

## XXII. Martinský bioptický seminár

Kúpele Lúčky, 4-5.11.2016

### Aktuálny pohľad na grading karcinómu prostaty.

J. Marcinek

Ústav patologickej anatómie

Univerzitná nemocnica Martin

Jesseniova lekárska fakulta UK v Martine

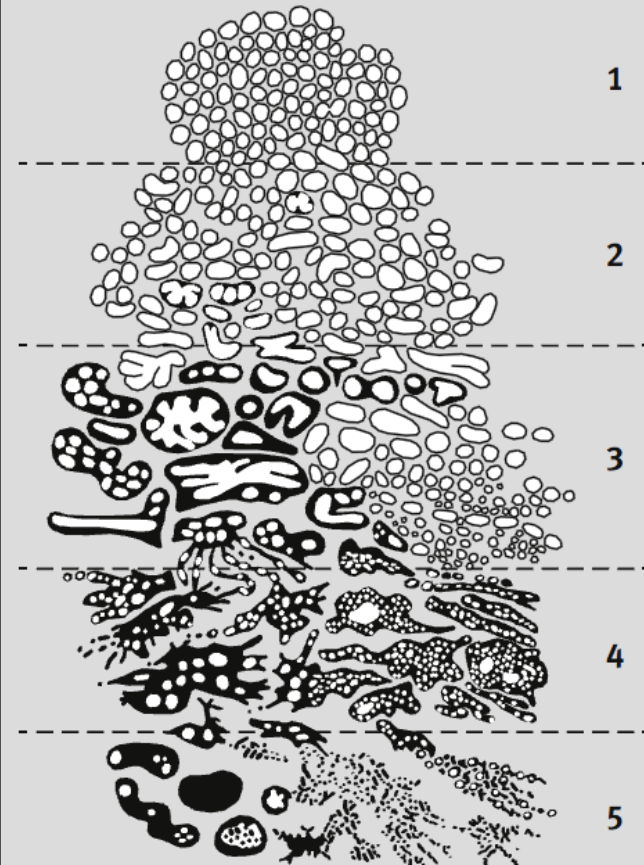


# Donald F. Gleason



- 1920 - 2008
- 1944 Título de Médico Universidad Minnesota
- 1947 Ingresa a la residencia de AP en Minneapolis
- 2002 Presidente Honorario AUA

## PROSTATIC ADENOCARCINOMA (Histological Patterns)



## The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Jonathan I. Epstein, MD,\* William C. Allsbrook, Jr, MD,† Mahul B. Amin, MD,‡  
and Lars L. Egevad, MD, PhD,§ and the ISUP Grading Committee<sup>1</sup>

Donald F. Gleason in 1966 created a unique grading system for prostatic carcinoma based solely on the architectural pattern of the tumor.<sup>1,14,22</sup> Another innovative aspect of this system was, rather than assigning the worst grade as the grade of the carcinoma, the grade was defined as the sum of the two most common grade patterns and reported as the Gleason score. The original description of this system, based on a study of 270 patients from the Minneapolis Veterans Administration Hospital, is seen in Table 1.

Initially, Gleason intended to classify carcinomas into four patterns, but a small group of distinctive tumors (clear cell) was observed and they were placed in a separate fifth category (pattern 4).<sup>14</sup> Certain aspects of the original Gleason system would be interpreted differently in today's practice. The cribriform pattern described as a component of Gleason's original patterns 2 and 3 would today typically be considered higher grade. Individual cells listed under Gleason's original pattern 3 would also be currently assigned a higher grade. Pattern 4 has become significantly expanded beyond Gleason's original description of tumors with clear cytoplasm that resembled renal cell carcinoma (Table 1).

By 1974, Gleason and the Veterans Administration Cooperative Urological Research Group expanded their study to

1032 men.<sup>13</sup> Gleason pattern 4 was described in a figure legend as "raggedly infiltrating, fused-glandular tumor, frequently with pale cells, may resemble hypernephroma of kidney." The Gleason system was further refined by Mellinger in 1977 when the papillary and cribriform tumor under Gleason pattern 3 was described as having a "smooth and usually rounded edge."<sup>23</sup> These modifications of the Gleason system are depicted in Table 1. In describing the breakdown of Gleason patterns among 2911 cases, Gleason pattern 1 was seen in 3.5%; pattern 2 in 24.4%; pattern 3 in 87.7%; pattern 4 in 12.1%; and pattern 5 in 22.6%.<sup>23</sup> These percentages added up to approximately 150% because 50% of the tumors showed at least two different patterns.

In 1977, Gleason provided additional comments concerning the application of the Gleason system.<sup>14</sup> "Grading is performed under low magnification (40-100X)." He also stated "an occasional small area of fused glands did not change a pattern 3 tumor to pattern 4. A small focus of disorganized cells did not change a pattern 3 or 4 tumor to pattern 5." The only comment relating to tertiary patterns was "occasionally, small areas of a third pattern were observed."

### WHY THE NEED FOR A CONSENSUS ON GLEASON GRADING?

It is a testament to the enduring power of the original Gleason grading system that it is the accepted grading system throughout the world, despite its inception almost 40 years ago. How many other things in medicine have stood the test of time so well? Nonetheless, medicine in general and prostate carcinoma in specific has changed dramatically since the late 1960s, when the Gleason grading system was derived. In the 1960s, there was no screening for prostate cancer other than by digital rectal examination, as serum PSA had not yet been discovered. In Gleason's 1974 study, most (86%) of the men had advanced disease with either local extension out of the prostate on clinical examination or distant metastases. Only 6% of patients had nonpalpable tumor diagnosed by transurethral resection and 8% of patients were diagnosed with a localized nodule on rectal examination.<sup>13</sup> The method of obtaining prostate tissue was also very different from today's practice. Typically, only a couple of thick-gauge needle biopsies were directed into an area of palpable abnormality. The use of 18-gauge thin biopsy needles and the concept of sextant needle biopsies to more extensively sample the prostate were not developed until the 1980s.<sup>17</sup> Consequently, the grading of

From the \*Department of Pathology, Urology and Oncology, Johns Hopkins Hospital, Baltimore, MD; †Departments of Pathology & Surgery (Urology), Medical College of Georgia, Augusta, GA; ‡Department of Pathology and Laboratory Medicine, Urology, Hematology & Oncology, Emory University School of Medicine, Atlanta, GA; and §Department of Pathology and Cytology, Karolinska Hospital, Stockholm, Sweden.

<sup>1</sup>Sheldon Bastacky, USA; Antonio López Beltrán, Spain; Aasmund Berner, Norway; Athanasios Biliy, Brazil; Liliane Boccon-Gibod, France; Liang Cheng, USA; Francisco Cventos, USA; Cynthia Cohen, USA; Michael B. Cohen, USA; Milton Datta, USA; Charles Davis, USA; Brett Delabant, New Zealand; Warwick Delprado, Australia; John N. Eble, USA; Christopher S. Foster, UK; Masakuni Furusato, Japan; Paul B. Gannin, USA; David J. Grignon, USA; Peter A. Humphrey, USA; Kenneth A. Iczkowski, USA; Edward C. Jones, Canada; Scott Lucia, USA; Peter A. McCue, USA; Tiju Nair, USA; Esther Oliva, USA; Chin-Chen Pan, Taiwan; Galina Puzov, Israel; Victor Reuter, USA; Hernando Sarmastranga, Australia; Thomas Sebo, USA; Isabella Senterberg, USA; Maria Shovchuk, USA; John R. Srigley, Canada; Sueli Szargan, Brazil; Hiroyuki Takahashi, Japan; Phemea Terribili, USA; Pany Hoon Tan, Singapore; Bernard Tebi, Canada; Satish Tickoo, USA; John E. Tomaszewski, USA; Patricia Troncoso, USA; Toyonori Tsumaki, Japan; Lawrence D. Truc, USA; Theo van der Kwast, Canada; Thomas M. Wheeler, USA; Kirk J. Wajno, USA; Robert H. Young, USA.

Reprints: Jonathan I. Epstein, MD, 401 N. Broadway Street, Johns Hopkins Hospital, Weisberg Building, Rm 2-242, Baltimore, MD 21231 (e-mail: jpepstein@jhmi.edu).

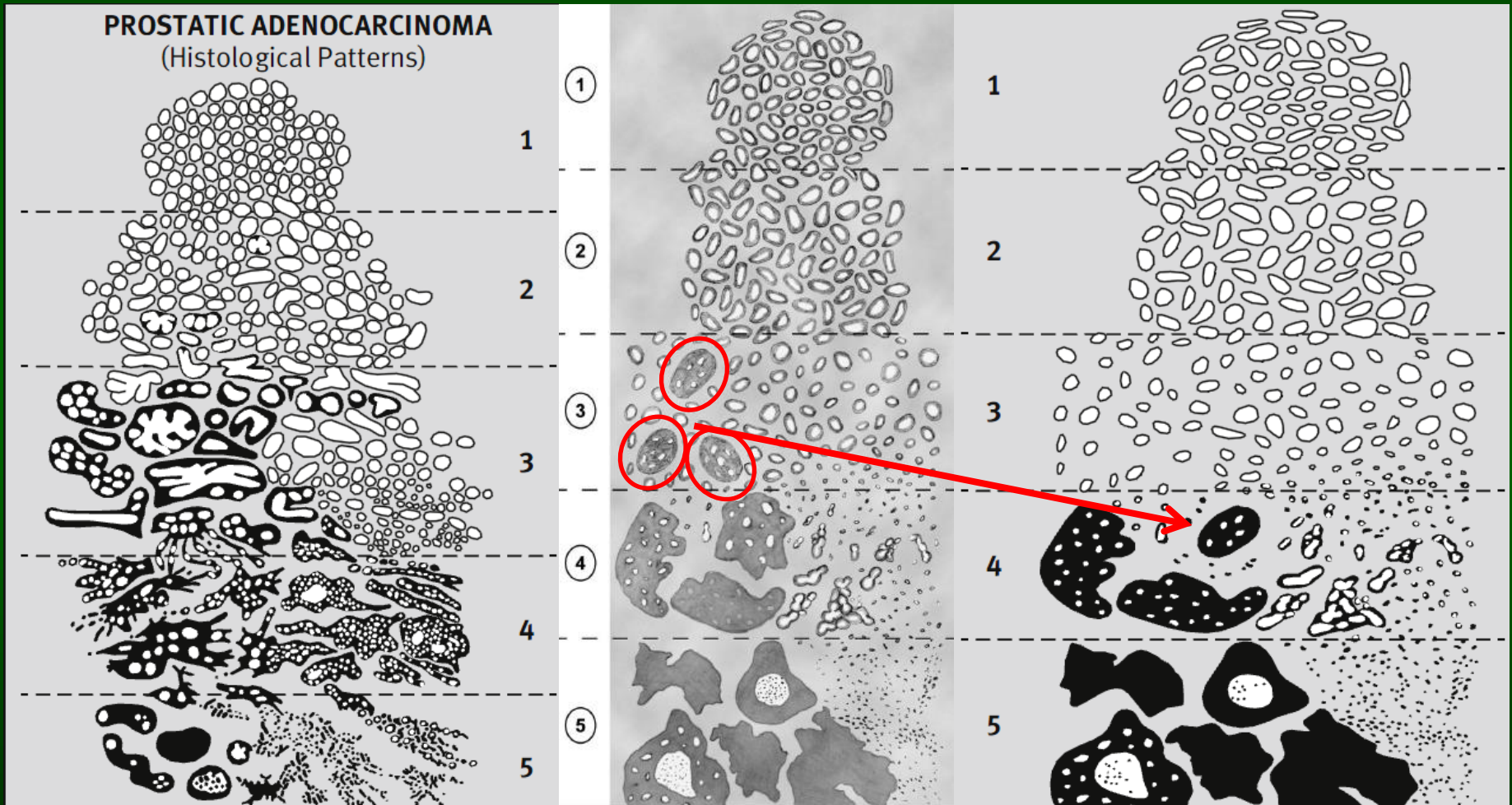
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# ❖ vývoj Gleasonovho grading systému karcinómu prostaty (KP)

Gleason 1992

ISUP 2005

Epstein 2010



# The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

## *Definition of Grading Patterns and Proposal for a New Grading System*

*Jonathan I. Epstein, MD,\* Lars Egevad, MD, PhD,† Mahul B. Amin, MD,‡ Brett Delahunt, MD,§ John R. Srigley, MD,|| Peter A. Humphrey, MD, PhD,¶ and the Grading Committee*

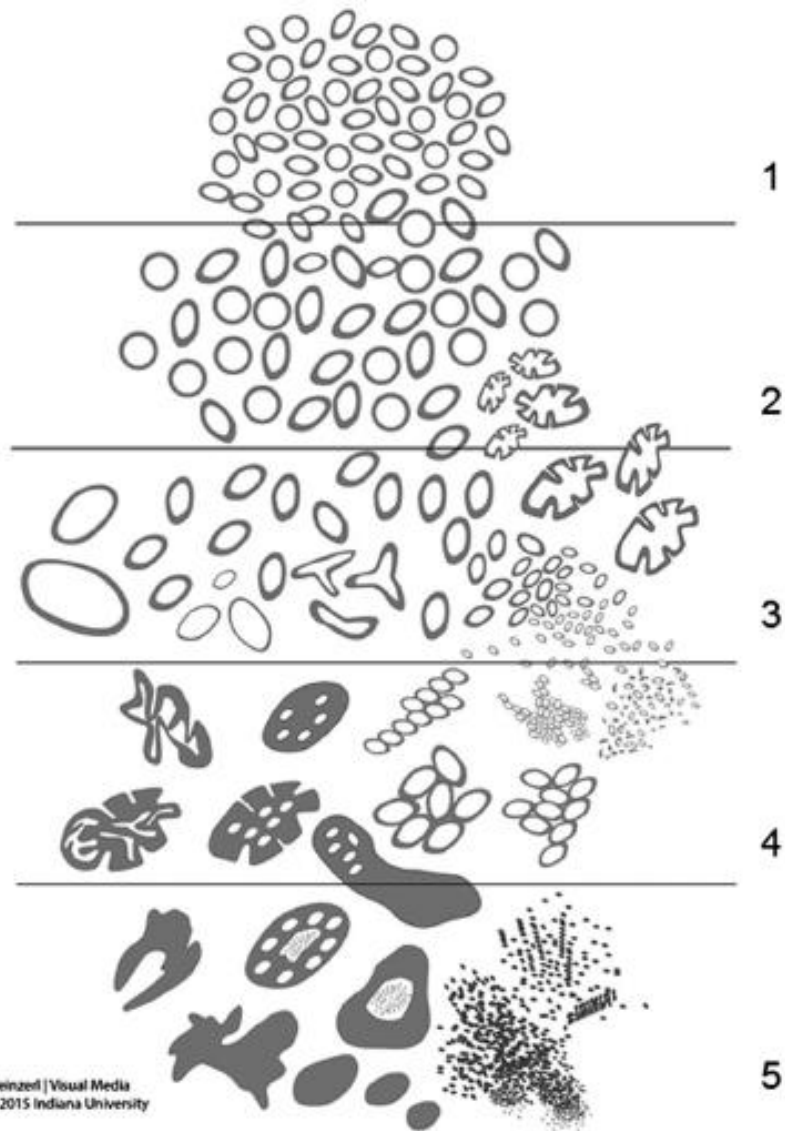
**Abstract:** In November, 2014, 65 prostate cancer pathology experts, along with 17 clinicians including urologists, radiation oncologists, and medical oncologists from 19 different countries

From the \*Departments of Pathology, Urology, and Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD; †Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden; ‡Department of Pathology & Laboratory Medicine, Cedars-Sinai, Los Angeles, CA; §Department of Pathology & Molecular Medicine, Wellington School of Medicine & Health Sciences, University of Otago-Wellington, Wellington South, New Zealand; ||Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada; and ¶Department of Pathology, Yale School of Medicine, New Haven, CT.

Members of Grading Committee: *Pathologists:* Turki Al-Hussain (Saudi Arabia), Ferran Algaba (Spain), Manju Aron (USA), David Berman (Canada), Daniel Berney (England), Fadi Brimo (Canada), Dengfeng Cao (China), John Cheville (USA), David Clouston (Australia), Maurizio Colechia (Italy), Eva Comperat (France), Isabela Werneck da Cunha (Brazil), Angelo De Marzo (USA), Dilek Ertoy (Turkey), Samson Fine (USA), Christopher Foster (England), David Grignon (USA), Nilesh Gupta (USA), Ruta Gupta (Australia), James Kench (Australia), Glen Kristiansen (Germany), Lakshmi Kunju (USA), Katia Ramos Moreira Leite (Brazil), Massimo Loda (USA), Antonio Lopez-Beltran (Spain), Tamara Lotan (USA), M. Scott Lucia (USA), Cristina Magi-Galluzzi (USA), Rodolfo Montironi (Italy), Jesse McKenney (USA), Jennifer Merrimen (Canada), George Netto (USA), Robert Orozco (Guatemala), Gladell Paner (USA), Anil Parwani (USA), Galina Pizov (Israel), Victor Reuter (USA), Jae Ro (USA), Hemamali Samaratunga (Australia), Luciana Schultz (Brazil), Jonathan Shanks (England), Isabell Sesterhenn (USA), Steven Shen (USA), Jeffrey Simko (USA), Sueli Suzigan (Brazil), Moushumi Suryavanshi (India), Puay Hoon Tan (Singapore), Hiroyuki Takahashi (Japan), Scott Tomlins (USA), Kiril Trpkov (Canada), Patricia Troncoso (USA), Lawrence

gathered in a consensus conference to update the grading of prostate cancer, last revised in 2005. The major conclusions were: (1) Cribriform glands should be assigned a Gleason pattern 4, regardless of morphology; (2) Glomeruloid glands should be assigned a Gleason pattern 4, regardless of morphology; (3) Grading of mucinous carcinoma of the prostate should be based on its underlying growth pattern rather than grading them all as pattern 4; and (4) Intraductal carcinoma of the prostate without invasive carcinoma should not be assigned a Gleason grade and a comment as to its invariable association with aggressive prostate cancer should be made. Regarding morphologies of Gleason patterns, there was clear consensus on: (1) Gleason pattern 4 includes cribriform, fused, and poorly formed glands; (2) The term hypernephromatoid cancer should not be used; (3) For a diagnosis of Gleason pattern 4, it needs to be seen at 10x lens magnification; (4) Occasional/seemingly poorly formed or fused glands between well-formed glands is insufficient for a diagnosis of pattern 4; (5) In cases with borderline morphology between Gleason pattern 3 and pattern 4 and crush artifacts, the lower grade should be favored; (6) Branched glands are allowed in Gleason pattern 3; (7) Small solid cylinders represent Gleason pattern 5; (8) Solid medium to large nests with rosette-like spaces should be considered to represent Gleason pattern 5; and (9) Presence of unequivocal comedonecrosis, even if focal is indicative of Gleason pattern 5. It was recognized by both pathologists and clinicians that despite the above changes, there were deficiencies with the Gleason system. The Gleason grading system ranges from 2 to 10, yet 6 is the lowest score currently assigned. When patients are told that they have a Gleason score 6 out of 10, it implies that their prognosis is relatively good

