ESGO-ESTRO-ESP Guideline for the management of Endometrial Cancer

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DISCLOSURE INFORMATION

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Consulting/Advisory: ImmunoGen, Seagen, Akesobio, Ensai, GSK, AstraZeneca, Mersana, Seattle Genetics, Kartos eTheRNA immunotherapies NV

Travel Expenses: Roche, Genmab, Amgen

Educational fees: Kartos, MSD, Medscape Oncology, TouchIME

Functions in societies:

President of ESGO

Chair of ENGOT Early Drug Development Network

ESGO-ESTRO-ESP Endometrial Cancer Guidelines

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Multidisciplinary, international working group

171 669 FULL ARTICLE + PDF DOWNLOADS

585 citations

(Dec 2020 - to Feb 2023)

Concin et al, Int J Gynecol Cancer 2021; Radiother Oncol 2021; Virchows Arch 2021

OPEN ACCESS: **https://ijgc.bmj.com/content/ijgc/31/1/12.full.pdf**.

ESGO-ESTRO-ESP Endometrial Cancer Guidelines

TOPICS

TUMOR BIOLOGY:
-Molecular Markers
-LVSI

SURGERY:
-MIS
-Sentinel Lymph Node

ESGO-ESTRO-ESP Endometrial Cancer Guidelines: PROGNOSTIC RISK GROUPS

ESMO-ESGO-ESTRO Consensus Conference 2015

TABLE 2. New risk groups to guide adjuvant therapy use

Risk group	Description	LOE
Low	Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative	I
Intermediate	Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative	I
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status	I
	Stage I endometrioid, 1–2, LVSI unequivocally positive, regardless of depth of invasion	II
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status	I
	Stage II	I
	Stage III endometrioid, no residual disease	I
	Non endometrioid (serous or clear cell or undifferentiated carcinoma, or carcinosarcoma)	I
Advanced	Stage III residual disease and stage IVA	I
Metastatic	Stage IVB	I

FIGO 2009 staging used; molecular factors were considered but not included; tumour size was considered but not included; nodal status may be considered for treatment recommendations.
LOE, level of evidence; LVSI, lymphovascular space invasion.

NOW
Integration of Molecular markers

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
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

Colombo et al, Ann Oncol, Jan 2016; Int J Gynecol Cancer, Jan 2016; Radiother Oncol, Dec 2015

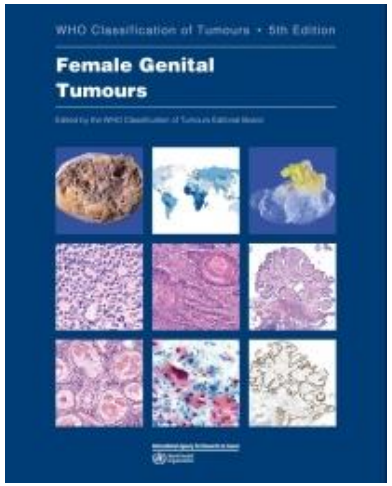
ESGO-ESTRO-ESP Endometrial Cancer Guidelines: major ADVANCEMENT

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 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

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
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

LVSI:
how to quantify? What is clinically meaningful?



Extent of LVSI is important

WHO definition

Focal LVSI is defined by the presence of a **single focus** around the tumor
Substantial LVSI as **multifocal** *or* d**iffuse** arrangement of LVSI *or*
the presence of tumor cells **≥ 5 lymphovascular spaces**.

Peters et al, International Journal of Gynecological Pathology 2021:

Quantitative analysis of LVSI & correlation with risk of pelvic lymph node recurrence using PORTEC-1 and 2 samples
Analyses repeated in Danish Gynecolgical cancer Database cohort

Clinically relevant: Numeric threshold **≥ 4 LVSI-involved vessels** in a least 1 H&E slide

Lyphvascular space involvement (LVSI)

S3 Leitlinie

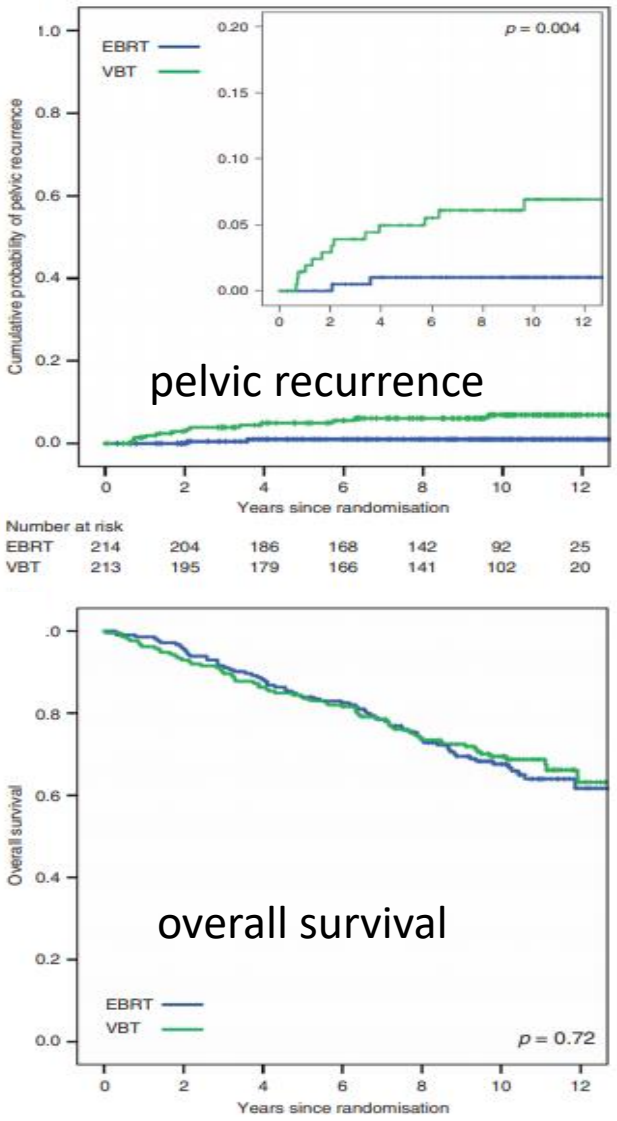
Lymphvascular space involvement (LVSI)

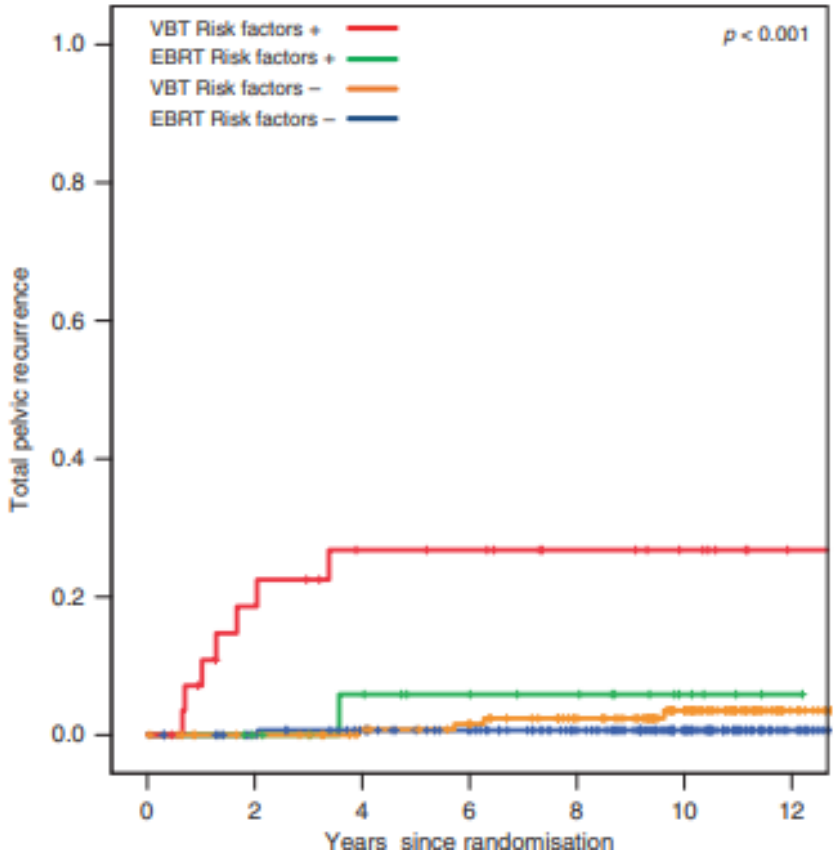
Focal LVSI is defined by the presence of a single focus around the tumor; **substantial LVSI** as multifocal or diffuse arrangement of LVSI or the presence of tumor cells in **five or more** lymphovascular spaces.

Substantial LVSI is defined as **four or more** LVSI-positive vessels in at least one H&E slide. In

Die fokale Lymphgefäßinfiltration ist definiert als Befall von <3 Lymphgefäßen und die extensive („**substantial**“) Lymphgefäßinfiltration als ein Befall von **≥ 3** Lymphgefäßen.

PORTEC-2 trial for high-intermediate risk EC: improving patient selection for adjuvant therapy





Total pelvic recurrence
by unfavourable risk factors:

LVSI

p53-mutant

L1CAM expression

Substantial LVSI is a strong independent risk factor for pelvic and distant recurrence & for EC-related survival

Wortman et al, BJC 2018

LVSI: in lymph node negative disease?

