ASGO Webinar Series #41

Understanding of New FIGO Staging of CA Endometrium

Distillation-Discussion

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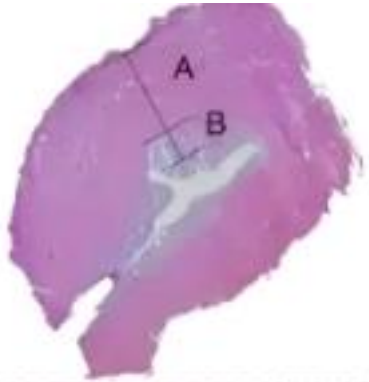
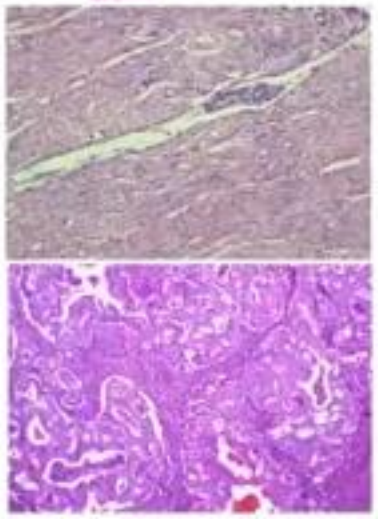
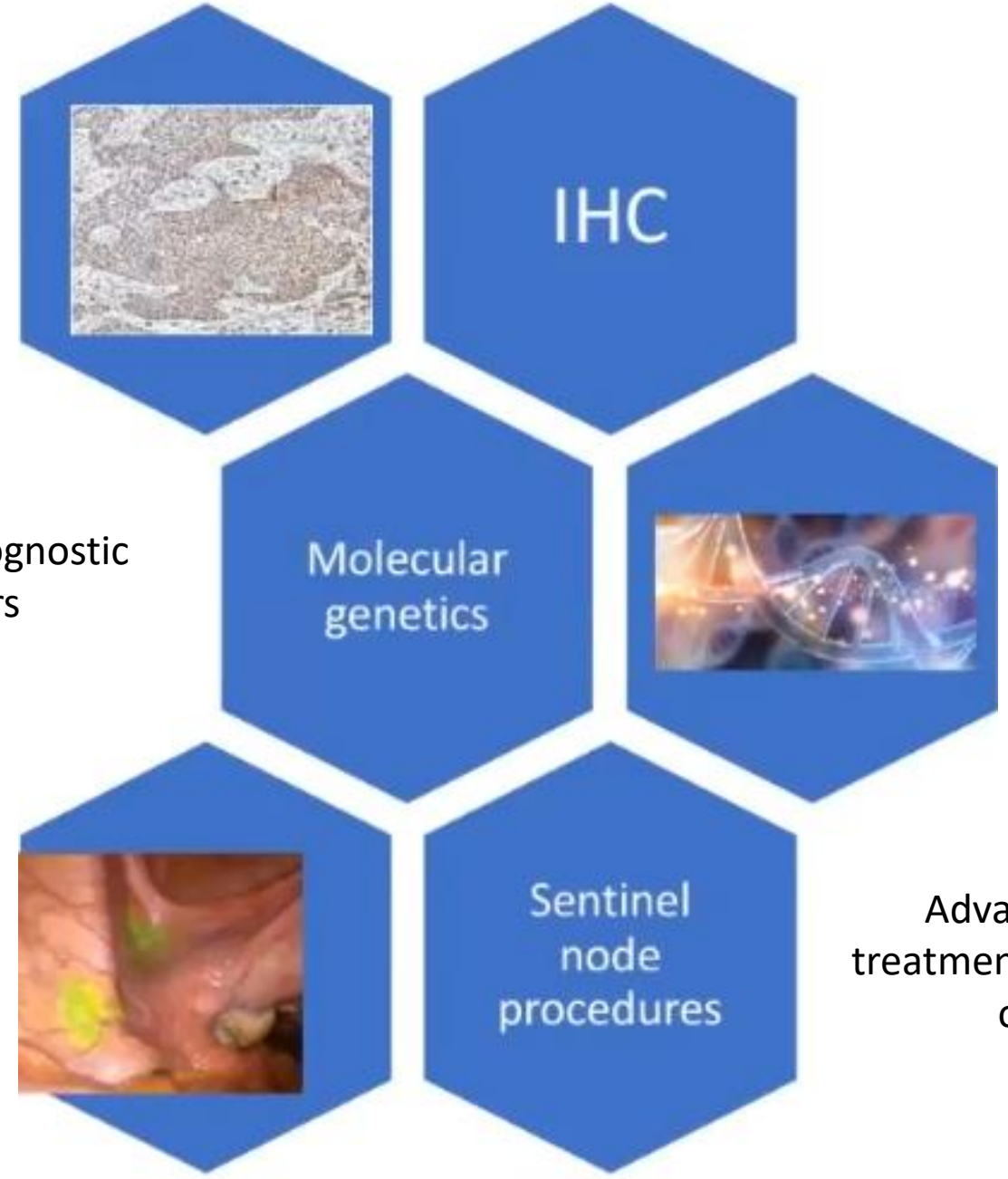
New CA Endometrium Staging

