Ontwikkelingen in de risicovoorspelling op terugkeer van baarmoederkanker en wat betekent dat voor radiotherapie

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DISCLOSURES

Research grants, paid to insitution:

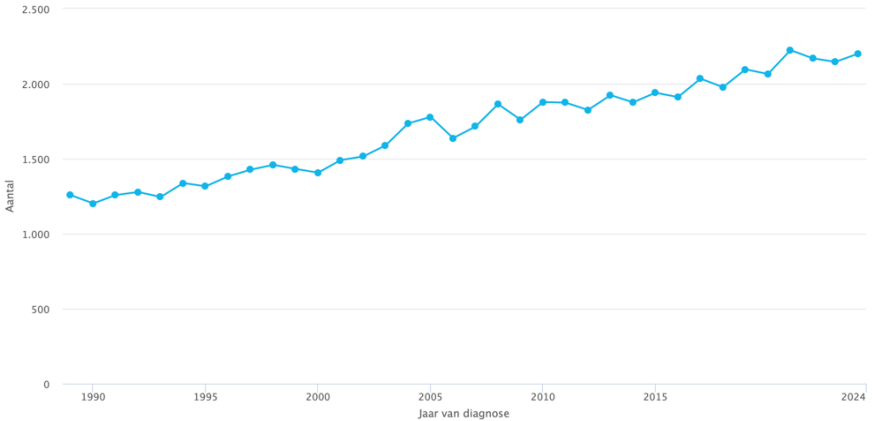
- Elekta, Varian, Accuray, Sensius, Sennewald, MSD

Speaker, advisory honoraria, paid to institution:

- Elekta, MSD, GSK

INCIDENCE

Incidentie per jaar, Aantal
Baarmoederlichaamkanker
Geslacht: Man en vrouw | **Leeftijdsgroep:** Totaal | **Regio:** Nederland | **Stadium:** Totaal



2024, 2023: Deze cijfers betreffen voorlopige gegevens.

Bron: NKR
Gewijzigd op: 27 januari 2025

Incidentie per jaar, Aantal
Baarmoederlichaamkanker
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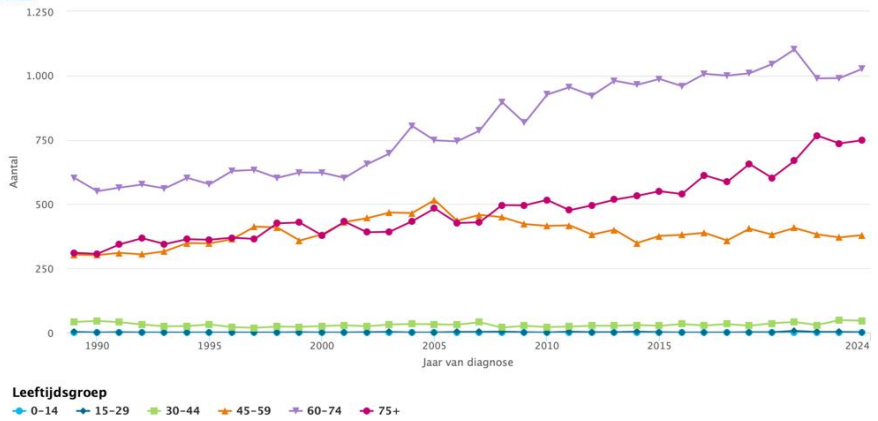


2024, 2023: Deze cijfers betreffen voorlopige gegevens.

Bron: NKR
Gewijzigd op: 27 januari 2025

FIGO 2023 STAGING

TABLE 1 2023 FIGO staging of cancer of the endometrium.[a,b]

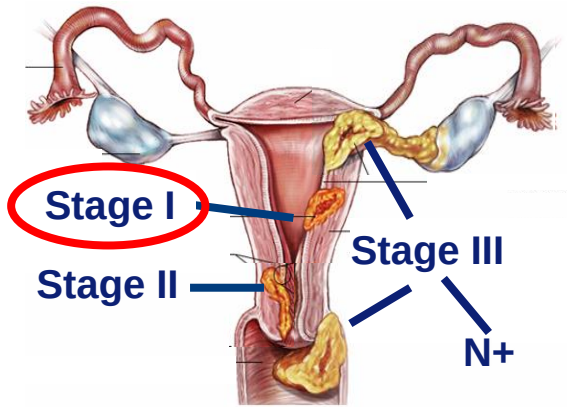
Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with 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
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIICii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
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

Molecular integrated

TABLE 2 FIGO endometrial cancer stage with molecular classification.[a]

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage IAm$_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage IICm$_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

?



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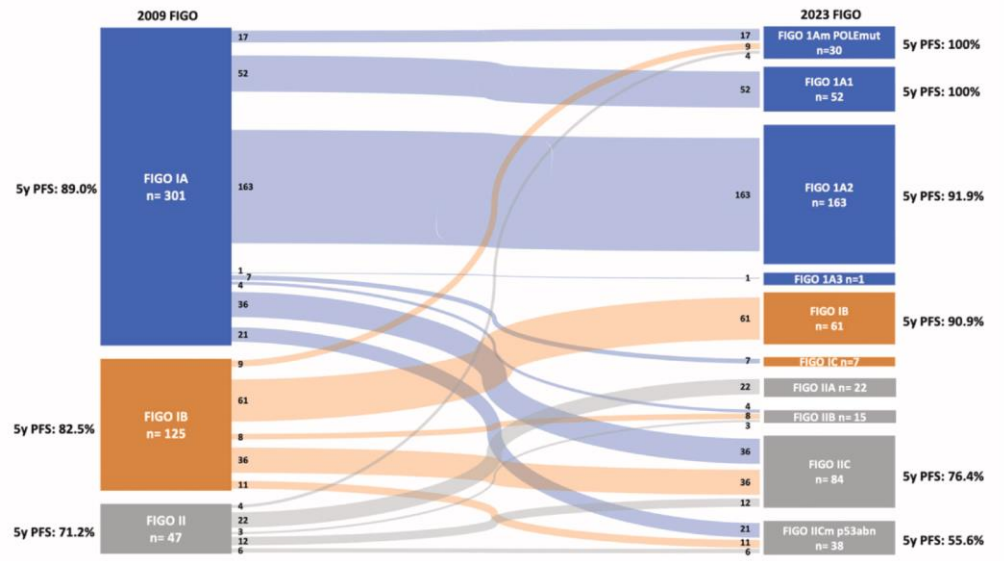
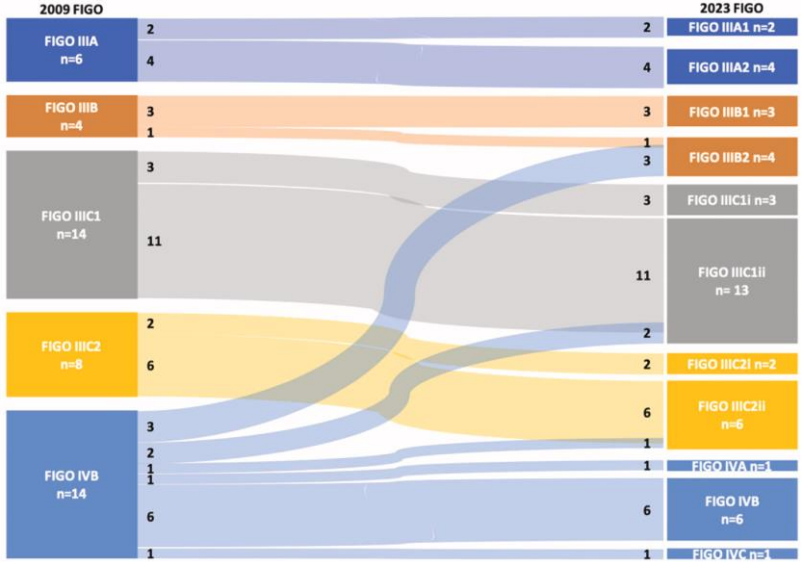
Berek et al. Int J Gyn Cancer 2023

