Molecular Classification of Endometrial Cancer and its Implications in Management

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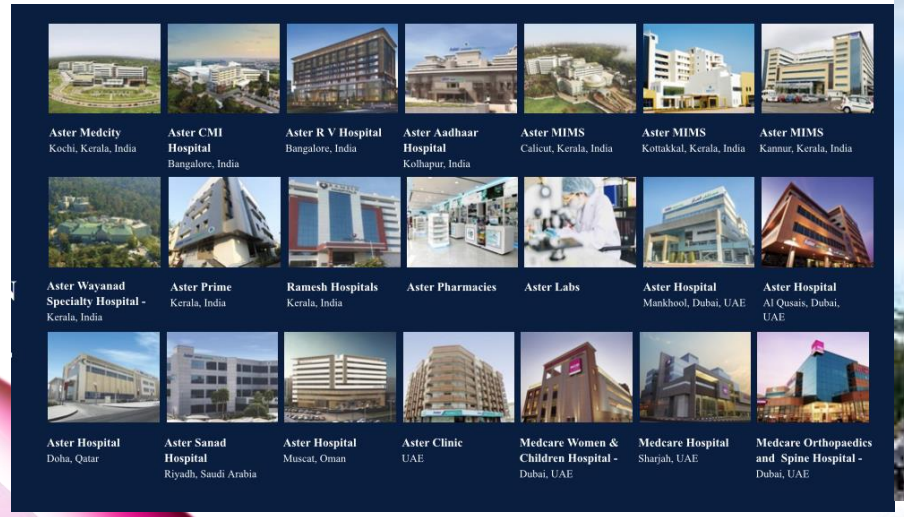


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INTRODUCTION

Although endometrial carcinoma (EC) is generally considered to have a good prognosis, over 20% of women with EC die due to their disease, having increased in its incidence and mortality over the few decades. The aim of accurate prognosis is to ensure patients receive optimal treatments.

Patients with EC can be categorized into prognostic risk groups based on clinicopathological findings:

- Tumour Type & Grade
- Groupings and Recommended management algorithms
- Age
- BMI
- Stage and presence of Lymphovascular space invasion

INTRODUCTION

The molecular classification of EC emerging from The Cancer Genome Atlas (TCGA) study provide additional, potentially superior, prognostic information. This classifier, however, does not replace clinicopathological risk assessment based on parameters other than histotype and grade.

While tumour typing and grading may be superseded by a classification based on underlying genomic abnormalities, accurate assessment of other pathological parameters will continue to be key to patient management. These include factors related to staging, such as:

- Depth of myometrial invasion
- Cervical, vaginal and serosal surface
- Adnexal and parametrial invasion

And those independent of Stages like lymphovascular space invasion.

CURRENT BASIS FOR TREATMENT DECISIONS

- Risk prediction algorithms like ESMO-ESGO/NCCN
- Stratify into LOW/INTERMEDIATE/HIGH-INTERMEDIATE/HIGH RISK based on:
  - Clinical: age, comorbidities, fertility
  - Pathological: FIGO stage, tumour type, grade, LVSI
  - Morphological:
    a) Endometrioid carcinoma and variants
    b) Mucinous carcinoma
    c) Serous endometrial intraepithelial carcinoma
    d) Serous carcinoma
    e) Clear cell carcinoma
    f) Carcinoid tumour
    g) Small cell neuroendocrine carcinoma
    h) Large cell neuroendocrine carcinoma
    i) Mixed cell adenocarcinoma
    j) Undifferentiated carcinoma
    k) Dedifferentiated carcinoma

CURRENT RISK STRATIFICATION

- LOW: G1/2 EEC, FIGO IA; no LVSI
- INTERMEDIATE: G1/2, FIGO IB, no LVSI

- HIGH-INTERMEDIATE: G1/2 with LVSI, G3 EEC IA
- HIGH: G3 EEC IB, all non-EEC, any stage, all stage II+

Factors influencing treatment planning for EC are:

- Preoperative Imaging
- Tumour profile
  - Morphology
  - Immunohistochemistry
  - Hormone receptor status
  - MMR status
  - Molecular profiling

Histomorphological assessment

	Type I	Type II
Associated clinical features	Metabolic syndrome: obesity, hyperlipidaemia, hyperglycaemia, and increased oestrogen concentrations	None
Grade	Low	High
Hormone receptor expression	Positive	Negative
Histology	Endometrioid	Non-endometrioid (serous, clear-cell carcinoma)
Genomic stability	Diploid, frequent microsatellite instability (40%)	Aneuploid
TP53 mutation	No	Yes
Prognosis	Good (overall survival 85% at 5 years)	Poor (overall survival 55% at 5 years)

Table 1: **Dualistic classification of endometrial cancers, by Bokhman subtype**

Risk stratification of endometrial cancer

Annals of Oncology 27: 16–41, 2016

Low	**IA, Grade1/2,** *LVSI negative*
Intermediate	1B, Grade1/2, *LVSI negative*
High Intermediate	IA, Grade3, regardless of LVSI
	IA/IB, Grade1/2, *LVSI positive*
High	IB, Grade3, regardless of LVSI
	Type 2 EC
	StageII

- *To guide adjuvant treatment and predict lymph node metastasis*

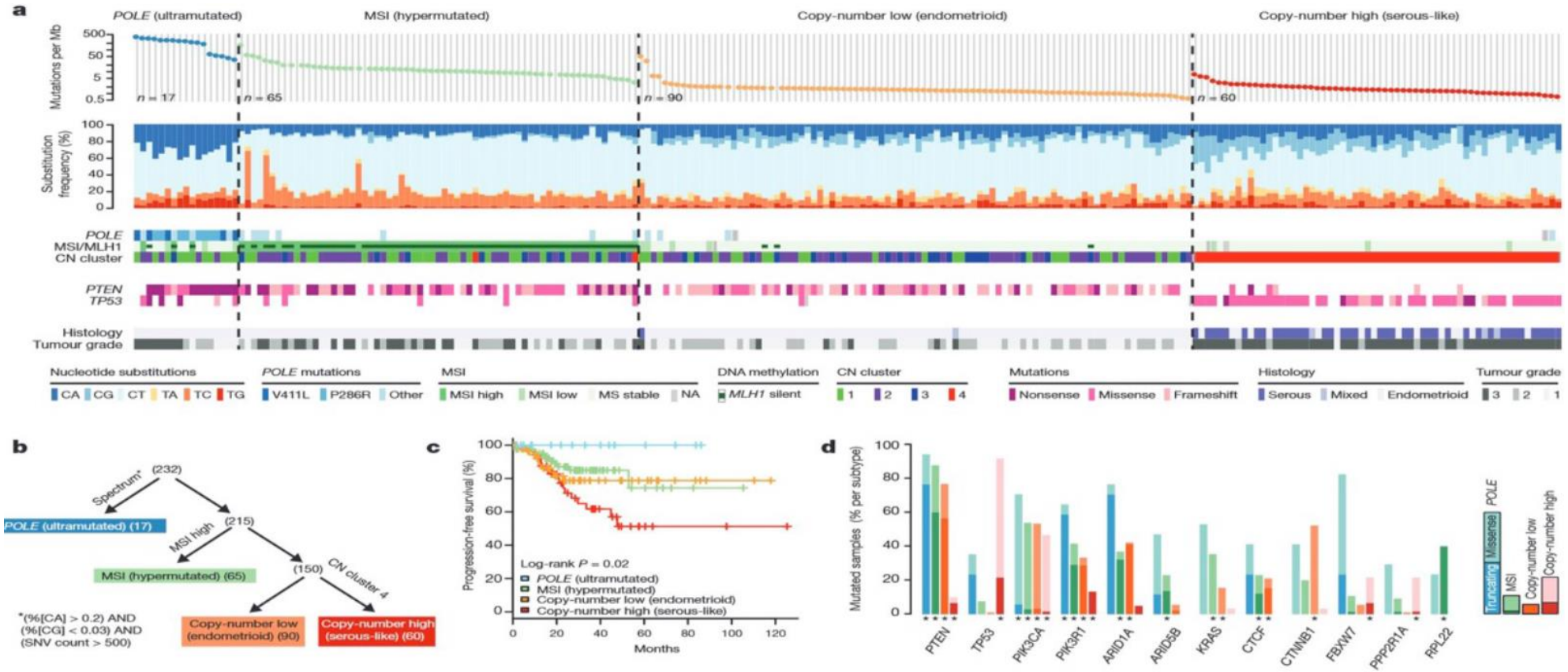
PROBLEMS

- Histotype diagnosis in EC shows higher inter-observer variation (especially in high grade EC)
- Histotype diagnosis in EC does not consistently predict clinical outcome
- **Prognostic separation of histotypes is therefore unreliable and inaccurate**

