Prípad SD IAP č. 602

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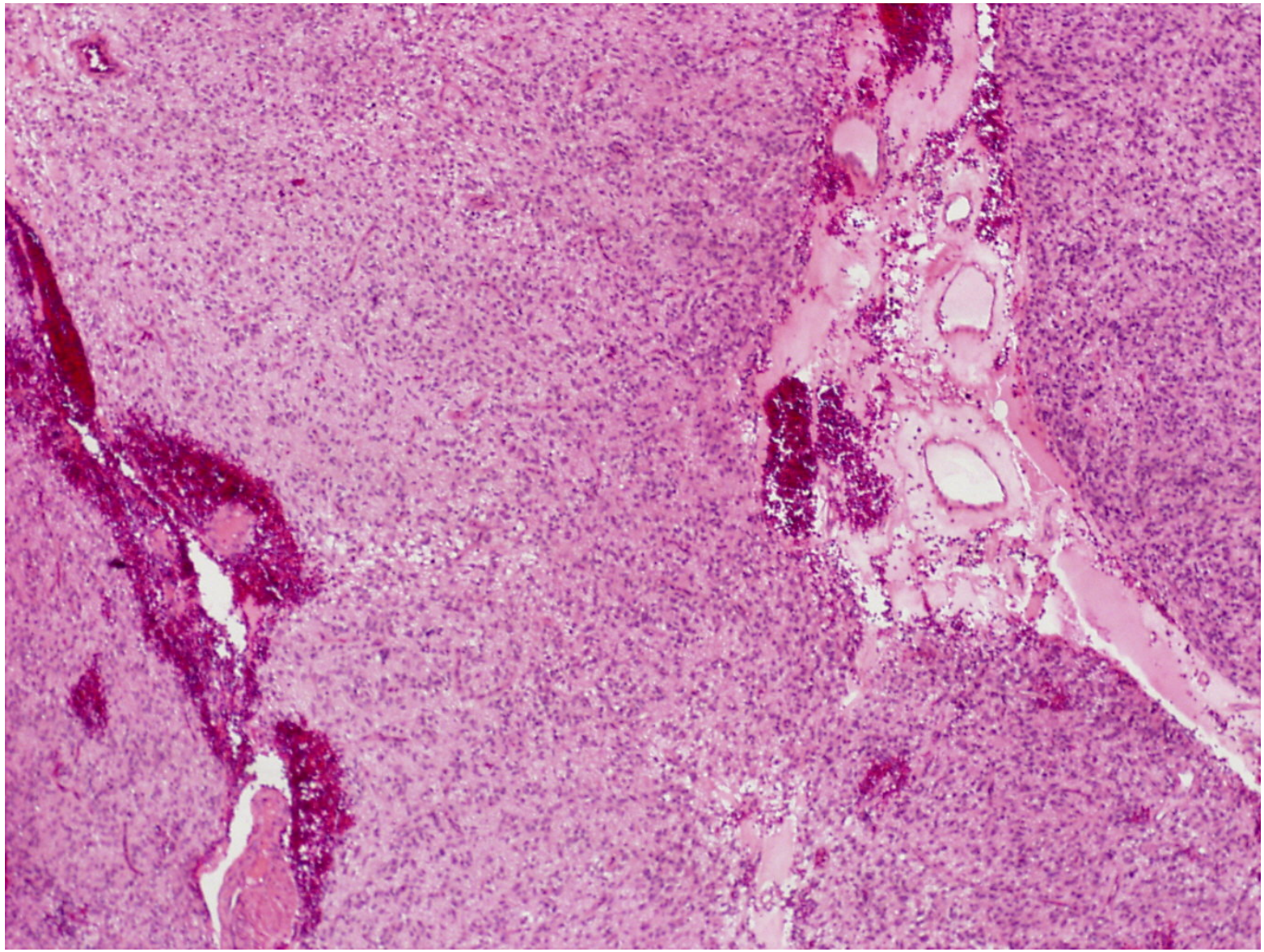
Letný bioptický seminár SD IAP, Senec, 17.-18.6.2016

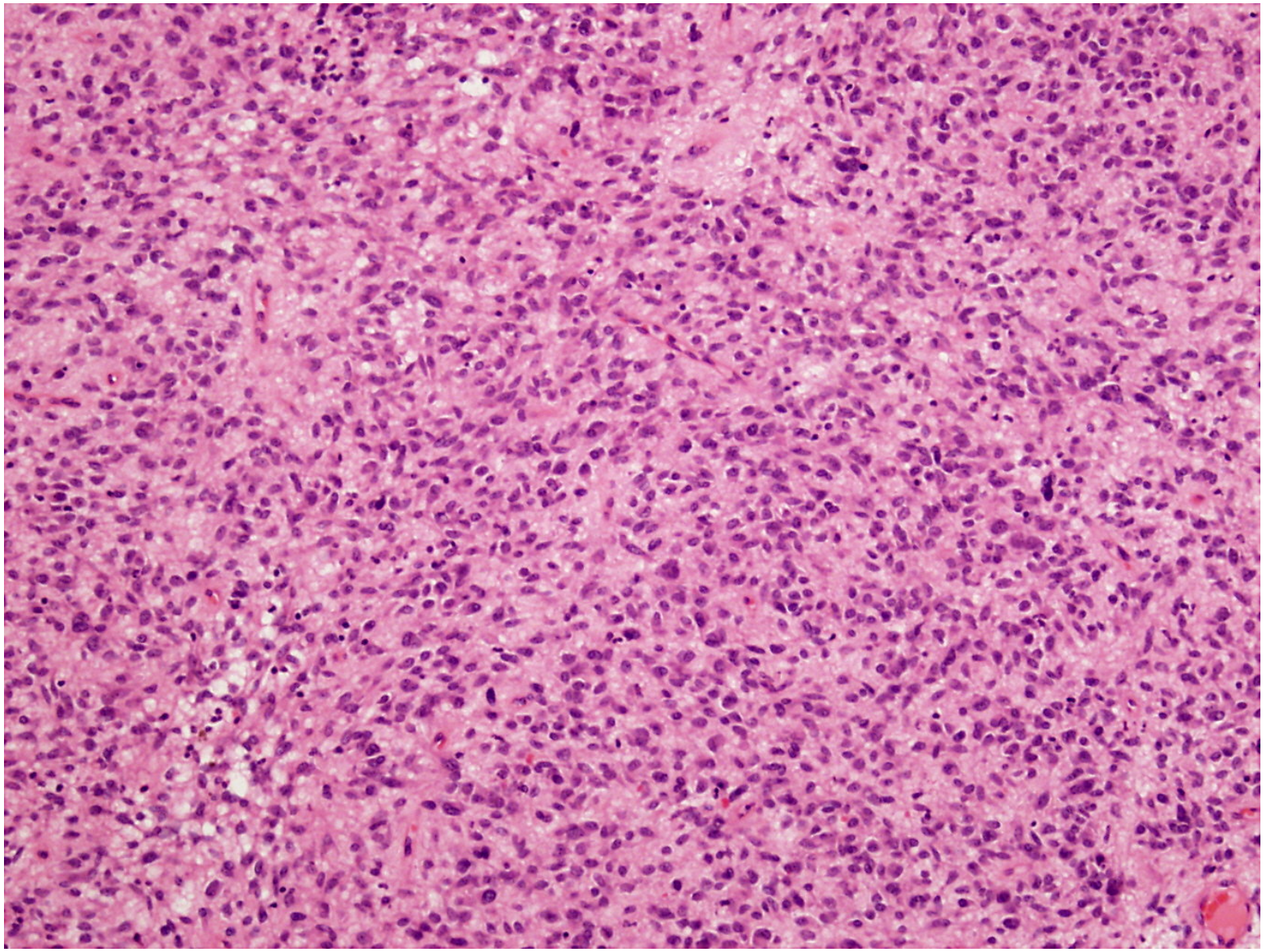
Poskytnuté údaje:

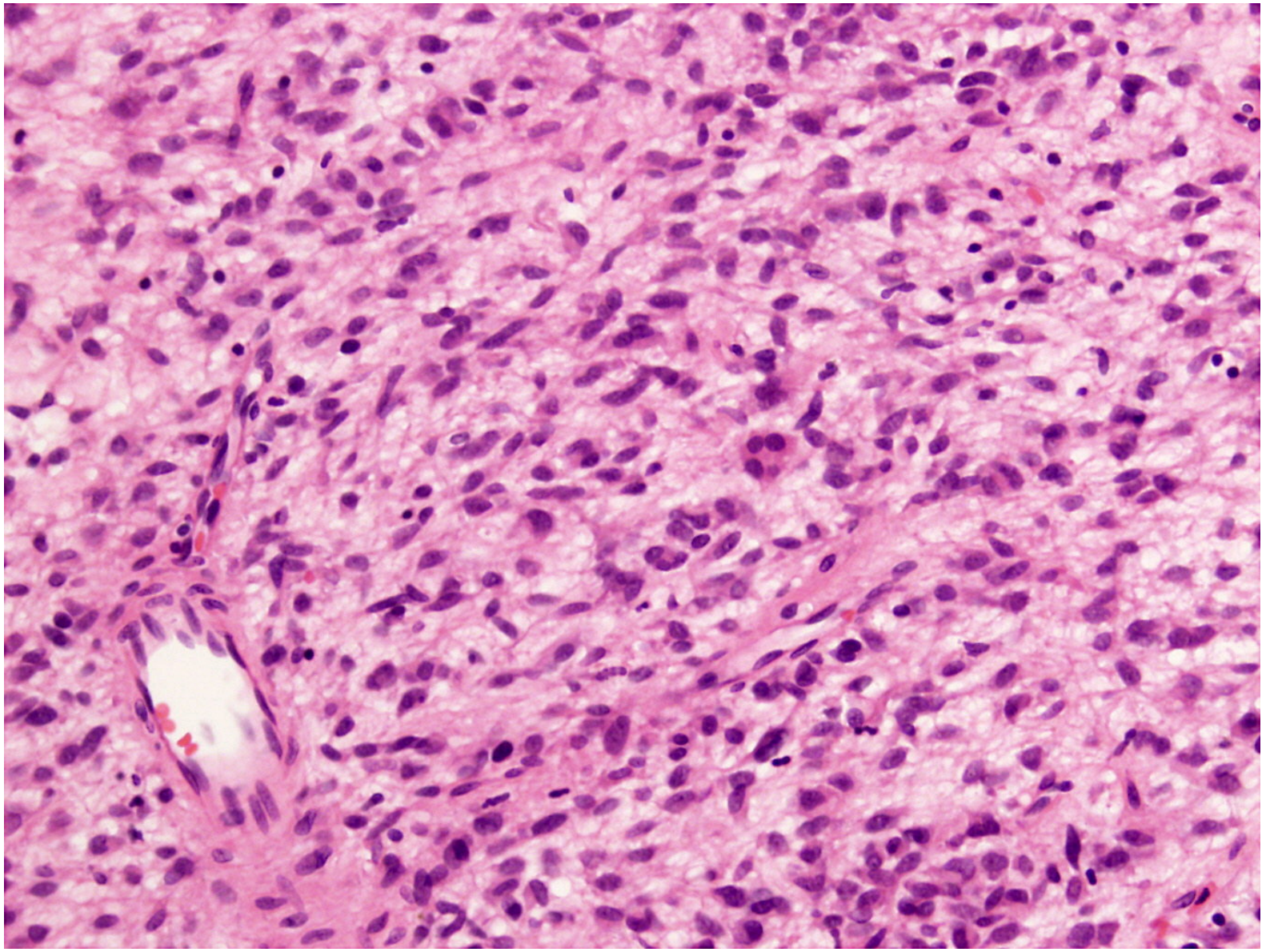
- muž, 68 rokov
- Makro: fragment tumoru d10 cm
  (prim. Dr. J. Macúch)

