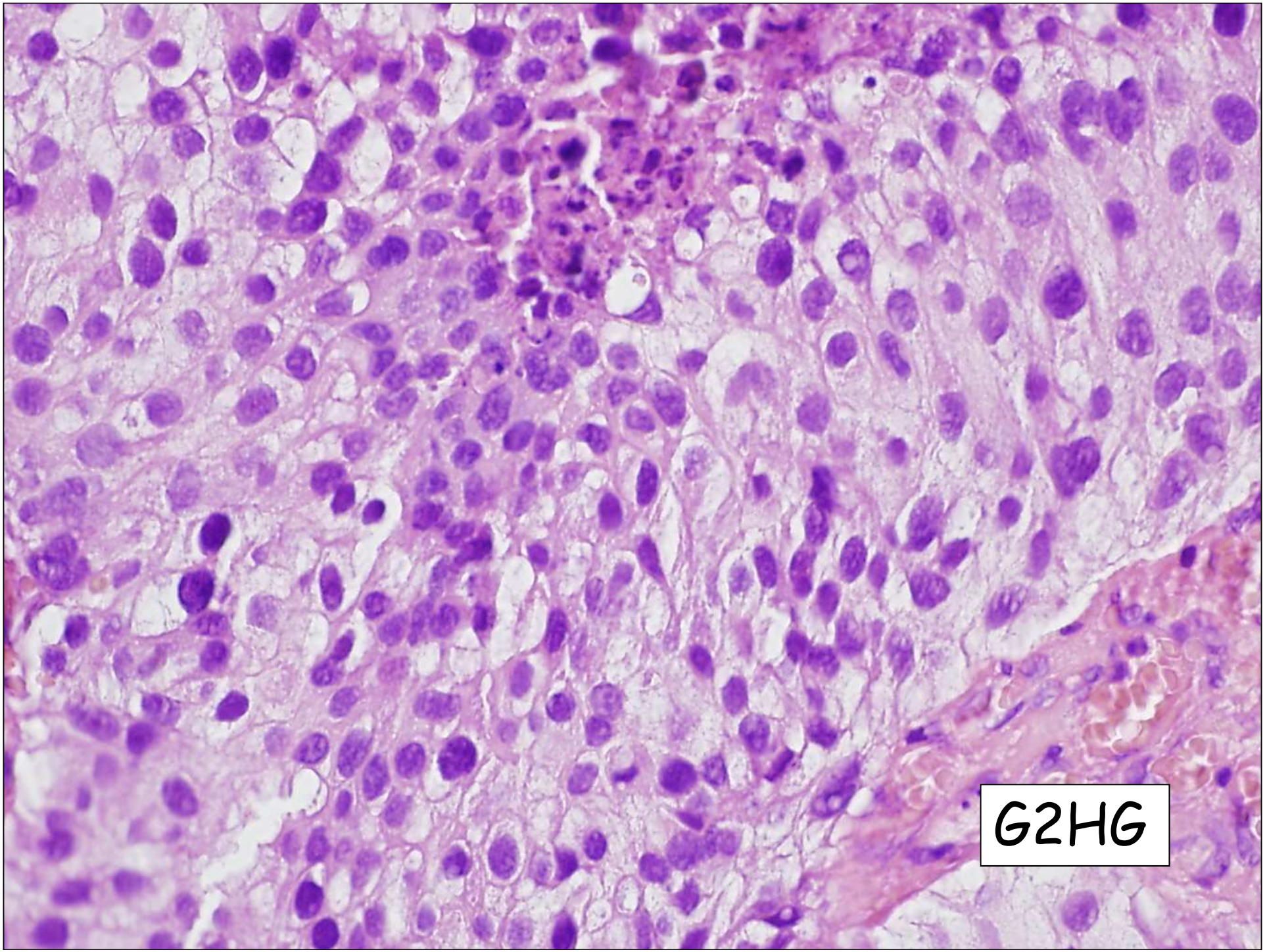
- Osztódások gyakoriak, előfordulhatnak bármely rétegben, atypusosak is