Study based on the Swedish Quality Registry for Gynecologic Cancer
by the Swedish Gynecologic Cancer Group

2010-2017:
endometrioid EC,
FIGO stages I-III
(N=1587)

Multivariable analyses of patients with **systematic pelvic and para-aortic lymphadenectomy** and **negative nodes** (N=404)
LVSI was associated with decreased OC

LVSI		
Not present	17/318 (5.4%)	Reference
Present	11/86 (13%)	2.50 (1.05–5.98)
Myometrial invasion		
<50%	12/230 (5.2%)	Reference
≥50%	16/174 (9.2%)	1.47 (0.63–3.44)
FIGO-grade		
Grades 1 and 2	15/224 (6.7%)	Reference
Grade 3	13/180 (7.2%)	0.92 (0.41–2.07)
DNA-ploidy		
Diploid	11/213 (5.2%)	Reference
Non-diploid	17/191 (8.9%)	1.42 (0.64–3.17)
Adjuvant treatment		
No	13/227 (5.7%)	Reference
Yes	15/177 (8.5%)	0.76 (0.32–1.82)
Age (continuous)[a]	28/404 (6.9%)	1.07 (1.02–1.13)

Stalberg et al, Acta Oncologica 2019

LVSI: in the presence of molecular markers?

Study based on the Danish Gynecological Cancer Database

Substantial LVSI was an important prognostic factor for **recurrence, OS & DSS**, **INDEPENDENT of molecular subgroups** and other clinicopathological features

2005-2012, molecularly profiled, **high grade, stages I-III EC** (N=367)

Multivarible analyses of patients with **lymphadenectomy** (N=251):
LVSI is an independend prognostic marker

	Recurrence			Overall survival			Disease specific survival		
	n events = 64			n events = 78			n events = 53		
Parameter	HR	95%CI	*p*-value	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Age									
<70	1			1			1		
≥70	0.896	0.516–1.553	0.695	1.779	1.081–2.926	0.023	1.073	0.581–1.984	0.821
Molecular subgroups									
MMRd	1			1			1		
p53abn	3.938	1.924–8.058	<0.001	1.875	1.064–3.304	0.030	3.244	1.510–6.969	0.003
*POLE*mut	–	–	–	0.622	0.180–2.156	0.454	–	–	–
NSMP	4.685	2.083–10.537	<0.001	2.031	1.007–4.096	0.048	3.954	1.648–9.486	0.002
Stage									
I-II	1			1			1		
III	0.379	0.122–1.176	0.093	0.498	0.167–1.485	0.395	0.448	0.123–1.625	0.222
LVSI									
Absent or focal	1			1			1		
Substantial	2.495	1.336–4.658	0.004	2.377	1.366–4.133	0.002	2.93	1.508–5.692	0.002
Adjuvant treatment									
No	1			1			1		
Yes	0.671	0.351–1.281	0.226	0.684	0.362–1.293	0.243	0.654	0.323–1.325	0.238
ASA score									
1–2	1			1			1		
3–5	1.440	0.466–4.455	0.526	2.248	0.980–5.158	0.056	1.314	0.362–4.770	0.678

Leon-Castillo et al, Gynaecol Oncol 2022

ESGO-ESTRO-ESP Endometrial Cancer Guidelines: major ADVANCEMENT

PROGNOSTIC RISK GROUPS

NOW

Integration of molecular markers

Risk group	Molecular classification unknown	Molecular classification known*†
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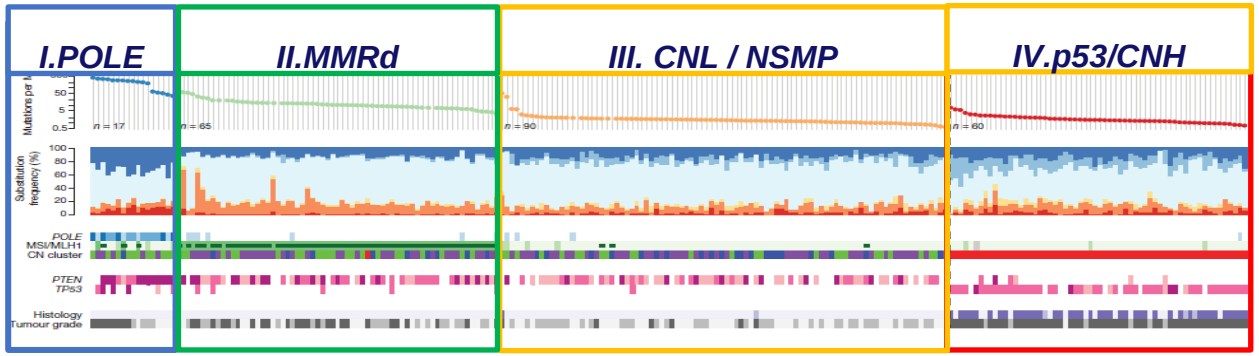
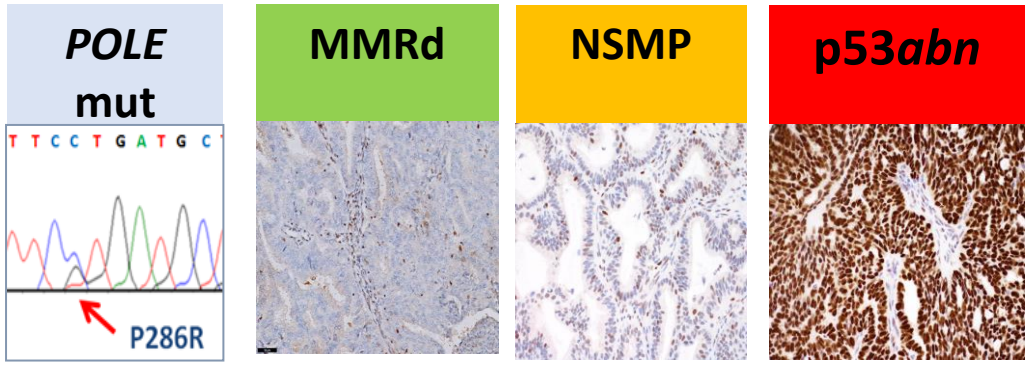
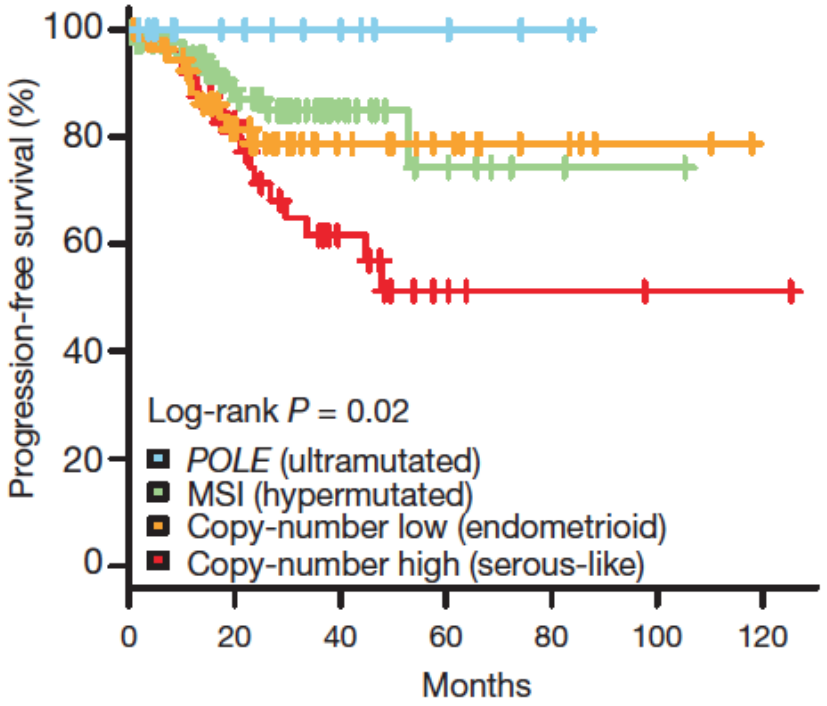
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** 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

TCGA molecular groups by surrogate markers



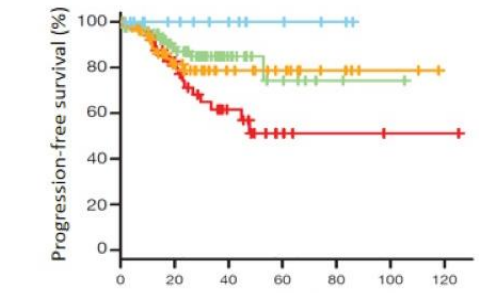




- **Immunohistochemistry** for **p53** & **mismatch repair proteins**
- **DNA sequencing** for ***POLE*** exonuclease domain mutations

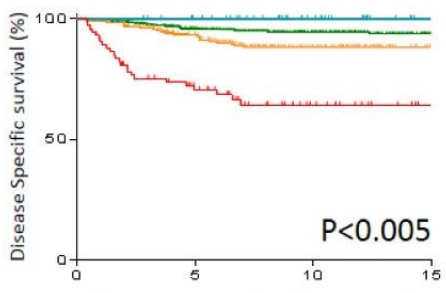
Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017

