CRITICITA' DELLE LINEE GUIDA ESGO NEL CARCINOMA DELL'ENDOMETRIO E DELLA CERVICE

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MaNGO
Mario Negri Gynecologic Oncology

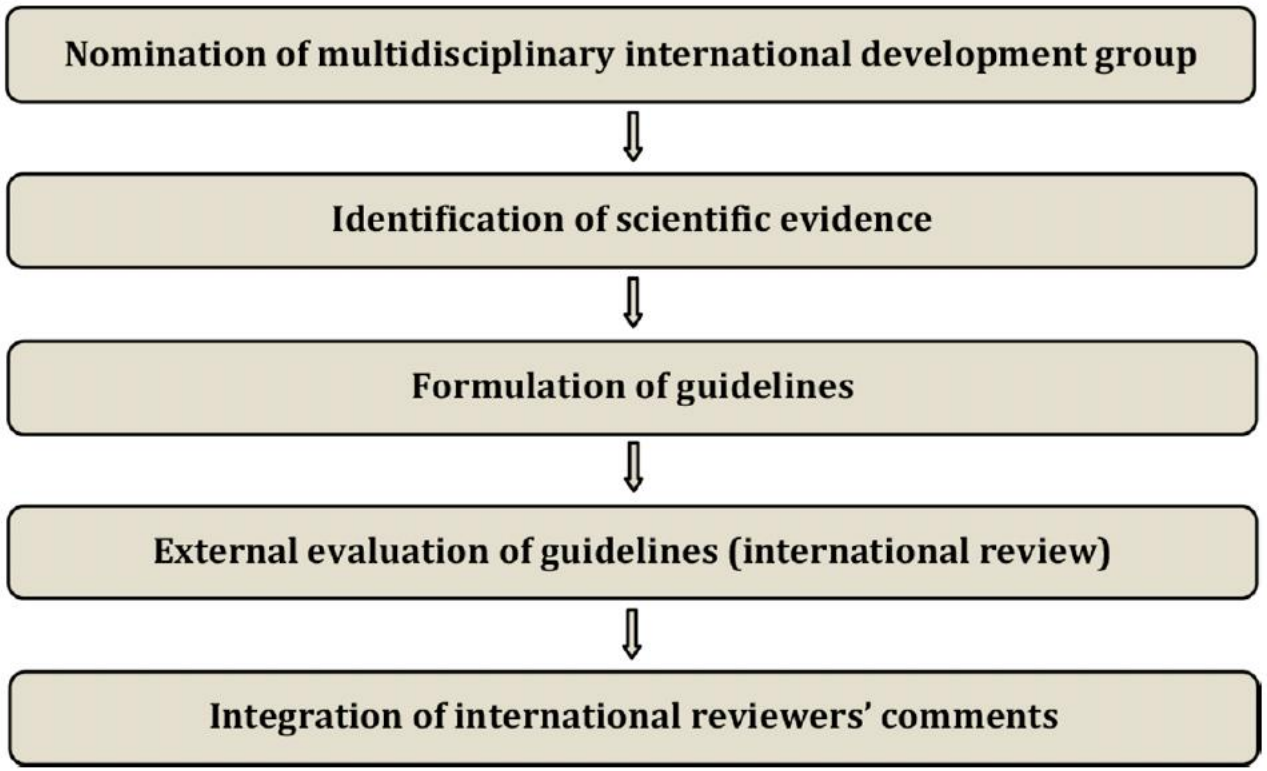


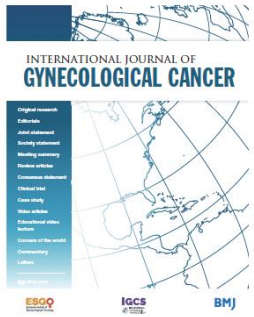
Figure 1 Guideline development process.

LEVELS OF EVIDENCE	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions

GRADES OF RECOMMENDATIONS	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Figure 2 Levels of evidence and grades of recommendations.