## ❖ modifikovaný ISUP Gleason grading systém



❖ **Gleason vzor 1 a 2:**

**1. Gleason skóre 2 (1+1) – nikdy nepoužívať (resp. „extrémne zriedkavo“)**

**2. Gleason skóre 3 a 4 (2+1, 2+2) – nikdy nepoužívať v PB**

**(nemožno posúdiť ohraničenosť lézie)**

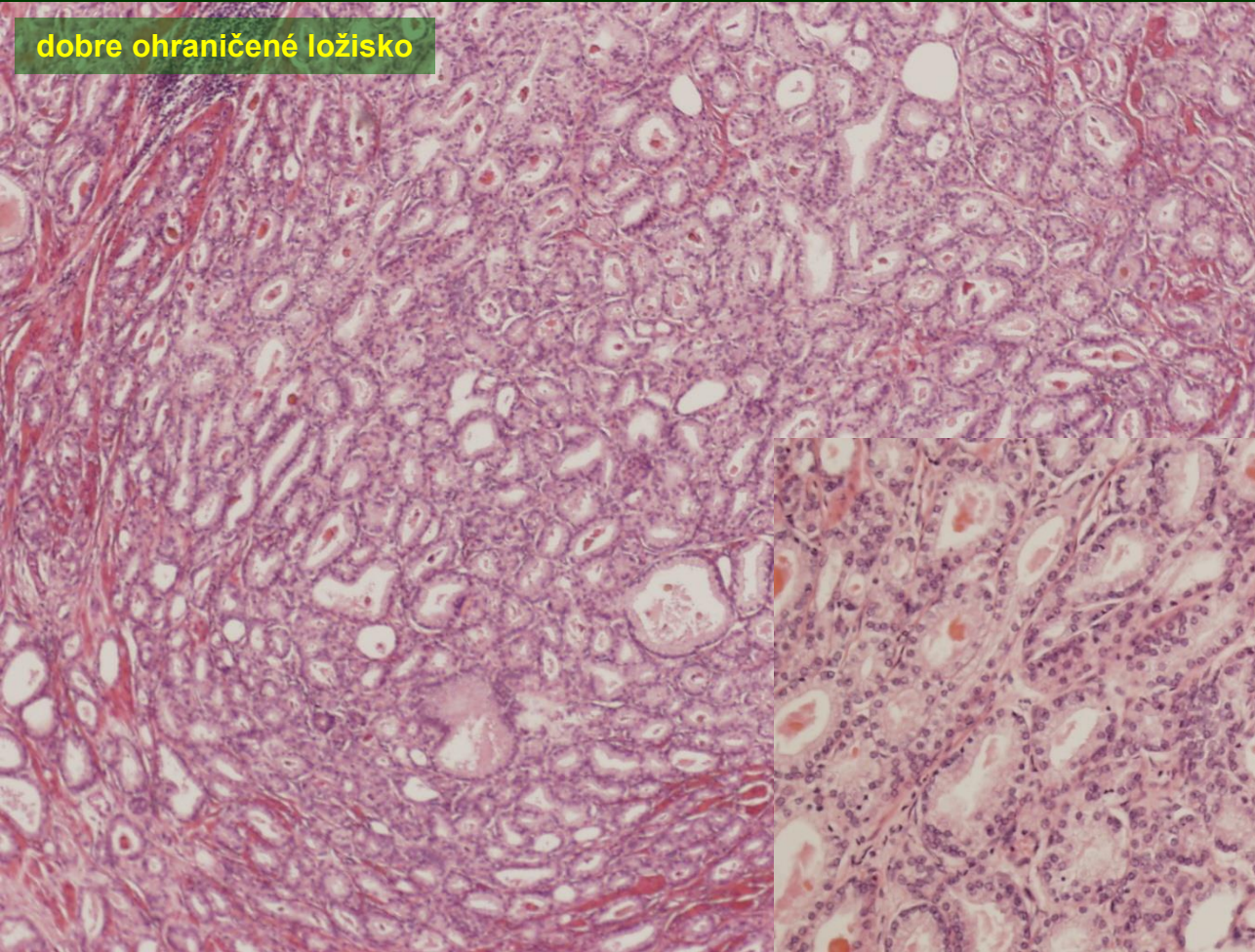
**- celkom ojedinele v TURP resp. RP**

**=>**

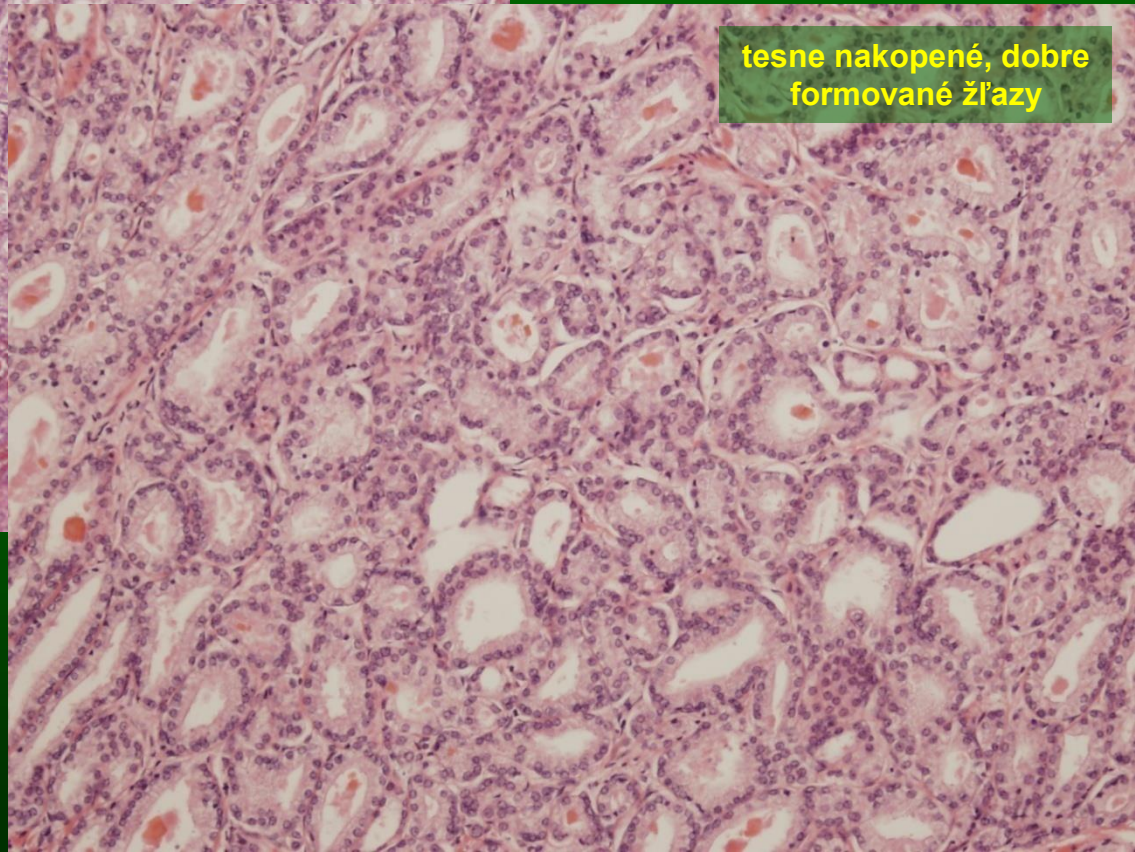
**3. Gleasonov vzor začína od 3 vo všetkých PB a drvivej väčšine TURP a RP**