Prognostic significance of molecular subgroups



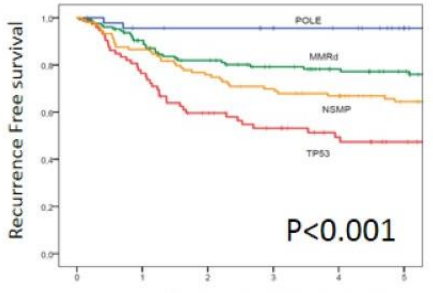
TCGA (n=373)

Kandoth et al., Nature 2013



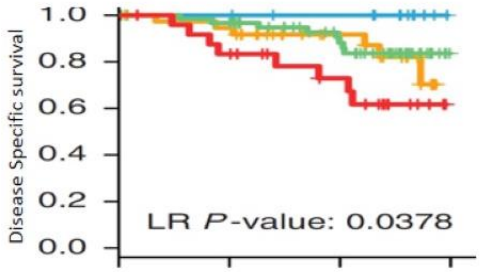
PORTEC-1/-2 (n=834)

Stelloo et al., CCR 2016



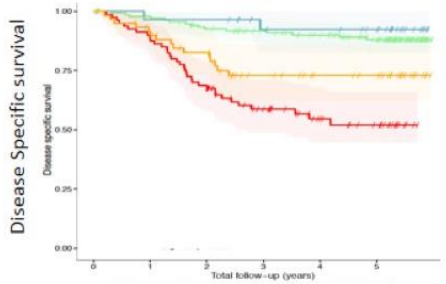
Grade 3 EEC (n=376)

Bosse et al., Am J Surg Path 2018



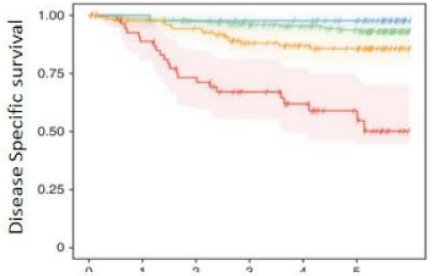
Unselected (n=142)

Talhouk et al, BJC 2015



Unselected (n=319)

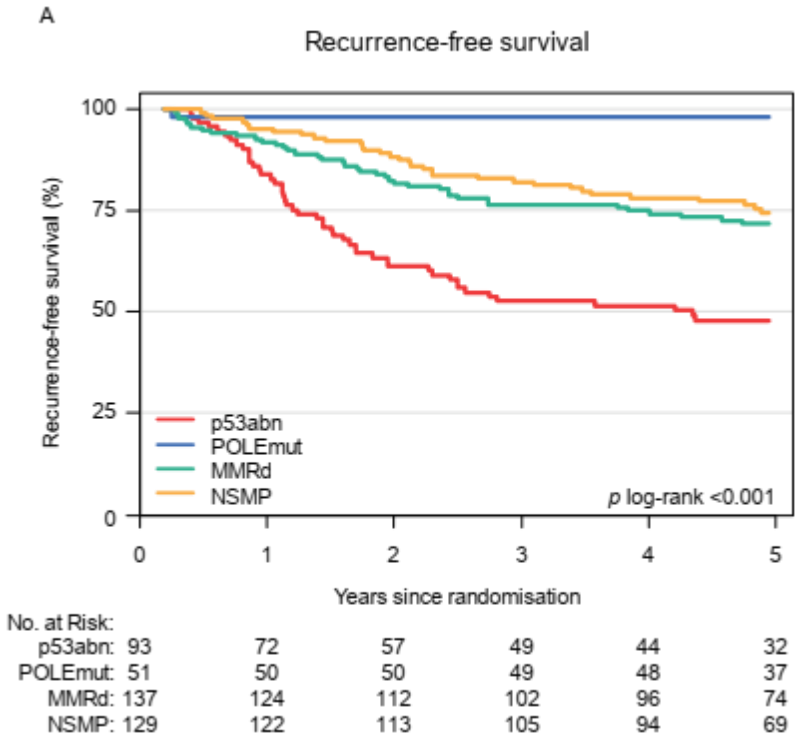
Talhouk et al, Cancer 2017



Unselected (n=415)

Kommoss et al, Ann of Onc 2018

PORTEC-3 translational results



----- *POLEmut* ------ MMRd ------ NSMP ------ p53abn

Leon del Castillo et al, JCO 2020

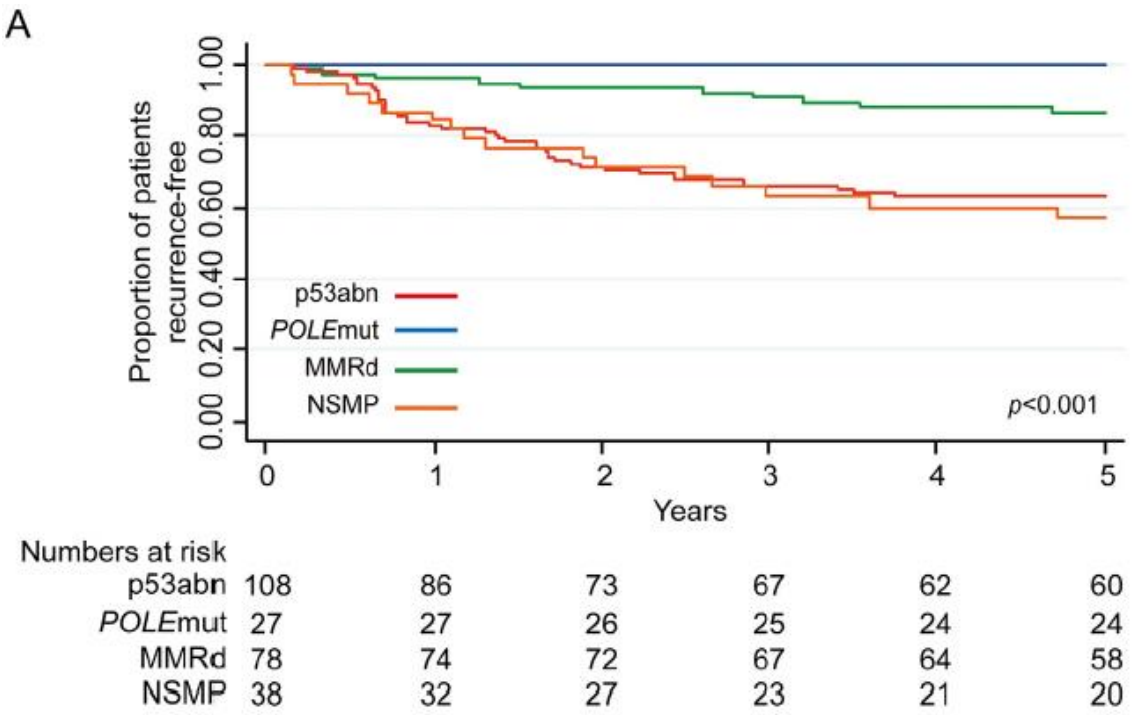
PROGNOSTIC significance of molecular subgroups in patients who underwent lymphadenectomy

Danish Gynaec. Cancer Database

High grade EC, stage I-III without residual disease after surgery
subgroup (N=251) lymph node staged

- Molecular subgroups were significantly associated with **RFS, OS, DSS**

- In **multivariable analysis**, molecular subgroups remain a strong prognostic factor for recurrence, OS, and DSS
  INDEPENDENT OF STAGE