- ***A papilláris mintázat még jól érzékelhető***

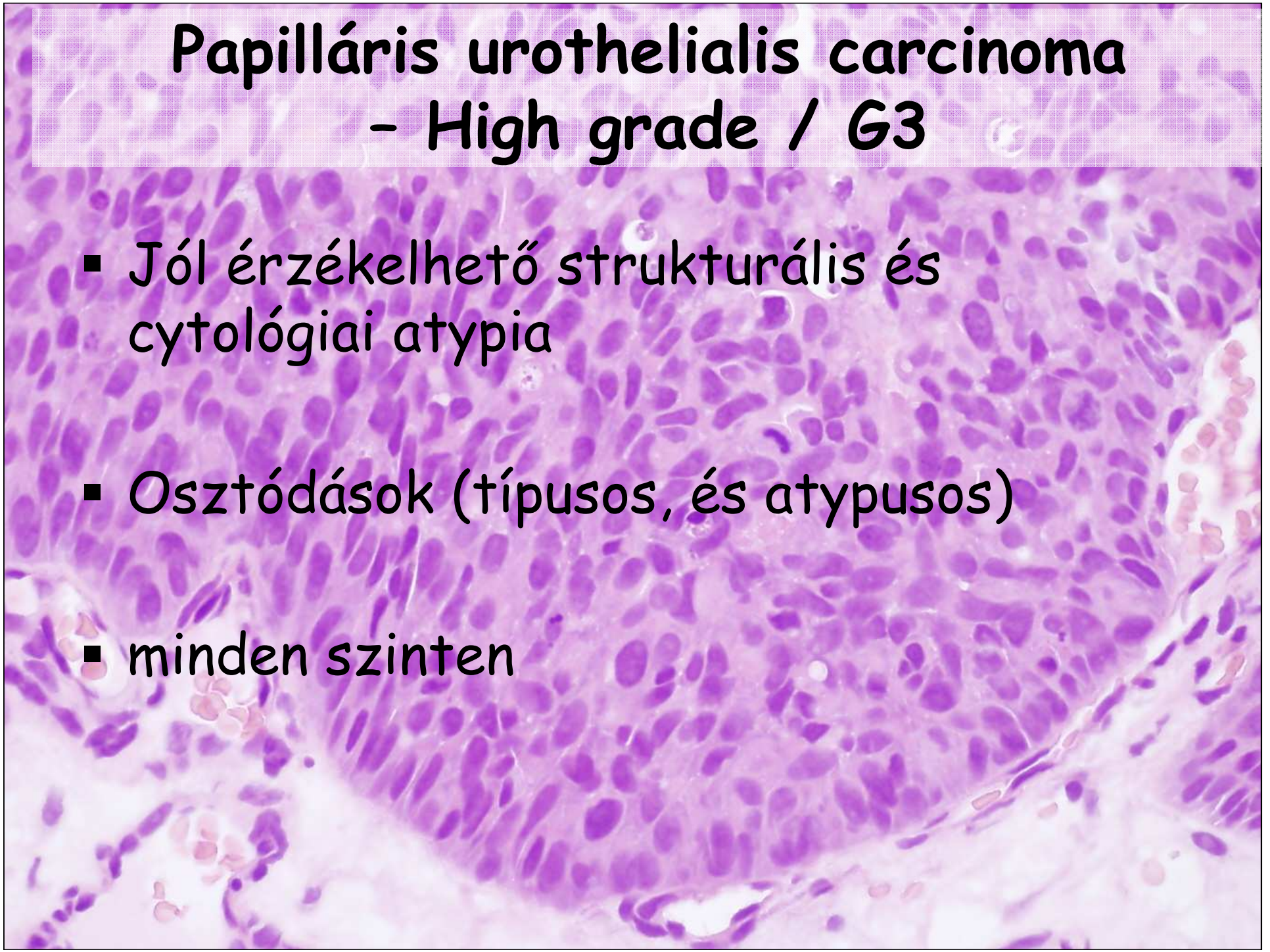



G2HG


G2HG

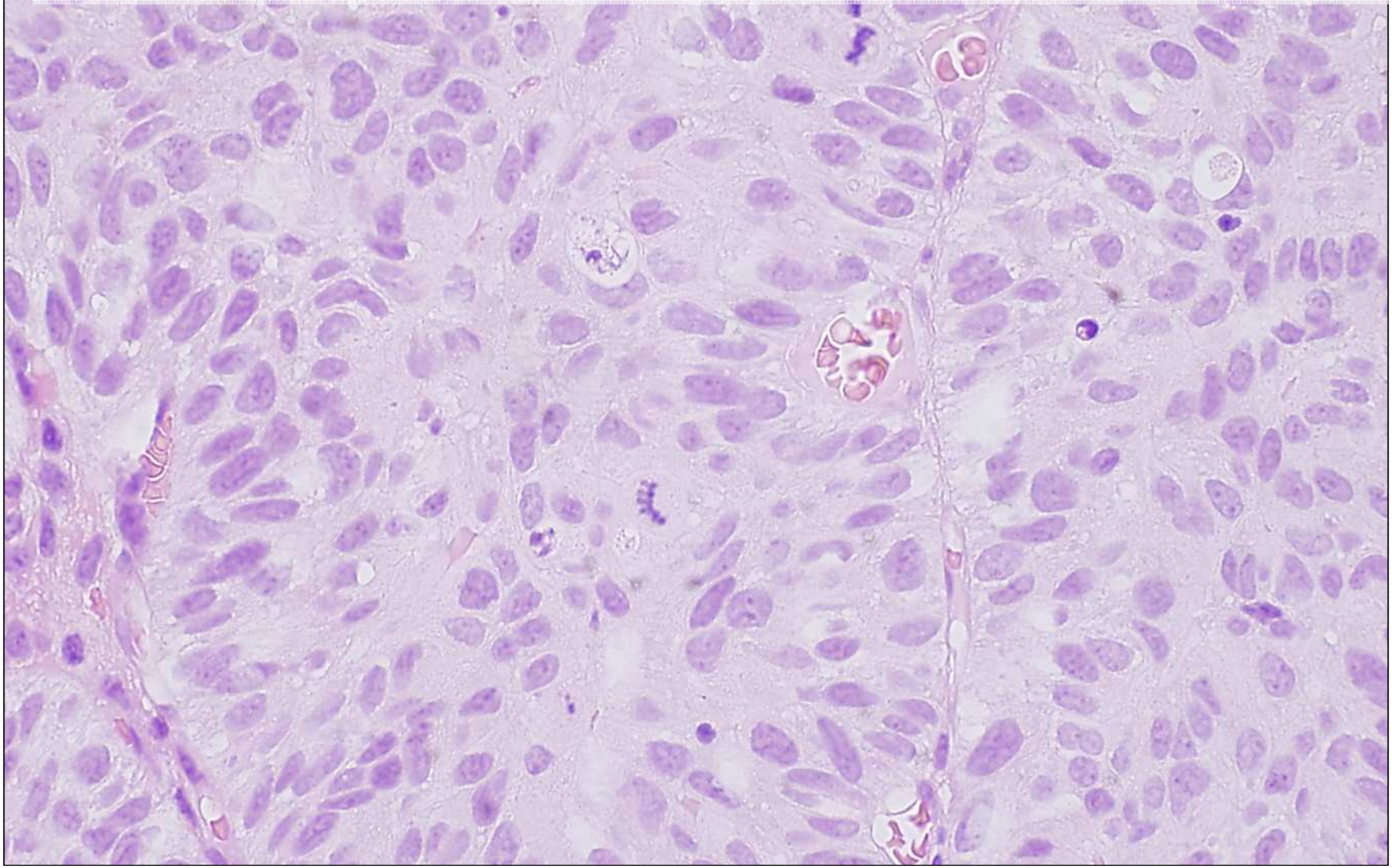

G2HG

Papilláris urothelialis carcinoma – High grade / G3

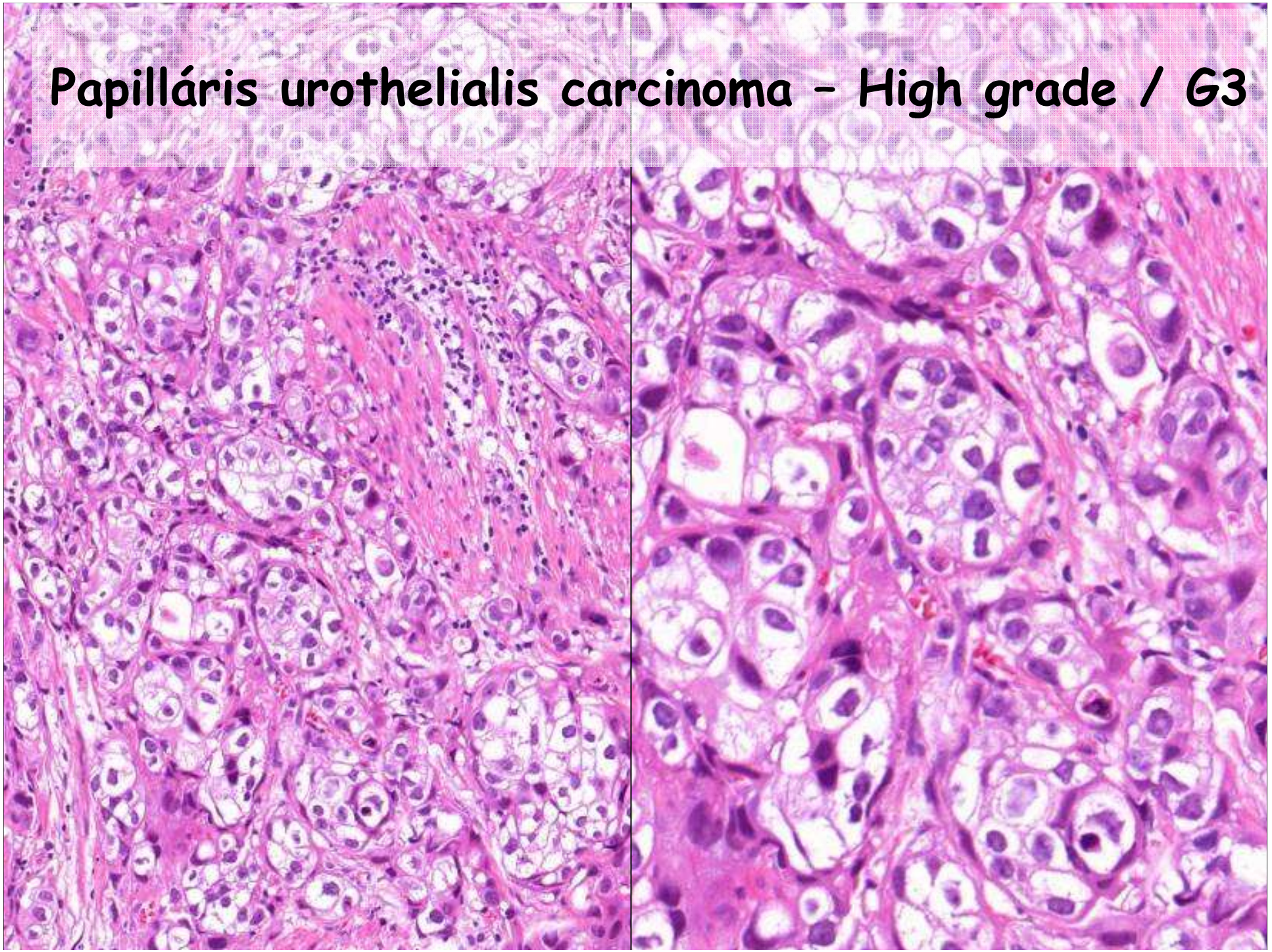


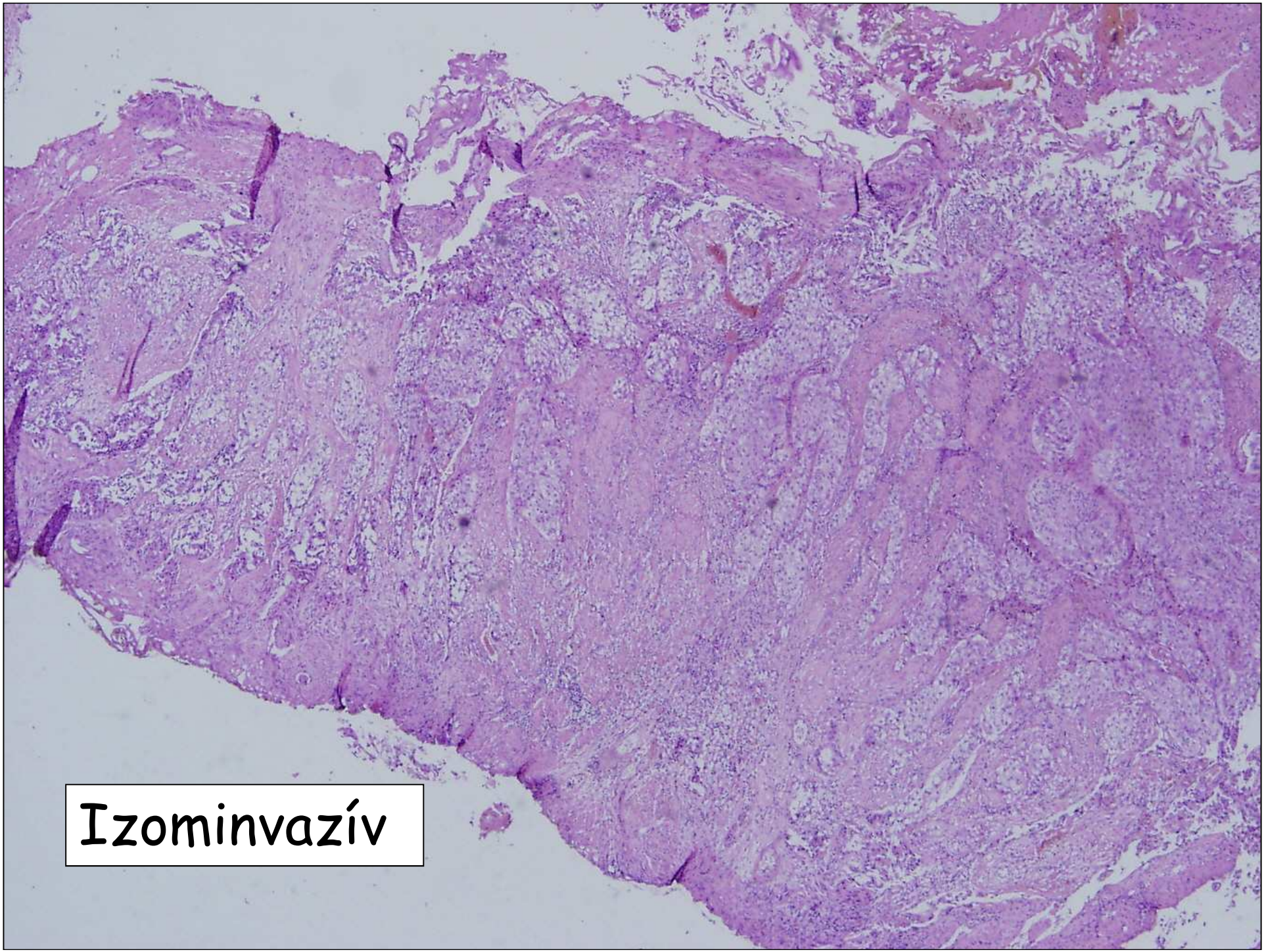
- Jól érzékelhető strukturális és cytológiai atypia
- Osztódások (típusos, és atypusos)
- minden szinten

