Nuovi algoritmi per la classificazione molecolare e il trattamento del carcinoma endometriale

Riunione del Gruppo di Miglioramento

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Ospedale Vizzolo Predabissi

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Epidemiologia

- Il carcinoma endometriale è il più comune cancro dell'apparato riproduttivo femminile;
- in Italia rappresenta il 3° tumore per frequenza nelle donne nella fascia di età 50-69 anni;
- complessivamente 4.6% dei tumori diagnosticati con circa 8300 nuovi casi/anno;
- insorge prevalentemente in età post-menopausale.

Aiom – Airtum: i numeri del cancro in Italia, 2020

Argomenti trattati

ANATOMIA PATOLOGICA

- I principali istotipi
- La nuova classificazione molecolare

ISTOTIPI

Istotipo	%
Adenocarcinoma endometrioide	75-80%
Adenocarcinoma sieroso-papillare	< 10%
Adenocarcinoma a cellule chiare	2-4%
Adenocarcinoma mucinoso	1%
Adenocarcinoma squamoso	< 1%
Adenocarcinoma misto	< 1%
Adenocarcinoma Indifferenziato	< 1%

Adenocarcinoma non-endometrioide

ISTOTIPI

Adenocarcinoma endometrioide: è l'istotipo più frequente ed è estrogeno correlato. È generalmente puro, in rari casi, tuttavia, può essere associato alla presenza di un carcinoma non endometrioide e la proporzione delle componenti influenza la diffusione della malattia e la prognosi. Per definizione, la componente di carcinoma non endometrioide deve rappresentare almeno il 10%, perché un carcinoma sia definito come misto. Il grado di differenziazione più frequentemente è il basso grado (G1-G2) rispetto all'alto grado (G3); il grado viene identificato in base alla percentuale di aree solide non squamose (G1 se <5%, G2 dal 6% al 50%, G3>50%). L'adenocarcinoma endometrioide può presentare una serie di aspetti morfologici che sono considerati espressione della potenzialità dell'epitelio mulleriano[9]. Tali aspetti possono essere focali o diffusi e, quando significativi, determinano una variante istologica.

ADENOCARCINOMA NON-ENDOMETRIODE

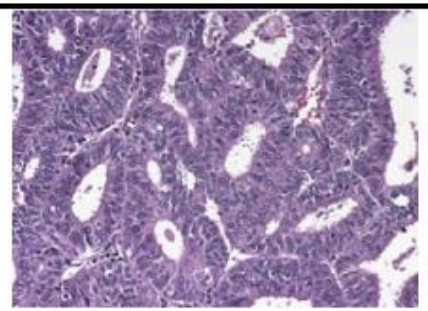
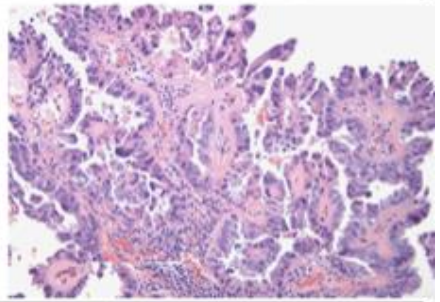
Adenocarcinoma sieroso-papillare: rappresenta il prototipo dell'adenocarcinoma non endometrioide. E' raro, circa il 5-10% dei carcinomi dell'endometrio, e va sospettato in donne in fascia di età di 10 anni superiore a quella dell'adenocarcinoma endometrioide o con anamnesi positiva per irradiazione pelvica, terapia prolungata con tamoxifene e cancro della mammella. Presenta invasione del miometrio ed associato ad invasione vascolare, spesso, sino al 75% dei casi, si presenta allo stadio III o IV, con metastasi ai linfonodi pelvici e para-aortici. Ha una prognosi peggiore rispetto alla forma endometrioide.

Adenocarcinoma a cellule chiare: tipico dell'età avanzata, ha prognosi sfavorevole. E' molto più raro dell'adenocarcinoma sieroso, circa l'1% dei carcinomi dell'endometrio. Appare come un gruppo eterogeneo, in quanto alcuni carcinomi hanno caratteristiche considerate tipiche ed altri, che rappresentano sino ai due terzi dei carcinomi a cellule chiare, presentano caratteristiche analoghe ai carcinomi sierosi. Il carcinoma a cellule chiare tipico, per definizione, ha gli stessi caratteri istologici architetturali del carcinoma a cellule chiare di altre sedi genitali.

Classical risk factors

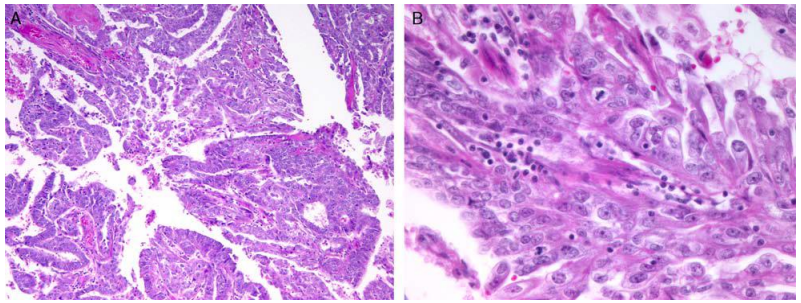
- Histological subtype
- Grade (G1-2 vs G3)
- Myometrial invasion
- LVSI
- Stage

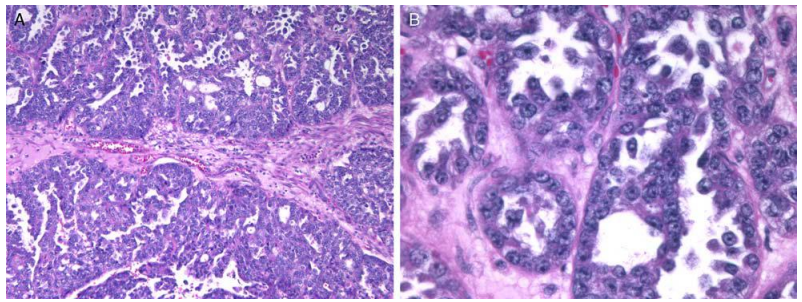
1983: a dualistic model for endometrial tumorigenesis

		Pathogenetic type	
		I	II
			
General clinical features	Menstrual function	History of anovulatory bleeding	Normal
	Reproductive function	Frequent infertility	Normal
	Onset of menopause	Often after age 50	Often before age 50
	Endometrial background or result of previous sampling	Hyperplasia	Atrophy
	Obesity	Present	Absent
	Hyperlipidemia	Present	Absent
	Diabetes mellitus	Present	Absent
	Hypertension	Associated with obesity and/or diabetes mellitus	Absent or not associated with obesity and/or diabetes mellitus
Tumor characteristics	Duration of symptoms	Usually long	Usually short
	Myometrial invasion	Frequently superficial	Frequently deep
	Potential for lymphovascular invasion	Low	High
	Progesterone sensitivity	High	Low
	Low grade ("G1 + G2")	79.9% of cases	34.3% of cases
	High grade ("G3")	20.1% of cases	65.7% of cases
	Prognosis	Favorable	Doubtful