FIGO 2023 STAGING: VALIDATION





Schwameis et al. EJC 2023

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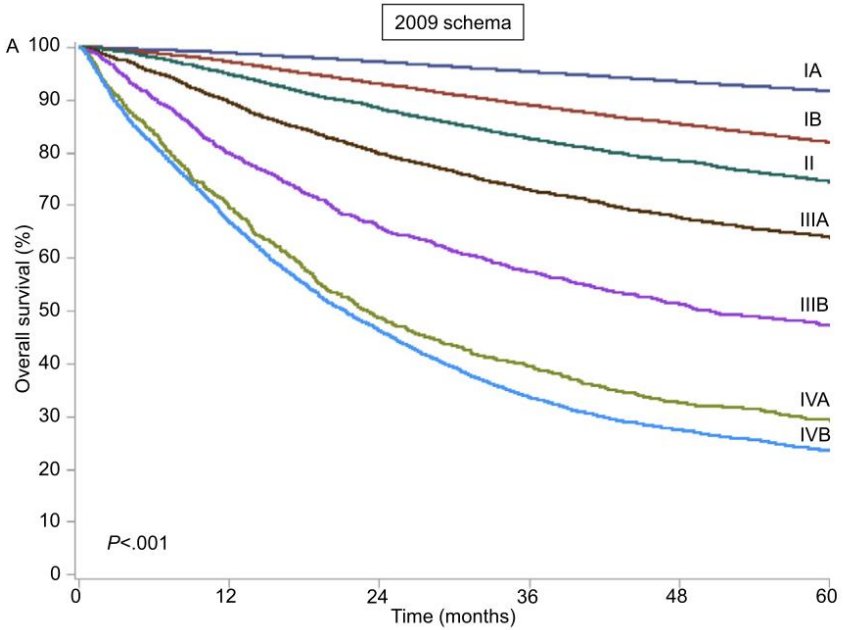
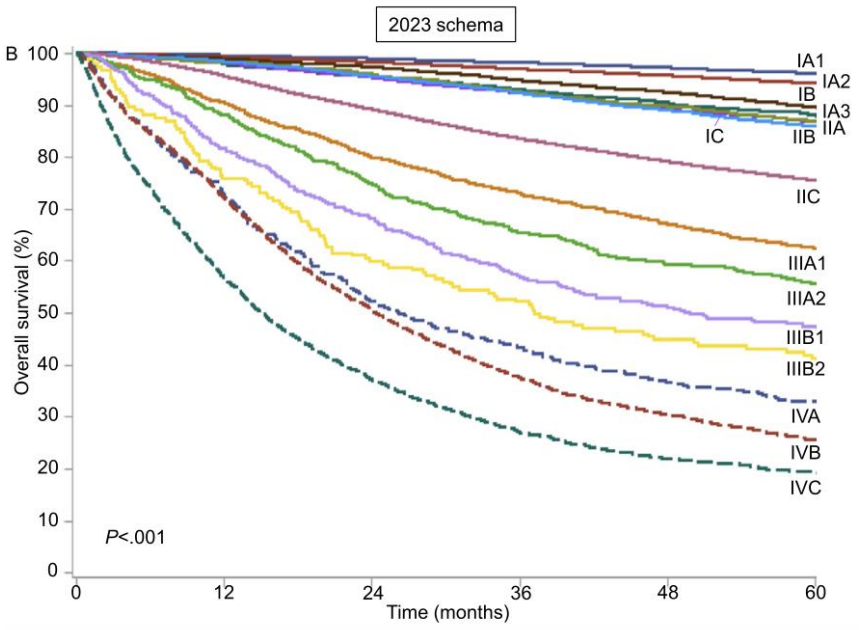
FIGO 2023 STAGING: VALIDATION





Matsuo et al. Gyn Onc 2023

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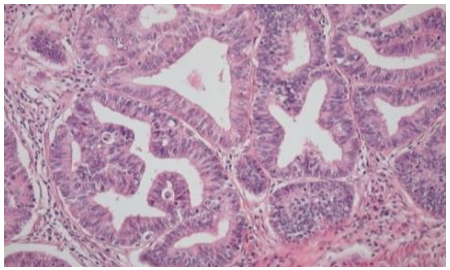
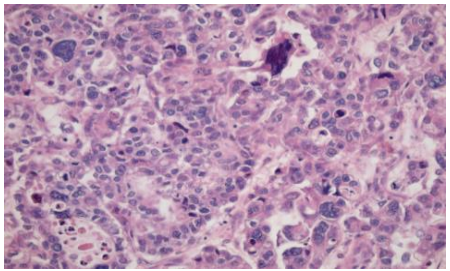
HISTORIC MAJOR PROGNOSTIC FACTORS

- Age
- Stage
  - Depth of myometrial invasion
- Histology
  - Histological type
  - Grade
  - Lymph-vascular space invasion