ATTRIBUTES OF A MEANINGFUL DIAGNOSIS

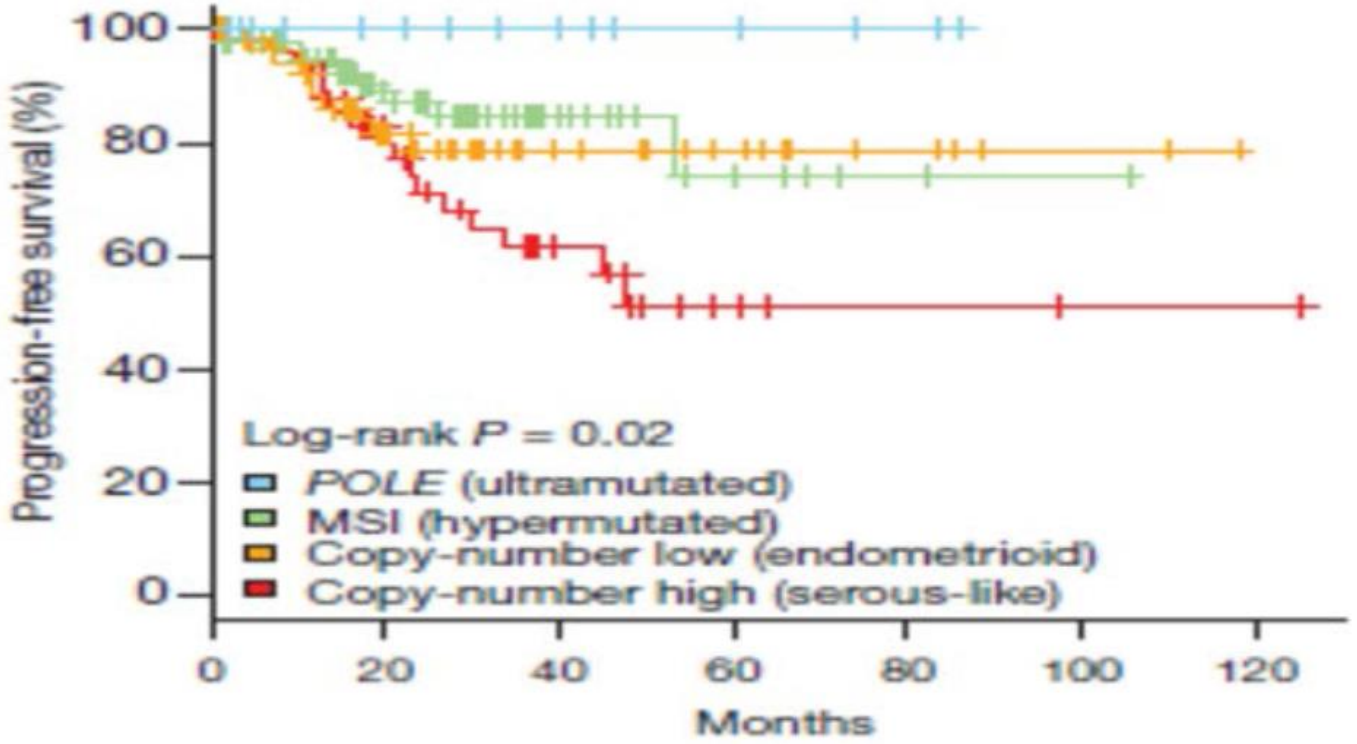
- Understandable by both clinicians and patients
- Objective
- Clinically relevant
- Sensitive and specific

THE CANCER GENOME ATLAS (TCGA): ENDOMETRIAL CARCINOMA



MOLECULAR CLASSIFICATION OF EC

Molecular classification of EC has clear prognostic implications

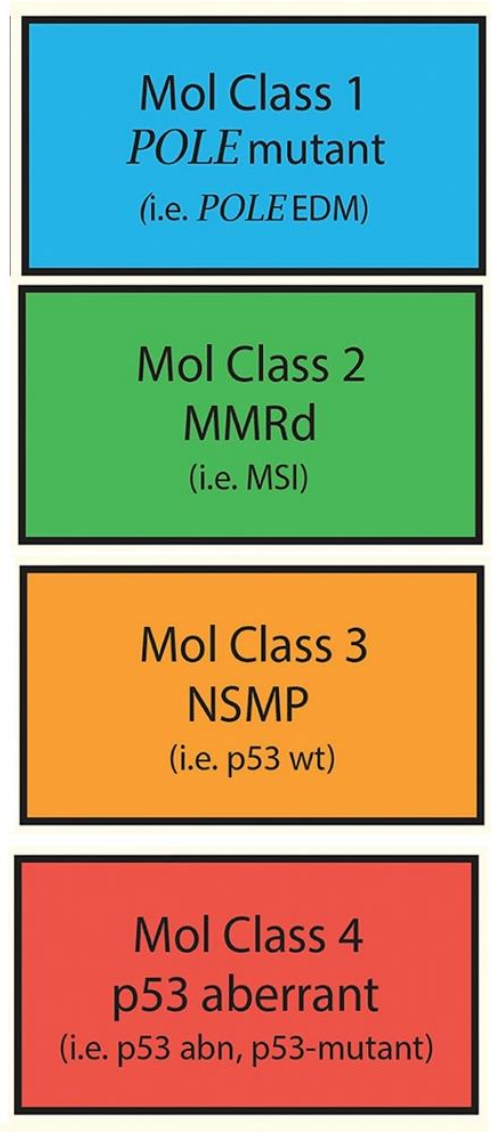


Pathological

	TYPE 1	TYPE 2
INCIDENCE	75-80%	20-25%
HISTOLOGY	Grade I, II Endometrioid	Grade III Endometrioid and other histologies (Serous, clear cell)
CLINICAL BEHAVIOUR	Subtle	Aggressive
OCCURS IN	Young women Nulliparous Obese	Older women Multiparous Non obese
ESTROGEN DEPENDENCE	Yes	No
PREMALIGNANT LESIONS	Yes	No
MUTATIONS	PTEN KRAS	P53
PROTECTIVE FACTORS	Combined OCP and smoking	Not protective
RACE	CAUCASIAN	NON WHITE

