Klasifikace nádorů ženského pohlavního systému WHO 2020

(Změny a novinky oproti WHO 2014)

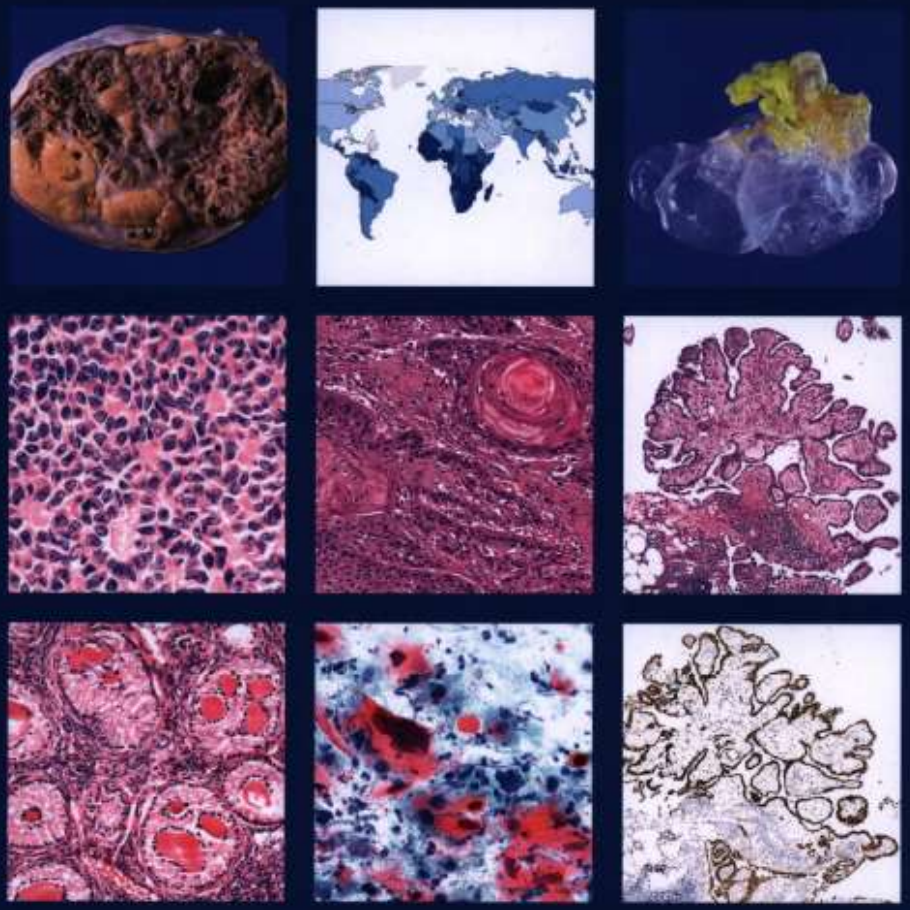
Medlov 2021
MUDr. Ondrej Ondič, PhD., FIAC
Šiklův ústav patologie, LF Plzeň.

Text přednášky neprošel jazykovou úpravou.

WHO Classification of Tumours • 5th Edition

Female Genital Tumours

Edited by the WHO Classification of Tumours Editorial Board



International Agency for Research on Cancer
World Health Organization

Hlavní rysy WHO 2020

- Důraz na specifické genetické charakteristiky nádorů (diagnostika, cílená léčba)
- Důraz na syndromy a asociace nádorů různych orgánů (zejména u raritních nádorů)
- Samostatné kapitoly: mezenchymální nádory, neuroendokrinní, hematologické malignity, metastázy, syndromy)

Dysonance

Dysonance

- Varianty LSIL vs pleiomorphic HSIL.

Dysonance

- Benigní metastazující leiomyom
- Karcinosarkom (vyniká z karcinomu)

Dysonance

- Borderline tumor ovária
- Monodermálni teratomy (patří mezi ně i ovariálni karcinoid a struma ovarii)

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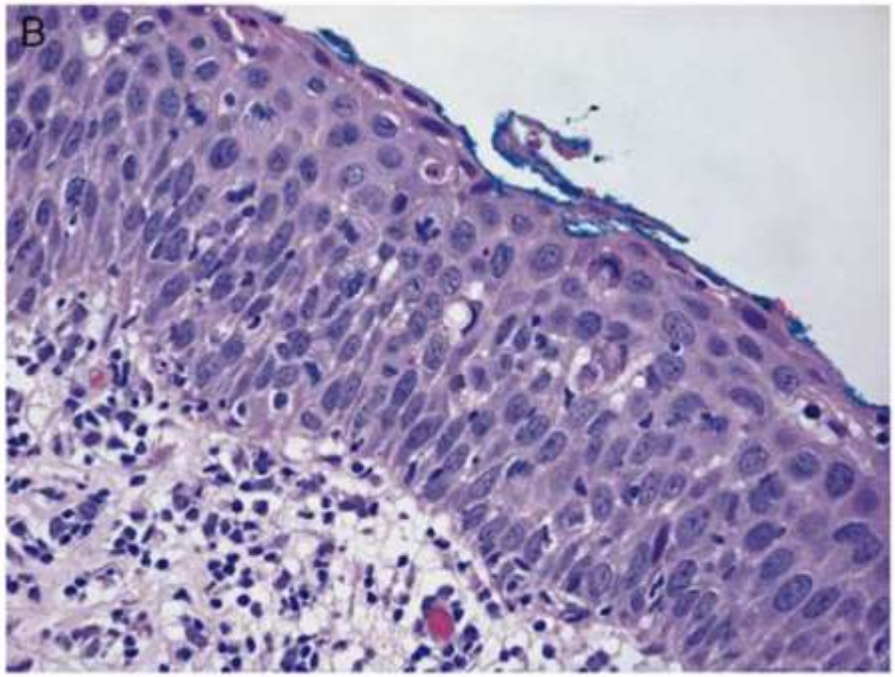
- Varianty LSIL vs pleiomorphic HSIL.

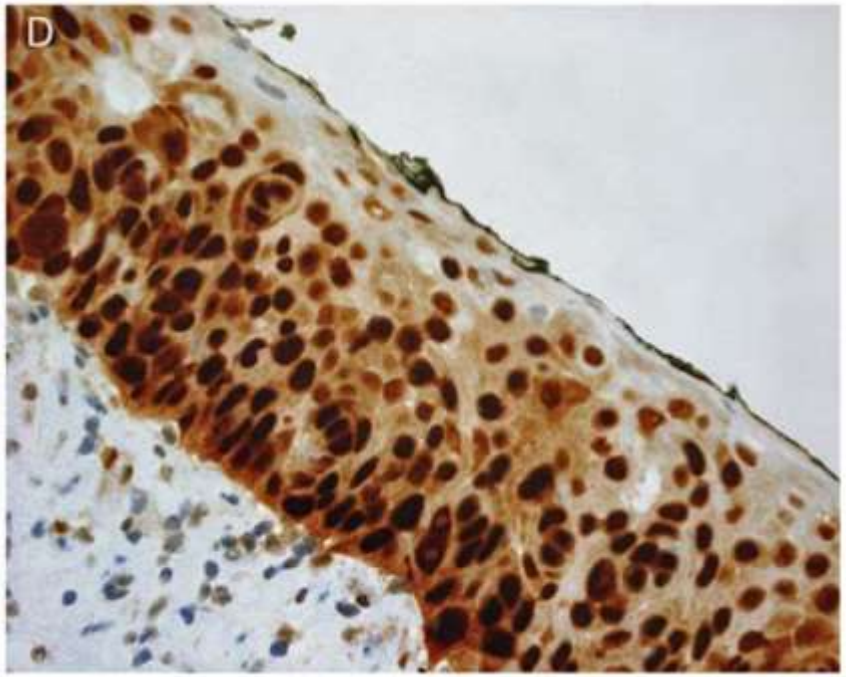
Vulva

Změny

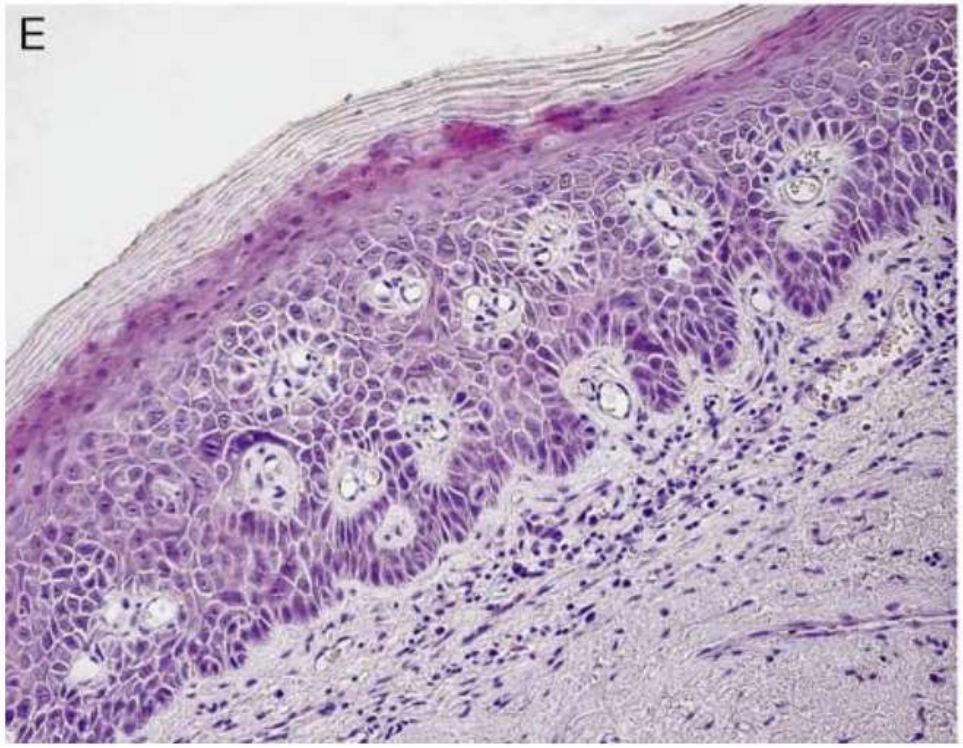
- Dělení dle vztahu k HPV infekci
- Nové druhy prekanceróz

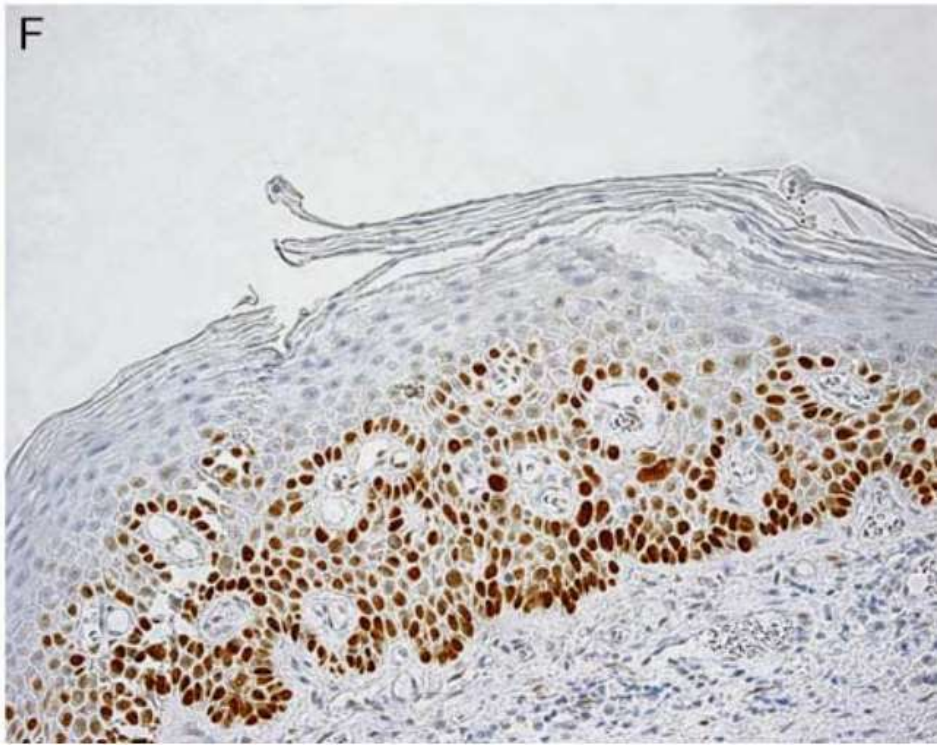
Usual VIN
běžná vulvárni intraepiteliálni neoplazie
(HPV +)





differentiated VIN
diferencovaná vulvárni intraepiteliálni neoplazie (HPV -)





Novější HPV- Prekurzory VAAS/DEVIL

status.[5] In the last few years, other distinctive precursors of HPV-independent VSCC have been described: vulvar acanthosis with altered differentiation (VAAD) and differentiated exophytic vulvar intraepithelial lesion (DEVIL), which has overlapping histologic features with VAAD, but is characterized by more prominent exophytic features.[6] Both lesions are defined by prominent acanthosis, parakeratosis, verruciform architecture, and lack of significant basal atypia. They are commonly associated with LSC and are considered precursors of verrucous carcinoma.[7] However, to date, both entities are still controversial due to their nonspecific histologic features, which overlap with LSC, and their uncertain prognosis.[8,9]

HPV-independent Precursors Mimicking High-grade Squamous Intraepithelial Lesions (HSIL) of the Vulva

Natalia Rakislova, MD, PhD, Laia Alemany, MD, PhD,†‡ Omar Clavero, MD,†‡ Maria del Pino, MD, PhD,§ Adela Saco, MD, PhD,* Lorena Marimon, BSc,* Beatriz Quirós, BSc,†‡ Belen Lloveras, MD, PhD,‖ Inmaculada Ribera-Cortada, MD, PhD,* Maria Alejo, MD, PhD,¶ Michael Pawlita, MD,# Wim Quint, MD, PhD,** Silvia de Sanjose, MD, PhD,†‡ and Jaume Ordi, MD, PhD,*‡*
On Behalf of VVAP Study Group

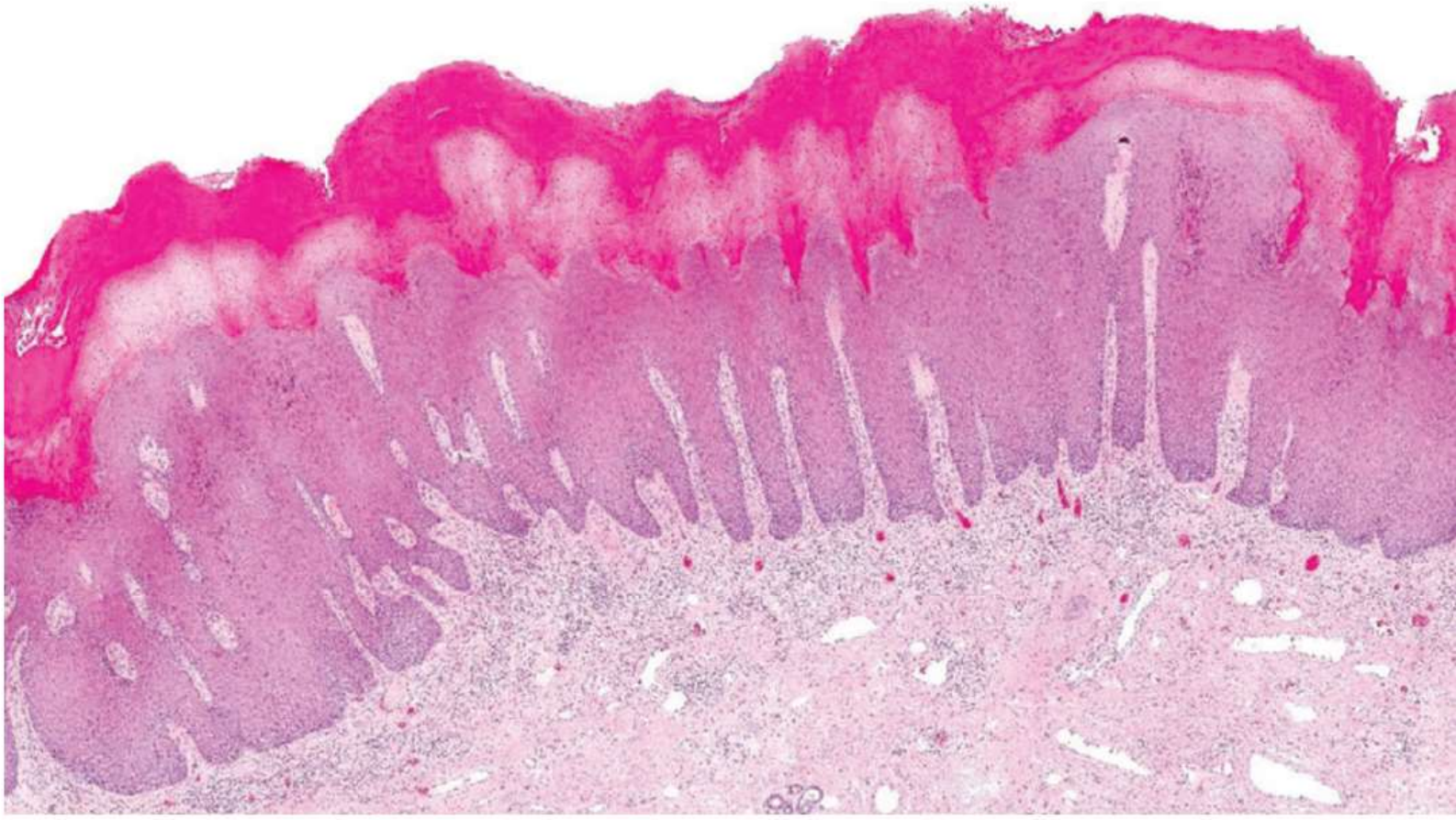
Abstract: Two etiopathogenic types of vulvar squamous cell carcinoma (VSCC) have been described: human papillomavirus (HPV)-associated and HPV-independent. Precursor lesions, frequently identified in the adjacent skin, are also distinct in the 2 types of VSCC: high-grade squamous intraepithelial lesions (HSILs) in HPV-associated VSCC and differentiated vulvar intraepithelial neoplasia (dVIN) or vulvar acanthosis with altered differentiation in HPV-independent VSCC. Although HPV-independent precursors mimicking HSIL have been described in the vulva, their frequency and morphologic spectrum have not been completely characterized. We explored, in a large series of HPV-independent VSSC, the frequency and the histologic features of precursors mimicking HSIL. We included 779 DNA

morphology, 13 warty, and 7 mixed basaloid/warty features. All the HSIL-like precursors were DNA HPV-negative/p16-negative; 74% of them showed p53 abnormal staining and 35% of them had areas of conventional dVIN. In conclusion, about one fifth of the HPV-independent precursors mimic HSIL, showing either basaloid or warty features. Older age and the presence of areas of typical HPV-independent intraepithelial lesions, together with p16 negativity, should raise suspicion of an HPV-independent etiology.

Key Words: vulvar cancer, HPV, HPV-independent precursor lesions in vulvar cancer, high-grade squamous intraepithelial lesions (HSIL), HPV-independent HSIL-like lesions

(*Am J Surg Pathol* 2020;44:1506–1514)

Nascimento AF, Granter SR, Cviko A, Yuan L, Hecht JL, Crum CP. Vulvar acanthosis with altered differentiation a precursor to verrucous carcinoma? Am J Surg Pathol 2004; 28: 638.

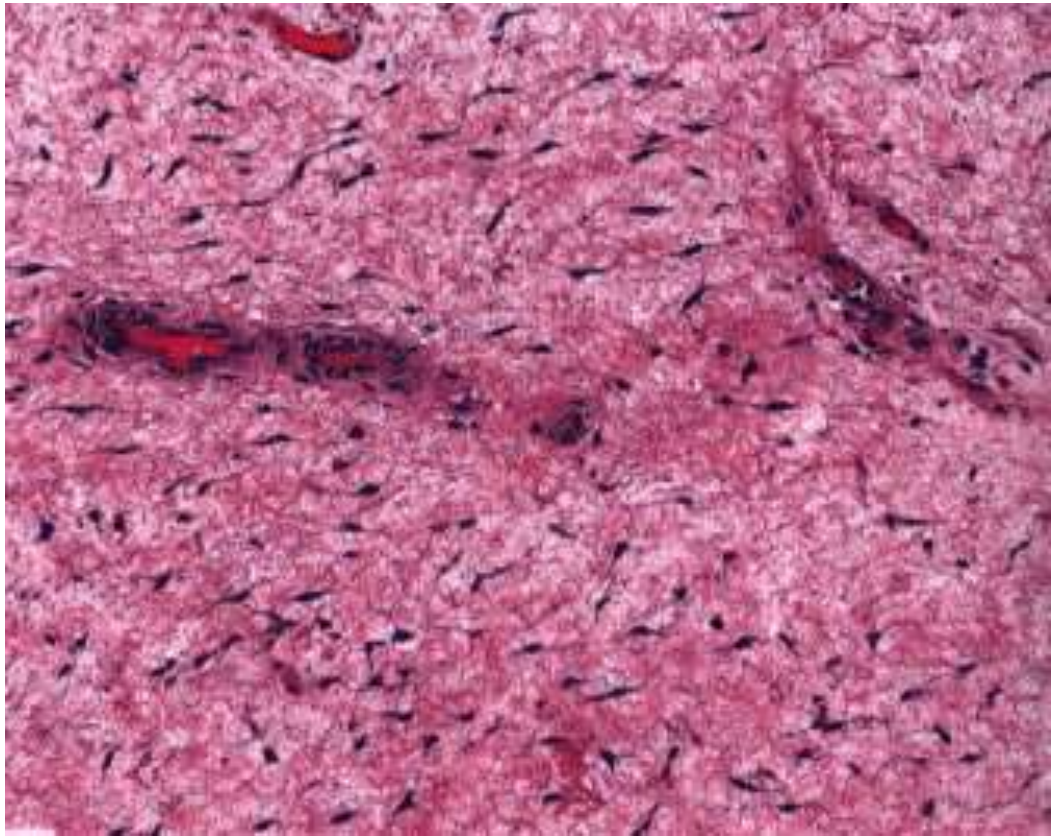


- Klinicky - leukoplakie
- Cytologicky - hyperkeratóza

Praktické dopady z pohledu patologa

- 1 HPV status – doplněk diagnozy
- 2 Imunohistochemie p16, p53 – doplněk diagnozy
- 3 Vyšetřováni okrajů karcinomů na prekurzory.
- 4 Manažment je (zatím) identický.

Deep (aggressive) angiomyxoma



Deep (aggressive) angiomyxoma

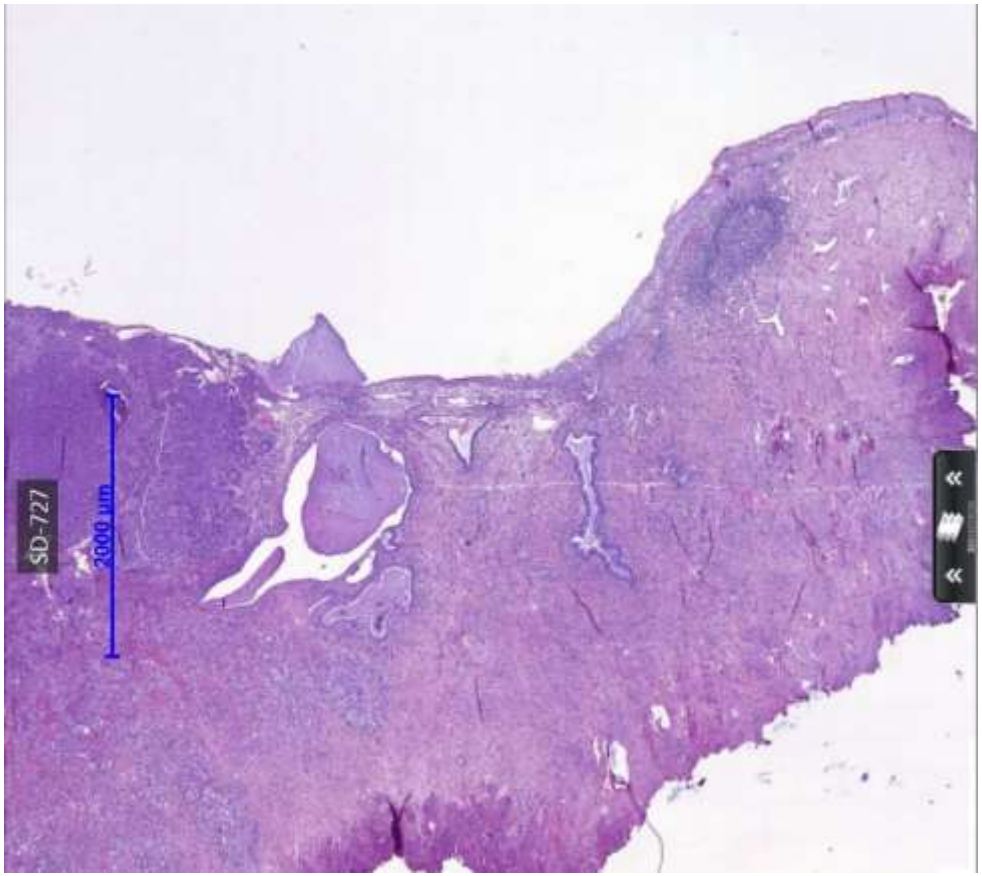
- Rekurence z důvodu inkompletní excize
- Okraje exize nelze dobře posuzovat pro blandní vzhled nádorových buněk
- Je asociace se zlomem genu HMGA2
- IHC HMGA2 **může** pomoci vyhodnotit okraje excize