## ❖ Gleasonov rastový vzor 2

dobře ohraničené ložisko



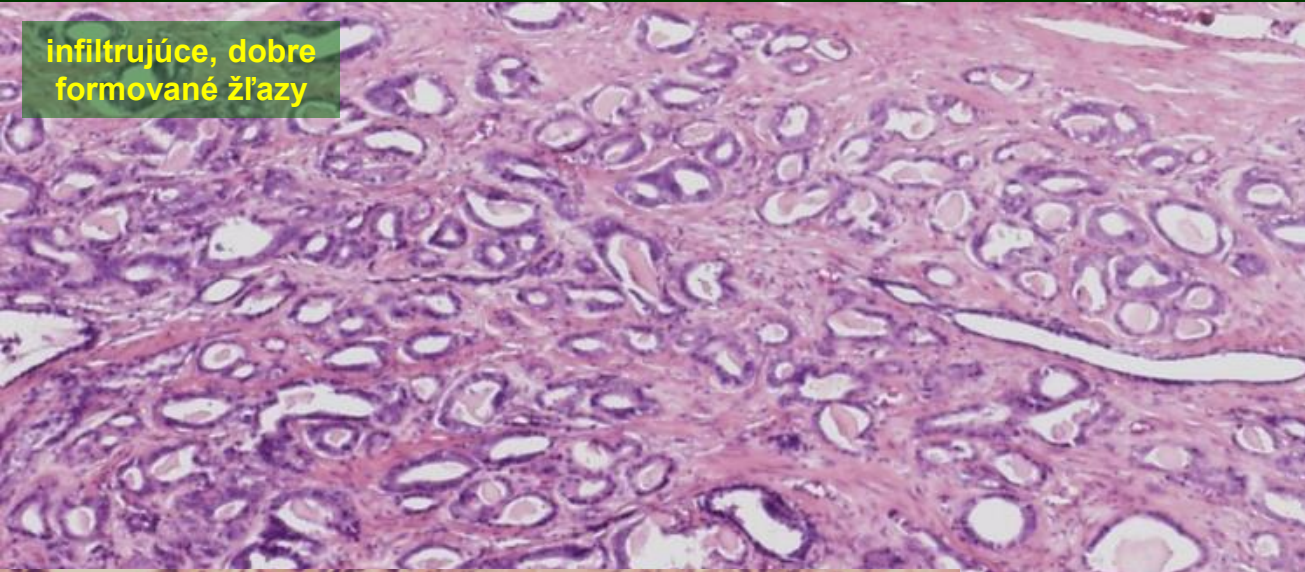
tesne nakopené, dobre formované žľazy



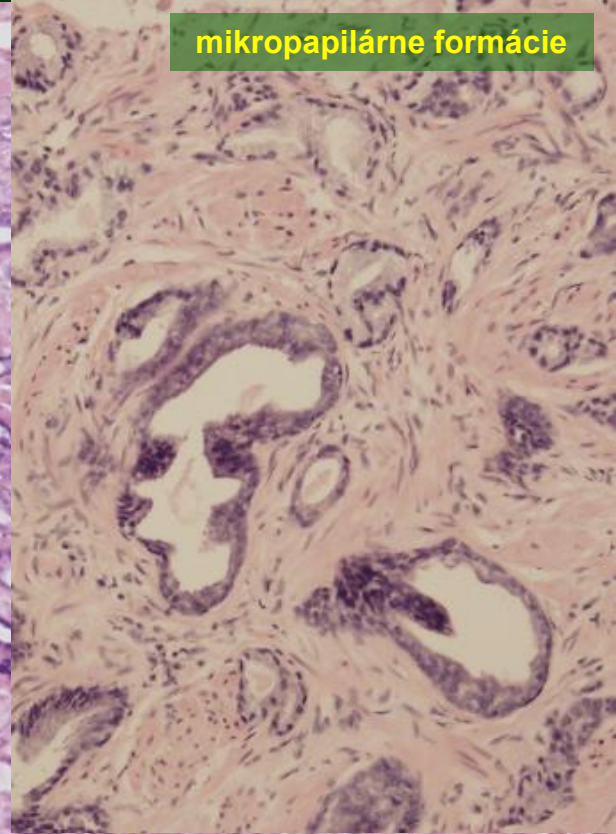


## ❖ Gleasonov rastový vzor 3

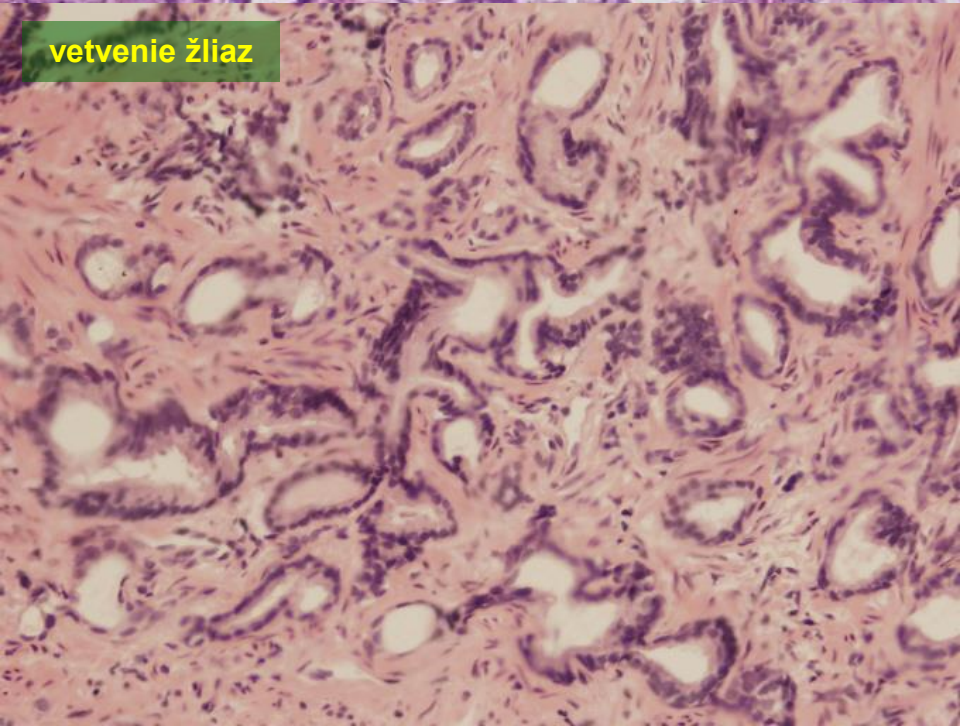
infiltrujúce, dobre formované žľazy



mikropapilárne formácie



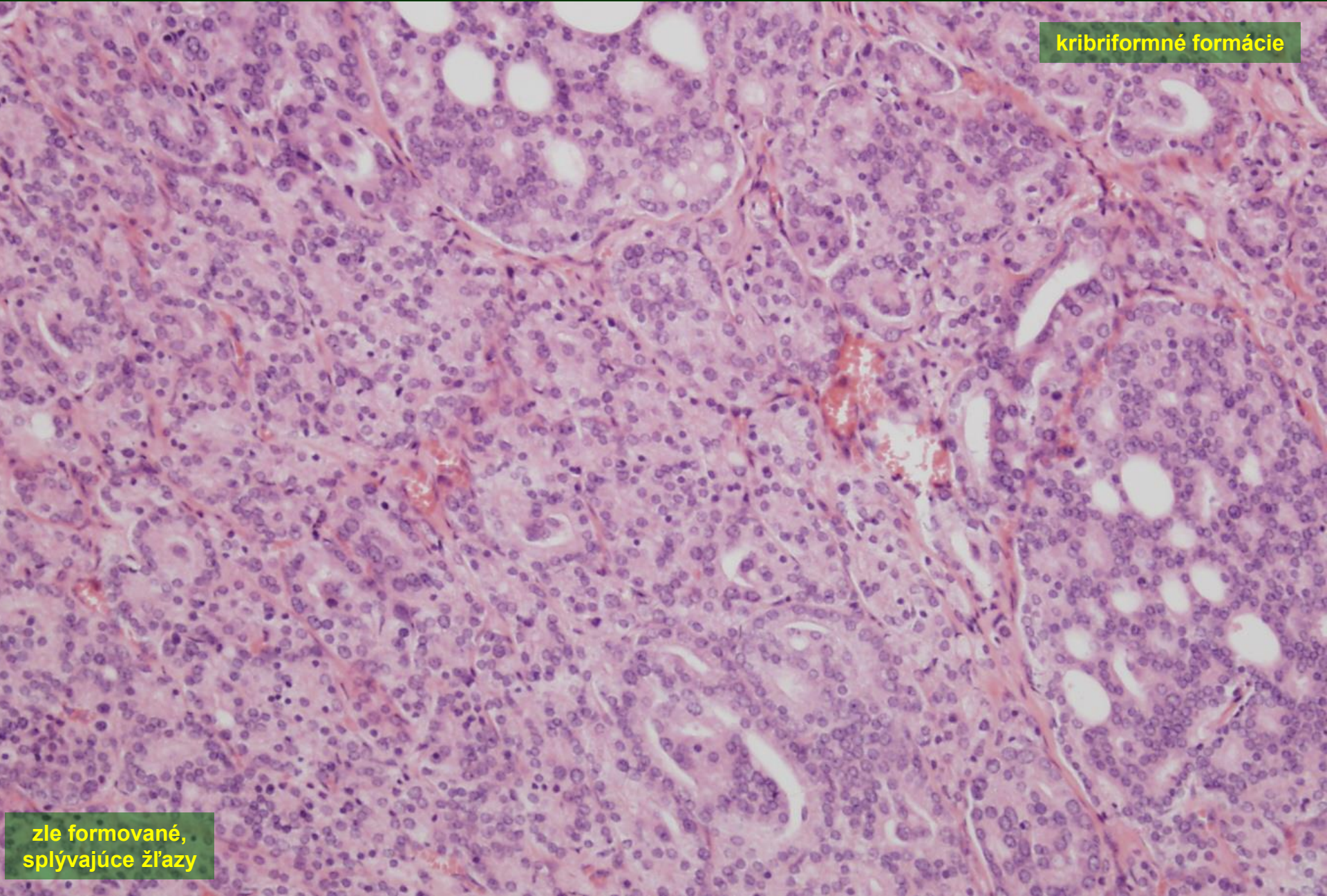
vetvenie žliaz



## ❖ Gleasonov rastový vzor 4

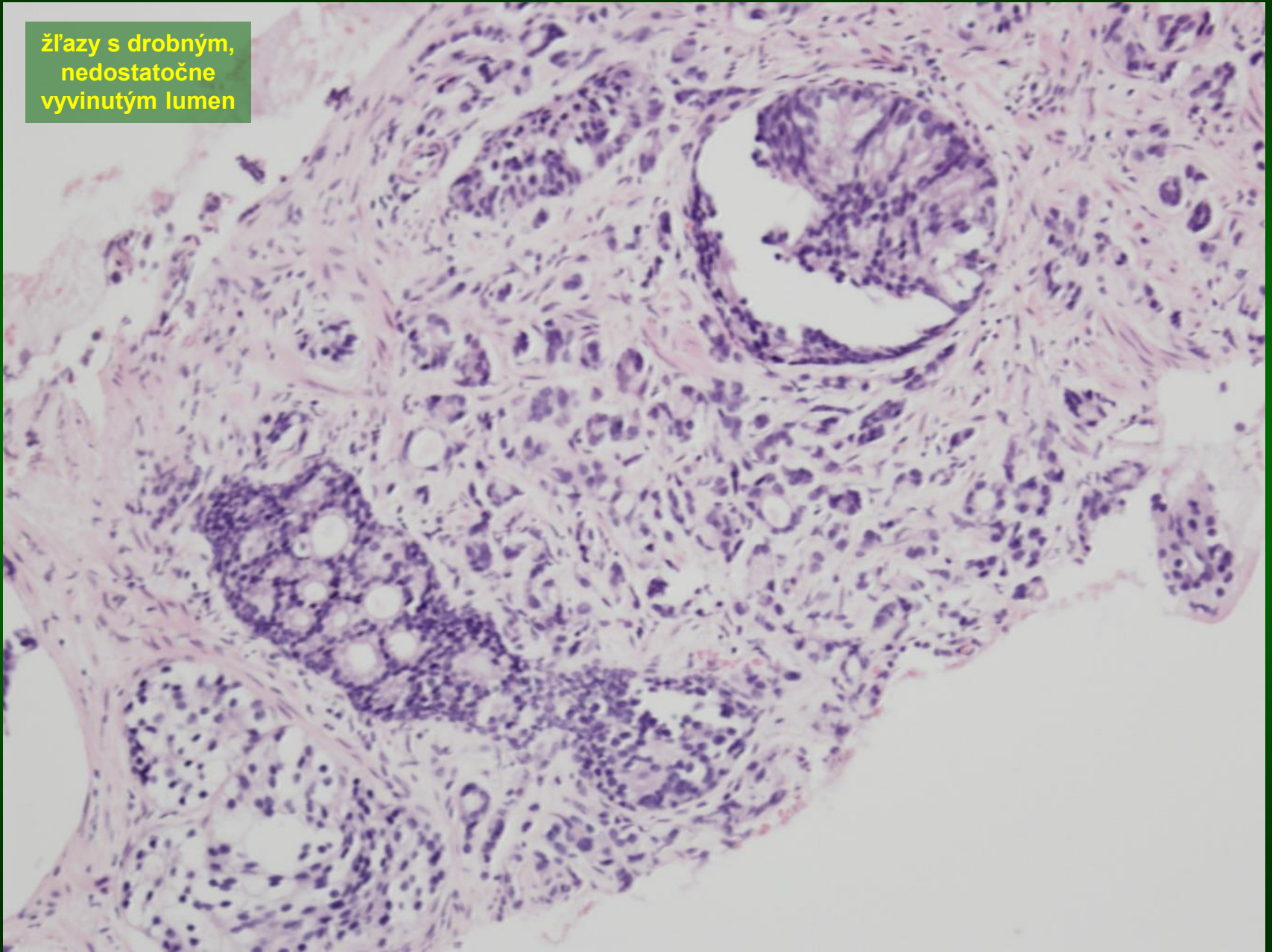
kribriformné formácie

zle formované,  
splývajúce žľazy

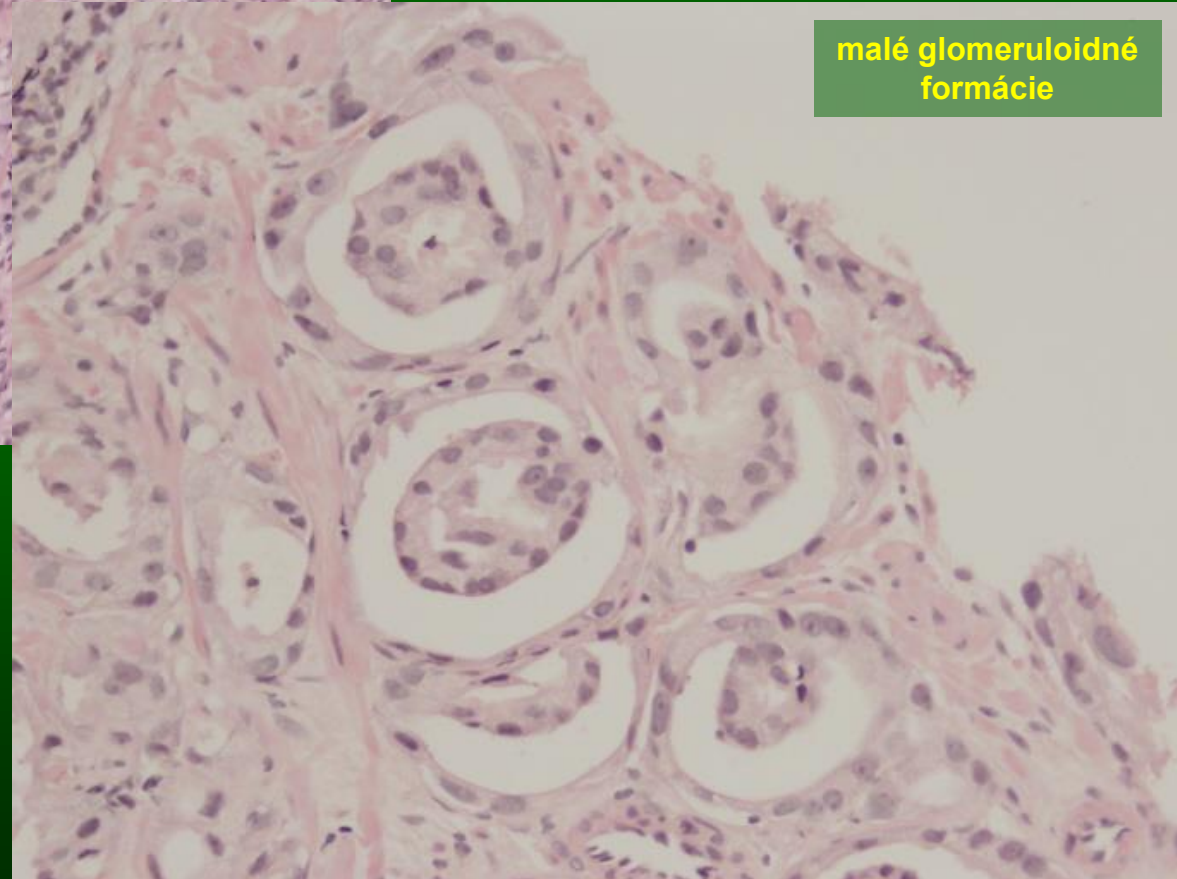
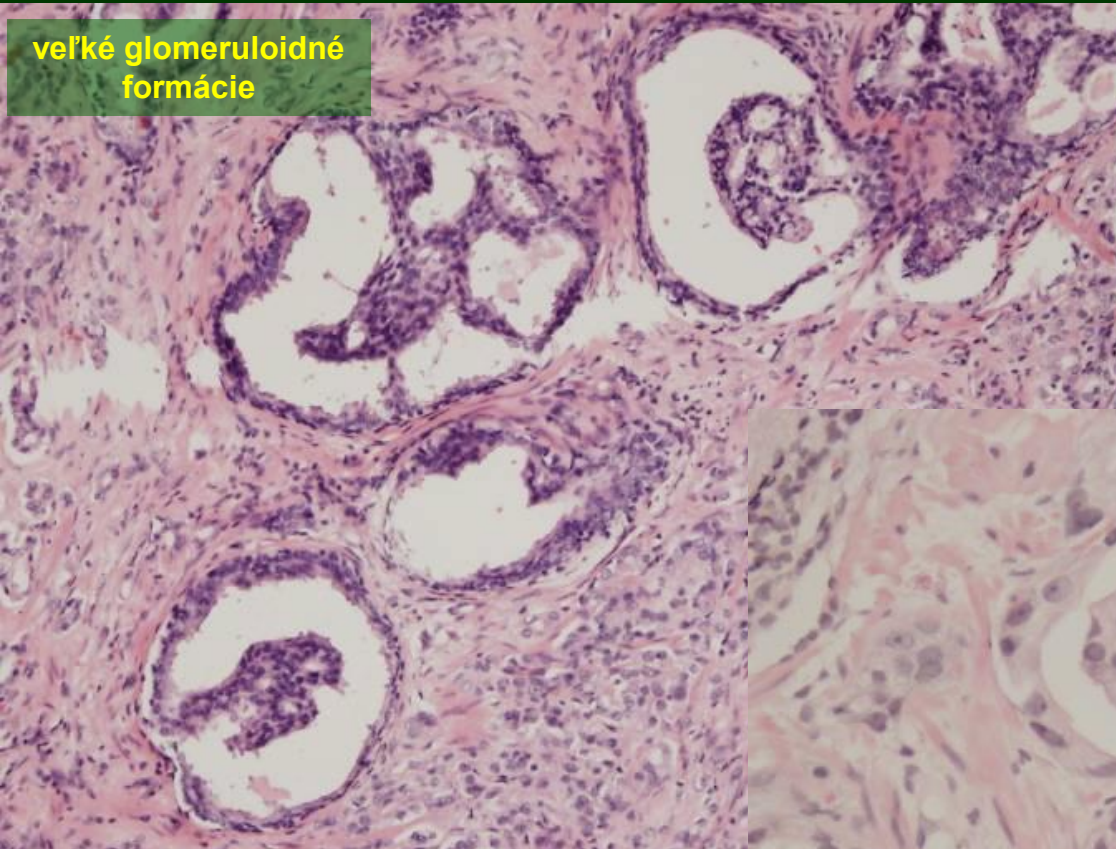


## ❖ Gleasonov rastový vzor 4

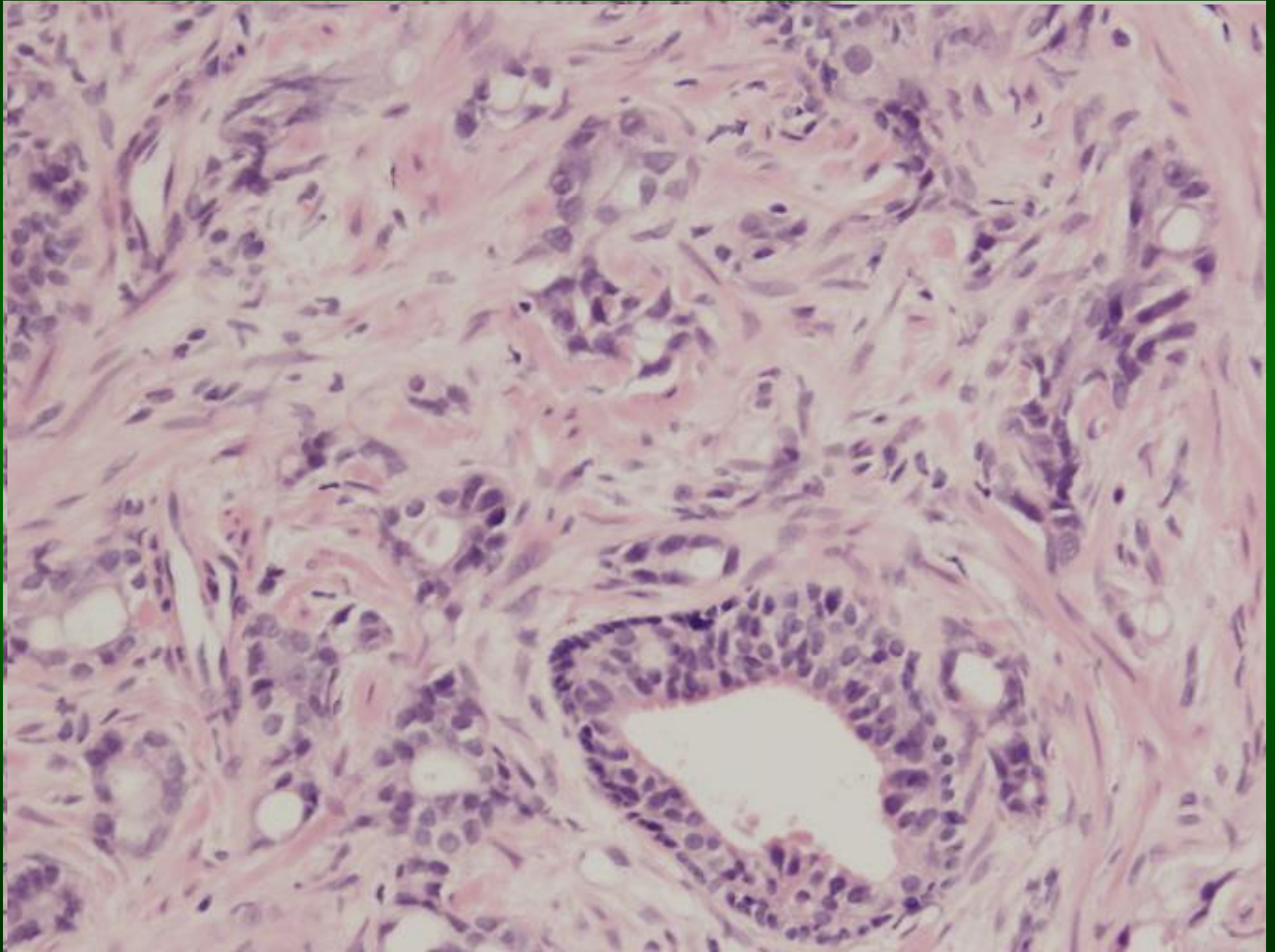
žlázy s drobným,  
nedostatočně  
vyvinutým lumen



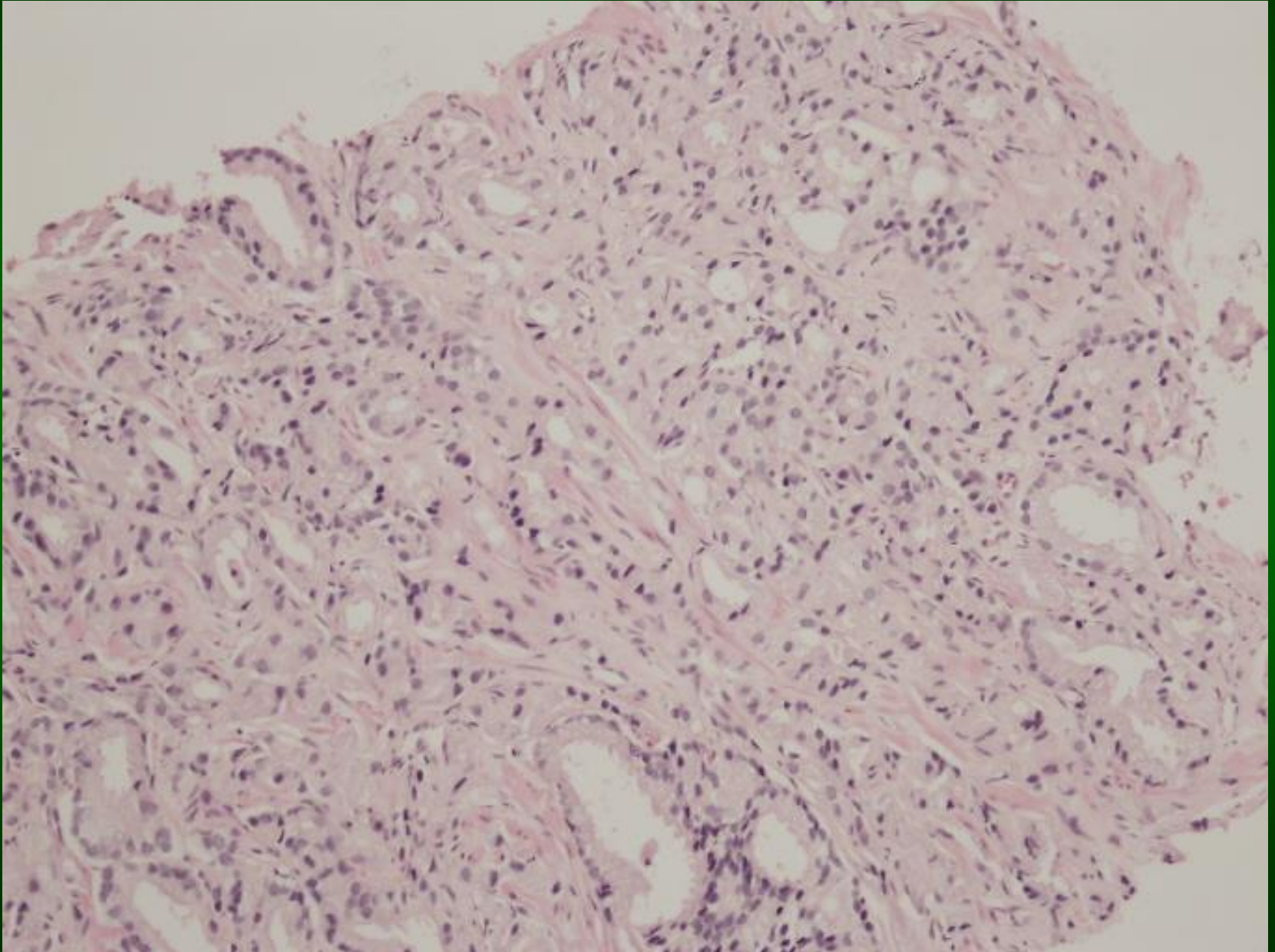
## ❖ Gleasonov rastový vzor 4



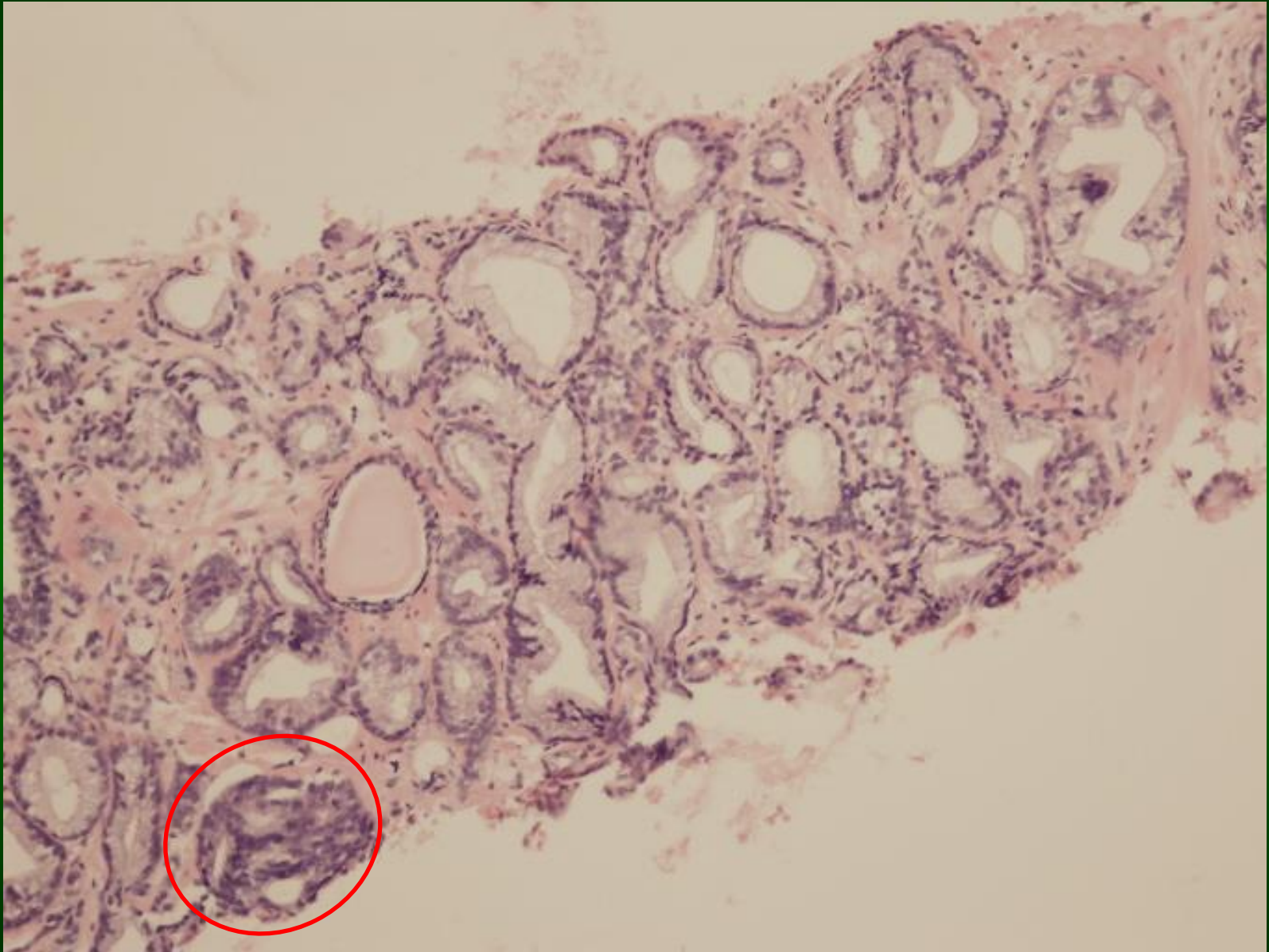
❖ Gleasonov rastový vzor 3 + ojedinelé „zle formované žľazy“ ( $\leq 5$ ) = 6 (3+3)



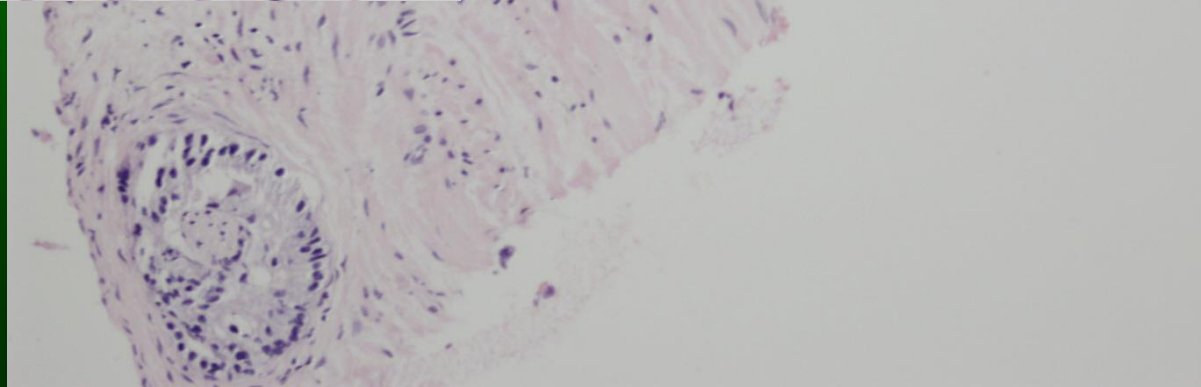
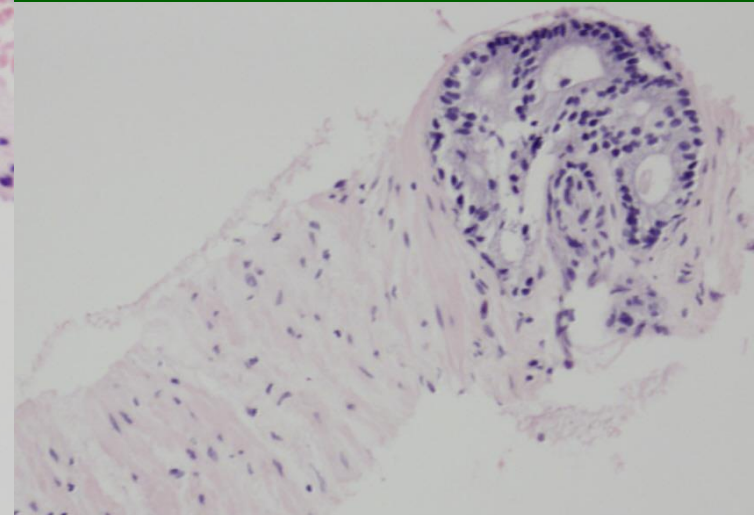
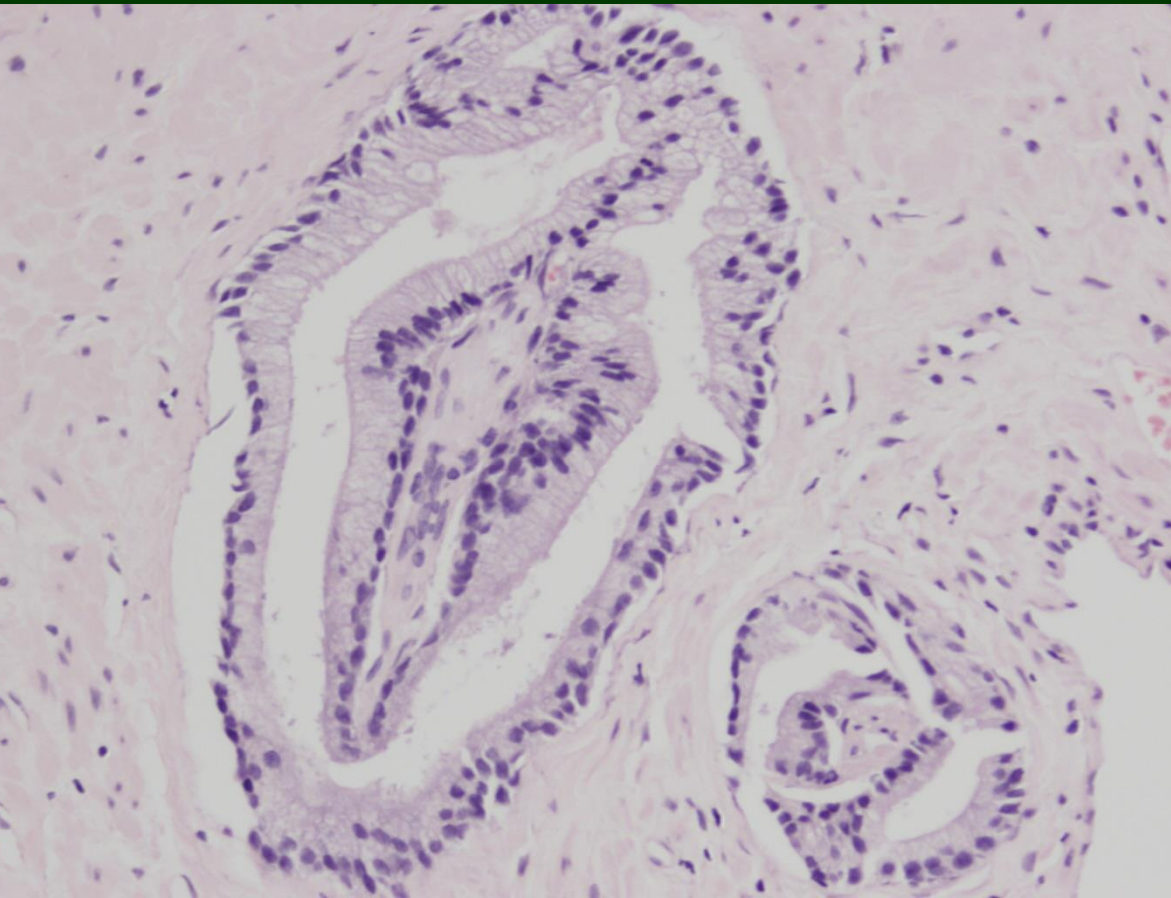
❖ Gleasonov rastový vzor 3 + viacero „zle formovaných žliaz“ ( $\geq 6$ ) = 7 (3+4)



