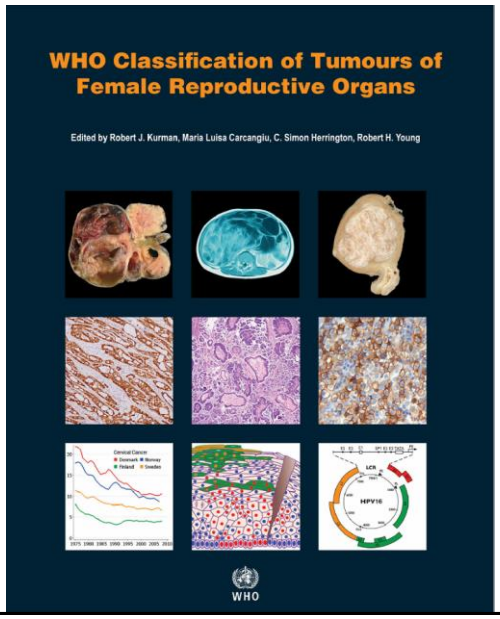
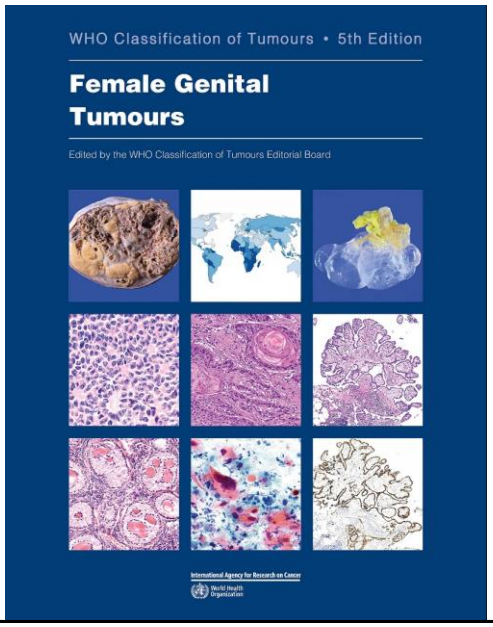
Молекулярная классификация и дифференциальная диагностика эпителиальных опухолей тела матки

А.С. Артемьева

2014



2020

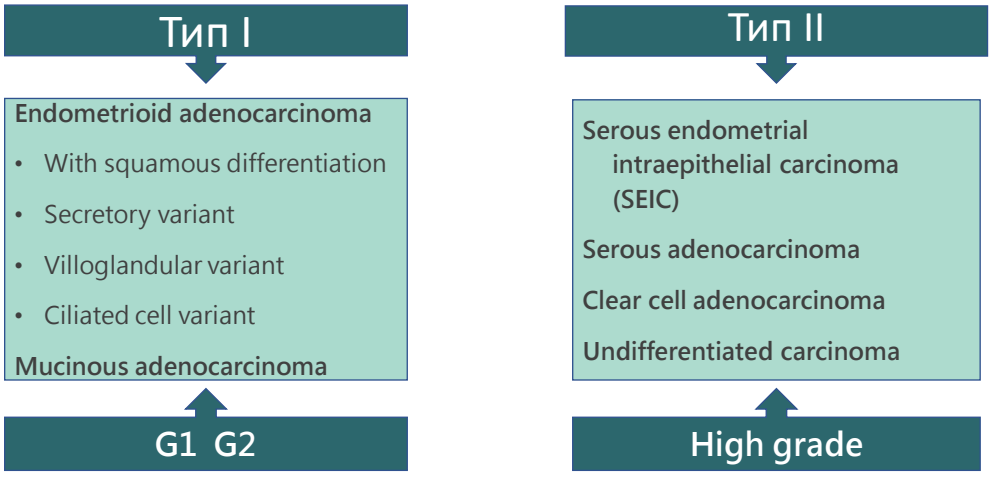


WHO classification

2014
- Endometrioid Ca
- Mucinous Ca
- Serous endometrial intraepithelial Ca
- Serous Ca
- Clear cell Ca
- Neroendocrine tumours
- Mixed cell adenoCa
- Undifferentiated Ca
- Dedifferentiated Ca

2020
- Endometrioid
- Serous
- Clear cell
- Undifferentiated and dedifferentiated
- Mixed
- Carcinosarcoma
- Other:
  Mesonephric adenocarcinoma
  Squamous cell carcinoma NOS
  Mucinous carcinoma, gastric (gastrointestinal)–type
  Mesonephric-like adenocarcinoma)