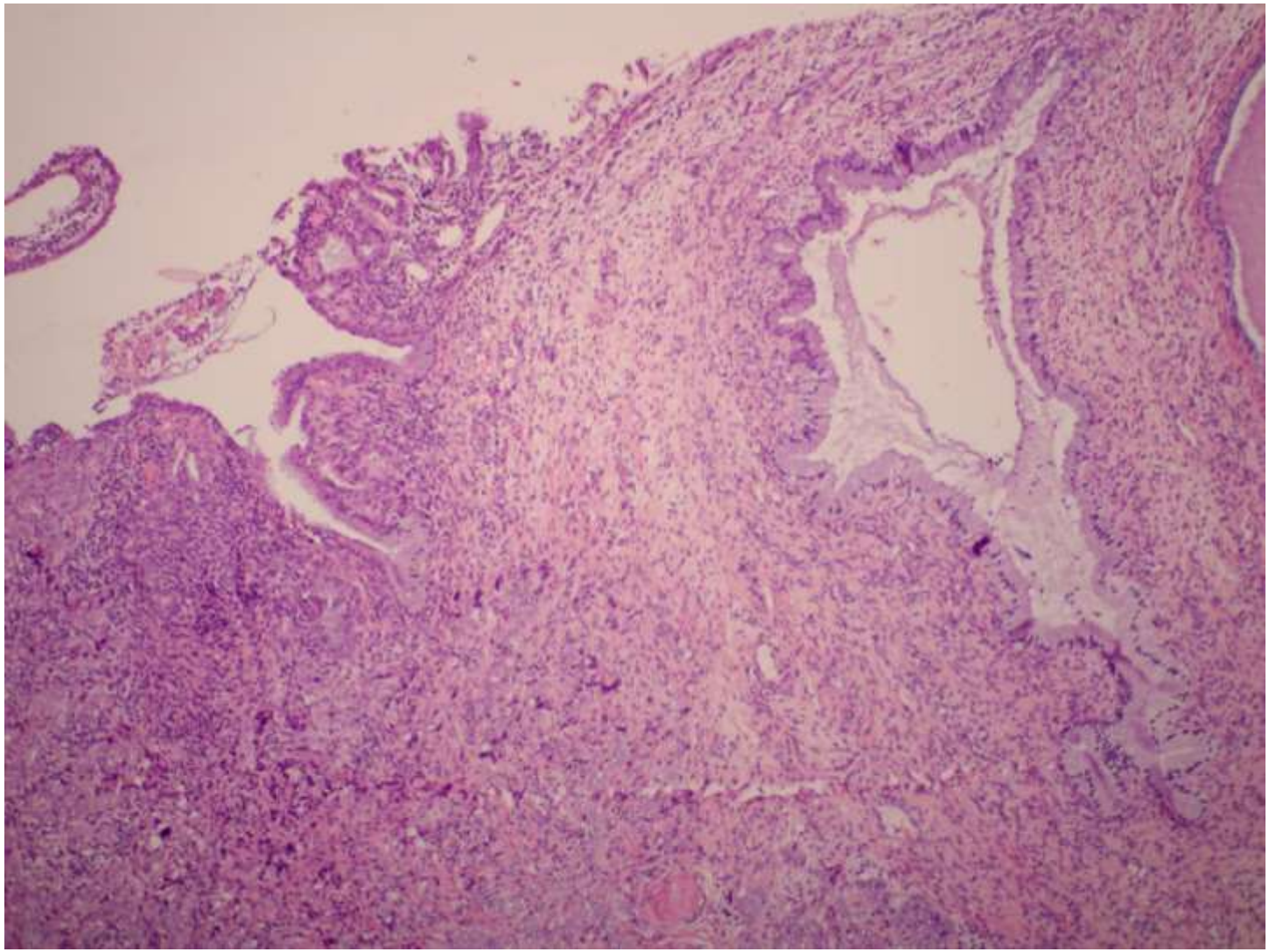
Cervix

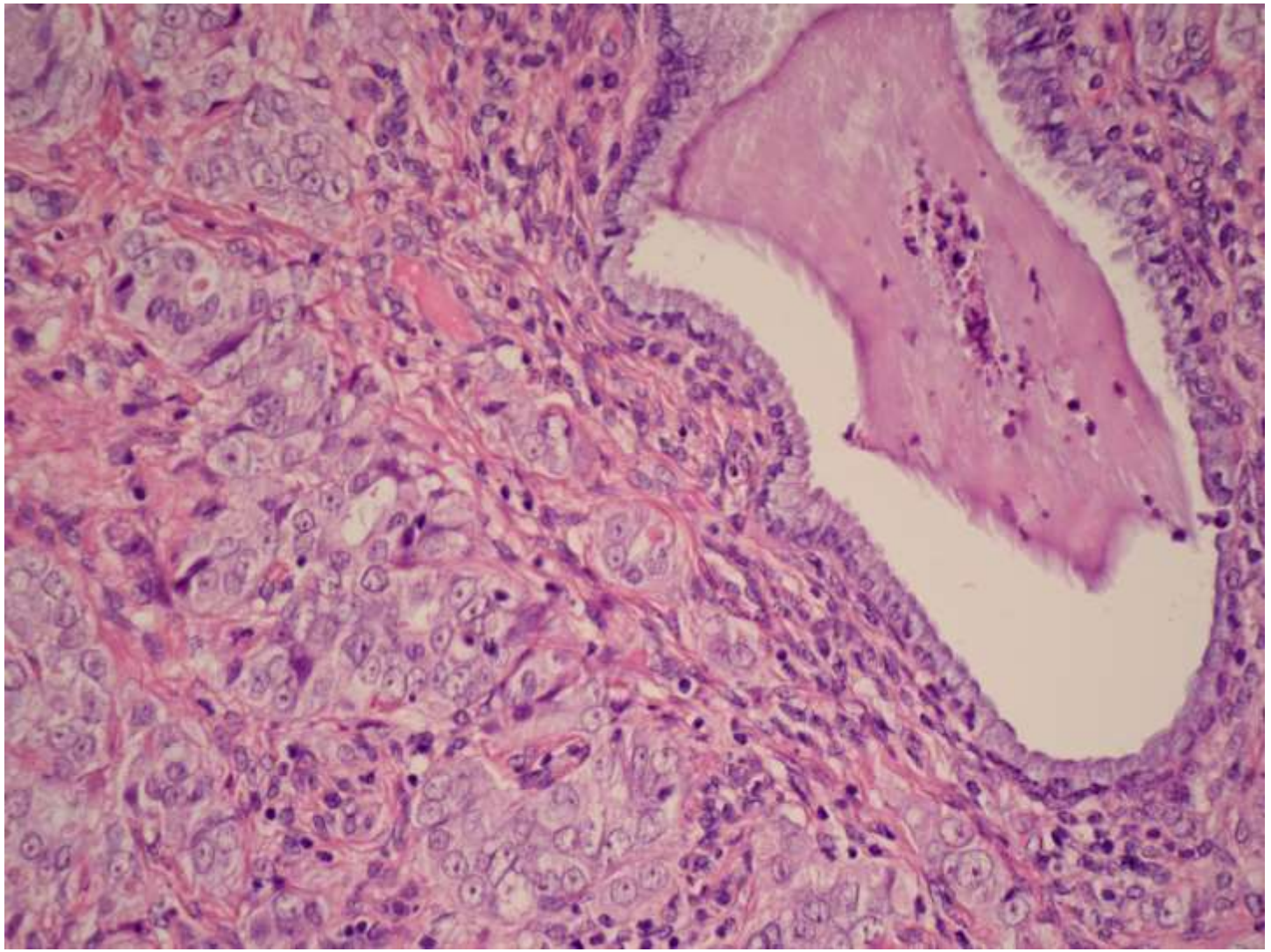
Neexistuje

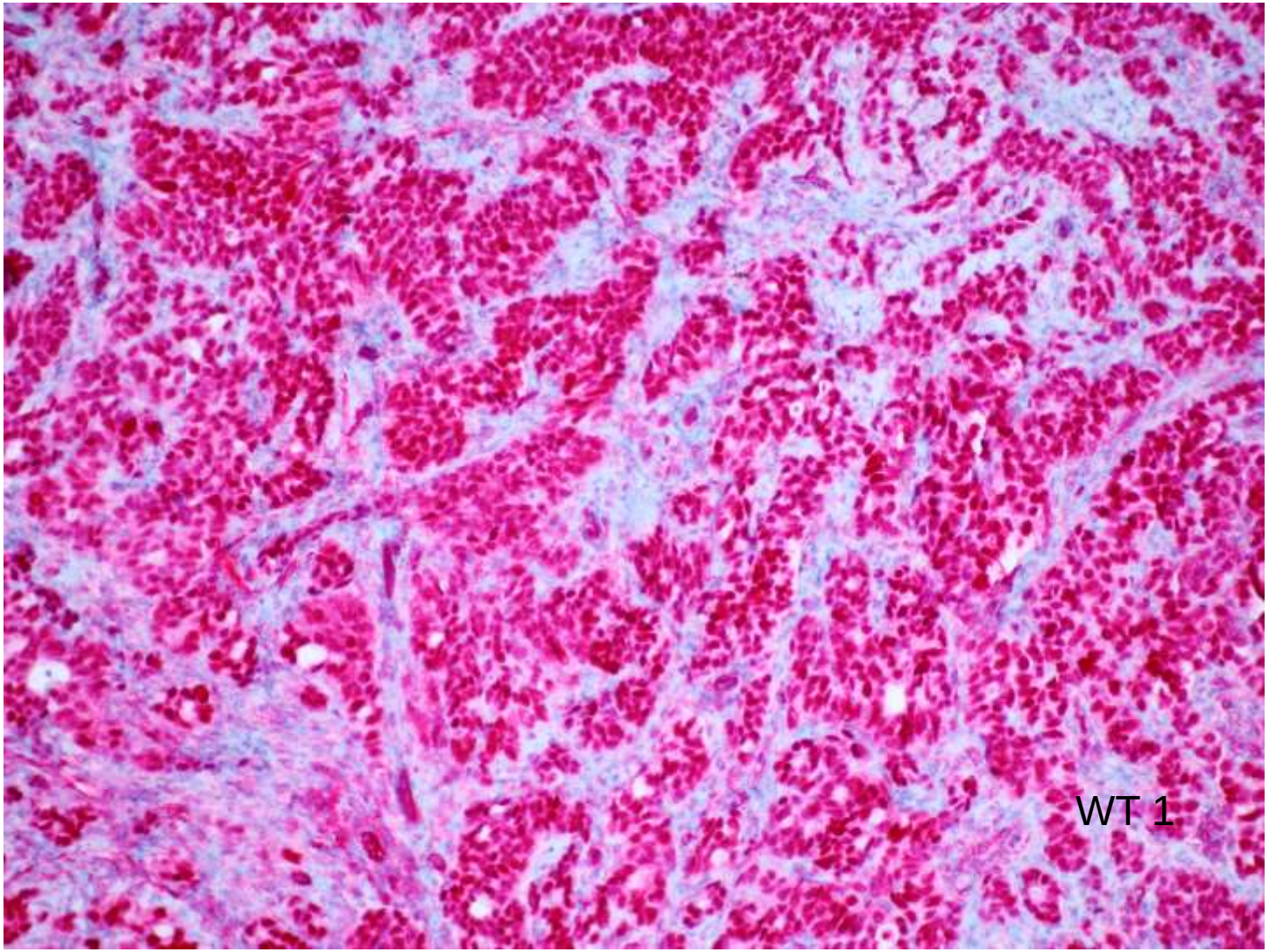
- High grade serózni karcinom čípku

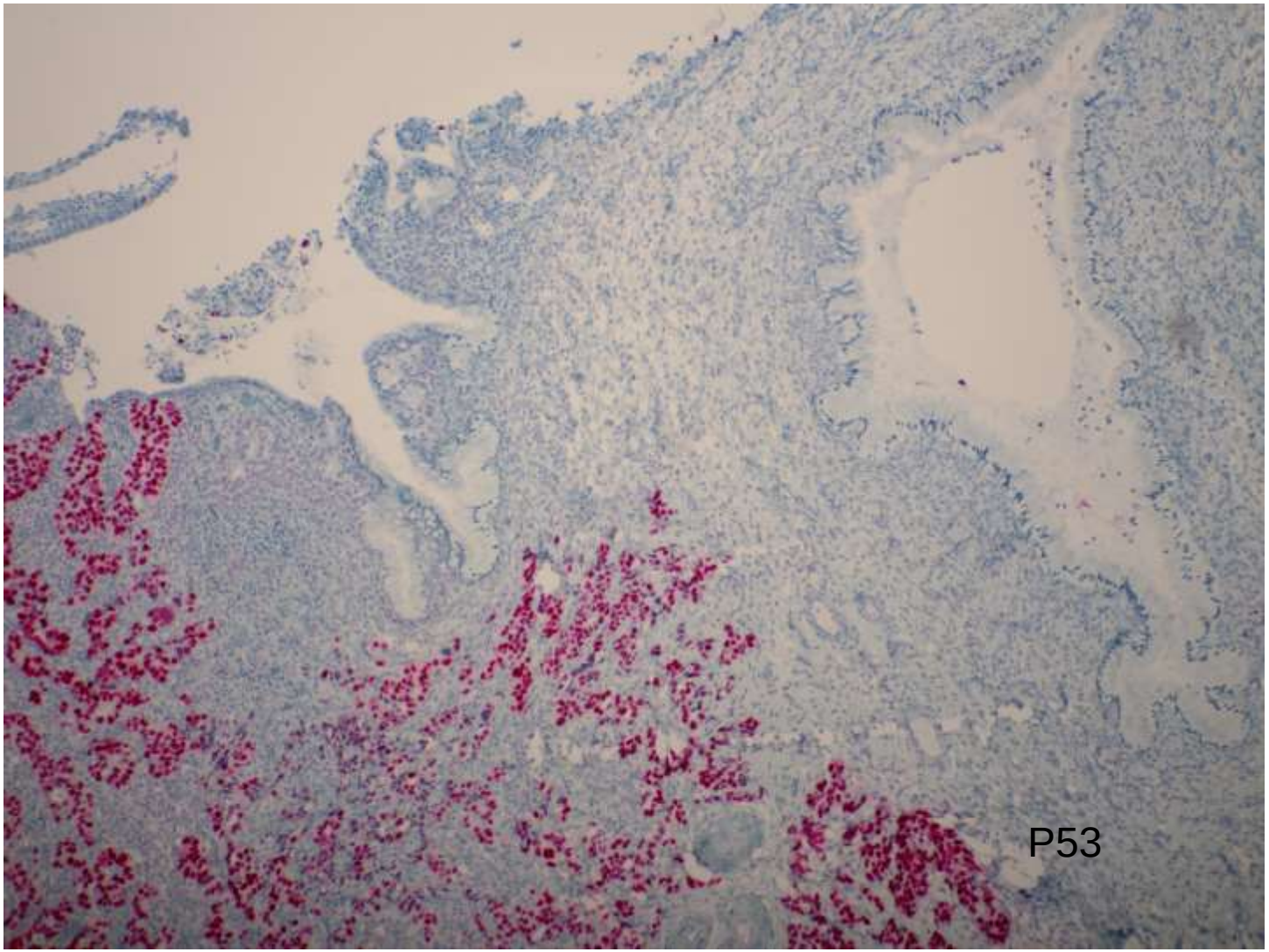
Histologický nález








WT 1


P53

Dodatočné klinické informácie

Pacientka bola liečená pre „triple negatívny karcinóm prsníka.“

Molekulová genetika

Na plzeňskom pracovisku: HPV detekcia a typizácia 3 metódami, ktoré cielia na HPV gén L1, E6/E7 – neprokazujeme přítomnost DNA HPV.

Na inom pracovisku: v minulosti potvrdená zárodočná mutácia génu BRCA1/c.5266dupC/p.Gln1756Profs*74 (431825413)

Kódy SCC cervix

- Dlaždicový karcinom čípku dělohy, NOS (tam, kde je vyšetřováni p16 a HPV nedostupné) 8070/3
- HPV asociovaný (HPV associated) SCC 8085/3
- HPV neasociovaný (HPV-independent) SCC 8086/3

Hlavní změny

- Dělení adenokarcinomů dle vztahu k HPV infekci (IECC)
- Patterny - Silva systém
- Nový druh dlaždicové prekancerózy – pleomorfní (bizarní) HSIL
- Nové jednotky

International Endocervical Adenocarcinoma Criteria and Classification (IECC)

A New Pathogenetic Classification for Invasive Adenocarcinomas of the Endocervix

Simona Stolnicu, MD, Iulia Barsan, MD,* Lien Hoang, MD,† Prusha Patel, MPH,‡ Cristina Terinte, MD,§ Anna Pesci, MD,‖ Sarit Aviel-Ronen, MD,¶ Takako Kiyokawa, MD,# Isabel Alvarado-Cabrero, MD,** Malcolm C. Pike, PhD,‡ Esther Oliva, MD,†† Kay J. Park, MD,‡ and Robert A. Soslow, MD‡*

TABLE 5. HPV Status and Immunophenotype of IECC-classified Cases*

IECC Subtypes	p16 Entire Cohort/ Selected Cohort† (N)	p16% Entire Cohort/ Selected Cohort†	HPV Entire Cohort/ Selected Cohort† (N)	HPV% Entire Cohort/ Selected Cohort†	p53%	PR%	VIM%
HPVA							
Usual	168/138	83/90	151/120	87/95	3.6	24	13
Mucinous NOS	4/4	100/100	2/2	100/100	0	0	0
Mucinous intestinal	4/4	75/75	4/4	100/100	25	25	0
Mucinous signet-ring	0/0	—	0/0	—	—	—	—
iSMILE	8/8	50/50	7/7	100/100	29	25	13
Villoglandular	2/2	50/50	1/1	100/100	50	0	0
All HPVA	186/156	82/87	165/134	88/96	5.4	24	12
Adenocarcinoma NOS	6/3	33/33	6/3	83/67	17	40	0
NHPVA							
Gastric	27/27	33/33	23/23	4/4	52	12	7.4
Clear cell	7/6	29/17	7/6	0/0	14	14	14
Endometrioid	3/3	67/67	2/2	0/0	33	33	0
Serous	2/1	50/100	1/0	0/—	0	—	100
Mesonephric	1/1	100/100	0/0	—	0	0	0
All NHPVA	40/38	38/37	33/31	3/3	40	14	10

*The number of evaluable TMA cores and cases varied from slide to slide. Cases from 1 center were not tested for HPV (n = 26).
†"Selected cohort" lacks data from 1 center whose IECC usual-type ECAs were only ~50% positive for p16 and HPV (n = 36).

International Journal of Gynecological Pathology
00:1–10, Lippincott Williams & Wilkins, Baltimore

Original Article

Invasive Endocervical Adenocarcinoma: Proposal for a New Pattern-based Classification System With Significant Clinical Implications: A Multi-institutional Study

Andrea Diaz De Vivar, M.D., Andres A. Roma, M.D., Kay J. Park, M.D., Isabel Alvarado-Cabrero, M.D., Golnar Rasty, M.D., Jose G. Chanona-Vilchis, M.D., Yoshiki Mikami, M.D., Sung R. Hong, M.D., Brent Arville, D.O., Norihiro Teramoto, M.D., Rouba Ali-Fehmi, M.D., Joanne K.L. Rutgers, M.D., Farah Tabassum, M.D., Denise Barbuto, M.D., Irene Aguilera-Barrantes, M.D., Alexandra Shaye-Brown, M.D., Dean Daya, M.D., and Elvio G. Silva, M.D.

Pattern C

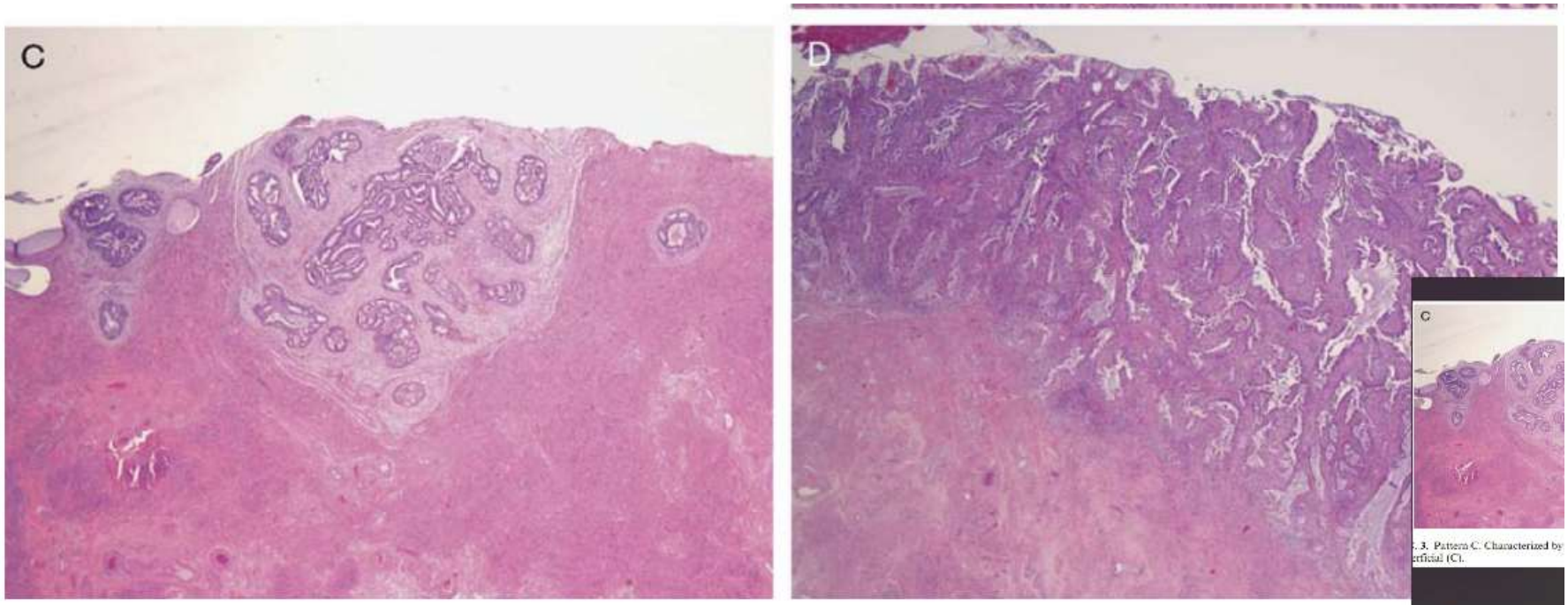
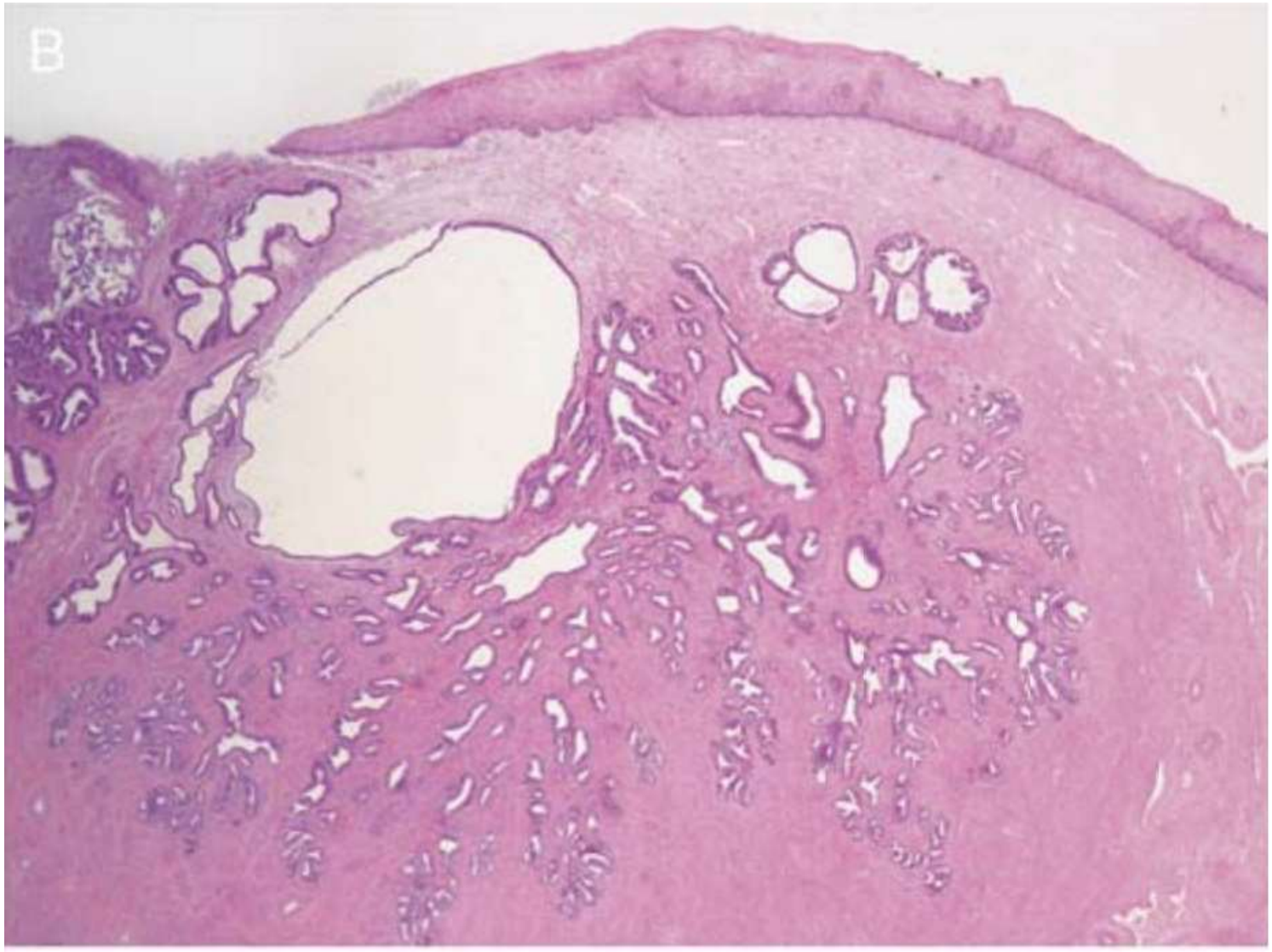


FIG. 3. Pattern C. Characterized by extensive and diffuse destructive stromal invasion (A, B, D). Tumors with this pattern o
superficial (C).

Pattern A !!!



Pattern A (Roma, 2015)

None of the cases had LVI. Over 1300 LNs were resected in patients with pattern A invasive adenocarcinoma, and every LN was negative for metastatic adenocarcinoma (range, 2 to 78 resected LNs per patient; mean 20.5; total 1333). Follow-up in 71 patients yielded no recurrences, and all patients were alive and well at last follow-up (range, 6 to 252 mo; mean 50.1 mo; median 44 mo).

Pattern A

- Řeší problematické histologické určení přítomnosti invaze.
- Vynikajíci prognóza

Nový typ prekancerózy **Pleiomorphic HSIL**

- Bizarre cell dysplasia = pleiomorphic HSIL

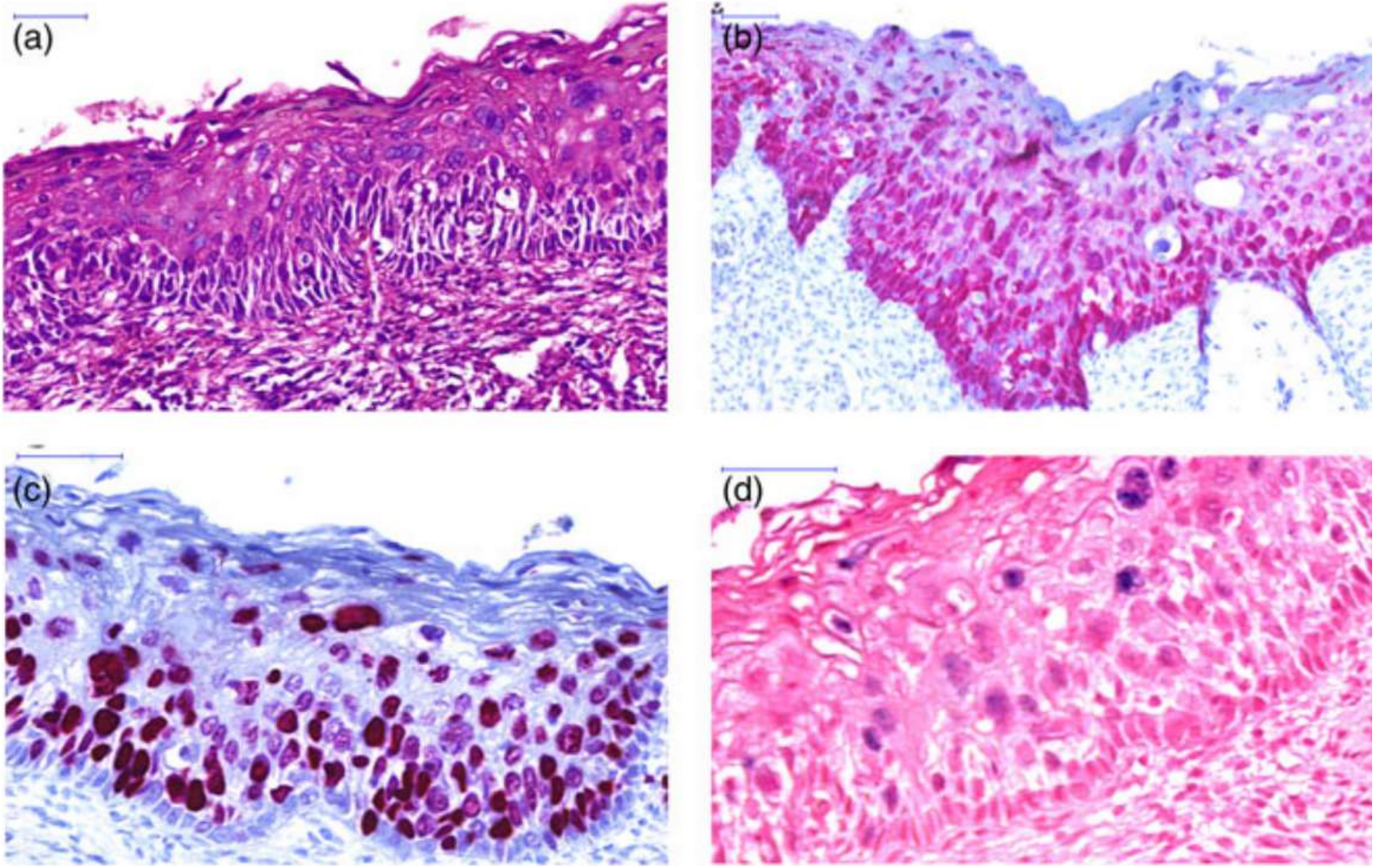
THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/jog.13196 J. Obstet. Gynaecol. Res. Vol. 43, No. 2: 345–351, February 2017

Bizarre cell dysplasia of the cervix

Ondrej Ondič[1,2], Radoslav Ferko[1,2], Jana Kašpírková[1,2], Marián Švajdler Jr[1,2], Boris Rýchly[4,5], Peter Talarčík[4,5], Jiří Bouda[3] and Michal Michal[2]

[1]Bioptická Laboratory, and [2]Šikl's Department of Pathology, [3]Department of Gynecology and Obstetrics, Medical Faculty Hospital, Charles University, Pilsen, Czech Republic and [4]Cytopathos, and [5]Department of Pathology, Slovak Medical University, Bratislava, Slovak Republic


(a)
(b)
(c)
(d)

Praktický význam

- HPV typy (HR 16; ale i možné HR 26, 67 – tj. negativní HPV testace !!!)
- Výjimečně asociace s imunosupresí.
- Cytologicko-histologická korelace

  (v anamnéze opakovaně LSIL)