❖ Gleasonov rastový vzor 3 + ojedinelé kribriformné formácie = 7(3+4)

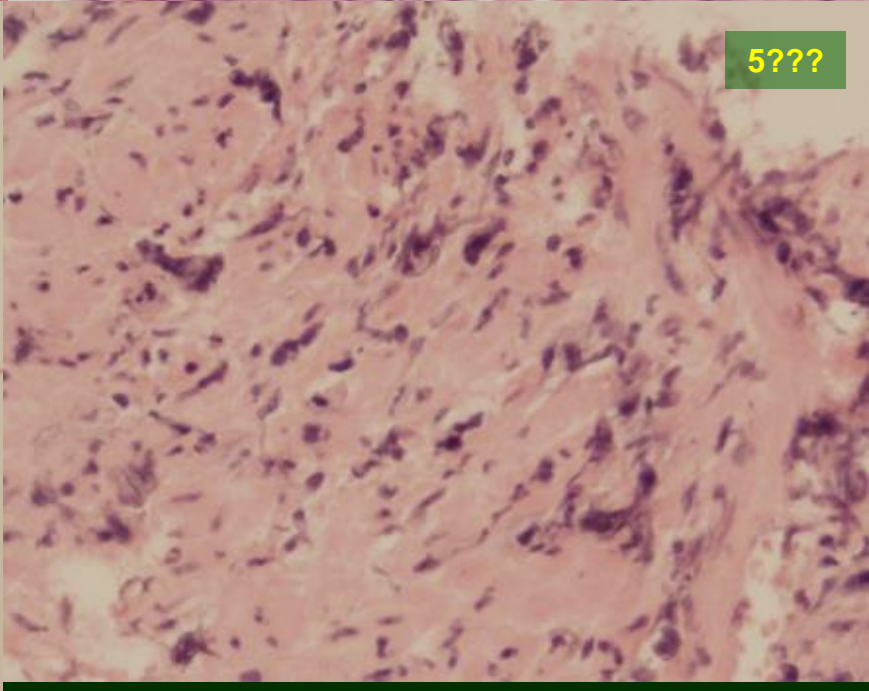
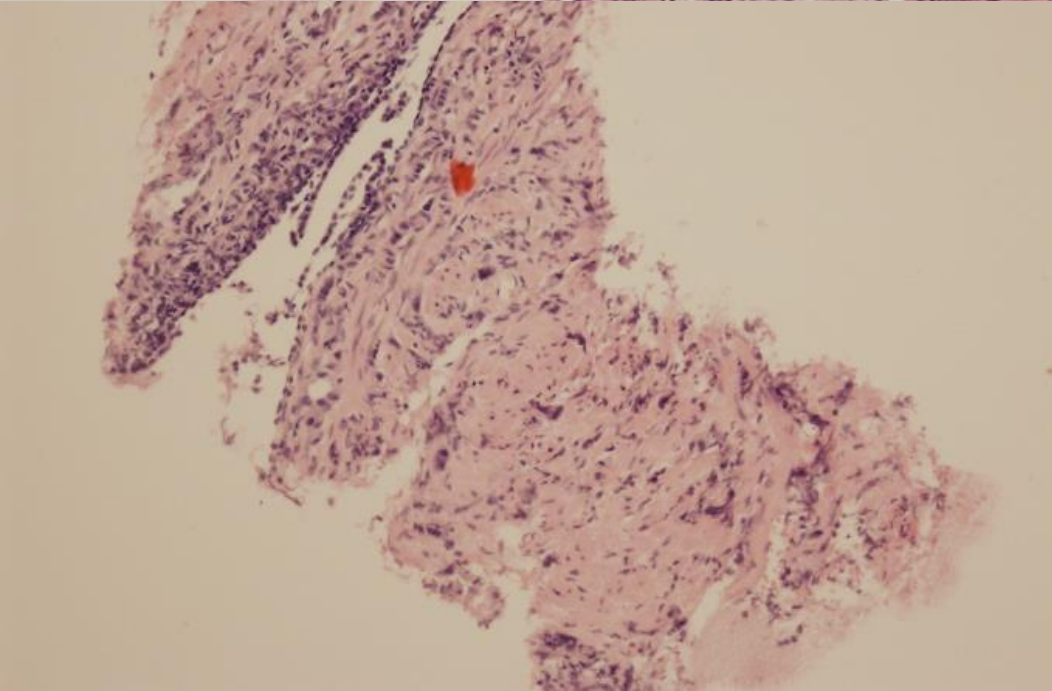
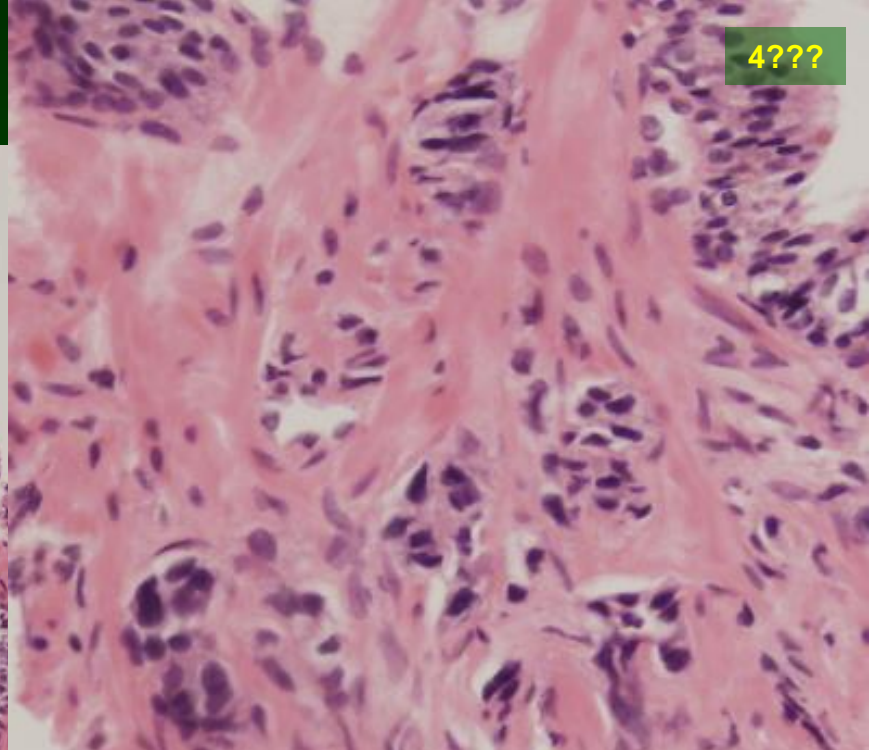
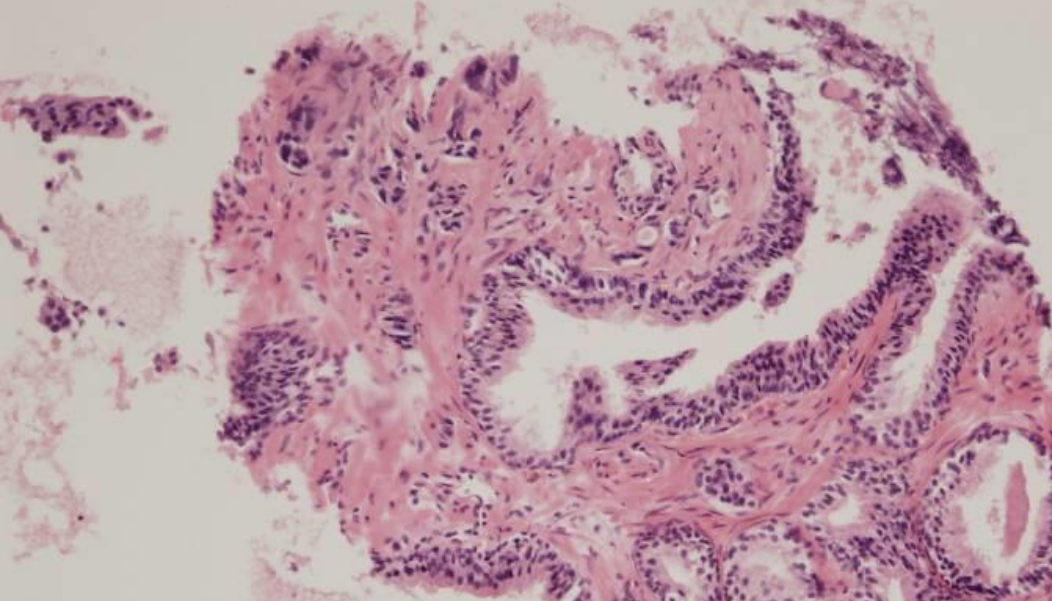


❖ perineurálne formácie sa neposudzujú (imitujú Gleasonov rastový vzor 4)