Bokhman JV et al, Gyn Onc 1983
Suarez AA, et al, Gyn Onc 2017

The dualistic model in crisis





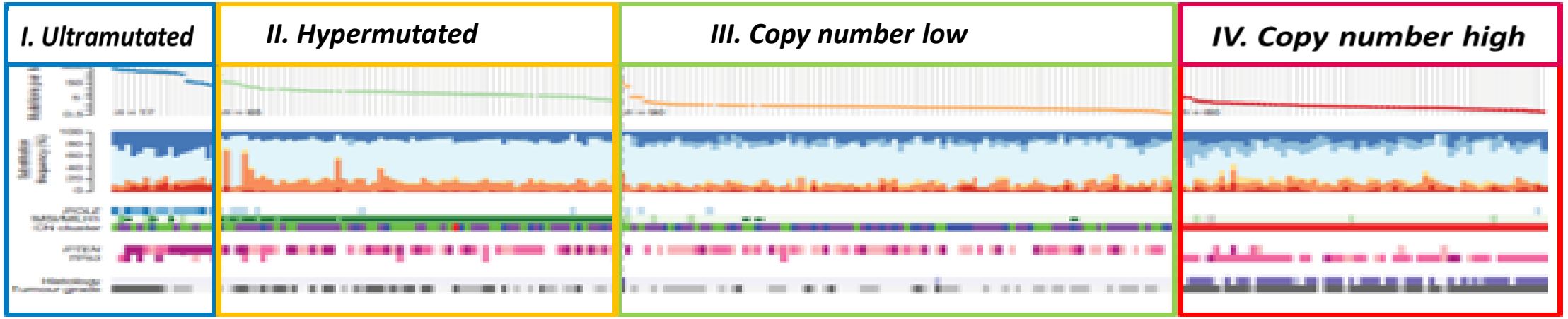
CURRENT SYSTEM OF CLASSIFICATION BASED ON HISTOMORPHOLOGY IS INADEQUATE

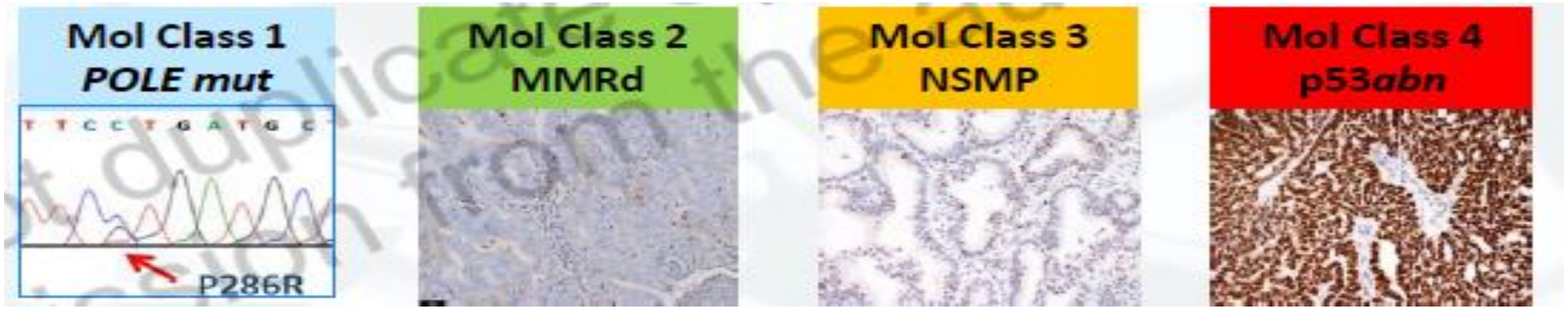
- ❖ POOR REPRODUCIBILITY OF HISTOTYPE, ESPECIALLY IN HIGH GRADE TUMORS
- ❖ POOR REPRODUCIBILITY OF GRADE BETWEEN BIOPSY AND HYSTERECTOMY
- ❖ POOR INTEROBSERVER REPRODUCIBILITY

- ➢ INCONSISTENT / POSSIBLY INAPPROPRIATE RISK STRATIFICATION WITH CONSEQUENCE OF UNDER AND OVER TREATMENT
- ➢ BATCHING OF MOLECULARLY DIVERSE TUMOURS IN CLINICAL TRIAL… DIFFICULT TO ASSESS EFFICACY OF TREATMENT

Gilks CB et al, Am J Surg Pathol 2013

TCGA molecular groups by surrogate markers
ProMisE molecular classifier





Molecular classification is more objective. Identifies 4 subtypes through pragmatic, clinically applicable tests: immunohistochemistry (IHC) for mismatch repair proteins and p53, and focused sequencing to detect *POLE* pathogenic mutations.

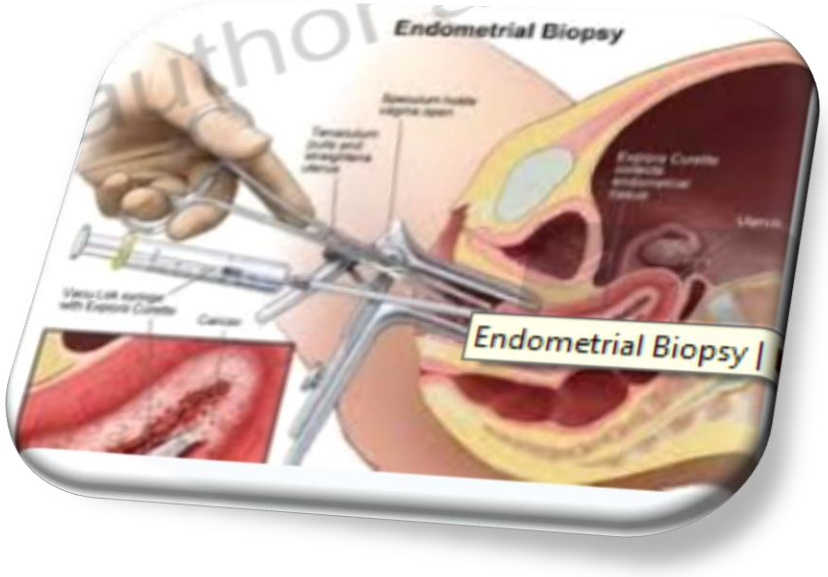
TGCA, Nature 2013
Stelloo et al, Clin Cancer Research 2016
Kommoset al, Annals of Oncology 2018

Timing of molecular classification

Current system of risk stratification requires staging.

<u>Molecular stratification provides earlier information to direct EC staging</u>

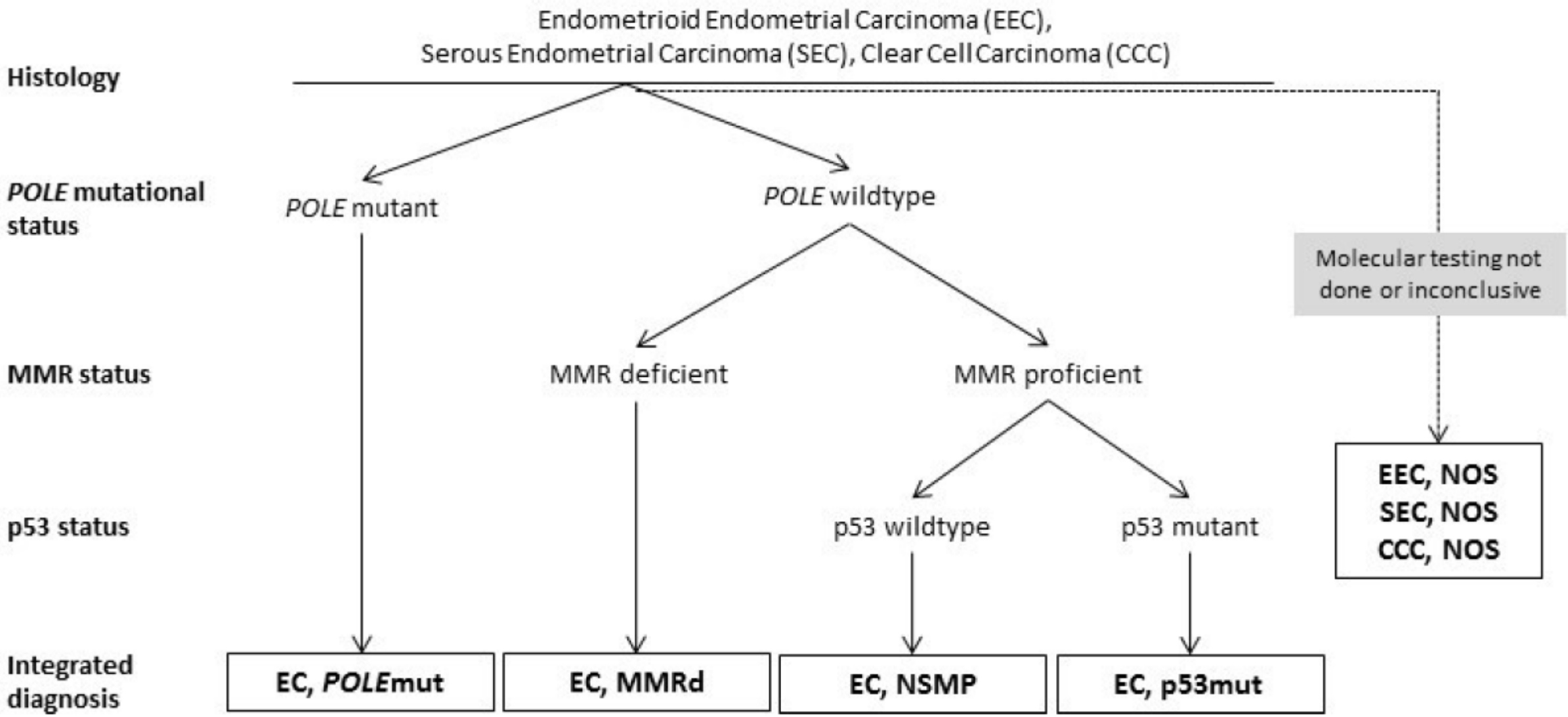
- ✓ Classification feasible and achievable on diagnostic biopsies
- ✓ High concordance in molecular subtype assessed on endometrial biopsy/curettage specimen to final hysterectomy



Stelloo et al, Gyn Onc 2014
Talhouk et al, Gyn Onc 2016
Kommoss et al, Ann Oncol 2018
Abdulfatah et al, Gyn Onc 2019

ALGORITMO DIAGNOSTICO

A hierarchical clustering



EC, endometrial cancer; MMR; mismatch repair; NSMP, no specific molecular profile; NOS, not otherwise specified

MOLECULAR CATEGORIES ATTRIBUTION

POLE	MMR	p53	MOLECULAR SUBTYPE
mut	MMR-p	normal	POLE
wt	MMR-d	normal	MMR-d
wt	MMR-p	normal	NSMP/p53wt
wt	MMR-p	abn	p53abn
mut	MMR-d	normal	double classifier → POLE
mut	MMR-p	abn	double classifier → POLE
wt	MMR-d	abn	double classifier → MMR-d
mut	MMR-d	abn	multiple classifier → POLE

Stelloo et al, Gyn Onc 2014
Talhouket al, Gyn Onc 2016
Kommoss et al, Onc 2018
Abdulfatah et al, Gyn Onc 2019
Leon-Castillo et al, J Path 2019

ARGOMENTI TRATTATI

DIAGNOSI E STADIAZIONE

- ESAMI INDICATI PER DIAGNOSI E STADIAZIONE
- STADIAZIONE FIGO

ESAMI INDICATI PER DIAGNOSI E STADIAZIONE

- diagnosi effettuata su **prelievo bioptico eseguito con isteroscopia o D&C** (dilatation and curettage).