Accepted: 21 September 2017

DOI: 10.1111/cyt.12494

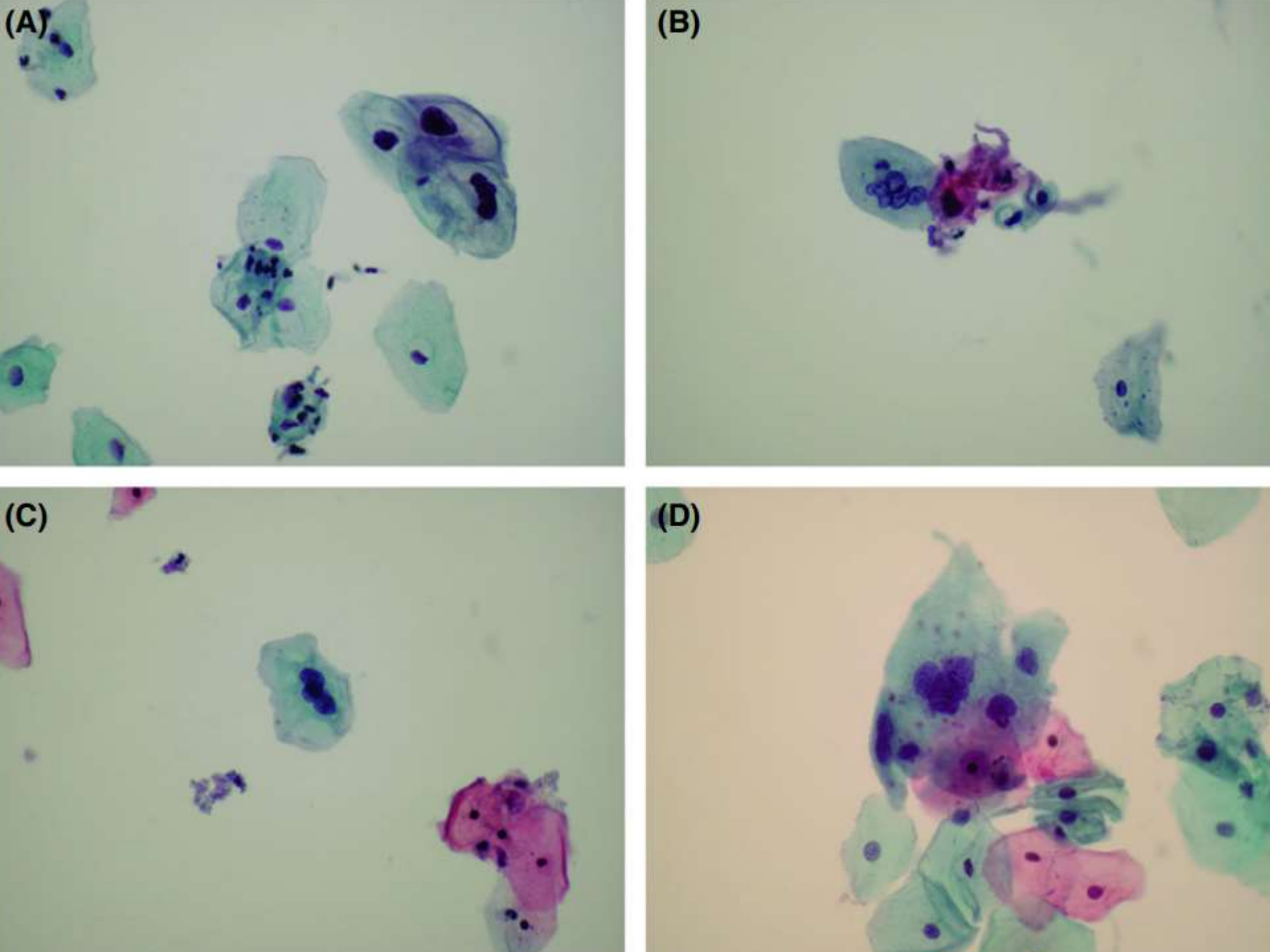
ORIGINAL ARTICLE

WILEY

Significance of bizarre cells in cervical screening liquid-based cytology: A prospective study of 15 cases

O. Ondič[1,2] | R. Ferko[1,2] | J. Kičinová[3] | J. Bouda[1] | I. Kinkorová-Luňáčková[1,2] | L. Kupcová[2] | M. Zůchová[1,2] | J. Chytra[1] | T. Waloschek[2] | M. Tůmová Bartošková[1,2] | R. Alaghehbandan[4] | J. Němcová[1,2]

FIGURE 1 Multinucleated cells of squamous origin and superficial level size – designated bizarre cells – were present in all 15 liquid-based cytology samples. Papanicolaou: (A) 400×, (B) 200×, (C) 200×, (D) 400×

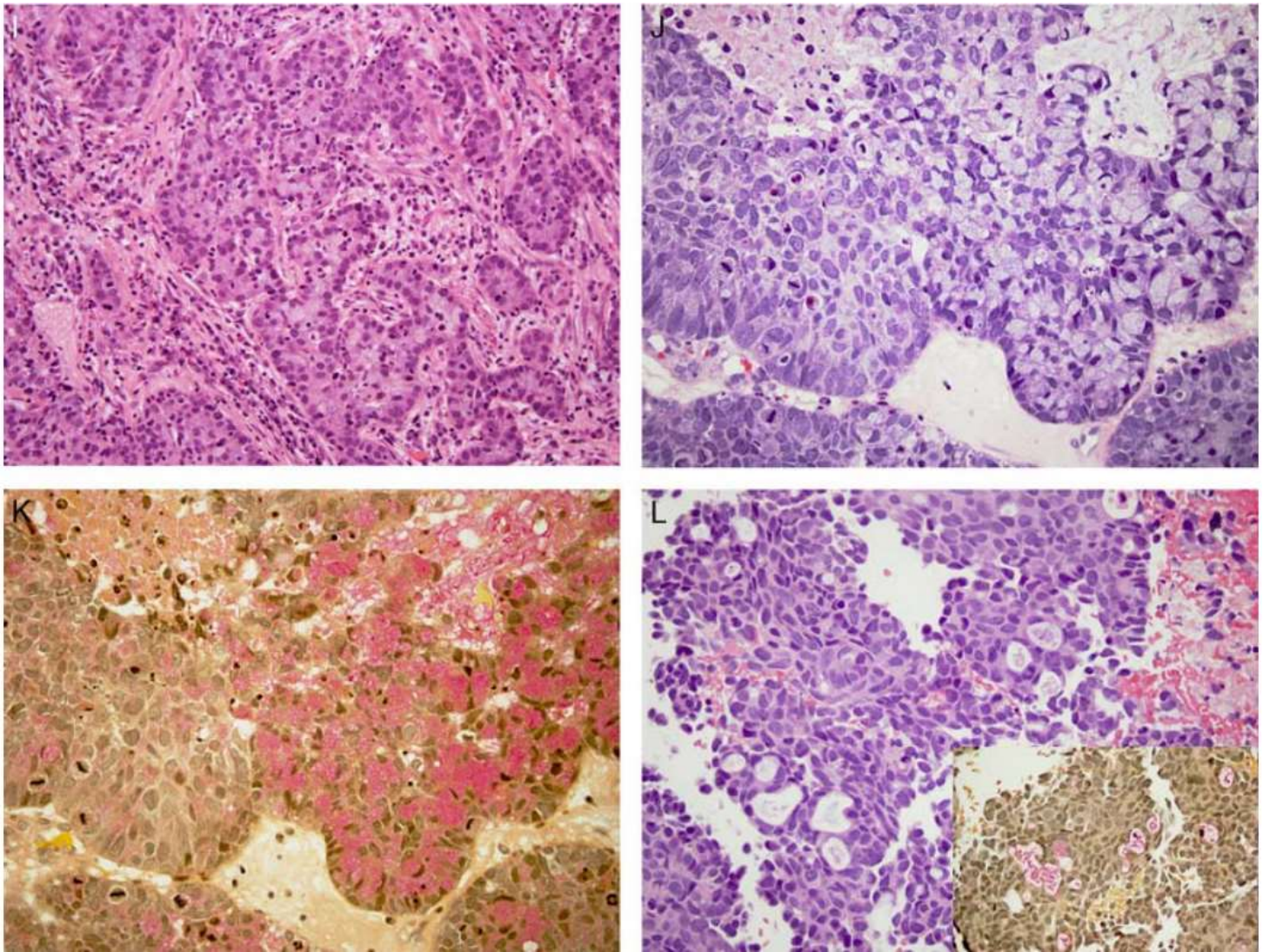

(A)
(B)
(C)
(D)

Nové a další jednotky

- Adenoskvamózni karcinom
- Adenoidně bazálni karcinom (adenoid basal carcinoma / tumor ?/)
- SMILE stratified mucinous intraepithelial lesion)
- Mukoepidermoidní karcinom (MAML2)

Adenoskvamózni karcinom (HPV+)

SMILE (HPV+)



Adenoid basal carcinoma (HPV+, netvoří masu, v čisté formě nemetastazuje,8098/3)

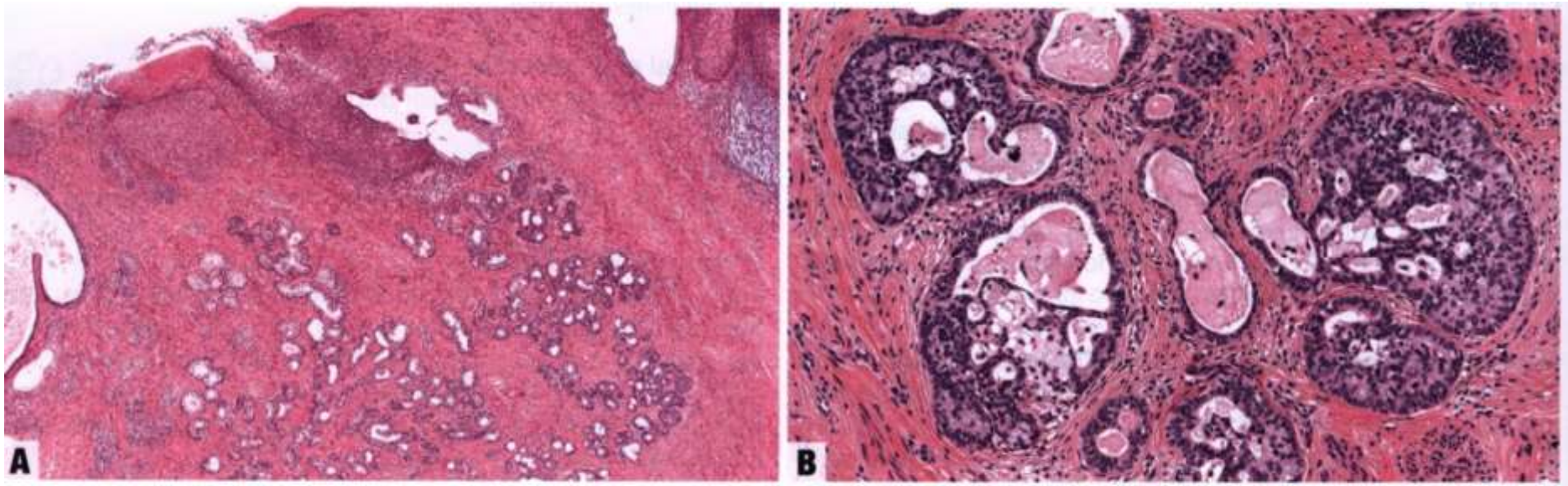


Fig. 8.47 Adenoid basal carcinoma. **A** This tumour shows a proliferation of small rounded nests of basaloid cells with some glandular differentiation. This case also shows overlying high-grade squamous intraepithelial lesion. **B** Adenoid basal carcinoma composed of nests of bland basaloid cells with central cystic change. There is a lack of significant stromal reaction to the tumour nests.

Mukoepidermoidní karcinom

Neklasifikovatelný karcinom čípku dělohy (HPV+)

Mezenchymální nádory s genovými translokacemi

- Samostatná kapitola

Germinálni nádory

- Teratom,
- Yolk sack tumor
- Choriokarcinom

Děloha

Změny

- Endometriální adenokarcinomy – molekulárni klasifikace dle TCGA, mesonephric–like adenokarcinom,
- Endometriální stromální sarkomy a jiné sarkomy – detekce genových translokací (zejména u HG ESS).
- Nové jednotky

Molekulární klasifikace dle TCGA

Cancer 2017;123:802-13.

Original Article

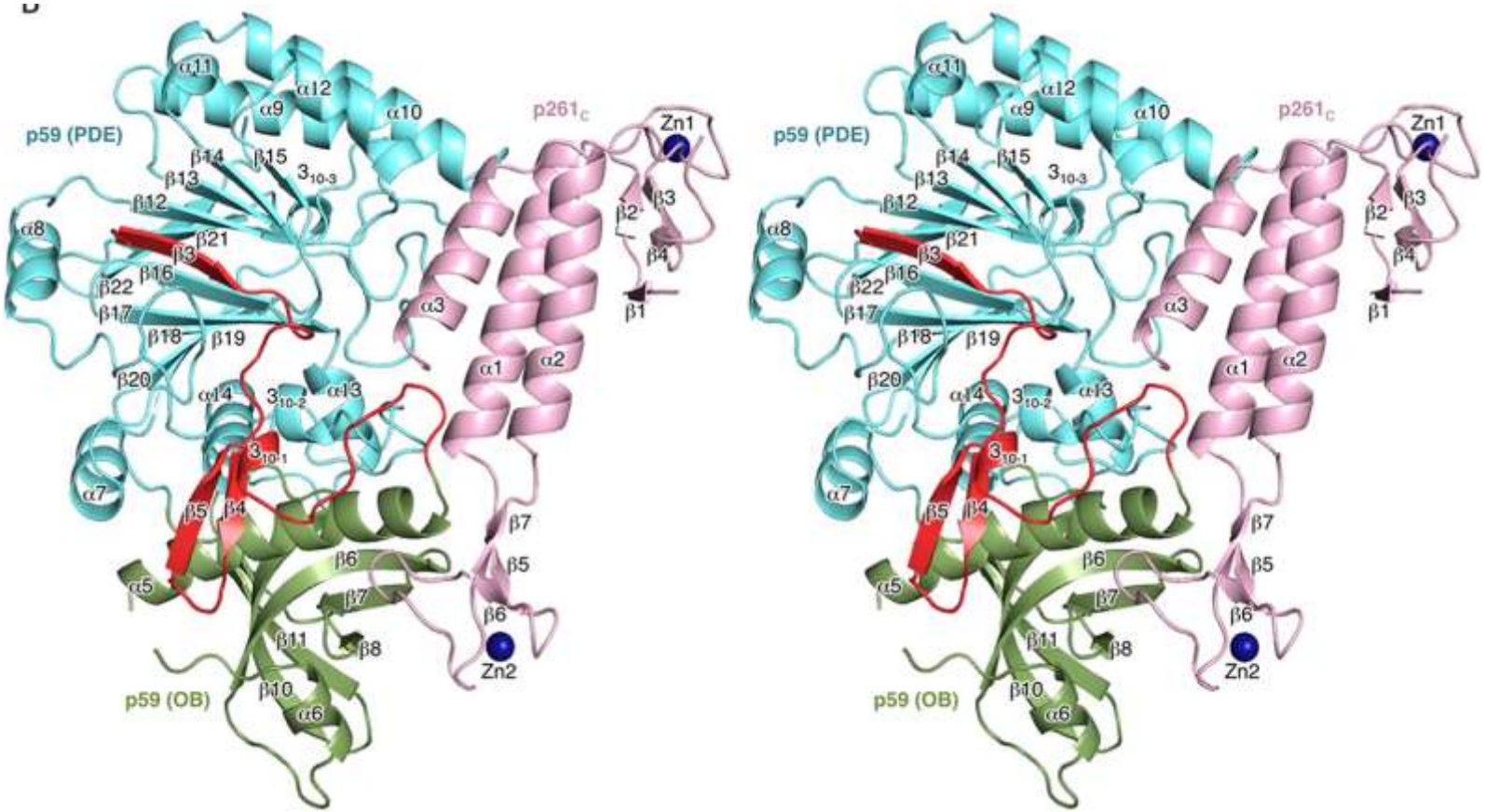
Confirmation of ProMisE: A Simple, Genomics-Based Clinical Classifier for Endometrial Cancer

Aline Talhouk, PhD[1]; Melissa K. McConechy, PhD[2]; Samuel Leung, MSc[3]; Winnie Yang, BSc[1]; Amy Lum, BSc[1]; Janine Senz, BSc[1]; Niki Boyd, PhD[1]; Judith Pike, MD[4]; Michael Anglesio, PhD[1]; Janice S. Kwon, MD, MSc[4]; Anthony N. Karnezis, MD, PhD[1]; David G. Huntsman, MD[1]; C. Blake Gilks, MD[5]; and Jessica N. McAlpine, MD[4]

The Journal of Pathology: Clinical Research
J Path: Clin Res October 2017; **3:** 279–293

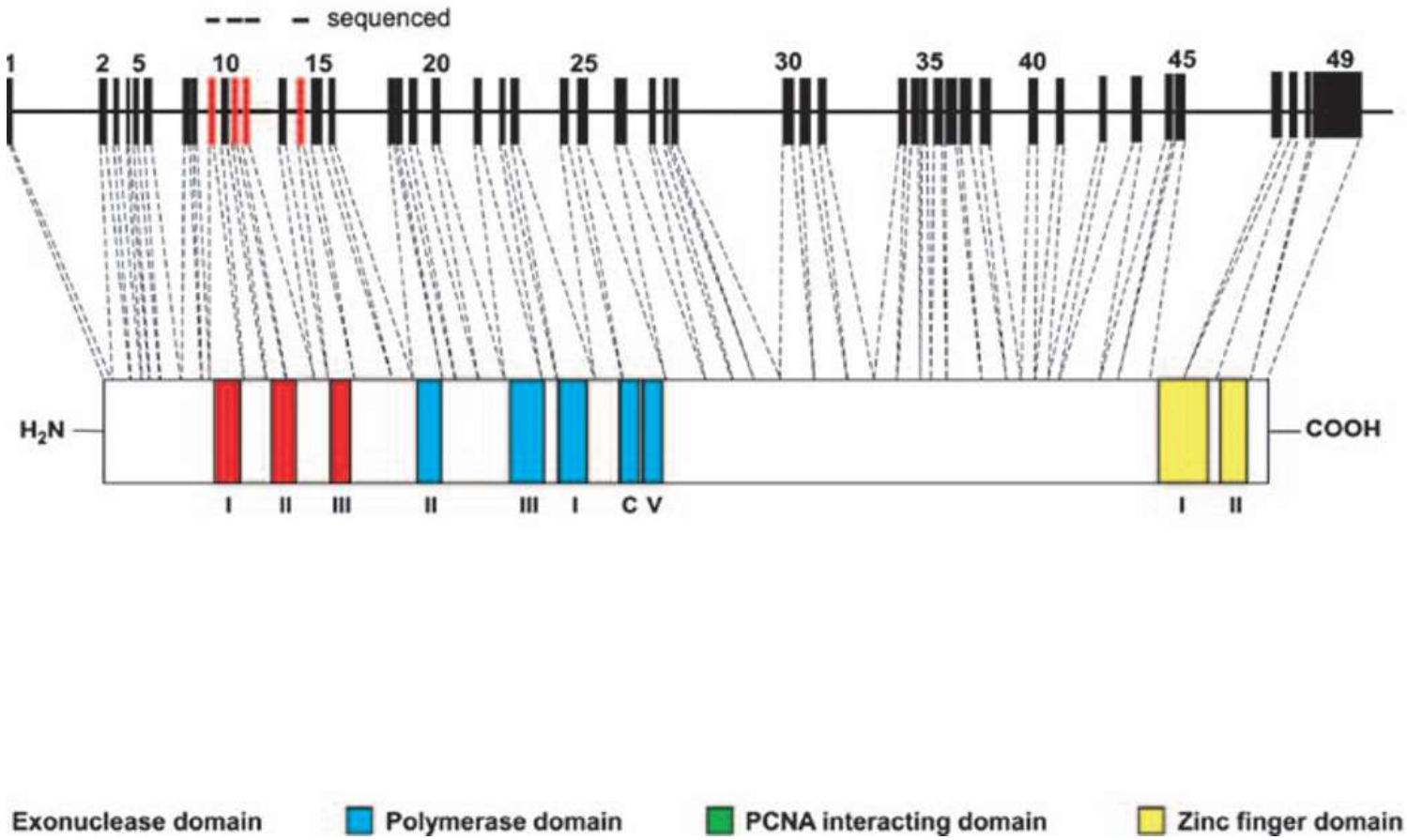
POLE struktura

Crystal structure of the human Pol B-subunit in complex with the C-terminal domain of the catalytic subunit
Received for publication, April 24, 2017, and in revised form, July 21, 2017 Published, Papers in Press, July 26, 2017, DOI 10.1074/jbc.M117.792705
Andrey G. Baranovskiy‡, Jianyou Gu‡1, Nigar D. Babayeva‡, Igor Kurinov§, Youri I. Pavlov‡¶, and Tahir H. Tahirov‡2



Proteín je složen jako origami

Genetický kód je ale lineárni


sequenced
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2
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H2N
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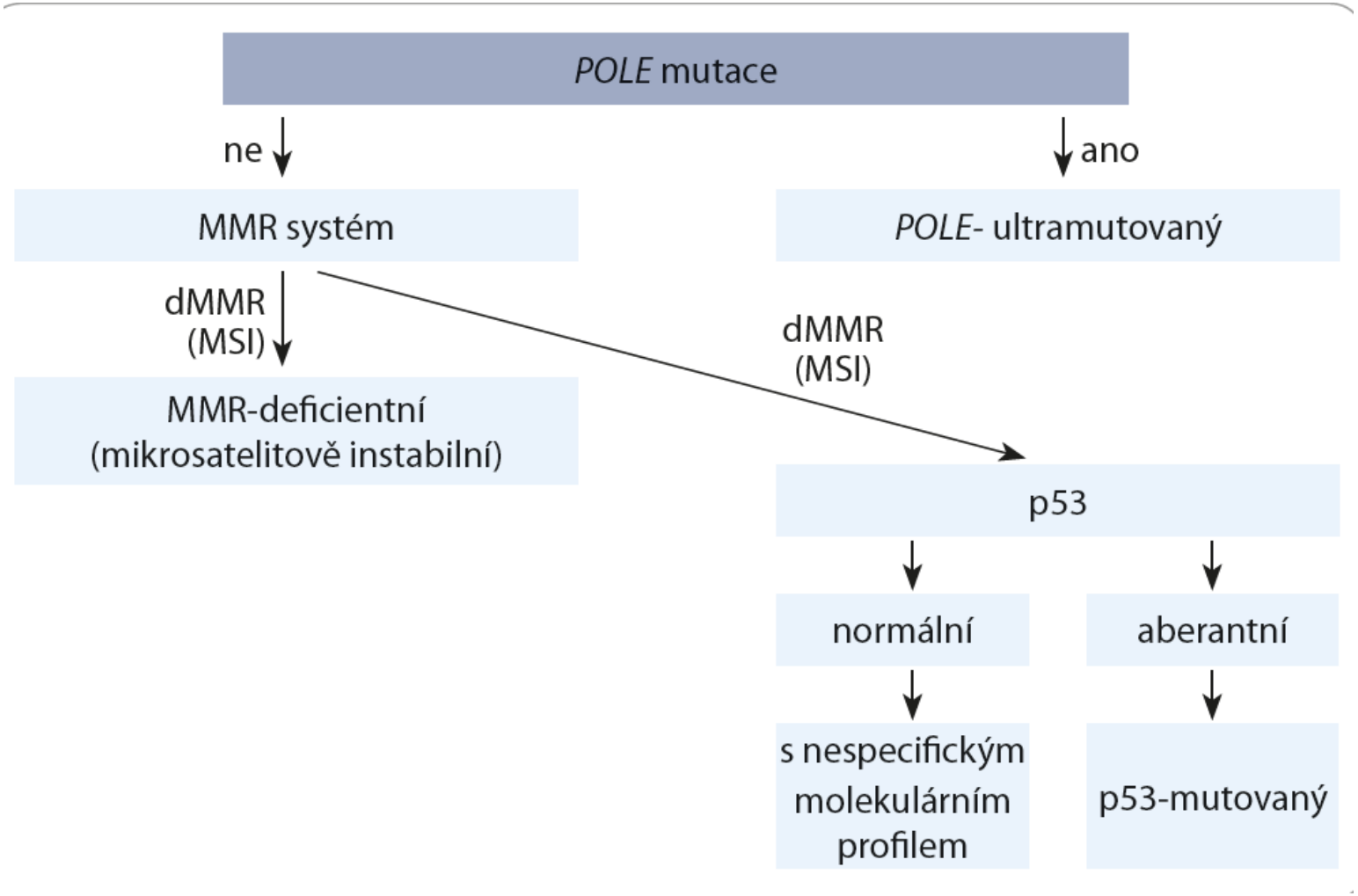
II
III
I
C
V
I
II
Exonuclease domain
Polymerase domain
PCNA interacting domain
Zinc finger domain

Journal of Pathology J Pathol 2020; 250: 323–335
Interpretation of somatic POLE mutations in endometrial carcinoma Alicia León-Castillo1† , Heidi Britton2†, Melissa K McConechy3, Jessica N McAlpine4, Remi Nout5, Stefan Kommoss6, Sara Y Brucker6, Joseph W Carlson7, Elisabeth Epstein8, Tilman T Rau9, Tjalling Bosse1 *‡ , David N Church10,11‡ and C Blake Gilks12‡

Table 3. Pathogenic POLE EDM based on POLE-score

Protein change	*Nucleotide substitution*
P286R	c.857C>G
V411L	c.1231G>T/C
S297F	c.890C>T
S459F	c.1376C>T
A456P	c.1366G>C
F367S	c.1100T>C
L424I	c.1270C>A
M295R	c.884T>G
P436R	c.1307C>G
M444K	c.1331T>A
D368Y	c.1102G>T

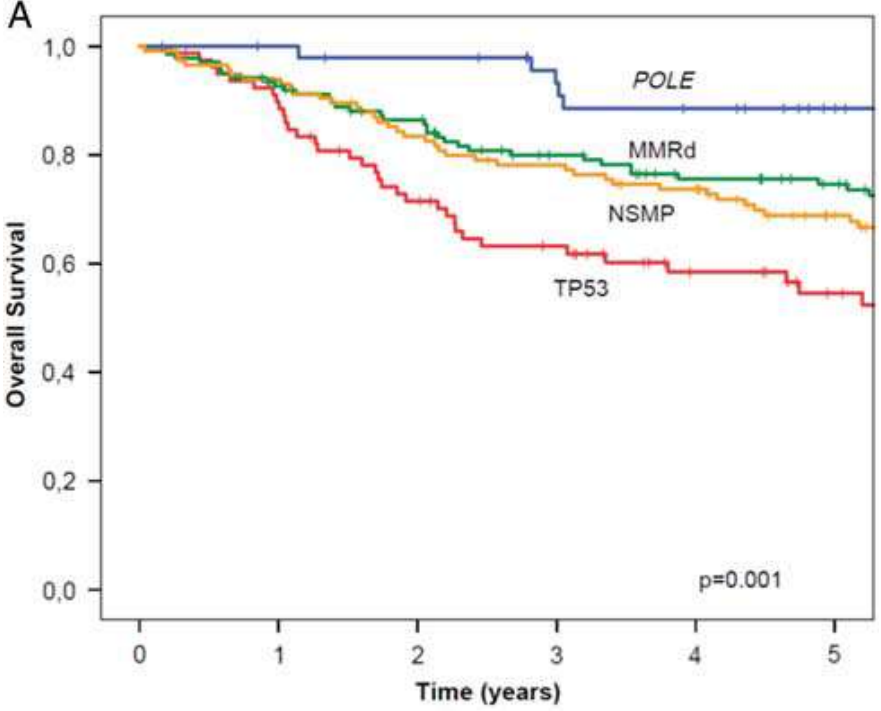
Algorytmus molekulárního testováni

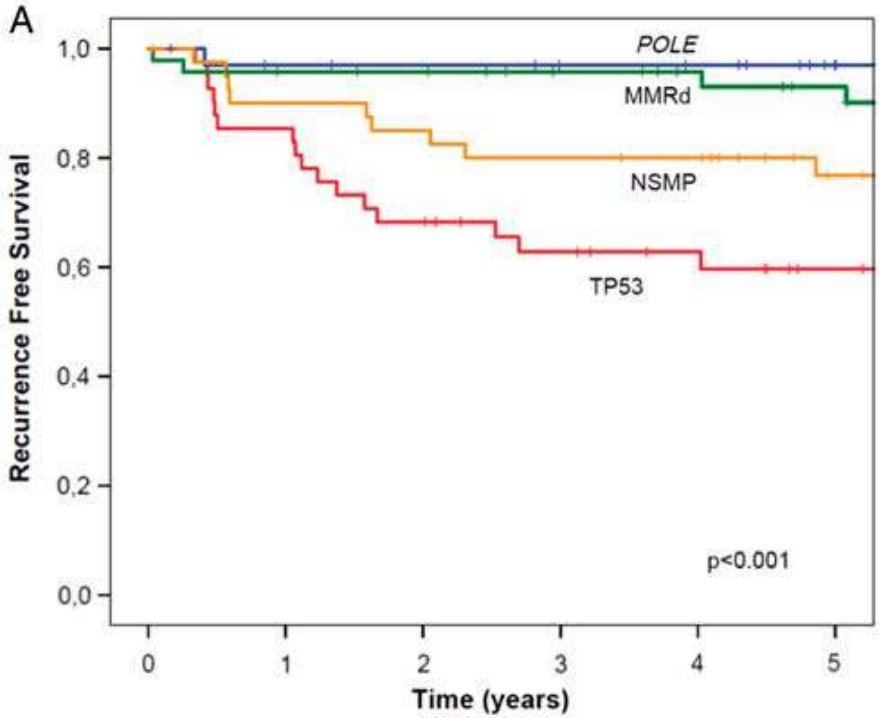


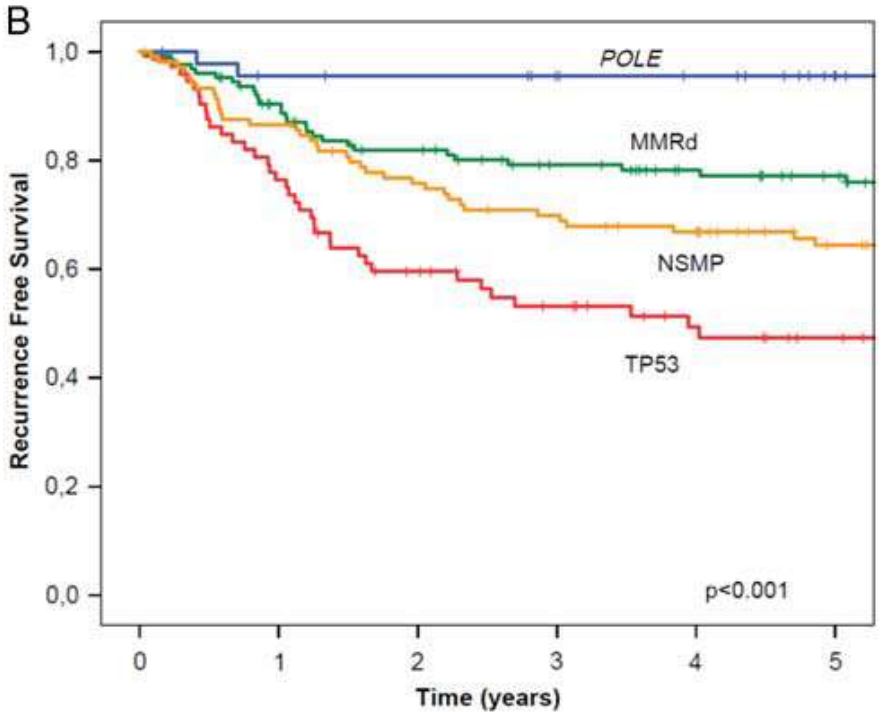
AJSP , 2018

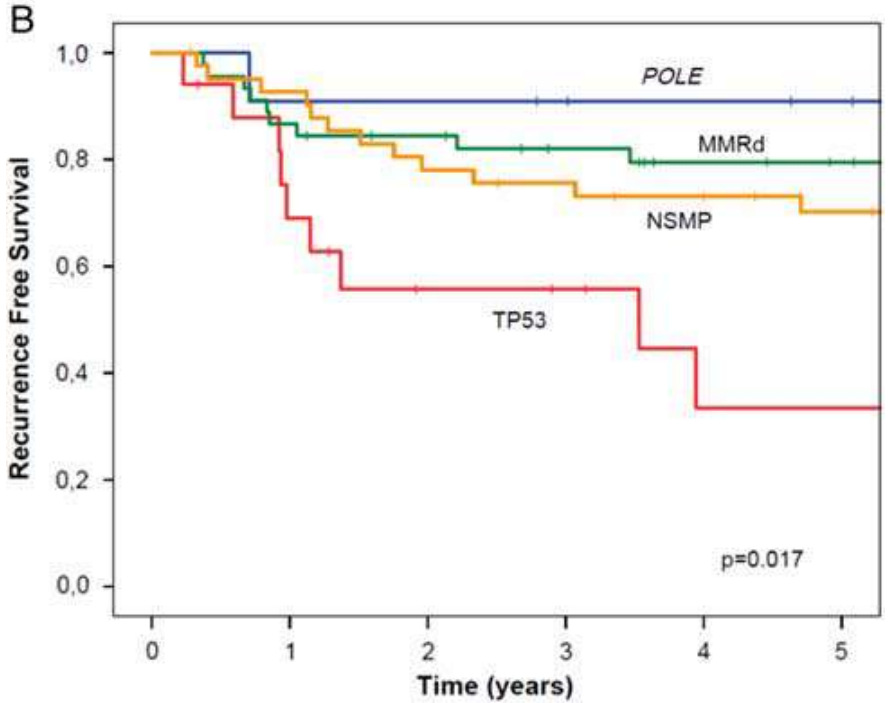
Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups

Tjalling Bosse, MD, Remi A. Nout, MD,* Jessica N. McAlpine, MD,† Melissa K. McConechy, MD,‡ Heidi Britton, MD,‡ Yaser R. Hussein, MD,§ Carlene Gonzalez, BA,§ Raji Ganesan, MD,‖ Jane C. Steele, MD,‖ Beth T. Harrison, MD,¶ Esther Oliva, MD,¶ August Vidal, MD,# Xavier Matias-Guiu, MD,# Nadeem R. Abu-Rustum, MD,** Douglas A. Levine, MD,** C. Blake Gilks, MD,‡ and Robert A. Soslow, MD§*


A
Overall Survival
1,0
0,8
0,6
0,4
0,2
0,0
POLE
MMRd
NSMP
TP53
p=0.001
0
1
2
3
4
5
Time (years)


A
Recurrence Free Survival
1,0
0,8
0,6
0,4
0,2
0,0
POLE
MMRd
NSMP
TP53
p<0.001
0
1
2
3
4
5
Time (years)


B
Recurrence Free Survival
1,0
0,8
0,6
0,4
0,2
0,0
POLE
MMRd
NSMP
TP53
p<0.001
0
1
2
3
4
5
Time (years)


B
Recurrence Free Survival
1,0
0,8
0,6
0,4
0,2
0,0
POLE
MMRd
NSMP
TP53
p=0.017
0
1
2
3
4
5
Time (years)

WHO 2020

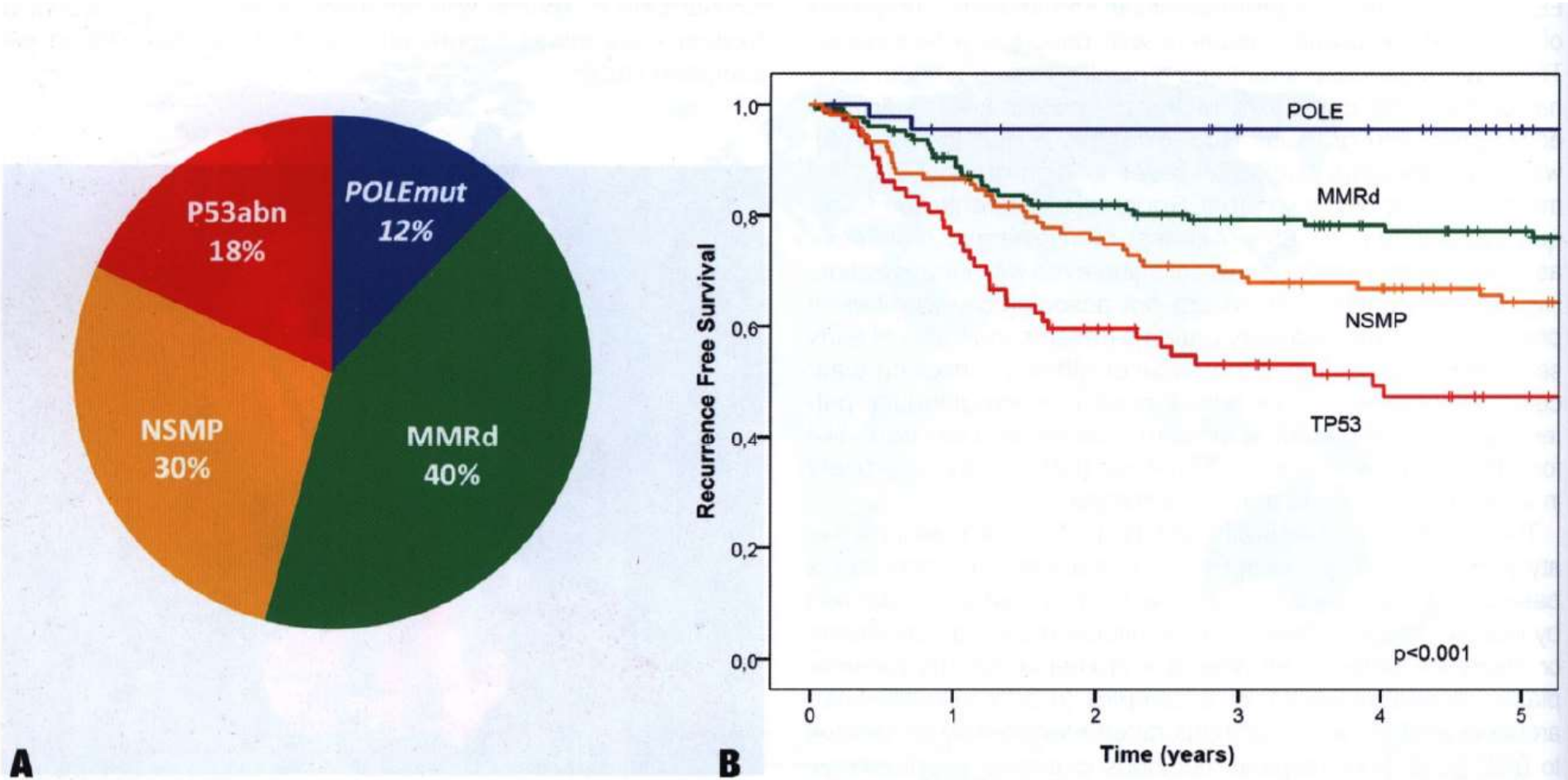


Fig. 6.09 Molecular subgroup prevalence (**A**) and recurrence-free survival (**B**) in FIGO grade 3 endometrioid endometrial carcinoma (*N* = 410). Molecular classification of grade 3 endometrioid endometrial cancers identifies distinct prognostic subgroups.

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CLINICAL OUTCOMES OF PATIENTS WITH *POLE* MUTATED ENDOMETRIOID ENDOMETRIAL CANCER

Marina Stasenko[a], Irina Tunnage[a], Charles W. Ashley[b], Maria M. Rubinstein[c], Alicia J. Latham[c,d], Arnaud Da Cruz Paula[b], Jennifer J. Mueller[a,d], Mario M. Leitao Jr.[a,d], Claire F. Friedman[c,d], Vicky Makker[c,d], Robert A. Soslow[b,d], Deborah F. DeLair[e], David M. Hyman[c,d], Dimitriy Zamarin[c,d], Kaled M. Alektiar[d,f], Carol A. Aghajanian[c,d], Nadeem R. Abu-Rustum[a,d], Britta Weigelt[b,d], Karen A. Cadoo[b,d]

HIGHLIGHTS

- In this prospective cohort, 5% of endometrioid endometrial carcinoma have *POLE* EDM
- 17% of *POLE*-mutant cases developed recurrences
- Recurrences were observed in uterine-confined G3 disease after adjuvant RT
- *De novo* metastatic disease was observed
- Further research is warranted before changes in treatment/management are considered

2021

Joint statement

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

Nicole Concin ,[1,2] Xavier Matias-Guiu,[3,4] Ignace Vergote,[5] David Cibula,[6] Mansoor Raza Mirza,[7] Simone Marnitz,[8] Jonathan Ledermann ,[9] Tjalling Bosse,[10] Cyrus Chargari,[11] Anna Fagotti,[12] Christina Fotopoulou ,[13] Antonio Gonzalez Martin,[14] Sigurd Lax,[15,16] Domenica Lorusso,[12] Christian Marth,[17] Philippe Morice,[18] Remi A Nout,[19] Dearbhaile O'Donnell,[20] Denis Querleu ,[12,21] Maria Rosaria Raspollini,[22] Jalid Sehouli,[23] Alina Sturdza,[24] Alexandra Taylor,[25] Anneke Westermann,[26] Pauline Wimberger,[27] Nicoletta Colombo,[28] François Planchamp,[29] Carien L Creutzberg[30]

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

*For stage III–IVA *POLE*mut endometrial carcinoma and stage I–IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk group in the molecular classification. Prospective registries are recommended.

†See text on how to assign double classifiers (eg, patients with both *POLE*mut and p53abn should be managed as *POLE*mut).

‡According to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade and grade 3 carcinomas are considered as high-grade.

LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal; *POLE*mut, polymerase-mutated.

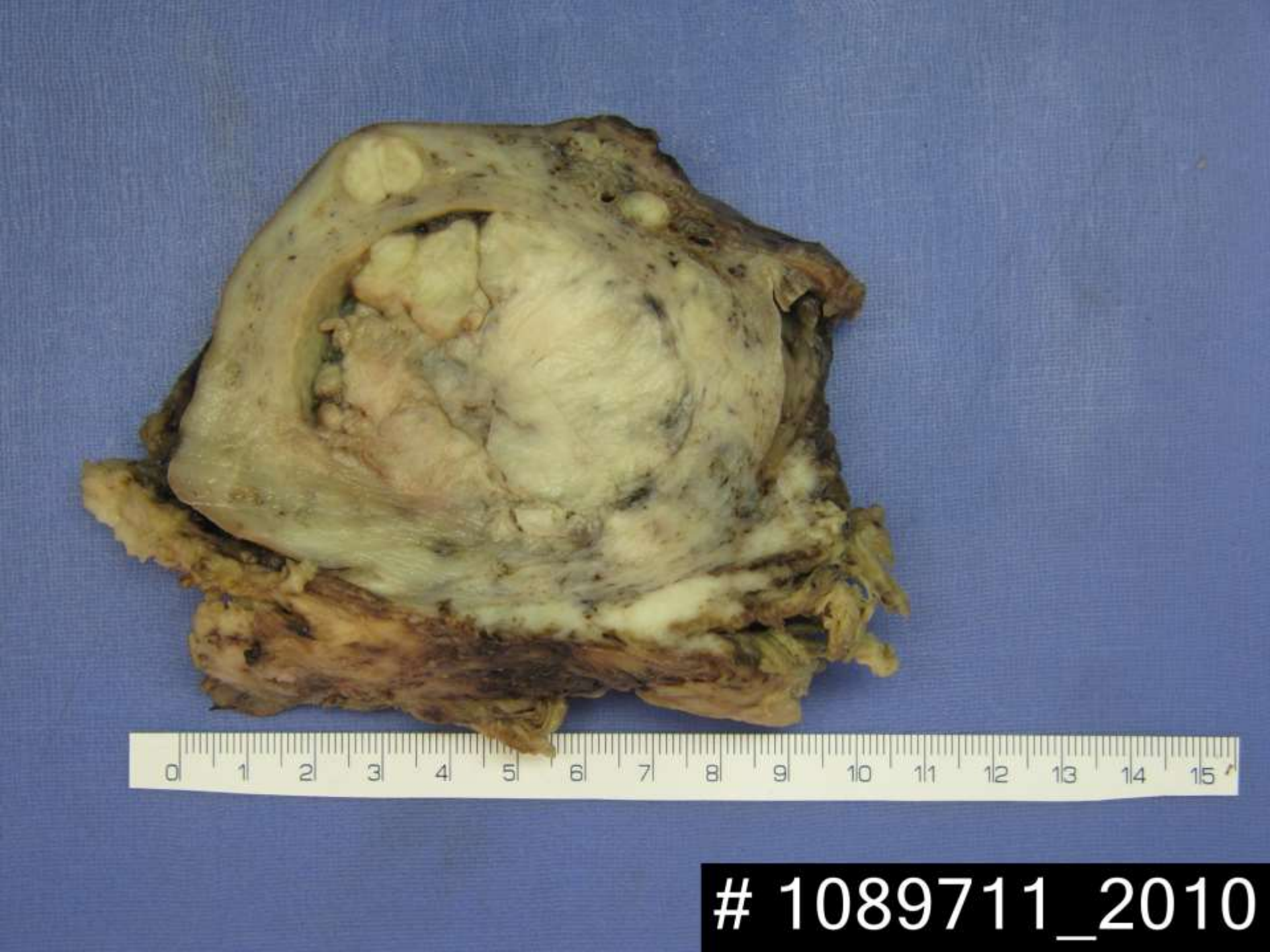
Praktické dopady z pohledu patologa

Recommendations

- Molecular classification is encouraged in all endometrial carcinomas, especially high-grade tumors (IV, B).
- POLE mutation analysis may be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology (IV, C).

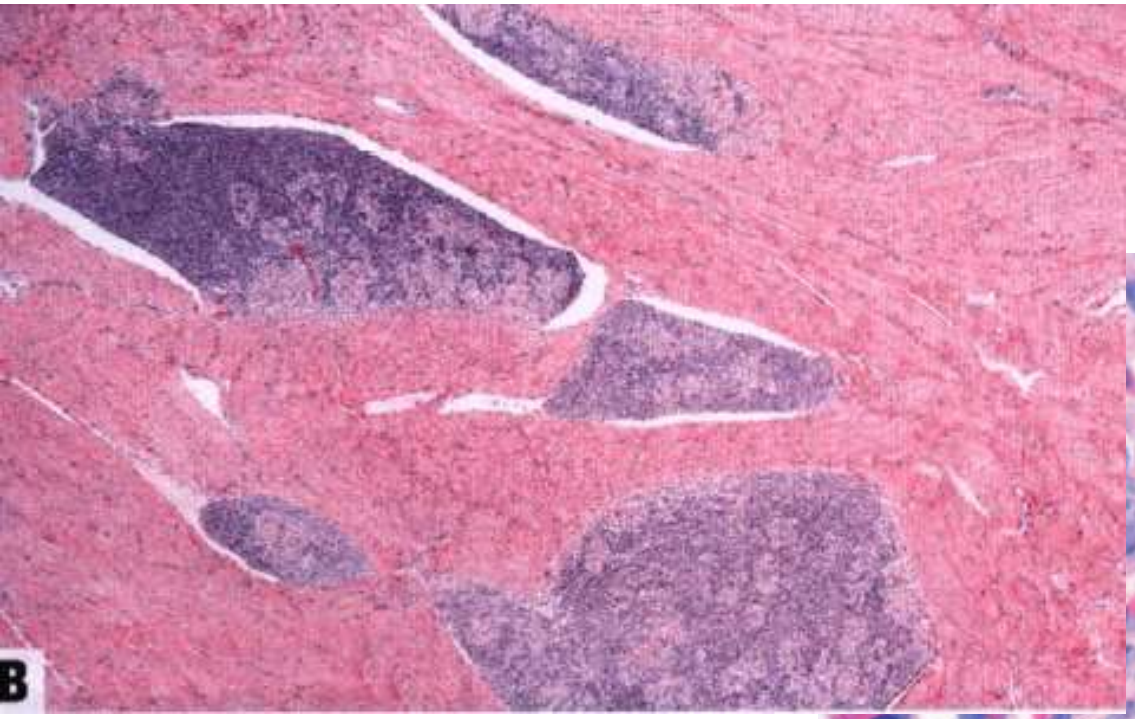
Endometriální stromální sarkomy (ESS)

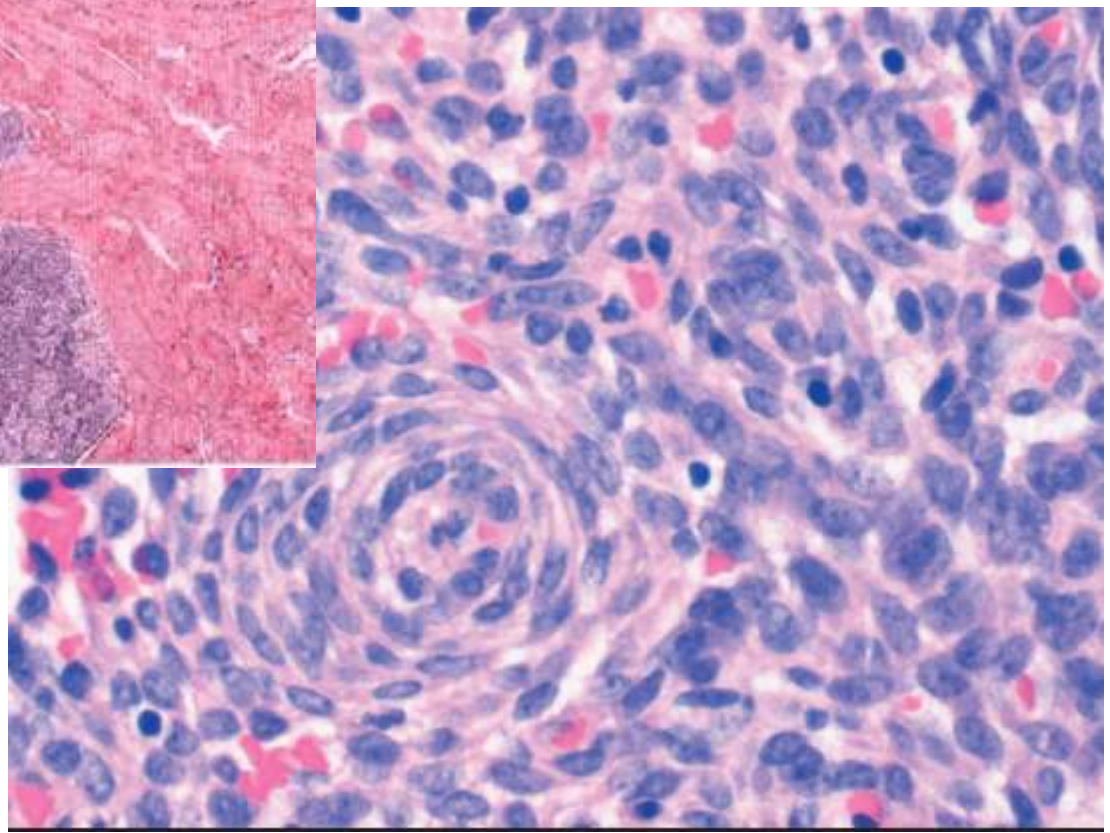
Makroskopický vzhled


0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
1089711_2010

Low grade ESS

Histologický vzhled





Biologické vlastnosti

- Indolentní low grade sarkom

<u>Dosud známe genové translokace:</u>

- *JAZF1-SUZ12, PHF1-JAZF1,*
- *PHF1-MEAF6, PHF1- EPC,*
- *PHF1-BRD8,*
- *MBTD1-CXorf67*

High grade ESS (vzácne)

- YWHAE-NUTM2 (FAM 22)
- BCOR-ZC3H7B,
- BCOR (ITD exon 15)

(BCOR – bcl6 interacting co-repressor)

- YWHAE-NUTM2 (NUTM2A, nebo NUTM2B) FAM 22 – *fúzni onkoprotein s neznámou funkcí*

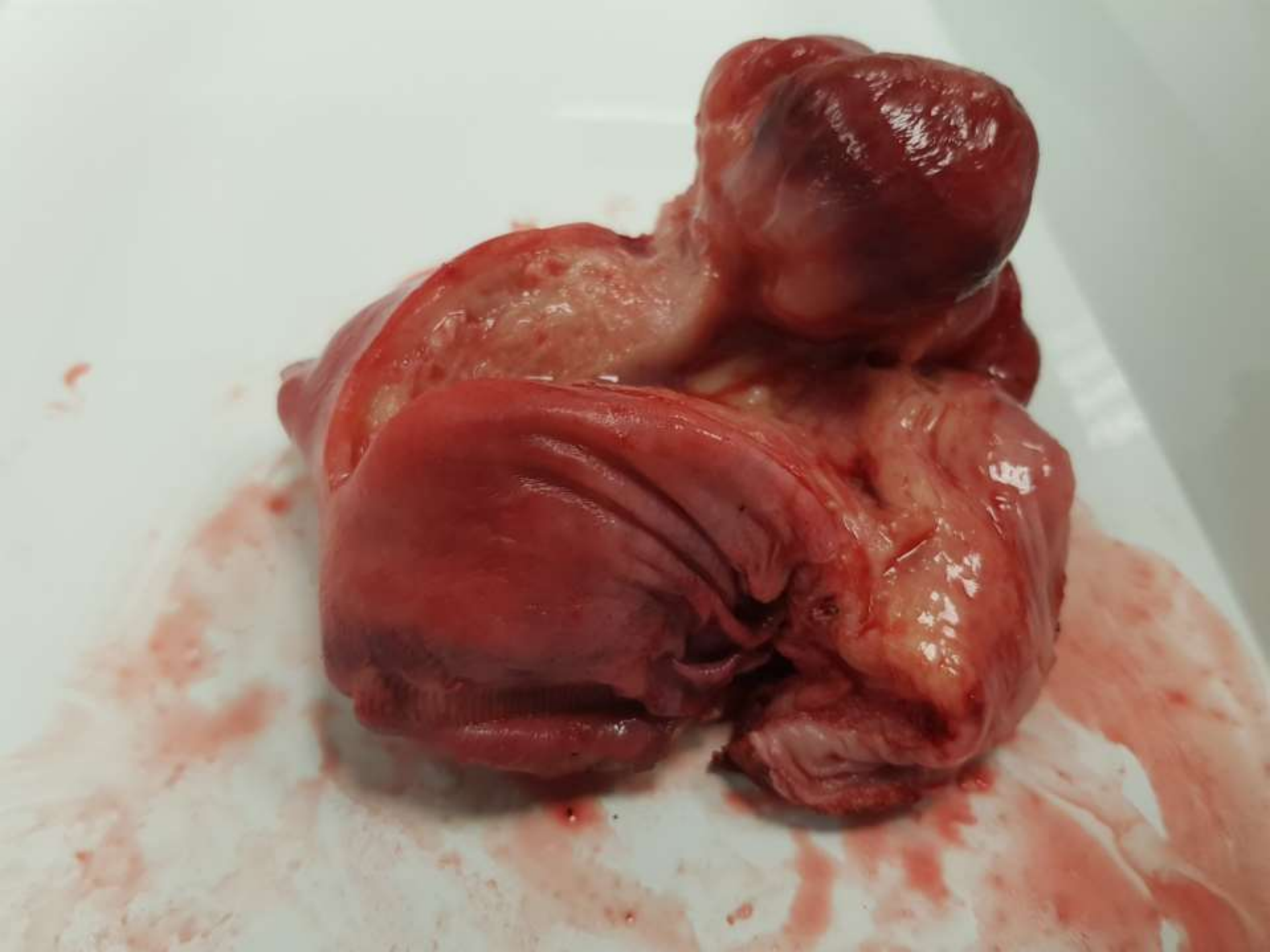
BCOR protein

- Gen: BCL-6 corepressor
- lokus Xp11.4
- Funkce:

- Zapojuje se do polycomb represive complex (PRC 1) a
- Suprimuje geny modifikací histonů.