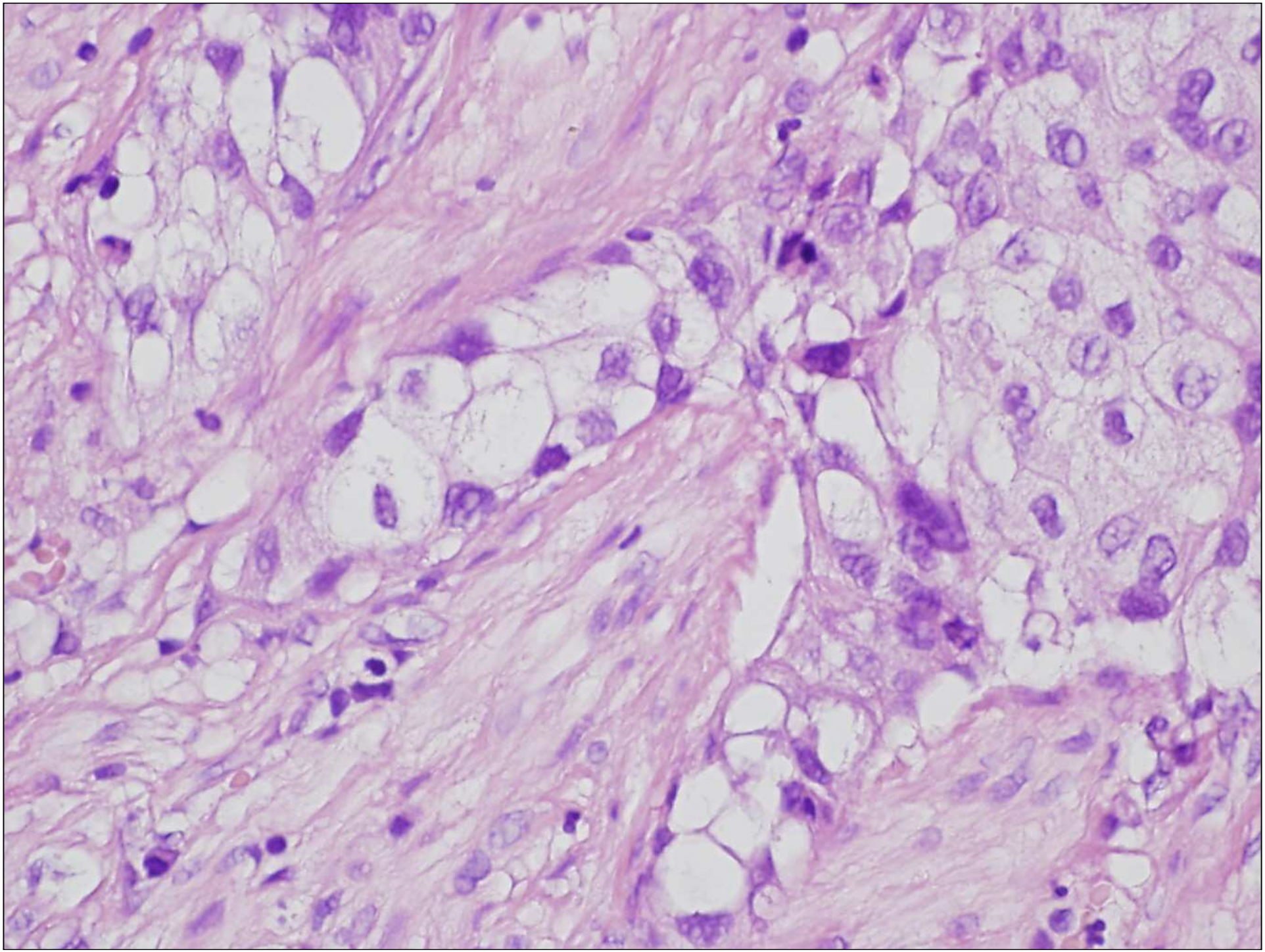
Papilláris urothelialis carcinoma – High grade / G3



Papilláris urothelialis carcinoma – High grade / G3




Izominvazív

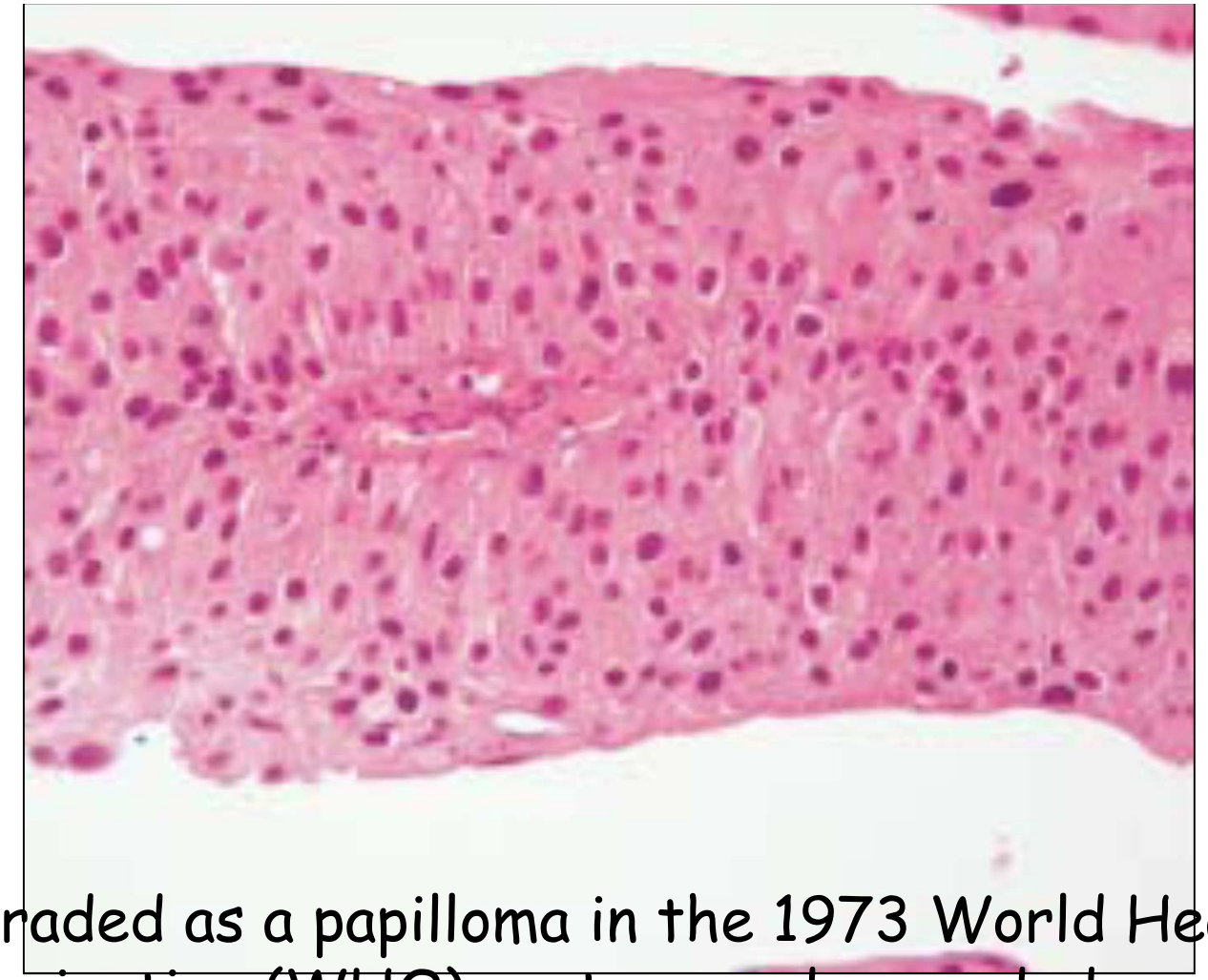


Histologic Grading of Noninvasive Papillary Urothelial Tumors

Validation of the 1998 WHO/ISUP System by Immunophenotyping and Follow-up

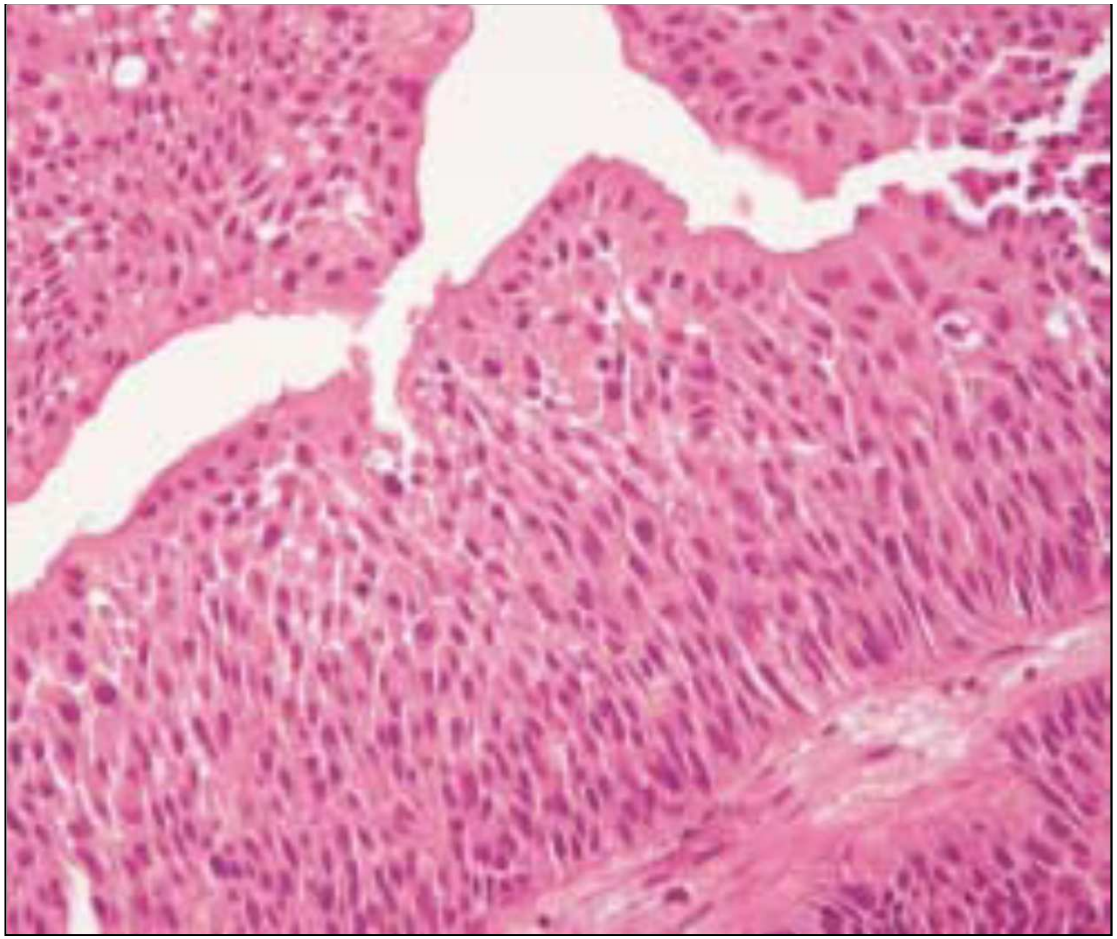
Hui Yin, MD, and Anthony S.-Y. Leong, MBBS, MD

Anatomic Pathology / VALIDATION OF WHO/ISUP CLASSIFICATION OF NONINVASIVE PAPILLARY UROTHELIAL TUMORS
DOI: 10.1309/0KATYHQBJD5XHQ8J