CANCER GENOME ATLAS

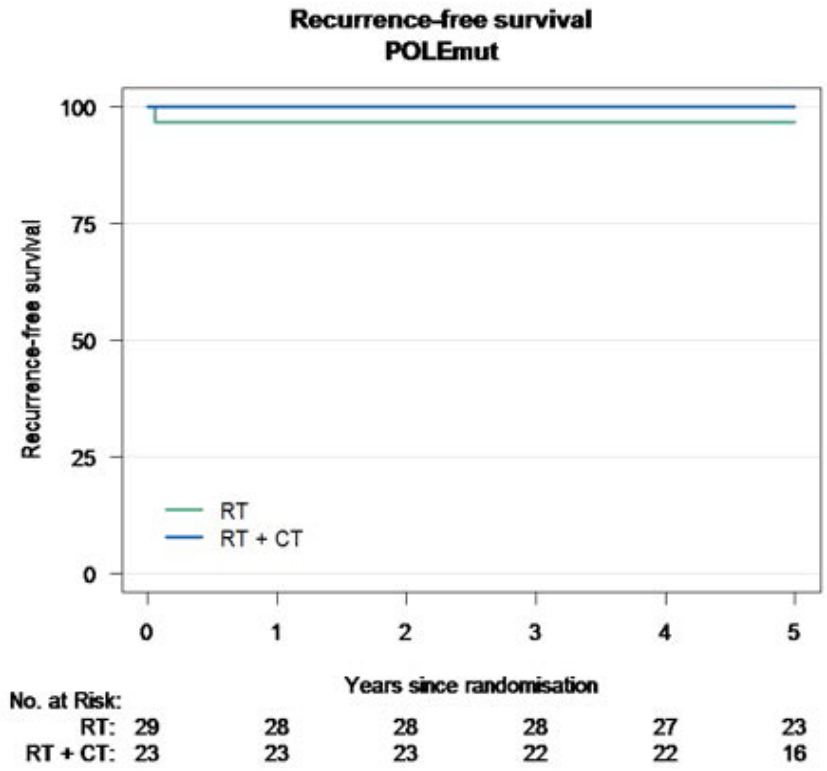
Molecular



	POLEmut (5-15%)	dMMR(MSI) (25-30%)	NSMP(p53 wt) (30-40%)	p53 mutated
DEFECT	Ultramutated (>100 mut/MB) MSS	Hypermutated (10-100 mut/MB) MSI	Copy number quiet <10 mut/MB MSS; p53 wt	High copy number alteration P53 mutation MSS
Histology	Endometroid High grade TIL + (Tumour infiltrating lymphocytes)	Endometroid High grade LVSI+ TIL +	Endometroid Low grade ER/PR + Squamous diff	ALL HISTOLOGIES High grade TIL -
Prognosis	Excellent	Intermediate	Intermediate	Poor
Diagnostic test	NGS/Sanger/Hotspot	MMR IHC/MSI assay	p53 IHC All others neg	p53 IHC
Clinical features	Low BMI Early Stage Early onset	Higher BMI Lynch associated	Higher BMI	Lower BMI Advanced age Late onset

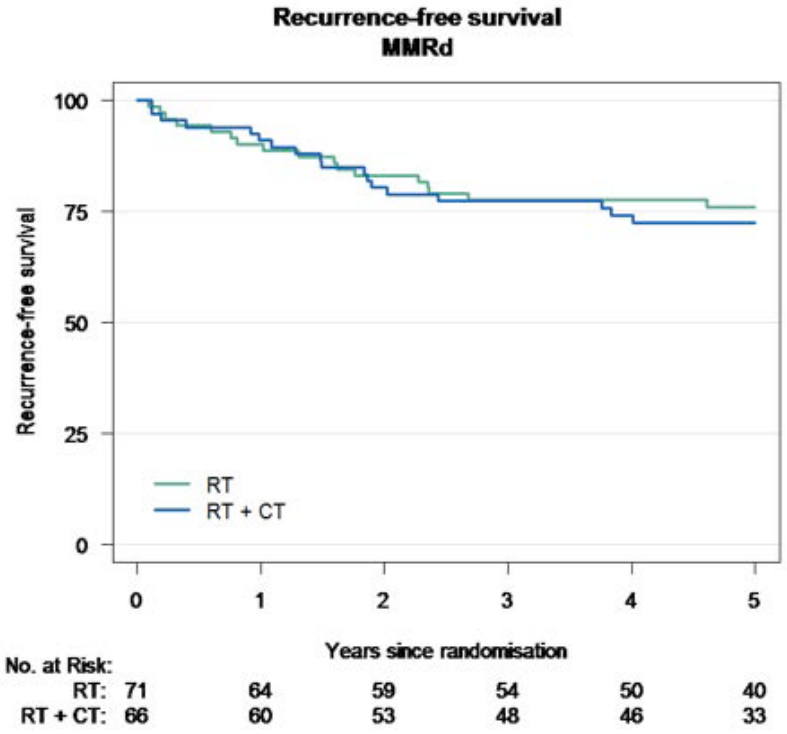
POLEMUT EC

- 10% of endometrioid EC
- Relatively young, low stage, high tumour grade, scattered tumour giant cells, prominent lymphocytic infiltrate
- High mutational burden (>100 mut/MB)
- **Classified as HIGH RISK by current algorithms**
- **<u>Exceptionally good prognosis</u>**
- Implications:
  - Treatment de-escalation
  - No RT for low stage
  - Omit chemo for high stage



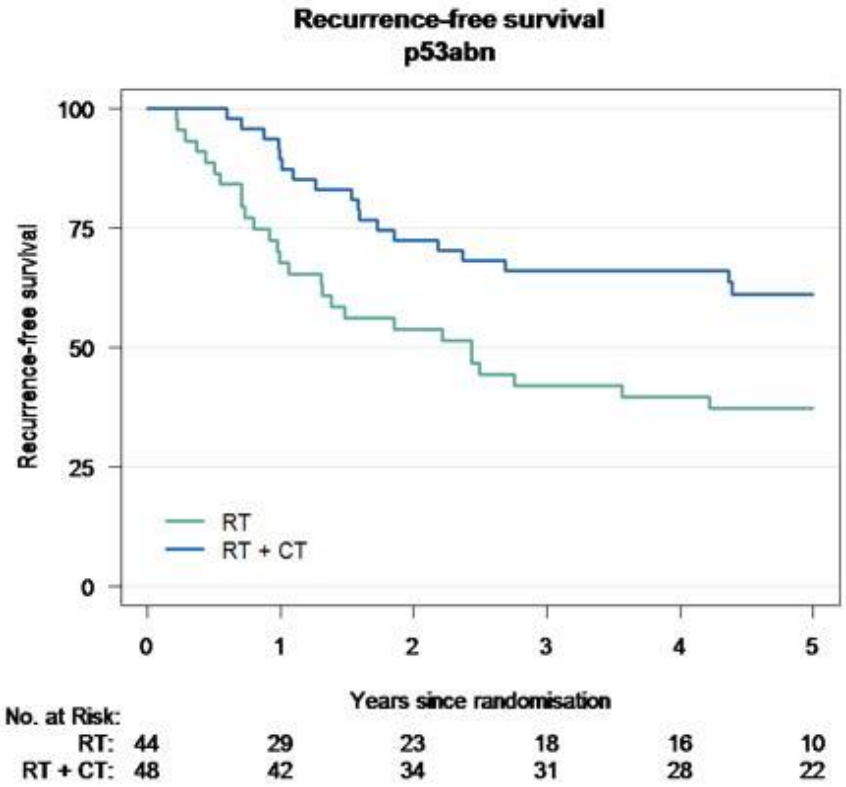
MMRd EC

- 25-30% of EC
- Majority sporadic (MLH1 promoter methylation)
- About 3% LS
- Higher grade, endometrioid, with large numbers of TIL's
- Higher prevalence of substantial LVSI
- Good response to RT (including just VBT in absence of unfavourable risk factors)
- Additional chemotherapy does NOT improve prognosis
- Immune checkpoint inhib Rx in recurrent cases