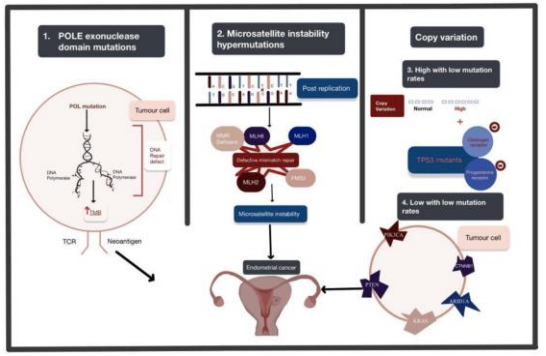
Cancer staging systems need periodic revision and modifications, when there are new data to inform advancements in treatment strategies, protocols and the outcome





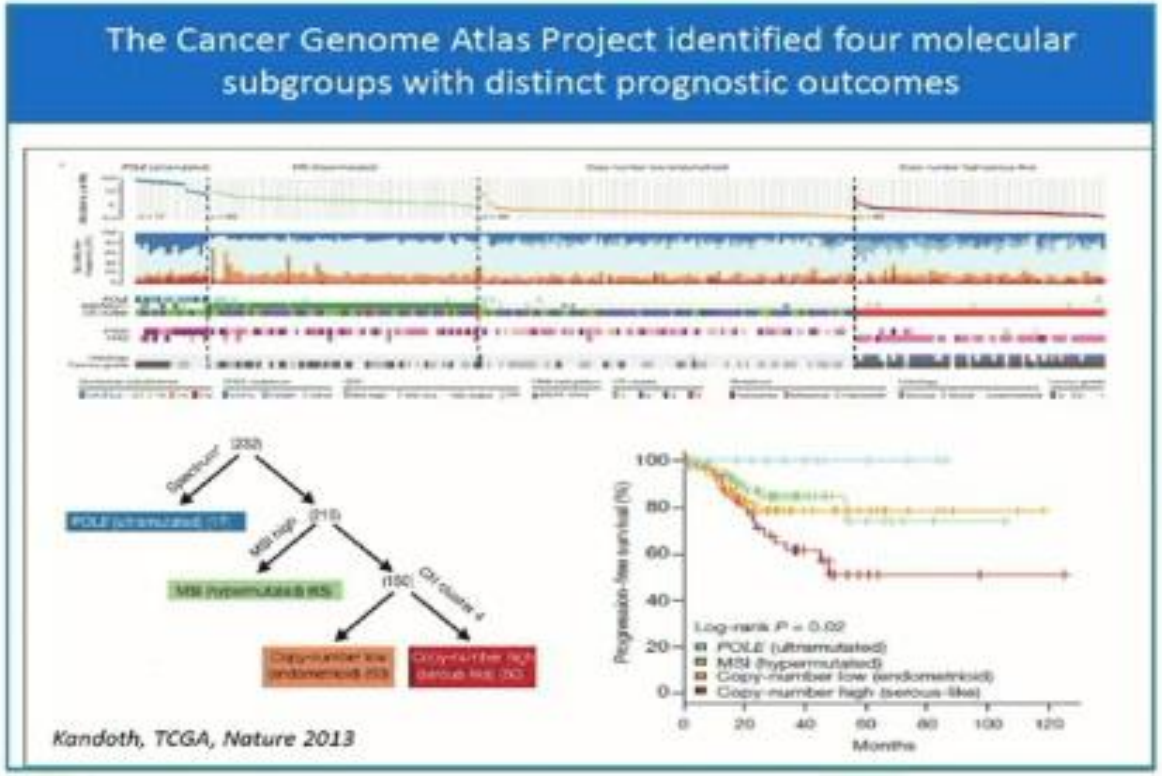
Adverse Prognostic factors

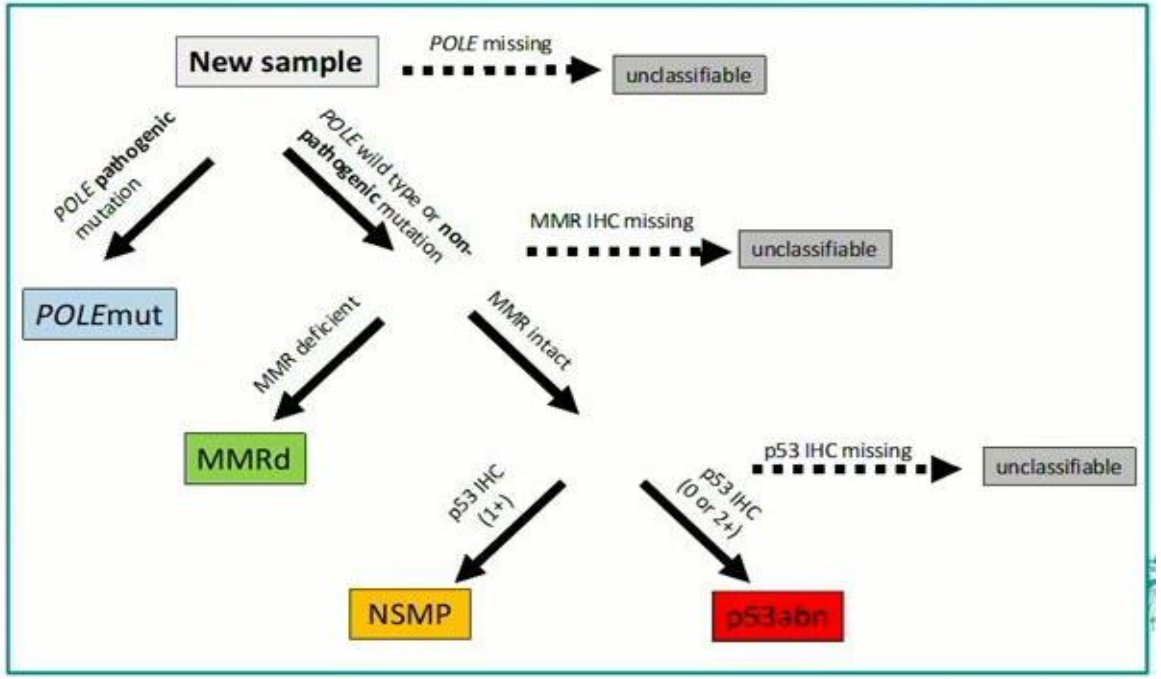




Advancements in treatment modalities and outcome

The “Modern” Molecular Classification: TCGA Classification





- POLE exonuclease sequencing (positive in TCGA ultramutated; i.e., group1)-mutational analysis
- MMR (microsatellite instability; immunohistochemistry; positive in TCGA hypermutated; i.e., group 2)
- P53 (immunohistochemistry); abnormal in TCGA serous-like; i.e., group 4)
- None of the above (TCGA low-copy number; i.e., group 3)

Cancer Genome Atlas Research Network. Nature. 2013;497:67.