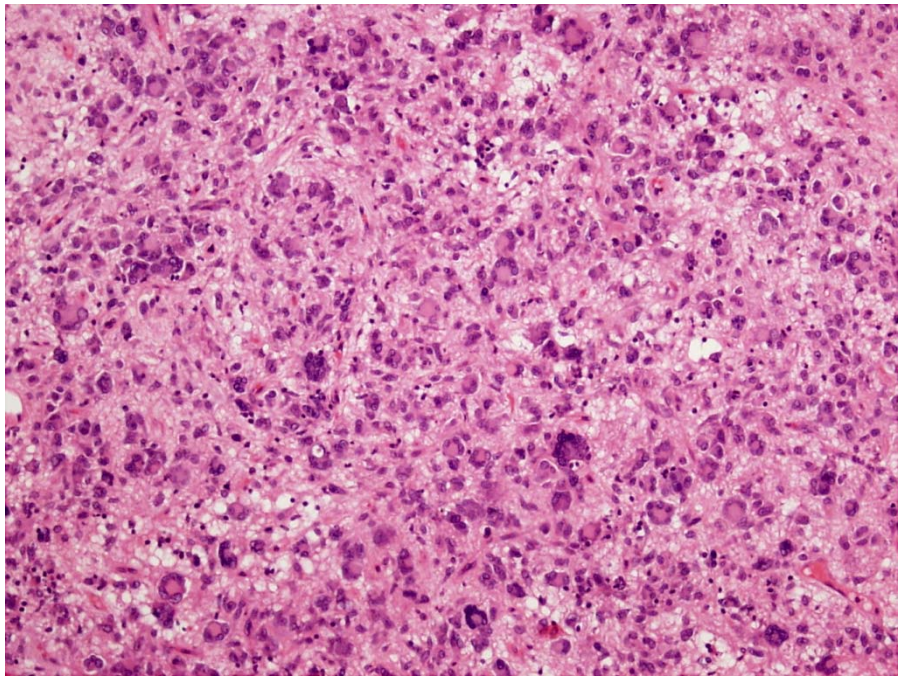
- **Klinická dg:** Tumor žalúdka, resp. burza omentalis - štúdia (C16.9)

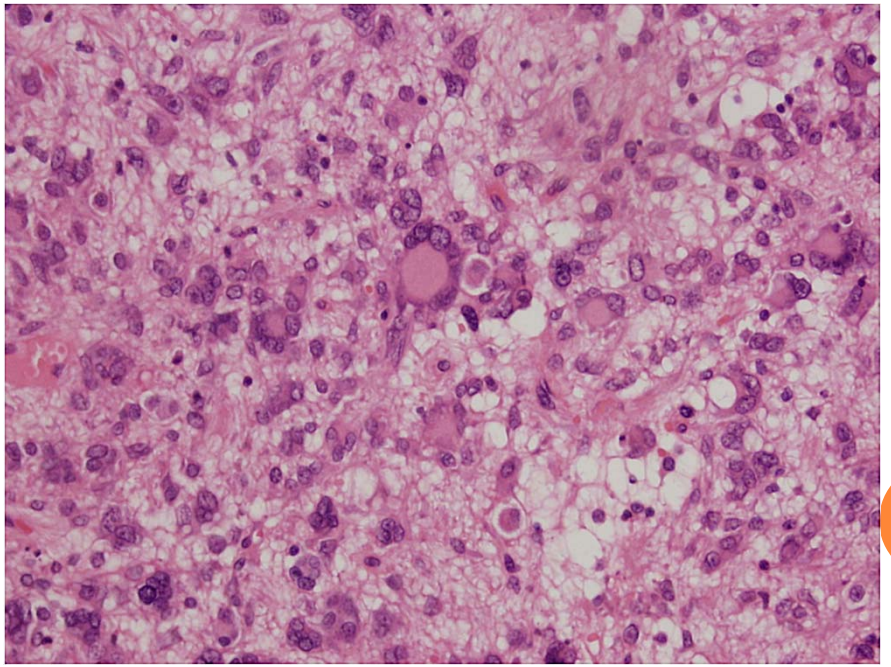
Fragment tumoru d.10cm (3 bloky)