Патогенетическая классификация 1983 - 2020



2014

Epithelial tumours and precursors
Precursors
- Hyperplasia without atypia
- Atypical hyperplasia / Endometrioid intraepithelial neoplasia 8380/2*

Endometrial carcinomas
- Endometrioid carcinoma 8380/3
  - Squamous differentiation 8570/3
  - Villoglandular 8263/3
  - Secretory 8382/3
- Mucinous carcinoma 8480/3
- Serous endometrial intraepithelial carcinoma 8441/2*
- Serous carcinoma 8441/3
- Clear cell carcinoma 8310/3
- Neuroendocrine tumours
  - Low-grade neuroendocrine tumour
    - Carcinoid tumour 8240/3
  - High-grade neuroendocrine carcinoma
    - Small cell neuroendocrine carcinoma 8041/3
    - Large cell neuroendocrine carcinoma 8013/3
- Mixed cell adenocarcinoma 8323/3
- Undifferentiated carcinoma 8020/3
- Dedifferentiated carcinoma

Tumour-like lesions
- Polyp
- Metaplasias
- Arias-Stella reaction
- Lymphoma-like lesion

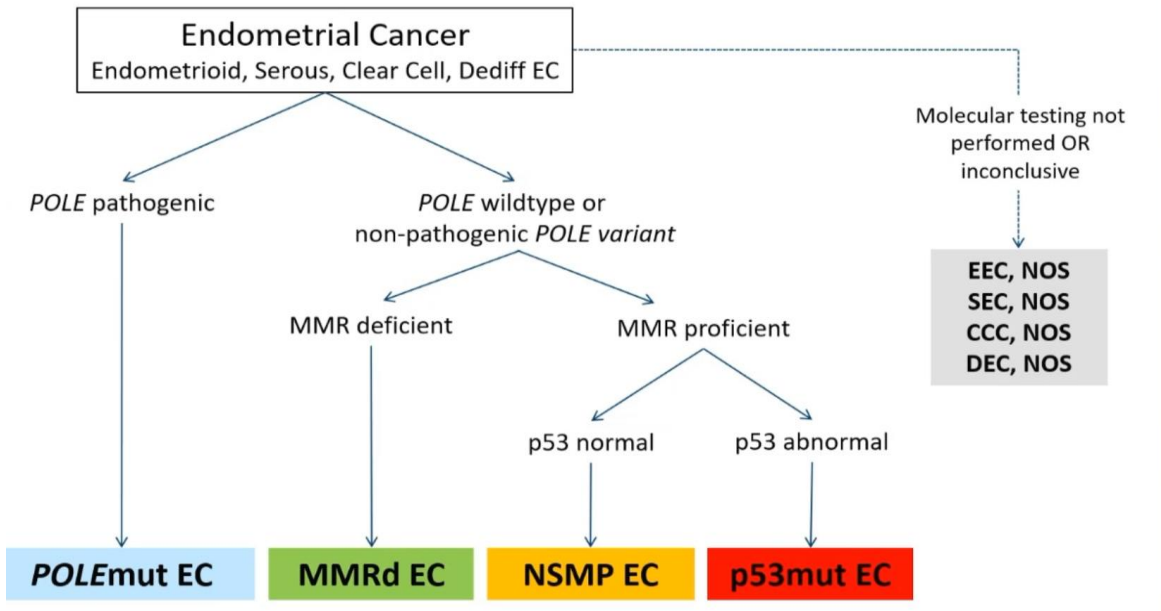
2020

Endometrial epithelial tumours and precursors
- Endometrial hyperplasia without atypia
- Atypical hyperplasia of the endometrium

8380/3 Endometrioid adenocarcinoma NOS
- *POLE*-ultramutated endometrioid carcinoma
- Mismatch repair–deficient endometrioid carcinoma
- p53-mutant endometrioid carcinoma
- No specific molecular profile (NSMP) endometrioid carcinoma

8441/3 Serous carcinoma NOS
8310/3 Clear cell adenocarcinoma NOS
8020/3 Carcinoma, undifferentiated, NOS
8323/3 Mixed cell adenocarcinoma
9110/3 Mesonephric adenocarcinoma
8070/3 Squamous cell carcinoma NOS
8144/3 Mucinous carcinoma, intestinal type
9111/3* Mesonephric-like adenocarcinoma
8980/3 Carcinosarcoma NOS