- il work-up preoperatorio ginecologico prevede la **colposcopia e il pap-test**.

- esami di imaging addominale: **ecografia trans-vaginale e RMN pelvica con mdc,** utili per valutare l'infiltrazione miometriale, l'interessamento cervicale, e l'eventuale coinvolgimento delle tube e/o delle ovaie.

- **TC torace/addome con mdc** utile per valutare lo stato dei linfonodi pelvici e aortici, e per evidenziare l'eventuale diffusione di malattia al fegato e al peritoneo e in sede sovradiaframmatica.

- ulteriori indagini (**cistoscopia, colonscopia, PET/CT**) eseguite su indicazione clinica.

Stadiazione FIGO (2009)

Stadio I			**Tumore limitato al corpo dell'utero**
	IA		Nessuna infiltrazione o < 1/2del miometrio
	IB		Infiltrazione > 1/2 del miometrio
Stadio II			**Tumore esteso allo stroma cervicale, ma non fuori dall'utero**
Stadio III			**Estensione locale o regionale**
	IIIA		Estensione alla sierosa uterina, o alle ovaie
	IIIB		Estensione alla vagina o ai parametri
	IIIC		Estensione ai linfonodi pelvici o lombo-aortici
		IIIC1	Linfonodi pelvici positivi
		IIIC2	Linfonodi lombo-aortici positivi, indipendentemente dai pelvici
Stadio IV			**Estensione alla mucosa vescicale o intestinale o metastasi a distanza**
	IV A		Estensione alla mucosa vescicale o intestinale
	IV B		Metastasi a distanza

ARGOMENTI TRATTATI

PERCORSI TERAPEUTICI

- CHIRURGIA
- TRATTAMENTI ADIUVANTI INTEGRATI POST-CHIRURGICI

  - GRUPPI DI RISCHIO IN FUNZIONE DEI FATTORI ANATOMO-PATOLOGICI

  - GRUPPI DI RISCHIO IN FUNZIONE DEI FATTORI ANATOMO-PATOLOGICI E DELLA CLASSIFICAZIONE MOLECOLARE

  - TRATTAMENTI ADIUVANTI (BRT, EBRT, CHT) IN BASE A STRATIFICAZIONE SU GRUPPI DI RISCHIO

FIGO 2009

Stadiazione chirurgica

- ✓ Procedura chirurgica standard: isterectomia totale extrafasciale con annessiectomia bilaterale (anche ad ovaie apparentemente normali) senza asportazione dell'orletto vaginale, per via laparotomica o mini-invasiva
- ✓ Accurata esplorazione della pelvi e dell'intero addome
- ✓ Ispezione e palpazione delle catene linfonodali pelviche e lomboaortiche
- ✓ Washing peritoneale

CHIRURGIA

- qualora la paziente non venga giudicata idonea per una chirurgia addominale soprattutto per obesità, è consigliabile inviarla per una **second opinion** presso un centro che dispone del robot per verificare se sia operabile con questo strumento.

- le pazienti **non operabili** neppure via vaginale sono trattate con radioterapia +/- ormonoterapia.

- l'**omentectomia** è indicata nel carcinoma sieroso, nel carcinoma indifferenziato e nel carcinosarcoma per l'alto rischio di metastasi microscopiche omentali, mentre non è suggerita nel carcinoma a cellule chiare.

LINFADENECTOMIA

LINEE GUIDA ESGO/ESTRO/ESP 2021 E AIOM

- **Basso rischio (G1-G2 con infiltrazione miometriale <50%):** non si effettua linfoadenectomia.

- **Rischio intermedio (G1-G2 con infiltrazione miometriale >50%:** linfoadenectomia stadiativa (pelvica o linfonodo sentinella).

- **Rischio intermedio/alto (G1-G2 con infiltrazione miometriale >50% con infiltrazione degli spazi linfovascolari oppure G3 con infiltrazione miometriale <50%):** linfoadenectomia stadiativa (pelvica o linfonodo sentinella).

- **Alto rischio (G3 con infiltrazione miometriale >50%):** linfoadenectomia pelvica e paraortica sistematica.

- La rimozione di linfonodi di volume aumentato è sempre raccomandata.
- Presence of both macrometastases and micrometastases (<2 mm, pN1(mi)) is regarded as a metastatic involvement (IV, C).
- The prognostic significance of ITCs, pN0(i+), is still uncertain (IV, C).

MALATTIA AVANZATA

- in presenza di metastasi a distanza o di malattia recidivante non suscettibile di chirurgia e/o radioterapia, la paziente viene trattata con chemioterapia.

- la combinazione **carboplatino + paclitaxel** è il regime standard.

- l'**ormonoterapia** con inibitori delle aromatasi, eventualmente associati ad everolimus, o con progestinici è una ulteriore opzione terapeutica per neoplasie a lenta crescita con positività dei recettori per estrogeni e progesterone.

- **pembrolizumab e dostarlimab** possono essere utilizzati in pazienti con carcinoma endometriale con MSI-high/MMRd in progressione dopo terapia convenzionale.

Trattamenti adiuvanti integrati

Risk Group	Molecular Classification Unknown
Low	• Stage IA endometrioid, grade 1–2, LVSI negative or focal
Intermediate	• Stage IB endometrioid, grade 1–2, LVSI negative or focal • Stage IA endometrioid, grade 3, LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	• Stage I endometrioid, substantial LSVI, regardless of grade and depth of invasion • Stage IB endometrioid, grade 3, regardless of LVSI status • Stage II
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
Advanced	• Stage III–IVA with residual disease
Metastatic	• Stage IVB

GRUPPI DI RISCHIO IN FUNZIONE DEI FATTORI ANATOMO - PATOLOGICI

Terapia adiuvante per classe di rischio

Classe di rischio	Trattamenti adiuvanti	Commenti
BASSO	Osservazione	▪ Le pazienti a basso rischio non necessitano di un ulteriore trattamento
INTERMEDIO	Brachiterapia (BCT) Osservazione	▪ Le pazienti a rischio intermedio possono ricevere una brachiterapia adiuvante, per ridurre il rischio di recidiva vaginale, o nessun ulteriore terapia specialmente se di età < 60 anni.
INTERMEDIO/ALTO	Radioterapia esterna (EBRT) Brachiterapia (BCT)	Le pazienti a rischio intermedio-alto sono trattate con: ▪ **radioterapia esterna pelvica** specialmente se in stadio II o se presentano LVSI sostanziale e non è noto lo stato linfonodale ▪ **brachiterapia** se hanno malattia in stadio I, grado G3 e LVSI negativo o in stadio II grado 1.
ALTO	Chemioterapia + EBRT Chemioterapia +/- BCT	▪ Le pazienti ad rischio alto sono trattate **sequenzialmente con chemioterapia e radioterapia esterna pelvica oppure con chemio-radioterapia concomitante seguita da chemioterapia adiuvante**. ▪ La chemioterapia esclusiva, con o senza brachiterapia, può rappresentare un'alternativa terapeutica soprattutto in presenza di una negatività linfonodale accertata istologicamente.

Colombo N, et al. Annals of Oncology, 2016

Risk Group	Molecular Classification Known
Low	• Stage I–II POLE EDM endometrial carcinoma, no residual disease • Stage IA MMRd/p53 wt endometrioid carcinoma + low grade + LVSI negative or focal
Intermediate	• Stage IB MMRd/p53 wt endometrioid carcinoma + low-grade + LVSI negative or focal • Stage IA MMRd/p53 wt endometrioid carcinoma + high-grade + LVSI negative or focal • Stage IA p53 abn and/or non-endometrioid without myometrial invasion
High-intermediate	• Stage I MMRd/p53 wt endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion • Stage IB MMRd/p53 wt endometrioid carcinoma high-grade regardless of LVSI status • Stage II MMRd/p53 wt endometrioid carcinoma
High	• Stage III–IVA MMRd/p53 wt endometrioid carcinoma with no residual disease • Stage I–IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease • Stage I–IVA p53 wt/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced	• Stage III–IVA with residual disease of any molecular type
Metastatic	• Stage IVB of any molecular type

GRUPPI DI RISCHIO IN FUNZIONE DEI FATTORI ANATOMO - PATOLOGICI E DELLA CLASSIFICAZIONE MOLECOLARE

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]

Concin N, *et al. Int J Gynecol Cancer* 2020;**0**:12–39. doi:10.1136/ijgc-2020-002230

Trattamenti adiuvanti
Linee guida ESGO/ESTRO/ESP 2020

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

Recommendations

For patients with low-risk endometrial carcinoma**, *no adjuvant treatment is recommended* (I, A).**

When molecular classification is known:

- For patients with endometrial carcinoma stage I–II, low-risk based on pathogenic *POLE*-mutation, omission of adjuvant treatment should be considered (III, A).
- For the rare patients with endometrial carcinoma stage III–IVA and pathogenic *POLE*-mutation, there are no outcome data with the omission of the adjuvant treatment. Prospective registration is recommended (IV, C).