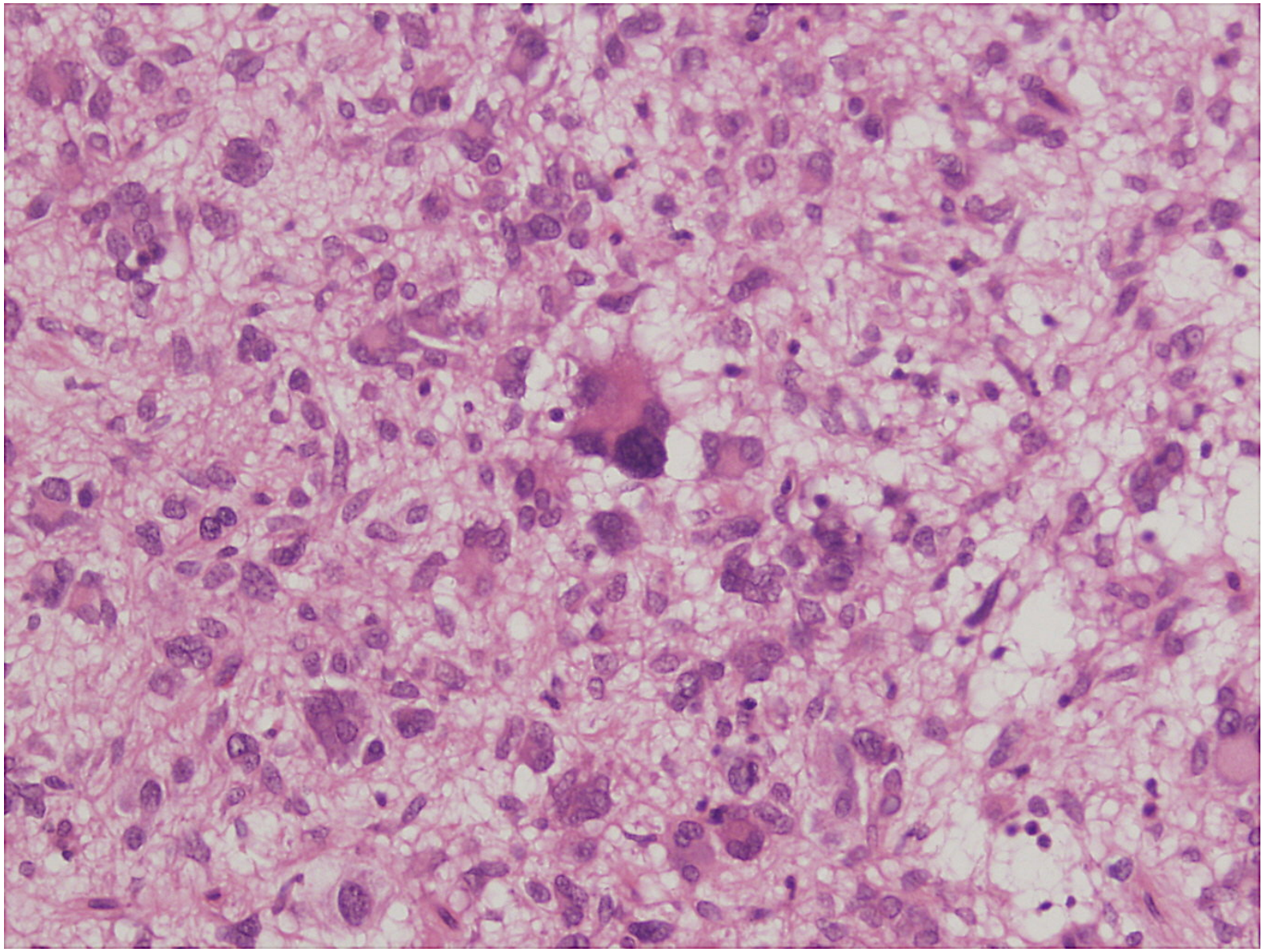


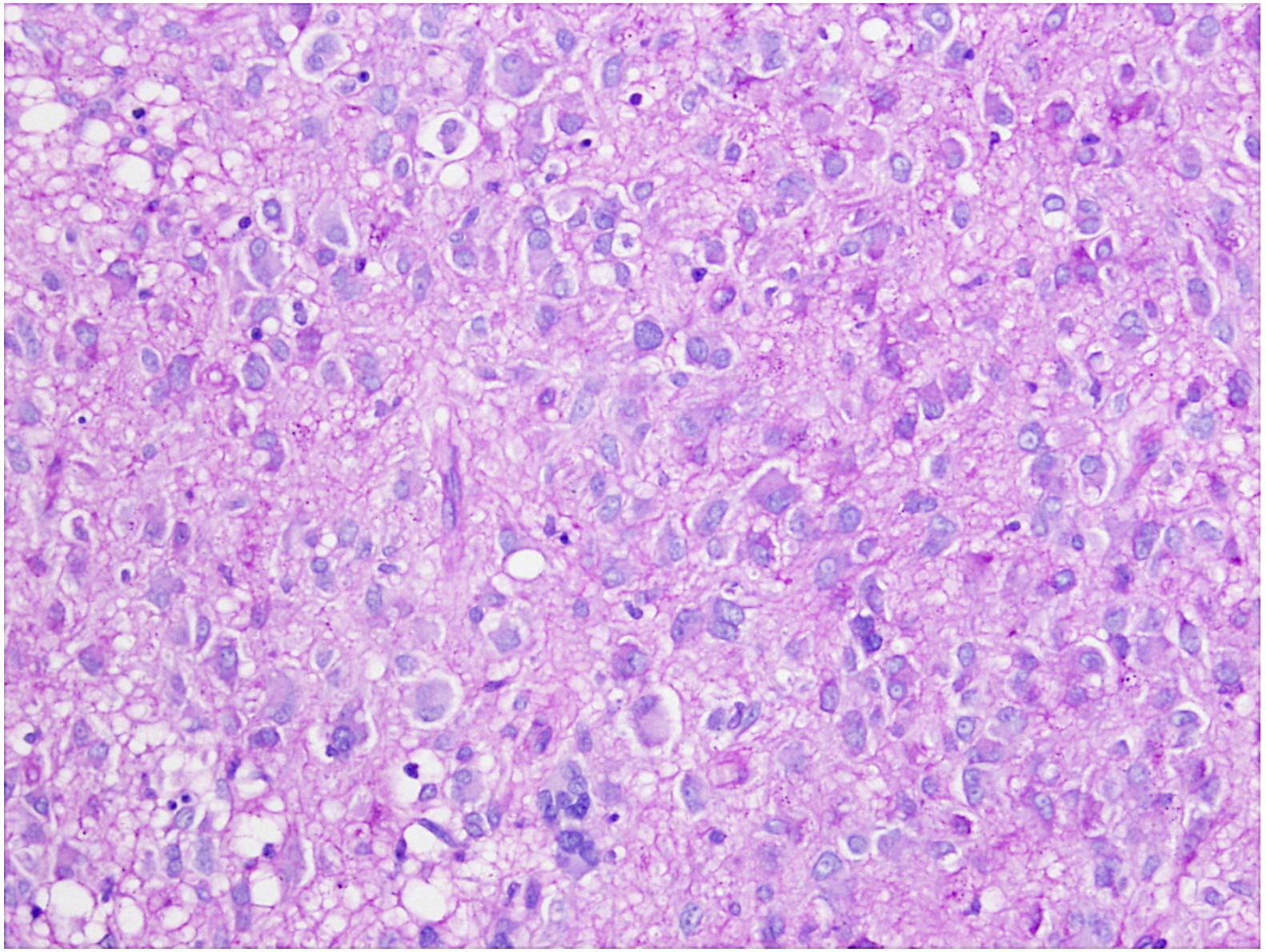


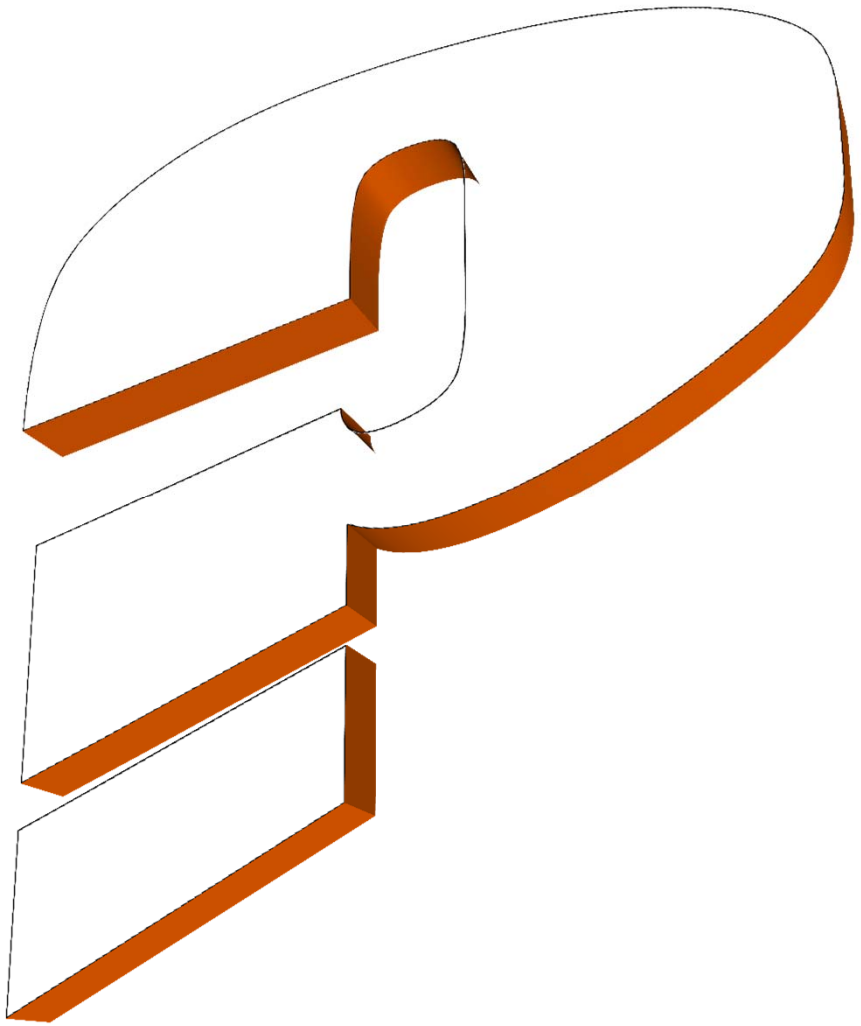




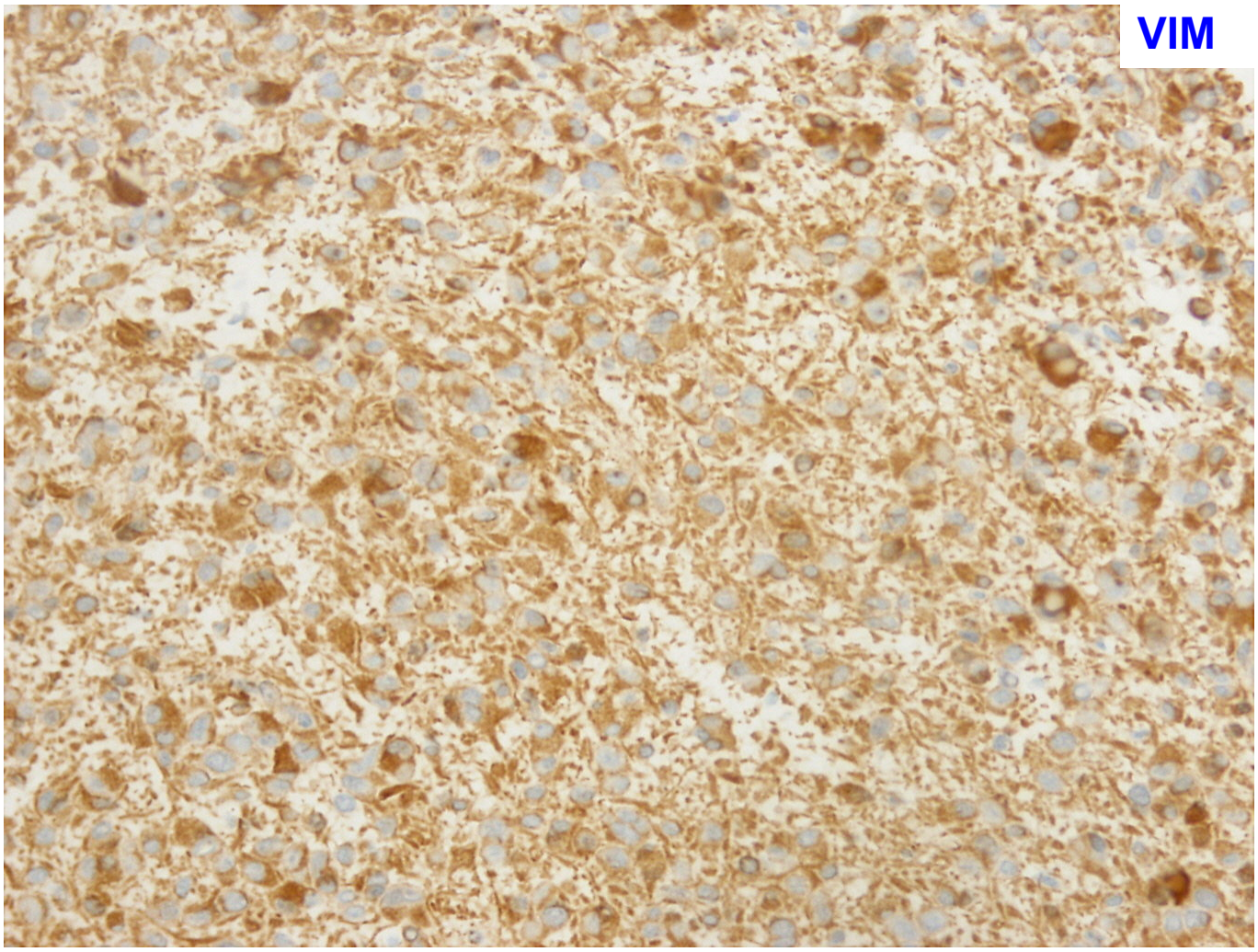


