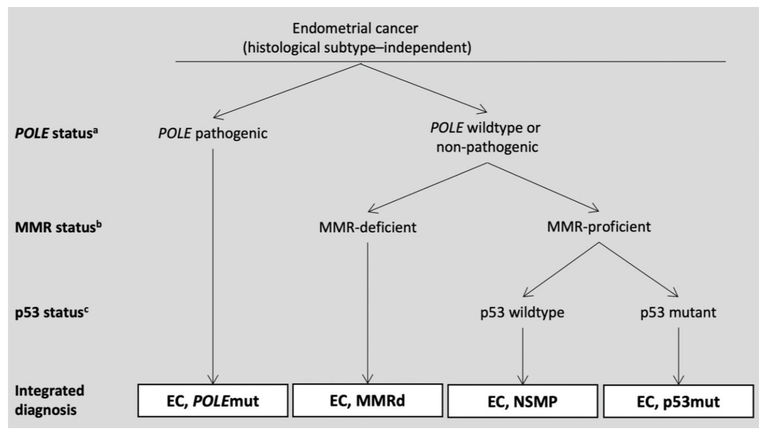
A retrospective audit of the distribution and clinicopathological association of endometrial cancer molecular subtypes

Dr de Gracia Hahn D, Dr Mohamed MB
University College London Hospital

Background

- The molecular classification of endometrial carcinoma into four molecular subgroups (*POLE*mut, MMRd, p53mut and NSMP) has been integrated into standard endometrial carcinoma reporting for the last few years and has a stronger prognostic significance than conventional histological classification.
- Recent guidelines have proposed further subclassification of NSMP tumours based on ER status, as ER positivity is considered a favourable prognostic factor in this group.
- A combination of immunohistochemistry and molecular testing is used for classification. *POLE*mut cases must show a specifically pathogenic mutation to be classified as such.
- In cases showing more than one molecular alteration ("multiple classifiers") a hierarchy is used to determine the final classification.
- **Audit aim:** To determine the distribution of molecular subtypes of endometrial carcinoma in our department and how this relate to the histological classification and stage.

Diagnostic algorithm for the integrated histomolecular endometrial carcinoma classification (image from WHO Female genital tumours, 5th ed.)