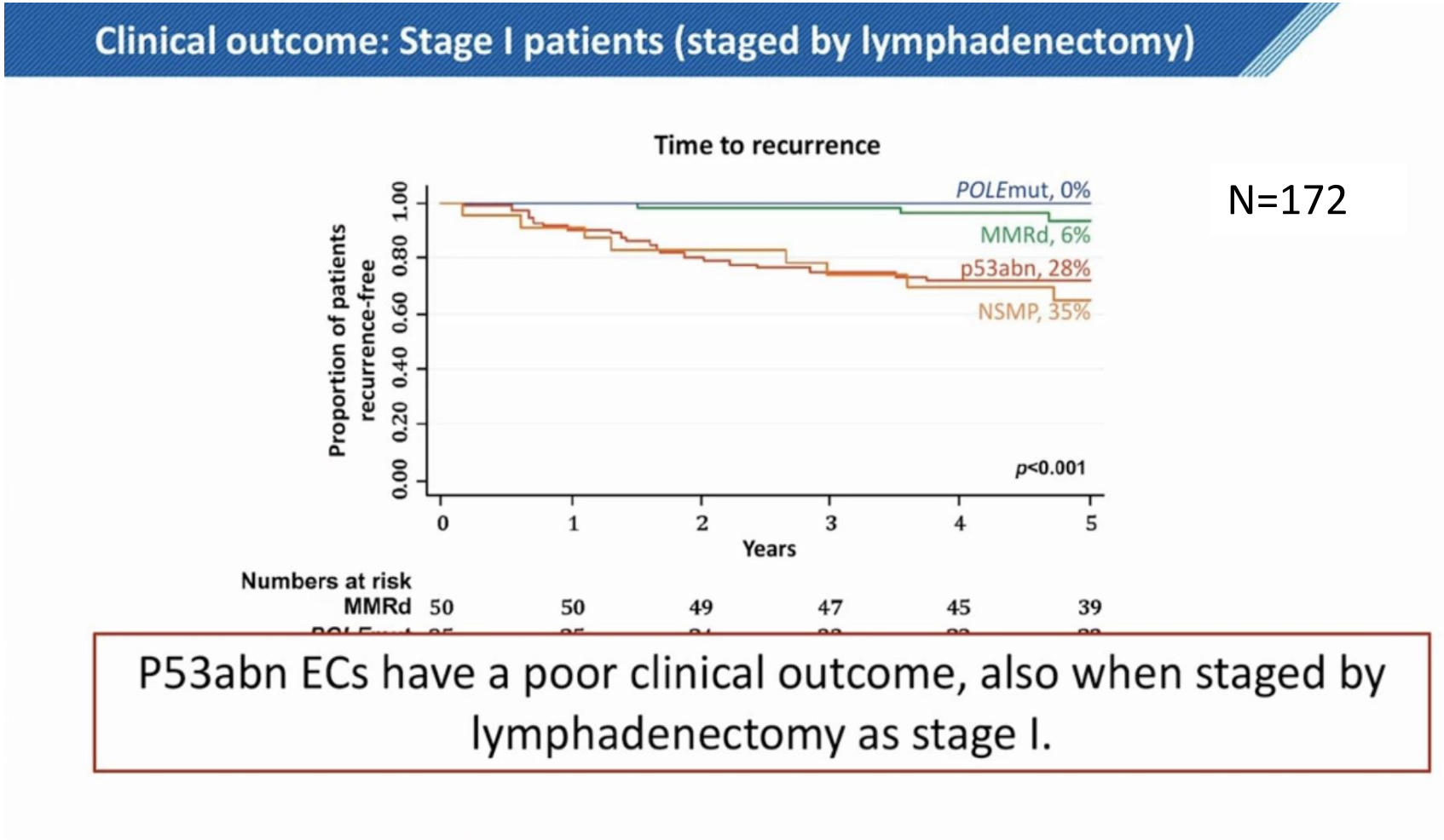


Leon Castillo et al, Gynecol Oncol 2022

PROGNOSTIC significance of molecular subgroups in stage I patients who underwent lymphadenectomy

Danish Gynaec. Cancer Database

High grade EC, stage I-III without residual disease after surgery incl. lymphadenectomy



Leon Castillo et al, Gynecol Oncol 2022 & ESGO Prague Congress 2021

MOLECULAR MARKERS FOR ENDOMETRIAL CARCINOMA DIAGNOSIS AND AS DETERMINANTS FOR TREATMENT DECISIONS

- Molecular classification **is encouraged in all** endometrial carcinomas, especially high-grade tumours [IV, B].

- POLE mutation analysis **may be omitted in low-risk and intermediate risk** endometrial carcinoma **with low grade histology** [IV, C].

ESGO-ESTRO-ESP Endometrial Cancer Guidelines: LOW RISK

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

[Δ] For **stage III-IVA *POLE*mut** endometrial carcinoma **insufficient data are available to allocate these patients to a prognostic risk-grou**p in the molecular classification. Prospective registries are recommended

- For patients with low-risk endometrial carcinoma, no adjuvant treatment is recommended [I, A].

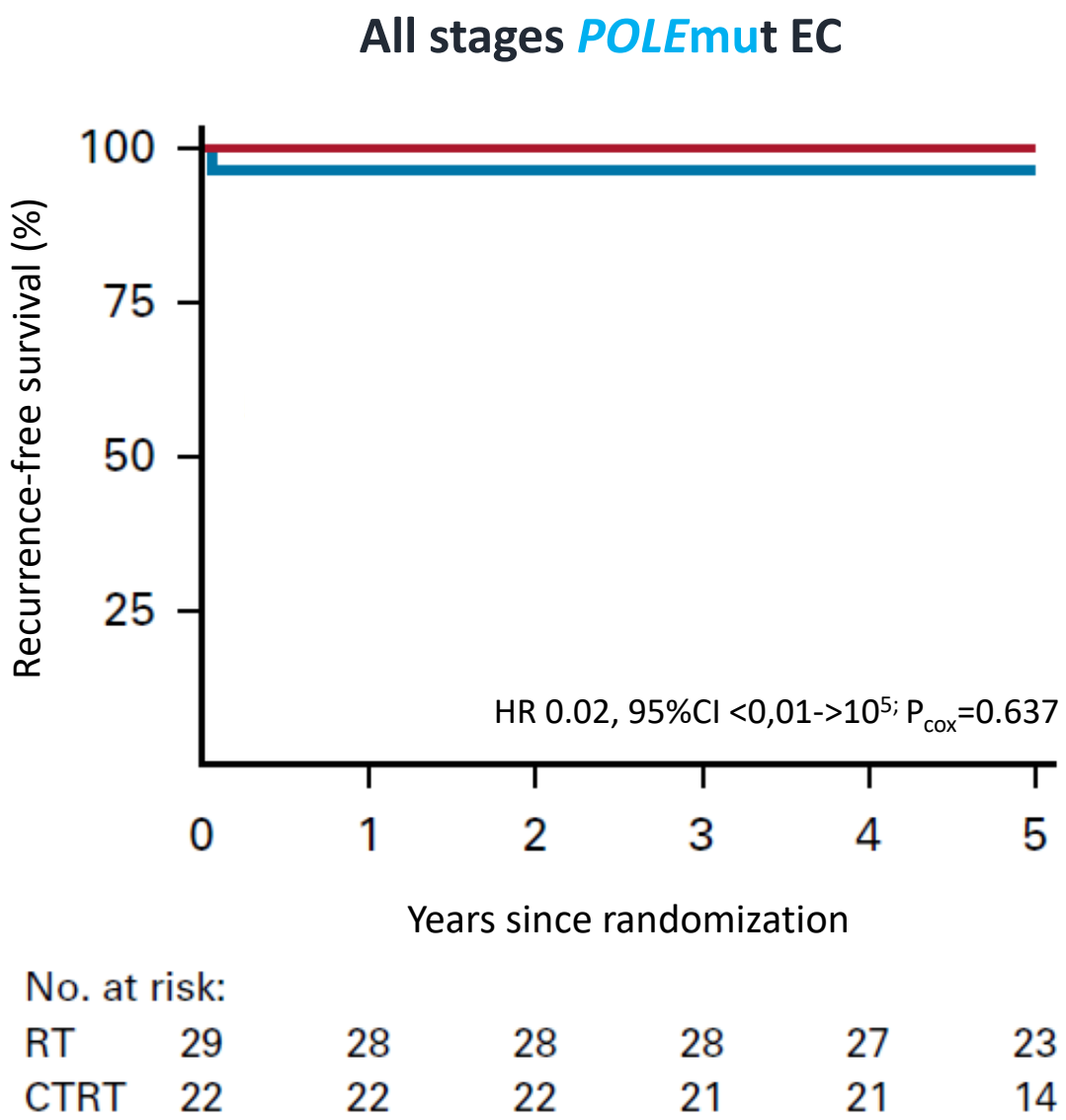
When molecular classification is known:

- 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].

Predictive potential of *POLE*mut for adjuvant platinum-based treatment

PORTEC-3: translational results

	Total	*POLE*mut
	n=410 (100%)	n=51 (12%)
Age, years		
Mean (range)	61 (27-81)	57 (43-72)
Histotype		
Low grade EEC	161 (39)	4 (8)
High grade EEC	113 (28)	29 (57)
NEEC	136 (33)	18 (35)
Stage		
I-II	232 (57)	39 (76)
III	178 (43)	12 (24)
LVSI		
Absent	155 (38)	18 (35)
Present	255 (62)	33 (65)
Treatment		
RT	200 (49)	29 (57)
CTRT	210 (51)	22 (43)



100% CTRT

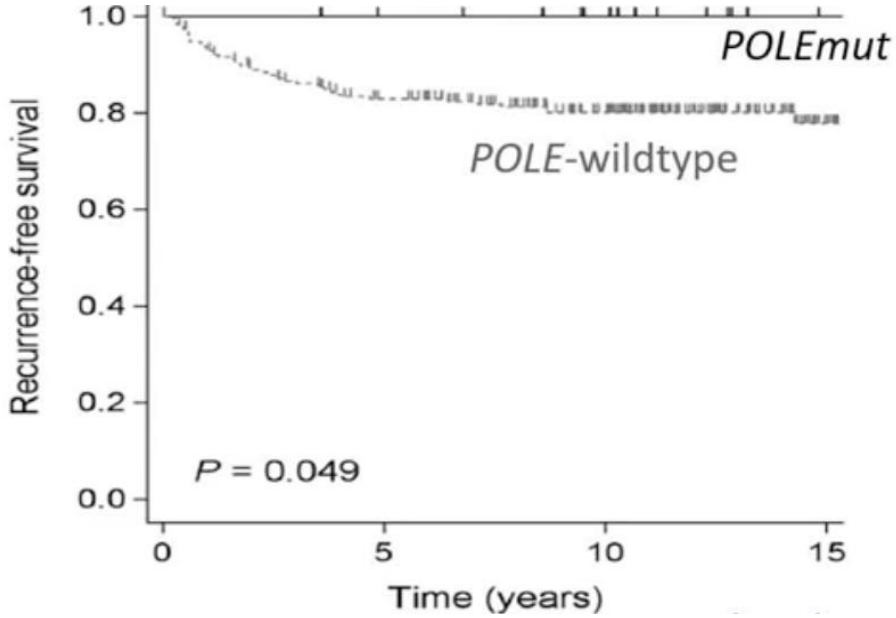
97% RT

Leon-Castillo et al, JCO 2020

POLEmut WITHOUT TREATMENT

PORTEC-1

no adjuvant treatment arm (N=276)