‡ Low grade: G1 – G2

Trattamenti adiuvanti
Linee guida ESGO/ESTRO/ESP 2020

Risk group	Molecular classification unknown	Molecular classification known*†
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

Recommendations

- ***Adjuvant brachytherapy can be recommended to decrease vaginal recurrence (I, A).***
- Omission of adjuvant brachytherapy can be considered (III, C), especially for patients aged <60 years (II, A).

- For p53abn carcinomas restricted to a polyp or without myometrial invasion, adjuvant therapy is generally not recommended (III, C).
- When molecular classification is known, POLEmut and p53abn with myometrial invasion have specific recommendations (see respective recommendations for low- and high-risk).

Trattamenti adiuvanti
Linee guida ESGO/ESTRO/ESP 2020

Risk group	Molecular classification unknown	Molecular classification known*†
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–intermediate risk (pN0 after lymph node staging)

Recommendations

- ***EBRT can be considered for substantial LVSI and for stage II*** (I, B).
- ***Adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI*** (II, C).
- ***Adjuvant brachytherapy can be recommended to decrease vaginal recurrence*** (II, B).

- Omission of any adjuvant treatment is an option (IV, C).
- When molecular classification is known, POLEmut and p53abn have specific recommendations (see respective recommendations for low- and high-risk).

Trattamenti adiuvanti
Linee guida ESGO/ESTRO/ESP 2020

Risk group	Molecular classification unknown	Molecular classification known*†
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–intermediate risk cN0/pNx (lymph node staging not performed)

Recommendations

- ***Adjuvant EBRT is recommended, especially for substantial LVSI and/or for stage II (I, A).***
- ***Additional adjuvant chemotherapy can be considered, especially for high-grade and/or substantial LVSI (II, B).***
- ***Adjuvant brachytherapy alone can be considered for high-grade LVSI negative and for stage II grade 1 endometrioid carcinomas (II, B).***

- When molecular classification is known, *POLE*mut and p53abn have specific recommendations (see respective recommendations for low- and high-risk).

Trattamenti adiuvanti
Linee guida ESGO/ESTRO/ESP 2020

Risk group	Molecular classification unknown	Molecular classification known*†
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

Recommendations

- ***EBRT with concurrent and adjuvant chemotherapy (I, A) or alternatively sequential chemotherapy and radiotherapy is recommended (I, B).***
- ***Chemotherapy alone is an alternative option (I, B).***
- *Carcinosarcomas should be treated as high-risk carcinomas (not as sarcomas) (IV, B).*

- When the molecular classification is known, p53abn carcinomas without myometrial invasion and *POLEmut* have specific recommendations (see respective recommendations for low and intermediate-risk) (III, C).

Trattamenti adiuvanti

Linee guida ESGO/ESTRO/ESP 2020

Risk group	Molecular classification unknown	Molecular classification known*†
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

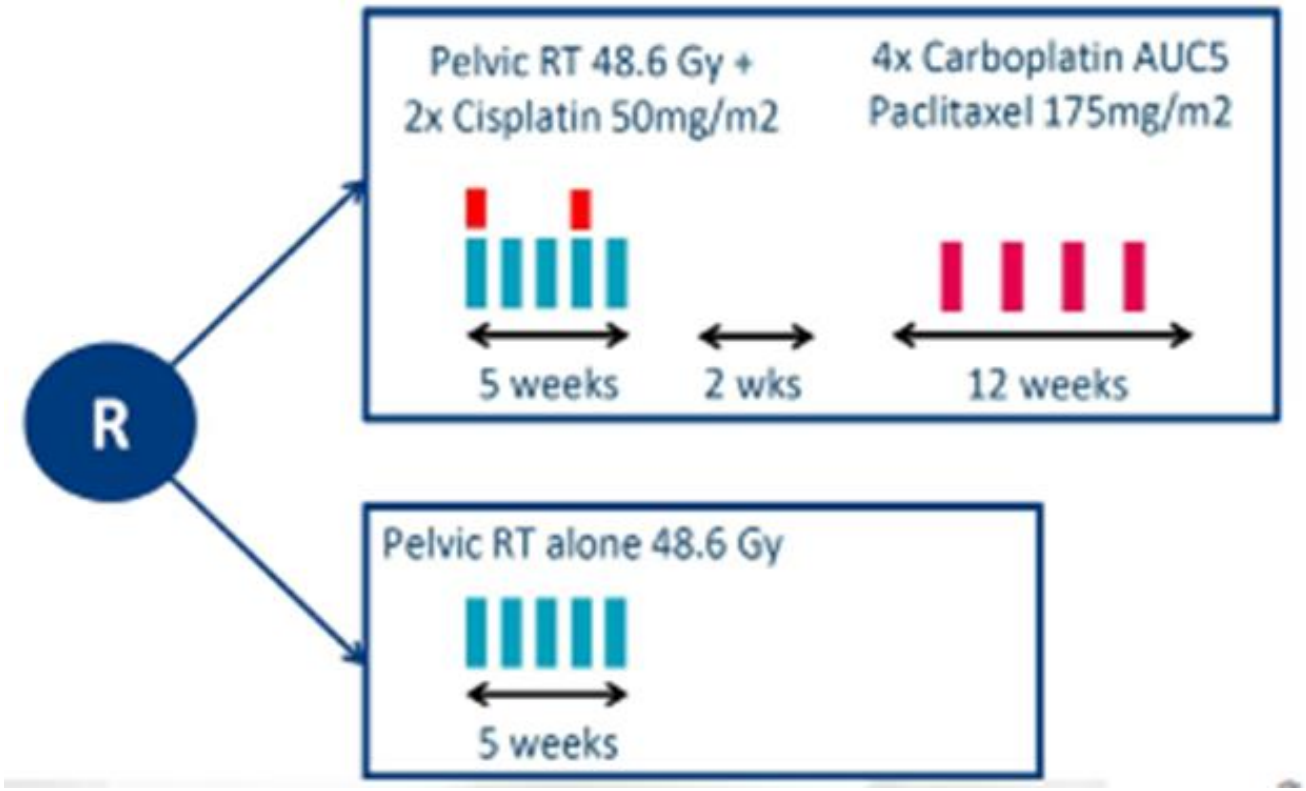
Recommendations

- In stage III and IV endometrial carcinoma (including carcinosarcoma), ***surgical tumor debulking including enlarged lymph nodes*** should be considered when complete macroscopic resection is feasible with an acceptable morbidity and quality of life profile, following full pre-operative staging and discussion by a multi-disciplinary team (IV, B).
- ***Primary systemic therapy should be used if upfront surgery is not feasible or acceptable*** (IV, A).
- In cases of a good response to systemic therapy, delayed surgery can be considered (IV, C).
- Only enlarged lymph nodes should be resected. Systematic lymphadenectomy is not recommended (IV, B).

PORTEC-3 trial – CTRT vs RT
high-risk endometrial cancer

Eligible pts (FIGO 2009):

- IA G3 EEC with documented LVSI;
- IB G3 EEC;
- II EEC;
- IIIA, IIIB (parametrial invasion), or IIIC EEC;
- IA (with invasion), IB, II, III serous or clear-cell.