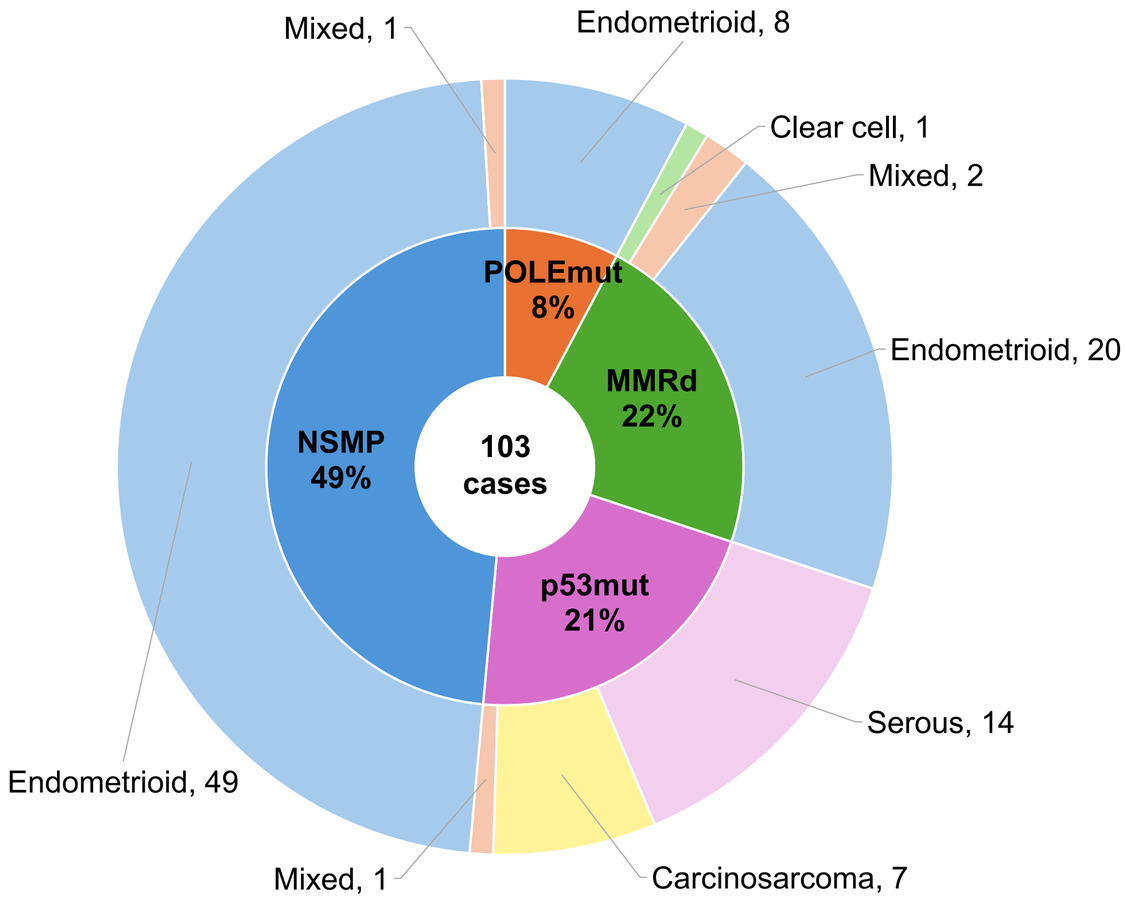


Method

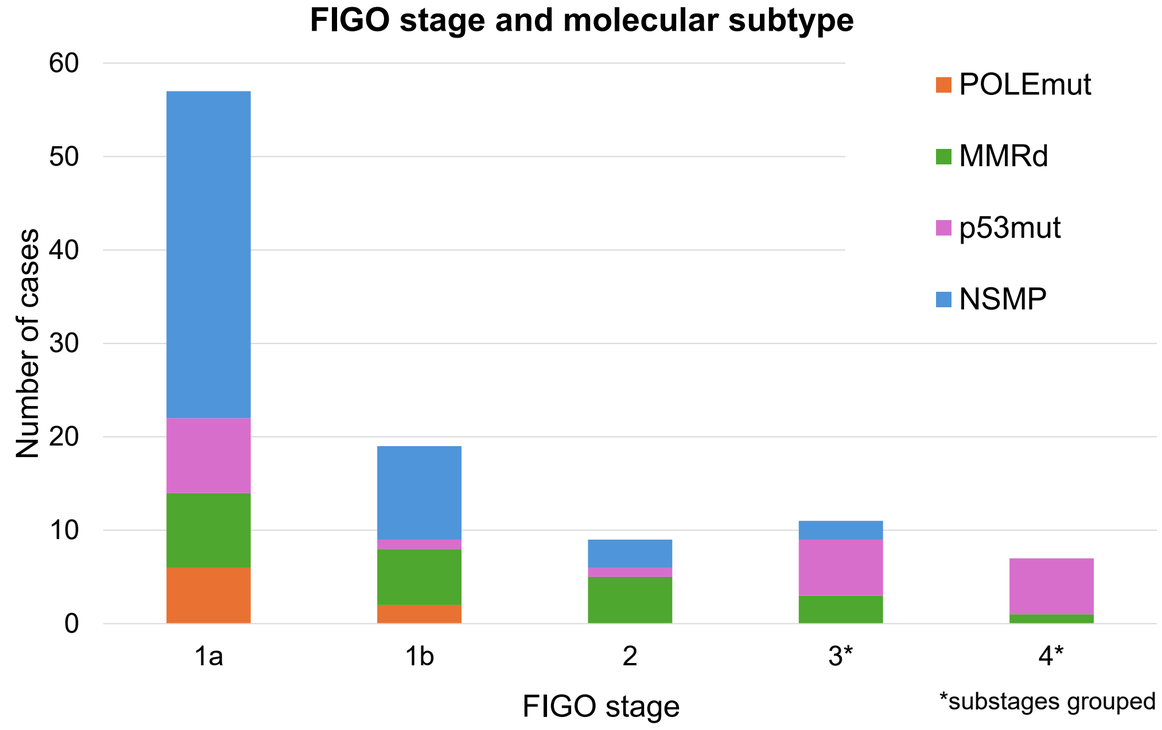
- Inclusion criteria: Endometrial carcinoma cases from January 2024 to July 2025 with molecular data (including *POLE* testing and IHC)
- Data collected:
  - Molecular subtype
  - Histological subtype
  - ER/PR status
  - FIGO stage

Results

- The distribution of molecular and histological subtypes in our cohort reflected the literature:



- High FIGO stage tumours correlated with higher risk molecular and histological subtypes.



Multiple classifiers

Histological subtype	POLE	p53	MMR	ER	PR	FIGO stage	Final molecular classification
Endometrioid grade 2	Mutant (c.1102G>T)	WT	Deficient (MLH1 hypermethylation AND sub-clonal MSH2 and MSH6 loss)	7/8	7/8	1a	*POLE*mut
Endometrioid grade 3	Mutant (c.857C>G)	X	Deficient (MSH2 and MSH6 loss)	3/8	0/8	1b	*POLE*mut
Endometrioid grade 2	Mutant p.Ser297Tyr (c.890C>A)	WT	Deficient (MLH1 hypermethylation detected)	6/8	8/8	1a	*POLE*mut*

- *Variant not on the standard pathogenic list published by BAGP
- Review of the molecular report revealed subtle difference in wording:
  - This case: "*A POLE variant was detected*"
  - Other cases: "*A POLE pathogenic variant was detected*" or "*No pathogenic variants were detected*"
- Clarified with the molecular team – variant considered "pathogenic/likely pathogenic"

- All NSMP cases were ER positive as per the Allred scoring system, with a score of ≥3 considered positive.
- Updated European guidelines recommend using tumour proportion score instead, with >10% staining considered positive, to subclassify tumours in the NSMP group (in addition to histological grade)
- These distinct scoring systems can result in different ER status in a subset of cases.

Conclusion

- Our findings closely align with reported behaviour of molecular subgroups, correlating with histological subtype and stage.
- Accurate identification of pathogenic *POLE* variants is crucial for correct tumour assignment.
- Recording the ER proportion score is recommended and may aid prognostic stratification within the NSMP group.

References

1. WHO Classification of Tumours Editorial Board. Female genital tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2020. (WHO classification of tumours series, 5th ed.; vol. 4).
2. Concin, N., Matias-Guïu, X., Cibula, D., Colombo, N., Creutzberg, C. L., Ledermann, J., … Planchamp, F. (2025). *ESGO–ESTRO–ESP guidelines for the management of patients with endometrial carcinoma: Update 2025*
3. Singh, Naveena, et al. *BAGP Guidance on POLE NGS Testing in Endometrial Carcinoma: Version 1.2*. British Association of Gynaecological Pathologists, July 2022