Endometrial cancer



ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

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 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

- No adj th
- When molecular classification available: I-II stage POLE mutated tumors no adj th

- Adj BT can be recommended to decrease local recurrence
- Omission of adj BT can be considered
- When molecular classification available: POLE and P53 mutated tumors have specific recommendations (P53 abn tumors restricted to a polyp or without myometrial is present on polyp orwithout myometrial invasion, adj th is generally not recommended)

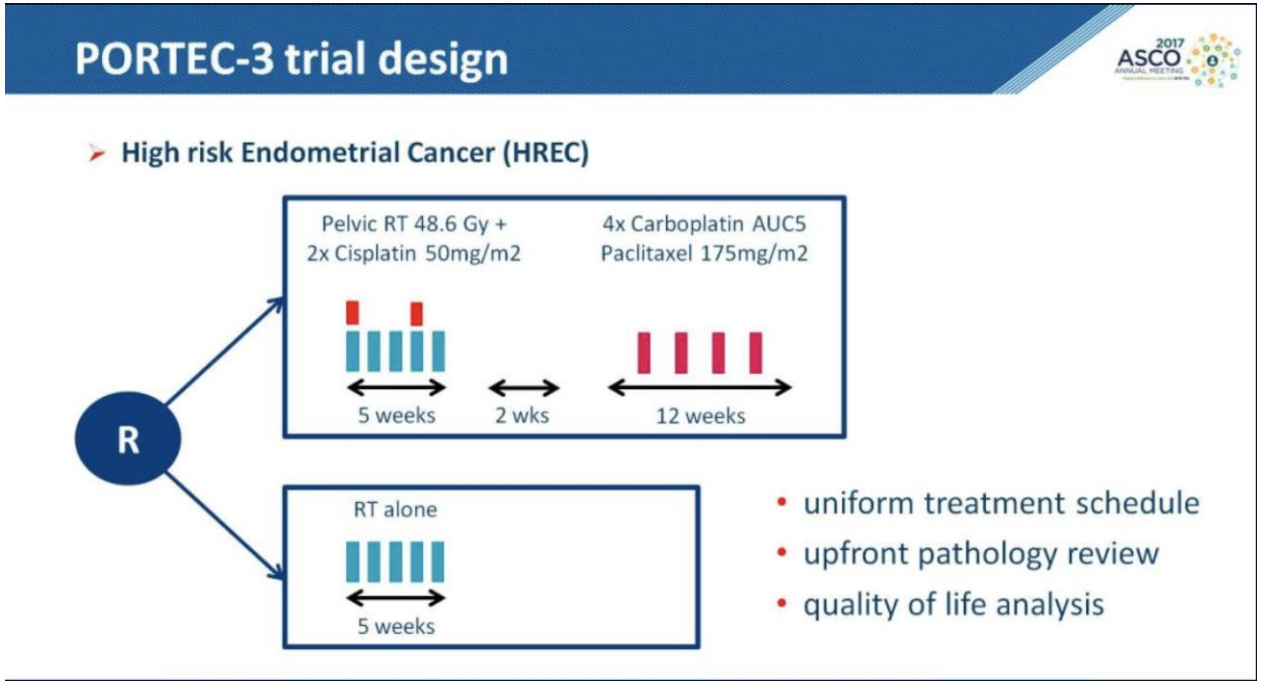
- Adj BT can be recommended to decrease local recurrence
- EBRT can be considered for substantial LVSI and for stage II
- Adj CT can be considere, especially for high grade and/or substantial LVSI
- Omission of any adj th is an option
- When mol class avail: POLE and P53 mutated tumors have specific recomm

- EBRT with concurrent and adj CT or with seq CT and RT
- CT alone is an alternative option
- When mol class avail: POLE and P53 mutated tumors have specific recomm

Concin N, et al. IJGC 2021

Mostly debated

POLE gene mutation in EC is observed EC in 7-12%



Post-hoc analysis

***POLE*mut**

- POLEmut endometrioid carcinoma had an excellent outcome in both arms.
- However, both trial arms included EBRT.
- Prospective registration preferably in national or international studies) of POLEmut endometrial carcinoma cases with treatment and outcome data is strongly recommended.

Stage					< .001
IA	54 (13.2)	23 (24.7)	12 (23.5)	13 (9.5)	6 (4.7)
IB	73 (17.8)	14 (15.1)	20 (39.2)	26 (19.0)	13 (10.1)
II	105 (25.6)	24 (25.8)	7 (13.7)	33 (24.1)	41 (31.8)
IIIA	46 (11.2)	8 (8.6)	2 (3.9)	10 (7.3)	26 (20.2)
IIIB	29 (7.1)	4 (4.3)	4 (7.8)	13 (9.5)	8 (6.2)
IIIC	103 (25.1)	20 (21.5)	6 (11.8)	42 (30.7)	35 (27.1)

Evaluation of Treatment Effects in Patients With Endometrial Cancer and *POLE* Mutations: An Individual Patient Data Meta-Analysis