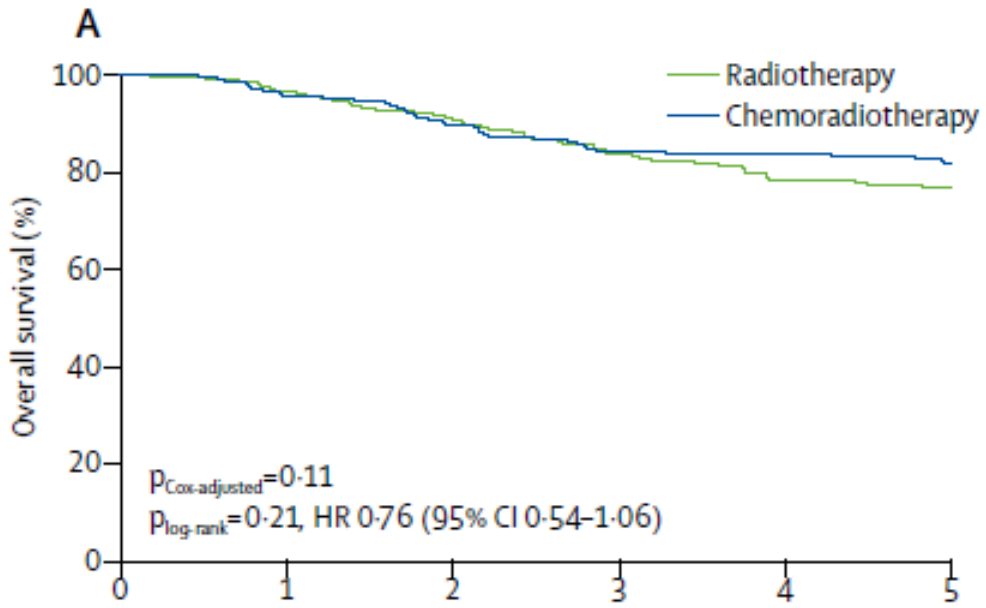


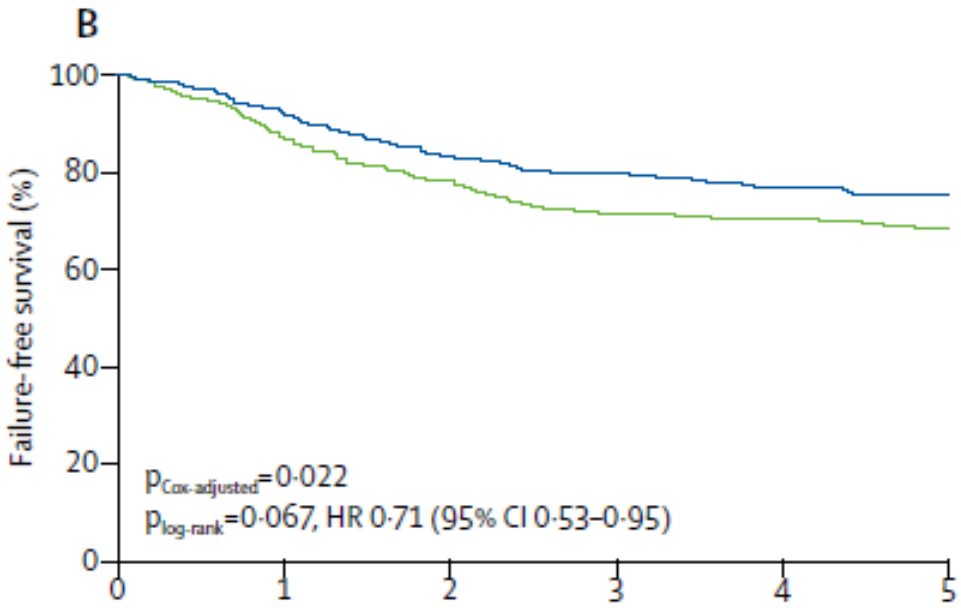
Coprimary endpoints:
- overall survival
- failure-free survival (FFS)

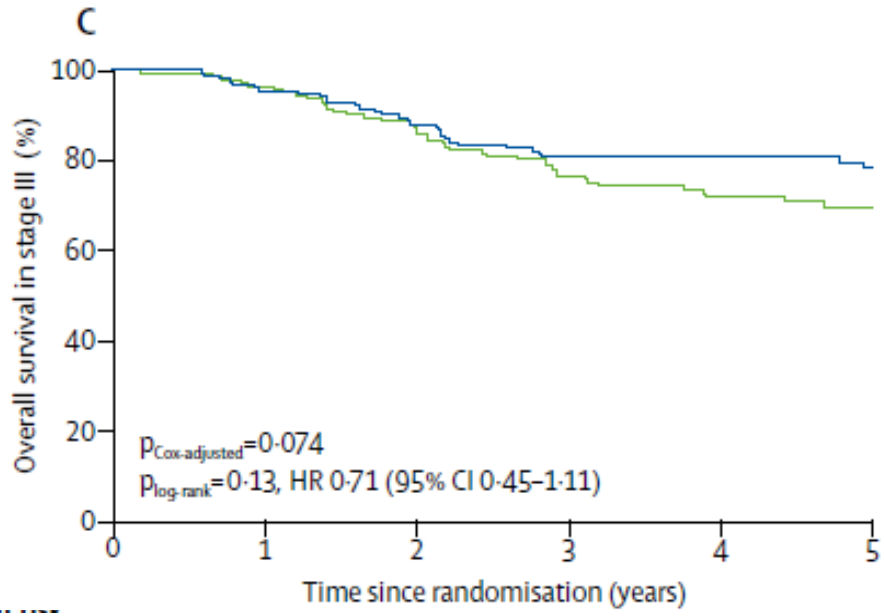
De Boer et al, Lancet Oncology 2019

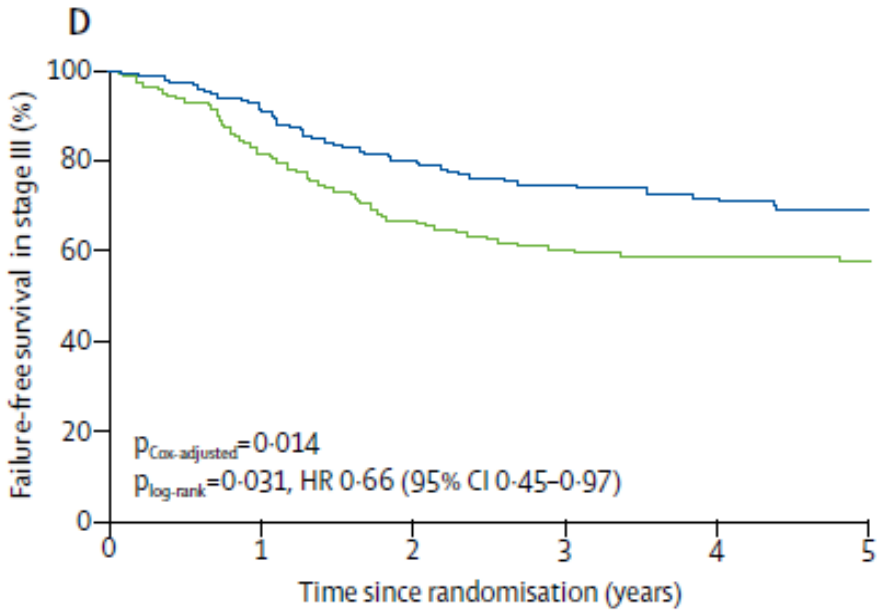
PORTEC-3 : results

A) OS in all pts
B) FFS in all pts





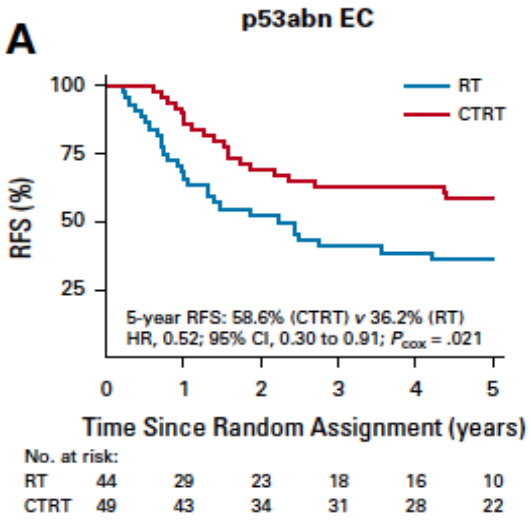


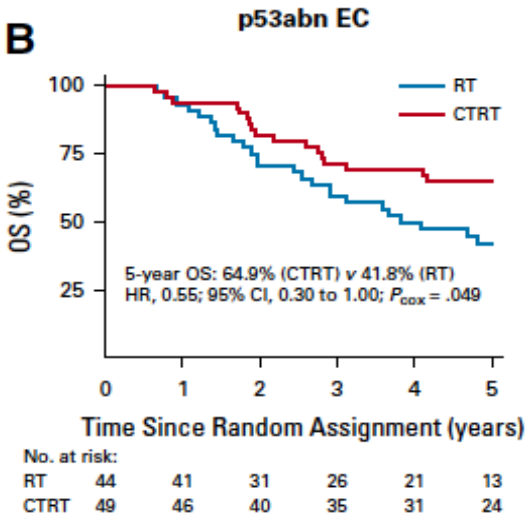


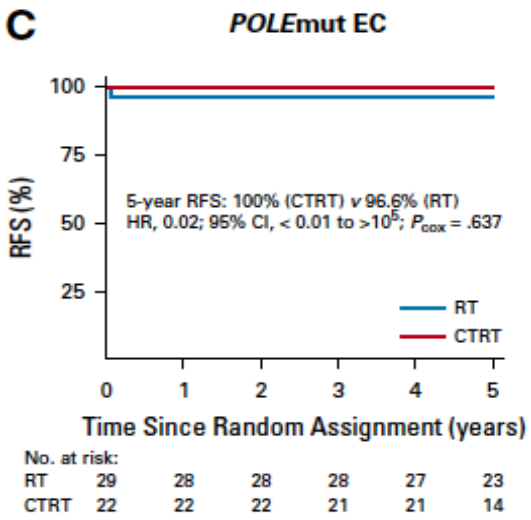
C) OS pts stage III
D) FFS pts stage III

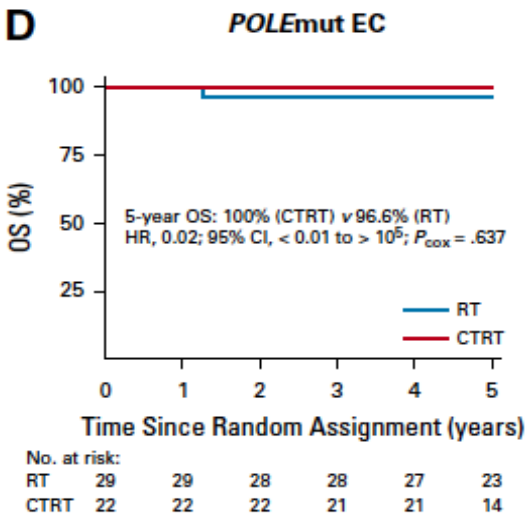
De Boer et al, Lancet Oncology 2019

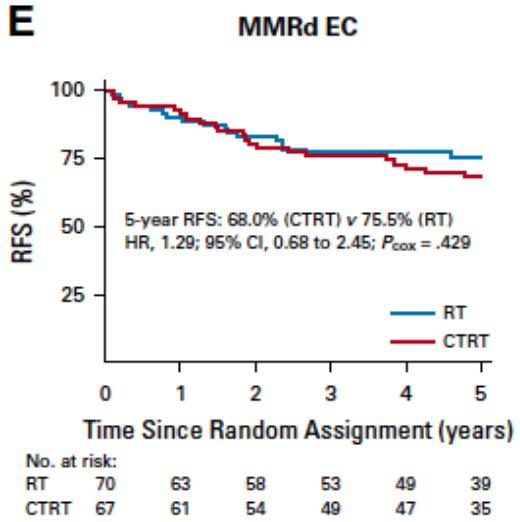
PORTEC-3
MOLECULAR CLASSIFICATION PREDICTIVE OF BENEFIT FROM ADJUVANT CHEMOTHERAPY?