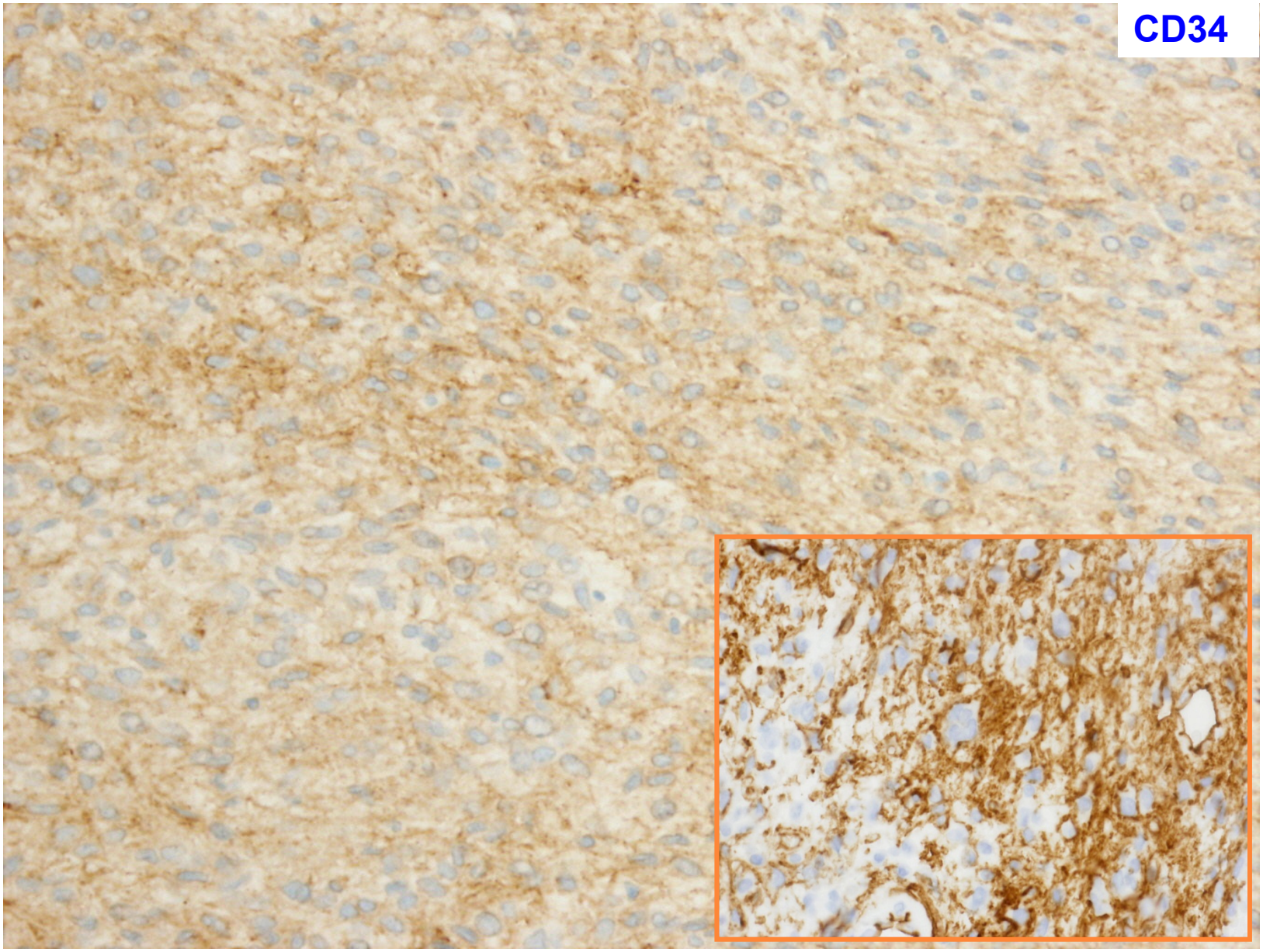


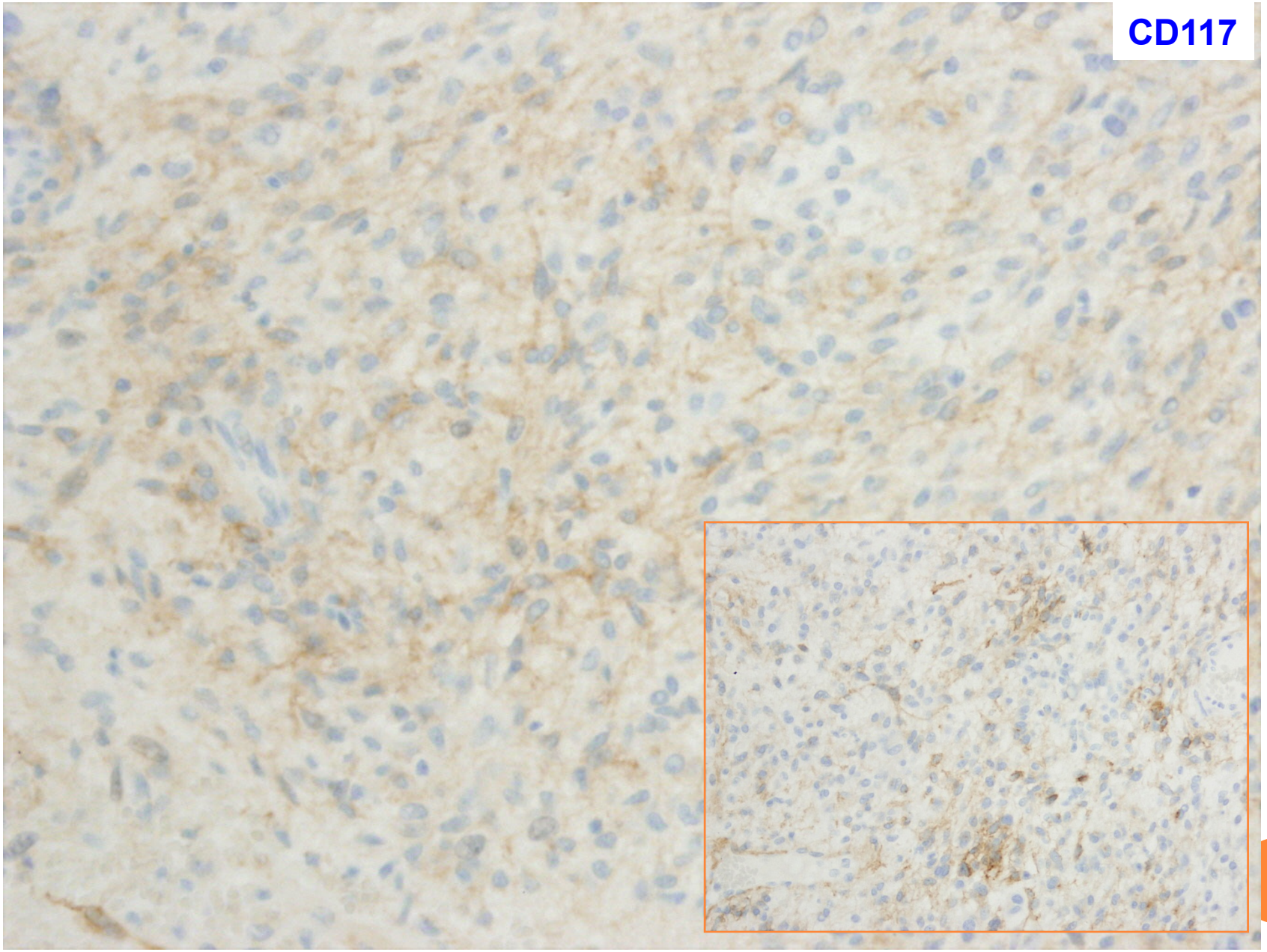


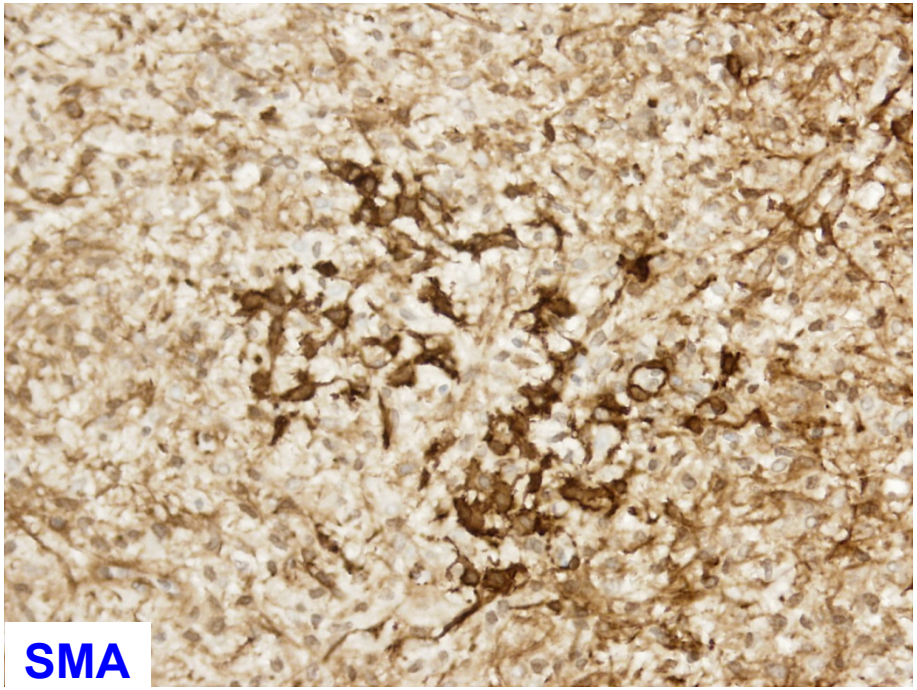


Imunohistochémia:

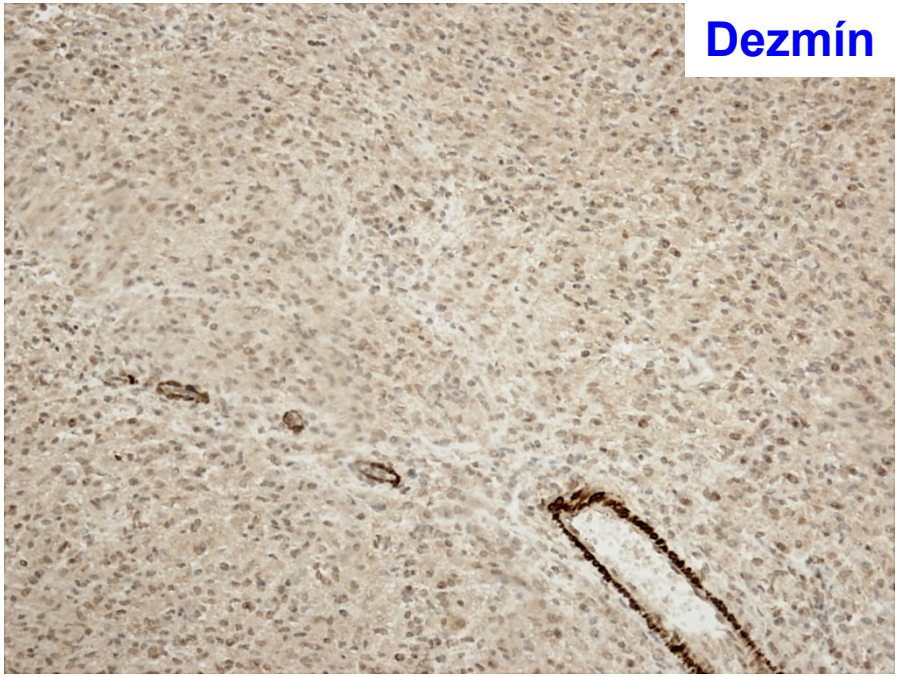



CD34

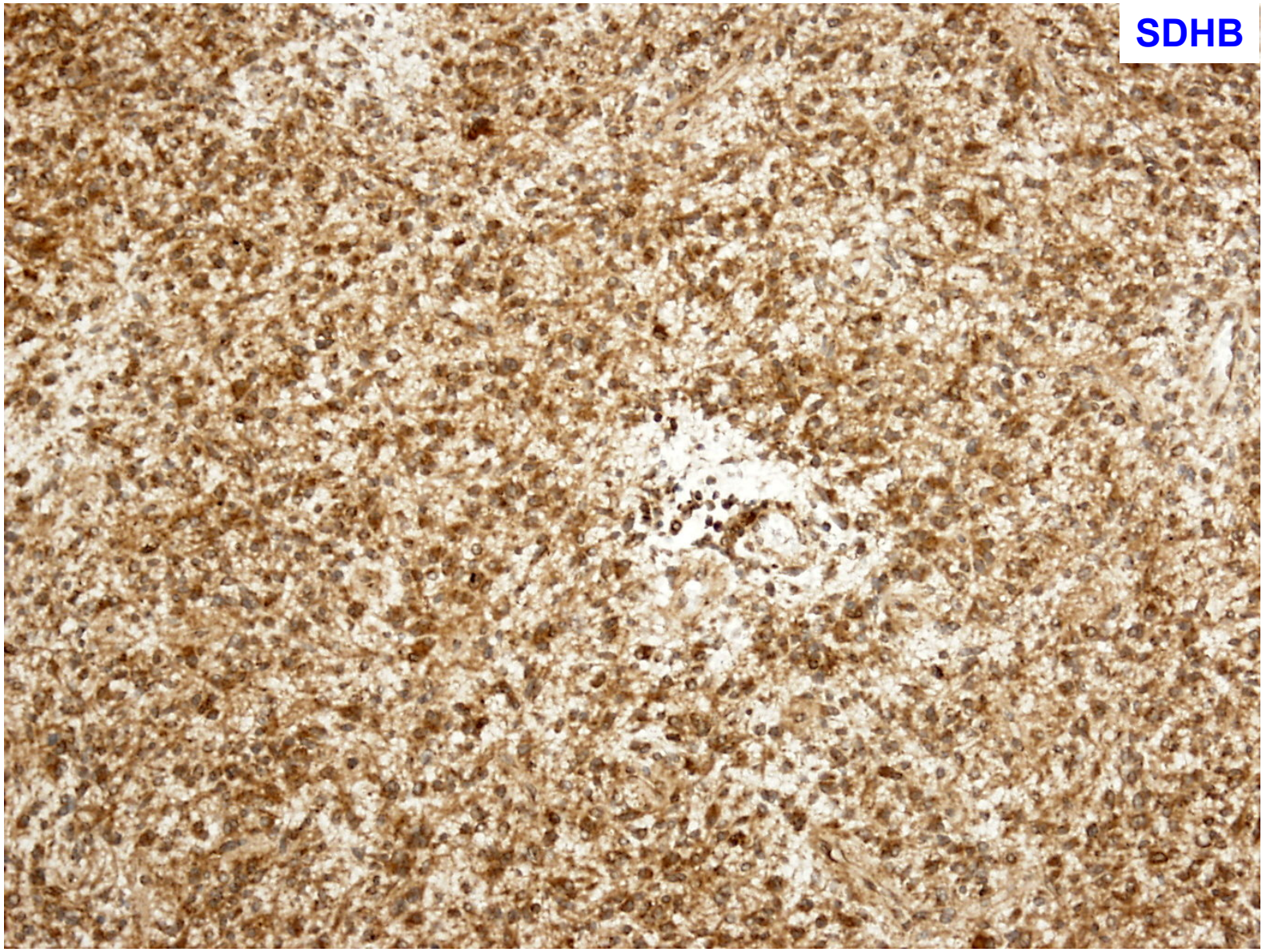

CD117

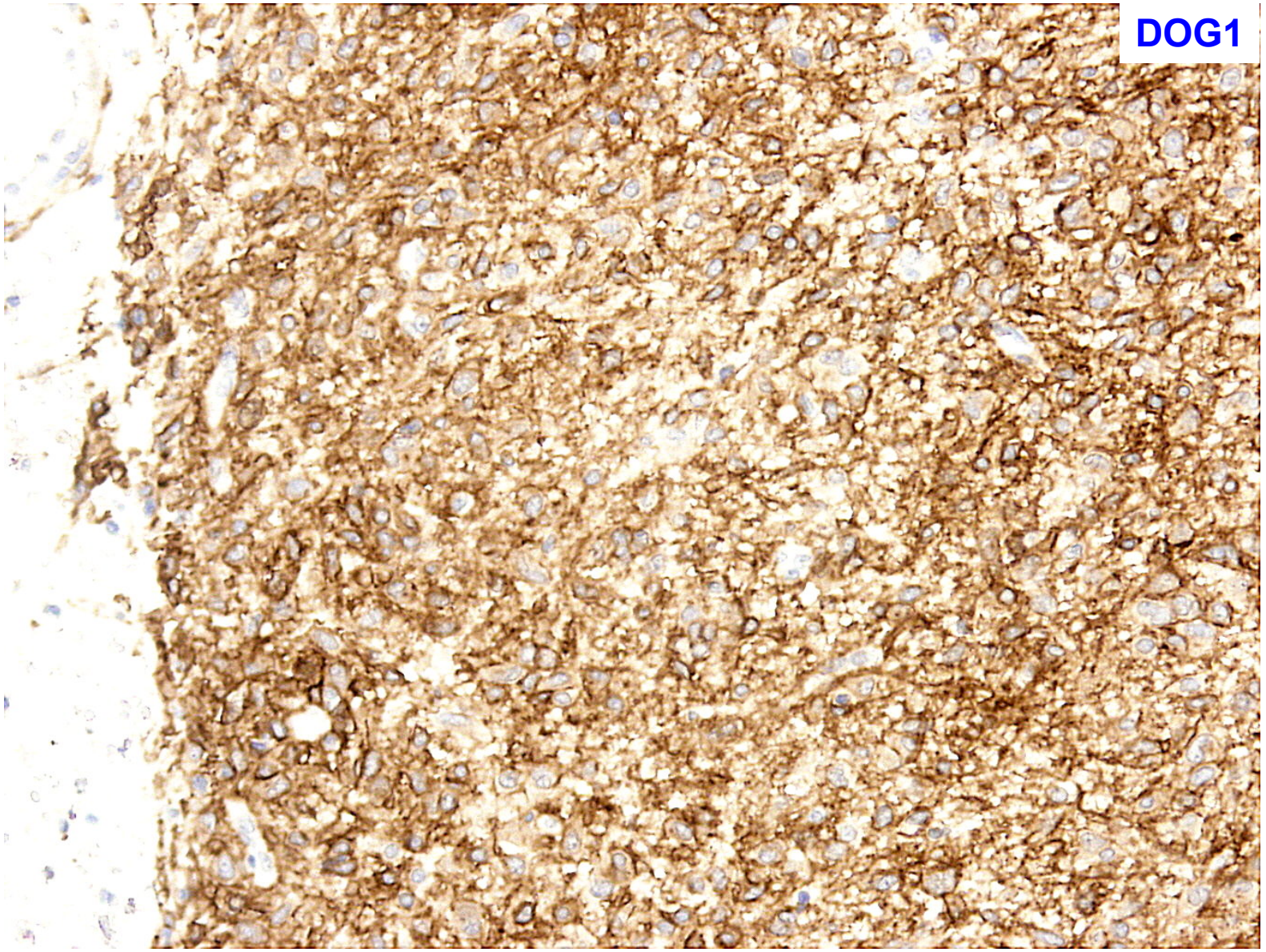


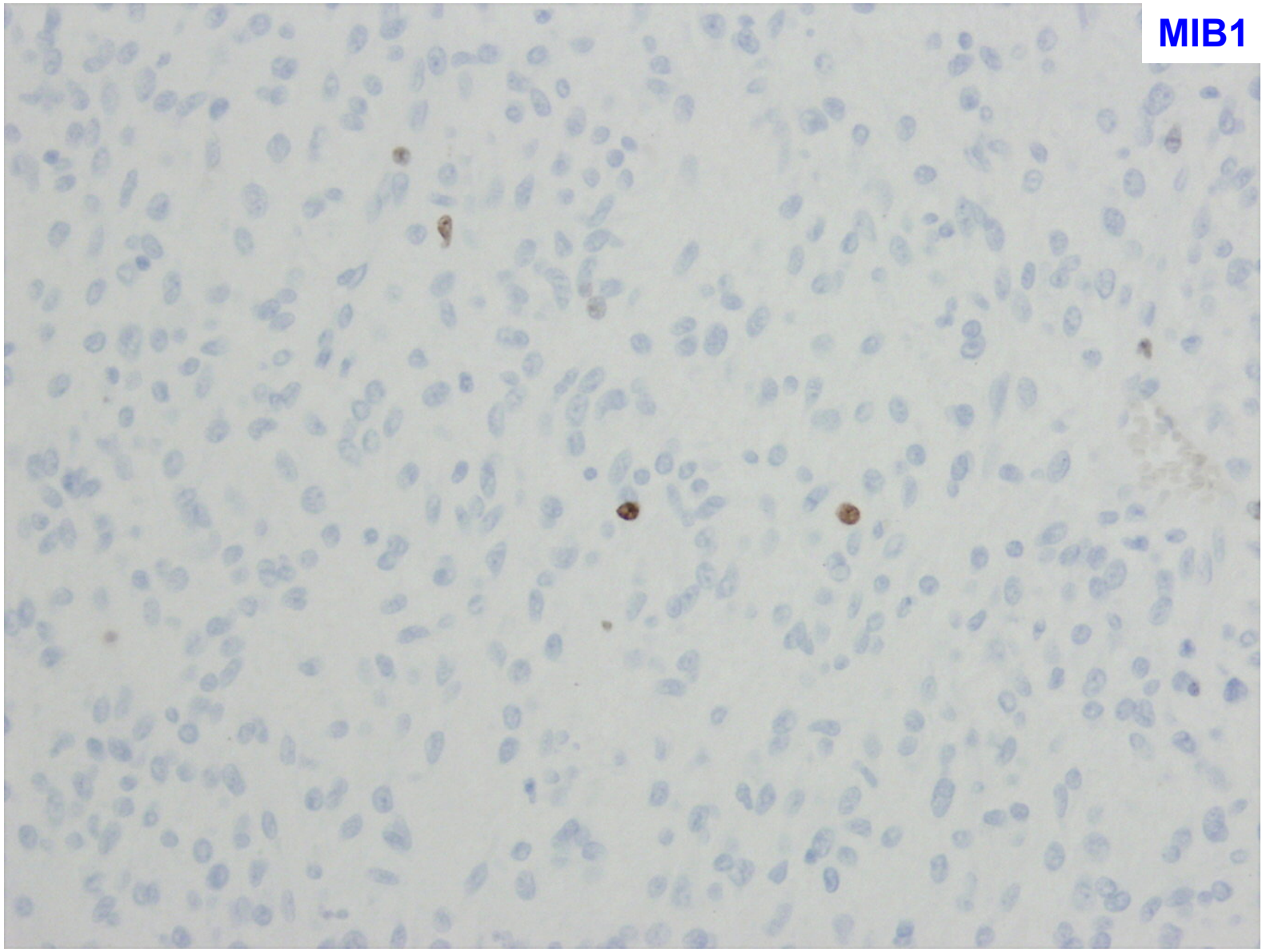
SMA



Dezmín


SDHB


DOG1


MIB1

Sumarizácia morfológie a fenotypu:

- výlučne nádorové tkanivo s ložiskami krvácania bez nekróz
- pleomorfné epiteloidné bunky bunky so širokou eozinofilnou, často vakuolizovanou cytoplazmou
- v časti nádoru dominujú viacjadrové bunky s nápadnými cytologickými a jadrovými atypiami
- mitotická aktivita je minimálna (0-1mf/50HPF, resp. 5 mm^2), proliferačná aktivita (index Ki-67) je menej ako 1%
- posúdenie vzťahu nádoru k okolitým tkanivám ani jeho celistvosti zaslané excízie neumožňujú.
- Imunohistochemicky: jednoznačná pozitivita dôkazu vimentínu, CD34, SDHB a DOG-1 so slabou koexpresiou CD117 v menej ako 10% a SMA vo viac ako 50% buniek

  - negativita dôkazu dezmínu a S-100 proteínu

DIAGNÓZA:

- ide o GIST epiteloidnebunkového typu nejasného origa (klinicky vychádzajúci zo žalúdka), bez možnosti morfologickej subtypizácie
- pri predpokladanej veľkosti nad 10 cm patrí podľa klasických kritérií (Fletcher a spol. 2002) do kategórie vysokého rizika a podľa kritérií AFIP (2006) do kategórie stredného rizika malígneho správania (v prípade ruptúry ide o vysoké riziko)
- podľa CAP a WHO (2010) ide o G1, T4, štádium III.B., prognostická skupina 3b (malígny GIST)

Výsledok mutačných analýz zašleme dodatočne, preto si dovolíme ponechať 2 Vaše bloky.


grafický seminář 2

68 ROČNÝ PACIENT

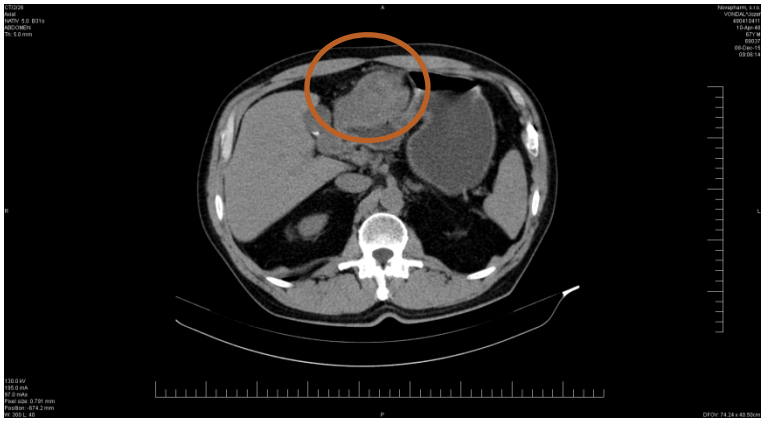
- **AA**:Neudáva
- **OA**: Struma nodosa, A.hypertenzia 2.st. ECS/ESH, BHP, asymptomatická mnohopočetná cholecystolitiáza, nodi hemoroidales,
- **SA,CA,EA**:Bez pozoruhodností.
- **RA**: Otec v 80 rokoch lymfóm
- **LA**: Euthyrox, Avodart,Kornam

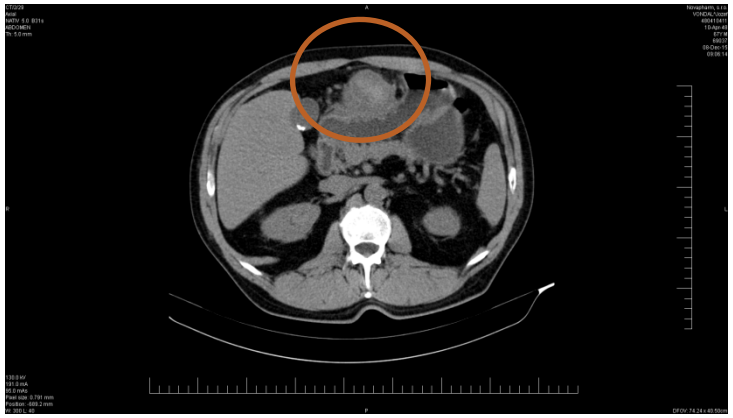
- **TO**:V máji 2015 epizóda bolestí epigastria. V novembri 2015 opätovné bolesti epigastria.

- **USG** 11/15 : Nález TU formácie 11x6x4cm v epigastriu - suspektne exofyticky vyrastajúci zo žalúdka alebo ezofagu.

- **EGD**12/15: Primeraný gastrofibroskopický nález.

CT 11.12.15:





V epigastriu ventrálne ostro ohraničené ložisko 78x68x52 mm naliehajúce na malú kurvatúru žalúdka a pylorickú časť so zhrubnutím steny žalúdka v tejto oblasti na 10 mm, heterogénnej štruktúry s hyper a hypodenznými / nekrotickými? / cystickými časťami s naznačenou septáciou. Bez lokoregionálnej lymfadenopatie.

Operačný a histologický nález:

- **Laparotómia** 4.2.2016 – z operačného nálezu:

.....HSL otvárame dutinu brušnú, nachádzame hemoperitoneum, prítomný perforovaný TU v omente veľkej kurvatúry antra žalúdka nejasnej príčiny. Odsávame koagulá a krv v množstve cca 1300 ml. Nejasná je príčina početných zrastov – opakované zakrvácanie? Evidentnú infiltráciu žalúdočnej steny nenachádzame a extirpujeme TU vcelku.....

- **Histologický nález**:

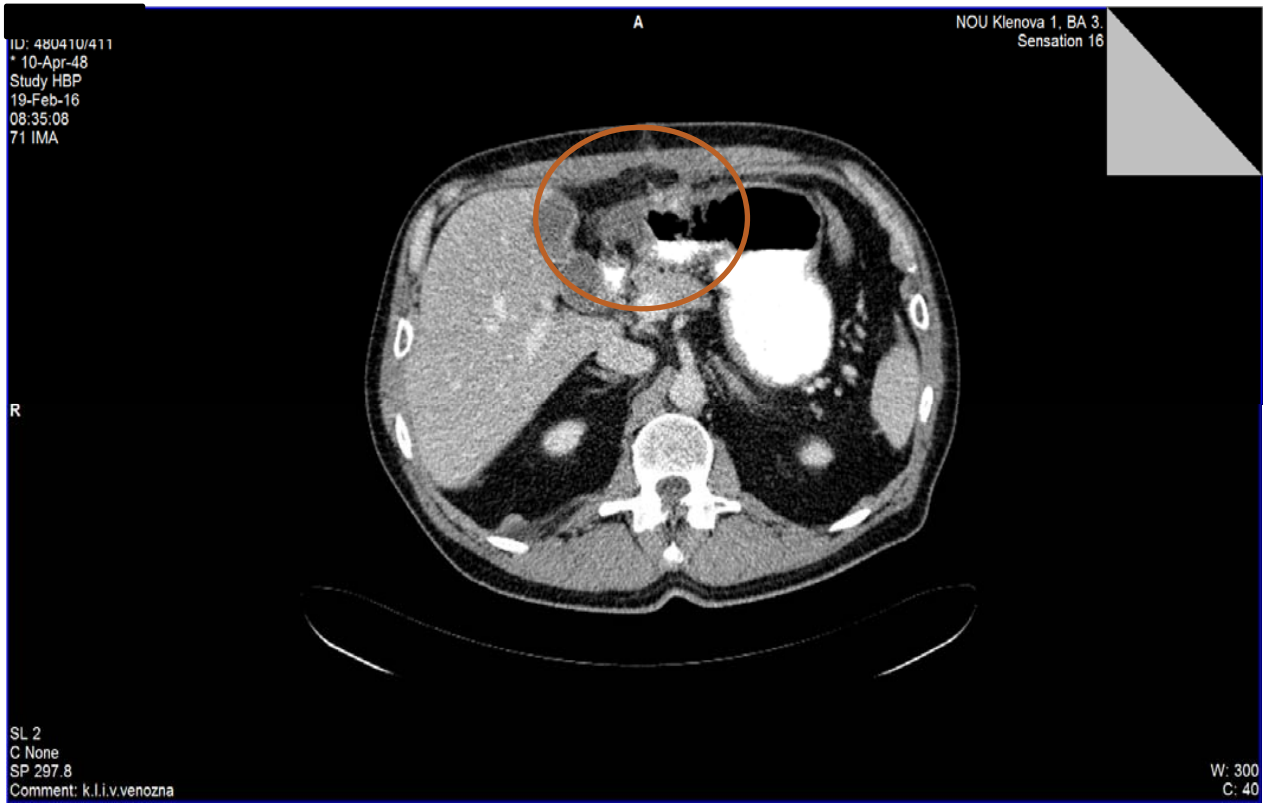
Makroskopicky: Fragment tumoru d 10cm

Mikroskopicky: Vcelku ohraničená nádorová proliferácia, tvorená epiteloidnejšími, miestami naznačene storiformnými formáciami, prítomné viacjadrové bunky, ložiská zakrvácania.

*Imunoprofi*l: AE1/3-, S100 ložiskovo +, VIM+, CD34+++, CD117-, SMA fokálne+, DEZ fokálne vo viacjadrových bb.+, MDM2-, CDK4-, CD68-. Mitotická aktivita 4 mi/50 HPF. Imunoprofil favorizuje najskôr léziu zo skupiny ***Solitary fibrous tumor –giant cell variant*** v.s. steny žalúdka. Ide o léziu s neistým malígnym potenciálom.

CT POOPERAČNE 19.2.2016

- St.p.op. TU omenta t.č. nepravidelné pruhovité štruktúry v tuku pod prednou brušnou stenou siahajúce po c. transverzum a na stenu antra žalúdka, ktorá je mierne zhrubnutá – len pooperačné zmeny? Min. reziduum sa nedá vylúčiť.