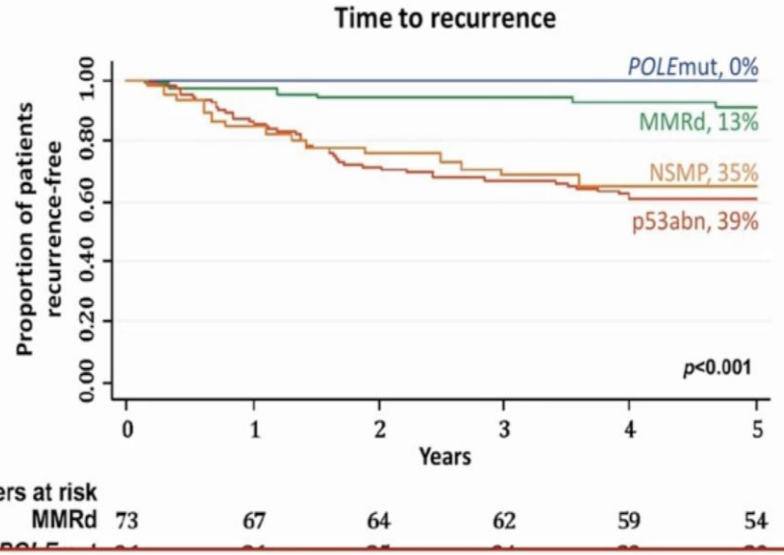
De-escalation

Danish Gynaec. Cancer Database

molecularly profiled **high grade EC, stage I-III** (N=367)

Clinical outcome: Patients not receiving adjuvant treatment

N=264



Patients with *POLE*mut EC have an excellent clinical outcome even when not receiving adjuvant treatment.

Leon Castillo et al, Gynecol Oncol 2022 & ESGO Prague Congress 2021; Nout et al, JCO 2011;

ESGO-ESTRO-ESP Endometrial Cancer Guidelines: HIGH RISK

ESGO
European Society of Gynaecological Oncology

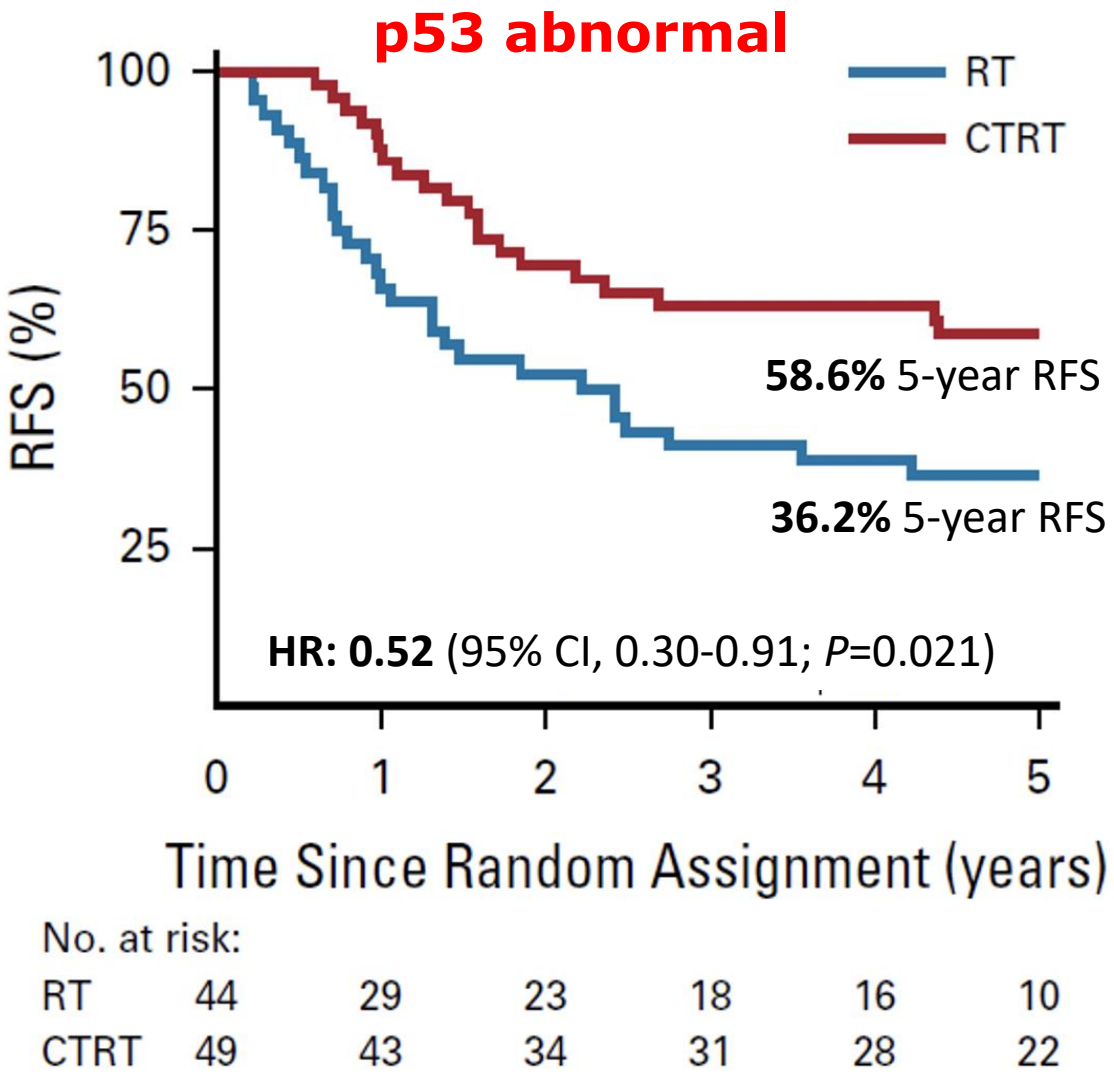
Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ],*
High	□ Stage III-IVA with no residual disease □ Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma mixed) with myometrial invasion, and with no residual disease	□ Stage III-IVA **MMRd/NSMP** 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

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

- **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].