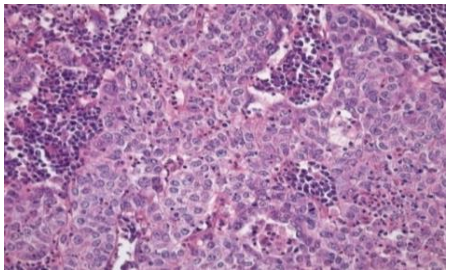
Grade 1



Grade 2



Grade 3



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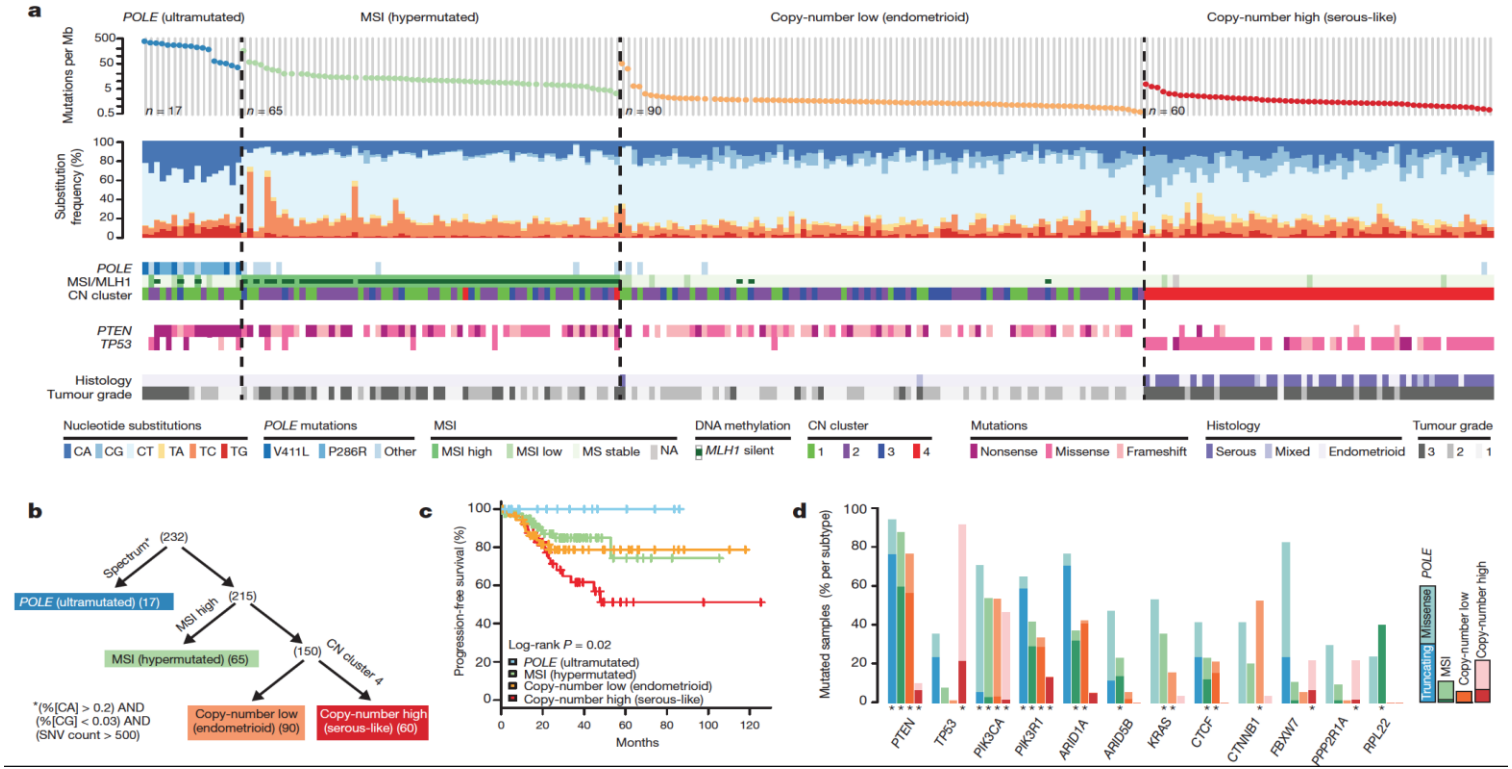
THE CANCER GENOME ATLAS 2013



TCGA (Kandoth et al), Nature 2013

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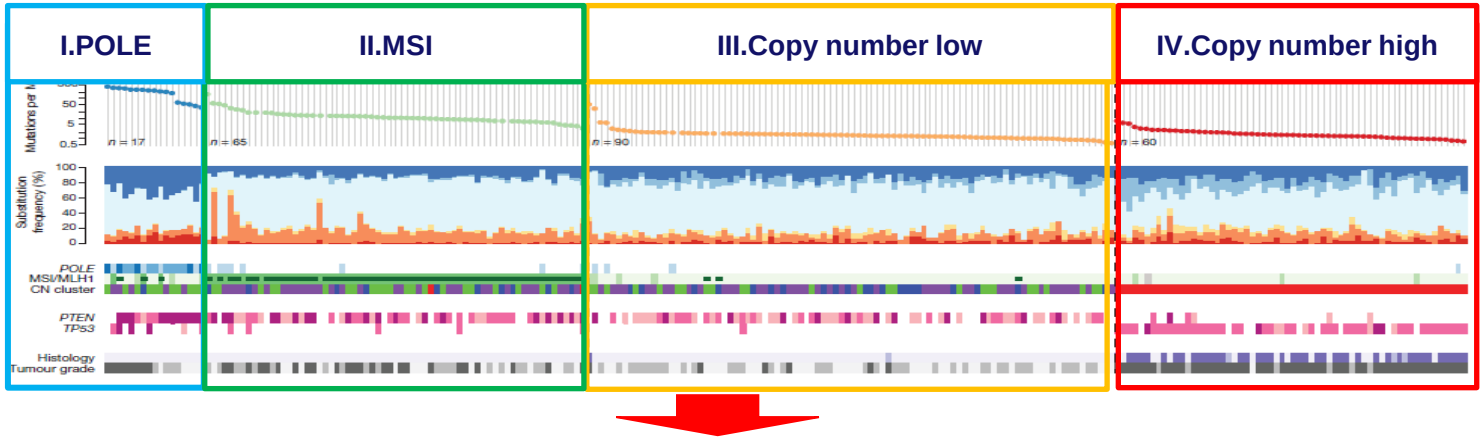
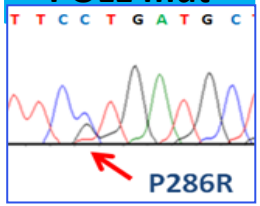
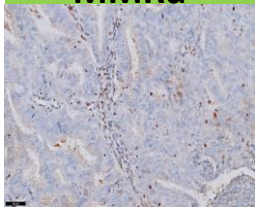
TCGA – SURROGATE MARKERS