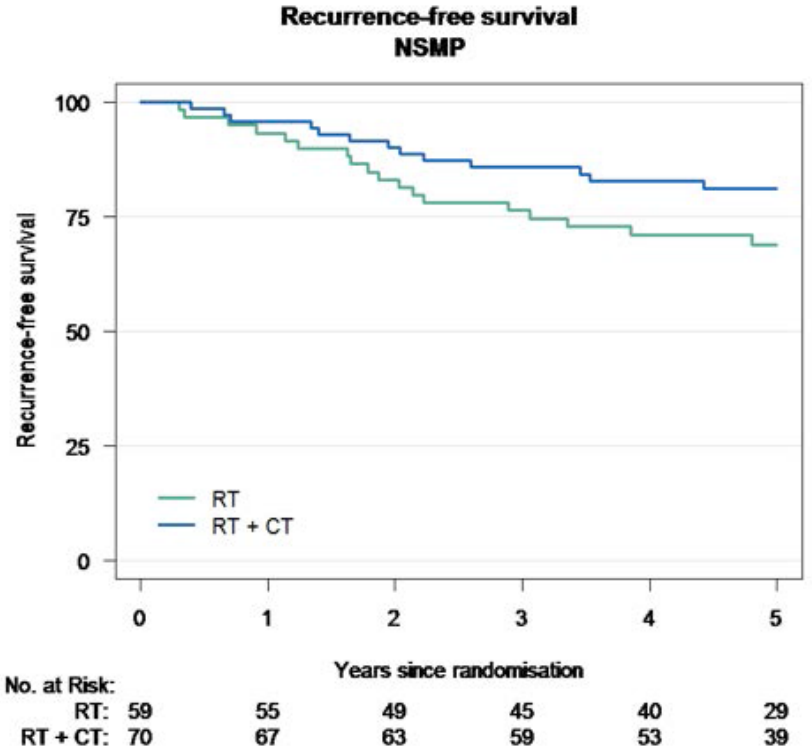
P53ABN (CNH/SEROUS-LIKE) EC

- Diagnosis is easy and reproducible once POLEmut and MMRd are excluded
- Significant improvement in survival with chemotherapy
- Targeting HER2 and HRD are being explored



NSMP EC

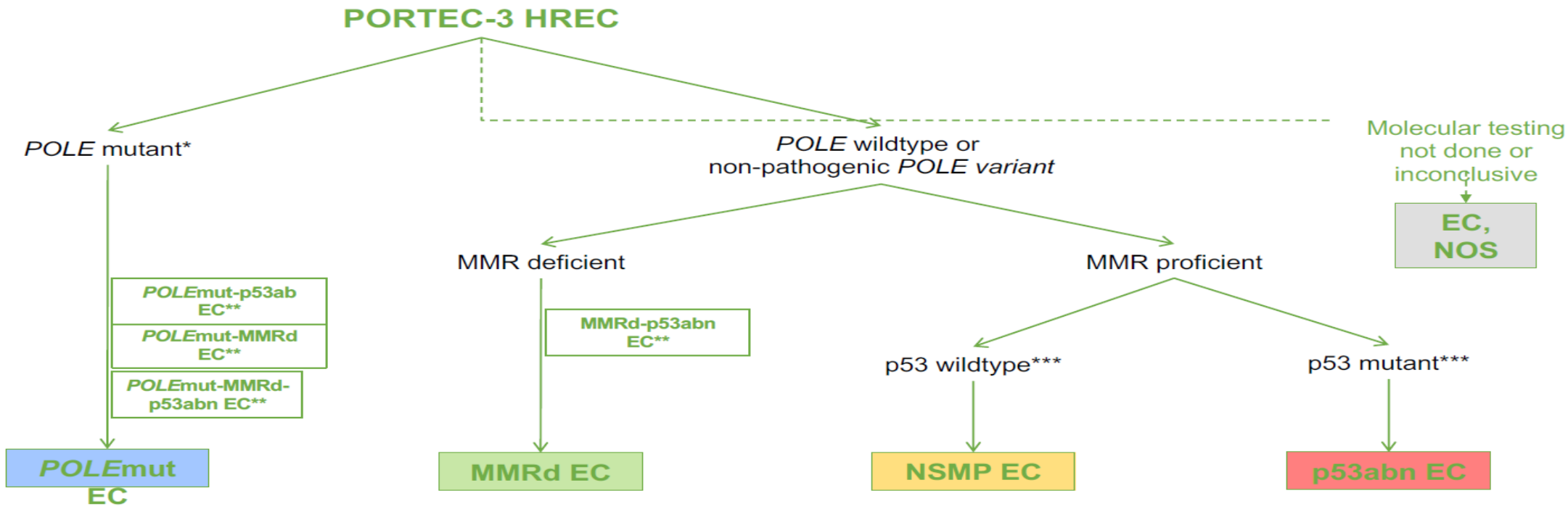
- Classic Type 1
- Oestrogen driven
- Amenable to conservative treatment
- Stage-dependent prognosis
- Largest group
- Requires further prognostic sub-grouping (beta-catenin; L1CAM)



FOUR MOLECULAR SUBTYPES OF EC

- Like ovarian cancer histotypes these are essentially non-overlapping
- In order of frequency: MMRd+p53; POLE+p53; MMRd+POLE; MMRd+POLE+p53
- About 3% of cases appear to fall into multiple groups
  - Not all POLE mutations are pathogenic
  - POLE, TP53 mutations and MMR defects can be secondary

EC MOLECULAR CLASSIFICATION



Adapted from Vermij et al, *Histopathology* 2020
*Pathogenic *POLE* exonuclease domain mutations (EDM) as per León-Castillo et al, *J Pathol* 2019
**León-Castillo et al, *J Pathol* 2019
****p53 IHC is as a excellent surrogate marker for mutational status (Singh et al, J Pathol 2019)*

FOUR MOLECULAR SUBTYPES OF EC

- Differential clinical settings (e.g. age, BMI), reflecting differences in pathogenesis
- Different genetic risk factors/associations with hereditary cancer susceptibility syndromes
- Different precursor lesions (wrt morphology & latency)
- Different prognoses (with prognostic information independent of/additive to clinical risk stratification)
- Excellent inter-observer/inter-lab diagnostic reproducibility
- Can be diagnosed accurately based on biopsy (thus can be used for planning of definitive treatment)
- Predictive of response to treatment (Pt-taxane CT, RT, immune, hormonal)

MOLECULAR CLASSIFICATION OF EC

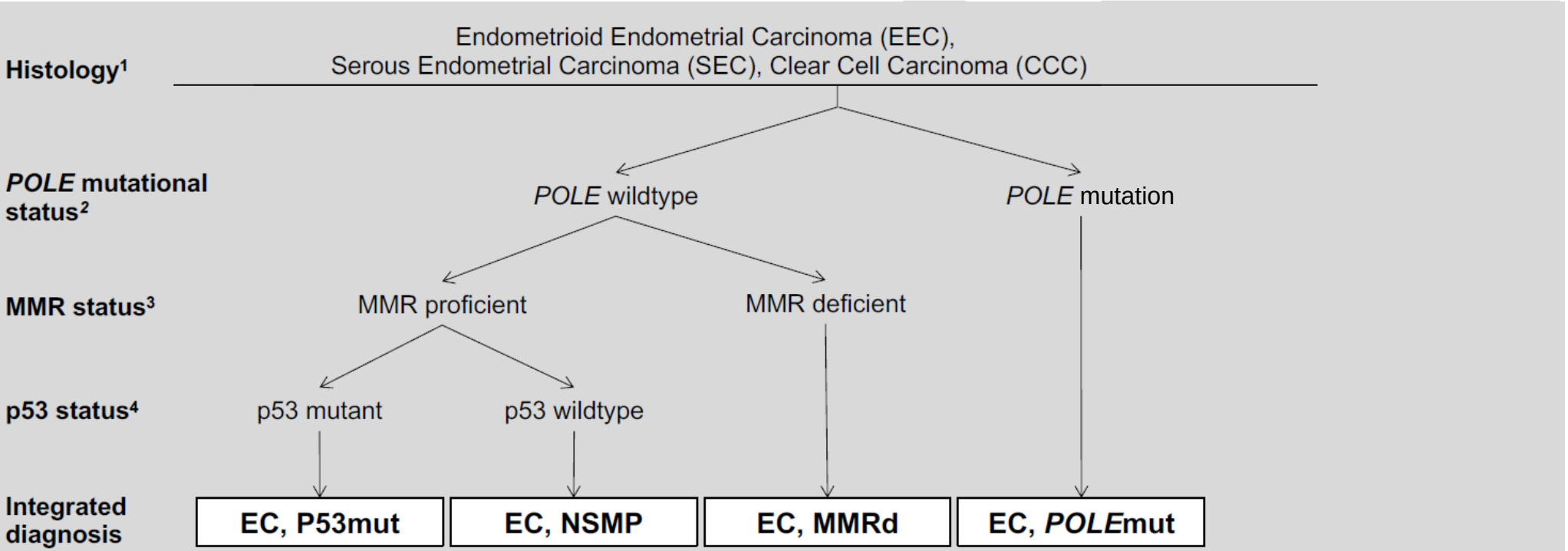
- By current classification:
  - 6/7 HIR EC patients receive unnecessary adjuvant RT
  - 7% EC patients suffer from potentially preventable recurrence/death
  - Only c20% HR EC (true 'serous-like') benefit from platinum-based chemotherapy