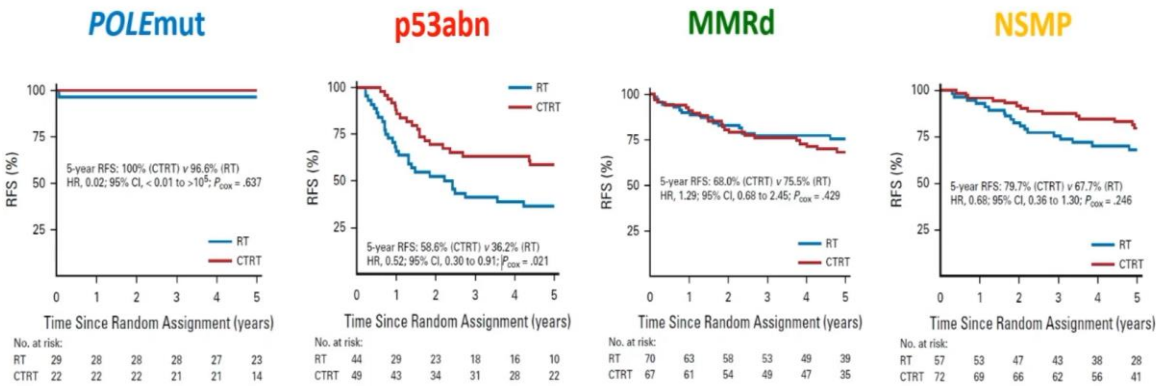
Tumour-like lesions
- Endometrial polyp
- Endometrial metaplasia
- Arias-Stella reaction



Adapted from Vermij et al; Histopathology 2020 (accepted)

	POLE-ultramutated EC	MMR-deficient EC	p53-mutant EC	NSMP EC
Associated molecular features	> 100 mutations/Mb, SCNA very low, MSS	10–100 mutations/Mb, SCNA low, MSI	< 10 mutations/Mb, SCNA high, MSS	< 10 mutations/Mb, SCNA low, MSS, 30–40% with *CTNNB1* mutations
Associated histological features	Often high-grade, ambiguous morphology with scattered tumour giant cells, prominent TILs	Often high-grade, prominent TILs, mucinous differentiation, MELF-type invasion, LVSI	Mostly high-grade with diffuse cytonuclear atypia; glandular and solid forms exist	Mostly low-grade with frequent squamous differentiation or morule, absence of TILs
Diagnostic tests	NGS / Sanger sequencing / hotspot analysis includes p.Pro286Arg, p.Val411Leu, p.Ser297Phe, p.Ala456Pro, and p.Ser459Phe	MMR-IHC: MLH1, MSH2, MSH6, and PMS2; MSI assay; NGS	p53-IHC: mutant-like staining[a]	MMR-proficient, p53-wildtype, and pathogenic *POLE* variant absent
Associated clinical features	Younger age at presentation	May be associated with Lynch syndrome	Advanced stage at presentation	Higher body mass index
Prognosis	Excellent	Intermediate	Poor	Intermediate to excellent

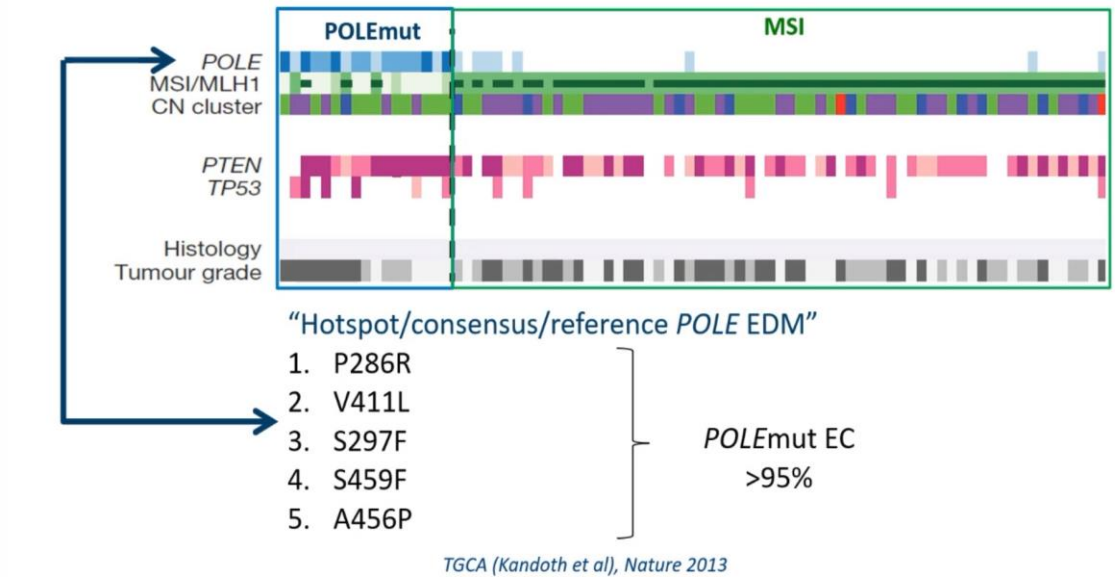
IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MELF, microcystic, elongated, and fragmented; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stability; NGS, next-generation sequencing; NSMP, no specific molecular profile; SCNA, somatic copy-number alteration; TIL, tumour-infiltrating lymphocyte.