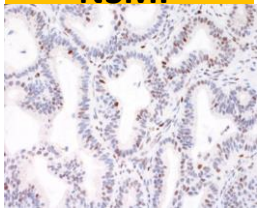
Mol Class 1
POLE mut



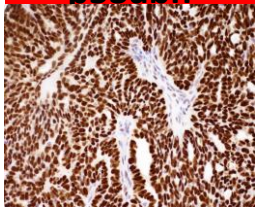
Mol Class 2
MMRd



Mol Class 3
NSMP



Mol Class 4
p53abn



Stelloo et al, CCR 2016

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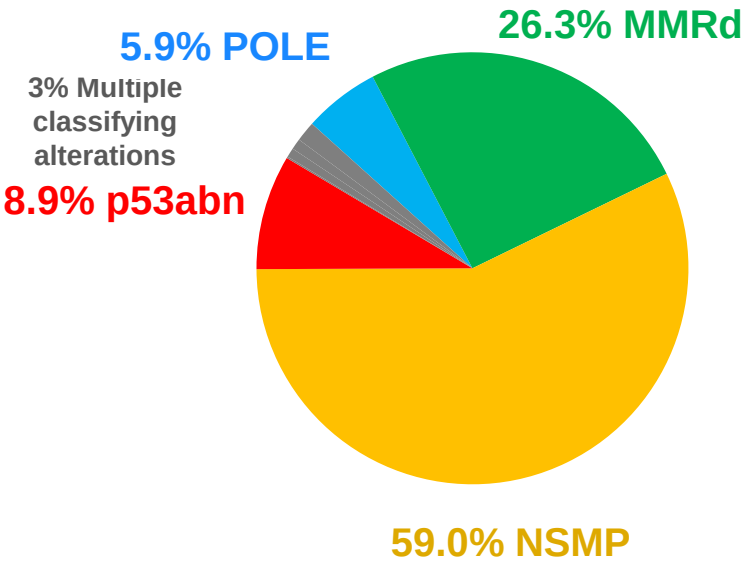
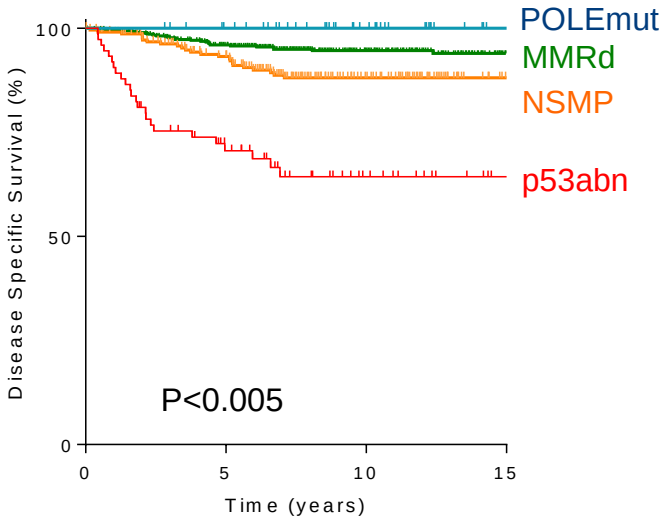
PORTEC-1&2 (N=834 HIR, ENDOMETRIOID)





High-intermediate risk

Surrogate markers improve prognostic accuracy in low stage, **intermediate risk** endometrial cancer

Stelloo et al, CCR 2016

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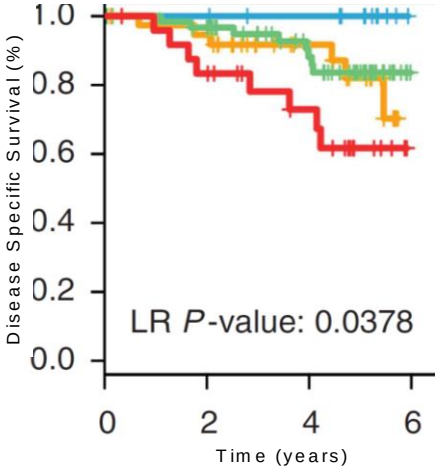
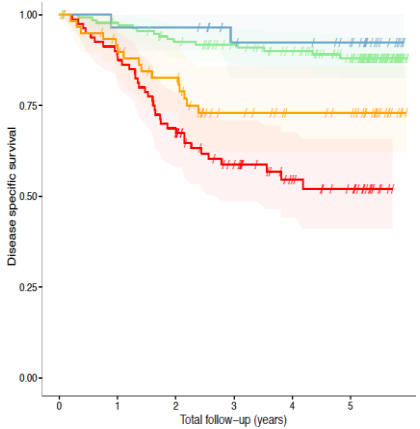
CONFIRMATION IN OTHER COHORTS

N=142



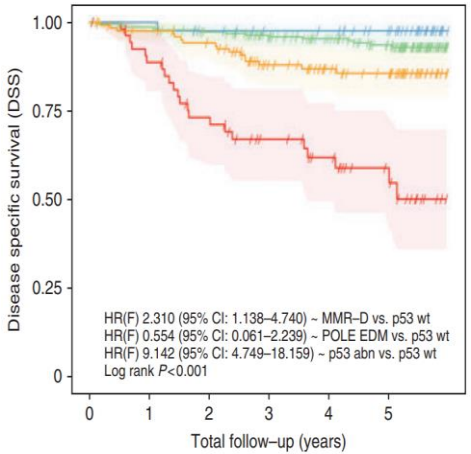
Unselected
Talhouk et al, BJC 2015

N=319



Unselected
Talhouk et al, Cancer 2017

N=451



Unselected
Kommoss et al, Ann of Onc 2018

POLEmut
MMRd
NSMP
p53abn

Prognostic capacity of surrogate marker approach is validated in a number of unselected cohorts

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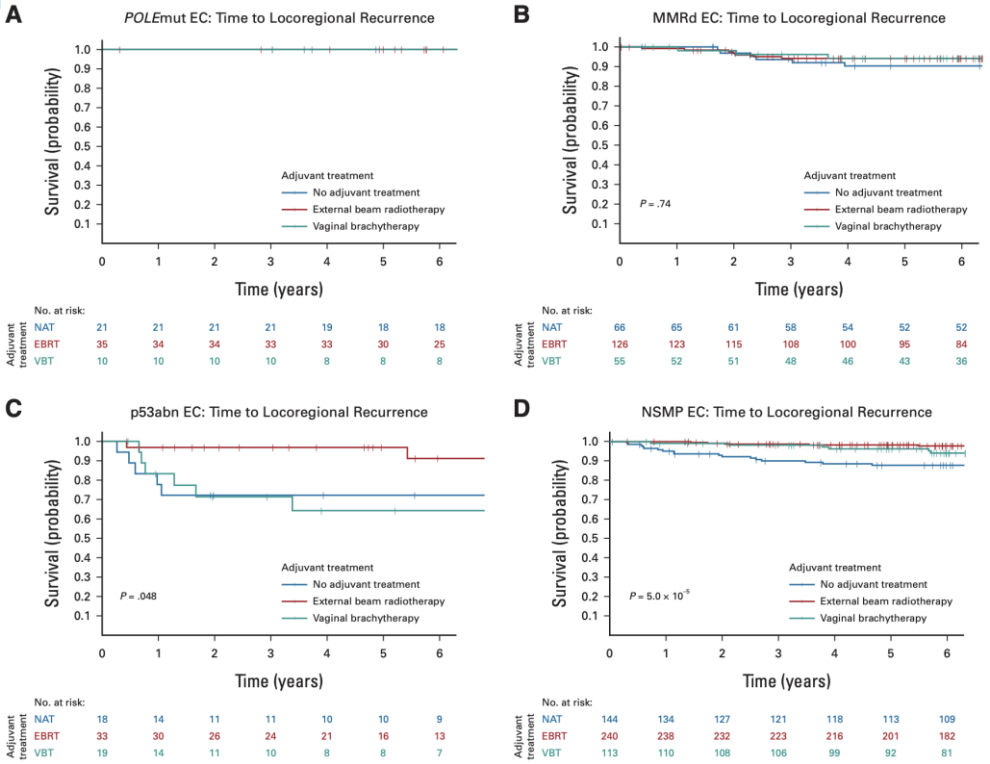
MOLECULAR CLASS PREDICTS RT-RESPONSE