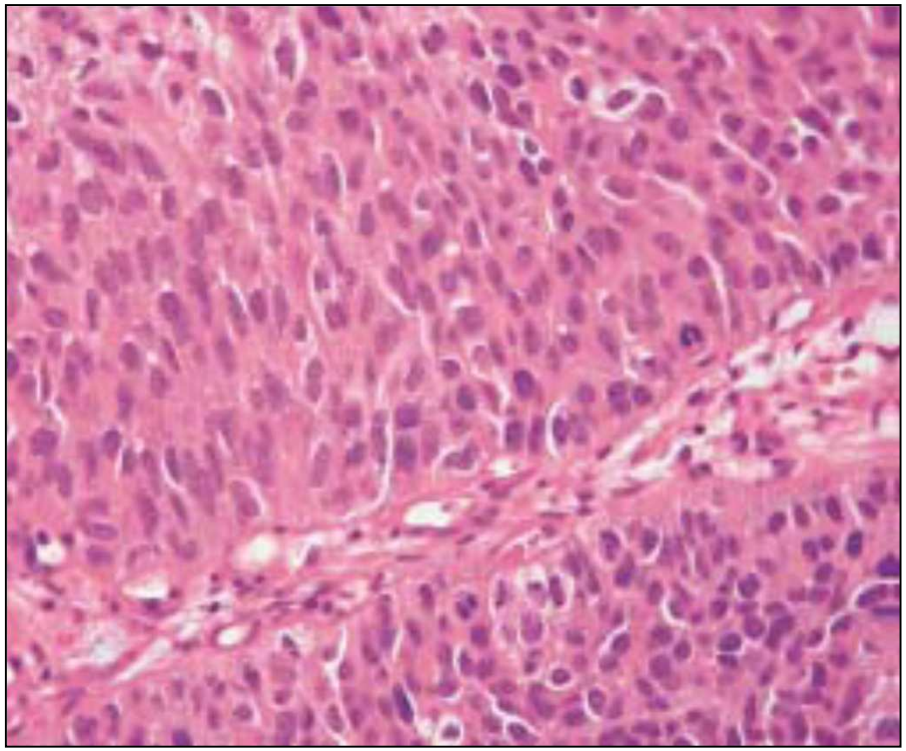


A, Graded as a papilloma in the 1973 World Health Organization (WHO) system, and regraded as papillary urothelial

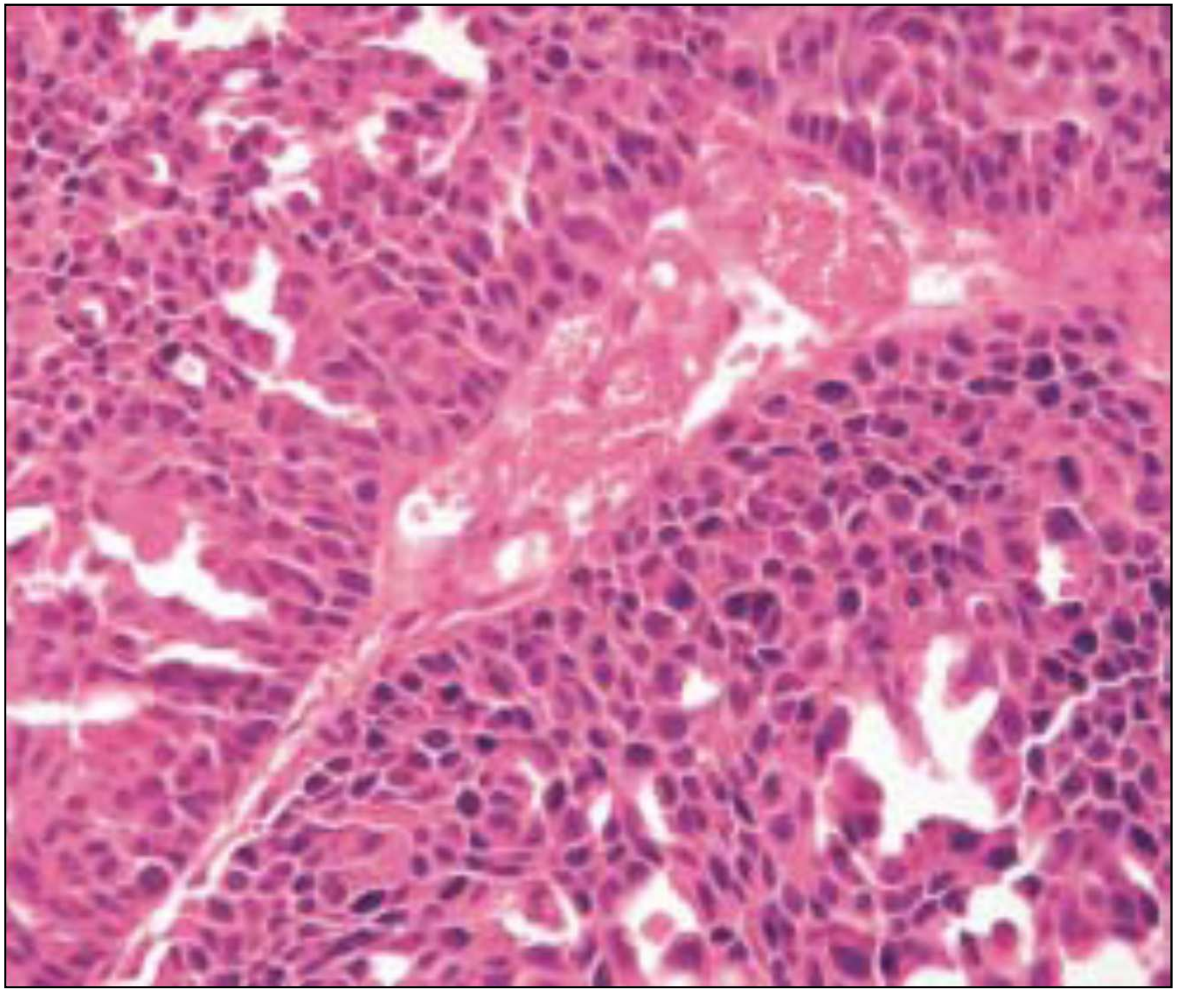
neoplasm of low malignant potential because of the mild variation in nuclear size and the mildly uneven nuclear distribution (H&E, ×20).



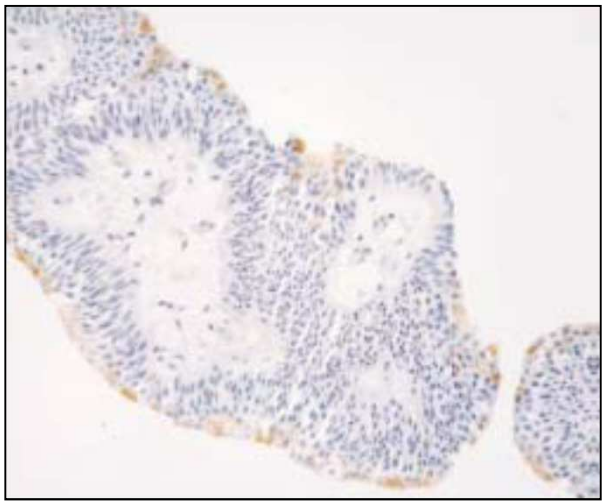
B, Graded as grade 1 carcinoma in the 1973 WHO system, and regraded as low-grade carcinoma. Note the variable nuclear pleomorphism and focal crowding. Scattered mitotic figures are present in the middle third of the epithelium (H&E, ×20).

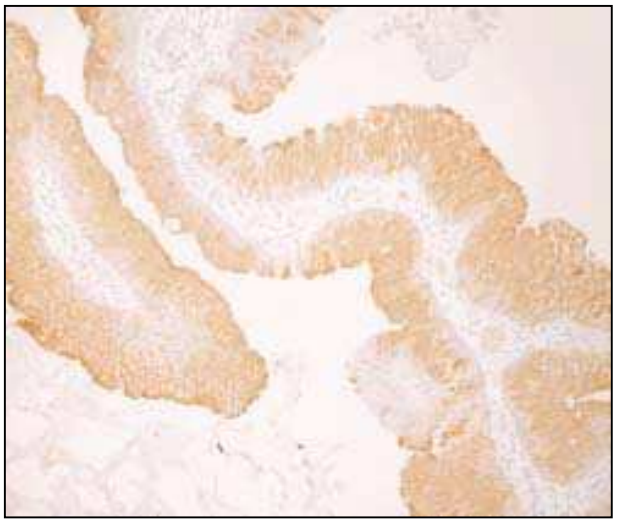


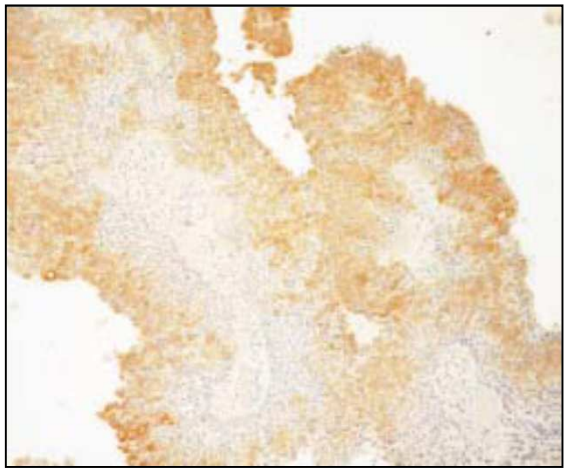
C, Graded as grade 2 carcinoma in the 1973 WHO system, and regraded as high-grade carcinoma. Nuclei are distinctly enlarged, and alignment is completely lost with marked unevenness of distribution of distinctly pleomorphic nuclei with coarse chromatin and distinct nucleoli. Mitoses were evident at all levels (H&E, ×20).



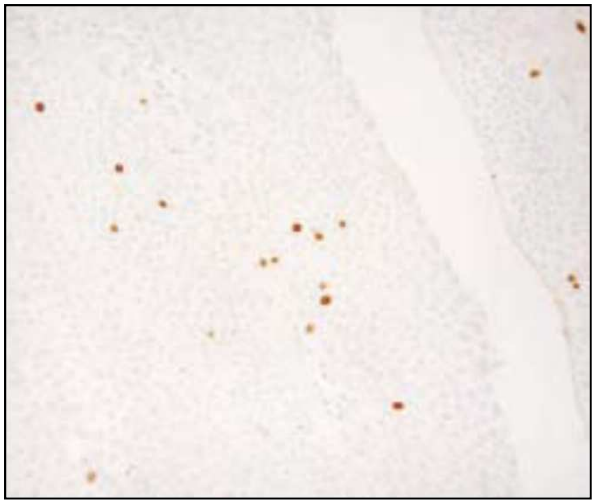
D, Graded as grade 3 carcinoma in the 1973 WHO system, and regraded as high-grade carcinoma. There is obvious loss of polarity, marked nuclear enlargement, pleomorphism, hyperchromasia, frequent mitosis at all levels, and dyscohesiveness (H&E, ×20).