Leon-Castillo et al., JCO 2020

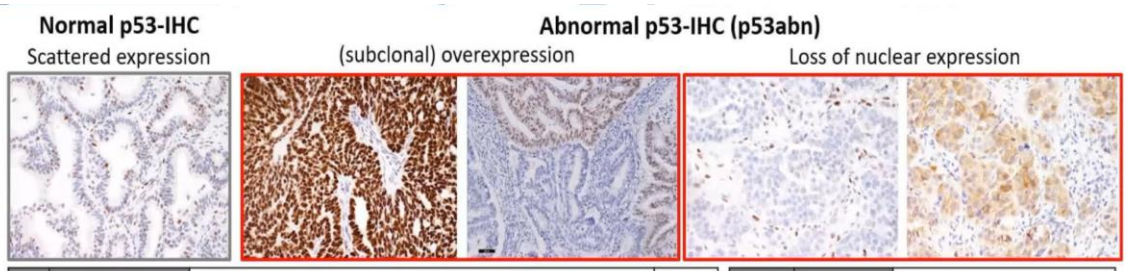
DNA Polymerase Epsilon Catalytic Subunit A

- более молодой возраст пациенток
- более низким индексом массы тела (ИМТ)
- более ранней стадией заболевания
- более благоприятный прогноз, несмотря на высокий grade опухоли.



Gene TP-53

- пожилой возраст пациенток
- нормальный индекс массы тела (ИМТ)
- продвинутые стадии заболевания
- серозноподобная (serous like) морфология опухоли
- неблагоприятный прогноз, независимо от grade или стадии в настоящее время.



		p53-IHC central					
		Normal	Overexpression	Absence	Cytopl	Subclonal	TOTAL
P53-IHC local	Normal	**68**	0	0	0	0	69
	Overexpression	1	**69**	0	1	0	72
	Absence	0	0	**14**	0	0	14
	Cytoplasmic	0	0	0	**1**	0	1
	Subclonal	1	0	0	0	**4**	5
	TOTAL	71	69	14	3	6	**164**

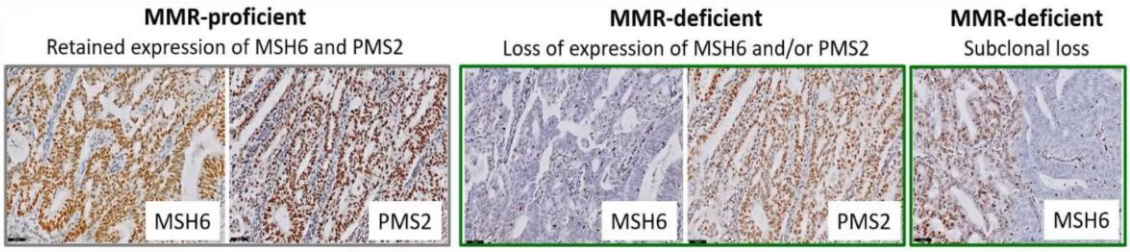
		TP53 mutation	
		Present	Absent
p53-IHC	Abnormal	**85**	4
	Normal	2	**32**
Sensitivity: 97.70% (95% CI 91.94% to 99.7%)			
Specificity: 88.89% (95% CI 73.94% to 96.89%)			
Accuracy: 95.12% (95% CI 89.68% to 98.19%)			

p53 IHC interpretation is reproducible, and an excellent surrogate marker for *TP53* mutations in EC with 95% accuracy

Singh et al., Journal of Pathology 2019, under consideration

DNA mismatch repair (MMR) system

- средний возраст пациенток
- высокий индексом массы тела (ИМТ)
- более ранней стадией заболевания
- имеют тенденцию к лимфоваскулярной инвазии и метастазированию.
- чаще встречаются в нижнем сегменте матки
- характерна высокая интратуморальная лимфоидная инфильтрация (TILs high)