Predictive potential of p53abn for adjuvant platinum-based treatment

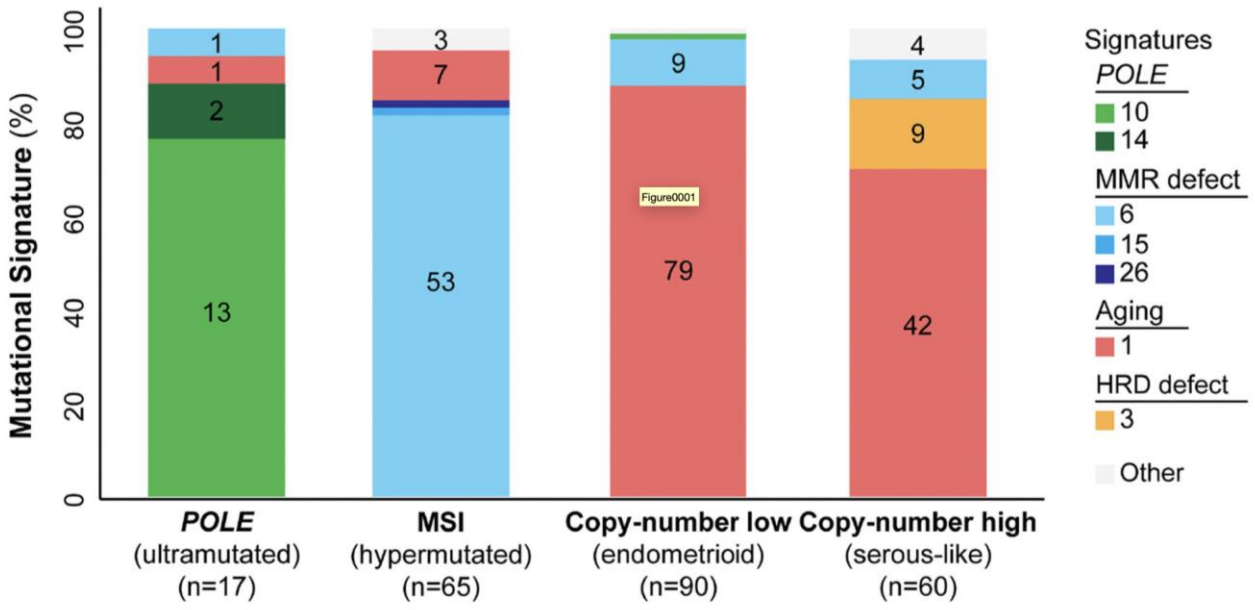
PORTEC-3: translational results



Leon-Castillo et al, JCO 2020

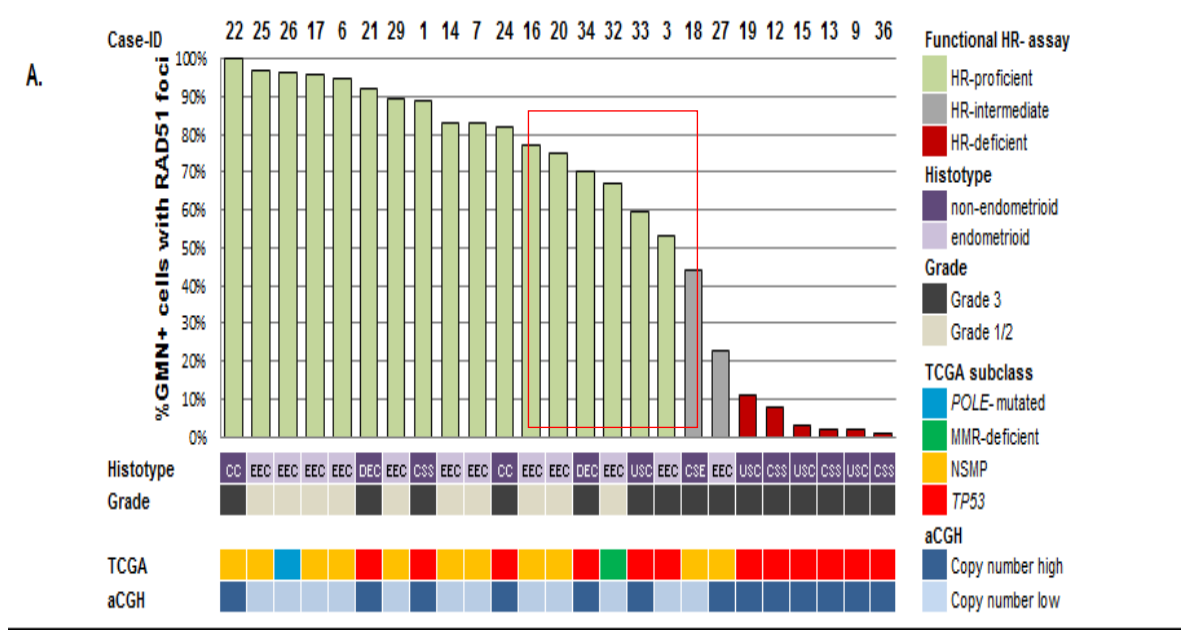
PREDICTIVE potential of p53abn for platinum-based treatment

HDR as a potential target for p53abn EC



50% of p53mut endometrial carcinomas **HRD pos**

n=36



Ashley et al Gynecol Oncol 2019; De Jonge et al, CCR 2018

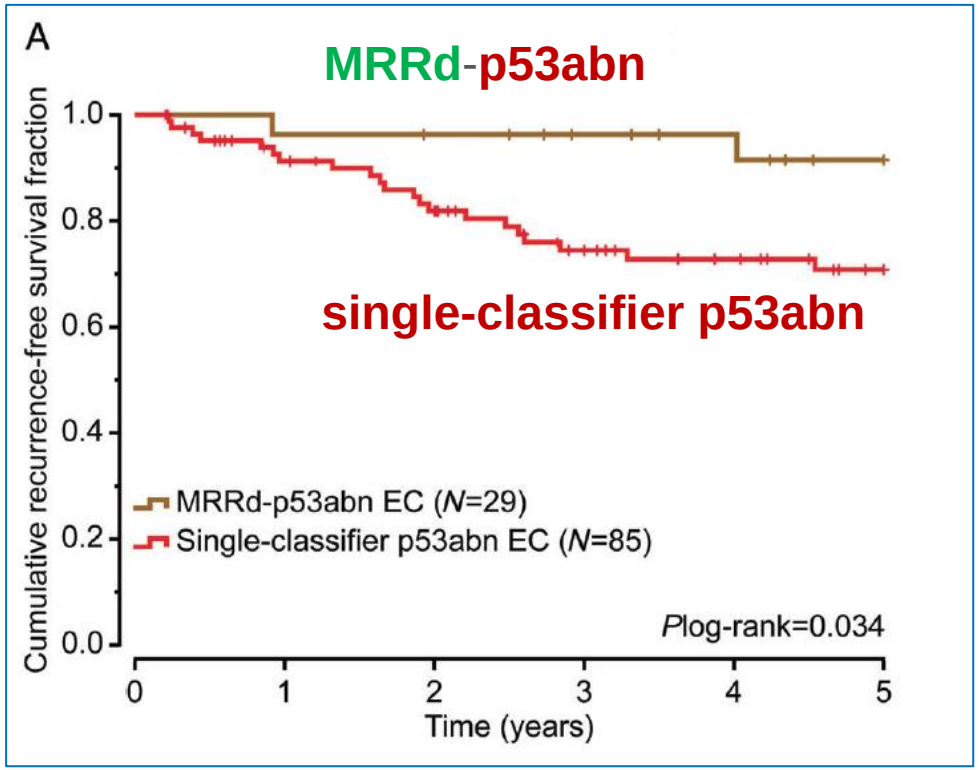
Endometrial cancer with more than one classifying feature: Multiple Classifiers

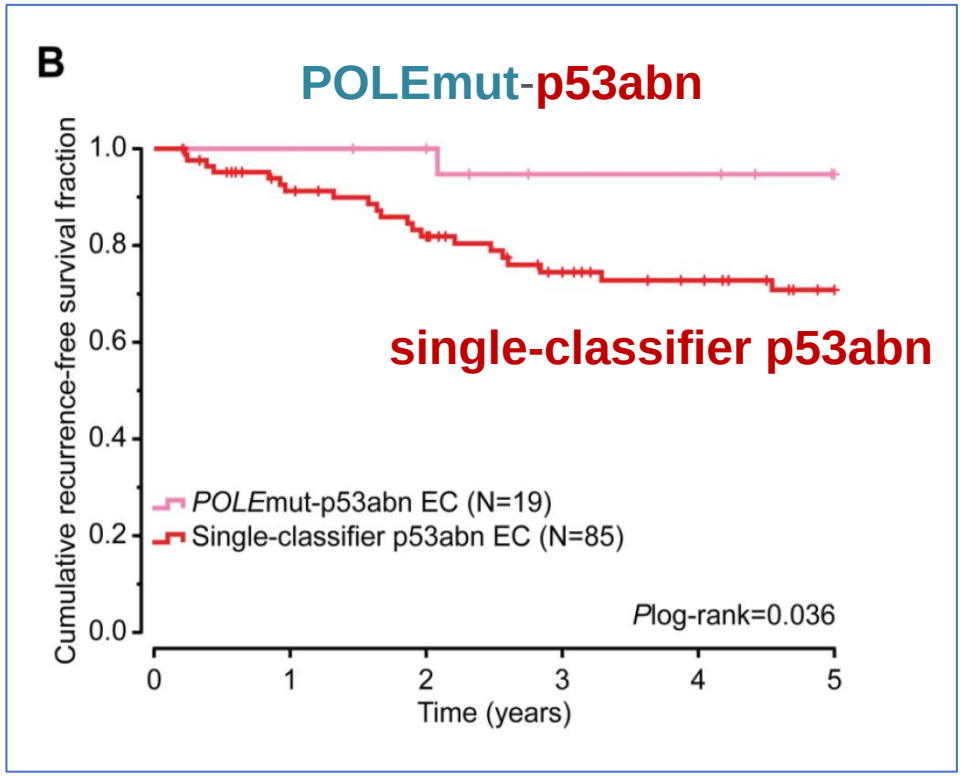
Molecular Profil EC
N=3518

→

Multiple Classifier
N=137 (3,9%)

Recurrenc free survival





León-Castillo et al. J Pathol 2019

Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ,*]
LOW risk	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLEmut*** **EC,** 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 risk	• 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 • **Stage I-IV p53 abn EC with myometrial invasion,** no residual disease carcinoma, carcinosarcoma with myometrial invasion, with no residual disease

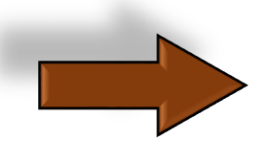
p53abn-*POLEmut* Double classifier

NEW FIGO 2023 Classification for Endometrial Carcinoma

FIGO 2009

Table 2
2009 FIGO Staging System for Endometrial Cancer

Stage	Description
IA	Tumor confined to uterus, <50% myometrial invasion
IB	Tumor confined to uterus, ≥50% myometrial invasion
II	Cervical stromal invasion
IIIA	Tumor invasion into serosa or adnexa
IIIB	Vaginal or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Paraaortic node involvement
IVA	Tumor invasion into bladder or bowel mucosa
IVB	Distant metastases (including abdominal metastases) or inguinal lymph node involvement



FIGO 2023

Integration of molecular markers into surgical-pathological FIGO Staging System

FIGO Endometrial Cancer Committee:

Jonathan Berek, USA (Chair)
Nicole Concin, Austria/Germany
Carien Creutzberg, Netherlands
Christina Fotopoulou, UK
David Gaffney, USA
Kristina Lindermann, Norway
Xavier Mathias-Guiu; Spain
David Mutch, USA

manuscript in press: Berek J…Concin N, Int J Gynecol Obstet 2023

Upcoming first public presentations: FIGO meeting, Paris Oct 2023
ESGO, Istanbul Sep 2023

STAGE I:
NEW FIGO 2023 Classification for Endometrial Carcinoma

Stage I	Confined to the uterine corpus and ovary*
• 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****
• IB	**Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI****
• IC	**Aggressive histological types*** limited to a polyp or confined to the endometrium**

Molecular Finding in early endometrial cancer patients (Stages I & II after surgically staging+)
POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type