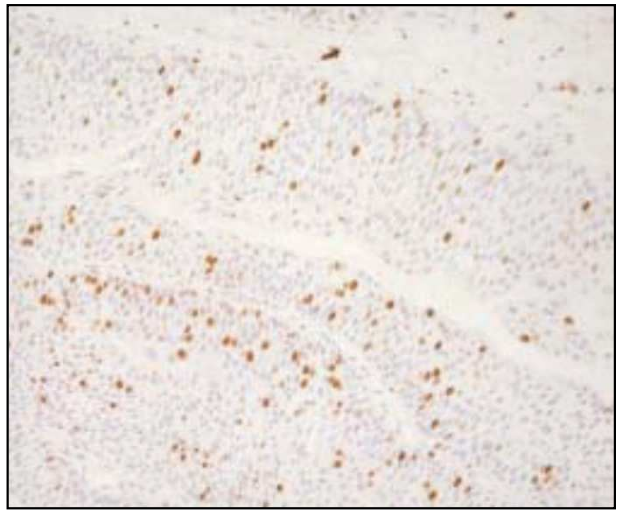


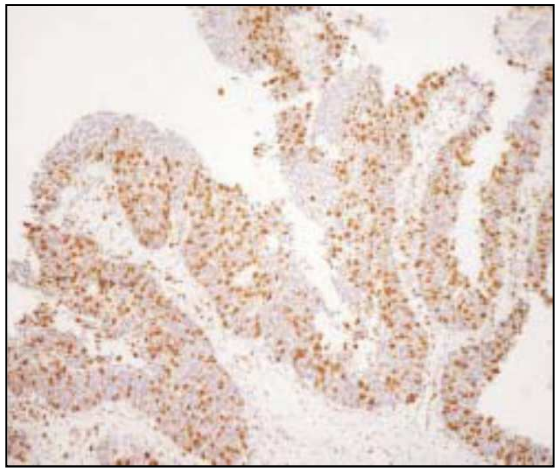




CK 20





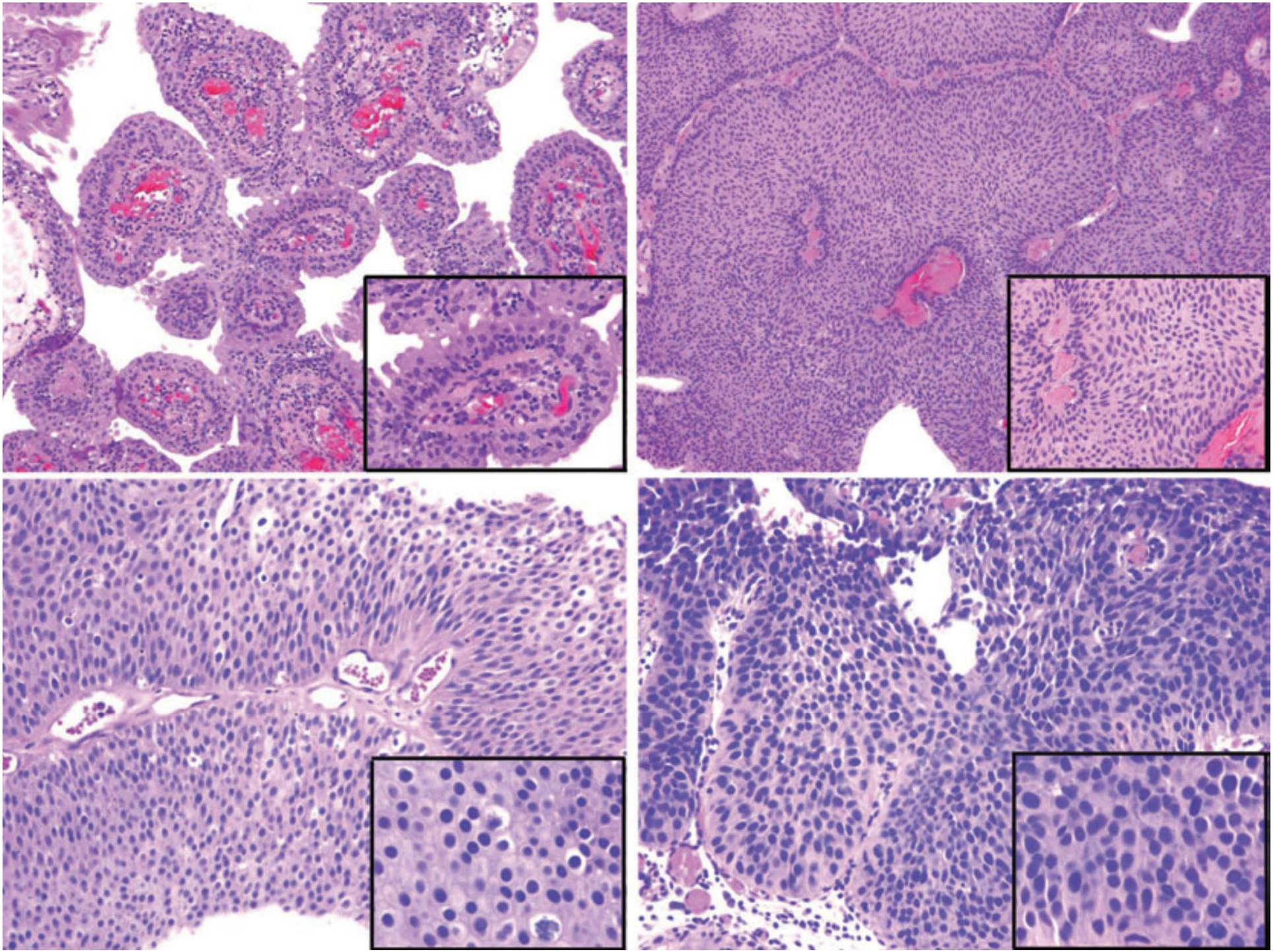


Ki 67

Non-invasive papillary urothelial neoplasms: The 2004 WHO/ISUP classification system

Hiroshi Miyamoto,1,2 Jeremy S. Miller,2 Daniel A. Fajardo,2 Thomas K. Lee,2 George J. Netto2–4 and Jonathan I. Epstein2–4

Pathology International 2010; **60**: 1–8 doi:10.1111/j.1440-1827.2009.02477.x



Beteg kezelés - követés

Nincs konszenzus

Prognosztikus faktorok

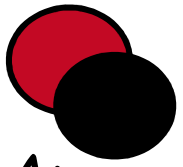
- Tumor gócok száma
  - Egy vagy több focus
- Tumor méret ≤ 3 cm ≥
- Stádium
- Van-e recidiva az első cystoscopos vizsgálatnál?

- Genetikai mintázat
  - C-ras amplifikáció
  - VEGF ″
  - TGFß1 ″
  - Fos ″
  - FGF3 mutáció

- Scand J Urol Nephrol. 2008;42(3):237-42.
- **Histological classification and stage of newly diagnosed bladder cancer in a population-based study from the Northeastern United States.**
- Schned AR, Andrew AS, Marsit CJ, Kelsey KT, Zens MS, Karagas MR.
- **Source**
- Department of Pathology, Dartmouth Medical School, Hanover, New Hampshire, USA. alan.schned@hitchcock.org
- **Abstract**

Interrelationships of papillary bladder tumors by WHO (1973) and WHO/ISUP classification systems.

WHO/ISUP classification	WHO (1973) CIS	Papilloma	Grade 1	Grade 2	Grade 3	Other	Total
Carcinoma in situ[CIS]	18	0	0	0	0	0	18
Papilloma	0	1	0	0	0	0	1
PUNLMP	0	0	84	0	0	0	84
PUC - low grade	0	0	60	52	0	0	112
PUC - high grade	0	0	0	5	69	0	74
Non-papillary UC	0	0	0	2	31	0	33
Other	0	0	0	0	0	5	5
Total	18	1	144	59	100	5	327



Virchows Arch. 2011 Jun;458(6):659-64. Epub 2011 Apr 12.

Histologic grading of urothelial papillary neoplasms: impact of combined grading (two-numbered grading system) on reproducibility.

Tuna B, Yörükoglu K, Düzcan E, Sen S, Nese N, Sarsık B, Akder A, Sayhan S, Mungan U, Kirkali Z.

Source

Department of Pathology, School of Medicine, Dokuz Eylul University, Izmir, Turkey.
burcin.tuna@deu.edu.tr

- 8 uropatológus
- 10 eset
- 6 hét után ugyanazt a 10 esetet újból megvizsgálták
- Nomenclatura: WHO1973, WHO-ISUP 2004, combinált score
- Mérték az intra-interobserver variabilitást

Primer grade	Secondary grade	Score	IO egyezés %
PUNLMP	PUNLMP	2	33.3
PUNLMP	LGPUC	3	38.1
LGPUC	PUNLMP	3	38.1
LGPUC	LGPUC	4	55.1
LGPUC	HGPUC	5	65.1
HGPUC	LGPUC	5	65.1
HGPUC	HGPUC	6	74.3

- Minél jobban differenciált a tumor, a variabilitás annál nagyobb

- Nem volt lényeges különbség a két grading rendszer eredményei között

- Am J Clin Pathol. 2010 May;133(5):788-95.
- **Prognostic significance of the 2004 WHO/ISUP classification for prediction of recurrence, progression, and cancer-specific mortality of non-muscle-invasive urothelial tumors of the urinary bladder: a clinicopathologic study of 1,515 cases.**
- Pan CC, Chang YH, Chen KK, Yu HJ, Sun CH, Ho DM.
- **Source**
- Department of Pathology, Taipei Veterans General Hospital, No. 201, Shi-Pai Rd, Sec 2, Taipei, 11217 Taiwan.