Interobserver agreement κ=0.919 (95% CI, 0.863-0.976)[1]

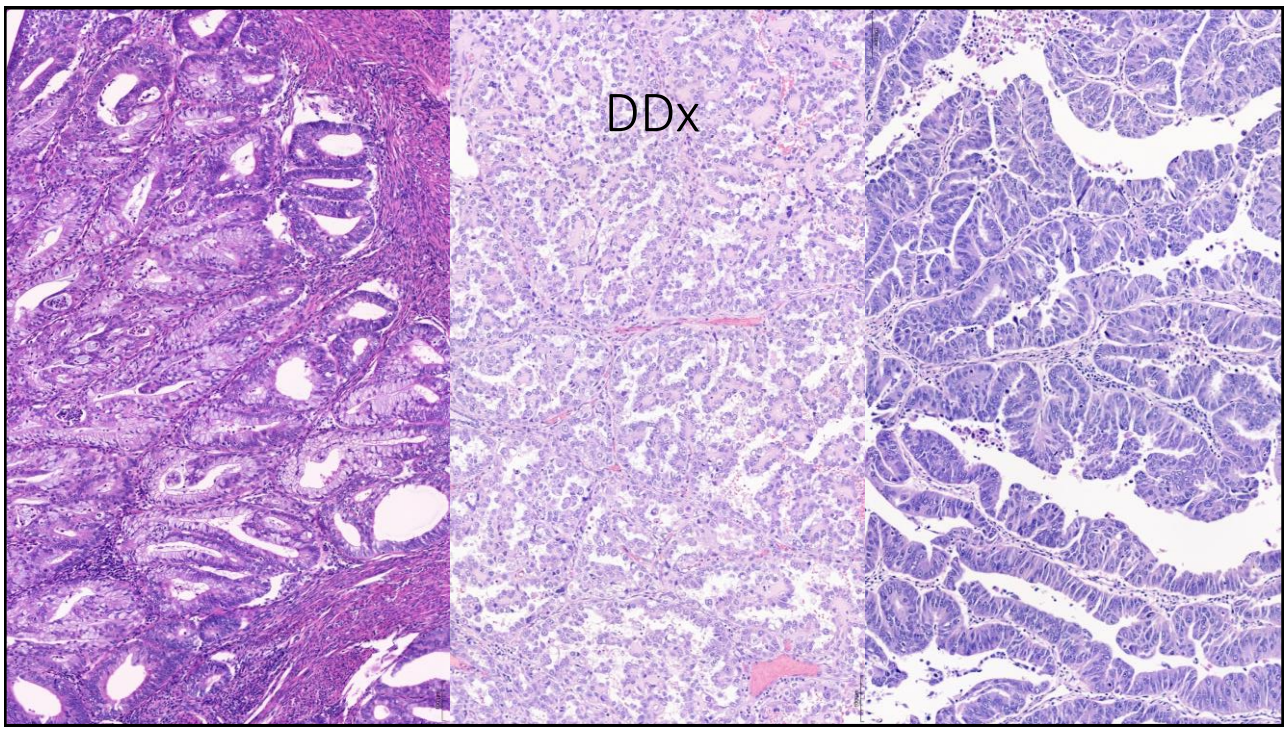
Study	Number of cases	Concordance with MSI
Stelloo et al., Annals of Onc 2016	696 ECs	95%
McConechy et al., GynOnc 2015	89 ECs	>93%
De Leeuw et al., JPath	31 LS-EC	94%
Chapusot et al., AJSP 2004	462 CRC	91%

MMR IHC interpretation is reproducible, and an excellent surrogate marker for MSI status in EC with 95% accuracy

[1]*Sari et al., Am J Surg Path 2019*

No specific molecular profile (p53 wt)

- составляет почти половину всех EC.
- средний возраст пациенток
- ожирение или высокий уровень эндогенного или экзогенного эстрогена
- большинство имеют низкий grade, встречаются на ранних стадиях
- в целом благоприятный прогноз



DDx

	EC	SC	CCC	UD/DD Ca
p53	mt 2-5% LG, 20% HG	mt	mt 22-72%	mt до 78%
p16	очагово	диффузно		
ER	+++	+	-	-
MMR	dMMR	pMMR	-	dMMR (50-66%)
PTEN	loss	wt	-	
other			Napsin A, AMACR	Loss E-cadherin, PAX-8, BRG1, INI1