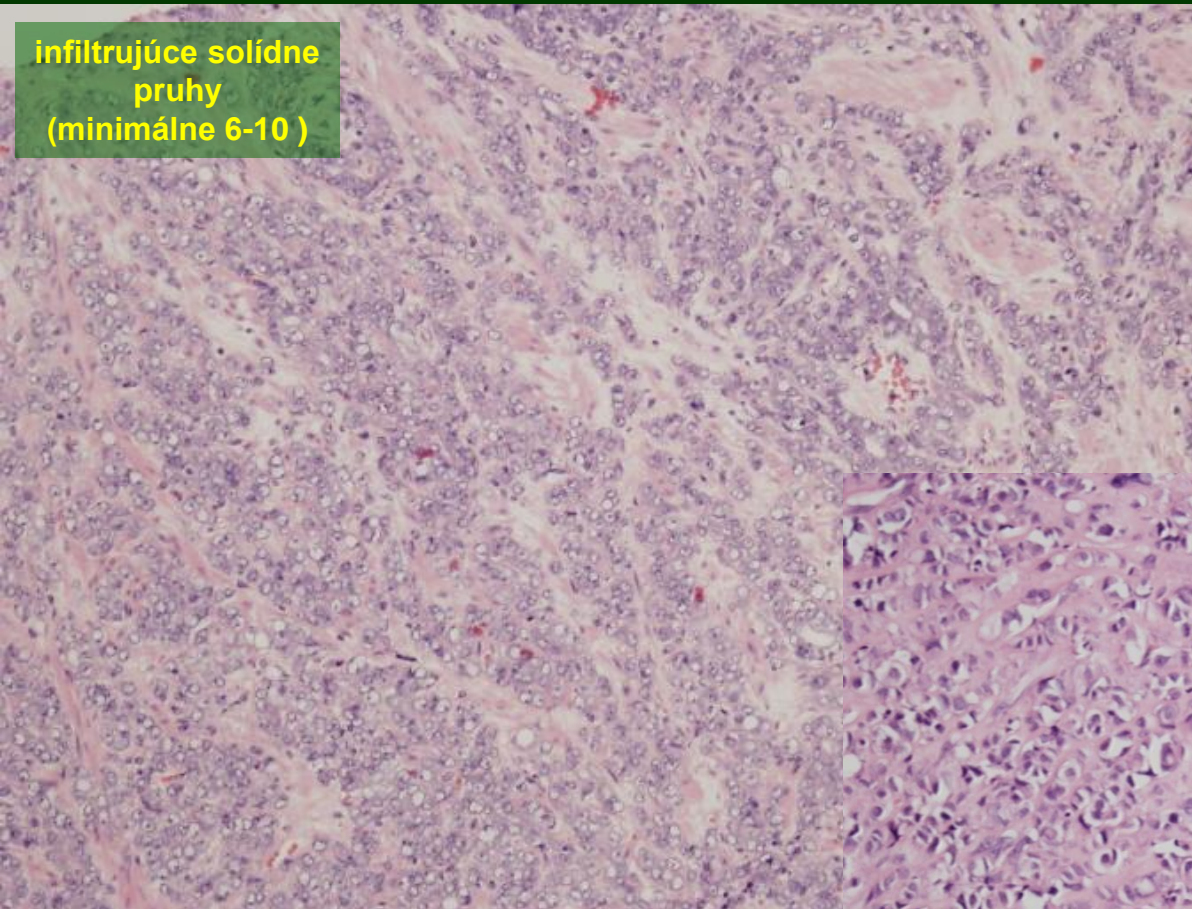


❖ artefakty imitující vyšší rastový vzor

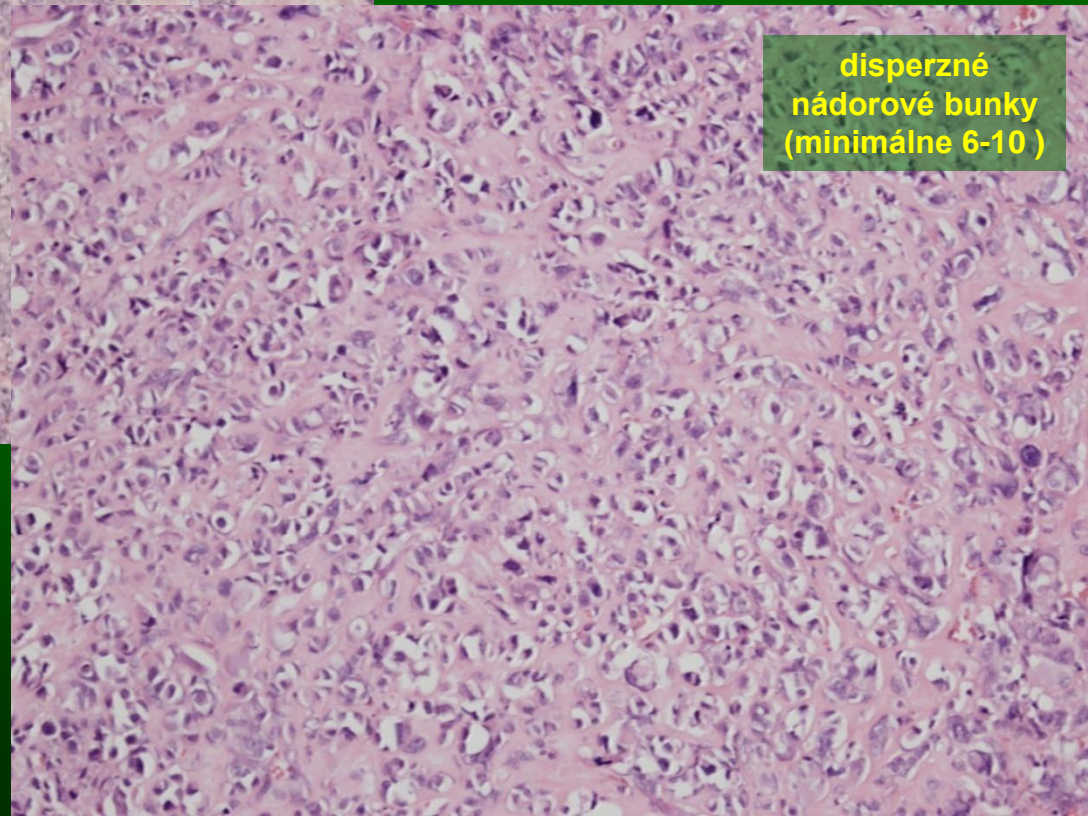


## ❖ Gleasonov rastový vzor 5

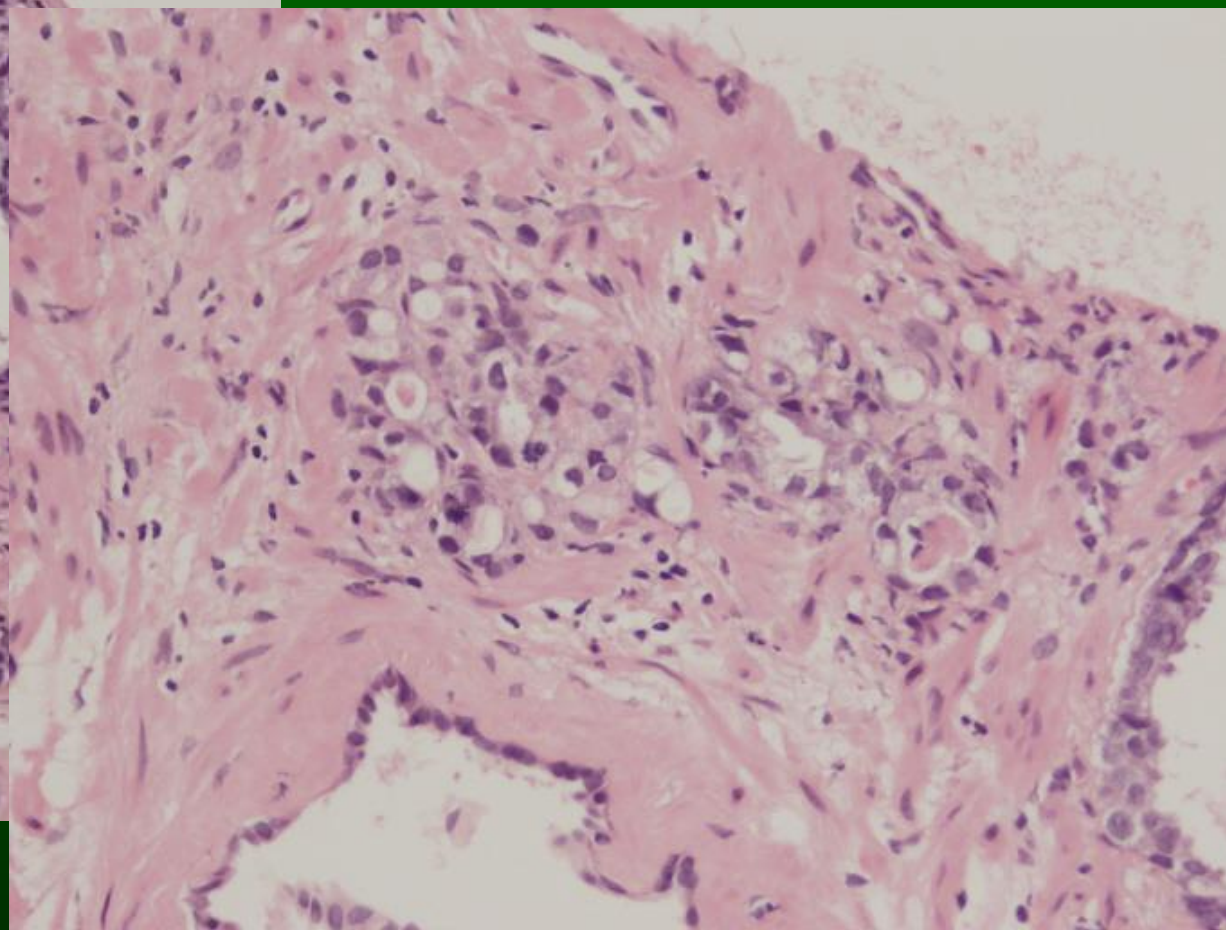
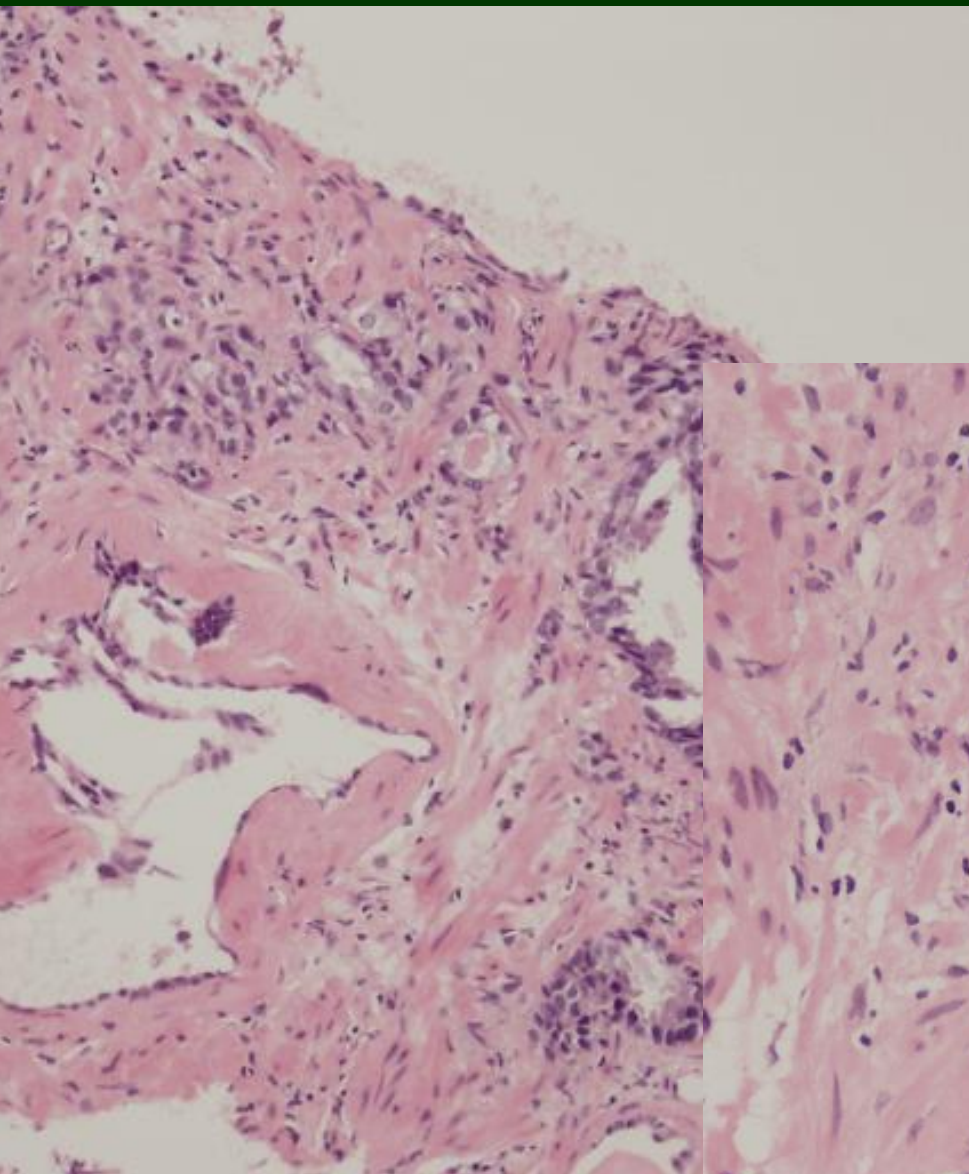
infiltrujúce solídne  
pruhy  
(minimálne 6-10 )



disperzné  
nádorové bunky  
(minimálne 6-10 )

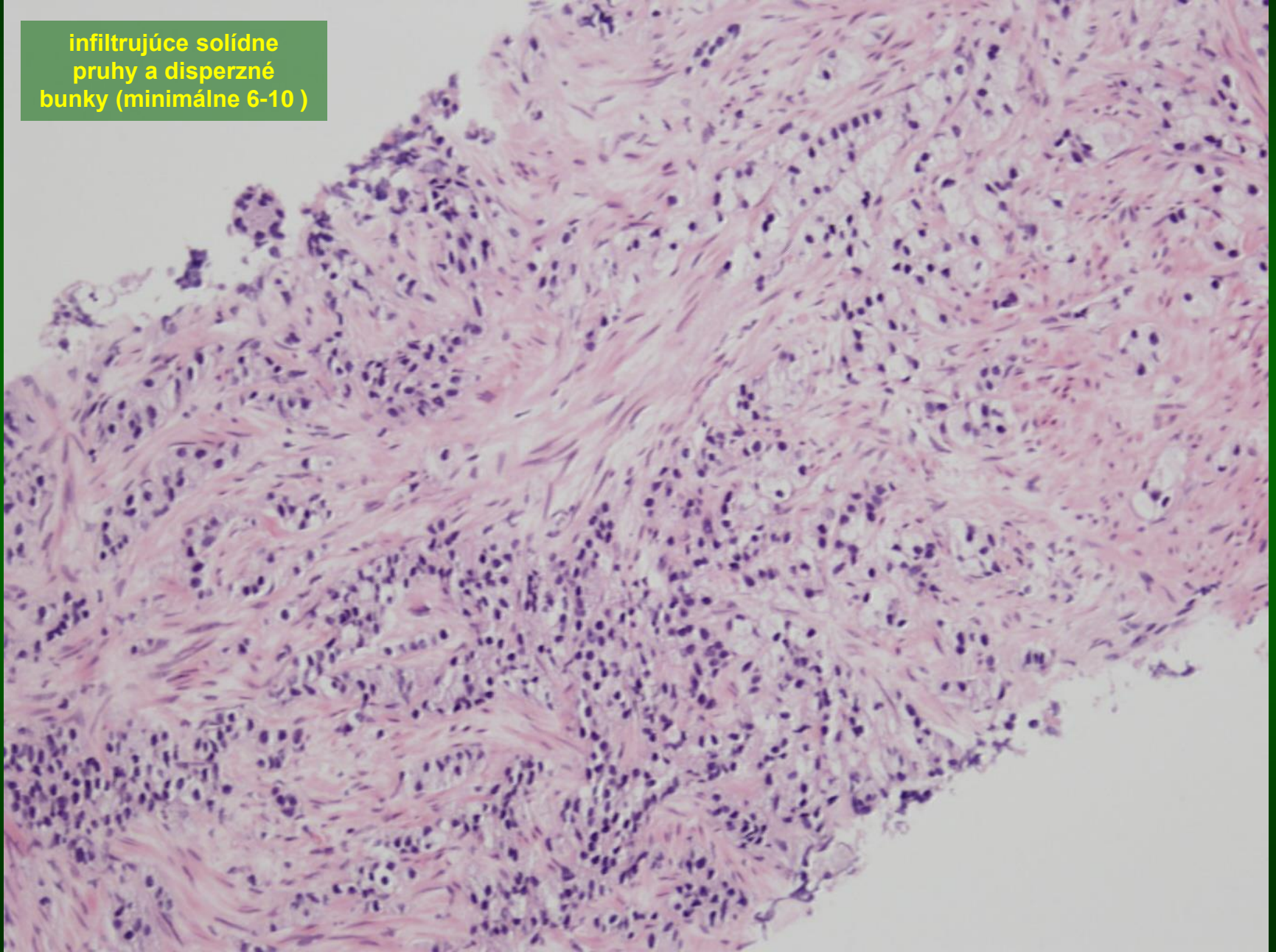


❖ niekoľko infiltrujúcich pruhov resp. disperzných buniek ( $\leq 5$ ) nie je 5 ale 4



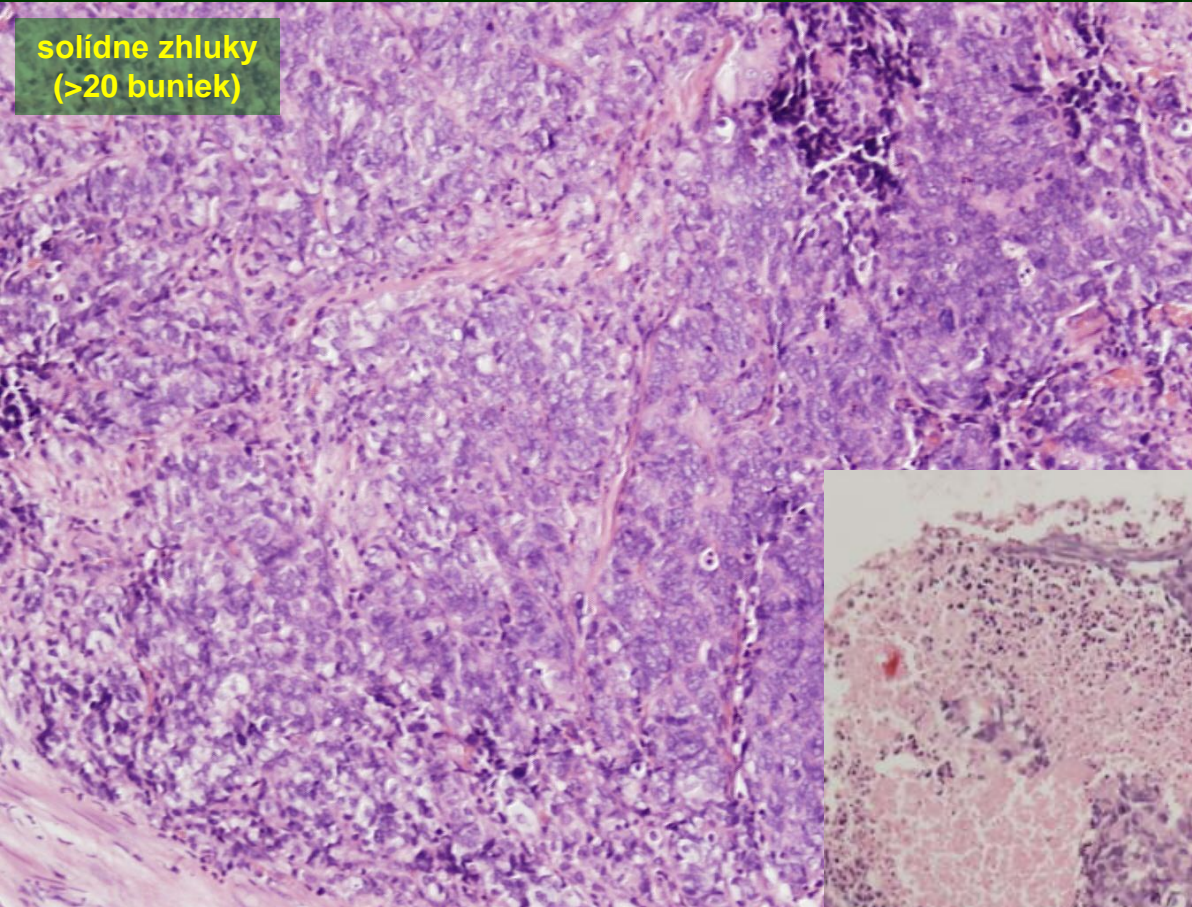
## ❖ Gleasonov rastový vzor 5

infiltrujúce solídne  
pruhy a disperzné  
bunky (minimálne 6-10)

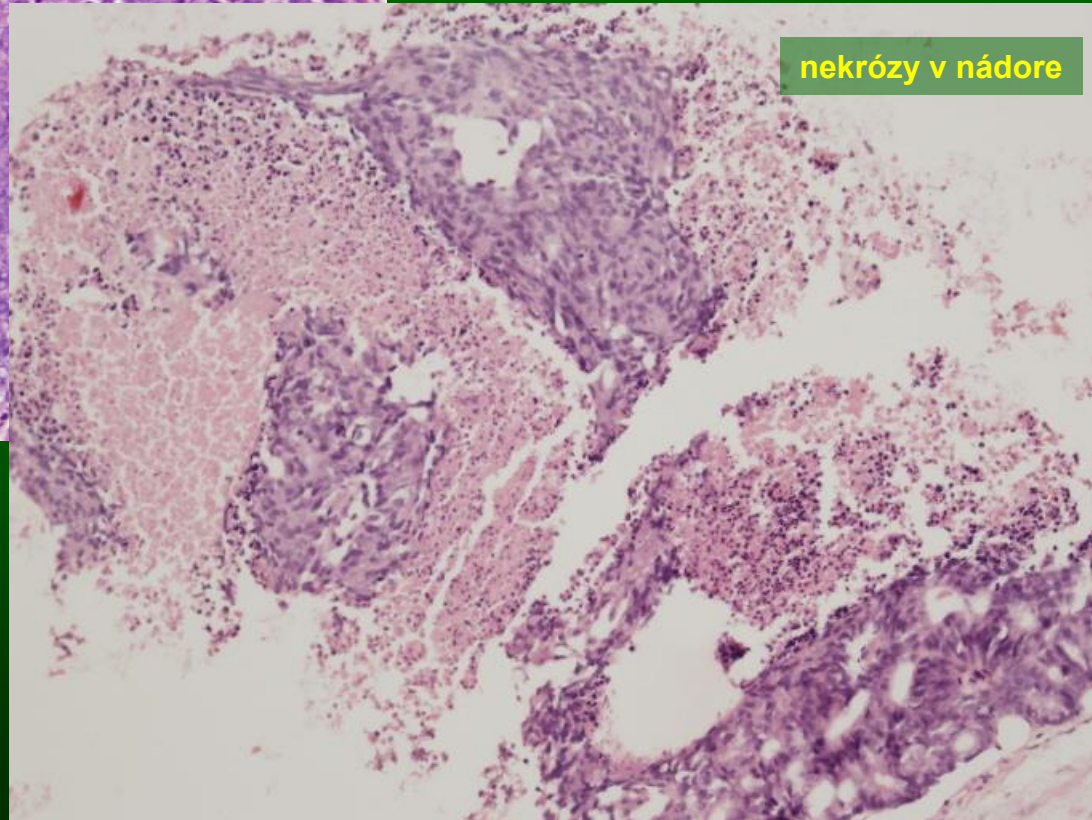


## ❖ Gleason rastový vzor 5

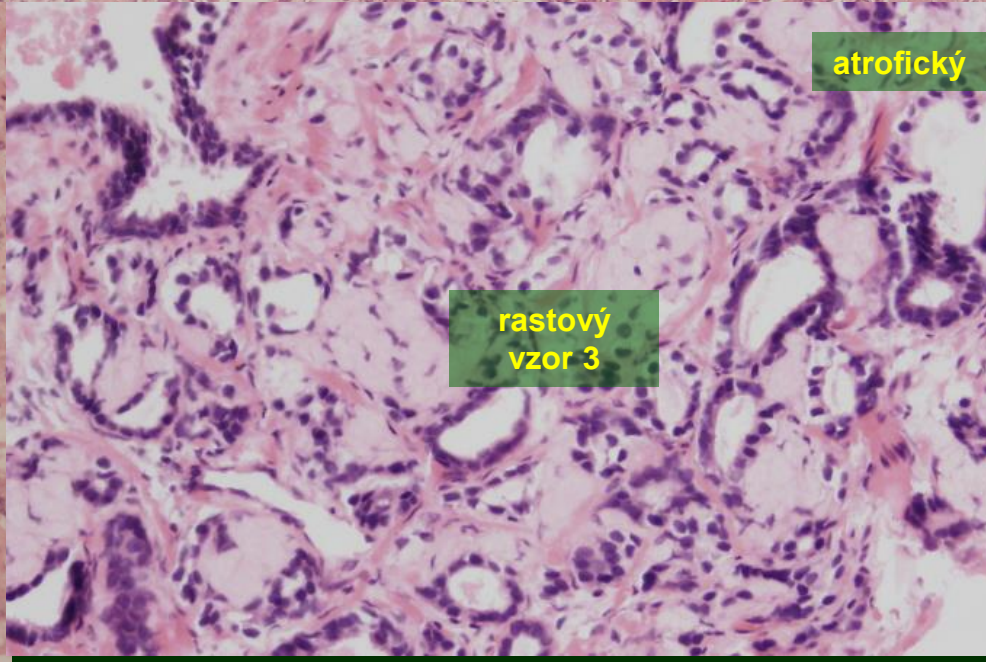
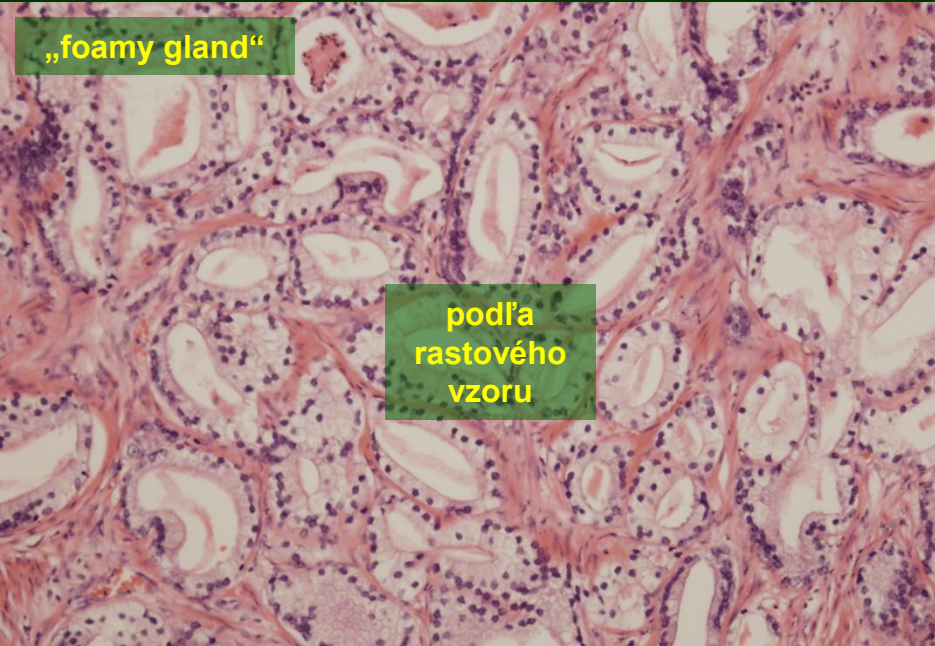
solidne zhluky  
(>20 buniek)