1.
Klinické údaje:

- muž 68 rokov
- tumor žalúdka - štúdia (C16.9)

TO:V máji 2015 epizóda bolestí epigastria. V novembri 2015 opätovné bolesti epigastria.
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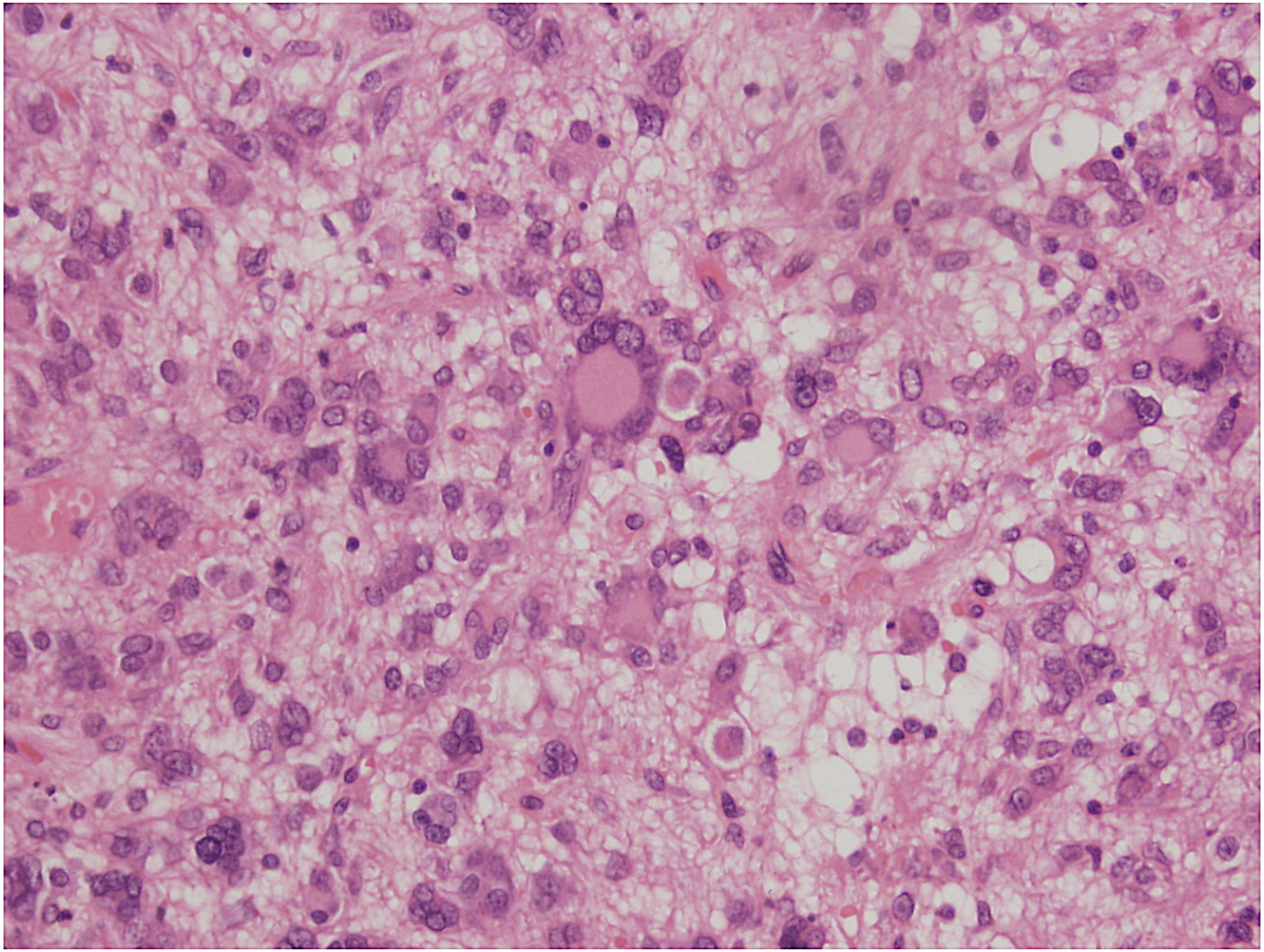
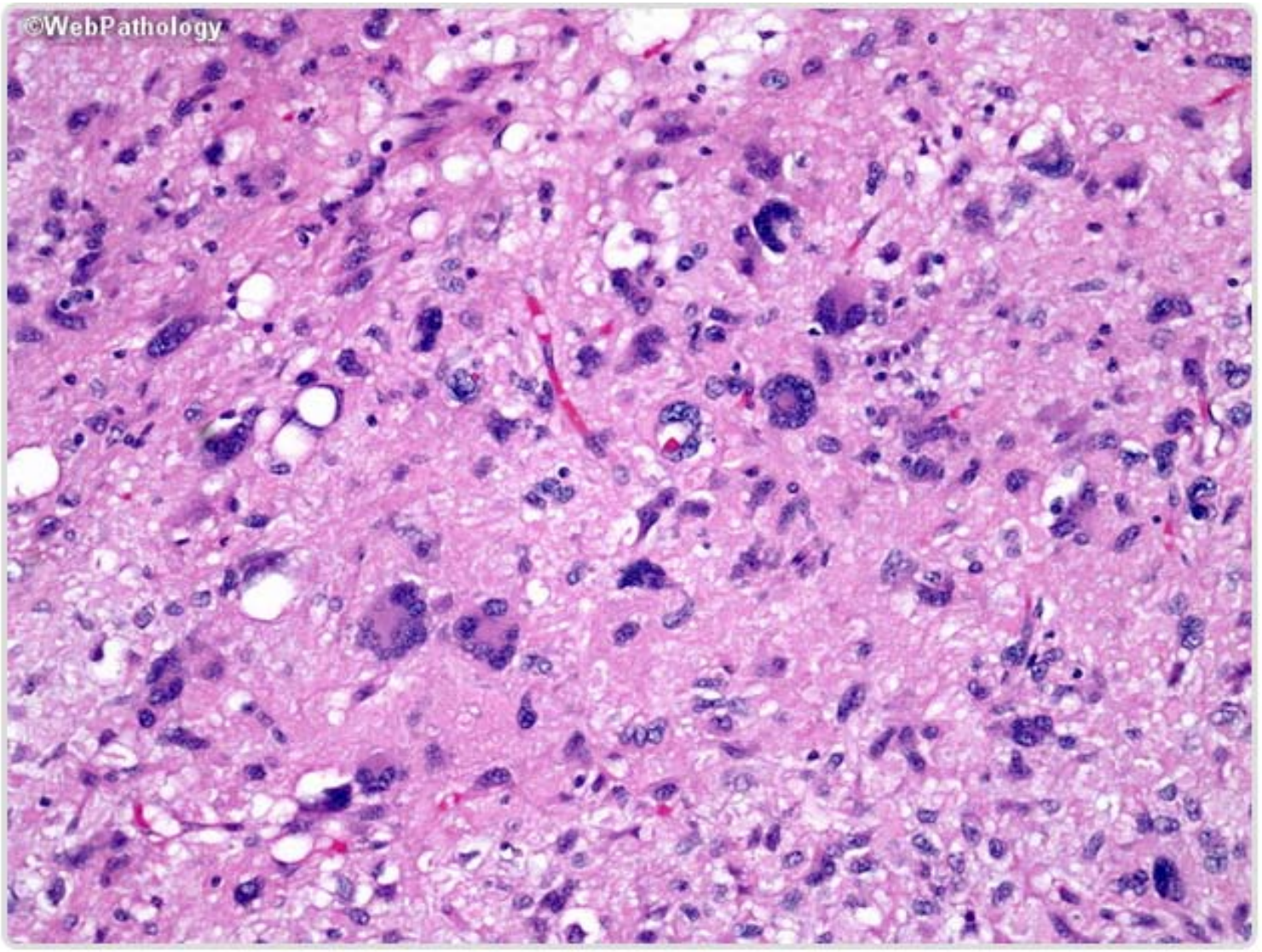
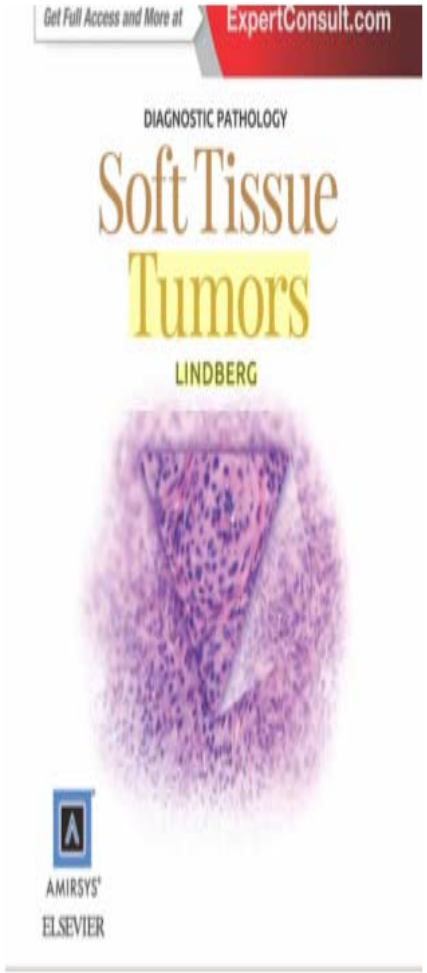
.....HSL otvárame dutinu brušnú, nachádzame hemoperitoneum, prítomný **perforovaný TU v omente veľkej kurvatúry antra žalúdka** nejasnej príčiny. Odsávame koagulá a krv v množstve cca 1300 ml. Nejasná je príčina početných zrastov – opakované zakrvácanie? Evidentnú infiltráciu žalúdočnej steny nenachádzame a exstirpujeme TU vcelku.....

2.
Morfologický obraz

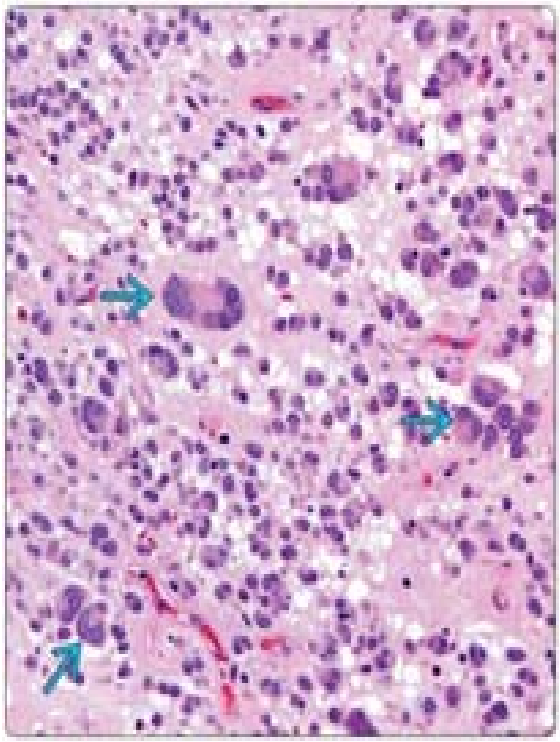


Epiteloidný GIST s obrovskými bunkami





Multinucleated Tumor Cells



(Left) *Prominent hyalinized or sclerotic stroma may be seen in epithelioid GIST. Individual tumor cells and small clusters of cells may resemble plasma cells or even osteoblasts.* **(Right)** *Scattered bi- or multinucleated tumor cells are relatively common in epithelioid GIST.*

3.
Diferenciálna diagnóza

SFT verzus GIST

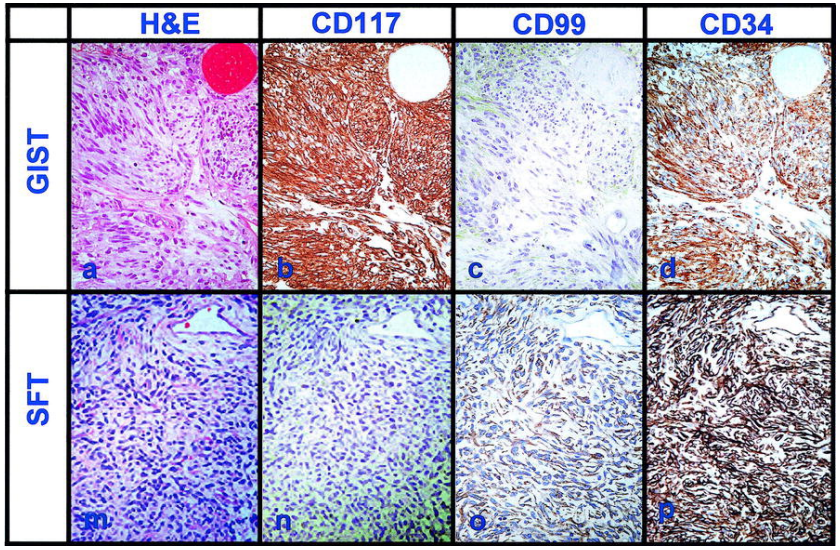
- „patternless“
- vretenobb., málo cytoplazmy
- cievy vetvené (HP-like)
- CD34 +
- CD117- / DOG1-/ aktín -/+
- STAT6+
- mutácia STAT6