- WHO/ISUP osztályozás jobb az 1973-nál
  PUNLMP a legjobb prognózisú daganat
    Nem vezet tumor-okozta halálozáshoz
- LGPUC Ta-T1 között nem látott prognosztikai különbséget

- Retrospective study- tumor méret, ill. concomittáló CIS jelenlétéről nem volt információ
- A tumor-grade volt a legfontosabb prognosztikai jegy

- Urol Int. 2007;78(4):338-44.
- **Comparison of 1998 WHO/ISUP and 1973 WHO classifications for interobserver variability in grading of papillary urothelial neoplasms of the bladder. Pathological evaluation of 258 cases.**
- Gonul II, Poyraz A, Unsal C, Acar C, Alkibay T.
- **Source**
- Department of Pathology, Gazi University Medical School, Ankara, Turkey. dripek@gmail.com
- **Abstract**
- **AIM:**
- Our aim was to compare the interobserver variability between the 1998 WHO/ISUP and 1973 WHO classifications.
- **METHODS:**
- 258 consecutive papillary urothelial carcinomas were reviewed by two pathologists and assigned a tumor grade according to the 1973 WHO and 1998 WHO/ISUP without the knowledge of primary diagnosis and clinical follow-up. All cases were also histologically staged by the two pathologists separately as follows: pTa (noninvasive), pT1 (lamina propria invasion only), pT2 (muscularis propria invasion). Findings of both pathologists and degree of agreement were compared statistically by using Pearson's chi(2) test and kappa statistics respectively. A kappa value of 0.21-0.40 is accepted as fair, 0.41-0.60 moderate and 0.61-0.80 substantial agreement.
- **RESULTS:**
- Regardless of the pathologist, tumor grades of two classifications correlated to each other and the pathological stage ($p < 0.05$). Overall degree of agreement between pathologists was higher in the 1998 WHO/ISUP (kappa 0.59) than the 1973 WHO (kappa 0.41), but both were still moderate. Papillary urothelial neoplasia with low malignant potential was the group of 1998 WHO/ISUP that showed the lowest degree of agreement and if excluded, interobserver variability of the 1998 WHO/ISUP decreased significantly (kappa 0.84).
- **CONCLUSION:**
- **The diagnosis of papillary urothelial neoplasia with low malignant potential and the criteria that differentiates it from low-grade carcinomas needs improvement in order to compare the different studies and therapies and to provide more accurate information for management.**

- J Ayub Med Coll Abbottabad. 2006 Apr-Jun;18(2):4-8.
- **Urothelial neoplasia of the urinary bladder--comparison of interobserver variability for WHO Classification 1972 with WHO/ISUP Consensus Classification 1998.**
- Mamoon N, Iqbal MA, Jamal S, Luqman M.
- **Source**
- Department of Histopathology, Armed Forces Institute of Pathology Rawalpindi, Pakistan. mamoon@isb.comsats.net.pk
- **Abstract**
- **BACKGROUND:**
- Classification of urothelial bladder tumours is an important factor in the treatment and prognosis of these lesions. Over the years many classifications have been proposed for this purpose. The objective of this study was to classify urothelial neoplasms of the urinary bladder using the latest WHO/ISUP Consensus Classification 1998 and WHO Classification 1972 and compare the two regarding interobserver variability.
- **METHODS:**
- This study included 100 consecutive biopsy specimens of urothelial neoplasms of the urinary bladder diagnosed at the department of Histopathology, Armed Forces Institute of Pathology, Rawalpindi. These were classified according to WHO Classification 1972 and WHO/ISUP Consensus Classification 1998 by 2 groups of pathologists independently. The tumour categories for WHO classification 1972; papilloma, and transitional cell carcinoma (TCC) grades I, II and III were compared with the WHO/ISUP Consensus Classification entities of papilloma, papillary neoplasm of low malignant potential, low grade and high grade papillary carcinomas. Kappa statistics were used to evaluate interobserver variability. Chi square test was used to calculate significance.
- **RESULTS:**
- There was agreement on 80 tumours between the two groups of histopathologists when using WHO classification 1972 while there was agreement on 95 tumours using WHO/ISUP consensus classification. The value of Kappa for WHO Classification was 0.68 (good agreement) whereas for WHO/ISUP Consensus Classification it was 0.91 (excellent agreement). The difference between the two systems was statistically significant (p<0,001). Kappa values were less for benign and borderline lesions using both systems.
- **CONCLUSIONS:**
- WHO/ISUP Consensus Classification **1998 showed less interobserver variability than WHO Classification 1972** in the evaluation of bladder tumours. It was found easier to apply by both groups. There was less agreement on the benign and borderline lesions using both the classifications.

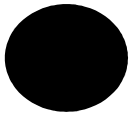
- Urol Int. 2004;73(3):201-8.
- **Comparison of WHO 1973, WHO/ISUP 1998, WHO 1999 grade and combined scoring systems in evaluation of bladder carcinoma.**
- Bircan S, Candir O, Serel TA.
- **Source**
- Department of Pathology, Suleyman Demirel University School of Medicine, Isparta, Turkey. bircans2000@yahoo.com
- **Abstract**
- **OBJECTIVES:**
- To compare WHO 1973, WHO/ISUP 1998 and WHO 1999 histologic grading systems, and also to evaluate the primary (most common) and secondary (second most common) patterns of cancer growth according to these three grading systems.
- **MATERIAL AND METHODS:**
- The study consisted of 87 bladder transurethral resections that were classified as grade 1, 2 and 3, and papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade (LG) and high grade (HG) carcinoma considering WHO 1973 and WHO/ISUP, respectively. The WHO 1999 system was subdivided high grade into grades 2 and 3 (HG-2 and HG-3). For combined scoring, primary (most common) and secondary (second most common) grades according to extension were recorded for three grading systems. The number was repeated when only grade was seen in all extension of the tissue examined. A final combined score was obtained which ranged from 2 to 6 for the WHO 1973 and WHO/ISUP 1998 systems and from 2 to 8 for the WHO 1999 schema. The TNM system was used for the pathologic staging.
- **RESULTS:**
- When considering the pathological stage, there were statistical differences between the WHO 1973 grades (p=0.011 and p=0.000), and LG and HG carcinomas of WHO/ISUP 1998 (p=0.000) and also the WHO 1999 grades (p=0.010 and p=0.003), except PUNLMP. Regarding the combined scoring, significant differences were found between score 4 (2+2) and 5 (2+3) of WHO 1973 (p=0.014) and score 5 (LG+HG) and 6 (HG+HG) of WHO/ISUP 1998 (p=0.011). There was also a significant difference between scores 4 and 6, and 6 and 8 of the WHO 1999 combined scoring system (p=0.019 and p=0.019). WHO 1973, WHO/ISUP 1998 and WHO 1999 systems were positively correlated with the pathological stage (r(s)=0.30, r(s)=0.52 and r(s)=0.50, respectively), whereas there was weak association between the combined scoring systems and stage (r(s)=0.20, r(s)=0.18 and r(s)=0.19). Comparing these grading systems, the grade 2 of WHO 1973 was subdivided into LG and HG in WHO/ISUP 1998 and also LG-1and HG-2 in WHO 1999 systems. The group of HG carcinoma in WHO/ISUP 1998 which was subdivided into HG-2 and HG-3 in the WHO 1999 system was different statistically in relation to the stage.
- **CONCLUSIONS:**
- Our results revealed that the WHO 1999 system may be more useful to evaluate the bladder carcinoma histopathologically in comparison to the WHO 1973 and WHO/ISUP 1998 systems.

- J Clin Pathol. 2002 Dec;55(12):900-5.
- **Histological grading of papillary urothelial carcinoma of the bladder: prognostic value of the 1998 WHO/ISUP classification system and comparison with conventional grading systems.**
- Oosterhuis JW, Schapers RF, Janssen-Heijnen ML, Pauwels RP, Newling DW, ten Kate F.
- **Source**
- Department of Pathology, Stichting Ziekenhuizen Noord-Limburg, PO Box 1926, 5900 BX, Venlo, The Netherlands. j.w.a.oosterhuis@isala.nl
- **Abstract**
- **AIM:**
- To test the prognostic value of the 1998 WHO/ISUP (World Health Organisation/International Society of Urologic Pathology) consensus classification system in Ta papillary urothelial neoplasms of the bladder.
- **METHODS:**
- The histological slides of 322 patients with a primary Ta tumour were classified according to the consensus classification system, and recurrence free survival (RFS) and progression free survival (PFS) were assessed for a mean follow up period of 79 months. In the same patient group, the RFS and PFS rates for the 1973 WHO grading system and a low grade/high grade system were analysed.
- **RESULTS:**
- Recurrent tumours were seen in all categories of the 1998 WHO/ISUP classification system and five year RFS was not significantly different between the groups (p = 0.12). The five year PFS showed a small but significant difference (p = 0.04) between papillary neoplasms of low malignant potential (PNLMP) and high grade papillary urothelial carcinomas (HGPUCs). In the 1973 WHO classification, no significant difference was found in RFS and PFS between the different grades. In the low grade/high grade classification PFS was significantly better for low grade tumours (p = 0.01).
- **CONCLUSION:**
- The prognostic value of the 1998 WHO/ISUP classification system is limited to predicting PFS, especially between PNLMP and HGPUC.
- **The prognostic value of this system over other grading systems is questionable.**

- Urology. 2002 Aug;60(2):315-9.
- **Comparison of WHO/ISUP and WHO classification of noninvasive papillary urothelial neoplasms for risk of progression.**
- Samaratunga H, Makarov DV, Epstein JI.
- **Source**
- Department of Pathology, Royal Brisbane Hospital, Brisbane, Australia.
- **Abstract**
- **OBJECTIVES:**
- To investigate the relation of the World Health Organization/International Society of Urological Pathology (WHO/ISUP) system for bladder neoplasia to prognosis.
- **METHODS:**
- A total of 134 patients with pTa bladder tumors were identified. We excluded cases with prior or concurrent carcinoma in situ or invasion (pT1 or pT2). Progression was defined as a tumor recurrence with either lamina propria (pT1) or muscularis propria (pT2) invasion or carcinoma in situ. Age at diagnosis, sex, tumor size, multifocality, and grade (WHO, WHO/ISUP) were entered into a Cox multivariate analysis to predict progression.
- **RESULTS:**
- The distribution of WHO papilloma, WHO G1, WHO G2, and WHO G3 was 5.2%, 31.3%, 59%, and 4.5%, respectively. The distribution of WHO/ISUP papilloma, tumors of low malignant potential, low-grade carcinomas, and high-grade carcinomas was 2.2%, 21.6%, 13%, and 21.6%, respectively. The mean and median follow-up was 56.2 and 50 months, respectively. The 90-month actuarial risk of progression for WHO papilloma, G1, G2, and G3 was 0%, 11%, 24%, and 60%, respectively. The corresponding progression rate for WHO/ISUP papilloma, tumors of low malignant potential, low-grade carcinoma, and high-grade carcinoma was 0%, 8%, 13%, and 51%, respectively. In separate analyses, WHO grade (P = 0.003) and tumor size (P = 0.03), as well as WHO/ISUP (P = 0.002) and tumor size (P = 0.04), independently predicted progression.
- **CONCLUSIONS:**
- WHO G3 has a more rapid progression rate and a slightly worse long-term progression rate compared with WHO/ISUP high-grade carcinoma. However, although only 4.5% of tumors were WHO G3, we were able to classify 21.6% as WHO/ISUP high-grade carcinoma with a poor prognosis. Use of the WHO/ISUP system allows urologists to more closely follow a larger group of patients at high risk of progression.