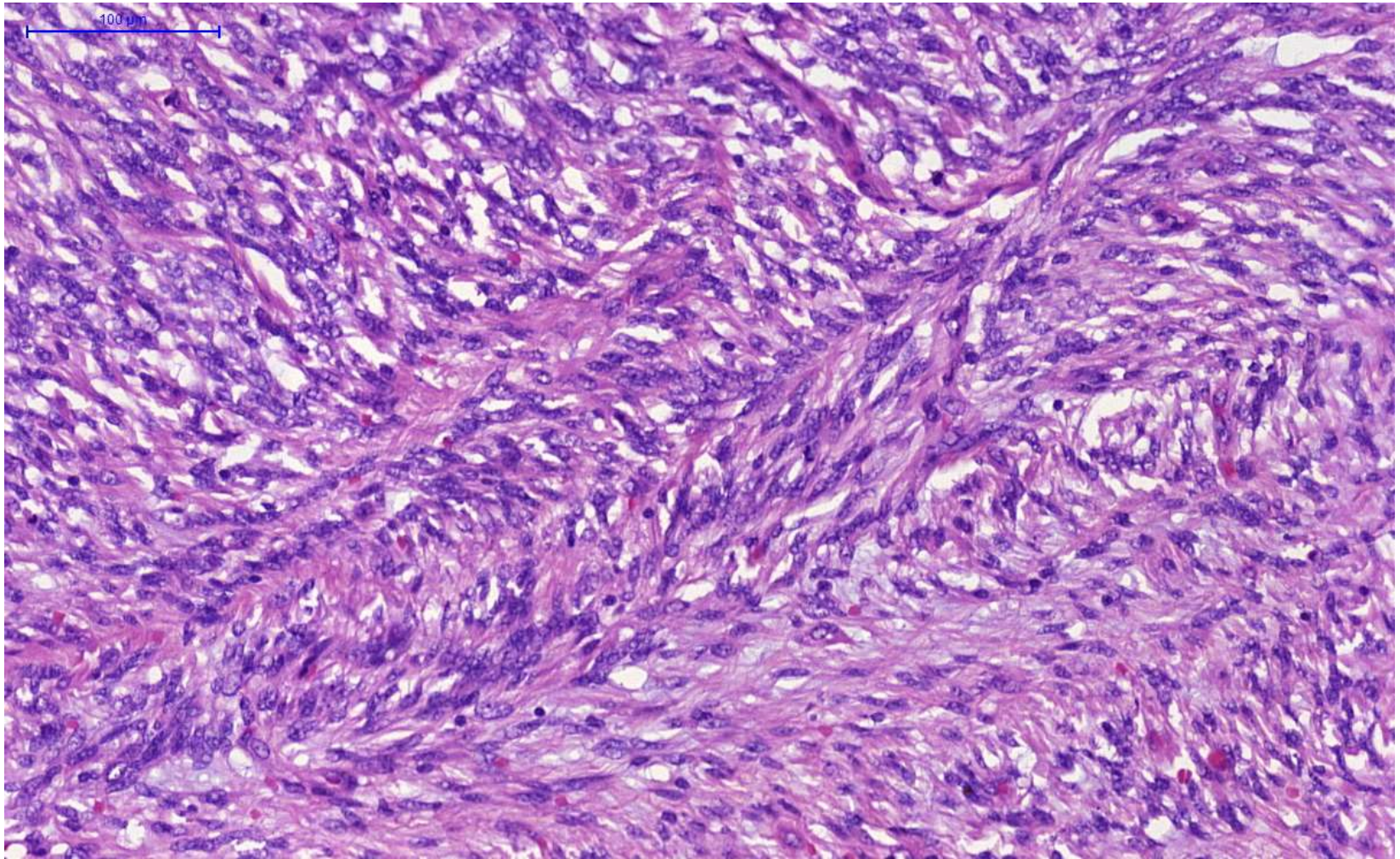
Fúzni gen ZC3H7B–BCOR t(X;22)(p11;q13)

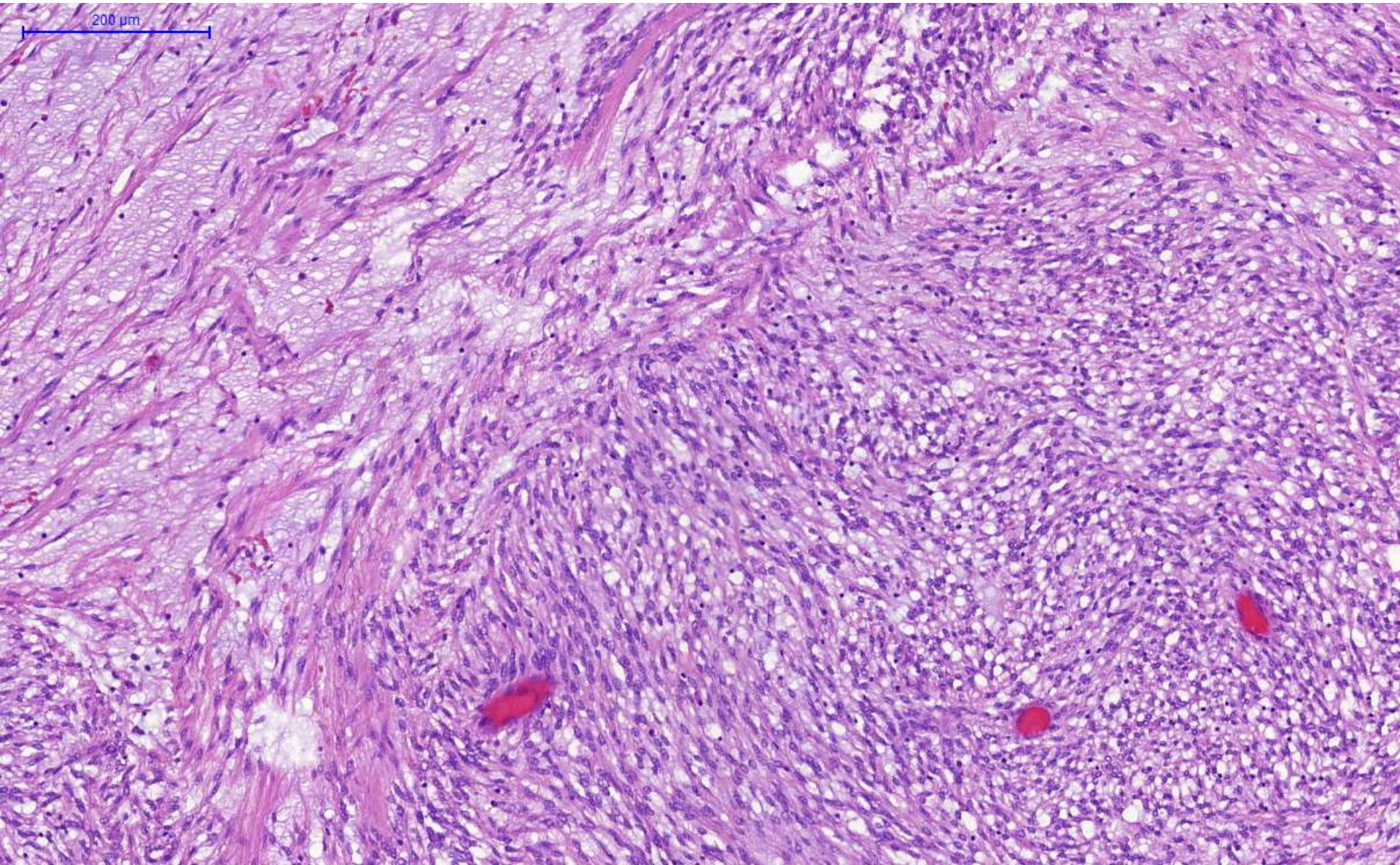
- 1. popis: Panagopoulos, 2013
- 1. minisérie: (3 případy) Hoang,AJSP, 2017
- 2. série: (17 případů) Lewis N, Mod Pathol, 2018



Histologký vzhled

Leiomyosarcoma-like




200 µm

Další sledování

- Pooperační chemoterapie (08,2018) - monoterapie, Doxorubicin
- Kontrola 05/2019 (MUDr. Arnetová) – subjektívně i objektívně bez obtíží a bez nálezu; objednané PET/CT vyšetření a kontrola (09/2019)
- Kontrola 09/2019 (MUDr. Franková) - **Subjektivně dobře, nastupuje do práce.**

V pánvi bez FDG akumulující lokální recidivy maligního onemocnění. Ojedinělé, drobné uzliny v levé polovině pánve, bez patol. zvýšené akumulace FDG, bez podstatné změny proti min. vyš. Nově jsou v levém třísle patrné nezvětšené uzliny s mírně vyšší akumulací FDG - v.s. reaktivní lymfadenopatie, vhodné USG sledování. (MUDr. Ferdová)

- Další kontrola Leden 2020.

Biologické vlastnosti

- Agresivnější než low grade endometriální stromálni sarkom

Praktické dopady z pohledu patologa

- 1. Diferenciálni diagnostika
- Zůžení skupiny nediferencovaných sarkomů dělohy
- 2. Cílená léčba zatím neexistuje.

Nejblíže tomu je léčba cílíci na bcl 6 u myelomu.

Možnosti léčby v budoucnu

Published OnlineFirst November 23, 2016; DOI: 10.1158/1078-0432.CCR-16-2071

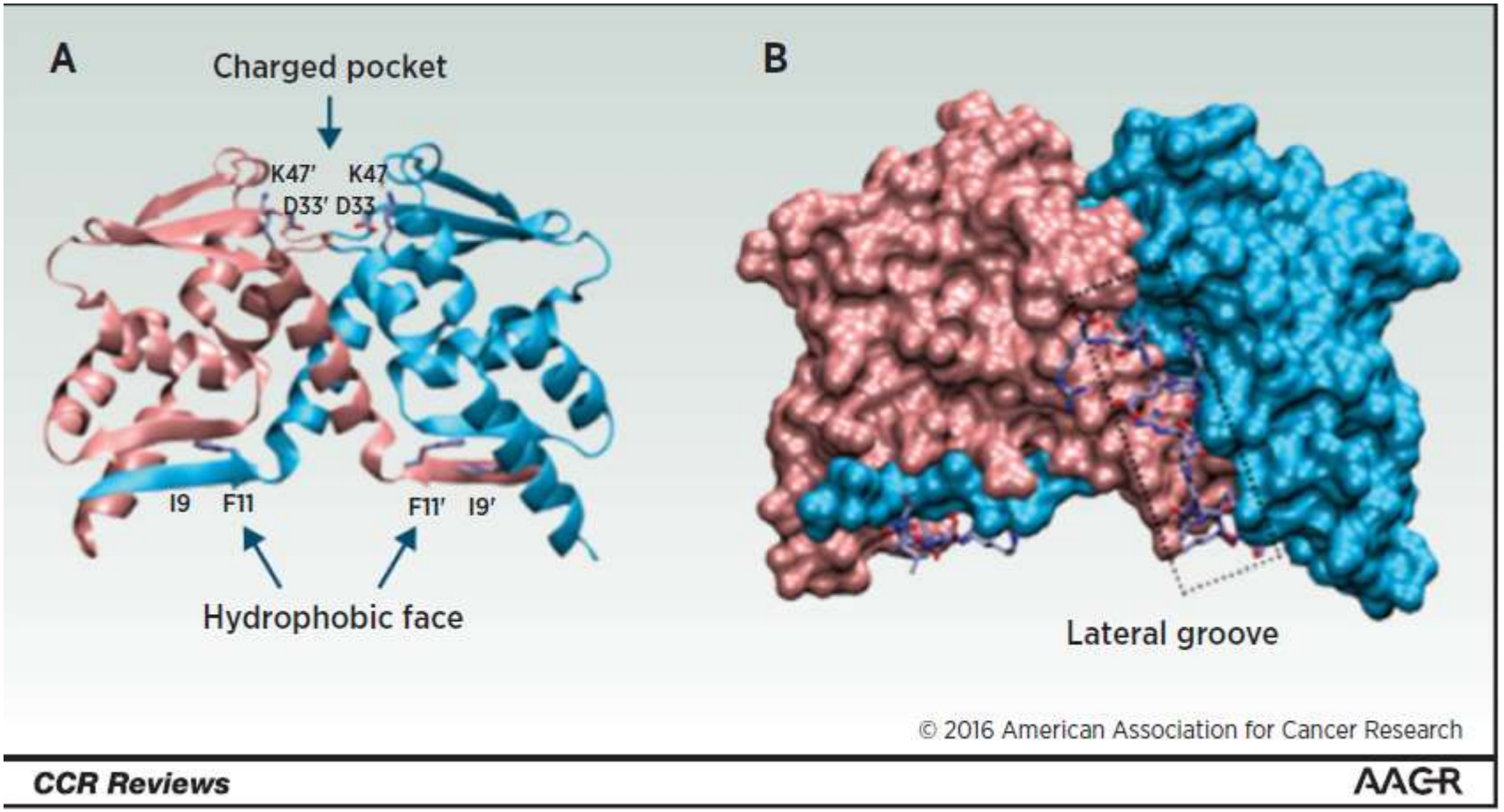
Review

Clinical Cancer Research

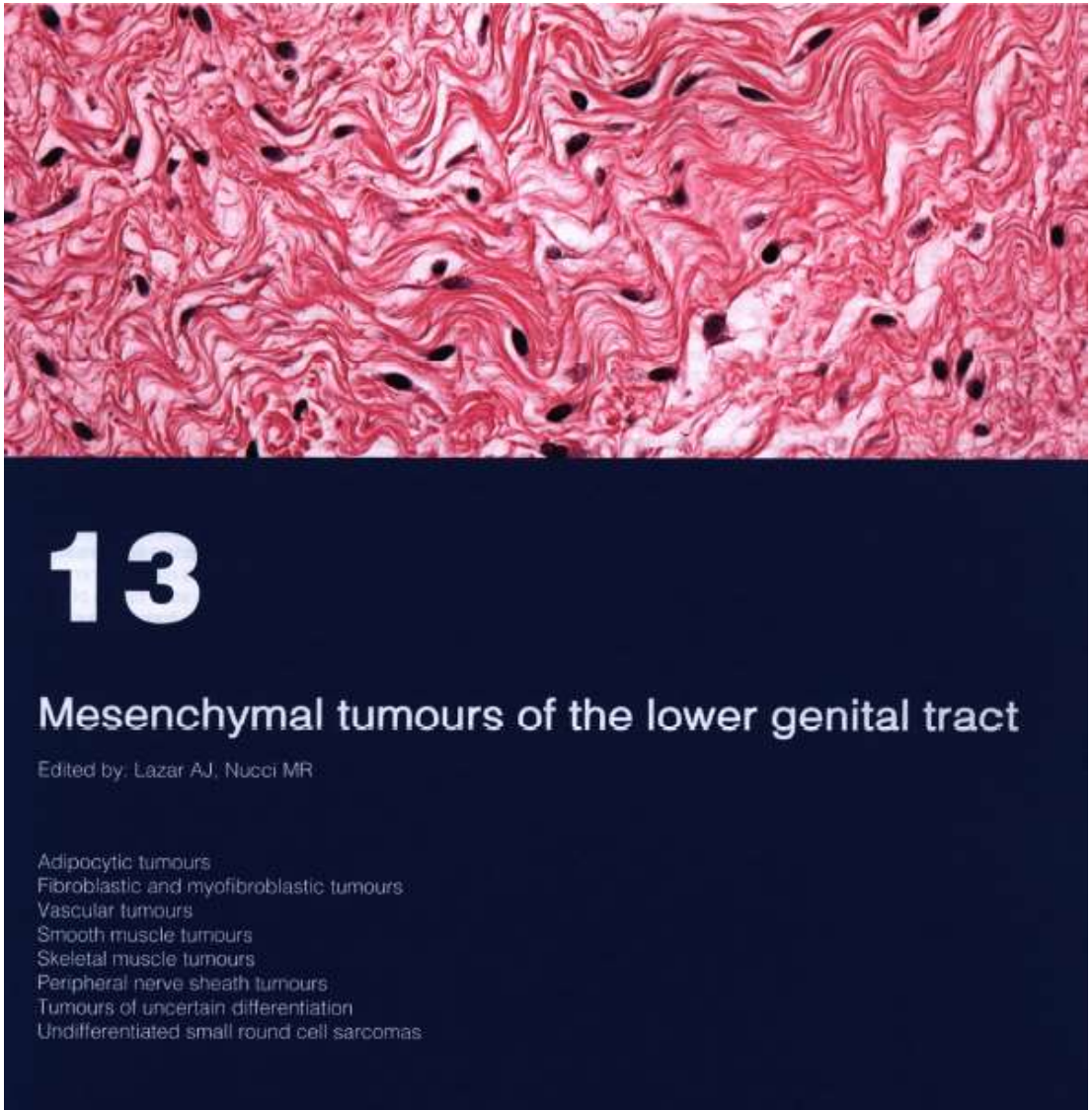
The Expanding Role of the BCL6 Oncoprotein as a Cancer Therapeutic Target

Mariano G. Cardenas[1], Erin Oswald[1], Wenbo Yu[2], Fengtian Xue[2], Alexander D. MacKerell Jr[2], and Ari M. Melnick[1]

BCL6 - štruktúra

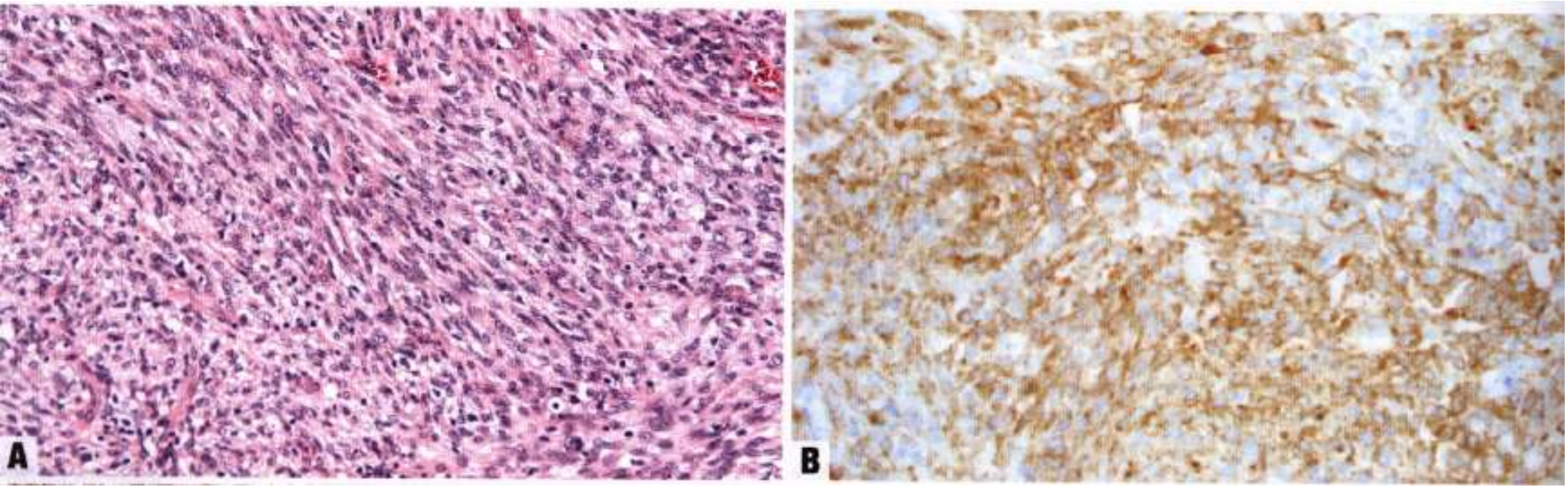


Mezenchymální nádory FGS



NTRK-rearranged spindle cell neoplasm (emerging)

Localization
Cervix and/or lower uterine segment



Prognóza

- Nejistá (málo případů), spíše příznivá.

Prognosis and prediction

The clinical course of NTRK-rearranged cervical sarcoma is variable, but at least some tumours are associated with metastasis and an aggressive clinical course. Data are limited, but older patients appear to be at higher risk of disease progression. The number of reported cases is too low for prognostic or predictive markers to be defined.

NTRK translokované sarkomy

- Gen NTRK (*Neurotropic Tyrosine Receptor kinase*)
- NTRK1, NTRK2, NTRK3 kóduje proteíny TrkA, TrkB, TrkC (*tropomyosin receptor kinase*)
- Funkce: ovlyvňuje vývoj neuronů t.j. přežívání, diferenciaci a plasticitu neuronů

NTRK sarkomy

- Obsahují rearanžovaný gen:

část NTRK genu + fúzni partner

Tento fúzni gen se chová ako efektivní onkogén – navozuje konstitutívni proliferaci buněk.

Sarkomy dělohy asociované s translokovaným genem NTRK

- V děloze jsou podobné fibrosarkomu, nebo MPNST (malignant peripheral nerve sheat tumor).
- Najčastěji postihují cervix, méně často telo dělohy, výjimečně vagínu.

Sarkomy dělohy asociované s translokovaným genem NTRK (první popis, USA, červen, 2018)

NTRK Fusions Define a Novel Uterine Sarcoma Subtype With Features of Fibrosarcoma

Sarah Chiang, MD, Paolo Cotzia, MD,* David M. Hyman, MD,† Alexander Drilon, MD,‡ William D. Tap, MD,§ Lei Zhang, MD,* Jaclyn F. Hechtman, MD,* Denise Frosina, BS,* Achim A. Jungbluth, MD, PhD,* Rajmohan Murali, MBBS, MD, FRCPA,* Kay J. Park, MD,* Robert A. Soslow, MD,* Esther Oliva, MD,‖¶ A. John Iafrate, MD, PhD,‖¶ Ryma Benayed, PhD,* Marc Ladanyi, MD,* and Cristina R. Antonescu, MD**

Abstract: Tropomyosin receptor kinase (Trk) inhibitors have shown high response rates in patients with tumors harboring *NTRK* fusions. We identified 4 *NTRK* fusion-positive uterine sarcomas that should

Key Words: *NTRK*, uterine sarcoma, fibrosarcoma

(*Am J Surg Pathol* 2018;42:791–798)

Společná USA-Evropská sestava (Květen, 2019)

Modern Pathology
https://doi.org/10.1038/s41379-018-0184-6

USCAP

ARTICLE

Uterine and vaginal sarcomas resembling fibrosarcoma: a clinicopathological and molecular analysis of 13 cases showing common *NTRK*-rearrangements and the description of a *COL1A1-PDGFB* fusion novel to uterine neoplasms

Sabrina Croce[1,2] · Isabelle Hostein[1] · Teri A. Longacre[3] · Anne M. Mills[4] · Gaëlle Pérot[1] · Mojgan Devouassoux-Shisheboran[5] · Valérie Velasco[1] · Anne Floquet[6] · Frédéric Guyon[7] · Camille Chakiba[6] · Denis Querleu[7] · Emmanuel Khalifa[1] · Laetitia Mayeur[1] · Flora Rebier[1] · Sophie Leguellec[8] · Isabelle Soubeyran[1] · W. Glenn McCluggage[9]

Table 2 Clinical and Pathological Features of Cases Included in Study

Case	Age (years)	Size (cm)	Tumor location	Follow-up (months)	Tumor Recurrence	Tumor stage	Predominant degree of nuclear Atypia	Mitoses per 10HPFs	Necrosis	Tumor Border	Lymphocytic Infiltrate	LVSI
1	32	5.5	Cervix	AWD 19	Bone, peritoneal	IB	Moderate	10	Yes	Infiltrating	Yes	No
2	47	5	Corpus/LUS	DOD 11	Adnexa and upper abdomen	IVB	Moderate	50	Yes	Not assessable	No	No
3	39	NA	Cervix	NA	Unknown	NA	Mild	3	Yes	Infiltrating	Yes	No
4	44	4.5	Cervix	NED 2	No	IA	Moderate	3	No	Not assessable	Yes	No
5	26	12	Cervix	AWD 52	Vagina	IB	Moderate	3	Yes	Not assessable	Yes	No
6	82	8.2	Cervix	NED 10	No	IB	Mild	8	Yes	Infiltrating	No	No
7	50	9	Vagina	DOD 34	Pelvis (bladder and rectum)	IIB	Mild	1	No	Infiltrating	Yes	No
8	23	3	Cervix	NED 33	No	IA	Moderate	5	Yes	Not assessable	Yes	No
9	30	2.5	Cervix	NED 12	No	IA	Mild	50	No	Infiltrating	No	No
10	60	5.8	Cervix	DOD 60	Pelvis and bladder	IIIB	Mild	20	No	Infiltrating	No	No
10			Recurrence case 10				Moderate	20	No	Infiltrating	No	No
11	33	5	Cervix	NED 108	No	IA	Mild	1	No	Infiltrating	Yes	No
12	23	2.8	Cervix	AWD 30	Left paracervical and ureterovesicle tissue, pelvic gutter, omentum, small bowel, ovary, liver	IIA	Mild	50	Yes	Infiltrating	No	No
12			Recurrence case 12				Marked	32	Yes	Infiltrating	No	No
13	48	12	Corpus	NA-Recent case		IB	Moderate	20	No	NE	No	No

NED no evidence of disease, *DOD* dead of disease, *AWD* alive with disease, *LUS* lower uterine segment, *NA* not available, *NE* not evaluable, *LVSI* lymphovascular invasion

Věk : 23-82 rokov

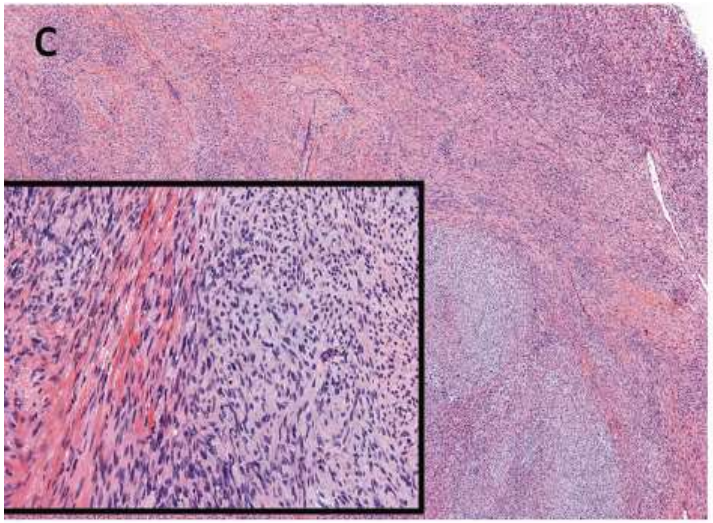
Velikost nádoru: 2,5 cm – 9 cm

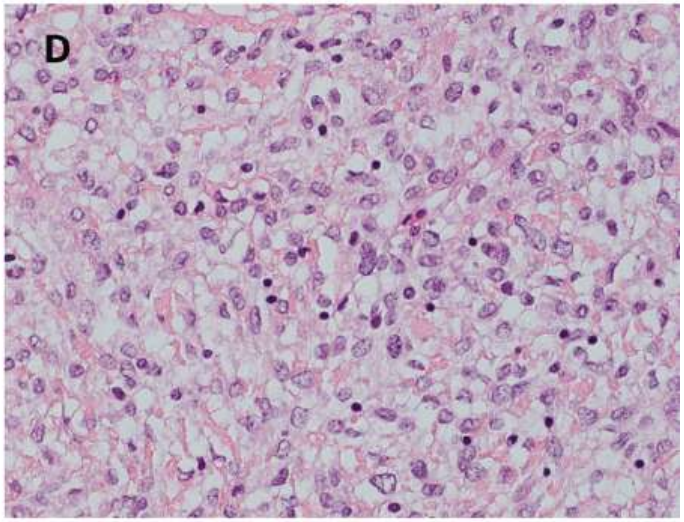
Přežití: úmrtí 11 měs. po dg (tu corpus 5 cm)

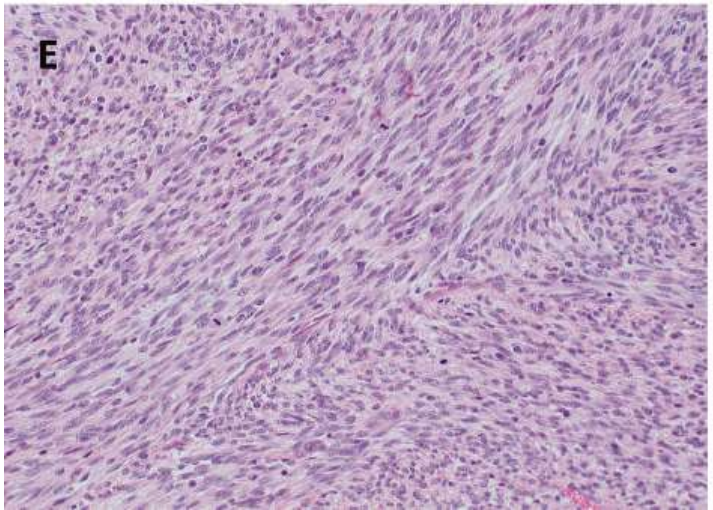
žije NED 108 měs. (tu cervix, 5cm)

Zemřely 3 pac. s inic. Dg. v st. TNM / FIGO IIIB, IVB.

Podobnost HG ESS a NTRK rearanžovaného sarkomu dělohy







Nediferencovaný sarkom dělohy

Undifferentiated Uterine Sarcomas Represent Under-Recognized High-grade Endometrial Stromal Sarcomas

Paolo Cotzia, MD, Ryma Benayed, PhD,† Kerry Mullaney, BS, MFS,† Esther Oliva, MD,‡ Ana Felix, MD, PhD,§ Joana Ferreira, MD,§ Robert A. Soslow, MD,† Cristina R. Antonescu, MD,† Marc Ladanyi, MD,† and Sarah Chiang, MD†*

Abstract: Undifferentiated uterine sarcoma is a diagnosis of exclusion with limited molecular genetic data available. Recent recognition of high-grade endometrial stromal sarcomas with diverse genotypes suggests that some tumors classified as undifferentiated uterine sarcomas may represent misdiagnosed high-grade endometrial stromal sarcomas. Archival material from 10 tumors diagnosed as undifferentiated uterine sarcomas in 2009 to 2017 were collected. BCOR immunohistochemistry and fluorescence in situ hybridization (FISH) using break-apart probes flanking *BCOR*, *ZC3H7B*, *CCNB3*, *YWHAE*, *NUTM2*, *JAZF1*, and *BCORL1* endometrial stromal sarcomas. BCOR expression in ≥50% of cells may help triage tumors for molecular confirmation of high-grade endometrial stromal sarcoma-related genetic abnormalities. Novel *YWHAE* rearrangements may define a subset of true undifferentiated pleomorphic sarcomas.

Key Words: endometrial stromal sarcoma, undifferentiated uterine sarcoma, undifferentiated endometrial sarcoma, *YWHAE*, *BCOR*, *PHF1*

(*Am J Surg Pathol* 2019;43:662–669)

Použitá metoda NGS

Targeted RNA Sequencing

Tumor samples lacking or harboring *BCOR*, *ZC3H7B*, *CCNB3*, *YWHAE*, *NUTM2*, *JAZF1*, and *BCORL1* rearrangements with no fusion partner by FISH were subjected to the Archer FusionPlex Custom Solid Panel (ArcherDX Inc., Boulder, CO), a next-generation targeted RNA sequencing assay utilizing the Anchored Multiplex PCR technology that detects gene fusions and oncogenic isoforms in selected protein-coding exons of 62 genes.[16] Tumor RNA was extracted from 5 µm, formalin-fixed, paraffin-embedded tumoral tissue sections followed by cDNA synthesis and library preparation. Final targeted amplicons were sequenced on an Illumina MiSeq. Data were analyzed using the Archer Software (version 4.0.10; ArcherDX Inc.).

Zjištění a metody

TABLE 1. Clinicopathologic and Molecular Features

Case	Age (y)	Stage	Year	Morphology	BCOR Expression	FISH	RNA Sequencing	Revised Diagnosis
1	58	IB	2009	Pleomorphic	M-S, 50%	*YWHAE* rearrangement only	Failed	UUS
2	50	IA	2010	Uniform	S, ≥95%	*YWHAE-NUTM2B*	Not performed	HGESS
3	53	IB	2011	Uniform	W, <5%	*ZC3H7B-BCOR*	Not performed	HGESS
4	55	IVA	2013	Uniform	M-S, 50%	Negative	*BRD8-PHF1*	HGESS
5	71	IB	2014	Uniform	S, ≥95%	*ZC3H7B-BCOR*	Not performed	HGESS
6	54	IB	2016	Uniform	Negative	Negative	Negative	UUS
7	52	IA	2016	Uniform	S, ≥95%	Negative	*BCOR* ITD	HGESS
8	57	IVA	2017	Pleomorphic	S, ≥95%	*YWHAE* rearrangement only	Negative	UUS
9	54	IB	2017	Uniform	S, ≥95%	Negative	*YWHAE-NUTM2B*	HGESS
10	61	IB	2017	Uniform	S, ≥95%	Negative	*BCOR* ITD	HGESS

HGESS indicates high-grade endometrial stromal sarcoma; ITD, internal tandem duplication; M, moderate; S, strong; UUS, undifferentiated uterine sarcoma; W, weak.