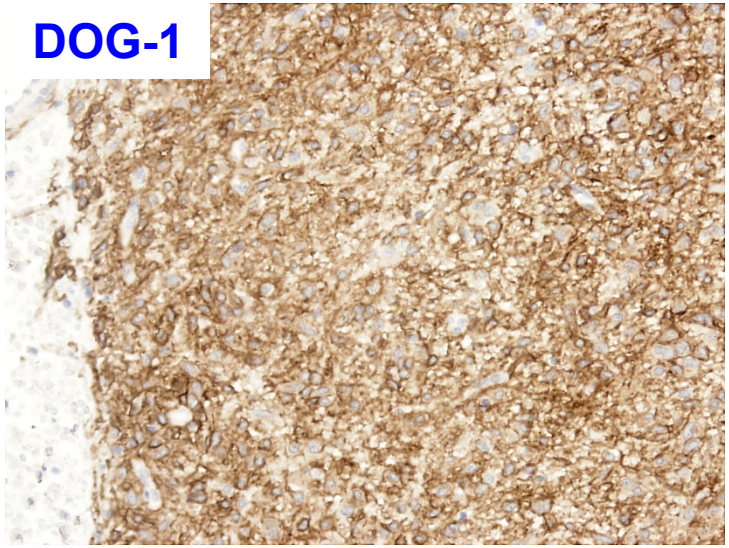
- palisádovanie, hniezda bb.
- vreteno- aj epiteloidnebunkový
- cievy nevetvené
- CD34 +/-
- CD117 +/- / DOG1+ / SMA+/-
- STAT6-
- mutácie C-KIT, PDGFRα, BRAF

SFT verzus GIST

Gastrointestinal Stromal Tumor	Solitary Fibrous Tumor
Spindled or epithelioid cytoplasm	Scant cytoplasm
Skeinoid fibers, if present are irregular, globular and have prominent retraction	Ropy collagen
Hemangiopericytoma-like vessels uncommon	HPC-like vessels common
CD117 (KIT) 74-95%, DOG1 87-95% positive	CD117, DOG1 negative
Actin 30-50% positive	Actin rare and focal

CD34 is usually positive in both





4.
Stanovenie stupňa rizika (dignity)

Table 3 Risk assessment of GIST, 2002 by NIH

Risk category	Size (cm)	Mitotic count (50 HPF)
Very low risk	<2	<5
Low risk	2-5	5
Intermediate risk	5	6-10
	5-10	5
High risk	>5	>5
	>10	Any mitotic rate
	Any size	>10

Adopted from Fletcher and colleagues [ref (99) Table 2].
Abbreviations: HPF, high-power field

Table 4 Risk assessment of GIST, 2006 by miettinen and lasota (ref 140)

Mitotic rate (50 HPF)	Tumor size (cm)	Stomach	Duodenum	Jejunum or ileum	Rectum
5	2	None	None	None	None
	>25	Very low	Low	Low	Low
	>510	Low	Moderate	Insufficient data	Insufficient data
	>10	Moderate	High	High	High
>5	2	None*	High*	Insufficient data	High
	>25	Moderate	High	High	High
	>510	High	High	Insufficient data	Insufficient data
	>10	High	High	High	High

Adopted from Miettinen and Lasota (ref 140). Abbreviation: HPF, high-power field; *Very small number of cases

Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts

Heikki Joensuu, Aki Vehtari, Jaakko Riihimäki, Toshirou Nishida, Sonja E Steigen, Peter Brabec, Lukas Plank, Bengt Nilsson, Claudia Cirilli, Chiara Braconi, Andrea Bordoni, Magnus K Magnusson, Zdenek Linke, Jozef Sufliarsky, Massimo Federico, Jon G Jonasson, Angelo Paolo Dei Tos, Piotr Rutkowski

Summary

Background The risk of recurrence of gastrointestinal stromal tumour (GIST) after surgery needs to be estimated when considering adjuvant systemic therapy. We assessed prognostic factors of patients with operable GIST, to compare widely used risk-stratification schemes and to develop a new method for risk estimation.

Methods Population-based cohorts of patients diagnosed with operable GIST, who were not given adjuvant therapy, were identified from the literature. Data from ten series and 2560 patients were pooled. Risk of tumour recurrence was stratified using the National Institute of Health (NIH) consensus criteria, the modified consensus criteria, and the Armed Forces Institute of Pathology (AFIP) criteria. Prognostic factors were examined using proportional hazards and non-linear models. The results were validated in an independent centre-based cohort consisting of 920 patients with GIST.

Findings Estimated 15-year recurrence-free survival (RFS) after surgery was 59·9% (95% CI 56·2–63·6); few recurrences occurred after the first 10 years of follow-up. Large tumour size, high mitosis count, non-gastric location, presence of rupture, and male sex were independent adverse prognostic factors. In receiver operating characteristics curve analysis of 10-year RFS, the NIH consensus criteria, modified consensus criteria, and AFIP criteria resulted in an area under the curve (AUC) of 0·79 (95% CI 0·76–0·81), 0·78 (0·75–0·80), and 0·82 (0·80–0·85), respectively. The modified consensus criteria identified a single high-risk group. Since tumour size and mitosis count had a non-linear association with the risk of GIST recurrence, novel prognostic contour maps were generated using non-linear modelling of tumour size and mitosis count, and taking into account tumour site and rupture. The non-linear model accurately predicted the risk of recurrence (AUC 0·88, 0·86–0·90).

Interpretation The risk-stratification schemes assessed identify patients who are likely to be cured by surgery alone. Although the modified NIH classification is the best criteria to identify a single high-risk group for consideration of adjuvant therapy, the prognostic contour maps resulting from non-linear modelling are appropriate for estimation of individualised outcomes.

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See Online/Comment
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The Lancet Oncology, Published online December 7, 2011
DOI:10.1016/S1470-2045(11)70299-6

Ruptúra a prežívanie

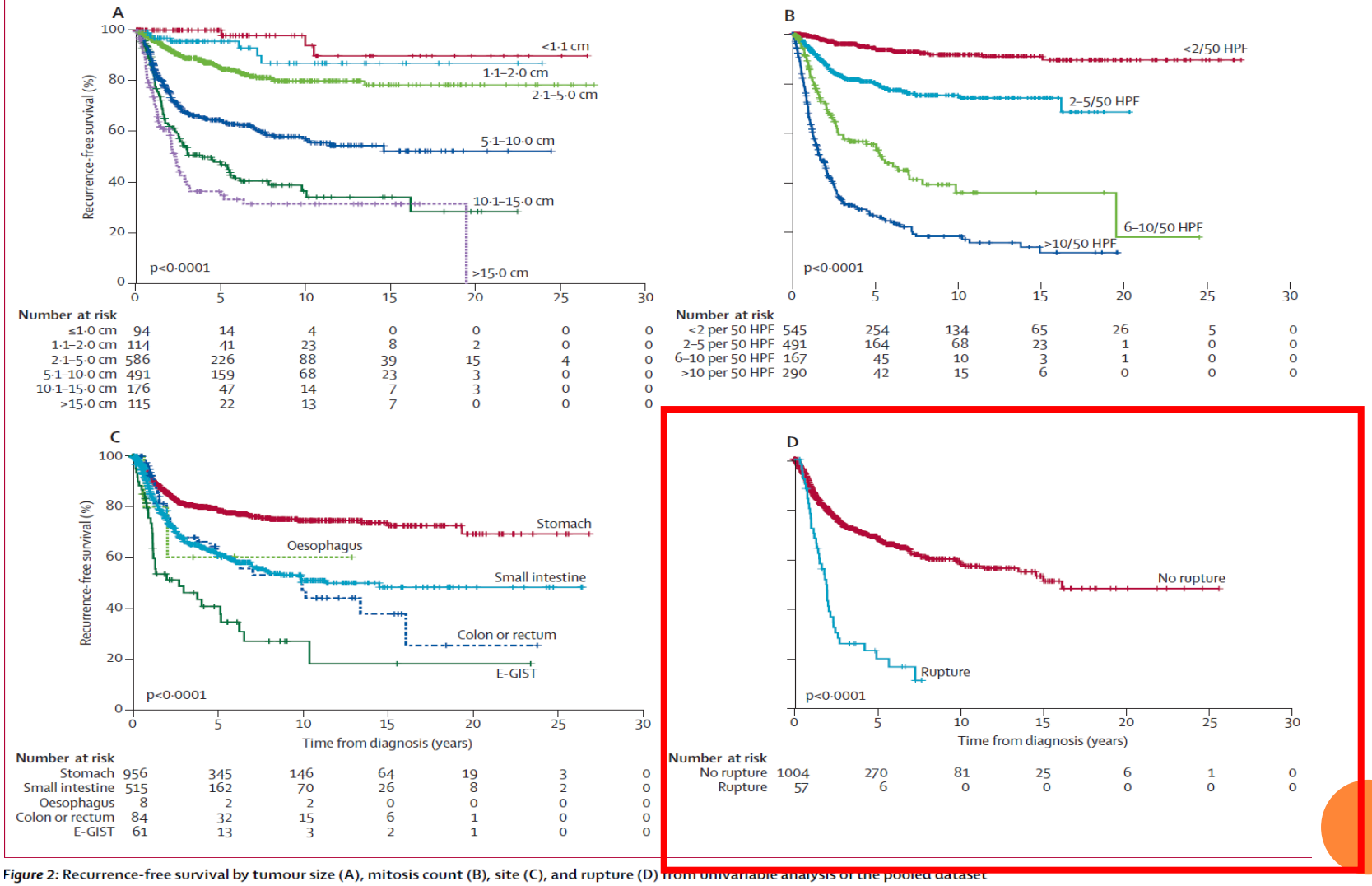

Figure 2: **Recurrence-free survival by tumour size (A), mitosis count (B), site (C), and rupture (D) from univariable analysis of the pooled dataset**
HPF=high power field of the microscope. E-GIST=extragastrointestinal stromal tumour (GIST that arises outside the gastrointestinal tract).

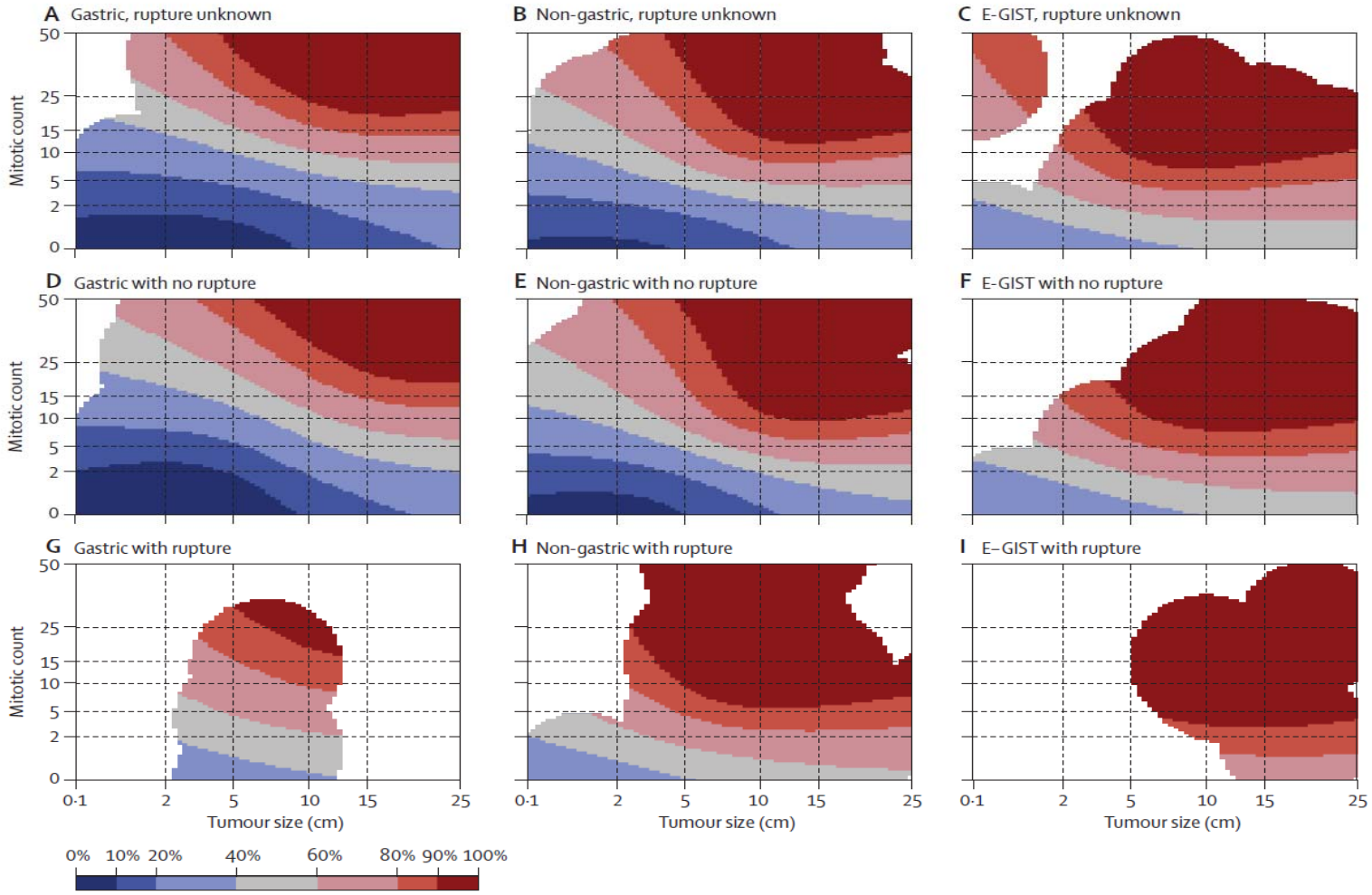

Figure 4: **Contour maps for estimating the risk of GIST recurrence after surgery**
The upper row maps are used when tumour rupture status is unknown (A,B,C), the middle row maps when the tumour has not ruptured (D,E,F), and the bottom row maps when tumour rupture has occurred (G,H,I). Red areas depict high risk, blue areas low risk, and white areas indicate lack of data. The percentages associated with each colour (key) indicate the probability of GIST recurrence within the first 10 years of follow-up after surgery. For example, the middle map of the far left column (D) shows that the 10-year risk of GIST recurrence of a patient diagnosed with a 10 cm gastric GIST with five mitoses per 50 high power fields (HPFs) of the microscope and no rupture is 20–40%. The 10-year risk associated with a similar tumour when the mitosis count is ten per 50 HPFs increases to 40–60%.
E-GIST=extragastrointestinal stromal tumour (arising outside the gastrointestinal tract).