MORPHOLOGY ALONE DOES NOT DISTINGUISH BETWEEN THESE CATEGORIES
(POLEmut, MMRd and p53abn variably appear endometrioid/non-endometrioid)

- If we are to apply our knowledge to the care of our patients & Do no harm
- *POLE and MMRd TESTING MUST BE INCORPORATED INTO ROUTINE DIAGNOSIS*

PATHOLOGISTS MUST FACILITATE THIS CHANGE

INTEGRATED HISTO-MOLECULAR EC CLASSIFICATION



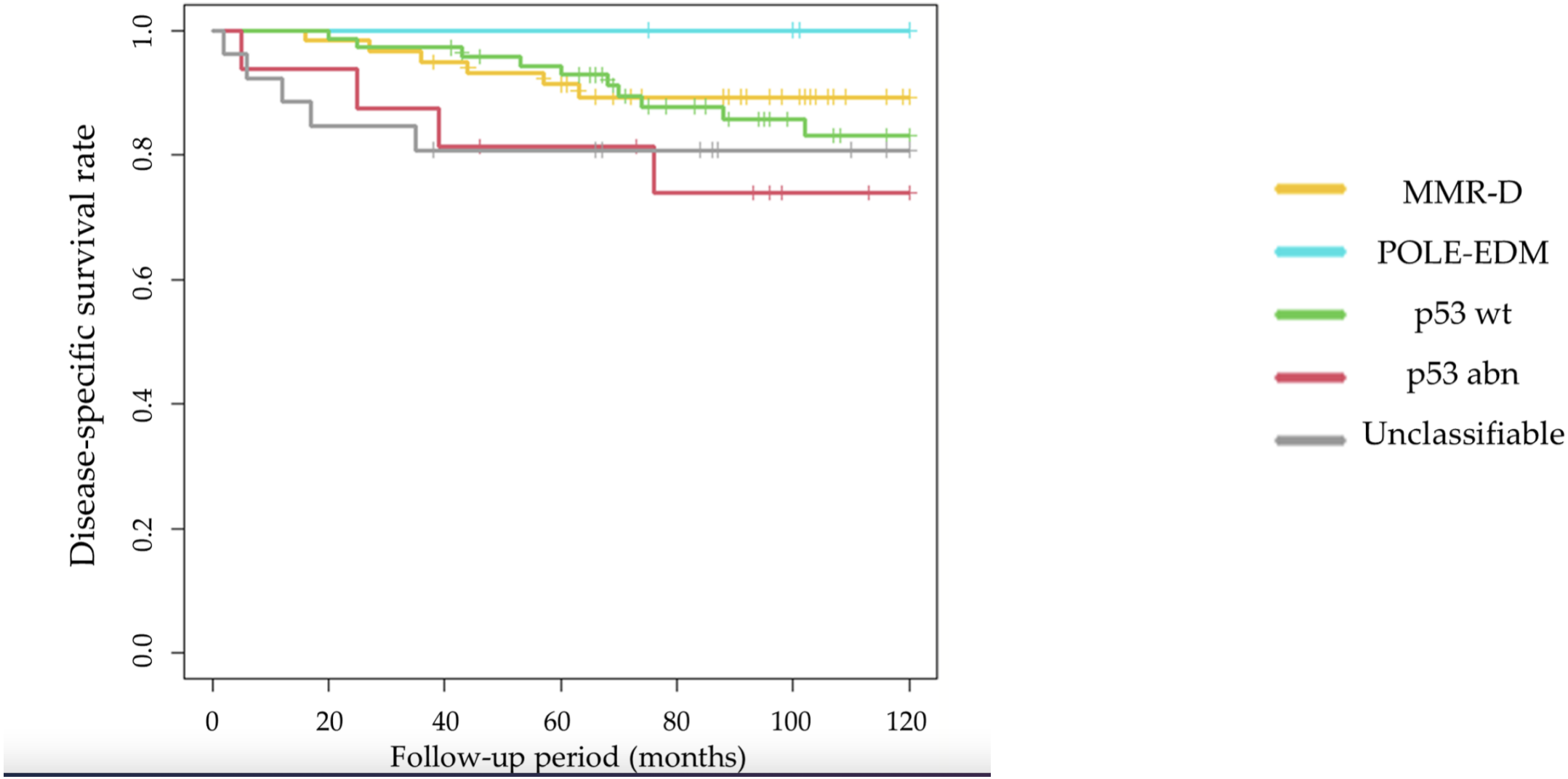
[1]*This approach is particularly valuable in high-grade endometrial carcinomas*
[2]*POLE mutant includes the 5 pathogenic variants P286R, V411L, S297F, A456P, and S459F (Leon et al., Journal of Path 2019)*
[3]*MMR deficiency is defined by loss of one or more MMR-proteins (MLH1, PMS2, MSH2 and MSH6)*
[4]*P53 IHC is as a excellent surrogate marker for mutational status (Singh et al, Journal of Path 2019)*

Molecular subtypes /Genomic classification

A

	POLE ultramutated	MSI hypermutated	Copy-number low, MSS	Copy-number high, serous-like
Mutation load				
Somatic copy number alterations load				
Histology	Endometrioid	Endometrioid	Endometrioid	Serous and endometrioid
Grade				
***PI3K* alterations**				
***KRAS* mutation**				
***TP53* mutation**	35%	5%	1%	>90%
Prognosis	Excellent	Intermediate	Intermediate	Poor

Disease-specific survival rates of patients according to the Proactive Molecular Risk Classifier for Endometrial Cancer classification system



PORTEC3- MOLECULAR CLASSIFICATION

- 410 Cases analysed:
  - Endometrioid grade 3 either 1B or LVSI or both stage II-III; or stage I–III disease with serous or clear cell histology
  - 93 cases p53 abnormal
    - 5 year PFS 48%. 5yr PFS chemo & RT vs RT 59% vs 36% P=0.019
  - 51 cases POLE mutant
    - 5 year PFS 98%. 5yr PFS chemo & RT vs RT 100% vs 97% P=0.637
  - 137 cases MMRd
    - 5 year PFS 72%. 5yr PFS chemo & RT vs RT 68% vs 76% P=0.019
  - 129 NSMP
    - 5 year PFS 74%. 5yr PFS chemo & RT vs RT 80% vs 68% P=0.243