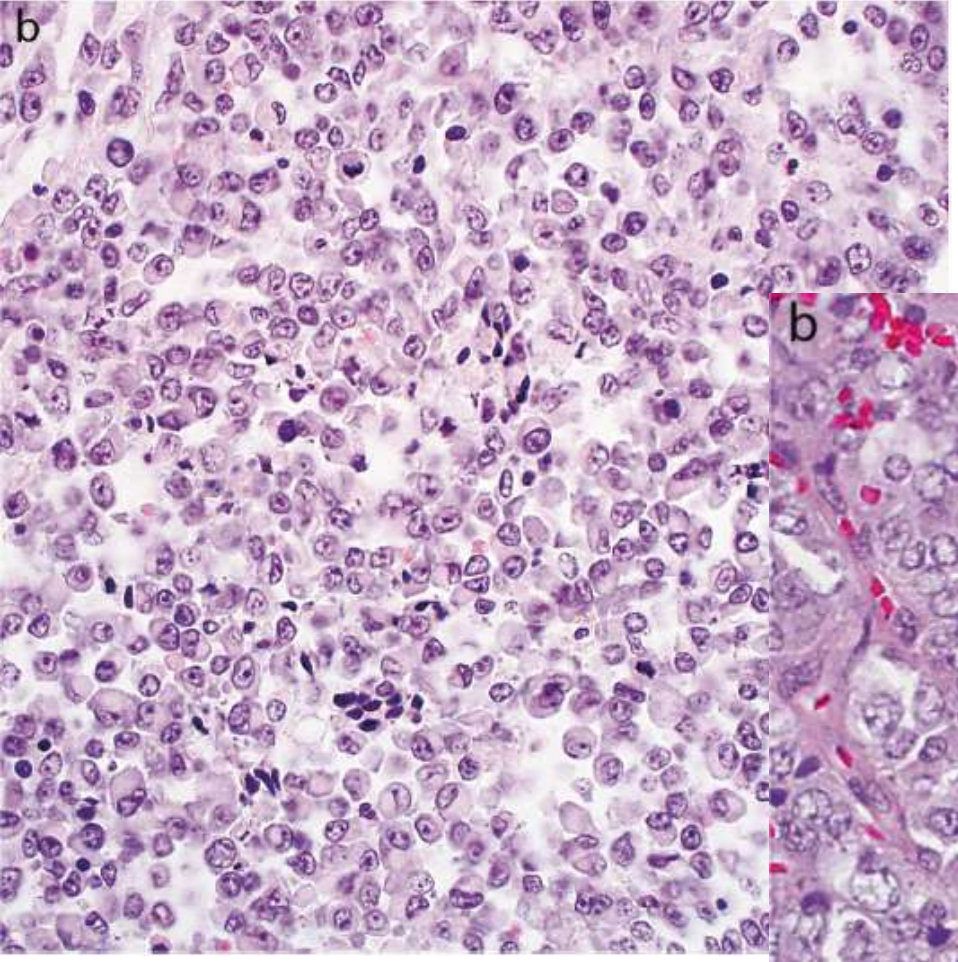
SMARCA4 – deficientní nediferencovaný sarkom dělohy

Modern Pathology (2018) 31:1442–1456
https://doi.org/10.1038/s41379-018-0049-z

ARTICLE

SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma

David L. Kolin[1] · Fei Dong[2] · Michele Baltay[2] · Neal Lindeman[2] · Laura MacConaill[2] · Marisa R. Nucci[1] · Christopher P. Crum[1] · Brooke E. Howitt[1,3]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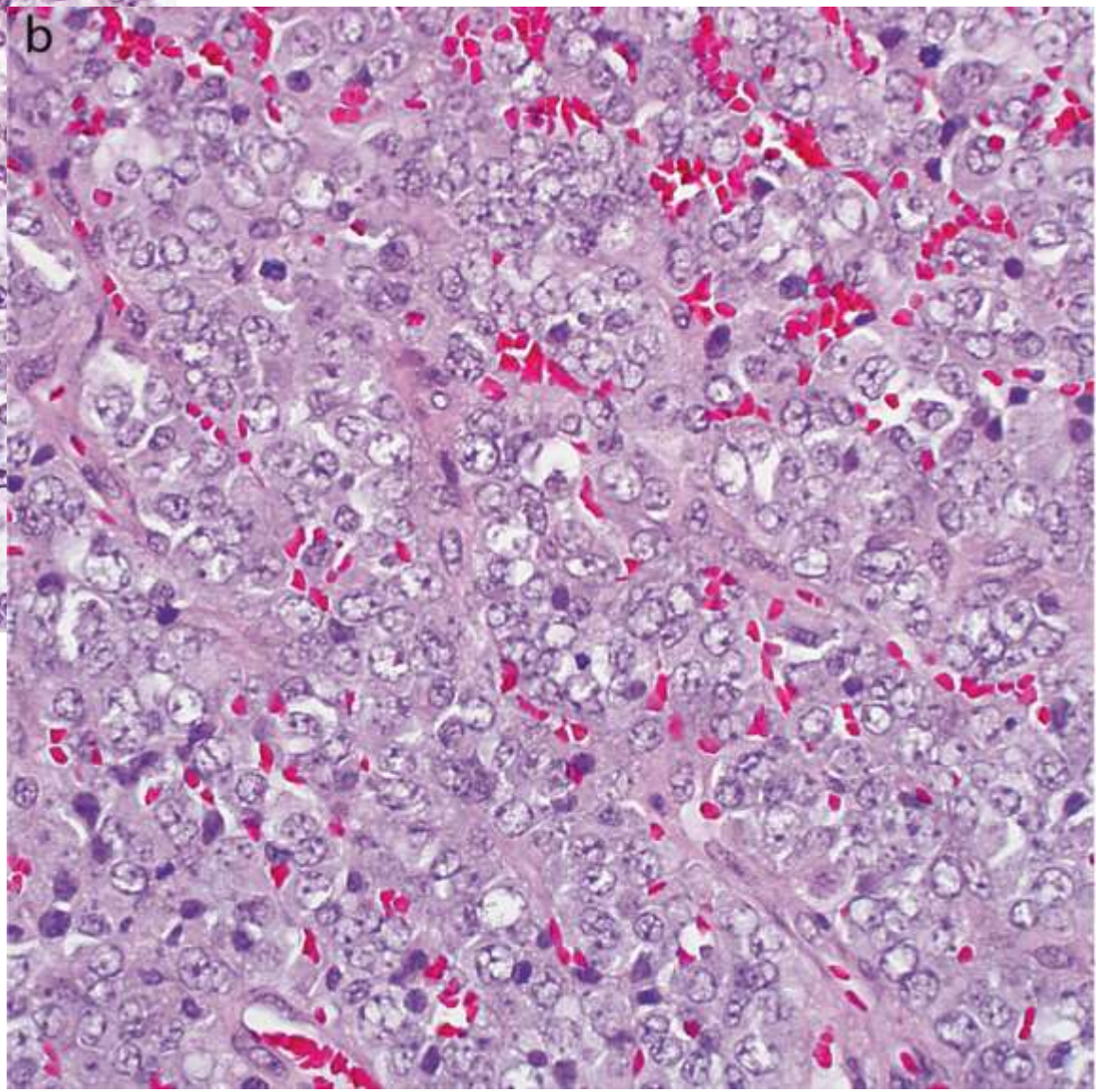

b

PD-1 antibody -možný léčebný přístup

Tomoyuki Naito et al. Successful treatment with nivolumab for SMARCA4-deficient non-small cell lung carcinoma with a high tumor mutation burden: A case report. Thorac Cancer. 2019 May; 10(5): 1285–1288.

Poznámka:

SMARCA4

is a subunit of the switch/sucrose non-fermentable (SWI/SNF) chromatin-remodeling complex.

Inflamatórni myofibroblastický tumor dělohy (IMT)

IMT dělohy - 1. kazuistika

- Gilks CB, Taylor GP, Clement PB. *Inflammatory pseudotumor of the uterus*. *Int J Gynecol Pathol* 1987;**6**:275–286.

IMT dělohy – první série a konzistentní popis

- Bennett JA, Nardi V, Rouzbahman M, Morales-Oyarvide V, Nielsen GP, Oliva E (2017) Inflammatory myofibroblastic tumor of the uterus: a clinicopathological, immunohistochemical, and molecular analysis of 13 cases highlighting their broad morphologic spectrum. Mod Pathol 30:1489–1503.

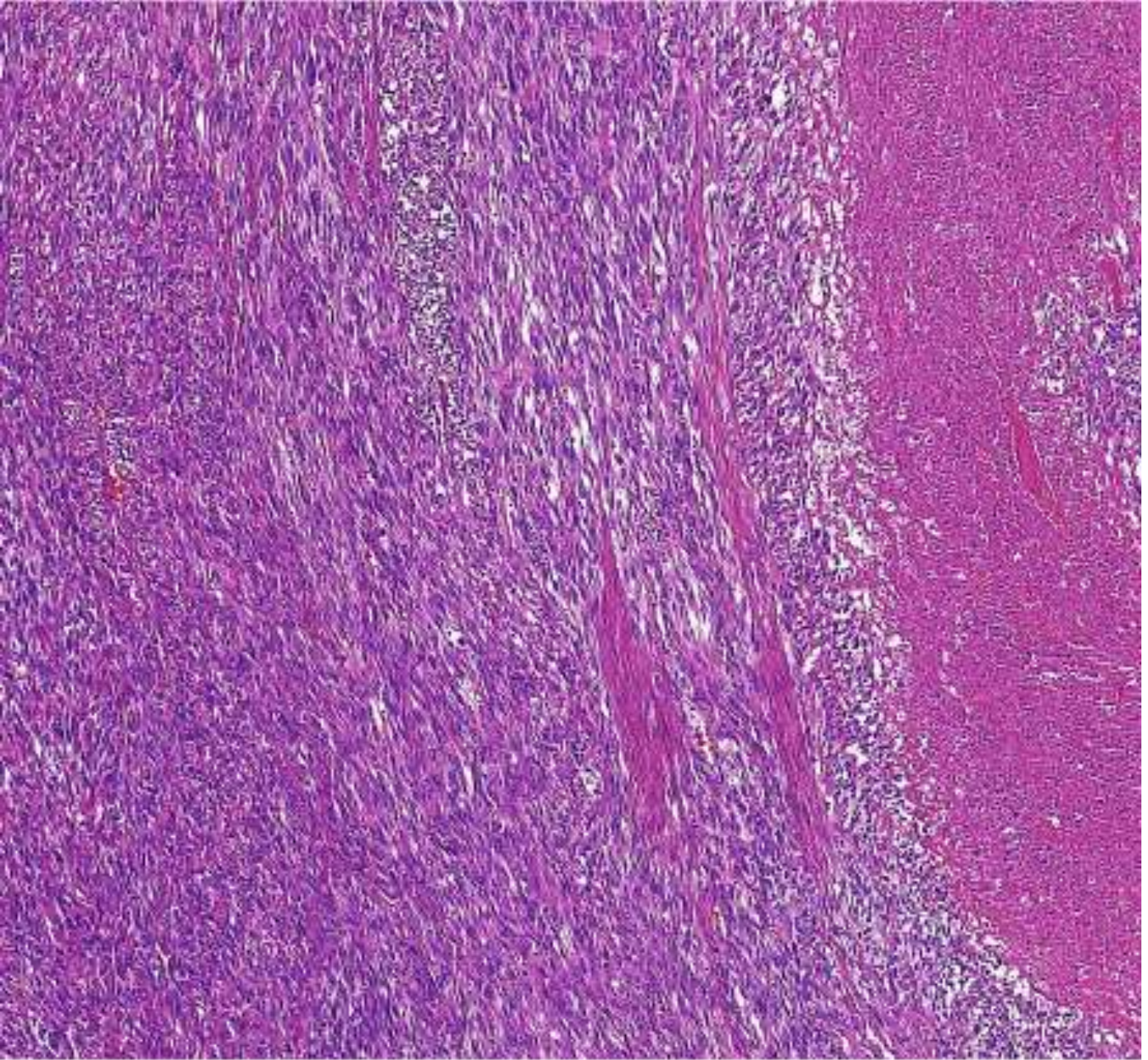
Inflamatórni myofibroblastický tumor dělohy

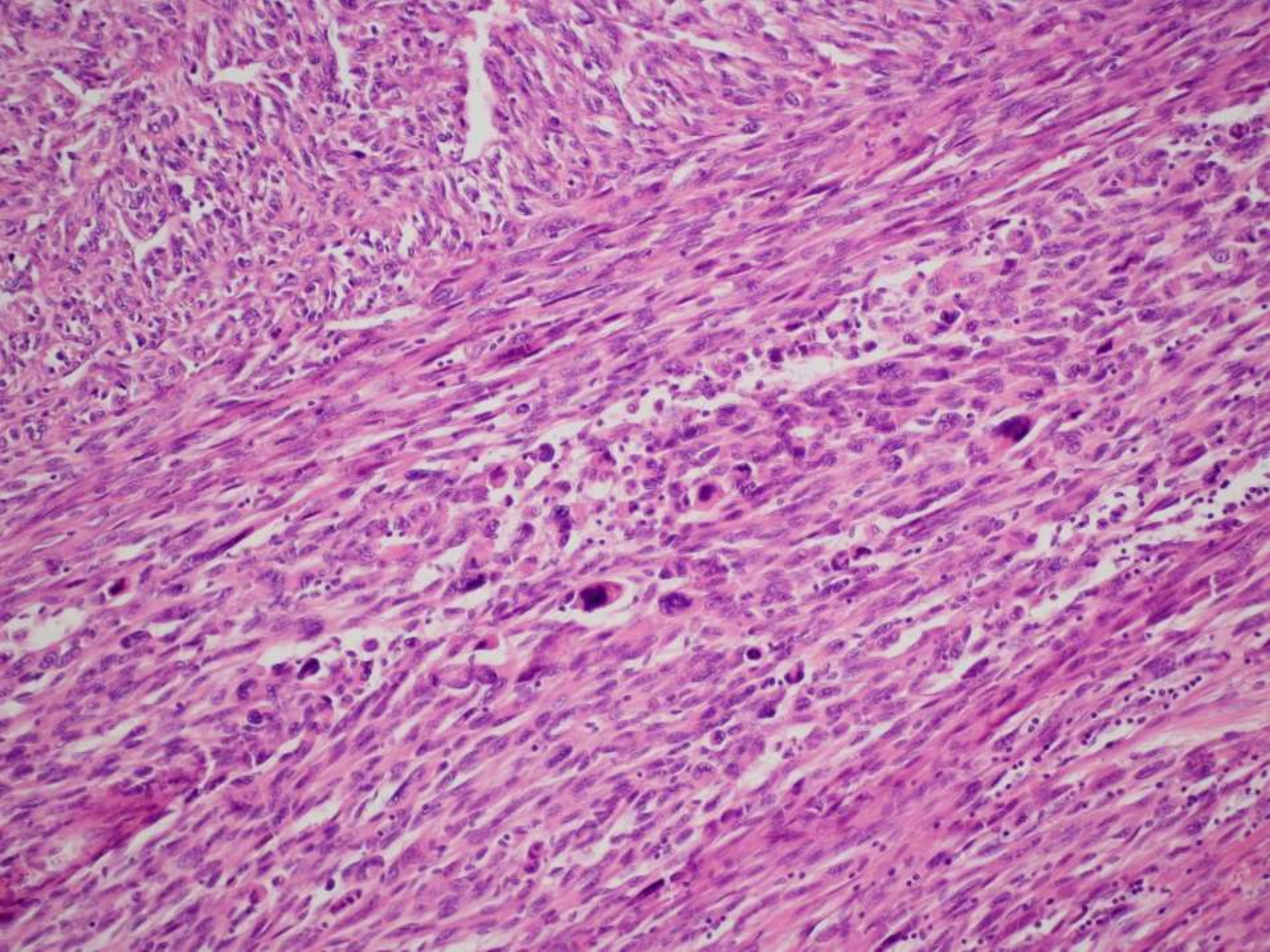
Virchows Archiv
https://doi.org/10.1007/s00428-018-2428-8

ORIGINAL ARTICLE

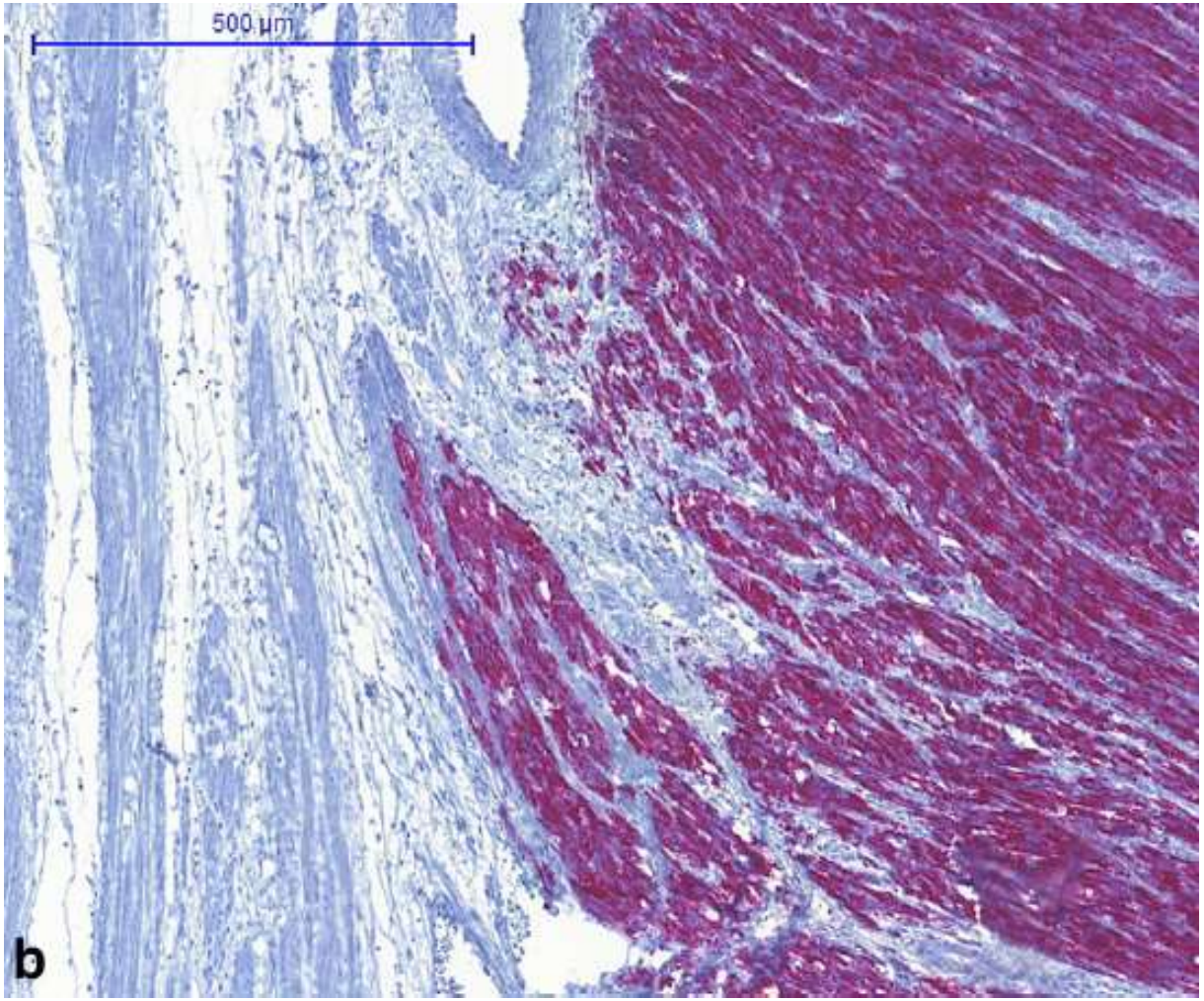
Immunohistochemical and selected genetic reflex testing of all uterine leiomyosarcomas and STUMPs for ALK gene rearrangement may provide an effective screening tool in identifying uterine ALK-rearranged mesenchymal tumors

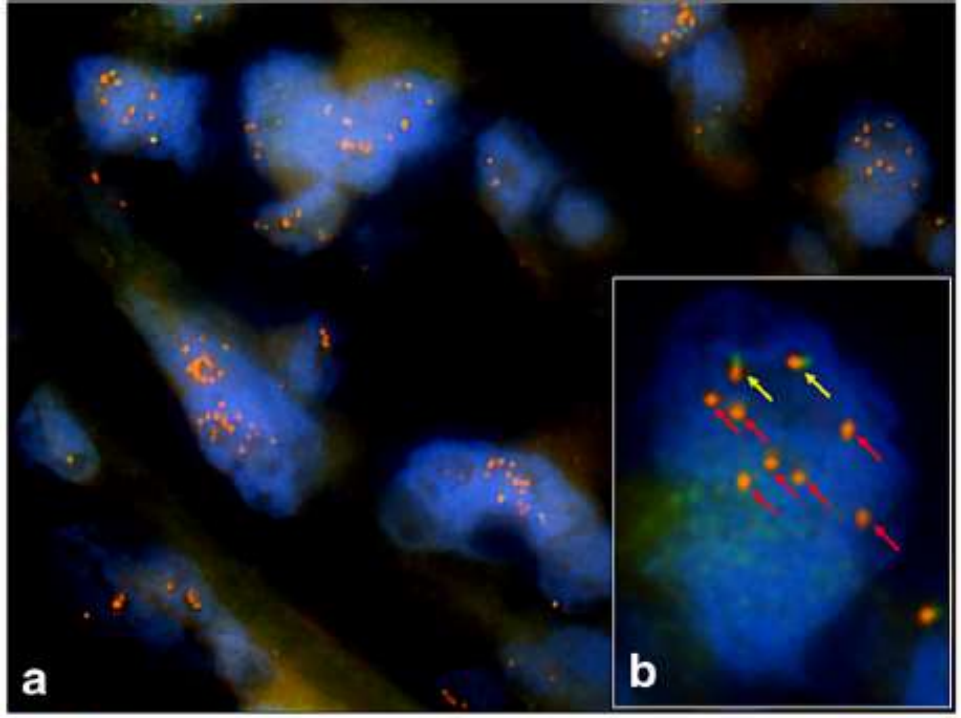
Nikola Ptáková[1,2] · Markéta Miesbauerová[1,2] · Ján Kosťun[3] · Petr Grossmann[1,2] · Henrieta Šidlová[4,5] · Jaroslav Pavelka[2,6] · Jiří Presl[3] · Reza Alaghehbandan[7] · Jiří Bouda[3] · Ondrej Ondič[1,2]





Exprese ALK

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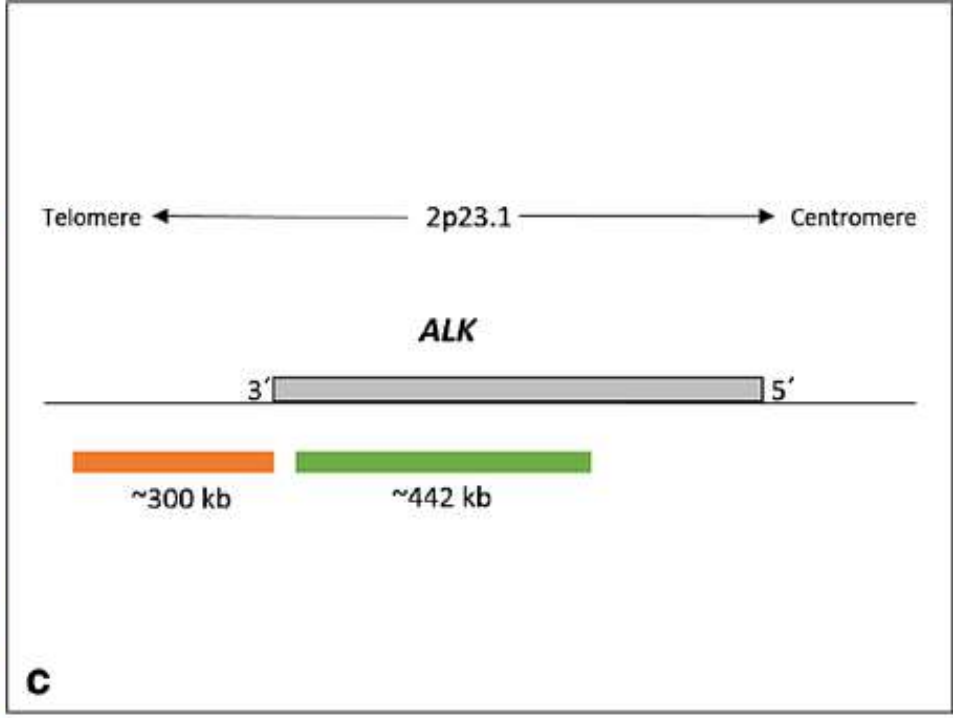
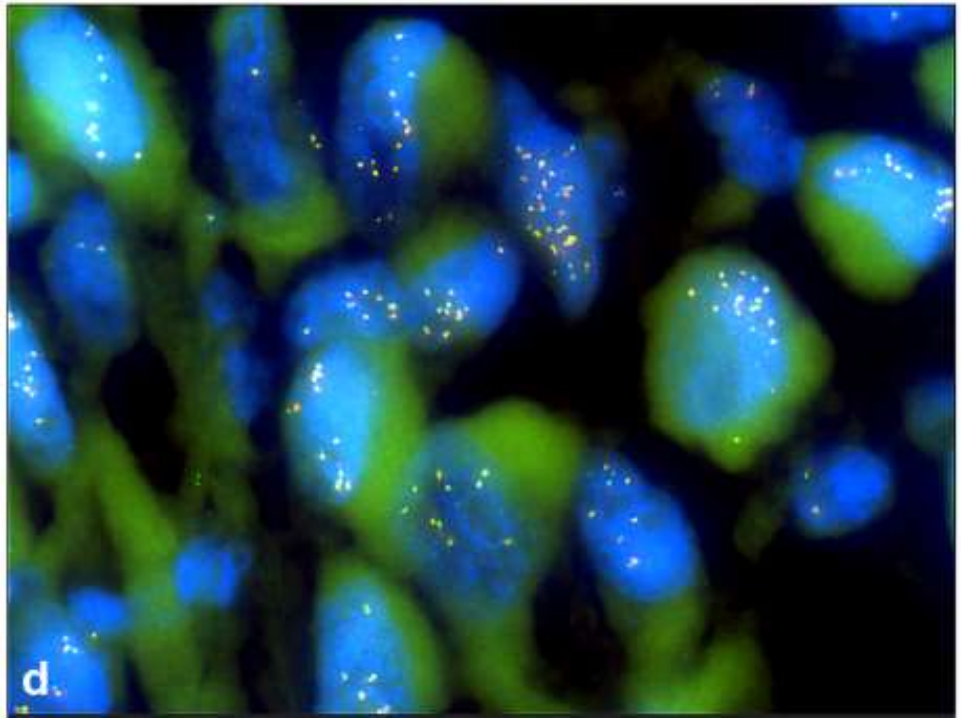
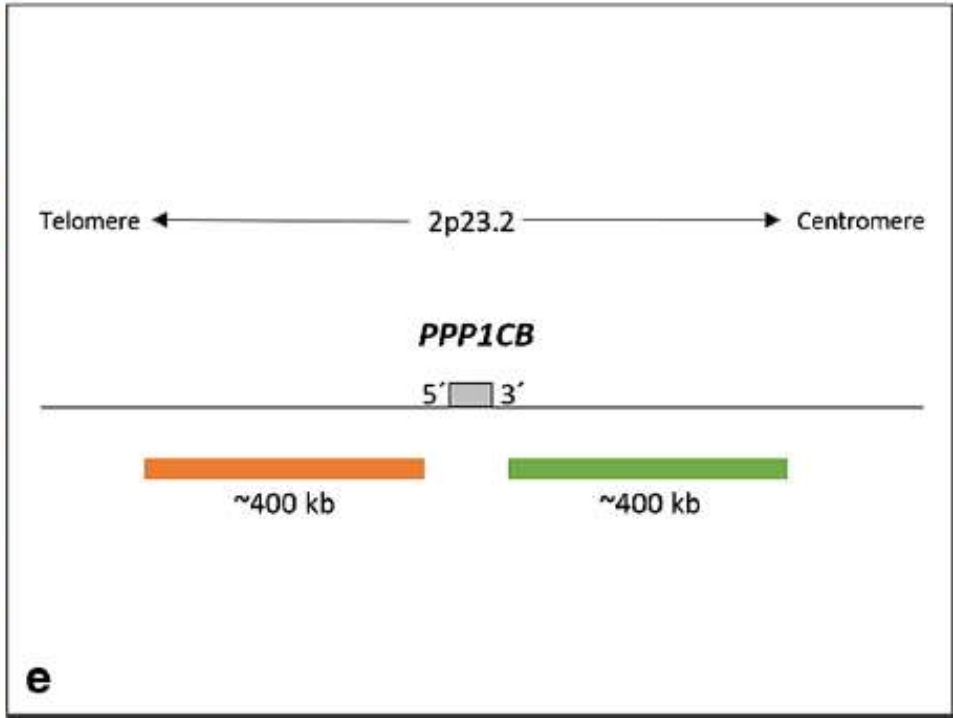
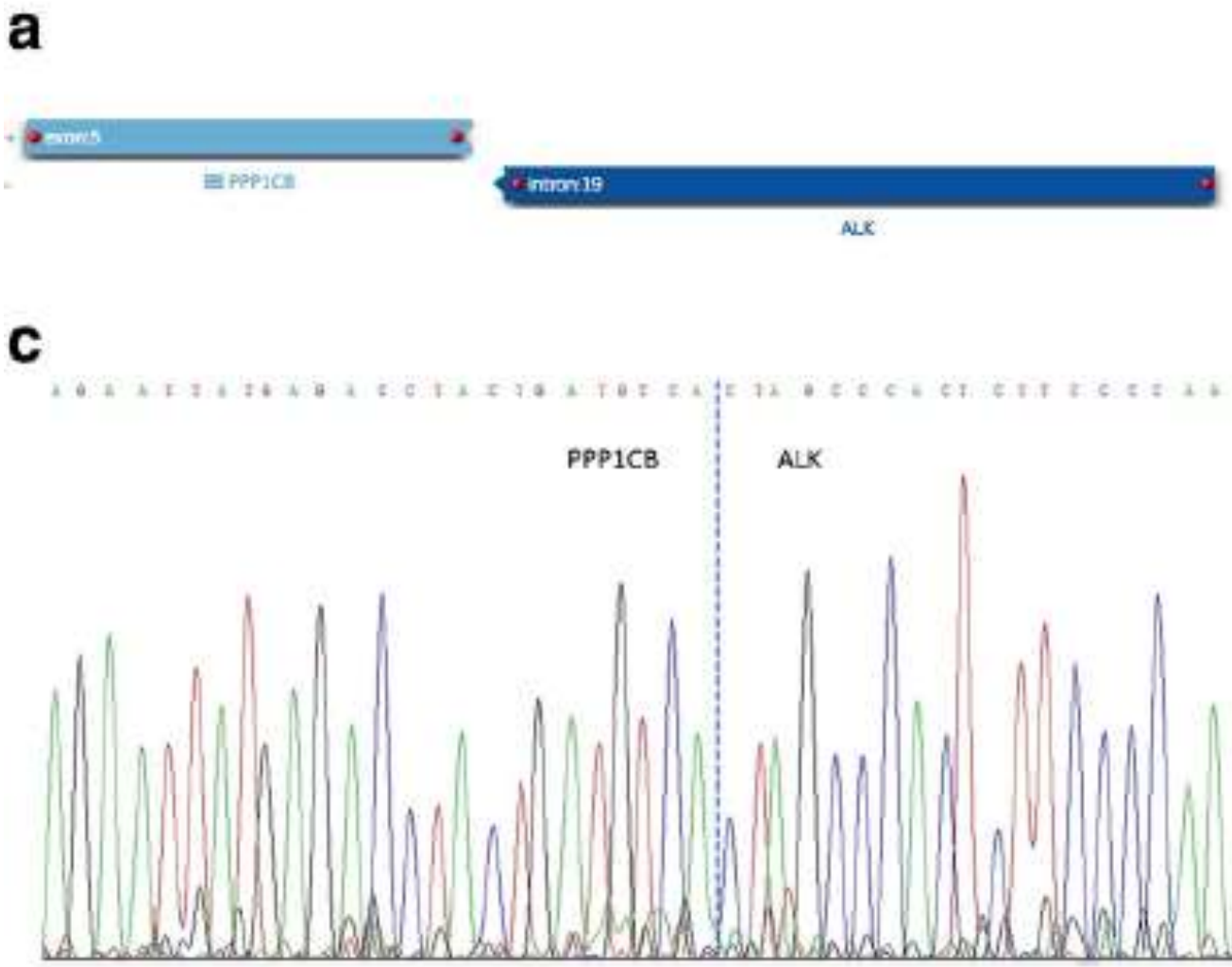