- 880 patients from PORTEC-1&2 randomised trials
- POLE: no recurrence
- MMRd: small ns benefit EBRT 94.2% or VBT 94.2% vs. No adj treatment 90.3% p=0.74
- p53abn: No adj treatement 72.2% and VBT 64.3% worse vs. EBRT 96.6% p=0.048
- NSMP: benefit for both EBRT 98.3% or VBT 96.2% vs. No adj treatment 87.7% p<0.001

Horeweg et al, JCO 2023

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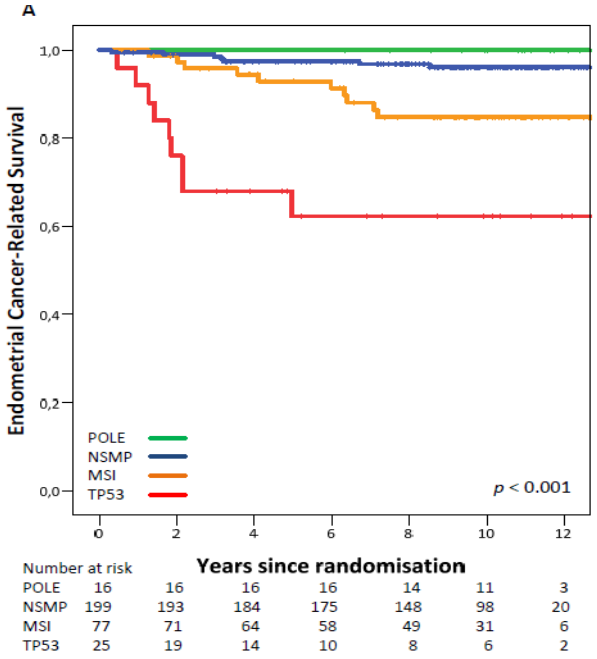
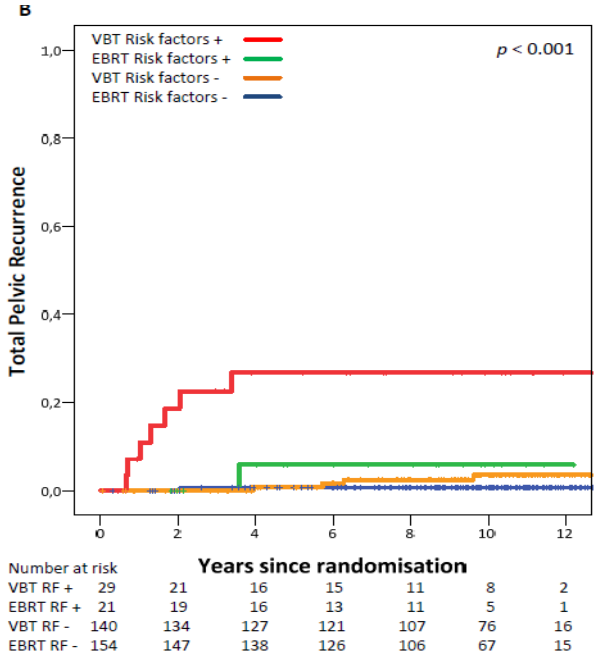
PORTEC-2 UNFAVORABLE FEATURES

Endometrial Cancer Related Survival



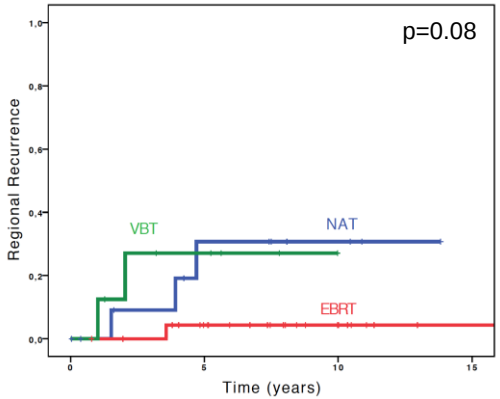
Pelvic Recurrence



Wortman et al, BJC 2018

Risk Factors:

- P53abn
- L1CAM>10%
- Substantial LVSI



Bosse et al, EJC 2015

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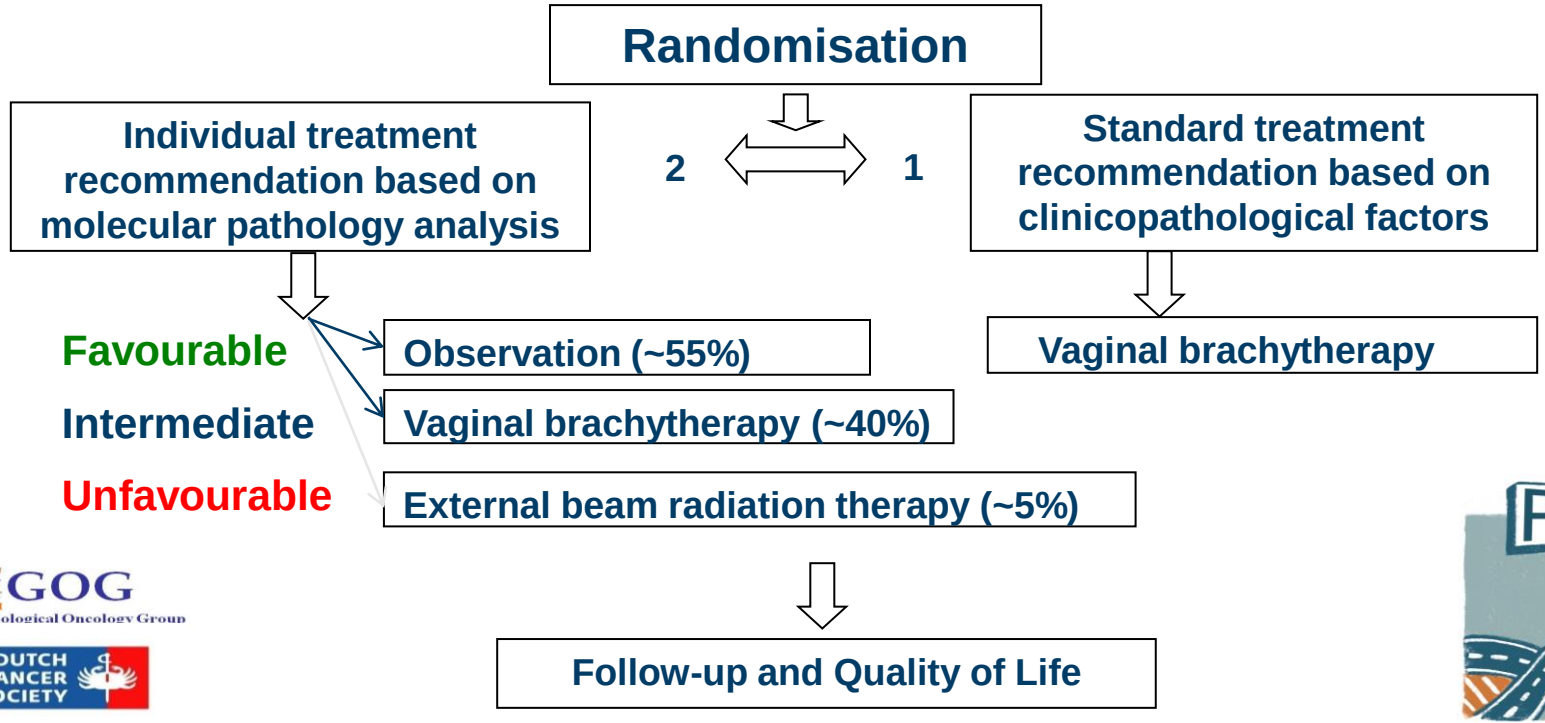
PORTEC-4A: MOLECULAR VS STANDARD



DUTCH GOG
Dutch Gynaecological Oncology Group

DUTCH CANCER SOCIETY

PORTEC 4a

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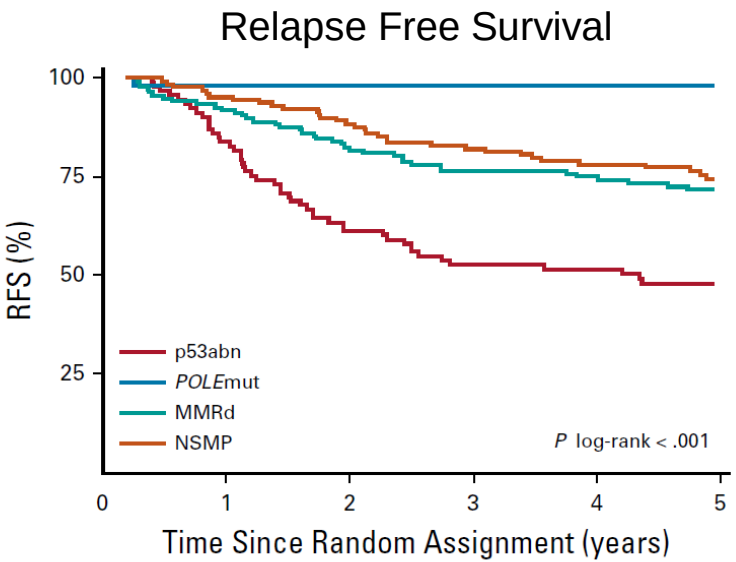
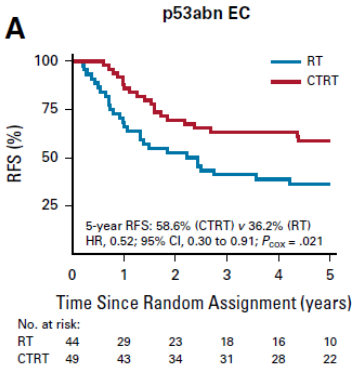
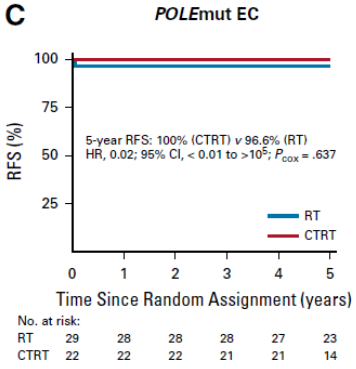
PORTEC-3 TRIAL IN HIGH RISK

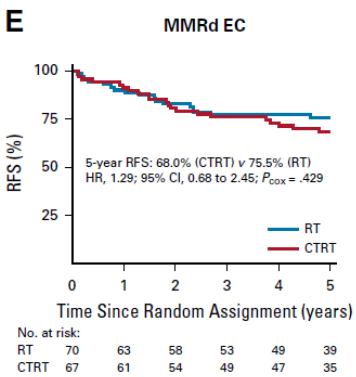


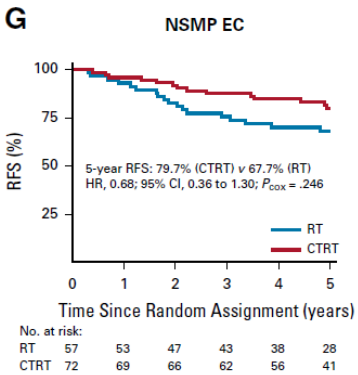
No. at risk:

p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
MMRd	137	124	112	102	96	74
NSMP	129	122	113	105	94	69