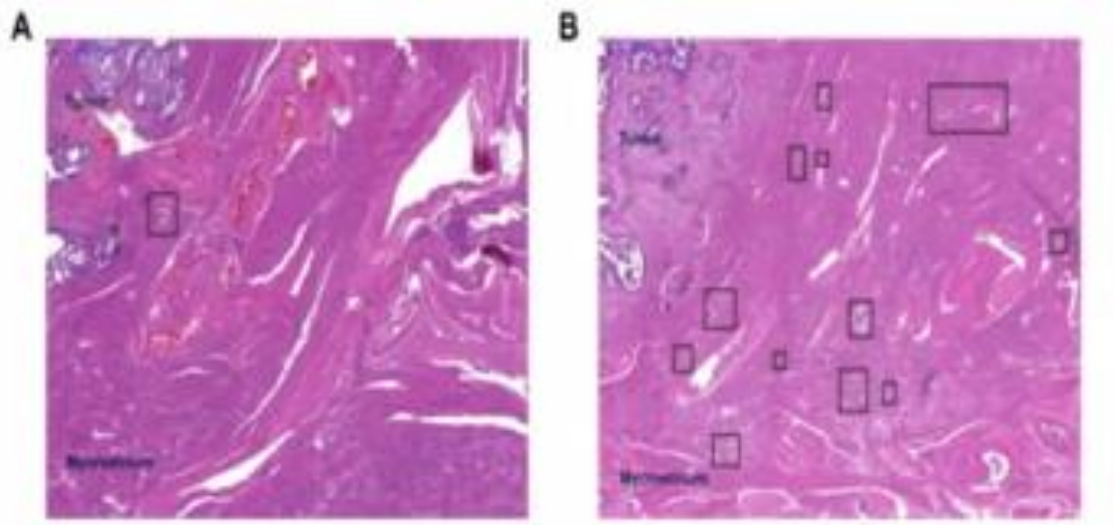
Lymphovascular Space Invasion

- Strong adverse prognostic parameter of endometrial cancer
- Independent of histologic grade or depth of myometrial invasion
- Correlates with nodal involvement
- Focal / no LVSI correlates with better prognosis, while substantial LVSI is associated with poorer prognosis (FIGO 2021)→ need to incorporate this in new staging

WHO (2021)

Focal LVSI - presence of a single focus around the tumour

Substantial LVSI - multifocal or diffuse arrangement of LVSI or the presence of tumour cells in ≥lymphovascular spaces



The impact of lymphovascular space invasion on survival in early stage low-grade endometrioid endometrial cancer

Fariba Yarandi[1], Elham Shirali[1], Setare Akhavan[2], Fatemeh Nili[3] and Sara Ramhormozian[1*]

European Journal of Medical Research (2023) 28:118

- Retrospective Cohort study
- 415 patients with stage I, grade 1, 2 endometrioid endometrial
-
-
- patients (12.8%)
- Multivariate analysis showed that LVSI has significant correlation with 3-year and 5-year overall survival rates

Parameter	LVSI-negative	LVSI-positive	*p*-value
Recurrence time (months)	33.65 ± 21.02	23.04 ± 14.88	0.043
			0
			0

Conclusion

LVSI in early stage endometrial cancer significantly and independently influences 3-year and 5-year survival rates and acts as a strong prognostic factor in these patients.

Positive LVSI	8 (66.7%)	92 (22.8%)	0.000
Adjuvant therapy			
No adjuvant therapy	6 (50%)	195 (48.8%)	0.012
Brachytherapy	3 (25%)	126 (31.5%)	
Brachytherapy and EBRT	1 (8.3%)	71 (17.8%)	
Recurrence	9 (75%)	44 (10.9%)	0.000
Recurrence time	9.22 ± 8.28	32.57 ± 17.94	0.000