5.
Genetické vyšetrenie

Očakávaný výsledok mol.-gen. analýzy:

1. bez mutácie génov C-KIT a PDGFRα (WT)
2. mutácia v exóne 11 C-KIT
3. mutácia v exóne 9 C-KIT
4. mutácia v exóne 18 PDGFRα
5. mutácia v exóne 15 BRAF
6. nemám krištáľovú guľu ...

Výsledok:

- zistená mutácia v exóne 18 PDGFRa, a to typu tzv. heterozygotnej missense mutácie (D842V).
- okrem toho bola zistená aj variácia v tom istom exóne, ktorá je z biologického hľadiska nevýznamná.

Doc. RNDr. Z.Lasabová, PhD., RNDr. A.Štanclová, CSc., Mgr. K.Gemzová, PhD.

Frekvencia mutácií GISTov

Table 2 Molecular classification of GISTs (134)*

Genetic type	Relative frequency	Anatomic distribution
***KIT* mutation (relative frequency 75-80%)**		
Exon 8	Rare	Small intestine
Exon 9 insertion AY502-503	10%	Small intestine and colon
Exon 11 (deletion, single nucleotide substitution and insertions	67%	All sites
Exon 13 K642E	1%	All sites
Exon 17 D820Y, N822K and Y823D	1%	All sites
***PDGFRA* mutation (relative frequency 5-8%)**		
Exon 12 (such as V561D)	1%	All sites
Exon 14 N659K	<1%	Stomach
Exon 18 D842V	5%	Stomach, mesentery and momentum
Exon 18 (such as deletion of amino acids IMHD 842-846	1%	All sites
***KIT* and *PDGFRA* wild-type (relative frequency 12-15%**		
BRAF V600E	~7-15%	
SDHA, *SDHB*, *SDHC* and *SDHD* mutations	~2%	Stomach and small intestine
HRAS and *NRAS* mutation	<1%	
Sporadic pediatric GISTs	~1%	Stomach
GISTs as part of the Carney triad	~1%	Stomach
NF1-related	Rare	Small intestine

Adopted from Corless and colleagues [ref (134) Table 1]. Abbreviation: GIST, gastrointestinal stromal tumor; NF1, neurofibromatosis type I; PDGFRA, platelet-derived growth factor receptor- ; SDH, succinate dehydrogenase

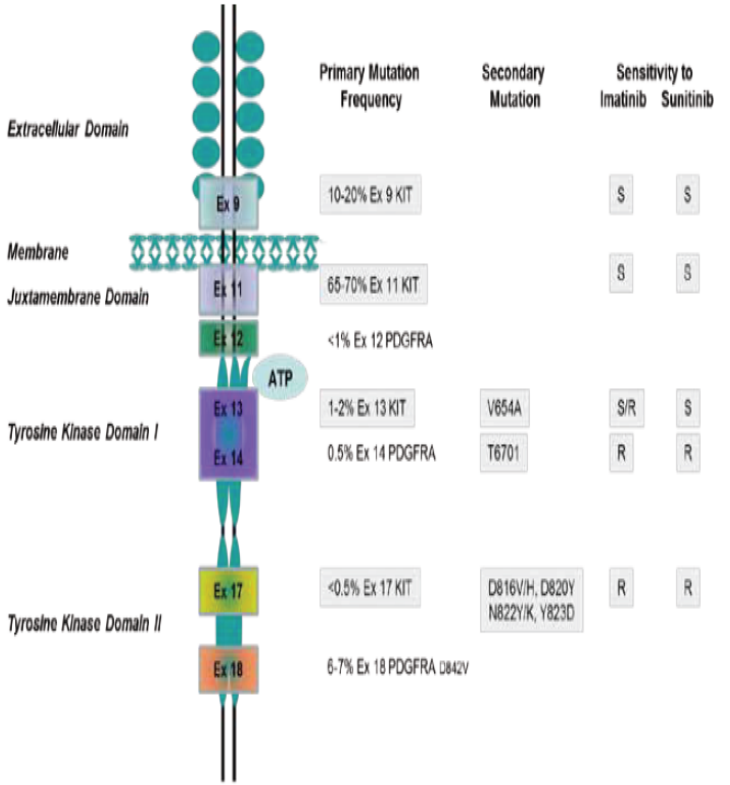

Figure 1 Schematic distribution of KIT or PDGFRA receptor mutations, frequency of mutations and TKI (Abbreviations: Ex, Exon; S, sensitive; R, resistant)

Liečba Imatinibom pri D842V PDGFRα

	n	PR	SD	PD
U.S-Finnish B2222 phase II trial,	3	0	0	3
EORTC phase III	4	0	0	4
US SWOG/CALGB phase III	4	0	1	3
ASCO 2009 an international survey	19	0	5	14

- Medián PFS 2,8 M, medián OS 12,7 M

Liečba Imatinibom pri D842V PDGFRα

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Clinical Cancer Research

Predictive Biomarkers and Personalized Medicine

Outcome of Patients with Platelet-Derived Growth Factor Receptor Alpha–Mutated Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era

Philippe A. Cassier[1], Elena Fumagalli[10], Piotr Rutkowski[11], Patrick Schöffski[12], Martine Van Glabbeke[14], Maria Debiec-Rychter[13], Jean-François Emile[2], Florence Duffaud[3], Javier Martin-Broto[15], Bruno Landi[5], Antoine Adenis[6], François Bertucci[4], Emmanuelle Bompas[7], Olivier Bouché[8], Serge Leyvraz[16], Ian Judson[17], Jaap Verweij[18], Paolo Casali[10], Jean-Yves Blay[1,9], and Peter Hohenberger[19] for the European Organisation for Research and Treatment of Cancer

Table 2. RR to imatinib per group of PDGFRA mutation and overall

	D842V[a]	Non-D842V exon 18	Exon 12	Exon 4	Overall[a]
Response	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
CR	0 (0)	1 (6)	1 (13)	0 (–)	2 (4)
PR	0 (0)	4 (24)	3 (38)	1 (–)	8 (14)
SD	10 (32)	10 (59)	3 (38)	0 (–)	23 (40)
PD	21 (68)	2 (12)	1 (13)	0 (–)	24 (42)

[a]One patient with a D842V-mutant GIST died of gastrointestinal hemorrhage before his first assessment and was therefore not evaluable for response.

Table 1. Main characteristic of the 58 patients included in this study

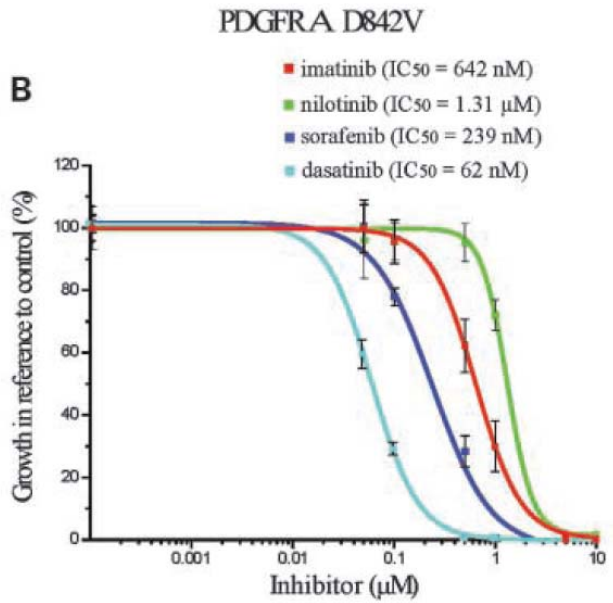
Characteristic	*N* (%)
Total	**58 (100)**
Gender	
Male	34 (59)
Female	24 (41)
Primary tumor location	
Stomach	40 (69)
Small bowel	7 (12)
Peritoneum/mesentery	3 (5)
Rectum/anus	1 (2)
Other[a]	3 (6)
Unknown	4 (7)
NIH risk group[b]	
NA	17 (—)
Very low	0 (0)
Low	2 (5)
Intermediate	2 (5)
High	37 (90)
Miettinen risk group[b]	
NA	24 (—)
Very low	1 (3)
Low	1 (3)
Intermediate	11 (32)
High	21 (62)
KIT/CD117 expression	
Positive	49 (84)
Negative	9 (16)
Type of mutation	
Exon 18 D842V substitution	32 (55)
Other exon 18 mutation	17 (29)
Exon 12 mutation	8 (14)
Exon 4 mutation	1 (2)
Metastatic sites	
Liver	36 (62)
Peritoneum	33 (57)
Liver and peritoneum	15 (26)
Other	15 (26)
WHO performance status	
0	28 (48)
1	19 (33)
2	2 (3)
Unknown	9 (16)

Iné možnosti liečby

Cancer Therapy: Preclinical

Activity of Dasatinib, a Dual SRC/ABL Kinase Inhibitor, and IPI-504, a Heat Shock Protein 90 Inhibitor, against Gastrointestinal Stromal Tumor – Associated PDGFRA^{D842V} Mutation

Barbara Dewaele,[1] Bartosz Wasag,[1] Jan Cools,[1,4] Raf Sciot,[2] Hans Prenen,[3] Peter Vandenberghe,[1] Agnieszka Wozniak,[3] Patrick Schöffski,[3] Peter Marynen,[1,4] and Maria Debiec-Rychter[1]



Clin Cancer Res 2008;14(18) September 15, 2008

Iné možnosti liečby

Published OnlineFirst June 27, 2012; DOI: 10.1158/1078-0432.CCR-12-0625

Clinical Cancer Research

Cancer Therapy: Preclinical

Crenolanib Inhibits the Drug-Resistant PDGFRA D842V Mutation Associated with Imatinib-Resistant Gastrointestinal Stromal Tumors

Michael C. Heinrich[1], Diana Griffith[1], Arin McKinley[1], Janice Patterson[1], Ajia Presnell[1], Abhijit Ramachandran[2], and Maria Debiec-Rychter[3]

Table 3. Biochemical IC_{50} values for inhibition of PDGFRA kinase activity in CHO cells expressing compound-mutant kinases

Kinase	Exons	Imatinib	Crenolanib	*P*
V561D +T674I	12 + 14	>1,000	>1,000	0.99
V561D + D842V	12 + 18	>1,000	26 ± 6	0.0002
T674I + D842V	14 + 18	>1,000	24 ± 12	0.006

NOTE: The values for crenolanib and imatinib represent the biochemical IC_{50} expressed in nmol/L units ± the SEM. Values represent the data from at least 3 replicate experiments per mutation.

Take home message (... zoberte si domov...):

- CD34 + tumory: GIST, SFT, IFP, DFSP, SCL, ASa, ...
- nezvyčajný výskyt viacjadrových buniek v GIST-e
- časť GIST-ov, najmä epiteloidnebunkových, môže byť CD117 negatívnych ...
- v prípade pochybností musí byť vyšetrenie DOG1 súčasťou panelu imunohistochémie
- akákoľvek ruptúra tumoru ho automaticky zaraďuje do kategórie vysokého rizika malígneho správania
- genetické vyšetrenie má priamy vplyv na spôsob liečby pacienta (KIT / PDGFRα / STAT6)