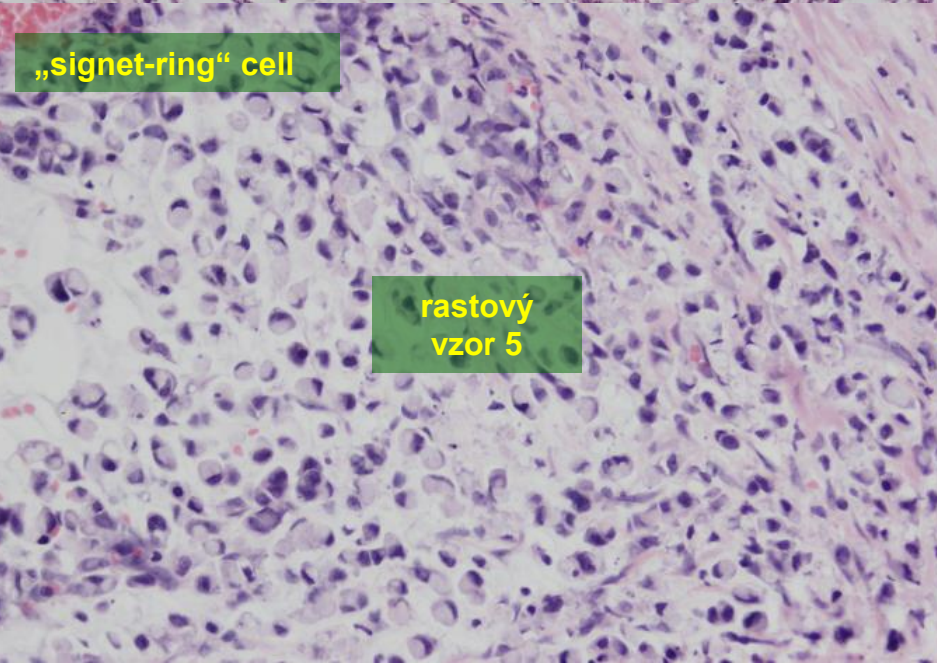
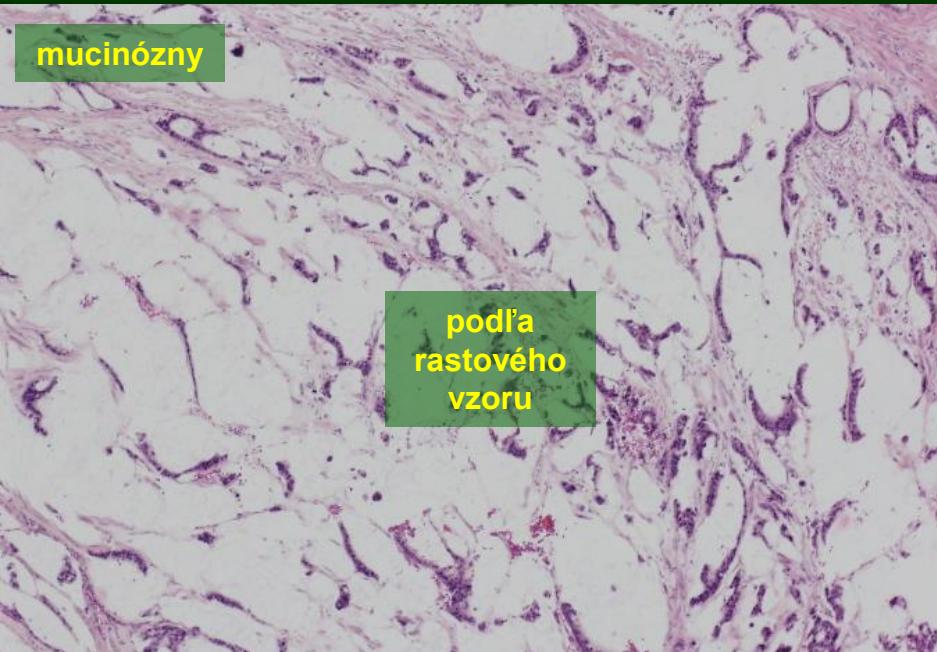
nekrózy v nádore



## ❖ hodnotenie Gleasonovho rastového vzoru variantov KP

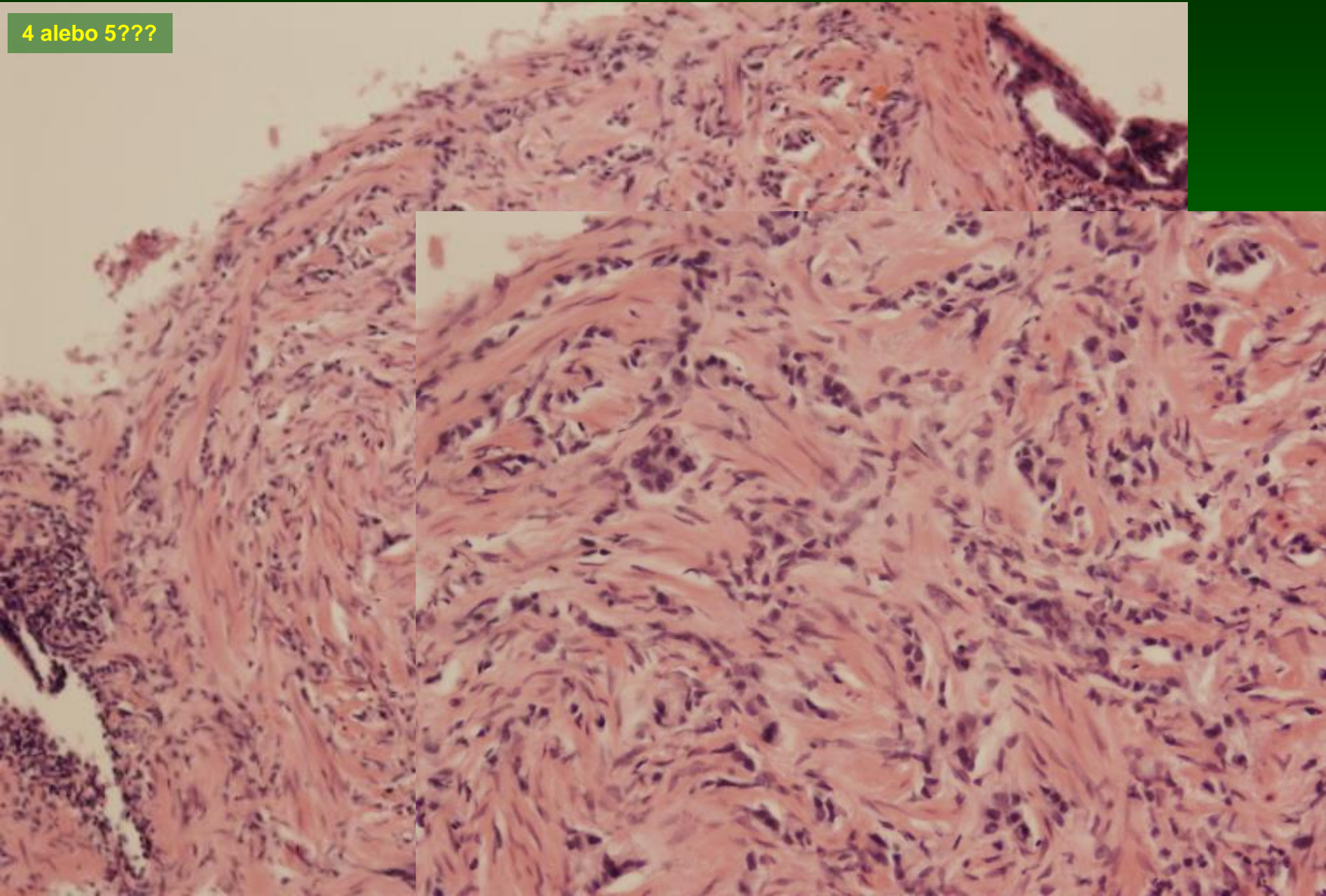


## ❖ hodnotenie Gleasonovho rastového vzoru variantov KP



❖ subjektívne hodnotenie rastového vzoru - v prípade neistoty voliť nižší vzor

4 alebo 5???





## ❖ Intraduktálny Ca prostaty – dôležitý nezávislý prognostický marker

- vždy súčasť boptického nálezu

- nezahŕňa sa do hodnotenia rastového vzoru KP

- dg. kritériá:

a). zachovaná vrstva bazálnych buniek

+

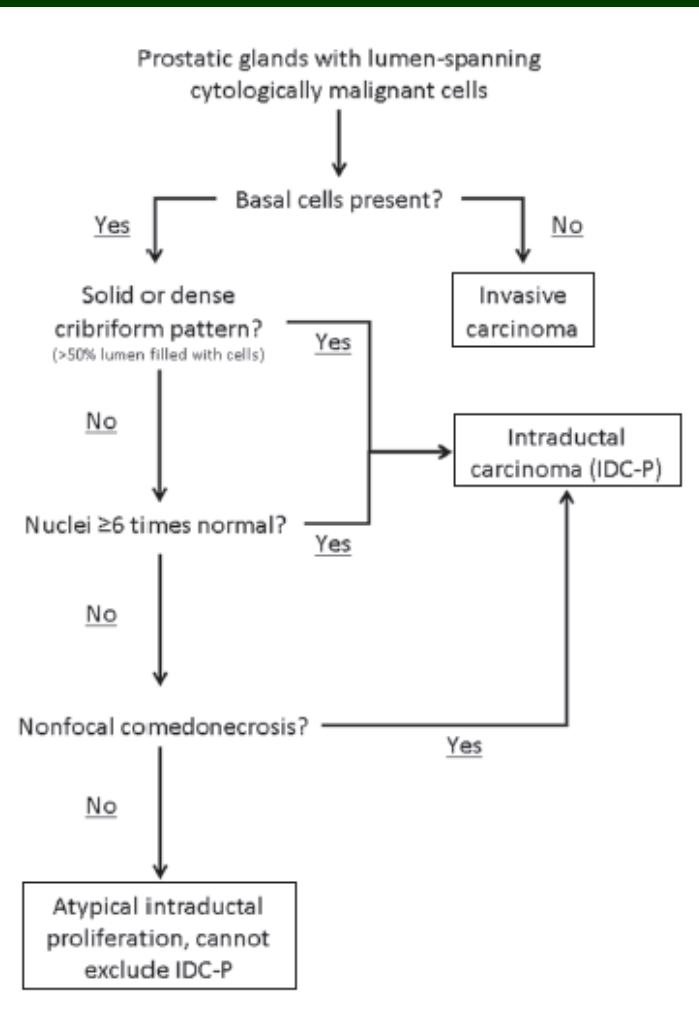
b). solídny resp. „denzný“ kribriformný rast. vzor  
(solídna komponenta  $\geq 70\%$  ložiska)

alebo

c). „riedky“ kribriformný rastový vzor (solídna komponenta  $< 70\%$  ložiska) s jadrami 6x väčšími ako jadrá normálnych žliaz v okolí

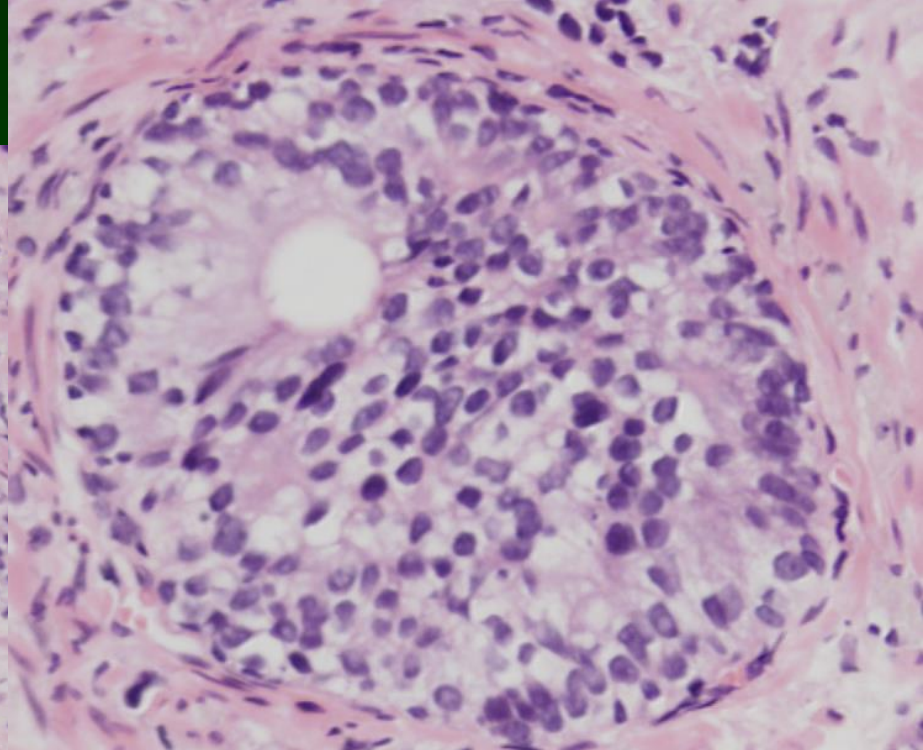
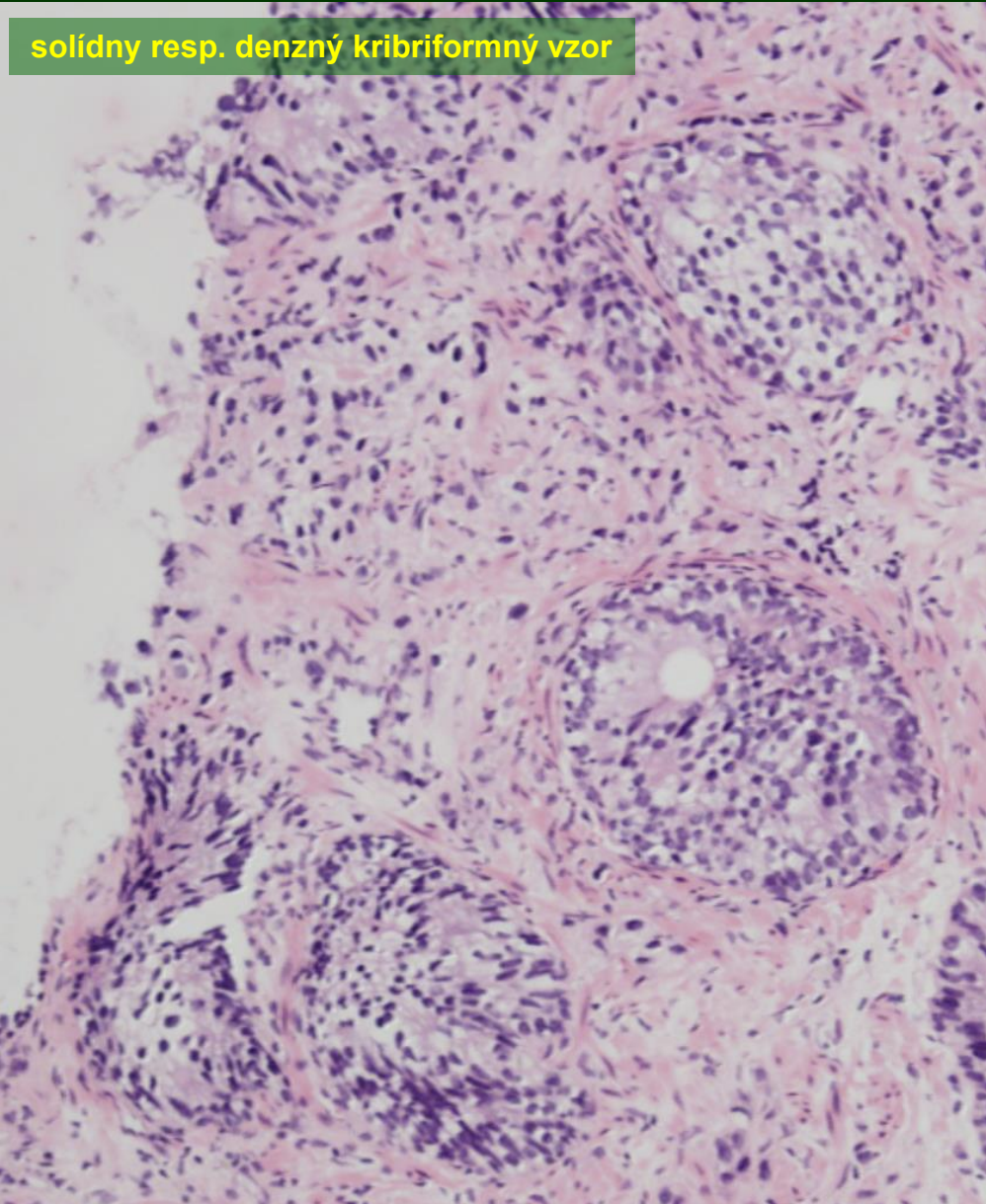
alebo

d). prítomnosť nekrózy v ložisku



## ❖ Intraduktálny Ca prostaty

solídny resp. denzný kribriformný vzor

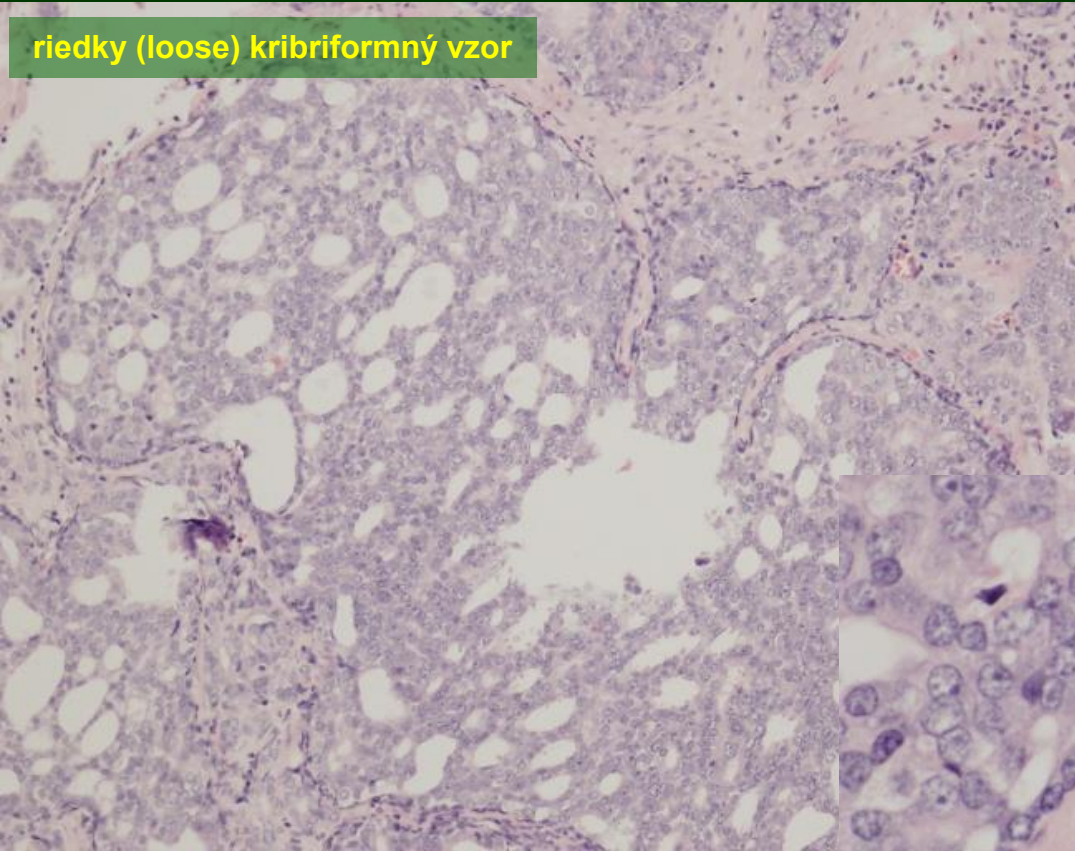


p63+ v bazálnych bb.