Undifferentiated/dedifferentiated Ca

- EMA
- PAX8
- CK18
- E-cadherin
- ER, PR
- MMR
- BRG1
- INI1

DDx:

- High grade endometrial stromal Sa
- NEC
- Myeloid Sa
- Lymphoma
- Melanoma

*PTEN loss = 0% staining; †p53-aberrant/mutation-type = strong staining in > 80% tumor cells or absent staining; ‡p16 is positive if > 90% strong staining; §ER positive if > 50% staining; ||DNA MMR protein loss is 0% staining. Controls should be appropriate.

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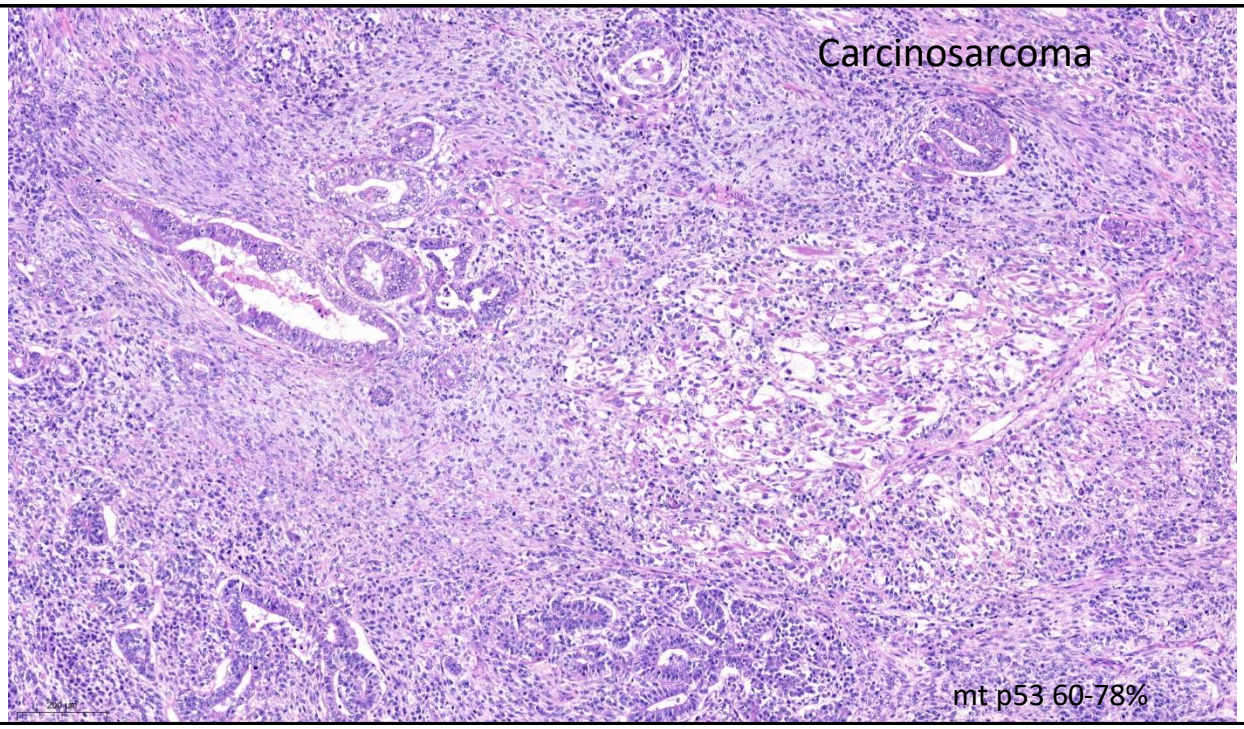
p53 Expression (Note F)

Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Endometrium

___ Normal expression
___ Abnormal strong diffuse overexpression (>90%)
___ Abnormal null expression (complete loss of expression)
___ Cannot be determined (explain): _____



Mixed cell carcinoma

- 2 и более компонентов, один из которых Serous Ca или Clear cell Ca
- Любое количество Serous Ca или Clear cell Ca
- Рекомендуется использовать ИГХ для подтверждения
- Репорт: указан каждый компонент, его grade и доля
- Общий grade 3 вне зависимость от доли Serous Ca или Clear cell Ca

- WHO classification of tumours of female reproductive organs
- AFIP atlas of tumor pathology: Tumors of the uterine corpus and trophoblastic diseases