Leon-Castillo A et al. J Clin Oncol 2020

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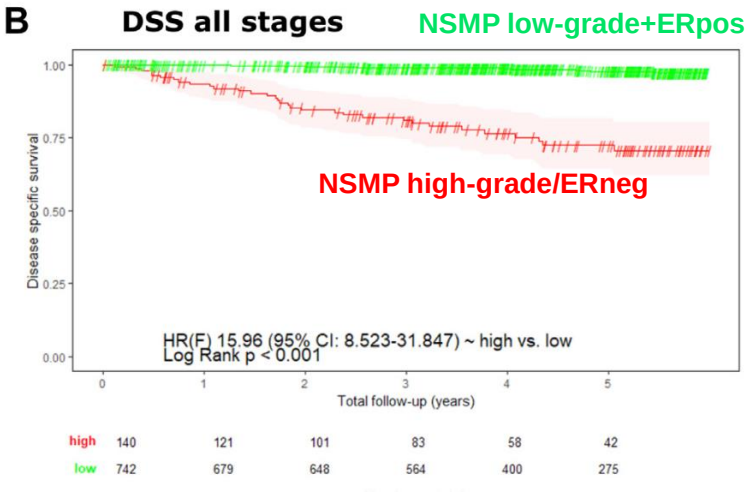
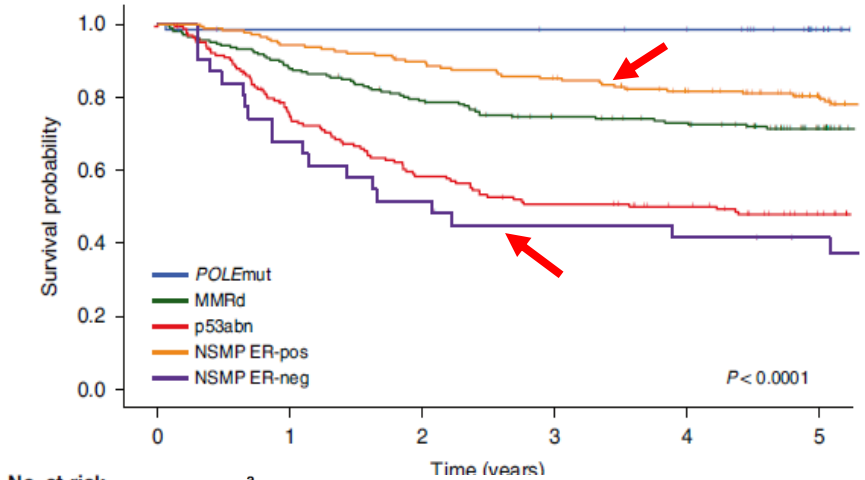
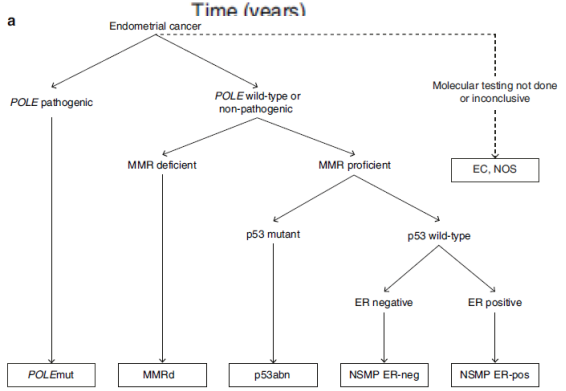
NSMP ROLE OF ER-STATUS

- Prognosis of NSMP ER-neg similar to p53abn
- Stongest model within NSMP: combination ER-neg OR grade 3 versus ER-pos AND endometrioid grade 1/2



Jamieson et al. Modern Pathology 2023





Vermij et al. BJC 2023

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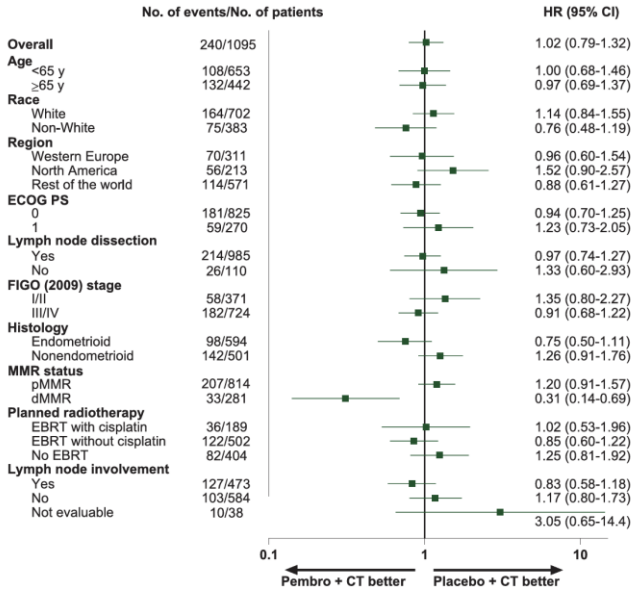
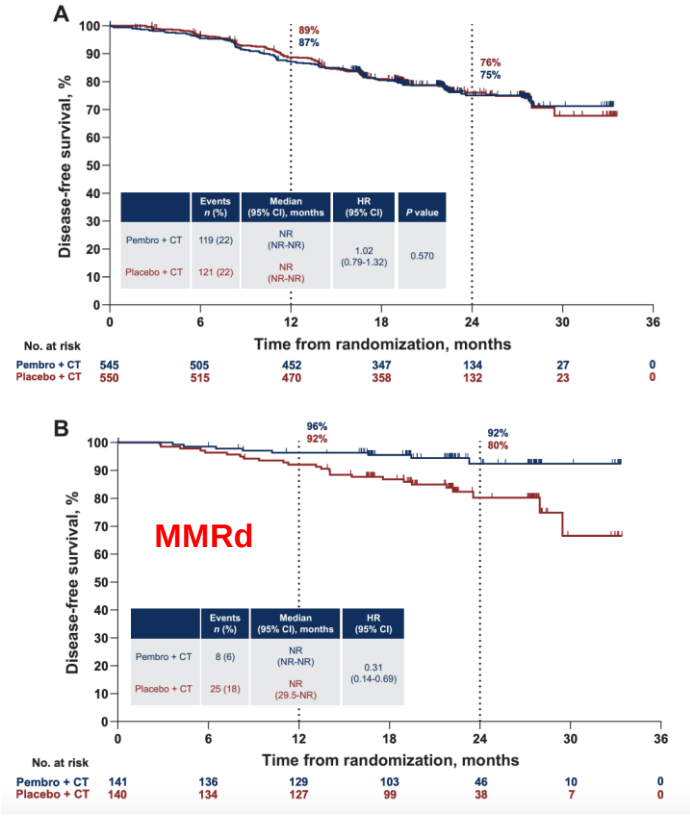
KEYNOTE B21

- Phase III trial investigating addition of pembrolizumab to adjuvant chemotherapy (+/- EBRT) -> *more than 80% EBRT*
- Stage III/IVA of any histology, or stage I/II of non-endometrioid histology or endometrioid histology with p53/TP53 abnormality





van Gorp et al. Ann of Onc 2024

Slomovitz et al. JCO 2024

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ESGO-ESTRO-ESP 2021 GUIDELINE

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal
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
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 with 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

[Δ]For stage III-IVA ***POLE*mut** endometrial carcinoma and stage I-IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk-group in the molecular classification. Prospective registries are recommended