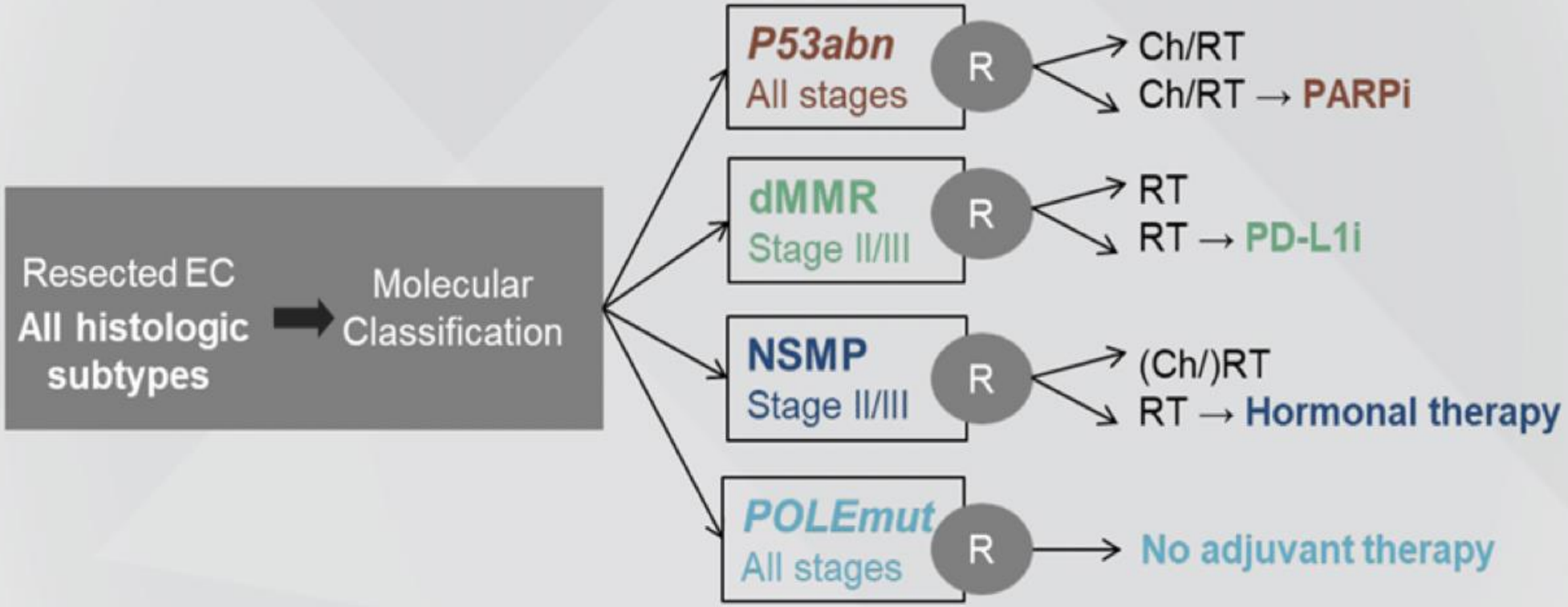
EC RISK CLASSIFICATION

Risk group	2014 ESMO-ESGO-ESTRO Consensus	2020 ESGO-ESTRO-ESP Guidelines	
		Molecular classification unknown	Molecular classification known
Low	· Stage IA endometrioid +low grade* +LVSI negative	· Stage IA endometrioid + low-grade* + LVSI negative or focal	· Stage I-II *POLE*mut endometrial carcinoma, no residual disease · Stage IA MMRd/NSMP endometrioid
Intermediate	· Stage IB endometrioid + low grade* + LVSI negative	· Stage IB endometrioid + low-grade* + LVSI negative or focal · Stage IA endometrioid + high-grade* + LVSI negative or focal · Stage IA non-endometrioid** 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** without myometrial invasion
High-intermediate	· Stage IA endometroid + high grade*, regardless of LVSI status · Stage I endometrioid + low grade* + LVSI unequivocally positive, regardless of depth of invasion	· 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 IB endometrioid + high grade* regardless of LVSI status · Stage II · Stage III endometrioid with no residual disease · Stage I-III non-endometrioid** with no residual disease	· Stage III-IVA with no residual disease · Stage I-IVA non-endometrioid** 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	· Stage III with residual disease · Stage IVA	· Stage III-IVA with residual disease	· Stage III-IVA with residual disease of any molecular type
Metastatic	· Stage IVB	· Stage IVB	· Stage IVB of any molecular type

IMPACT OF MOLECULAR CLASSIFICATION ON RISK STRATIFICATION

- **New guidelines in 2020 which included molecular classification which led to changes in risk stratification**
  - All **POLEmut stage 2** or less considered **low risk-** POLEmut are often HG (35%) so previously would have been considered intermediate or greater risk
  - All **P53abn** with myometrial invasion considered **high risk**(or greater if residual disease)
  - **High grade NSMP/MMRd** stage 1A and non-endometroid **p53abn** without myometrial invasion moved to **intermediate risk** not high intermediate risk
  - Stage **1B high grade** with **LVSI** and stage **2 NSMP/MMRd now high intermediate risk** not high risk
  - Stage 3-4 POLEmut tumours no risk classification currently

How Endometrial Cancer Molecular Classification Can Define Risk Categories

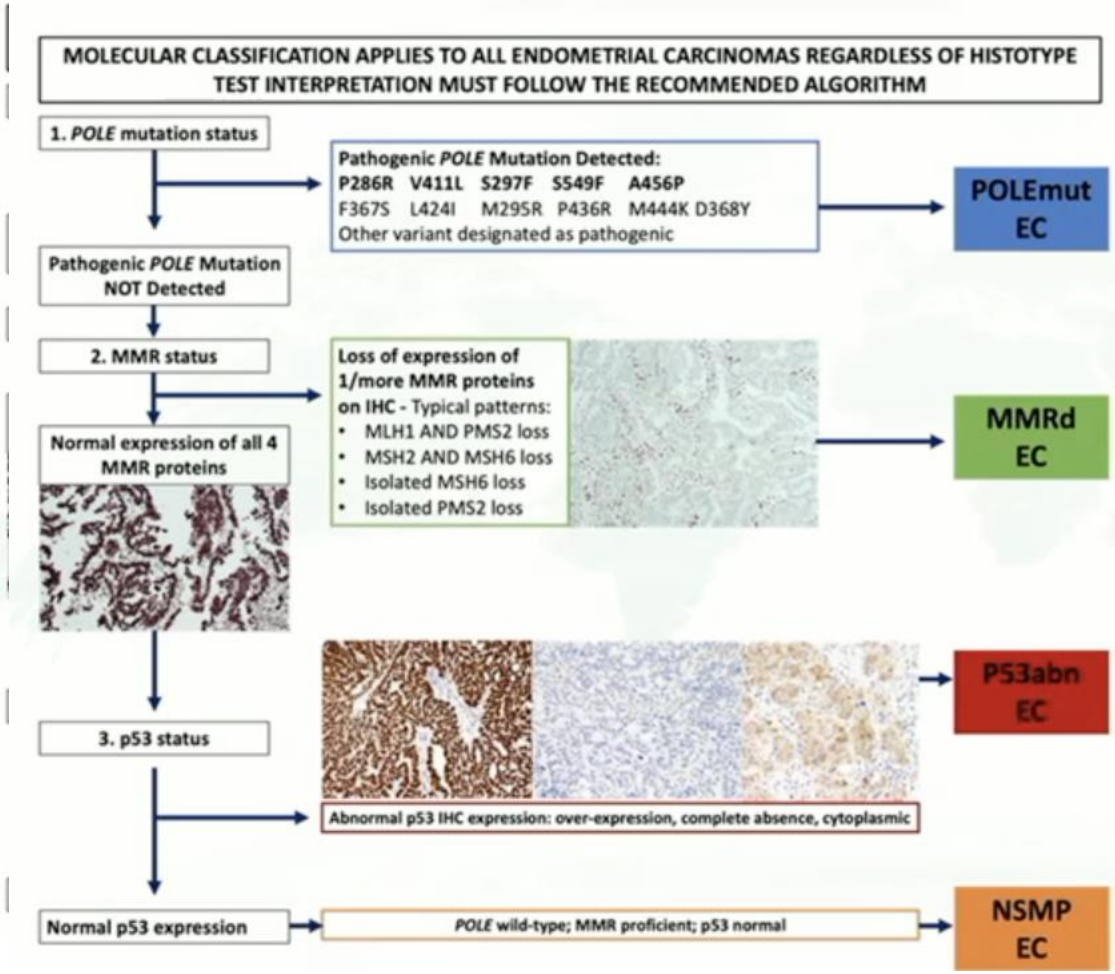


RAINBO umbrella programme coordinated by *Trans*PORTEC consortium will allocate patients with endometrial cancer into 4 international academically sponsored trials