Telomere
2p23.1
Centromere
ALK
3′
5′
~300 kb
~442 kb
c


d


Telomere
2p23.2
Centromere
PPP1CB
5′
3′
~400 kb
~400 kb
e

Fúzní transkript: PPP1CB-ALK



Inflamatórny myofibroblastický tumor – identifikace případů

- Rutinní analýza exprese **ALK** u **leiomyosarkomů a STUMP**.
- Následné potvrzení metodami molekulárni genetiky.

Léčba IMT dělohy - crizotinib

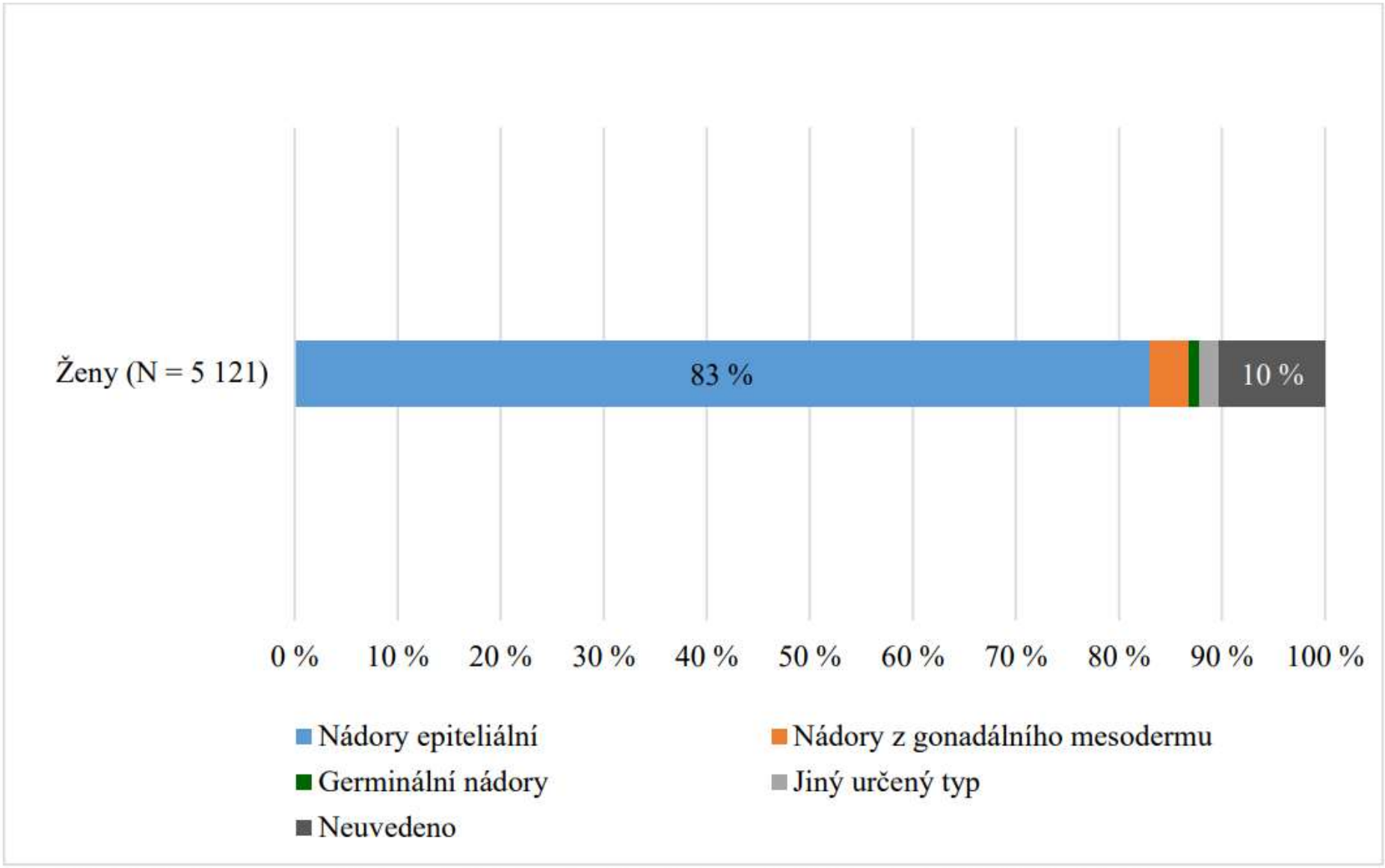
- Vivek Subbiah, Caitlin McMahon, Shreyaskumar Patel, Ralph Zinner, Elvio G Silva, Julia A. Elvin, Ishwaria M. Subbiah, Chimela Ohaji, Dhakshina Moorthy Ganeshan, Deepa Anand, Charles F. Levenback, Jenny Berry, Tim Brennan, Juliann Chmielecki, Zachary R. Chalmers, John Mayfield, Vincent A. Miller, Philip J. Stephens, Jeffrey S. Ross, and Siraj M. Ali (**2015)** STUMP un“"stumped”": anti-tumor response to anaplastic lymphoma kinase (ALK) inhibitor based targeted therapy in uterine inflammatory myofibroblastic tumor with myxoid features harboring DCTN1-ALK fusion. J Hematol Oncol. Jun 11;8:66. doi: 10.1186/s13045-015-0160-2.

- Pickett JL, Chou A, Andrici JA, Clarkson A, Sioson L, Sheen A, Reagh J, Najdawi F, Kim Y, Riley D, Maidens J, Nevell D, McIlroy K, Valmadre S, Gard G, Hogg R, Turchini J, Robertson G, Friedlander M, Gill AJ. (**2017**) Inflammatory mMyofibroblastic tTumors of the fFemale gGenital tTract aAre uUnder-recognized: aA lLow tThreshold for ALK iImmunohistochemistry iIs rRequired. Am J Surg Pathol 41:1433–-1442. doi: 10.1097/PAS.0000000000000909.

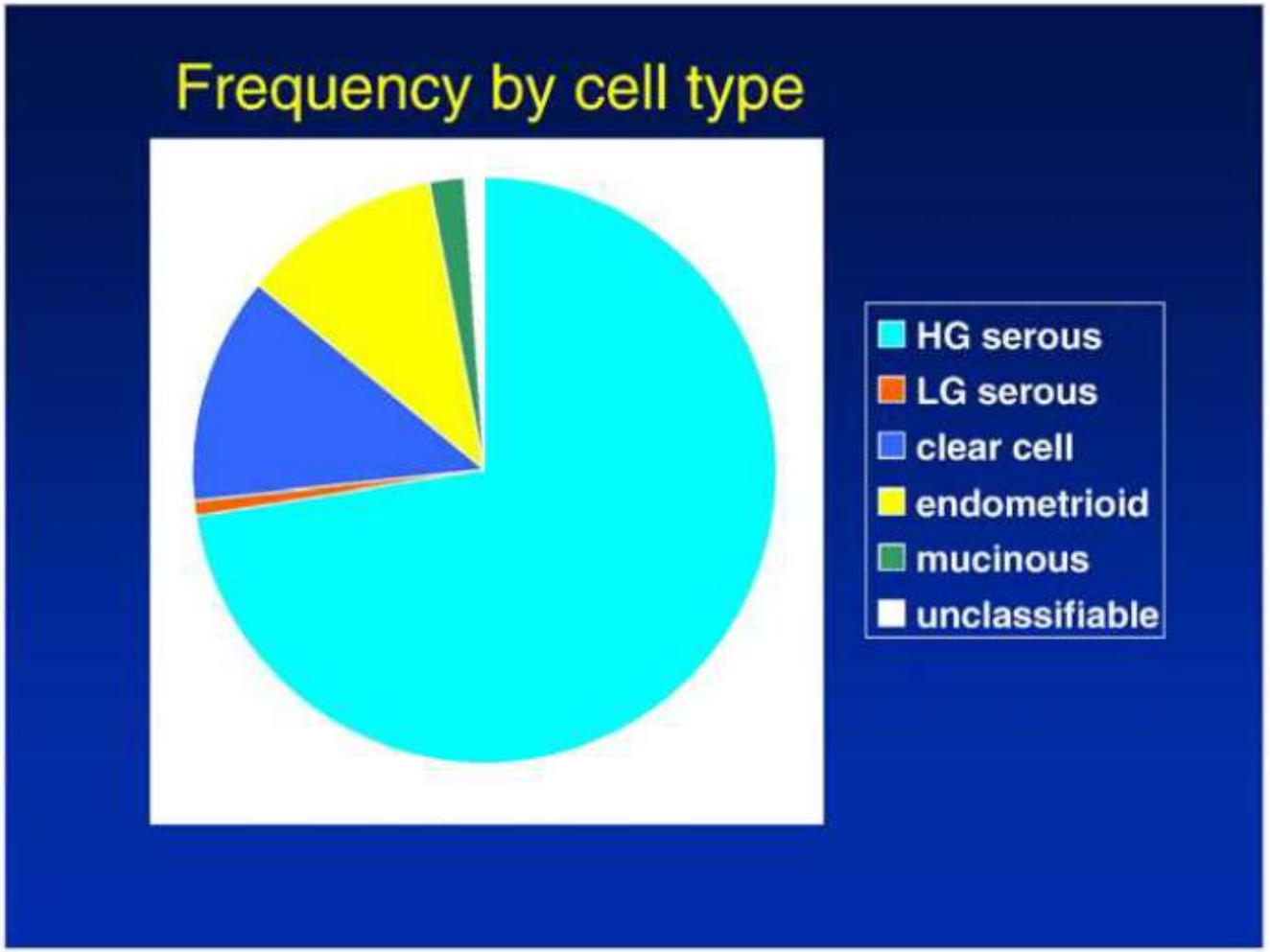
- Devereaux K, Kunder CH, Longacre T. (**2018**) ALK-rearranged Tumors are Highly Enriched in the STUMP Subcategory of Uterine Tumors AJSP: May 22; doi: 10.1097/PAS.0000000000001083.

Většina sarkomů a mezenchymálnich nádorů FGS by měla být sekvenována metodou
mRNA NGS

Ovárium



Graf 3.19.9: Zastoupení hlavních histologických typů C56, období 2013–2017



Gilks and Prat. Human Pathology (2009) 40, 1213–1223

Klasifikace nádorů z povrchového epitelu

Histologický TYP

- Serous
- Mucinous
- Endometroid
- Clear cell
- Seromucinous
- Brenner

Dignita

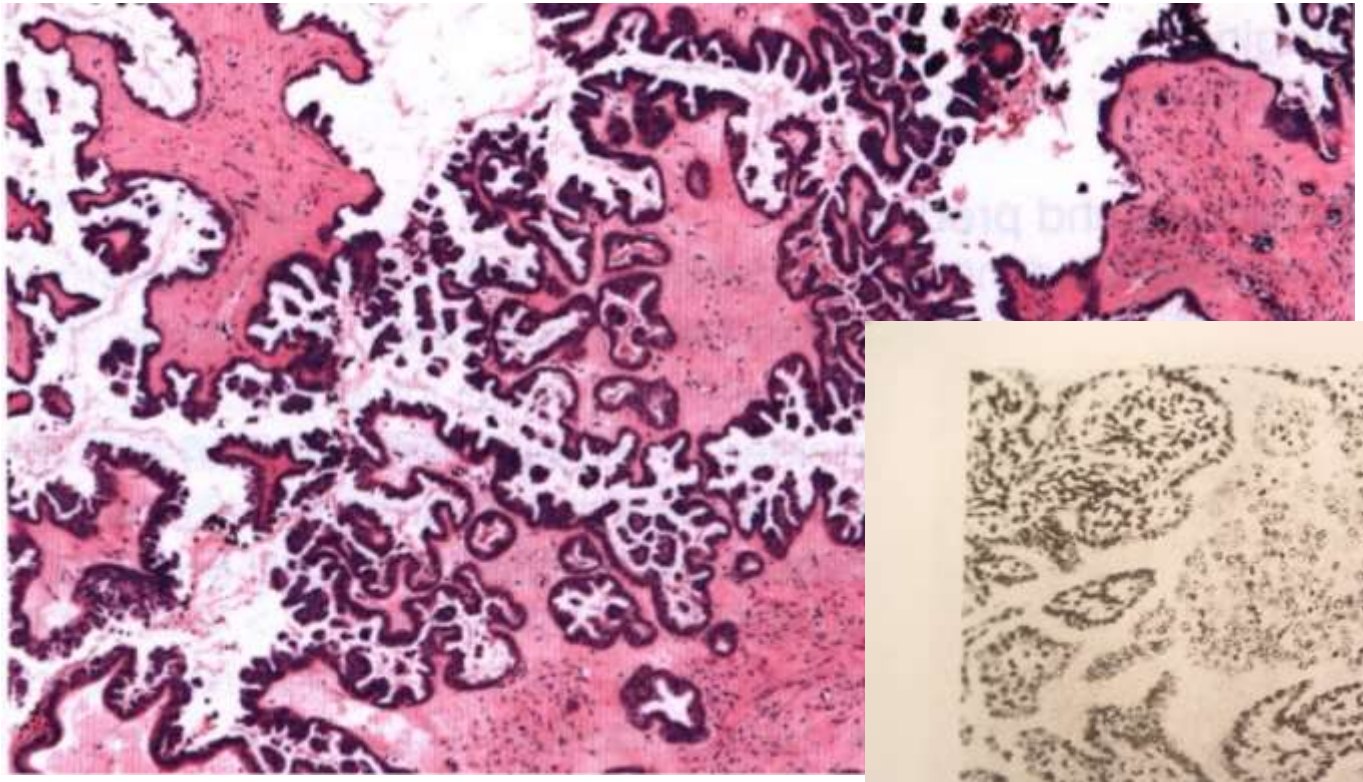
- Cystadenoma

(nad 1 cm)

- Cystadenofibroma
- Borderline
- Adenocarcinoma

(except seromucinous)

Serous borderline tumor



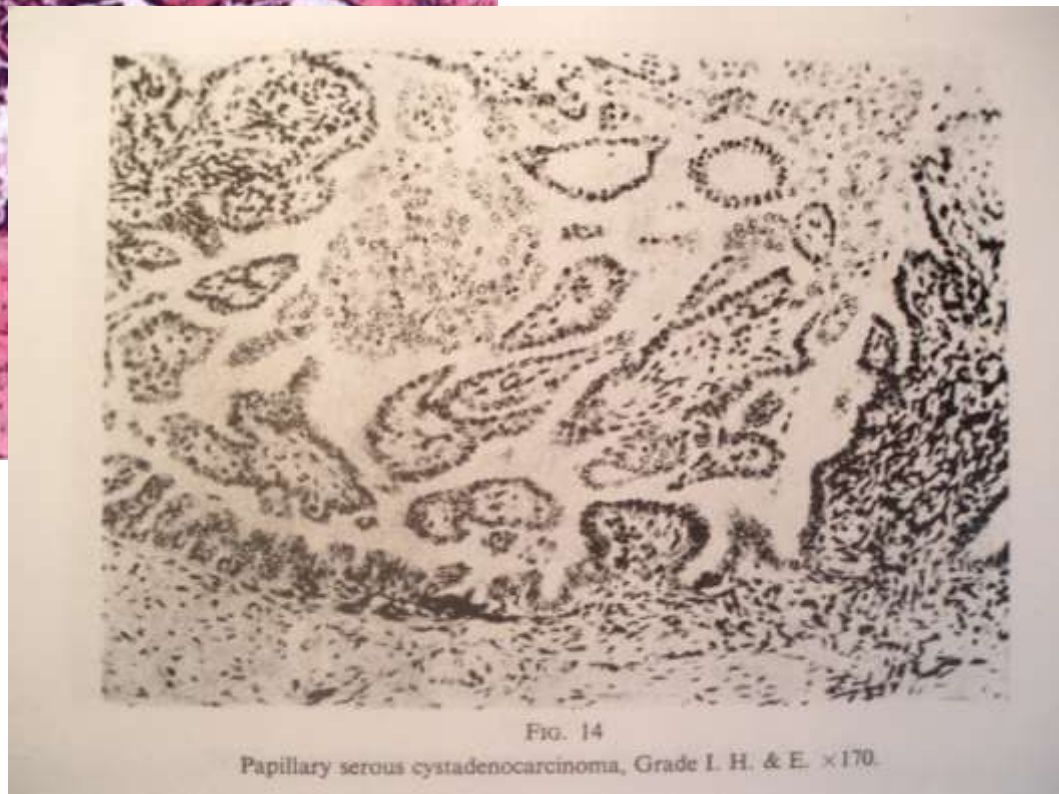


FIG. 14

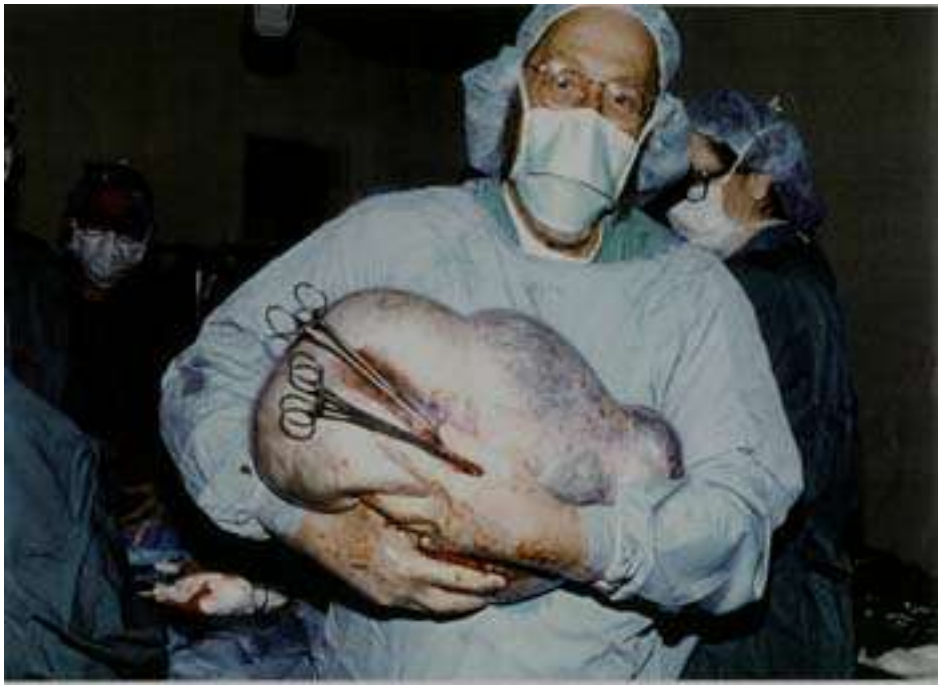
Papillary serous cystadenocarcinoma, Grade I. H. & E. ×170.

SBOT

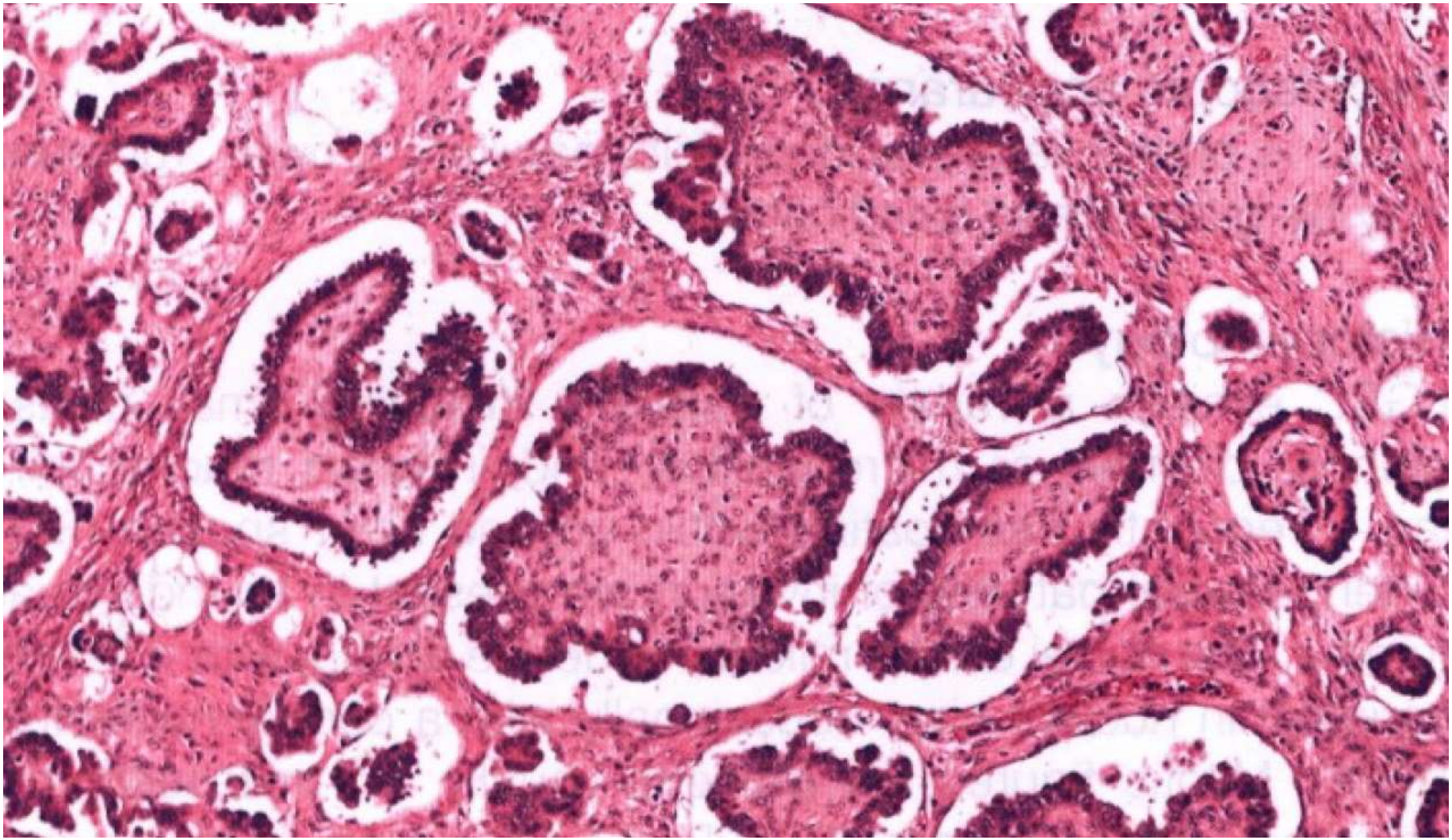
- Serózni borderline tumor
- Nádor bez invaze. Implanty jsou neinvazivní.
- Mutace genu **KRAS** –prognostický význam: její **absence je příznivým znakem**.
- Mikroinvaze (méně než 5 mm – sampling ???) význam nejasný, většinou není nepříznivý.
- Uzliny – subkapsulárně (odlišení od inkluzí!?) není nepříznivý znak, stage N1.

Tsang YT, Deavers MT, Sun CC et al. KRAS (but not BRAF) mutations in ovarian serous borderline tumour are associated with recurrent low-grade serous carcinoma. J Pathol 2013; 231(4): 449–456.