Cesk Patol. 2008 Apr;44(2):29-34.

[Difficulties in routine diagnostics of urothelium lesions].



[Article in Czech]

Dusková J, Babjuk M, Soukup V.

Source

Ustav patologie, LF UK a VFN, Katedra patologie IPVZ a Vysoká skola zdravotní, Praha. jaroslava.duskova@lf1.cuni.cz

Abstract

BACKGROUND:

Facing the increasing frequency of urothelial neoplasms and stratified therapeutic strategy pathologists have to meet the demands of urologists for constantly increasing preciseness of the histopathology reports influencing the application of tailored therapeutic schemes. The WHO/ISUP consensus conference in 1998 resulted into adoption of a new classification of the urothelial lesions. Its employment requires considering of features that can be difficult to find in the material provided.

MATERIAL AND METHODS:

parallel typing of more than 200 urothelial neoplasms from the daily routine biopsy samples provided by the faculty of medicine urology clinic according to the previous Mostofi 1973 and the new WHO/ISUP 1998 classification.

RESULTS:

Realizing the consultation demands we have identified some repetitive problems in the urothelium lesions diagnostics considering typing, grading, and staging of the lesions. Typing was a less frequent source of problems. It appeared in classifying lesions with inverted growth, and mucin producing urothelial neoplasms vs. adenocarcinomas. Less important typing problems are represented by uncommon rare diagnoses, as they manifest from the beginning as a specialty solvable mostly with the help of immunohistochemistry. Grading was experienced as troublesome in the following items:

- papillary hyperplasia vs. LG papillary ca,
- PUNLMP vs. LG papillary ca, HG papillary ca with a majority of LG material,
- monotonous types of HG flat lesions, and combined lesions.

Staging difficulties applied mostly in identification of the initial unequivocal invasion and the substaging of pT1 into pT1a and pT1b with learning to find the decisive mucosa structures described in detail as late as 1983 (2). We have implemented reporting the presence/absence of the detrusor muscle in the material as a marker describing the representativness of the sample provided; we consider this approach less confusing than introduction of clinical staging terminology Ta, T1 instead of pTa, pT1. To help the practising pathologists accustomed to the previous classification system we have organized postgraduate courses dealing with the application of the new diagnostic criteria adopted by the new version WHO 2004 urothelial neoplasms classification. A slide collection from the routine biopsy material comparing the previous and the new classification and a reference image database with commented reference images are being developed in the LUCIA Net image archiving system. Free access for study is available at http://www.laboratory-imaging.com. Recently, it includes over 80 images.

CONCLUSION:

adopting the new system of urothelial lesions classification requires consideration of formerly not employed features. The learning can be simplified with both classical slide collection & e-learning image database.

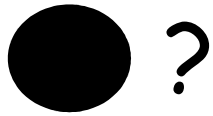
- Pathol Res Pract. 2008;204(10):707-17. Epub 2008 Jun 24.
- **Relationship of Ki67, TP53, MDM-2 and BCL-2 expressions with WHO 1973 and WHO/ISUP grades, tumor category and overall patient survival in urothelial tumors of the bladder.**
- Gönül II, Akyürek N, Dursun A, Küpeli B.
- **Source**
- Department of Pathology, Gazi University School of Medicine, Ankara, Turkey. dripek@gmail.com
- **Abstract**
- Using the 1998 World Health Organization/International Society of Urological Pathology (WHO/ISUP) (2004 WHO), 1999 WHO/ISUP, and 1973 WHO classifications, we examined Ki67, BCL-2, TP53, and MDM-2 expressions in invasive and noninvasive urothelial neoplasias of the bladder of 72 patients, and compared the results regarding tumor category and grade with clinical outcome to determine the clinicopathological relevance of these classifications. Ki67 and TP53 expressions were correlated with tumor grades of the 1973 WHO classification, and they also distinguished "papillary urothelial neoplasm with low malignant potential" from other WHO/ISUP grades ($p < 0.05$). No difference was observed for Ki67 and TP53 expressions between the other WHO/ISUP grades ($p > 0.05$). Neither tumor grade nor tumor category correlated with MDM-2 or BCL-2 expressions ($p > 0.05$). **WHO/ISUP classifications are obviously not superior to the 1973 WHO classification for grading urothelial neoplasia of the bladder.**
- However, if the "papillary urothelial neoplasm with low malignant potential" is distinguished from grade 1 tumors of the 1973 WHO classification, more precise prognostic information may be obtained.

- BJU Int. 2004 Jun;93(9):1228-31.
- **Papillary urothelial neoplasm of low malignant potential: reliability of diagnosis and outcome.**
- Campbell PA, Conrad RJ, Campbell CM, Nicol DL, MacTaggart P.
- **Source**
- Department of Urology, Princess Alexandra Hospital, Brisbane, Australia. camppa@bigpond.com.au
- **Abstract**
- **OBJECTIVE:**
- To determine the ability of pathologists to reproducibly diagnose a newly defined lesion, i.e. the papillary urothelial neoplasm of low malignant potential (PUNLMP) using the published criteria, defined by the 1998 World Health Organisation/International Society of Urological Pathology (WHO/ISUP) classification system; in addition, debate remains about the clinical behaviour of these lesions, thus the rates of recurrence and progression of PUNLMP lesions were assessed and compared with low-grade papillary urothelial carcinomas (LG-PUC) and high-grade (HG-PUC) over a 10-year follow-up.
- **PATIENTS AND METHODS:**
- Forty-nine cases of superficial bladder cancer (G1-3 pTa) representing an initial diagnosis of transitional cell carcinoma made in 1990 were identified and re-graded using the 1998 WHO/ISUP classification by two pathologists. Inter-observer agreement was assessed using Cohen weighted kappa statistics. After re-classification the clinical follow-up was reviewed retrospectively, and episodes of recurrence and progression recorded.
- **RESULTS:**
- The inter-observer agreement was moderate, regardless of whether one (kappa 0.45) or two (kappa 0.60) pathologists were used to grade these lesions. Re-classification identified 12 PUNLMP, 28 LG-PUC and nine HG-PUC. PUNLMP lesions recurred in 25% (3/12) of cases; no progression was documented. Recurrence rates were 75% (21/28) and 67% (6/9) for LG- and HG-PUC, respectively, and progression rates were 4% (1/28) and 22% (2/9).
- **CONCLUSION:**
- **The 1998 WHO/ISUP classification of urothelial neoplasms can be reproducibly applied by pathologists**, with a moderate level of agreement. There is evidence that PUNLMP lesions have a more indolent clinical behaviour than urothelial carcinomas. However, the risk of recurrence and progression remains, and clinical monitoring of these patients is important.

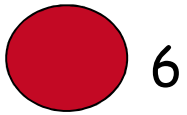
- Am J Clin Pathol. 2004 May;121(5):679-87.
- **Histologic grading of noninvasive papillary urothelial tumors: validation of the 1998 WHO/ISUP system by immunophenotyping and follow-up.**
- Yin H, Leong AS.
- **Source**
- Division of Anatomical Pathology, Hunter Area Pathology Service, Newcastle, NSW, Australia.
- **Abstract**
- Cytokeratin (CK) 20, Ki-67, and p53 were applied to 84 noninvasive papillary urothelial tumors graded by the 1973 World Health Organization (WHO) and 1998 WHO/International Society of Urological Pathology (ISUP) systems. In the WHO/ISUP classification, all benign lesions showed normal CK20 staining and all carcinomas showed abnormal staining. The Ki-67 index was significantly different between benign and malignant lesions ($P < .05$) and between low- and high-grade carcinomas ($P < .001$). p53 was negative in all benign lesions, with a significant difference between low- and high-grade carcinomas ($P < .001$). Tumor recurrence was significantly different between low- and high-grade carcinomas (no recurrences among the papillary urothelial neoplasms of low malignant potential).
- By the 1973 WHO classification, normal CK20 staining was present both in benign lesions and in carcinomas. Ki-67 staining did not distinguish between grade 2 and grade 3 carcinomas ($P > .05$), and there was no difference in p53 staining in grades 1 and 2 carcinomas ($P > .05$). Recurrences were not different between grades 1, 2, and 3 carcinomas.
- **All biologic markers studied and tumor recurrences were significantly different among papillary lesions classified by the WHO/ISUP system but not by the 1973 WHO system**, validating the predictive value of the WHO/ISUP system and providing objective markers for the grading of papillary urothelial tumors.

- Virchows Arch. 2003 Dec;443(6):734-40. Epub 2003 Oct 8.
- **Reproducibility of the 1998 World Health Organization/International Society of Urologic Pathology classification of papillary urothelial neoplasms of the urinary bladder.**
- Yorukoglu K, Tuna B, Dikicioglu E, Duzcan E, Isisag A, Sen S, Mungan U, Kirkali Z.
- **Source**
- School of Medicine, Department of Pathology, Dokuz Eylul University, 35340 Inciralti, Izmir, Turkey. kutsal.yorukoglu@deu.edu.tr
- **Abstract**
- **OBJECTIVES:**
- This study assessed the diagnostic agreement and intra- and inter-observer reproducibility of the World Health Organization/International Society of Urologic Pathology Consensus Classification of Urothelial Neoplasms (1998 WHO/ISUP classification) and the 1973 WHO classification.
- **METHODS:**
- A teaching set with 5 slides of each papillary neoplasm of low malignant potential, low-grade papillary carcinoma, high-grade papillary carcinoma, and a guideline, as well as a study set of 30 slides containing ten cases of each category, were sent to participants. Six pathologists expert in urological pathology reviewed the 30 slides of non-invasive papillary urothelial tumors in the study set. Diagnostic accuracy and reproducibility were evaluated using intra- and inter-rater techniques (kappa statistic).
- **RESULTS:**
- A moderate to substantial intra- and inter-observer reproducibility was achieved for both the 1998 WHO/ISUP and 1973 WHO classification. The results of the two classification systems were not different statistically (P>0.05). Reproducibility was lower in low-grade tumors for both classifications.
- **CONCLUSIONS:**
- **The new proposed classification system for non-invasive urothelial neoplasms does not increase the reproducibility**. There is still a need for uniformity in grading in order to compare the different studies and therapies and to provide more accurate information for management.