	POLEmut	MMRd/NSMP	P53abn
Low Risk	Stage I/II, no residual disease	Stage IA, low-grade endometrioid, negative/focal LVSI	-
Intermediate Risk	-	Stage IB, low-grade endometrioid, negative/focal LVSI	Stage IA without myometrial invasion
	-	Stage IA, high-grade endometrioid negative/focal LVSI	
	-	Stage IA serous, mixed, undifferentiated or carcinosarcoma without myometrial invasion	-
High-Intermediate Risk	-	Stage I with substantial LVSI, regardless of grade or depth of invasion	-
	-	Stage IB, high-grade regardless of LVSI	-
	-	Stage II endometrioid	-
High Risk	-	Stage III-IVA with no residual disease	Stage I-IVA with myometrial invasion and no residual disease
	-	Stage I-IVA serous, mixed, undifferentiated or carcinosarcoma with myometrial invasion and no residual disease	-

ESGO risk groups, Concin et al, 2020

ProMise >>>>>>>ProMisE-2

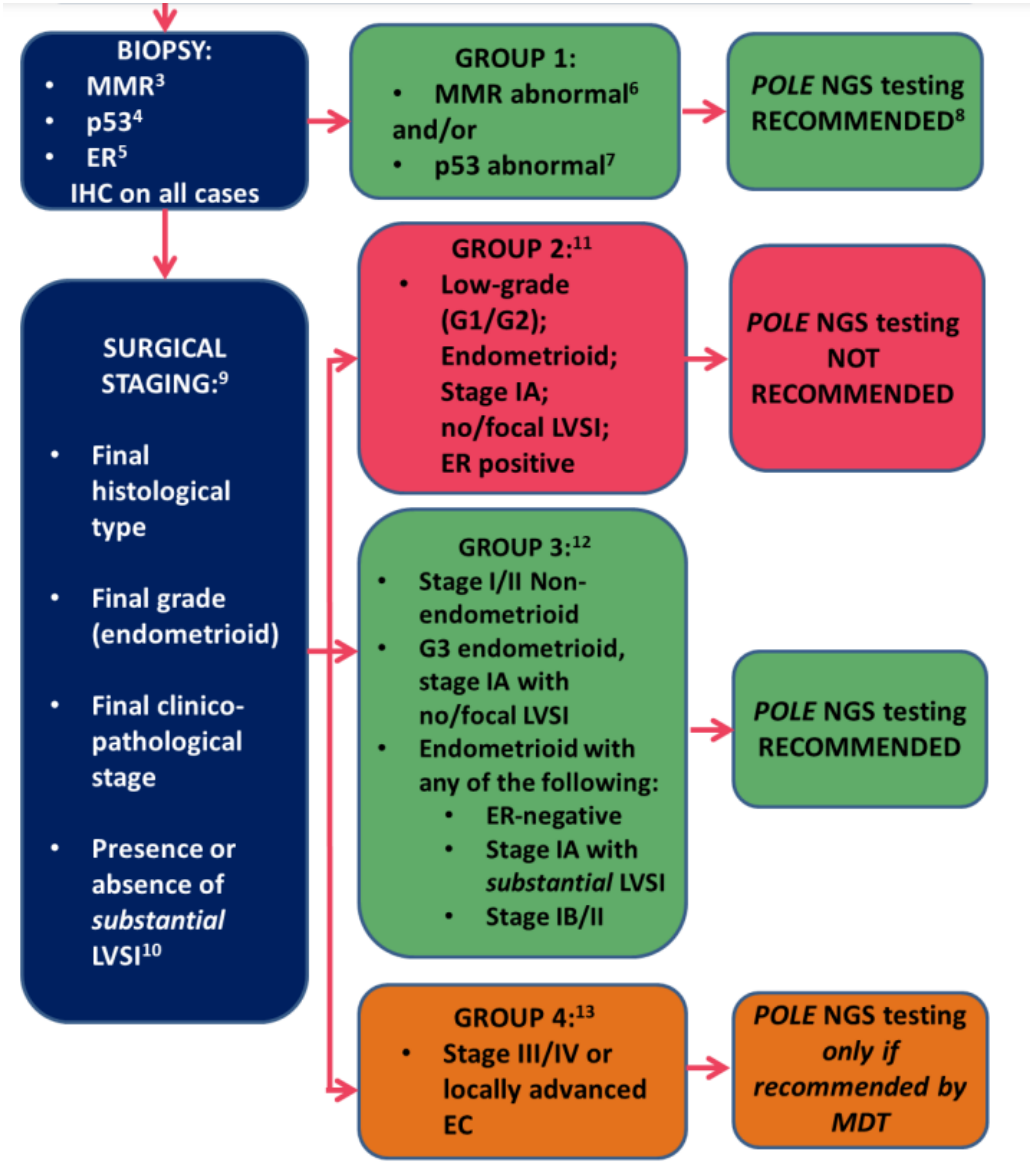


Cosbie et al Lancet 2022

One step molecular classifier

- DNA is extracted from tumor
- Next generation sequencing for *POLE* and *TP53* mutations (replacing p53 IHC)
- Microsatellite instability (MSI) assay (replacing MMR IHC)

WHO TO TEST (POLE)



BAGP &BGCS guidelines April 2022

SUMMARY OF MOLECULAR TESTING

- POLEmut has excellent prognosis
- PORTEC 4a will give further evidence of the use of any adjuvant treatment in Intermediate & high intermediate risk EC
- POLE testing should be carried out in all non-low risk patients as if found can obviate need for adjuvant treatment.