Problém samplingu



LGSCA histologie



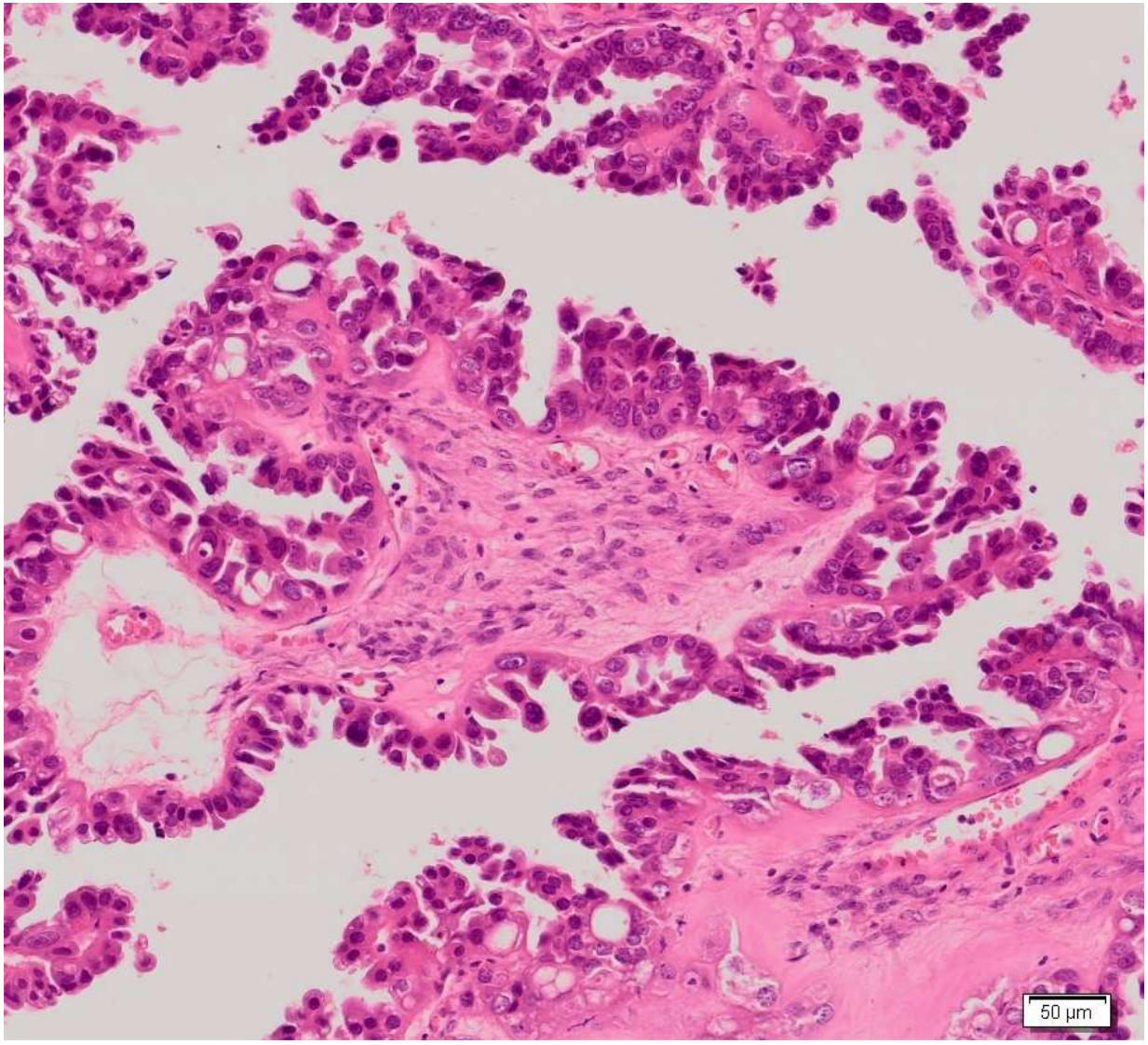
Low grade serous carcinoma

- Je invaze. Jsou invazivní implanty.
- Prognóza (stage II-IV):

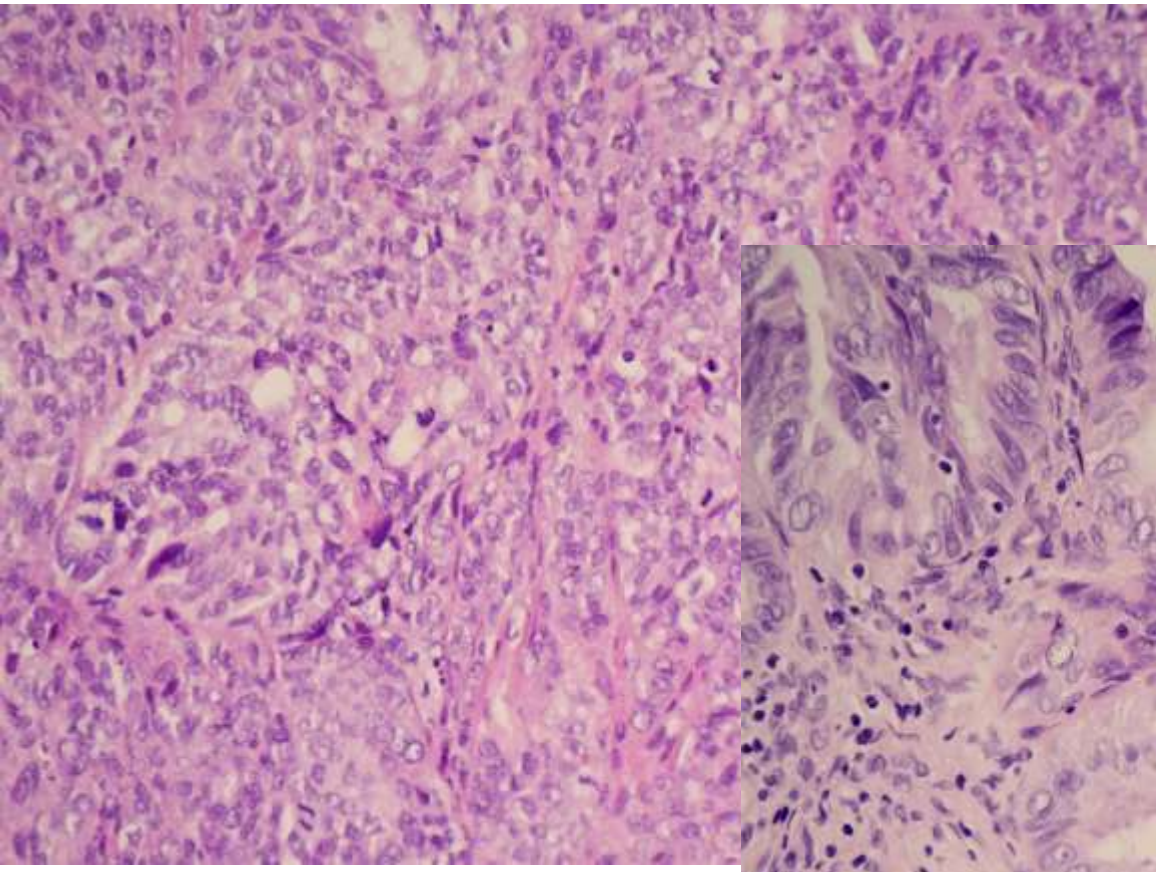
Median Progression free 28 m,

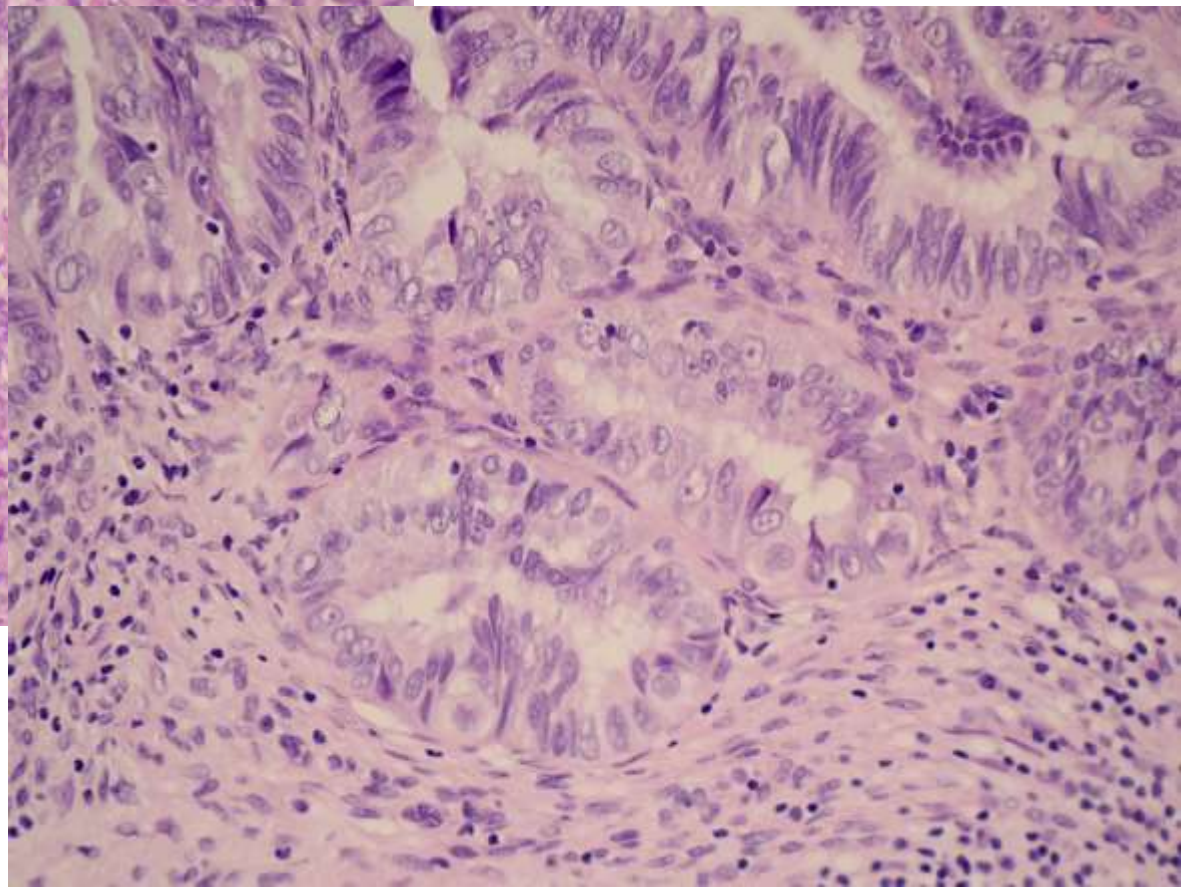
Median Overall survival 100 m.

High grade serous carcinoma



MUTACE BRCA1,2 - SET pattern (solid , endometrioid, transitional)





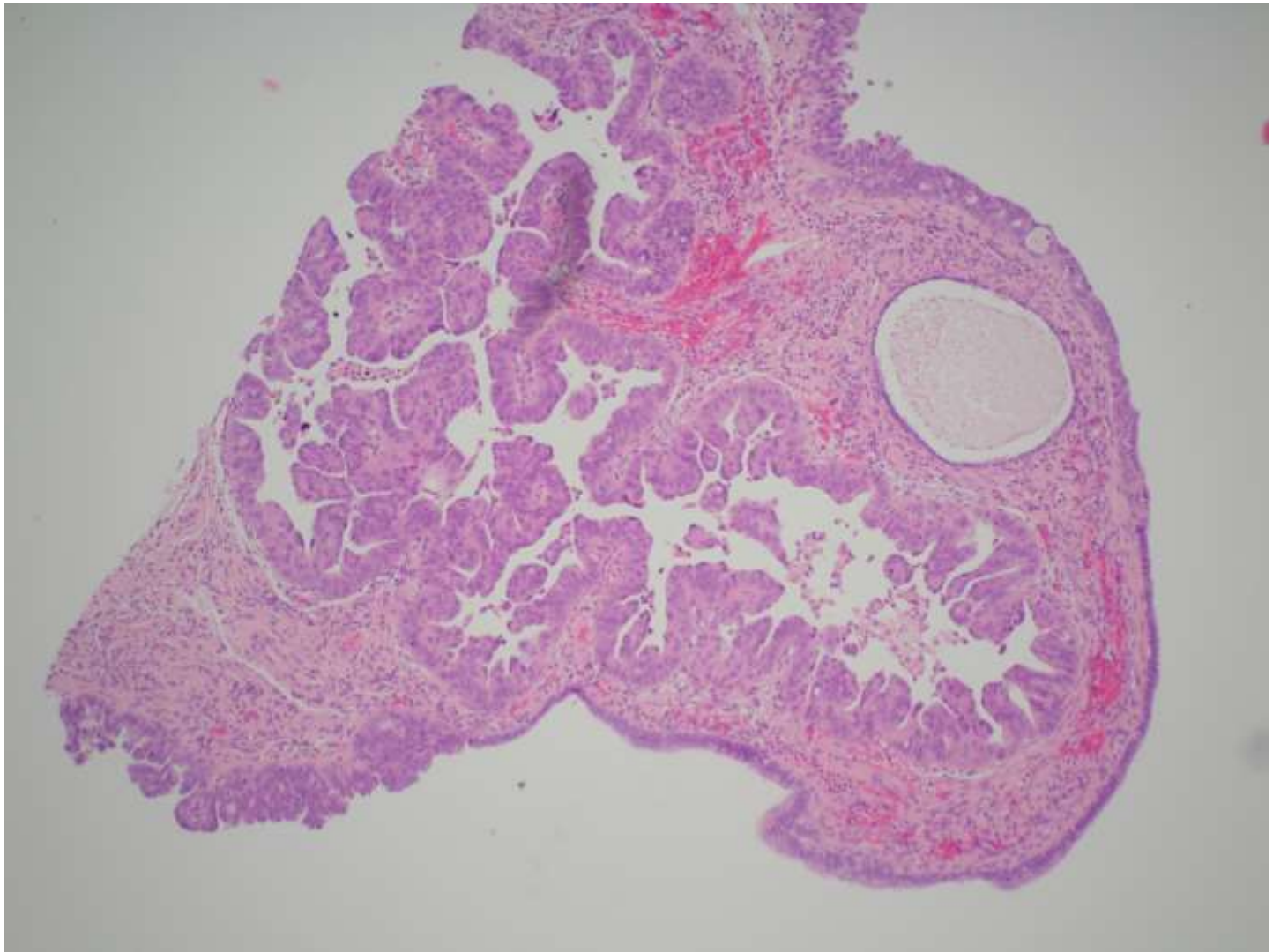
- Mutace BRCA1, BRCA2 je

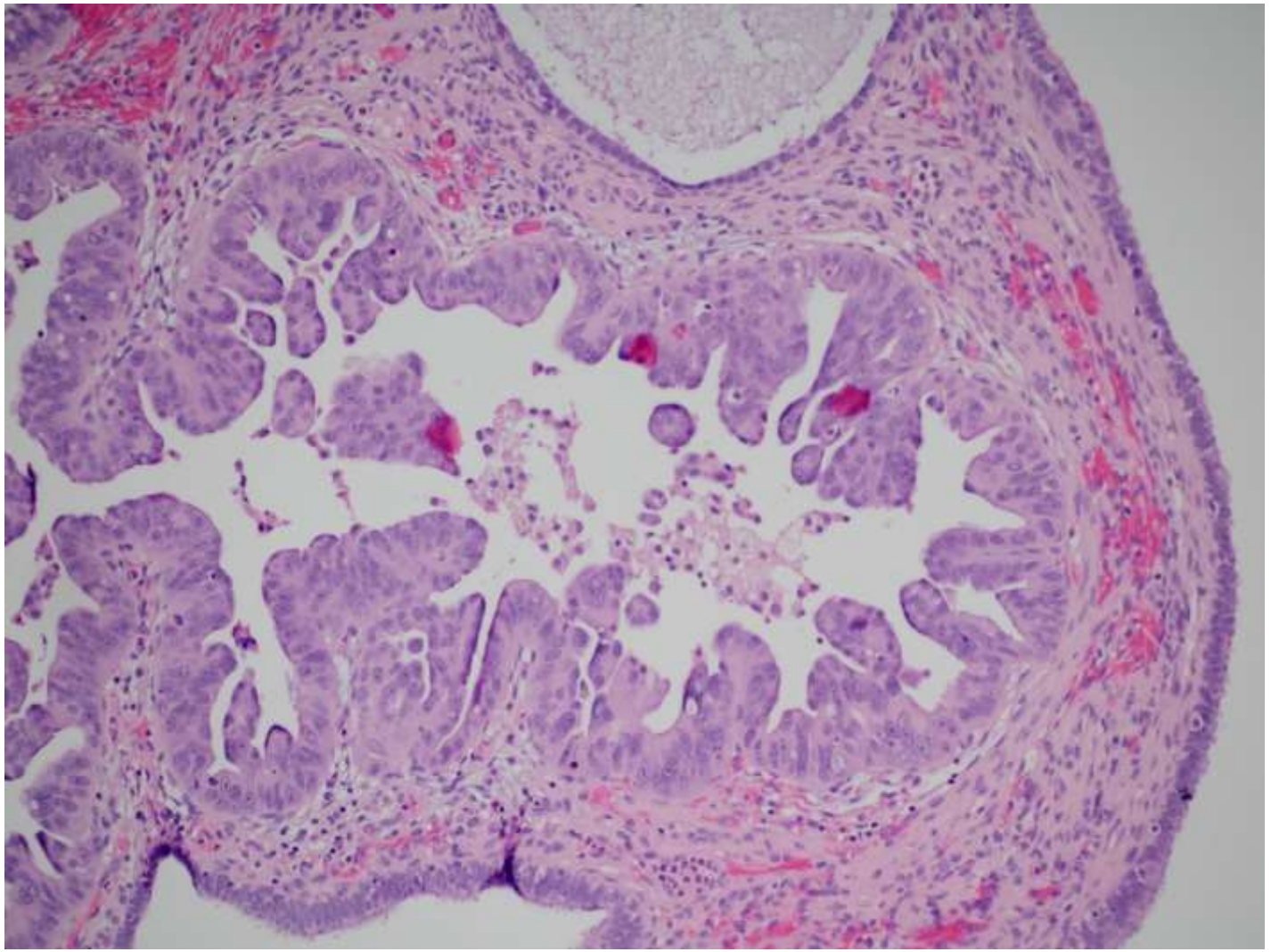
u cca 15% HGSCA

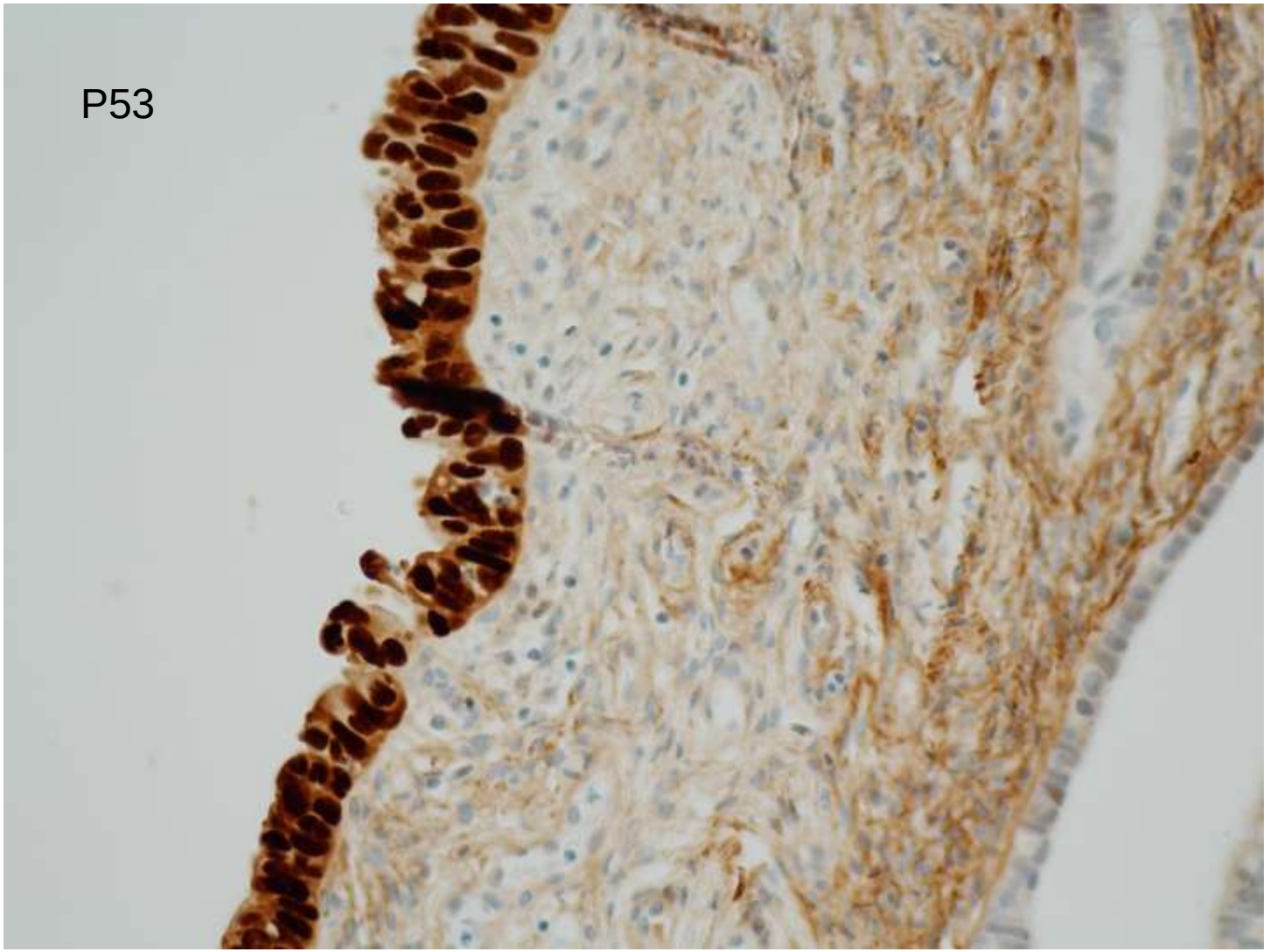
- Méně než 1% (mutace RAD51C/D, BRIP, metylace (somatická) BRCA1,2)
- Léčba PARP inhibitory s vynikající dlouhodobou odpovědí u cca 10-15 % pac.
- Genetické poradenství

Prekurzorova leze STIC -

Fimbrie tuby - STIC






P53

Sex cord stromálni tumory

- Geneticky definované jednotky

Germinální nádory

- Vzácne, rozhodující je STAGE
- Dysgerminom 10-leté přežití 90% pac.
- Yolk sack tumor – rekapituluje extraembryonální struktury
- Embryonální karcinom – high grade malignita
- Smíšené germinální nádory (nejčastěji dysgerminom+Yolk sack)
- Gonadoblastom: dívky, mladé ženy s dysgenetickými gonádami

Nezralý teratom

- Obsahuje nezralou neuroektodermální buněčnou populaci

- **Grading** (podle objemu této komponenty)

- **Staging:**
- Stage I – příznivá prognóza.
- Pozor na gliomatózu peritonea – formálně stage 3, ale biologicky indolentní.

Monodermal teratomas and somatic-type tumors arising from dermoid cyst

- Struma ovarii
- Ovarian carcinoid
- Neuroectodermal-type tumors
- Monodermal cystic teratoma
- Somatic neoplasms arising from teratoma

Germinálni a sex-cord tumory: Vyjmenované maligní jednotky

1 Adult granulosa cell tumor recidiva i po 10-20 letech /bodové mutace FOXL2; histologické znaky nemají prognostický význam. (Juvenilní GCT nemá mutaci FOXL2 a je řazen mezi tumory s nejistým maligním potenciálem, odvislým od stage)

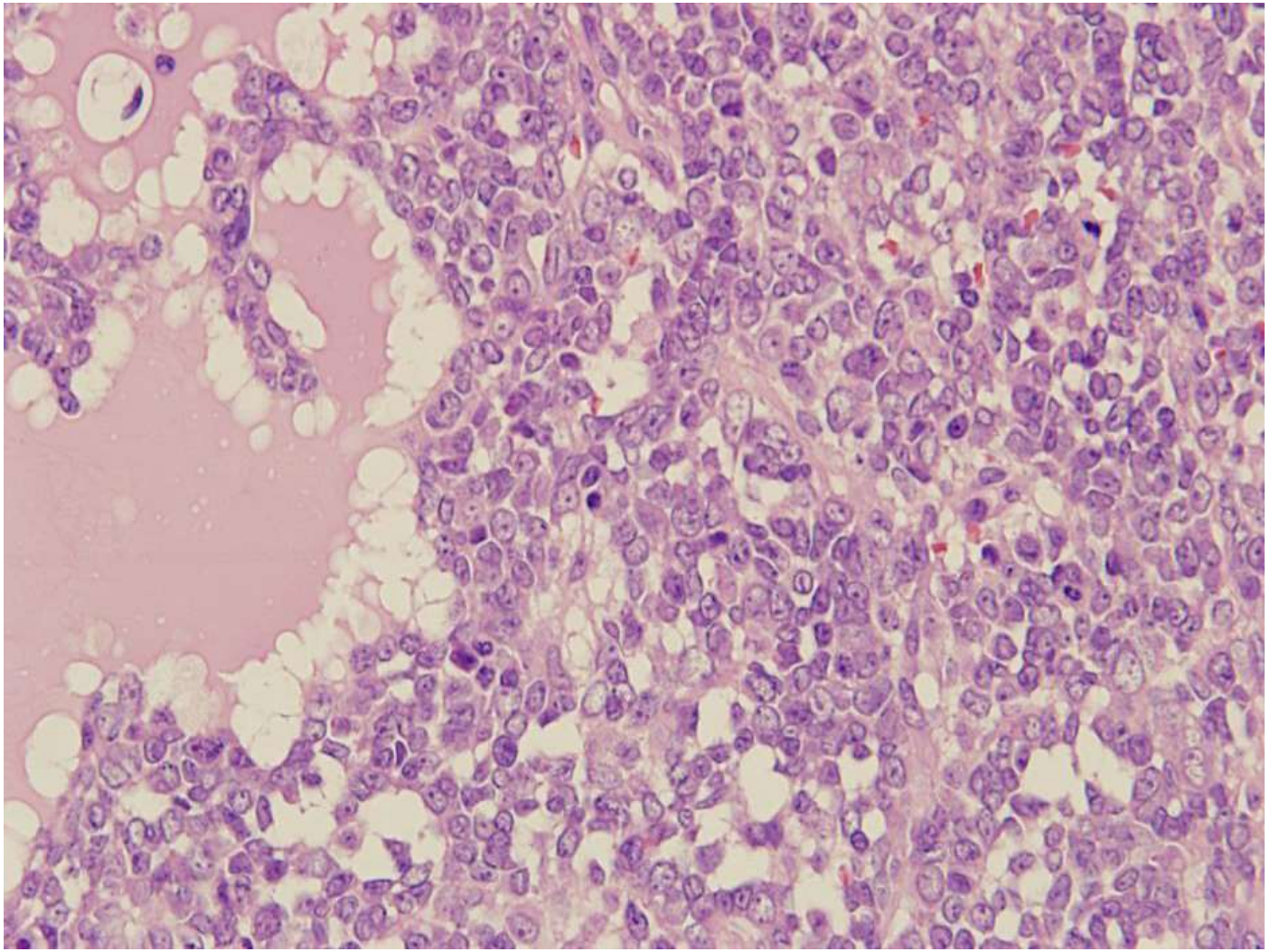
2 Sertoli-Leydig cell tumor grade 2,3- DICER1;

3. Nezralý teratom (viz výše)

4. Ovariálni karcinoid (mucinózni a insulárni nebo nízce diferencovaný)

5. Steroid cell tumor (1/3 případů)

Small cell carcinoma of the ovary, hypercalcemic type

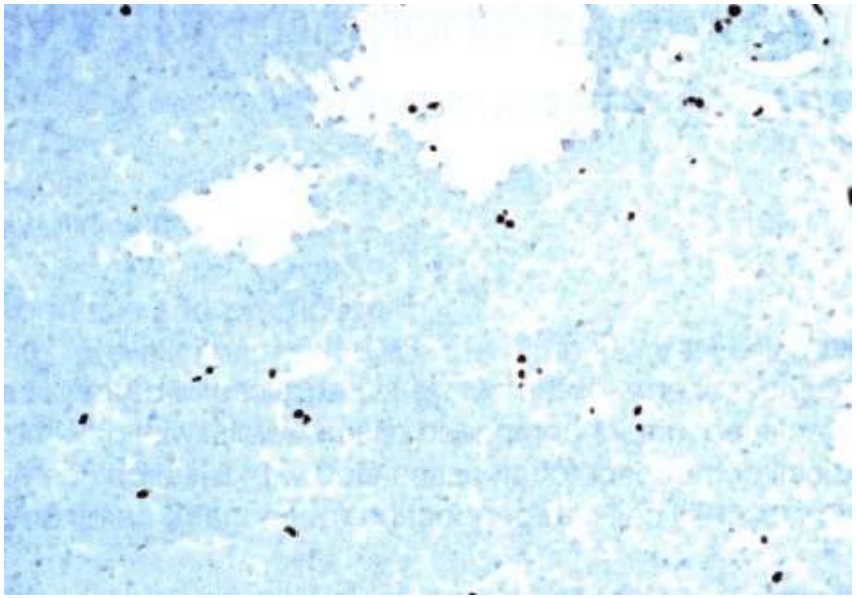


Small cell carcinoma of the ovary, hypercalcemic type

- Mladé ženy, hyperkalémie, špatná prognóza
- Výpadek exprese proteinu BRG1 (gen SMARCA4) z důvodu mutace.
- Dysfunkce SWI/SNF komplexu.

BRG1

- Plní úlohy při remodelaci chromatinu



Nádory a možné syndromy

Nádory a možné syndromy

orgán	nádor	syndrom
čípek	mezenchymálni nádory	Carney
	gastric endocervical adenocarcinoma	Peutz-Jeghers
	embryonálni rhabdomyosarkom	DICER1
	myxoidní leiomyom	Carney
děloha	PECom	Tuberózni skleróza
	endometroidní karcinom (gr 1)	Lynch, Cowden
	lymphangioleiomyomatosis	Tuberózni skleróza
	FH deficit. Leioyom	HLRCC
	high grade serózni karcinom	BRCA
ovárium	endometroidní karcinom	Lynch
	sex cord tumor with anular tubules (SCTAT)	Peutz-Jeghers
	dysgerminoma	ataxia-teleangiectasia (AT)
	gonadoblastoma	ataxia-teleangiectasia (AT), Ovariální dysgenéza
	Yolk sack tumor	ataxia-teleangiectasia (AT)
	Sertoli-Leydig cell tumor grade 2,3	DICER 1
	fibrom	Basal cell carcinoma sy (Gorlin sy)
	Ovarian hypercalcemic small cell CA	SMARCA4
široký vaz	papilárni cystadenom	vHL
vejcovod	papilom	vHL

Kdyby ste později narazily na nesrovnalosti, dejte mi prosím vědět. Nepochybně, vždy lze něco vylepšit.

ondic@biopticka.cz

Děkuji za pozornost