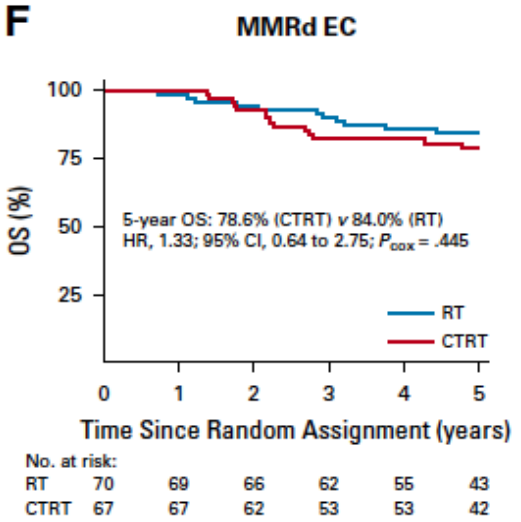


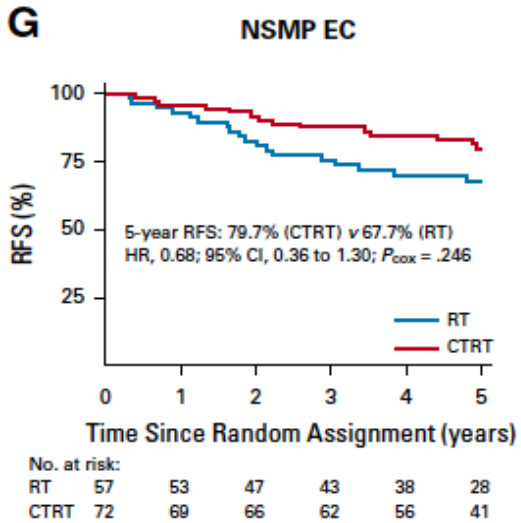


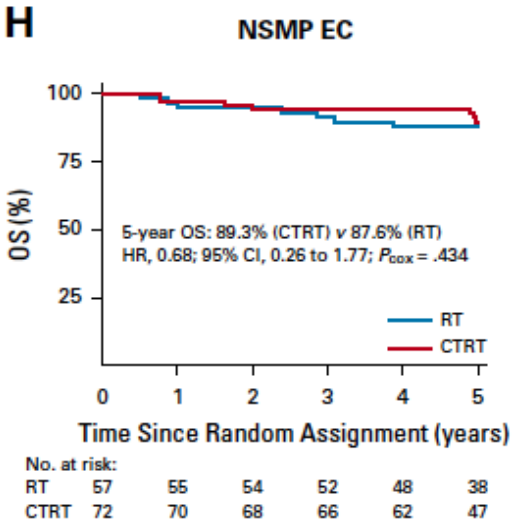








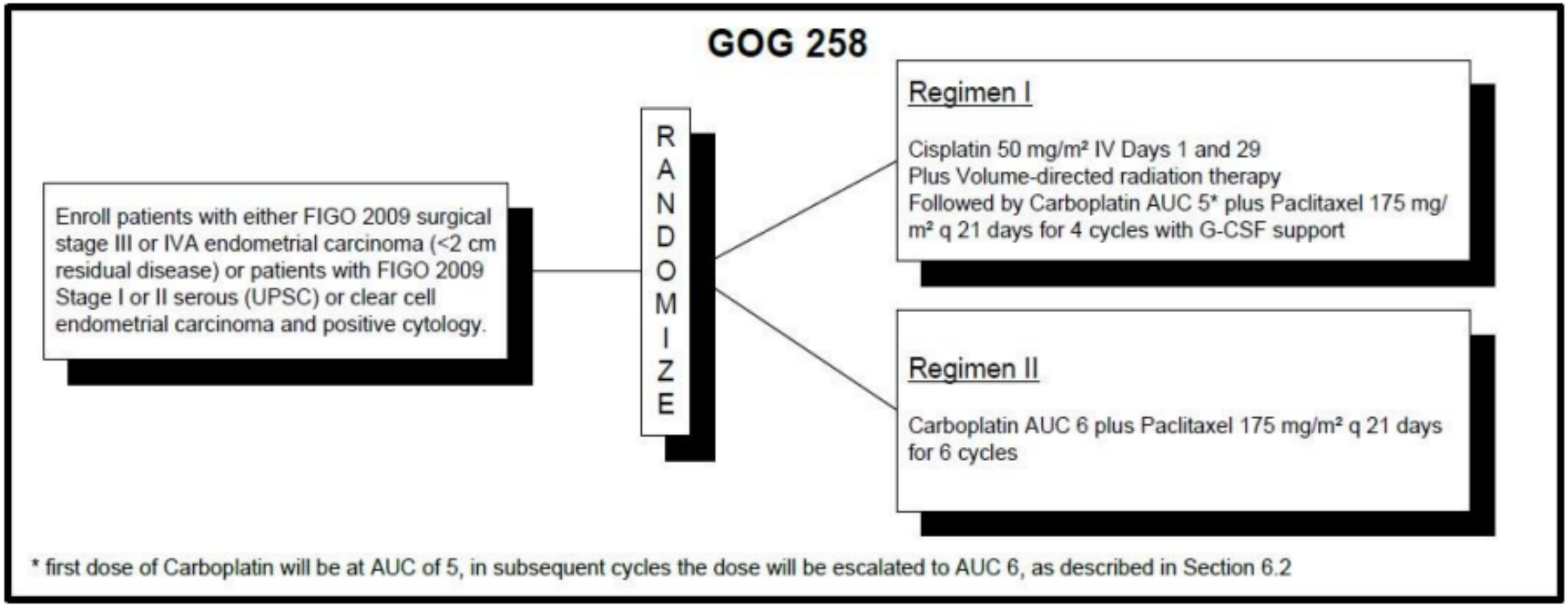




Leon-Castillo et al, JCO 2020

The NEW ENGLAND JOURNAL of MEDICINE

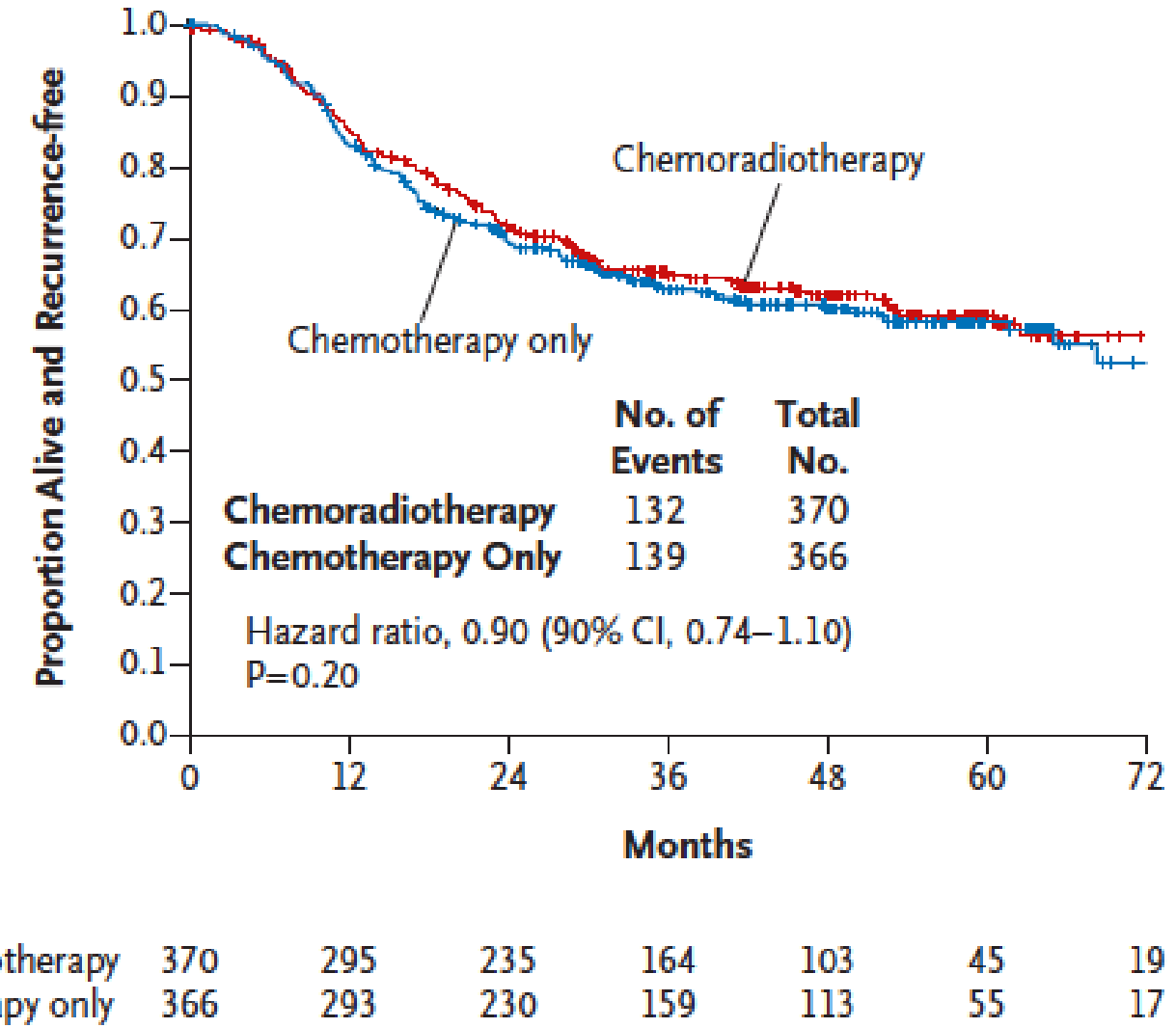
Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer



Matei D. et al, N Engl J Med 2019

GOG 258 : results

Primary endpoint:
- relapse-free survival



Matei D. et al, N Engl J Med 2019

Phase III Trial: Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/ Carboplatin in High-Intermediate and High-Risk Early-Stage Endometrial Cancer

Journal of Clinical Oncology

Endometrial cancer
1) stage I with high-intermediate risks with +/- cytology
2) stage II (any histology), +/- risk factors
3) stage I/II serous or clear cell cancers with neg cytology
n= 562

→ Pelvic RT
optional vaginal cuff boost

→ Vaginal cuff brachy +
3 cycles of
paclitaxel 175 mg/m2 +
carboplatin AUC 6

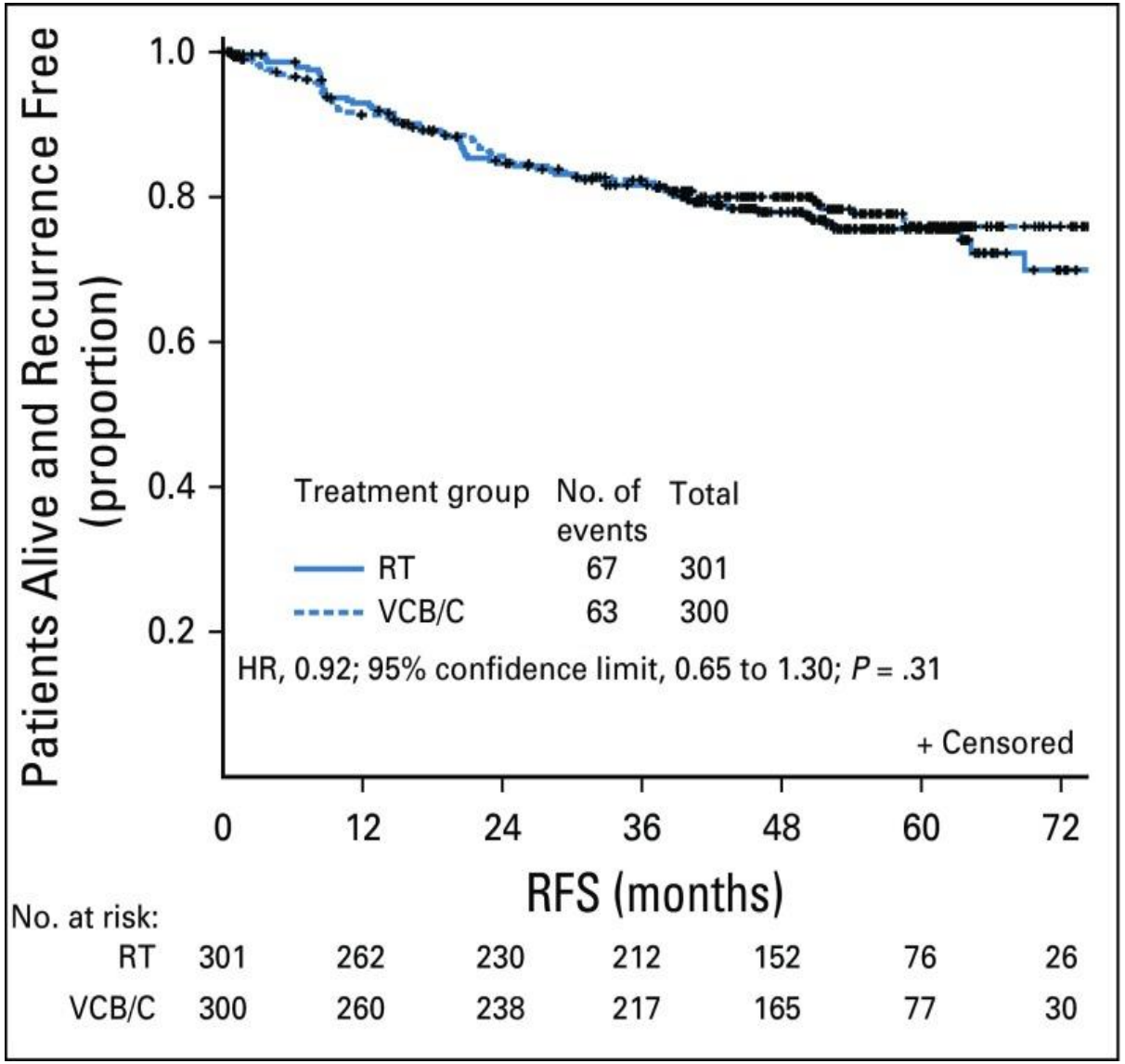
Primary endpoint:
- recurrence-free survival (RFS)

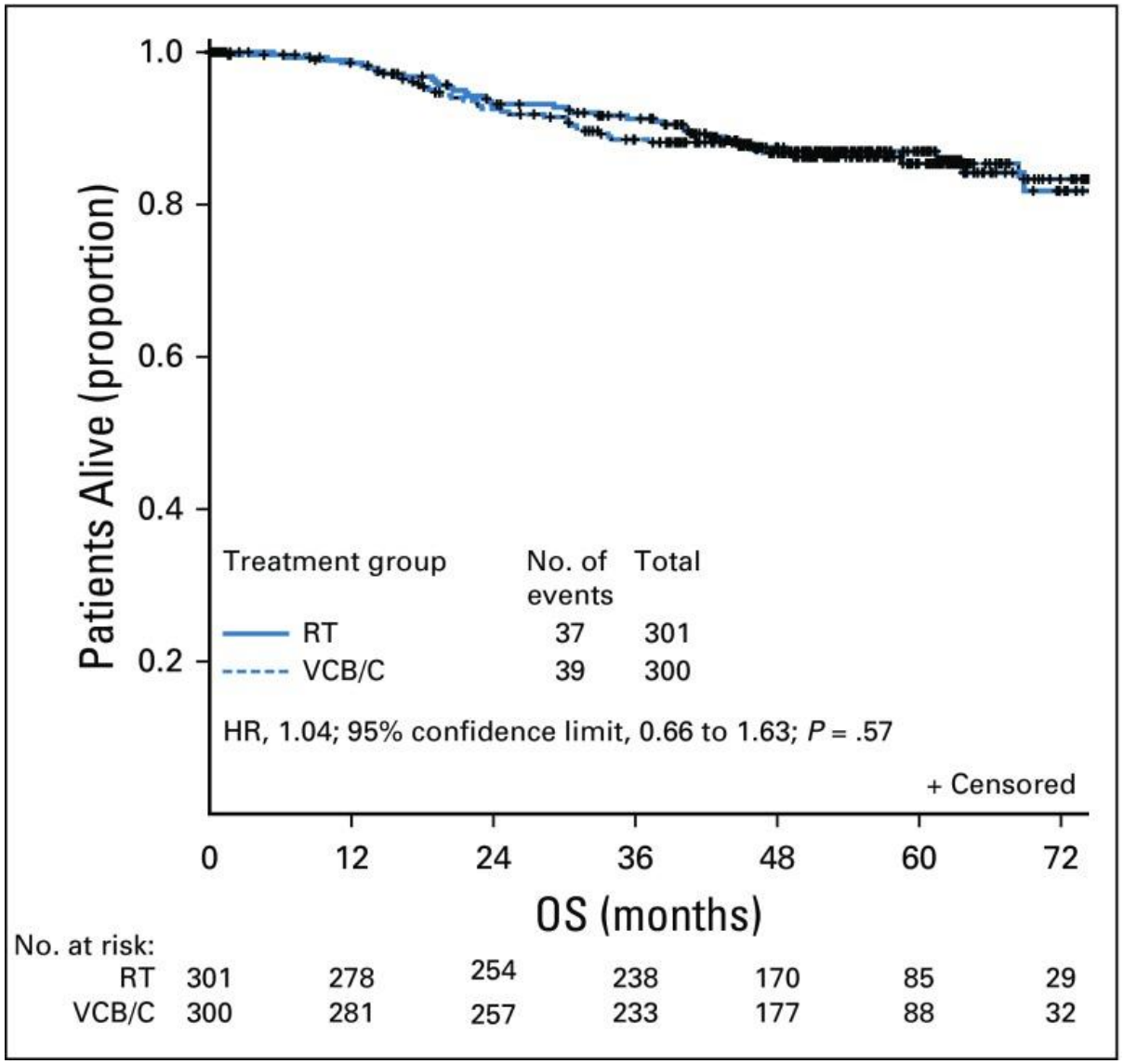
High-intermediate risks:
age ≥ 70 yrs with one risk factor
age ≥ 50 yrs with 2 risk factors
age ≥ 18 yrs with 3 risk factors

Risk factors:
grade 2 or 3 tumor
+LVI
outer ½ myometrial invasion

Randall et al, JCO 2019

GOG 249 : results





Randall et al, JCO 2019

European School of Oncology

Summary - Can molecular classification help with adjuvant treatment decision?