Distinguishing true LVSI from its mimics can be challenging

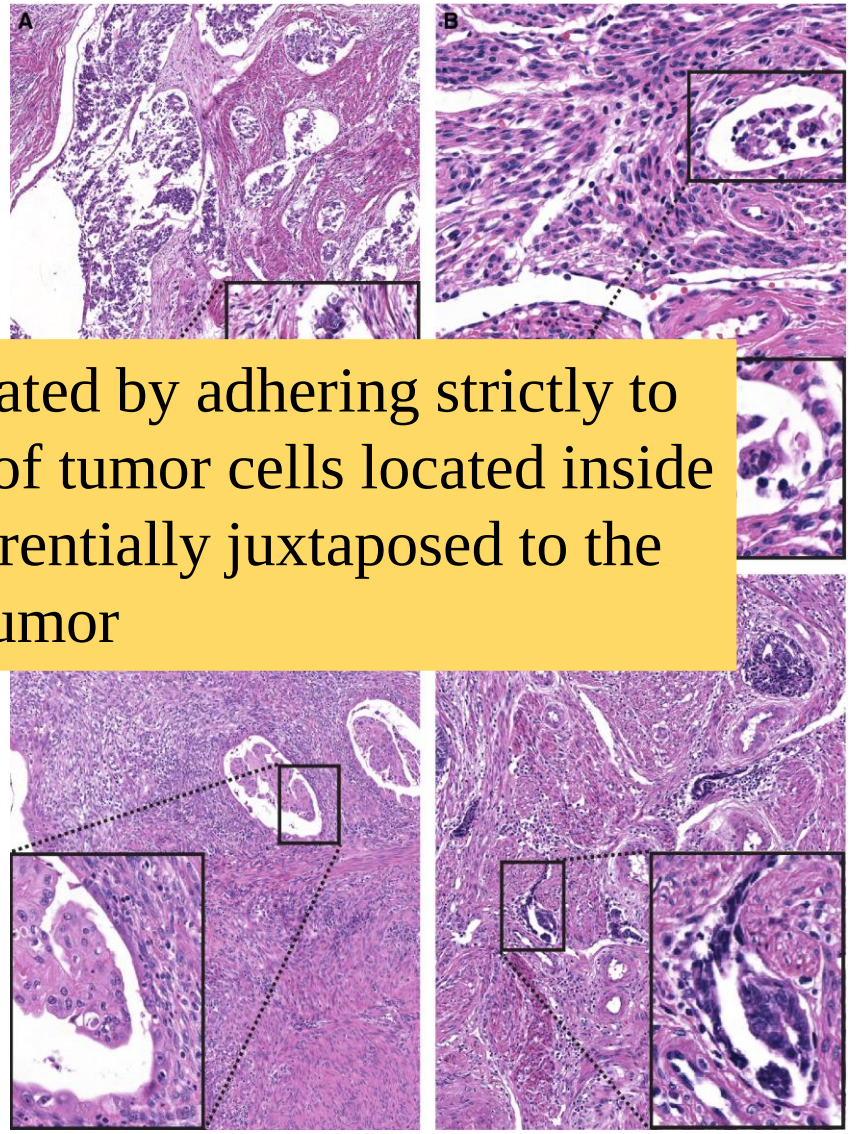
What are the common mimics that can be encountered and how to overcome them?

- Frequently encountered LVSI mimic is artefactual displacement of tumour within myometrial clefts or large endothelial-lined vessels
  - ➢ Probably results from surgical manipulation or
  - ➢

True invasion from pseudoinvasion can be differentiated by adhering strictly to the histologic criteria defined as cohesive aggregates of tumor cells located inside a vascular space lined by endothelial cells and preferentially juxtaposed to the vessel wall, outside the main tumor

- Another frequent artefact that mimics LVSI is stromal retraction around invading tumour glands

- 'Microcystic elongated and fragmented (MELF)-type invasion' - specific type of myometrial invasion, may also be another potential mimicker



Stage I

- Although the updated classification preserves the notion of confining the disease to the uterine corpus and ovary, it introduces sub-classifications depending on histological type and depth of myometrial invasion
- Increased number of subgroups within Stage IA

Do you think this will complicate communication among clinicians, and pathologists, thus jeopardizing the genuine interpretation and application of the staging criteria?

- Use of histological types and degree of invasion as classification criteria (stage I) could be challenging due to the inherent variability in assessment of invasion extent and of histological interpretation esp. in mixed histologies.

What is your opinion?

Do you think this variability could result in differences of opinion among observers and consequently can influence the treatment decisions

Stage II

- The second stage remains centered on cervical stromal invasion with varying levels of lymphovascular space involvement and histological presentation