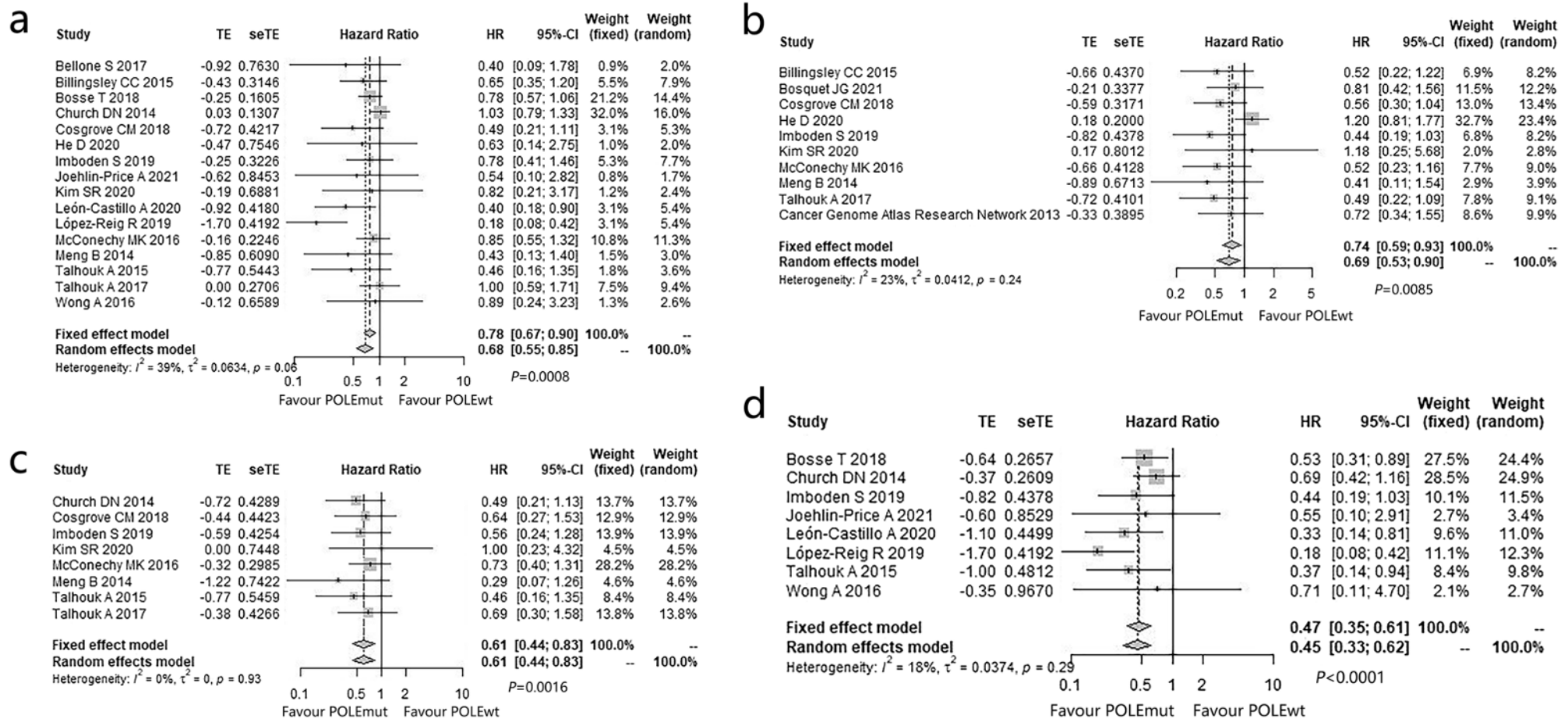


Fig. 3 Forest plot of the meta-analysis estimating the hazard ratio (HR) with 95% confidence interval (CI) of **a** overall survival (OS), **b** progression free survival (PFS), **c** disease specific survival (DSS), and **d** relapse free survival (RFS) for POLEmut compared with POLE-wild-type (POLEwt) EC patients

McAlpine JN et al., Cancer 2021

Evaluation of Treatment Effects in Patients With Endometrial Cancer and *POLE* Mutations: An Individual Patient Data Meta-Analysis