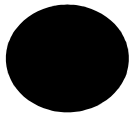
- Virchows Arch. 2002 Aug;441(2):109-16. Epub 2002 Jun 13.
- **Urothelial papillary (exophytic) neoplasms.**
- Bostwick DG, Mikuz G.
- **Source**
- Bostwick Laboratories, 2807 N. Parham Rd Richmond, VA 23294, USA. bostwick@bostwicklaboratories.com



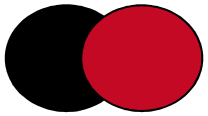
- **Abstract**
- The contemporary classification and grading of human papillary urothelial neoplasms remains unsettled, with multiple recent suggestions by groups of pathologists with little or no clinical input. One of the chief motivations for these new approaches was to avoid use of the term "cancer" for neoplasms with a low likelihood of invasion, recurrence, and death. Also, critics contended that earlier grading schemes were too imprecise to be clinically useful. We summarize the work carried out by the majority of members of Committee No. 1 at the International Consultation on the Diagnosis of Non-Invasive Urothelial Neoplasms held in Ancona, Italy (11-12 May 2001). Our deliberations represent a multidisciplinary international effort based on the best available data and the perception of existing practical methods of classification by clinicians, pathologists, and cancer registrars. The WHO 1973 classification for papillary urothelial neoplasms (papilloma, grade 1, grade 2, and grade 3 carcinoma) is still superior to all existing alternatives (such as WHO/ISUP 1998 and WHO 1999), although some refinement of diagnostic criteria would be useful. Some pathologists may prefer additionally to report synonymous classification in other schemes, but this is discouraged owing to variations and difficulties in translations.



6



5



2

- Am J Surg Pathol. 2001 Dec;25(12):1528-33.
- **Biologic differences between noninvasive papillary urothelial neoplasms of low malignant potential and low-grade (grade 1) papillary carcinomas of the bladder.**
- Pich A, Chiusa L, Formiconi A, Galliano D, Bortolin P, Navone R.
- **Source**
- Department of Biomedical Sciences and Human Oncology, Section of Pathology, University of Turin, Turin, Italy. achille.pich@unito.it
- **Abstract**
- We investigated the expression of oncogenes p53, c-erbB-2, and bcl-2 and cell proliferative activity in 62 newly diagnosed superficial pTa papillary bladder tumors. Based on the 1998 World Health Organization/International Society of Urological Pathology (WHO/ISUP) and 1999 WHO classifications, 19 were urothelial neoplasias of low malignant potential (LMP) and 43 low-grade (grade 1) papillary carcinomas. All the patients underwent transurethral resection and were followed up to 97 months; 42 had recurrences. Initial biopsies were tested for p53, c-erbB-2, and bcl-2 proteins using DO7, CB11, and bcl-2 124 monoclonal antibodies. Cell proliferation was assessed by MIB-1 mAb and mitotic count. **LMP had significantly lower MIB-1 (p = 0.002) and p53 immunopositivity (p = 0.03), mitotic count (p = 0.006), and recurrence rates (p = 0.04) than did grade 1 cases, whereas no difference was observed for c-erbB-2 and bcl-2 expression.** The median disease-free survival for LMP was 76 months but only 15 months for grade 1 cases (p = 0.002). Although the cohort is small, the results indicate that the **distinction between LMP and low-grade (grade 1) papillary urothelial neoplasias, as proposed by the 1998 WHO/ISUP and 1999 WHO classifications, reflects different biologic activity and clinical behavior; however, a long-term follow-up is advisable also for patients with LMP.**

- J Pathol. 2002 Oct;198(2):245-51.
- **Frequent FGFR3 mutations in urothelial papilloma.**
- van Rhijn BW, Montironi R, Zwarthoff EC, Jöbsis AC, van der Kwast TH.
- **Source**
- Department of Pathology, Josephine Nefkens Institute, Erasmus University, 3000 DR Rotterdam, The Netherlands.
- **Abstract**
- Activating point mutations in the FGFR3 gene occur frequently in low-grade and low-stage bladder carcinomas, whereas they are rare in high-grade carcinomas. This study investigates the incidence of FGFR3 mutations in 12 urothelial papillomas and 79 pTaG1 tumours which were regraded according to the 1998 WHO/ISUP classification system, resulting in 62 papillary urothelial neoplasms of low malignant potential (PUNs-LMP) and 17 low-grade papillary urothelial carcinomas (LG-PUCs). FGFR3 mutation analysis of 21 ovarian Brenner tumours was also performed. Seventy-seven cases were detected with a mutation in the FGFR3 gene. The mutations were exclusively found in bladder neoplasms. In urothelial papilloma, generally considered a benign lesion, 9/12 (75%) mutations were found. This report is the first to describe a genetic defect in urothelial papilloma. A comparable percentage of mutations was found in PUNs-LMP (85%) and LG-PUCs (88%). No mutations were found in matched normal DNA from bladder tumour patients. The mean follow-up was 5.78 years (range 0.21-17.60 years). Five patients developed high-grade papillary urothelial carcinoma from 2.5 to 12 years after first diagnosis. Two patients died of bladder cancer. The mean number of recurrences (recurrence rate) per year was 0.03, 0.21, and 0.46, respectively, for papilloma, PUN-LMP, and LG-PUC. **Urothelial papilloma is a rare lesion with a benign natural behaviour compared with PUN-LMP and LG-PUC of the bladder, but from a molecular perspective, papillomas should be classified together with all well-differentiated urothelial neoplasms.**

- Pathol Int. 2010 Jan;60(1):1-8.
- **Non-invasive papillary urothelial neoplasms: the 2004 WHO/ISUP classification system.**
- Miyamoto H, Miller JS, Fajardo DA, Lee TK, Netto GJ, Epstein JI.
- **Source**
- Department of Pathology and Laboratory Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642, USA. hiroshi_miyamoto@urmc.rochester.edu
- **Abstract**
- The classification and grading of papillary urothelial neoplasms has been a long-standing subject of controversy. Previously, numerous diverse grading schemes for bladder tumor, including the 1973 World Health Organization (WHO) classification, existed whereby one of the major limitations was poor inter-observer reproducibility among pathologists. The WHO/International Society of Urological Pathology (ISUP) consensus classification system of urothelial neoplasms of the urinary bladder was developed in 1998 and was revised most recently in 2003 (published in 2004). Importantly, the current classification system provides detailed histological criteria for papillary urothelial lesions and allows for designation of a lesion (papillary urothelial neoplasm of low malignant potential) with a negligible risk of progression. Thus, the latest system is designed to be a universally acceptable one for bladder tumors that not only could be effectively used by pathologists, urologists, and oncologists, but also stratifies the tumors into prognostically significant categories. This article outlines the 2004 WHO/ISUP classification system regarding the specific histological criteria for non-invasive papillary urothelial neoplasms and the clinical significance of each category.


458
ITALIA

- Arch Pathol Lab Med. 2010 Aug;134(8):1160-3.
- **Low-grade papillary urothelial carcinoma of the urinary bladder: a clinicopathologic analysis of a post-World Health Organization/International Society of Urological Pathology classification cohort from a single academic center.**
- Miyamoto H, Brimo F, Schultz L, Ye H, Miller JS, Fajardo DA, Lee TK, Epstein JI, Netto GJ.
- **Source**
- Department of Pathology, Johns Hopkins University, Baltimore, Maryland, USA.
- **Abstract**
- **CONTEXT:**
- Few large cohort studies have addressed outcome in patients with noninvasive low-grade papillary urothelial carcinoma (LG-UrCa) following implementation of the 2004 World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification.
- **OBJECTIVE:**
- To evaluate our cohort of LG-UrCa cases classified according to 2004 WHO/ISUP to reassess outcome and interobserver agreement.
- **DESIGN:**
- Files were searched for all patients diagnosed with LG-UrCa between 1998 and 2008. All sections were reevaluated for accuracy of classification.
- **RESULTS:**
- A total of 112 cases initially diagnosed as LG-UrCa were identified. Of those, 8 of 55 cases (15%) initially diagnosed by nonurologic pathologists were reclassified as high-grade papillary urothelial carcinoma and were excluded. The mean length of follow-up was 40.1 months (range, 2-113 months). Tumor recurrence was encountered in 56 of 104 patients (53.8%), including 37 (35.6%) with LG-UrCa or lower-grade tumors and 19 (18.3%) with high-grade papillary urothelial carcinoma. Of the 19 patients demonstrating grade progression, 7 (37%) also developed stage progression (invasive carcinoma, n = 5; metastatic carcinoma, n = 2). Seven patients eventually underwent radical cystectomy. None of the 104 patients died of bladder cancer. The mean number of recurrence episodes was 3.11. The mean durations of time to first recurrence and time to grade progression were 13.9 months and 25.1 months, respectively. The mean size of initial tumors was 1.73 cm. There was no significant correlation between tumor size, patient age, sex, or smoking history and the likelihood for recurrence or grade progression. A significantly higher rate of recurrence was seen in patients with multiple tumors at initial diagnosis (P = .04).
- **CONCLUSIONS:**
- A tendency to underdiagnose high-grade papillary urothelial carcinoma continues to exist. More than half (53.8%) of patients with LG-UrCa developed recurrence, with an 18.3% incidence of grade progression and a 6.7% incidence of stage progression. Patients with multiple initial tumors had significantly higher risk of developing recurrence.

- Histopathology. 2011 Mar;58(4):579-85. doi: 10.1111/j.1365-2559.2011.03784.x. Epub 2011 Feb 23.
- **Handling and reporting of transurethral resection specimens of the bladder in Europe: a web-based survey by the European Network of Uropathology (ENUP).**
- Lopez-Beltran A, Algaba F, Berney DM, Boccon-Gibod L, Camparo P, Griffiths D, Mikuz G, Montironi R, Varma M, Egevad L.