## ❖ Intraduktálny Ca prostaty

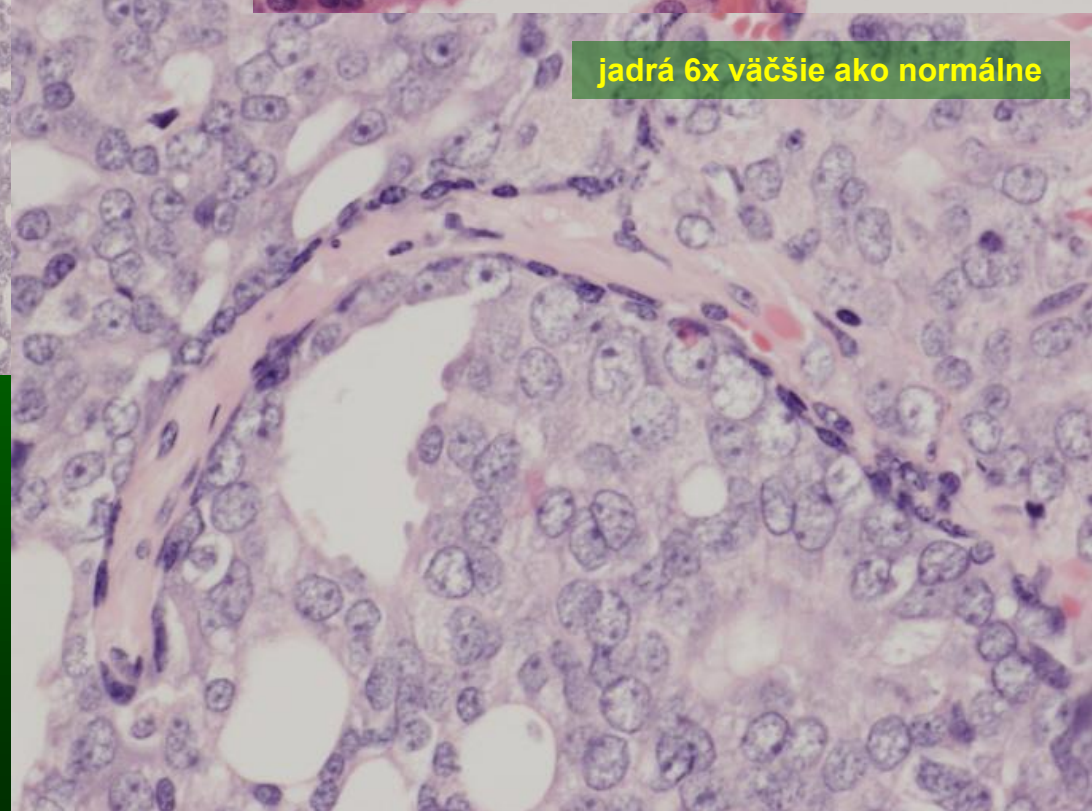
riedky (loose) kribriformný vzor



normálne žľazy prostaty

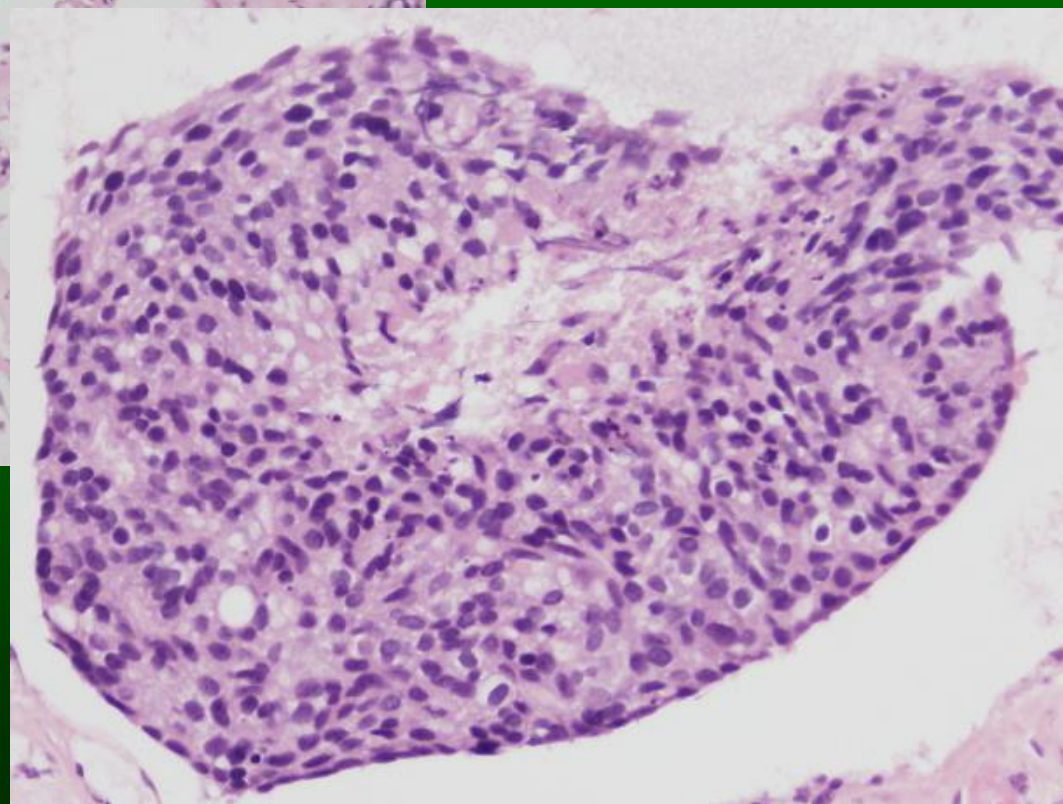
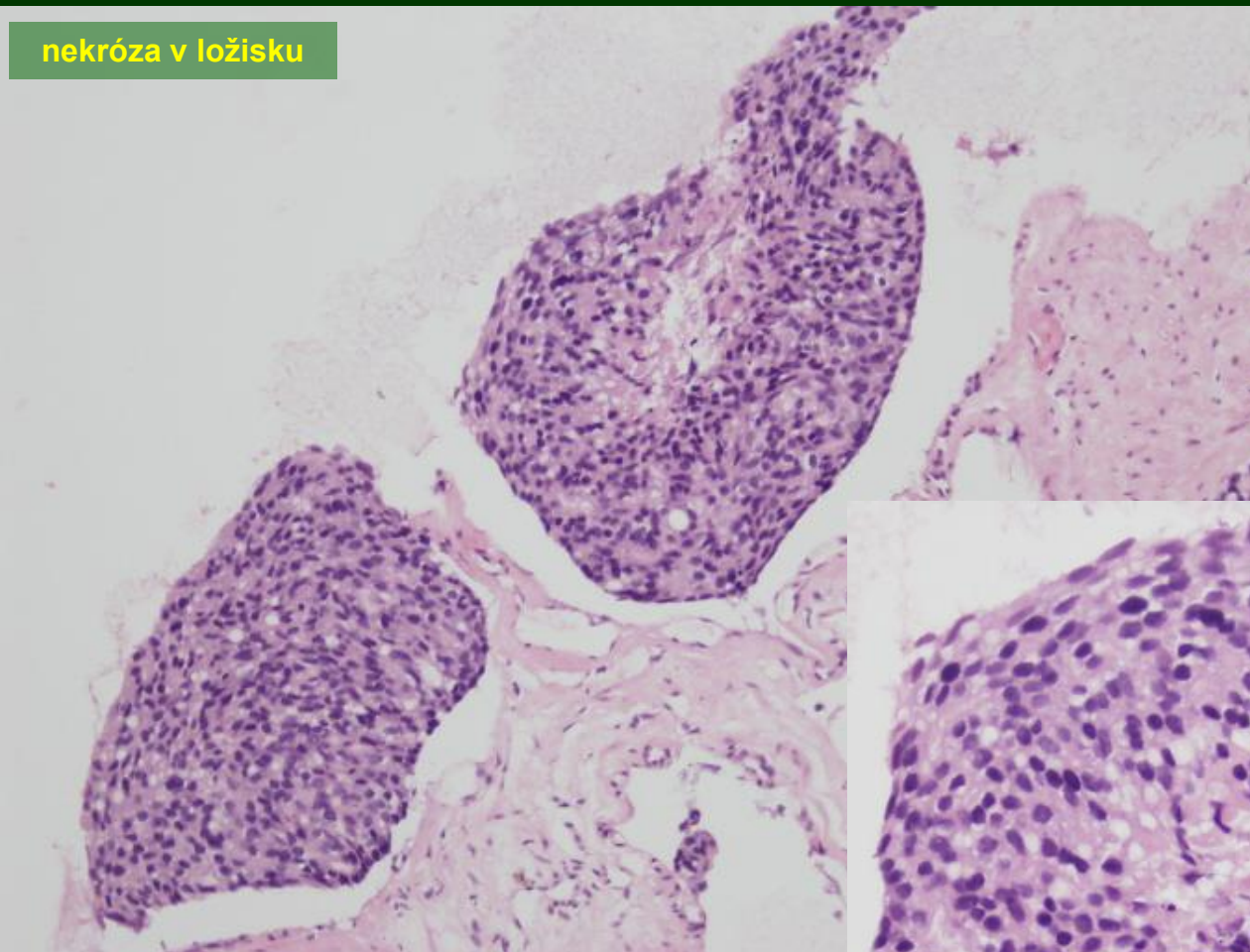


jadrá 6x väčšie ako normálne

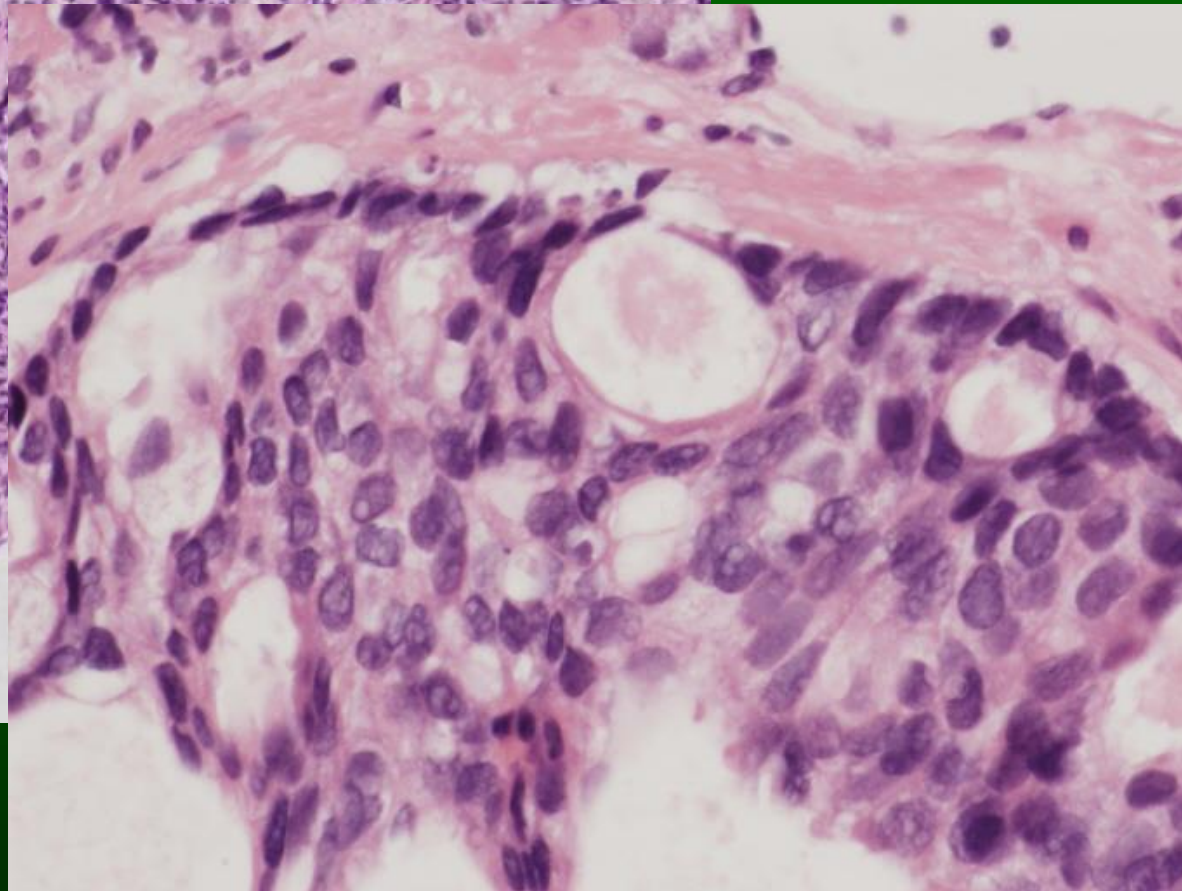
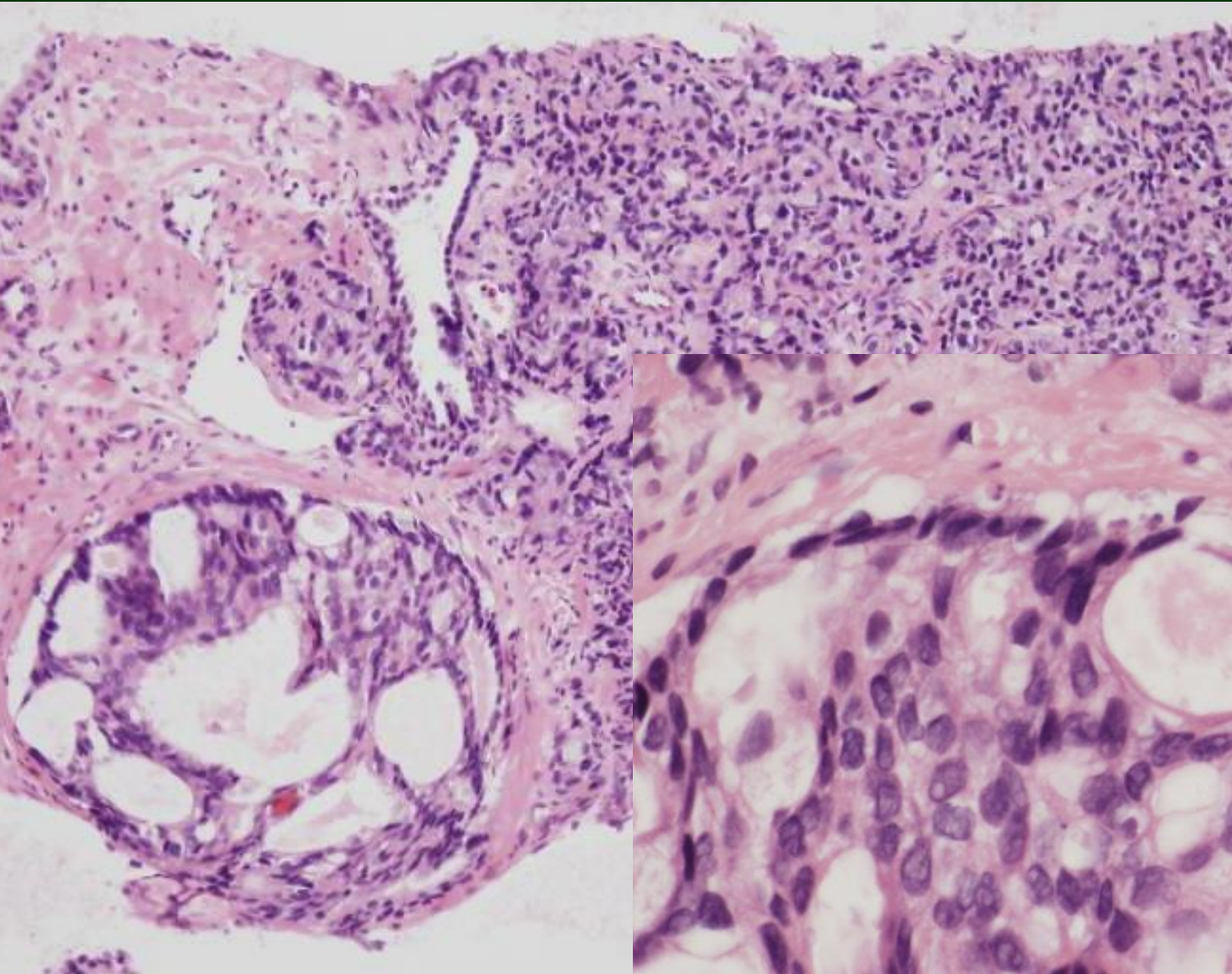


## ❖ Intraduktálny Ca prostaty

nekróza v ložisku

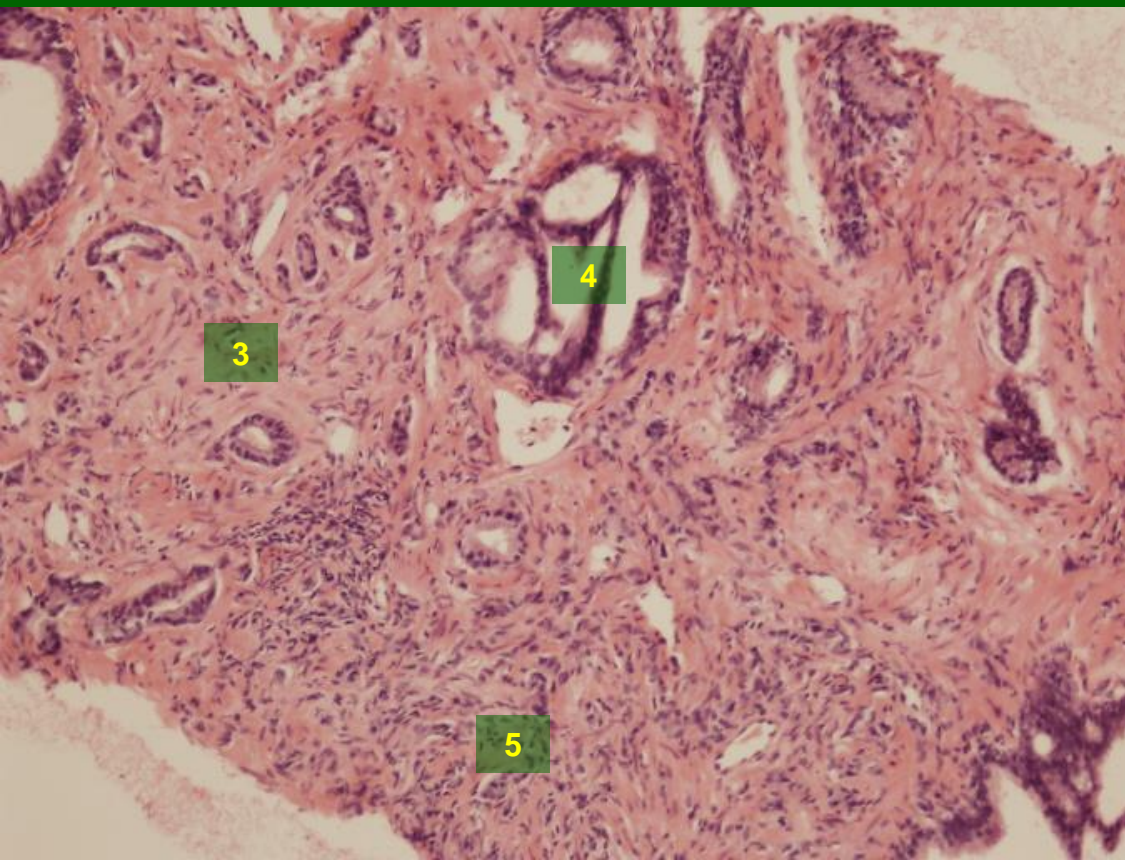


❖ **Atypická intraduktálna proliferácia – nemožno vylúčiť intraduktálny KP**



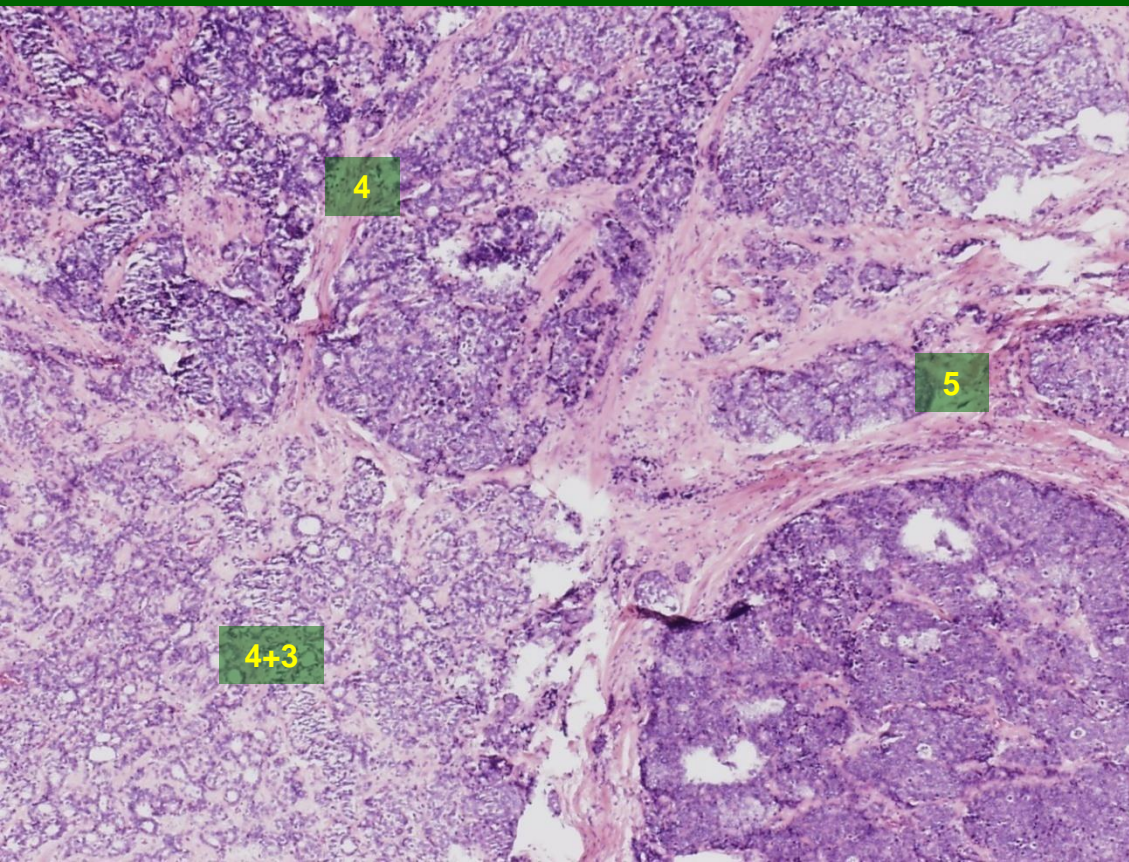
❖ **Hodnotenie Gleasonovho skóre (GS) v punkčnej biopsii (PB):**

- najrozsiahlejší rastový vzor + najvyšší rastový vzor
- nižší rastový vzor tvoriaci <5% možno ignorovať
- hodnotenie GS v každom punktáte
- zhodnotenie výsledného GS vo všetkých vzorkách
- v prípade GS 7 (3+4) kvantifikovať % rozsah vzoru 4



❖ **Hodnotenie Gleasonovho skóre (GS) v radikálnej prostatektómii (RP):**

- najrozsiahlejší rastový vzor + druhý najrozsiahlejší rastový vzor
- nižší rastový vzor tvoriaci <5% možno ignorovať
- terciárny rastový vzor sa uvádza len v prípade kombinácie vzorov 3, 4, 5
- terciárny rastový vzor nižší ako primárny a sekundárny sa neuvádza
- rastový vzor 5: >5% nádoru = sekundárny r. vzor / <5% = terciárny r. vzor