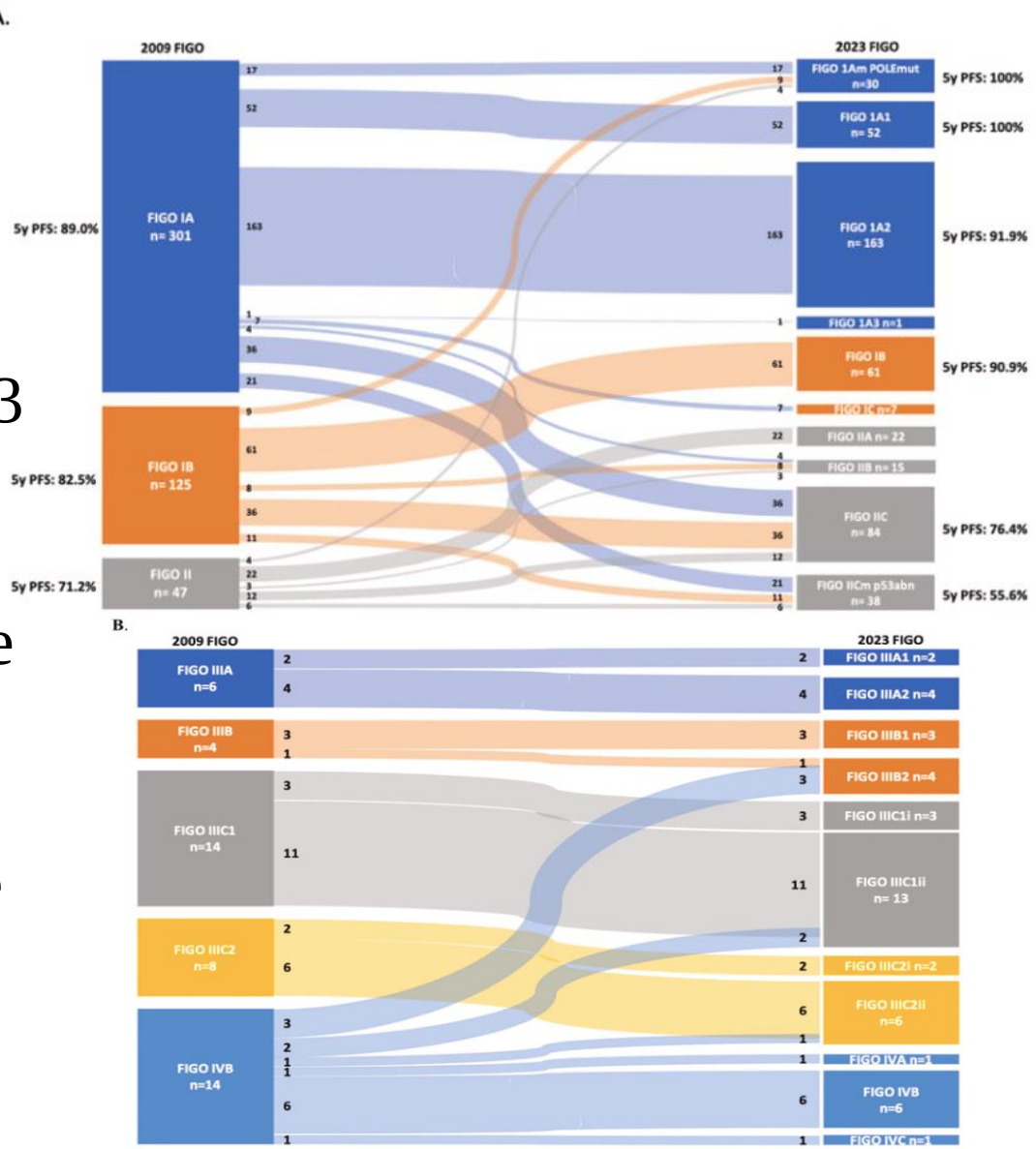
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement

What about aggressive histology with substantial LVSI?

Verification of the prognostic precision of the new 2023 FIGO staging system in endometrial cancer patients – An international pooled analysis of three ESGO accredited centres

Richard et al. European Journal of Cancer 193 (2023) 113317

- International, pooled retrospective study
- 519 EC patients 3 ESGO accredited centres in Austria/Italy
- Categorised according to the 2009 and the 2023 FIGO staging systems
- In early stage (I/II) 90% of stage shifts concerned upshifts to a higher FIGO (sub)stage based on aggressive histological subtypes or presence of p53 abn with myometrial invasion
- All downshifts encountered in early stage were caused by the presence of pathogenic *POLE* mutations



If there is an aggressive histology say serous carcinoma with no myometrial and no LVSI but P53 abn

Will this tumor be classified as Ic or due to P53abn it will be upstaged to stage IIcmP53?

Stage III

- Addresses the local and regional dissemination of the tumor, encompassing uterine serosa, adnexa, vagina, parametria and lymph nodes

- 2023 guidelines now introduces categories for micrometastasis and macrometastasis in pelvic and *para*-aortic lymph nodes

- Precise detection of micrometastasis necessitates scrupulous histopathological methodologies (ultrastaging)

Routine clinical applicability ⟶ **Is it feasible?**

- Small subset of tumors (~5%) exhibit more than one molecular feature referred to as “multiple classifiers

How to classify based on molecular feature in presence of multiple classifiers?

If a patient has both POLE and MMRd? Which should be considered and what is its implication?

Stage IV

Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

- Stage IV is subclassified into 3 (A,B & C) where abdominal disease is further classified into IV A and B

How will management differ for LN spread above renal vessels (now IVB)

Thank You