Molecular subtypes /Genomic classification

A

	POLE ultramutated	MSI hypermutated	Copy-number low, MSS	Copy-number high, serous-like
Mutation load				
Somatic copy number alterations load				
Histology	Endometrioid	Endometrioid	Endometrioid	Serous and endometrioid
Grade				
***PI3K* alterations**				
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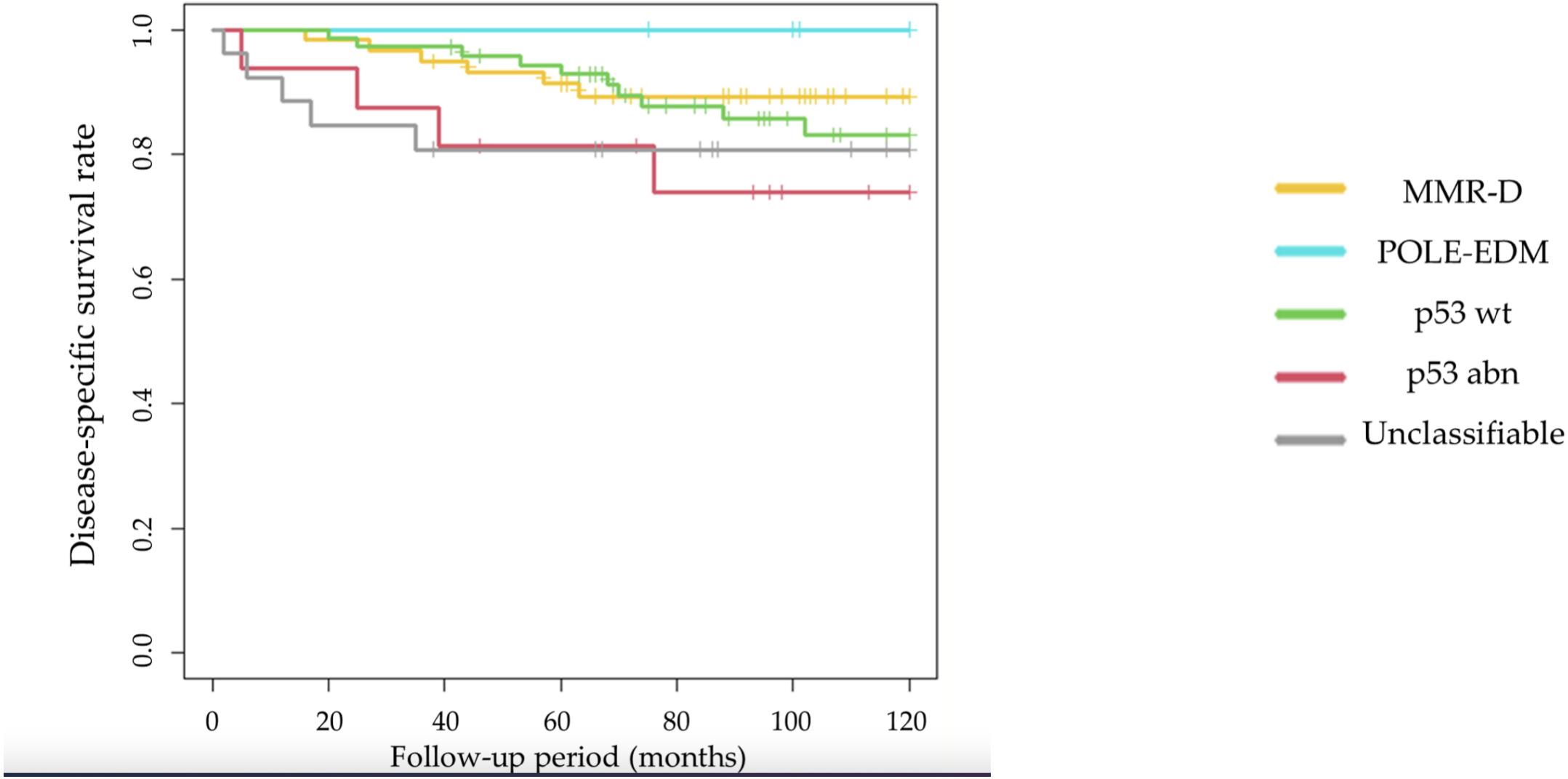
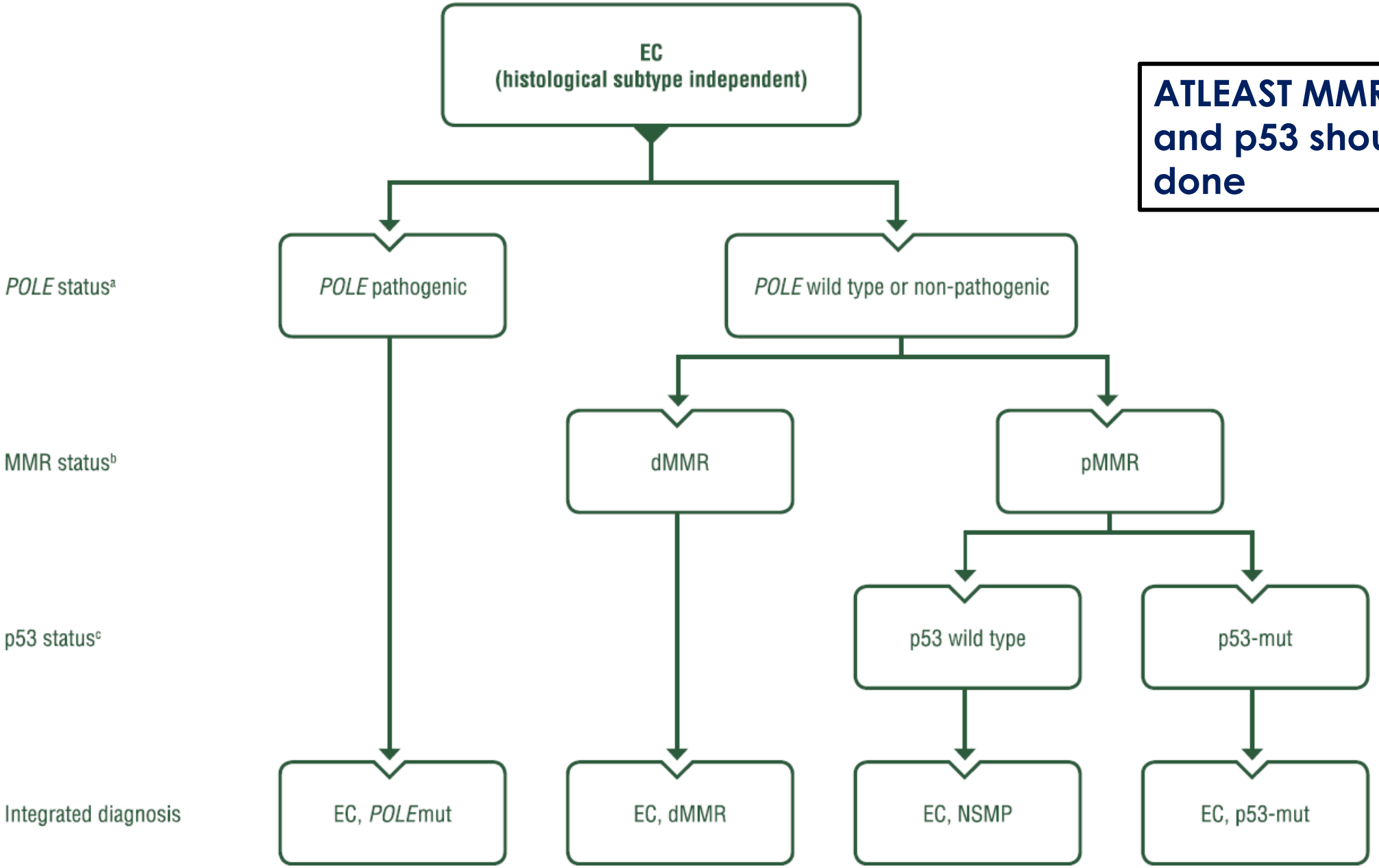
Disease-specific survival rates of patients according to the Proactive Molecular Risk Classifier for Endometrial Cancer classification system



2020 ESGO-ESTRO-ESP Recommendatio

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 foca
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 foca ► 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 wit 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



ATLEAST MMR IHC and p53 should be done

CONCISE, READY TO USE TREATMENT GUIDELINES FOR ENDOMETRIUM CANCER AFTER SURGERY

Endometrial cancer treatment guidelines post surgery: ESGO ESTRO 2020

Stage I

No further treatment if-

Stage IA Grades 1-3, pole m , Whatever LVSI

Stage IA Low Grade, MMRd/NSMP, LVSI Negative or focal

Brachytherapy only

Stage IA Grade 3, Endometroid, MMRd/NSMP, LVSI negative or focal

Stage IA, no myometrium invasion,

P53 abn or non endometroid

External Radiation (no chemo)

Stage IA or B, Grades 1-3, MMRd/NSMP

Substantial LVSI

External Radiation and chemo

Stage IA with myometrium invasion or stage B , Grades 1-3, p53 abnormal and/

or non endometroid

Stage II

Observation
If pole mutated for all grades and histologies

External Radiation (no chemo)
All grades, endometroid, NSMP/MMRd

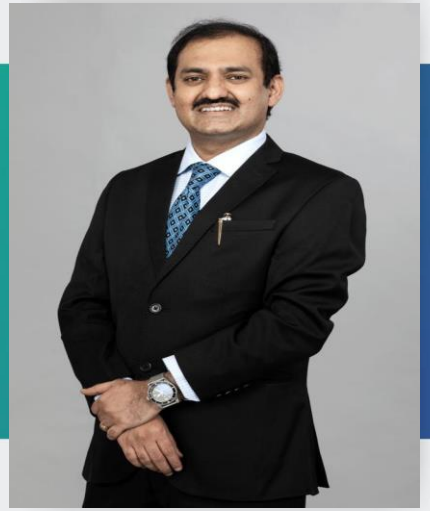
External radiation and chemo
P53 m or non endometroid

Stage III & IV - all need radiation and chemo

CONCLUSION

- The decision for adjuvant treatment in early endometrial cancer is taken based on surgical-pathological risk stratification after surgery
- The advent of molecular classification has revamped the risk stratification system
- MMR and p53 IHC can be adopted as a routine in LMIC resource setting. POLE sanger/NGS testing doesn't appear to be feasible in all.
- Appropriate Radiotherapy (EBRT/VBT) is the mainstay of adjuvant treatment in intermediate and high-intermediate groups.
- Chemotherapy appropriately sequenced with Radiotherapy is indicated in high-risk endometrial cancer.

Thanks



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