StageIAm$_{POLEmut}$

manuscript in press: Berek J…Concin N, Int J Gynecol Obstet 2023

Upcoming first public presentations: FIGO meeting, Paris Oct 2023
ESGO, Istanbul Sep 2023

STAGE II:
NEW FIGO 2023 Classification for Endometrial Carcinoma

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 ** of non-aggressive histological type**
•	**IIC**	**Aggressive histological types *** with any myometrial involvement**

Molecular Finding in early endometrial cancer patients (Stages I & II after surgically staging+)
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

StageIICm$_{p53abn}$

manuscript in press: Berek J…Concin N, Int J Gynecol Obstet 2023

Upcoming first public presentations: FIGO meeting, Paris Oct 2023
ESGO, Istanbul Sep 2023

Surgery in endometrial carcinoma: Mainstay of treatment

Major Advancements in Surgery **in Early Stage Disease**

2015

ESMO-ESGO-ESTRO Consensus Conference

2020

ESGO-ESTRO-ESP Guidelines

Minimal invasive surgery

Sentinel Lymph Node

Minimal invasive surgery (MIS)

ESMO-ESGO-ESTRO
Consensus Conference 2015

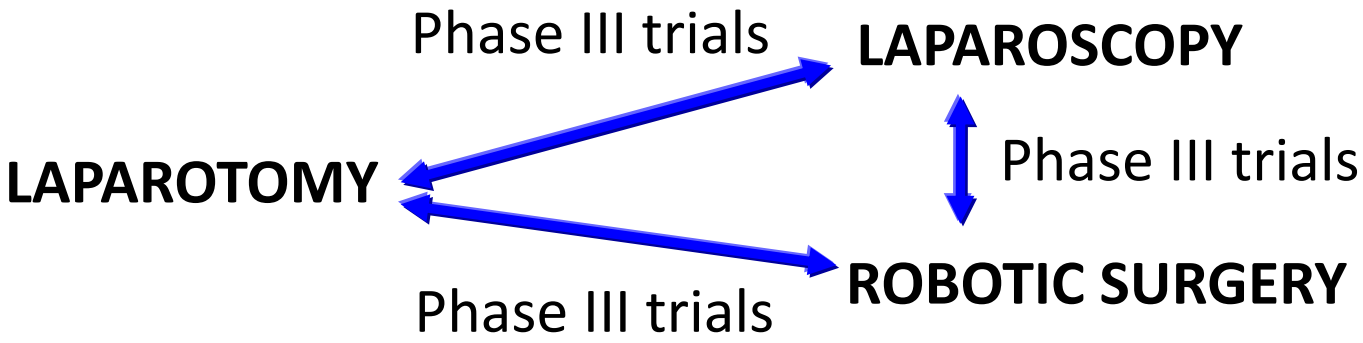
MIS **is recommended** in the surgical management of **low-and intermediate-risk** endometrial cancer
*Level of evidence: **I***
Strength of recommendation: A

MIS **can be considered** in the management of **high-risk endometrial cancer**
*Level of evidence: **IV***
Strength of recommendation: C

Colombo N et al, Ann Oncol. 2016 & Int J Gynecol Cancer 2016 & Radiother Oncol 2015

ESGO-ESTRO-ESP Guidelines NOW

Minimally invasive surgery is the preferred surgical approach, including patients with high-risk endometrial carcinoma (I, A).



Concin N et al, Int J Gynecol Cancer 2020 & Radiother Oncol 2021 & Virchows Arch 2021

Surgical management in apparent stage I/II endometrial carcinoma

- **Total Hysterectomy (HE) & bilateral salpingo-oophorectomy (BSO) [II, A]**
- **Staging infracolic omentectomy in serous, undifferentiated carcinoma & carcinosarcoma [IV, B]**
- **Stage II: HE+BSO & lymph node staging, more extensive procedures admitted only to achieve free surgical margins [IV, B]**

Minimally Invasive Surgery preferred surgical approach (I,A)

- Intraperitoneal tumour spillage, including tumour rupture or morcellation (including in a bag), should be avoided [III, B]
- If vaginal extraction risks uterine rupture, other measures should be taken (eg. mini-laparotomy, use of endobag [III, B]
- Tumours with metastasis outside the uterus and cervix (excluding lymph node metastases) are relative contra-indications [III, B]

Concin N *et al*, Int J Gynecol Cancer & Radiother Oncol & Virchows Arch 2020/21

Quality assurance

Quality Indicators for Endometrial Cancer Surgery

ESGO Accredited Centre in Endometrial Cancer Surgery

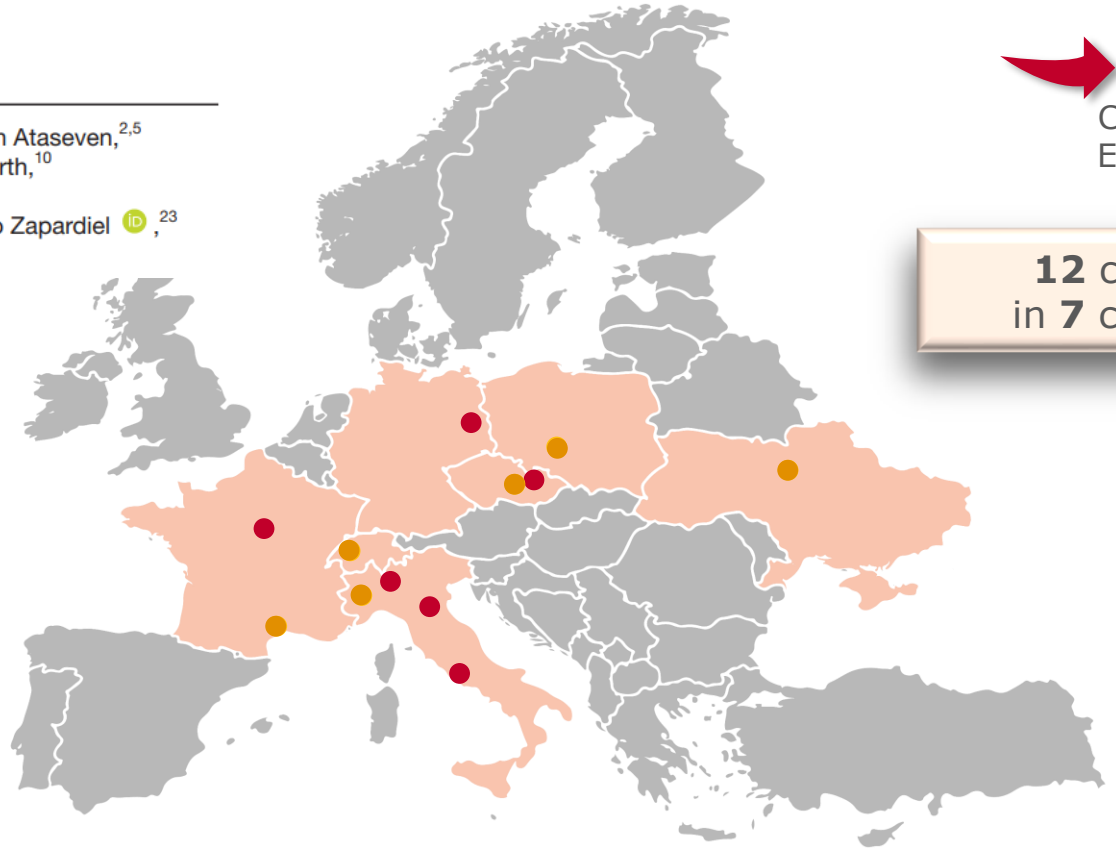
European Society of Gynaecological Oncology quality indicators for the surgical treatment of endometrial carcinoma

Nicole Concin [1,2] François Planchamp,[3] Nadeem R Abu-Rustum [4] Beyhan Ataseven,[2,5] David Cibula,[6] Anna Fagotti,[7] Christina Fotopoulou,[8] Pawel Knapp,[9] Christian Marth,[10] Philippe Morice,[11] Denis Querleu [7,12] Jalid Sehouli,[13] Artem Stepanyan [14] Cagatay Taskiran [15,16] Ignace Vergote,[17] Pauline Wimberger,[18,19,20,21,22] Ignacio Zapardiel [23] Jan Persson[24,25]

2021

6 Accredited centres

6 Centres of Excellence



12 centers in **7** countries

accreditation launched in Sept 2022

Concin et al, Int J Gynecol Cancer 2021

Quality Indicator 8

Proportion of early stage endometrial carcinoma cases with non ruptured uterus after hysterectomy