**3+4+5: GS 8 (3+5)**

**GS 7 (3+4) + terciárny  
vzor 5 (<5%)**

**4+3+5: GS 9 (4+5)**

**GS 7 (4+3) + terciárny  
vzor 5 (<5%)**

**3+5+4: GS 8 (3+5)**

**5+3+4: GS 8 (5+3)**

**4+5+3: GS 9 (4+5)**

**5+4+3: GS 9 (5+4)**

- ❖ **Hodnotenie gradingu v radikálnej prostatektómii s multifokálnym KP**
  - hodnotiť najväčšie nádorové ložisko – zvyčajne najvyššie GS a stage
  - v prípade multifokality – zhodnotiť najväčšie nádorové ložisko a jeho GS
    - zhodnotiť ložisko s najvyšším GS
    - opísať ložisko s najvyššími parametrami stagingu resp. vzt'ahom k resekčnej línii





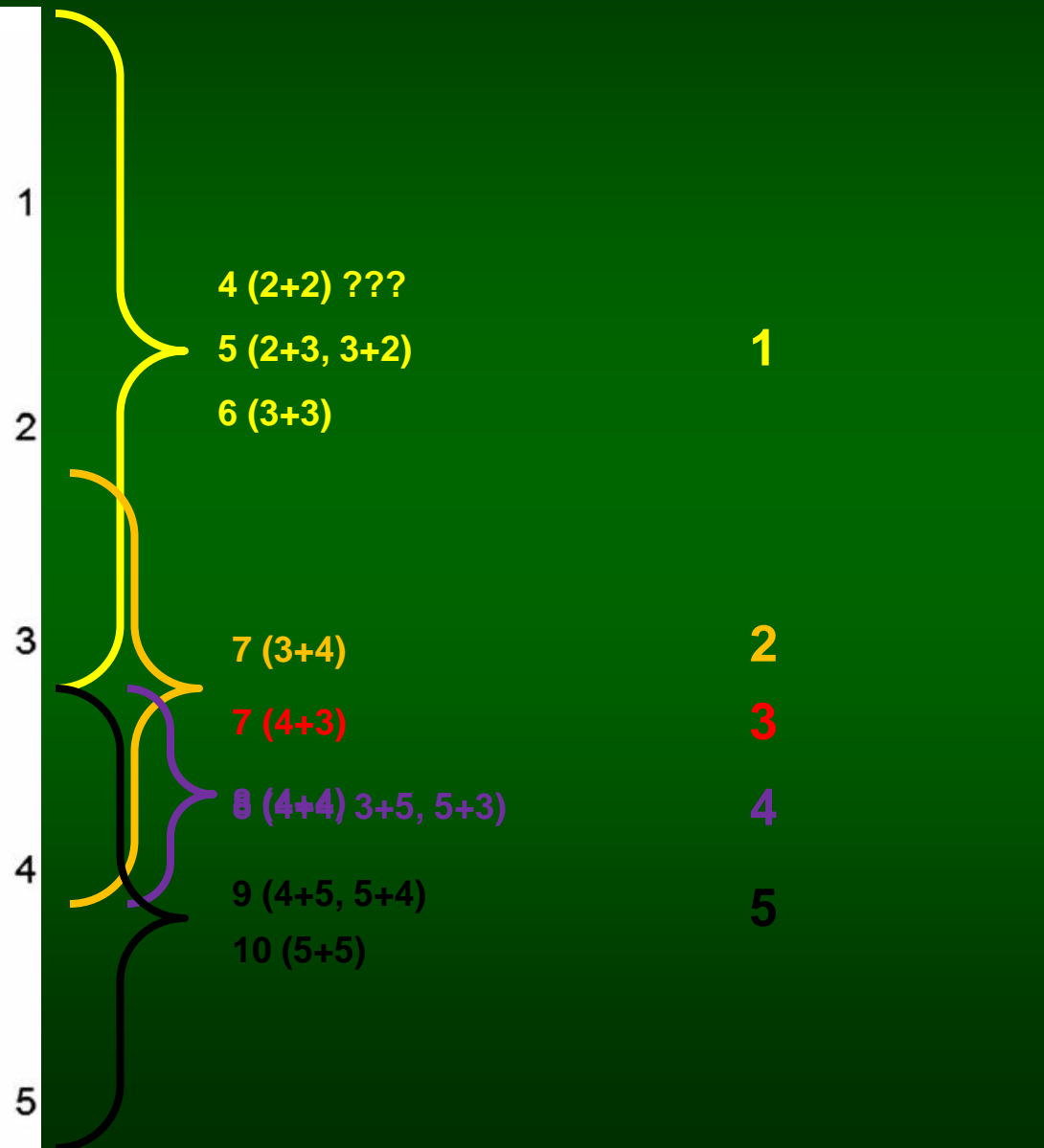
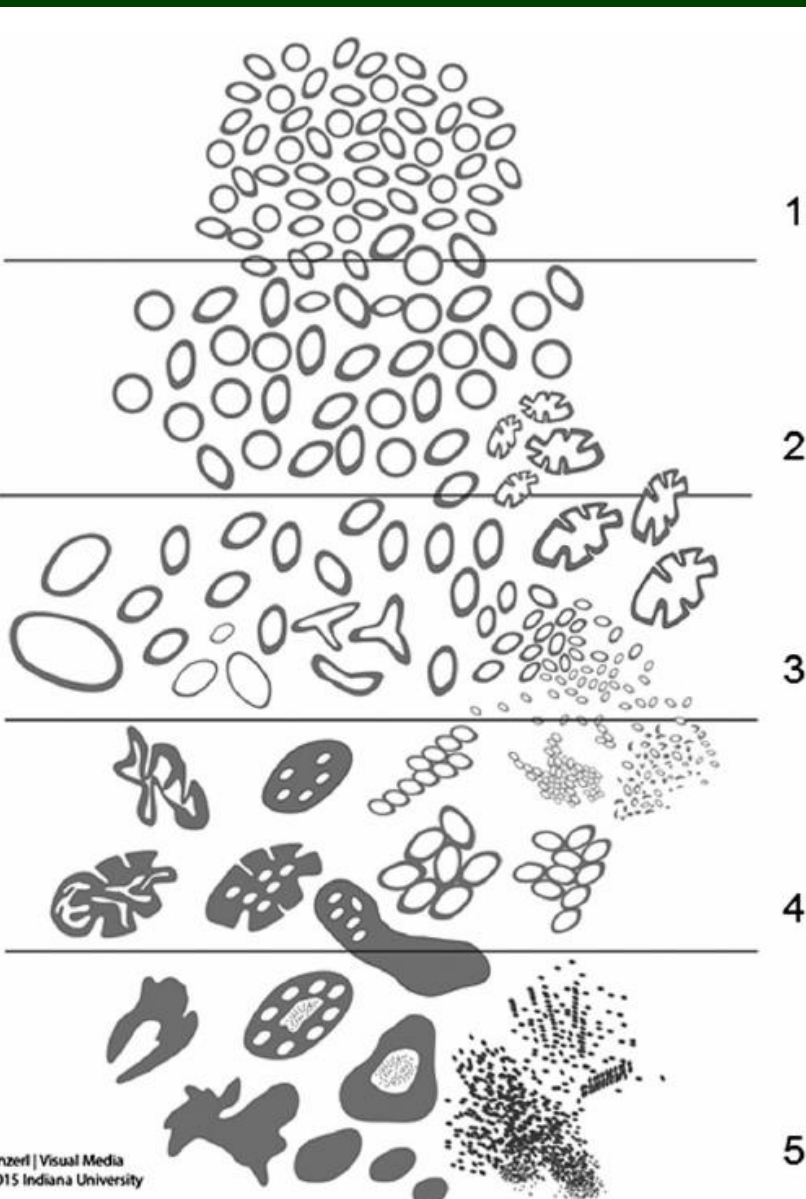
# ❖ Nový grading systém karcinómu prostaty:

ISUP 2014 / WHO 2016

rastový vzor

Gleason score:

ISUP 2014 / WHO 2016  
prognostické „grade groups“



## ❖ Morfológická definícia „grade groups“ (ISUP 2014/WHO 2016)

**Grade group 1 = Gleason score  $\leq 6$ : len jednotlivé dobre formované žľazy**

**Grade group 2 = Gleason score 7(3+4): prevažne dobre formované žľazy s menej početnými zle formovanými, splývajúcimi resp. kribriformnými žľazami**

**Grade group 3 = Gleason score 7(4+3): prevažne zle formované, splývajúce resp. kribriformné žľazy s menej početnými dobre formovanými žľazami**

**Grade group 4 = Gleason score 8 (4+4): len zle formované, splývajúce resp. kribriformné žľazy**

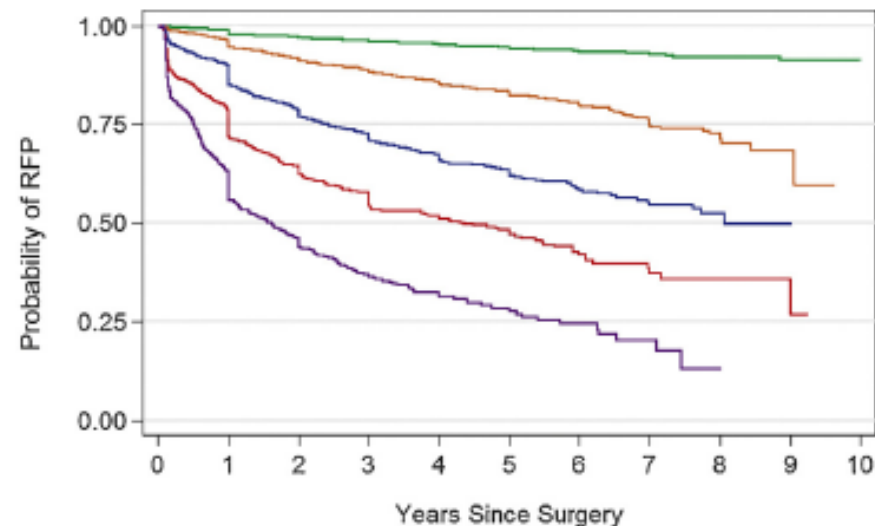
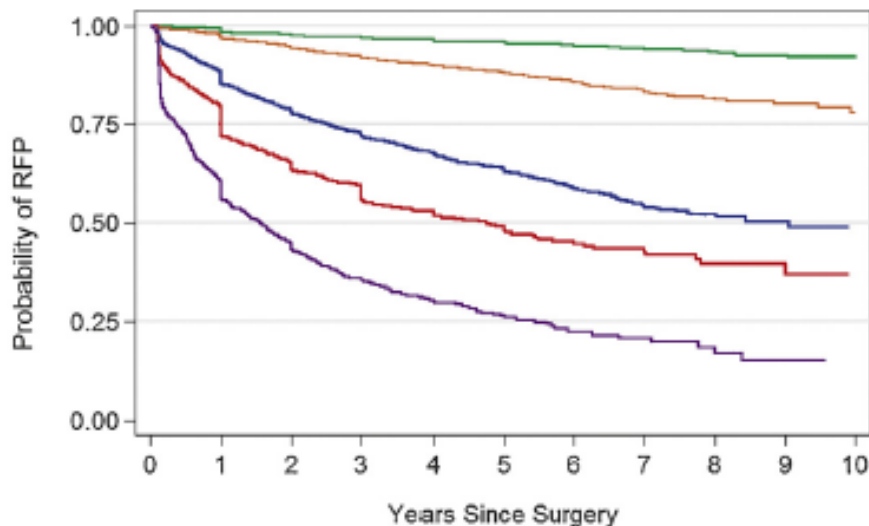
**Gleason score 8 (3+5): prevažne dobre formované žľazy a menšia časť nádoru bez tvorby žliaz**

**Gleason score 8 (5+3): nádor prevažne bez žliaz s menšou účasťou dobre formovaných žliaz**

**Grade group 5 = Gleason score 9 – 10 : nádor bez tvorby žliaz (s resp. bez nekróz) s resp. bez účasti zle formovaných, splývajúcich resp. kribriformných žliaz**

## ❖ Prínosy nového gradovacieho systému

1. lepšia stratifikácia pacientov vzhľadom na ich prognózu a liečbu
2. rozdelenie GS 7 na dve skupiny (3+4, 4+3) s odlišnou prognózou



Number at risk

	≤6	7-8	9-10	11-12	13-14	15-16	17-18	19-20	21-22	23-24	25-26
≤6	7397	6973	5104	4054	3226	2451	1768	1169	670	278	108
3+4	8363	7202	6298	5983	5955	5091	4299	3778	3393	3135	245
4+3	3198	2452	1805	1152	839	569	350	199	90	38	15
8	917	678	412	280	191	125	86	59	35	14	7
≥9	1051	578	325	194	118	73	41	24	12	4	2

Number at risk

	≤6	7-8	9-10	11-12	13-14	15-16	17-18	19-20	21-22	23-24	25-26
≤6	8030	7284	5154	3943	3018	2177	1383	818	371	80	1
3+4	4695	3875	2624	1845	1291	845	470	244	102	21	0
4+3	1872	1511	934	534	432	282	157	90	35	5	0
8	1095	710	413	279	185	120	68	33	13	4	0
≥9	661	365	199	118	75	41	25	11	2	0	0

## ❖ Prínosy nového gradovacieho systému

1. lepšia stratifikácia pacientov vzhľadom na ich prognózu a liečbu
2. rozdelenie GS 7 na dve skupiny (3+4, 4+3) s odlišnou prognózou
3. vyššia interpersonálna reproducibilita (80%)
4. vyššia zhoda v GS medzi PB a RP (nezhody najmä v zmysle podhodnotenia v PB – problém samplingu)
5. zjednodušenie gradovacieho systému z GS 2-10 (2+2, 2+3, 3+2, 3+3, 3+4, 4+3, 4+4, 4+5, 5+4, 5+5, 3+5, 5+3 => 12 možností!) na 5 „grade groups“ (GG)
6. najnižší grade KP je 1 z 5 a nie 6 z 10 (konfúzia časti klinikov a strach pacientov s GS 6 zo „stredne malígneho“ ochorenia)



Nový grading systém a „grade groups“ je plne akceptovaný v novej WHO klasifikácii uropatológie z r. 2016

# ❖ Gleasonov grading???

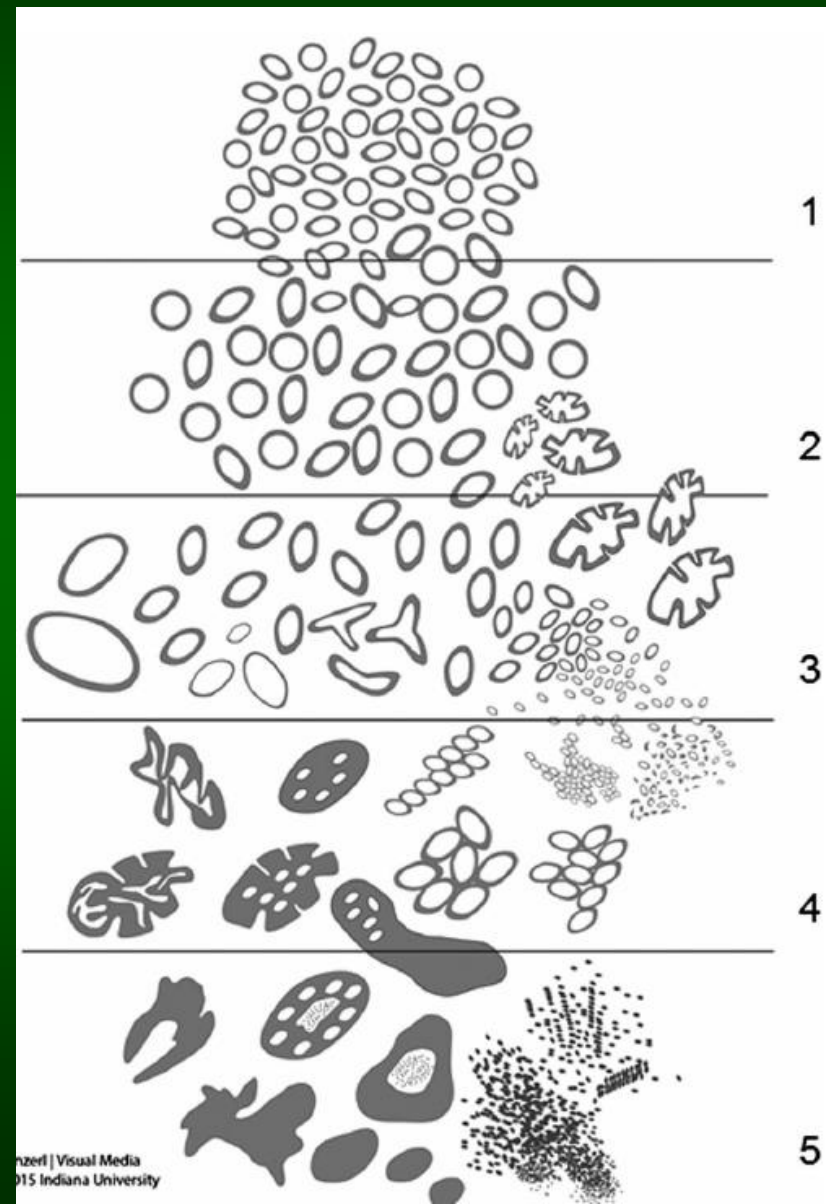
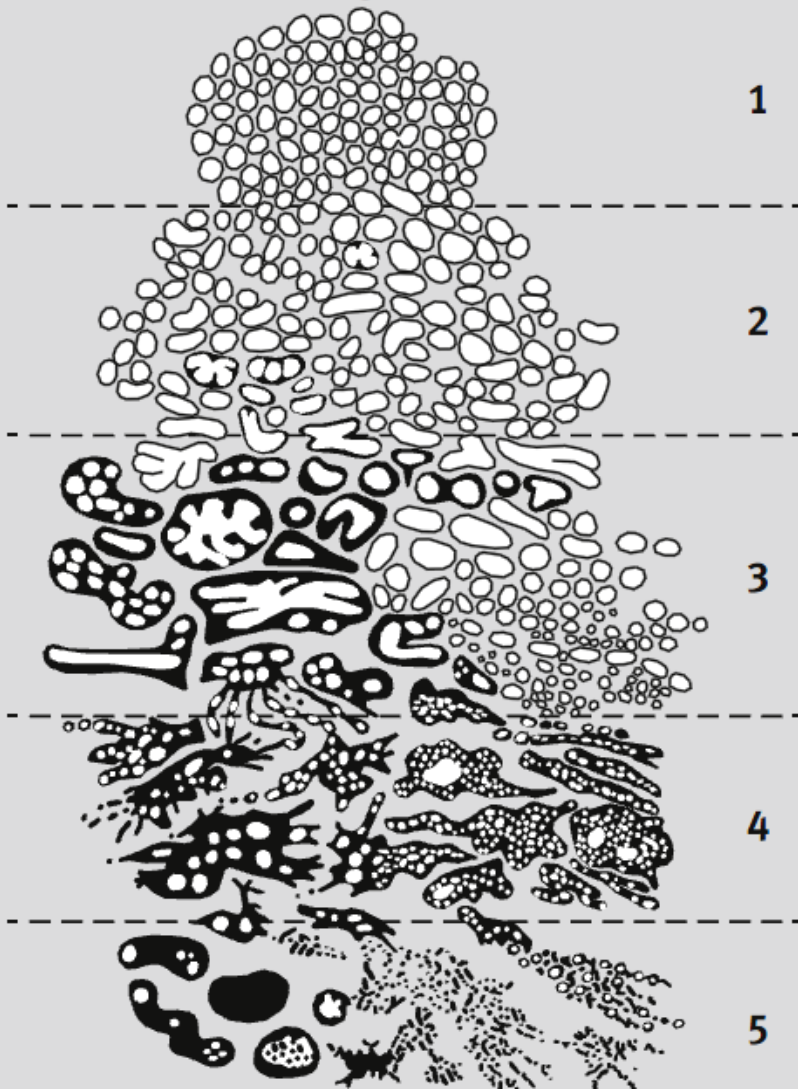
Gleason 1992

rastový vzor / Gleason score

ISUP 2014 / WHO 2016

„grade groups“

## PROSTATIC ADENOCARCINOMA (Histological Patterns)



❖ **Otázky do budúcnosti:**

**Nádor s GG 1 volať „karcinóm“???**

**Rozdeliť GG 4 na podskupiny vzhľadom na prítomnosť rast. vzoru 5?**

**Gradovať intraduktálny KP?**

**Začleniť mol-genetické analýzy do štandardne vyšetrovaných prognostických markerov?**



Jane, obávám se, že tohoto pána nezajímá, zda Ježíš spasí jeho duši