* see text on how to assign double classifiers (e.g. patients with both *POLE*mut and p53abn should be managed as *POLE*mut)

** according to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade, and grade 3 carcinomas are considered as high-grade.

p53abn: p53 abnormal, MMRd: Mismatch Repair Deficient, NSMP: nonspecific molecular profile, *POLE*mut: polymerase Ɛ mutated

First integration of histopathological and molecular features in risk groups:

- POLE good
- MMRd & NSMP intermediate
- p53abn poor

Shifts in historical risk groups:

Shift from high to high-intermediate

- Endometrioid stage I grd3 & II; substantial LVSI

Shift from high-intermediate to intermediate

- Endometrioid low-grade IB and high-grade IA

Shift from intermediate to low

ESGO-ESTRO-ESP guidelines

Concin et al. Int J Gyn Onc 2021

Erasmus MC Cancer Institute

TRANSPORTEC - RAINBO

RAINBO

TransPORTEC

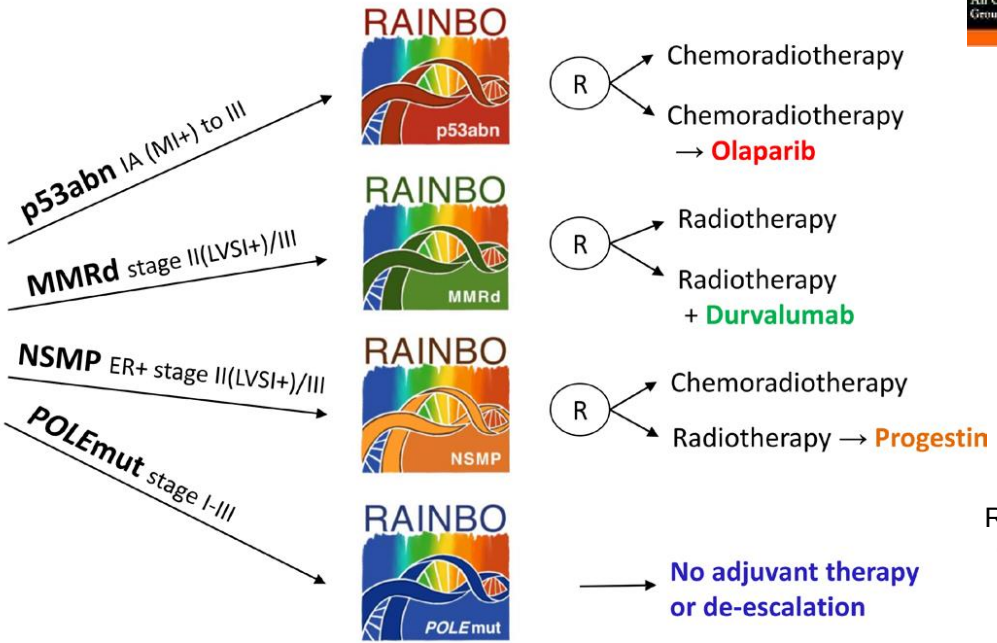
GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Completely resected endometrial cancer

Eligible histotypes:
endometrioid,
serous,
clear cell,
un/dedifferentiated,
mixed and
carcinosarcoma

→ Molecular Classification



RAINBO Research Consortium. Int J Gynecol Cancer 2023

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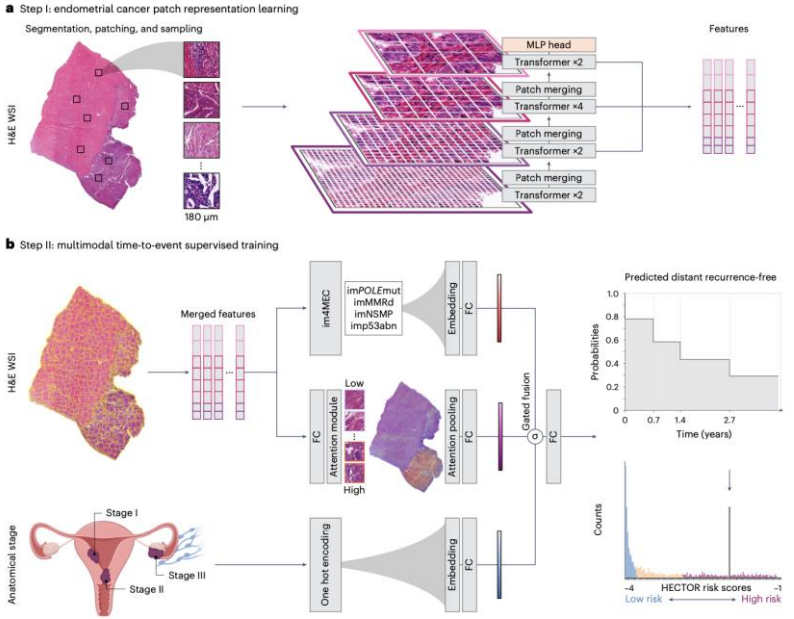
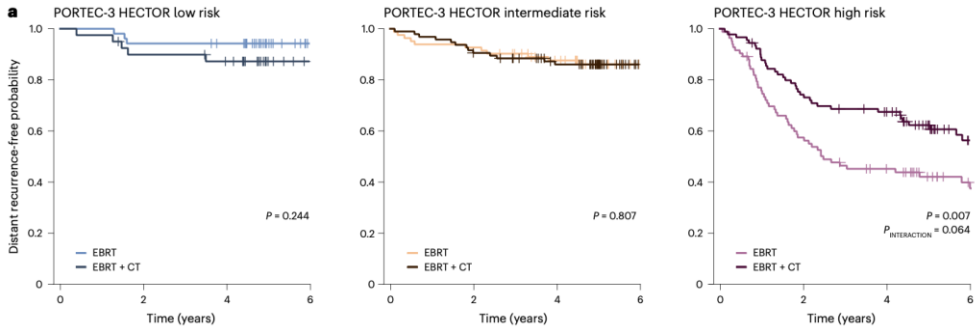
MULTIMODAL DEEP LEARNING



- HECTOR developed with 2072 patients including PORTEC studies
- H&E-stained, whole-slide images and tumor stage as input
- C-index internal 0.789 validation 0.828 and 0.815 distant recurrence
- Predicted adjuvant chemotherapy benefit better



Fremond et al, Nature Med 2023

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CONCLUSIE

- Moleculaire risico factoren moeten meegenomen worden in diagnostiek, behandel adviezen en nieuwe studies:
  - Reduceren van over- en onderbehandeling
  - Studies onderweg
- Moleculaire risicofactoren predictief voor respons op radiotherapie
- Toekomstig gebruik van deep learning in de pathologie is veelbelovend vanuit een modiaal perspectief


Thank you!
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