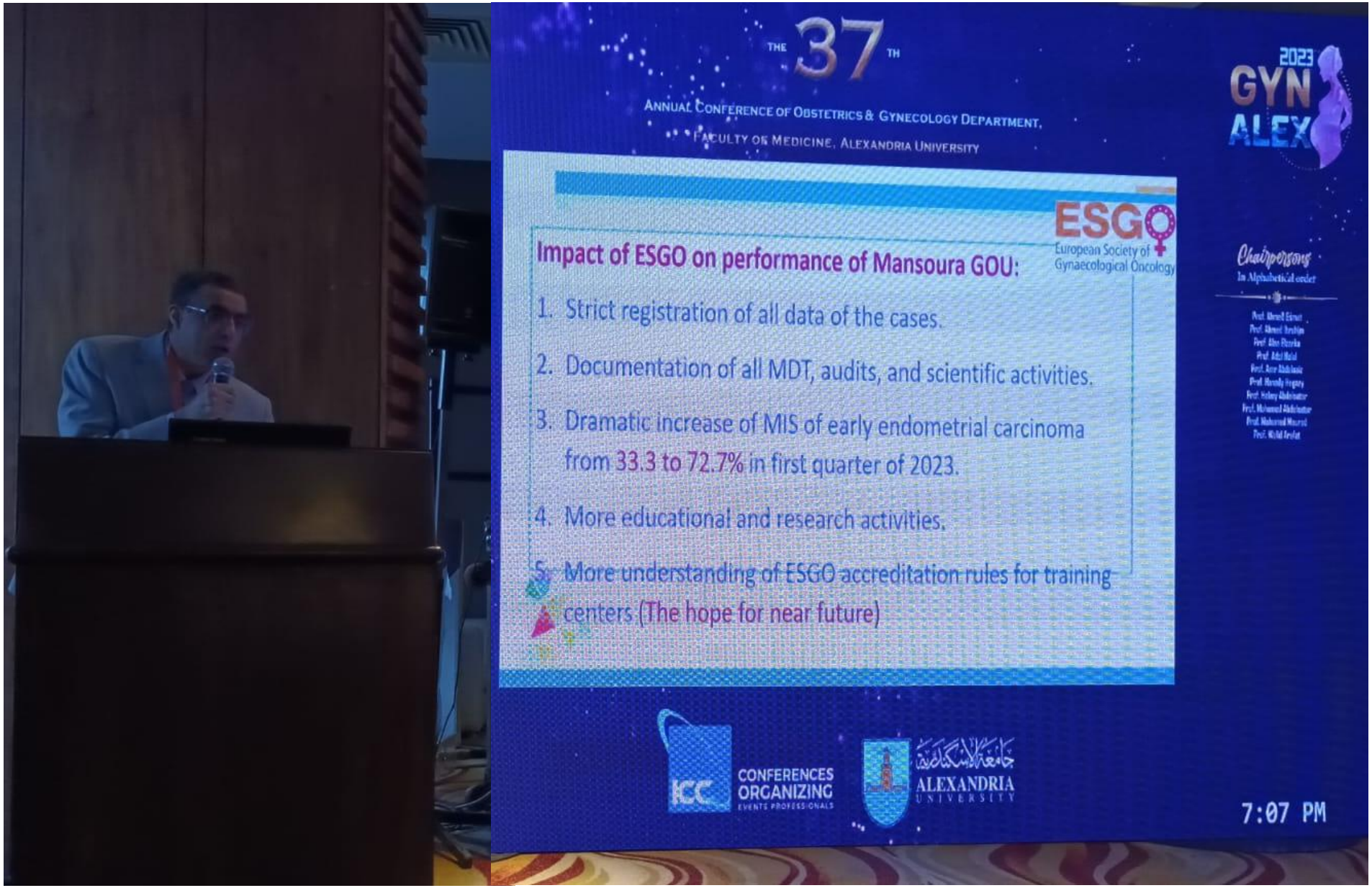
Type	Outcome indicator
Description	Uterus should be removed intact. Intraoperative rupturing/fragmentation/morcellation of the uterus must be avoided. Any intra-peritoneal tumour spillage, including tumour rupture or morcellation (including in a bag), should be avoided.
Specifications	*Numerator*: number of patients with early-stage endometrial carcinoma after hysterectomy with intact/non ruptured/non fragmented/non morcellated uterus. *Denominator*: all patients with early stage (I-II) endometrial carcinoma who underwent hysterectomy.
Target	99%

Quality Indicator 9

Proportion of patients with early-stage endometrial carcinoma who have undergone successful minimally invasive surgery

Type	Outcome indicator
Description	Minimally invasive surgery (laparoscopic or robotic surgery) is considered successful if performed without any intra-peritoneal tumour spillage, tumour rupture or morcellation (including in a bag). If vaginal extraction risks uterine rupture, other measures should be taken (e.g, mini-laparotomy, use of endobag). If a mini-laparotomy for such purpose is performed within a minimal invasive procedure, the surgery is still considered a successful minimal invasive surgery.
Specifications	*Numerator*: number of patients with preoperative early-stage endometrial carcinoma who have undergone successful minimally invasive surgery. *Denominator*: all patients who have undergone surgery for preoperative early stage (I-II) endometrial carcinoma.
Targets	Optimal target: ≥80% Minimum required target: 60%

May 2023: Annual Conference Department Obs&Gynae, Alexandria University in Egypt



Lymph node staging in apparent stage I/II endometrial carcinoma

ESGO
European Society of Gynaecological Oncology

ESMO-ESGO-ESTRO
Consensus Conference 2015

Sentinel Lymph Node biospy is still experimental

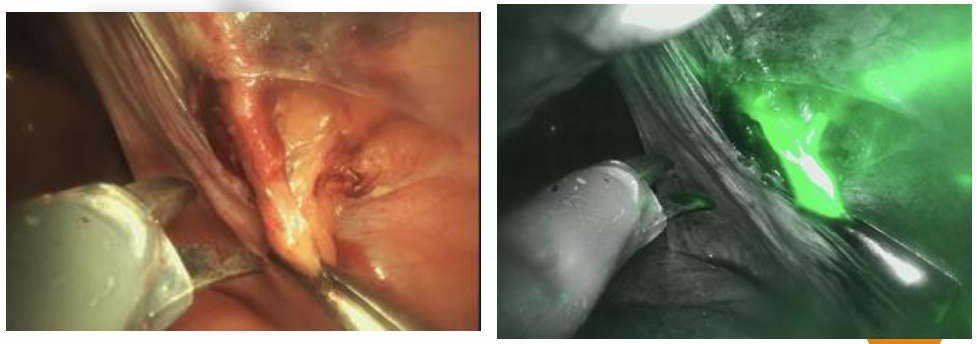
Level of evidence: IV
Strength of recommendation: D

Colombo N et al, Ann Oncol 2016 & Int J Gynecol Cancer 2016 & Radiother Oncol 2015

ESGO-ESTRO-ESP Guidelines NOW

Sentinel Lymph Node biopsy as an alternative to systematic lymphadenctomy for LYMPH NODE STAGING

A negative SLN is accepted to confirm pN0



Concin N et al, Int J Gynecol Cancer 2020 & Radiother Oncol 2021 & Virchows Arch 2021

Prospective cohort studies: Sentinel Lymph Node Mapping in high risk endometrial carcinoma patients

Studies	FIRES Rossi et al., Lancet Oncol 2017	MDA/Soliman et al., Gynecol Oncol 2017	SHREC Persson et al., EJC 2019	SENTOR Cusimano et al., JAMA Surg Nov 2020
Patients	**Stage I all histotypes and grades (~ 30% high risk)**	**Stage I-II High risk** (44% endometrioid grade 3 or grade 1/2 stage Ib, 30% serous, 16% clear cell, 10% carcinosarcoma 12% stage II)	**Stage I-II High-risk** (13% endometrioid grade 3, 23% serous 5% clear cell 5% carcinosarcoma 5% stage II)	**Stage I intermediate & high grade**
N	N=385	N=123	N=**257**	N=156
N of metastatic nodes	N=41 (12%) (high risk: 22%)	N= 23 (23%)	N=54 (21%)	N=27 (17%)
Sensitivity	**97.2%**	**95%**	**98%**	**96%**
False-negative-rate	**3%**	**5%**		**4%**
Negative predictive value	**99.6%**	**98.6%**	**99.5%**	**99.0%**
SLN detection rate: -per patient -per hemipelvis -bilateral		89% 40% 58%	95%	97.4 87.5 77.6%

Lymph node staging in apparent stage I/II endometrial carcinoma

- **Sentinel lymph node biopsy can be considered** for staging purposes in patients with **low/intermediate risk disease**. It can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended in this group [II, A].

- Surgical lymph node staging should be performed in patients with **high intermediate risk/high risk** disease. **Sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy for lymph node staging in stage I/II** [**III, B**].

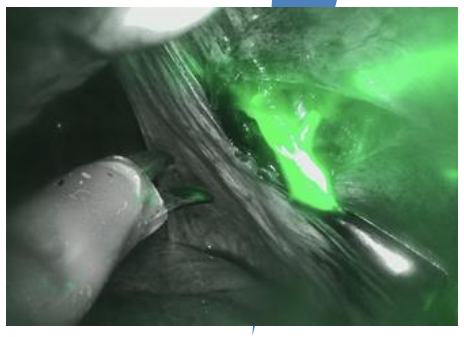
Sentinel Lymph node in apparent stage I/II endometrial carcinoma

High intermediate/ high risk

SLN

low/intermediate risk

Pelvic & para-aortic Lymphadenectomy



No Lymph node staging

- **lower risk of post-operative morbidity especially lower leg lymphedema**
- **Identification of true low risk disease**

- **Increase detection rate of positive pelvic nodes by ultrastaging and immunohistochemistry**

Key: adequate surgeons experience
defined and structured surgical algorithm
clear definition of SLNs based on one tracer, ICG

Persson J et al, European Journal of Cancer 2019; Accorsi et al, J Minim Invasive Gynecol 2020; Kim CH et al, Gynecol Oncol 2013

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