- p53abn improved response to chemotherapy
- POLEmut de-escalation of treatment > observation
- MMRd improved response to RT

Howitt et al, JAMA 2015
Le et al, NEJM 2015
Van Gool et al, CCR 2018
Reijnen et al, Gyn Onc 2019
Leon-Castillo et al, JCO 2020

Istotipo	Terapia
Recidiva locoregionale	
Tutti gli istotipi	Chirurgia o radioterapia in pazienti non irradiate +/- chemioterapia
Recidiva sistemica	
Endometrioide basso grado	Ormonoterapia Opzione: Chemioterapia con Carboplatino e Taxolo
Alti gradi ed istotipi speciali	Carboplatino e taxolo per sei cicli Nessuna seconda linea standard
Terapia palliativa	Terapia di supporto o radioterapia

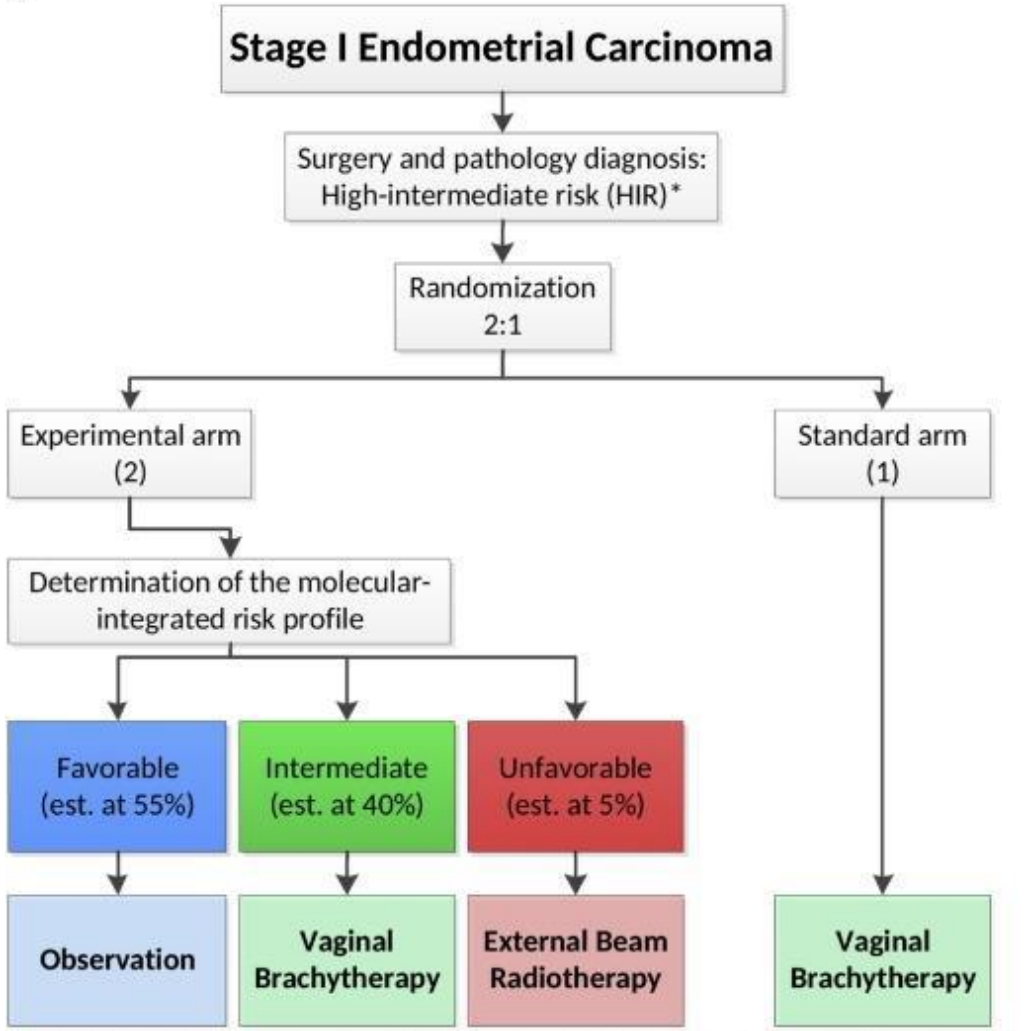
Trattamento della malattia avanzata o recidivata

AIOM 2021

FUTURE DIRECTIONS

PORTEC 4a

A



**High-intermediate risk (HIR) endometrial cancer:* stage IA (with invasion) and grade 3; stage IB, grade 1 or 2; with either age ≥ 60 or substantial lymph-vascular space invasion (LVSI); stage IB, grade 3 without LVSI; or stage II (microscopic) with grade 1. Est = estimated.

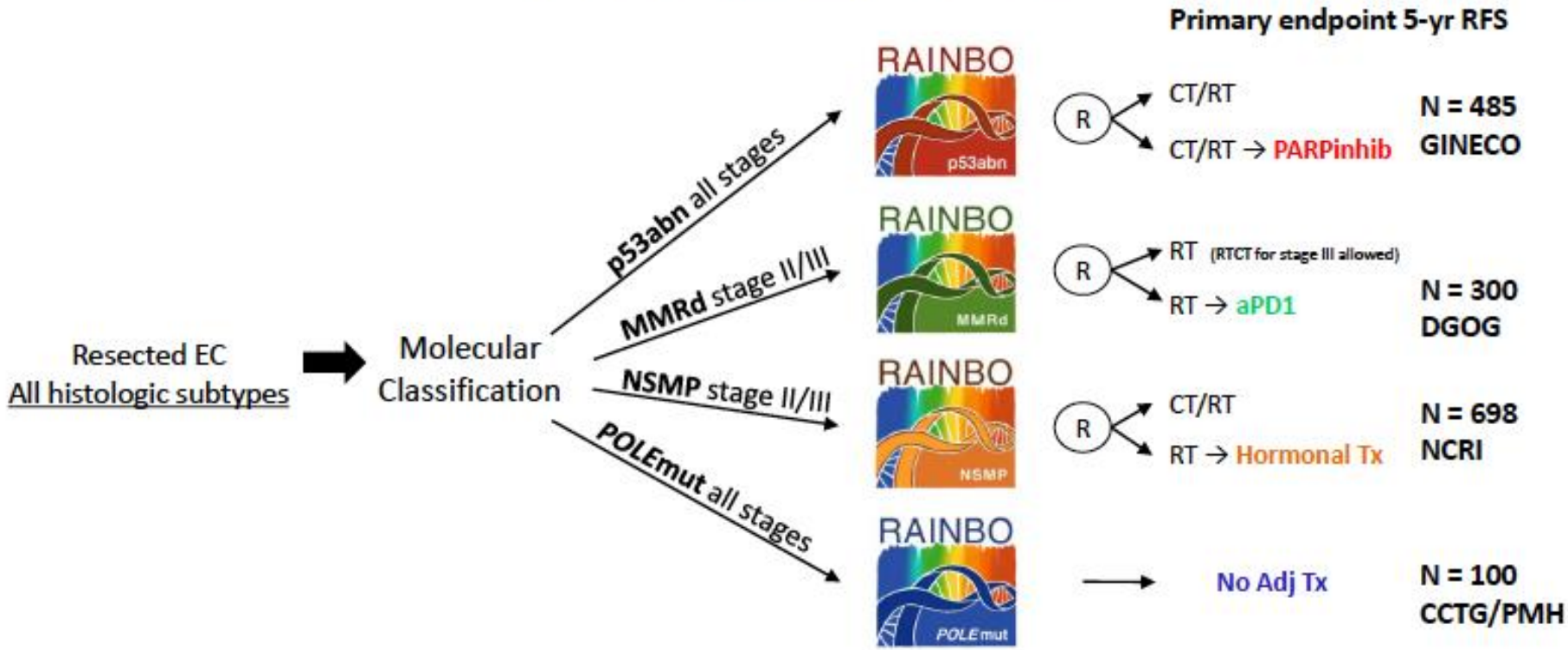
RAINBO umbrella program

Refining **A**djuvant treatment **IN** endometrial cancer **B**ased
On molecular profile (RAINBO)

a TransPORTEC collaboration and initiative
DGOG, GINECO, NCRI, CCTG, ANZGOG

Carien Creutzberg and Judith Kroep for TransPORTEC Consortium

RAINBO umbrella Program



RAINBO umbrella program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group