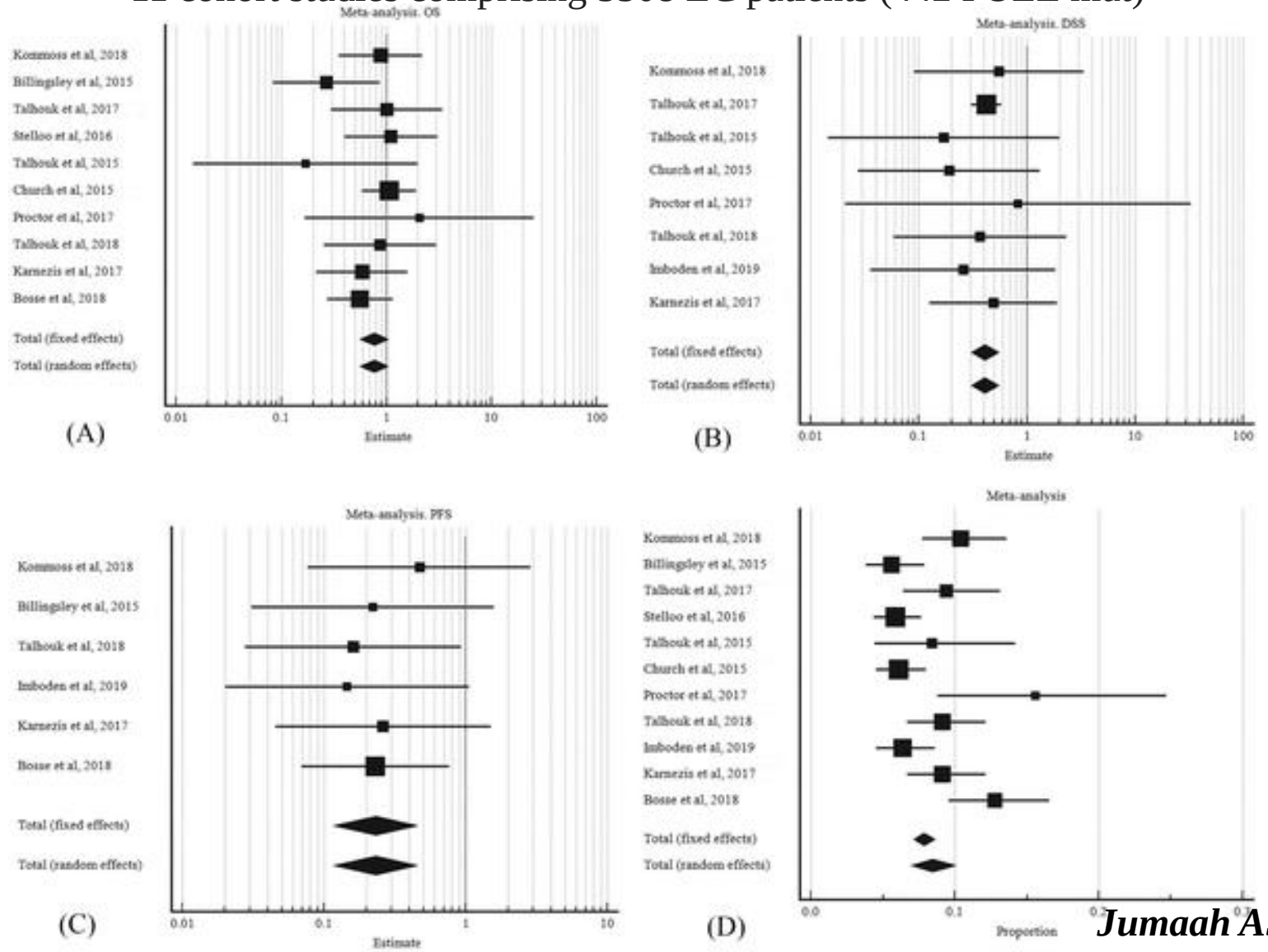
TABLE 1. Clinicopathological Characteristics, Treatments, and Outcomes for *POLE* Pathogenic and Nonpathogenic/Variant of Uncertain Significance Endometrial Cancers

Variable	Total (n = 359)	Pathogenic (n = 294)	Nonpathogenic (n = 65)	*P*
Age, y[a]				.002
Median (range)	58.0 (31.0-92.6)	57.0 (31.0-92.6)	64.0 (35.0-82.3)	
BMI, kg/m^2				.359
Median (range)	27.3 (17.4-213.5)	27.1 (18.0-54.2)	28.3 (17.4-213.5)	
Missing	104	95	9	
Stage, No. (%)[a]				.095
IA	193 (53.8)	165 (56.1)	28 (43.1)	
IB	101 (28.1)	81 (27.6)	20 (30.8)	
II	22 (6.1)	19 (6.5)	3 (4.6)	
IIIA	16 (4.5)	10 (3.4)	6 (9.2)	
IIIB	5 (1.4)	3 (1.0)	2 (3.1)	
IIIC	15 (4.2)	12 (4.1)	3 (4.6)	
IV	7 (1.9)	4 (1.4)	3 (4.6)	

McAlpine JN et al., Cancer 2021

POLE mutations and survival analysis meta-analysis.

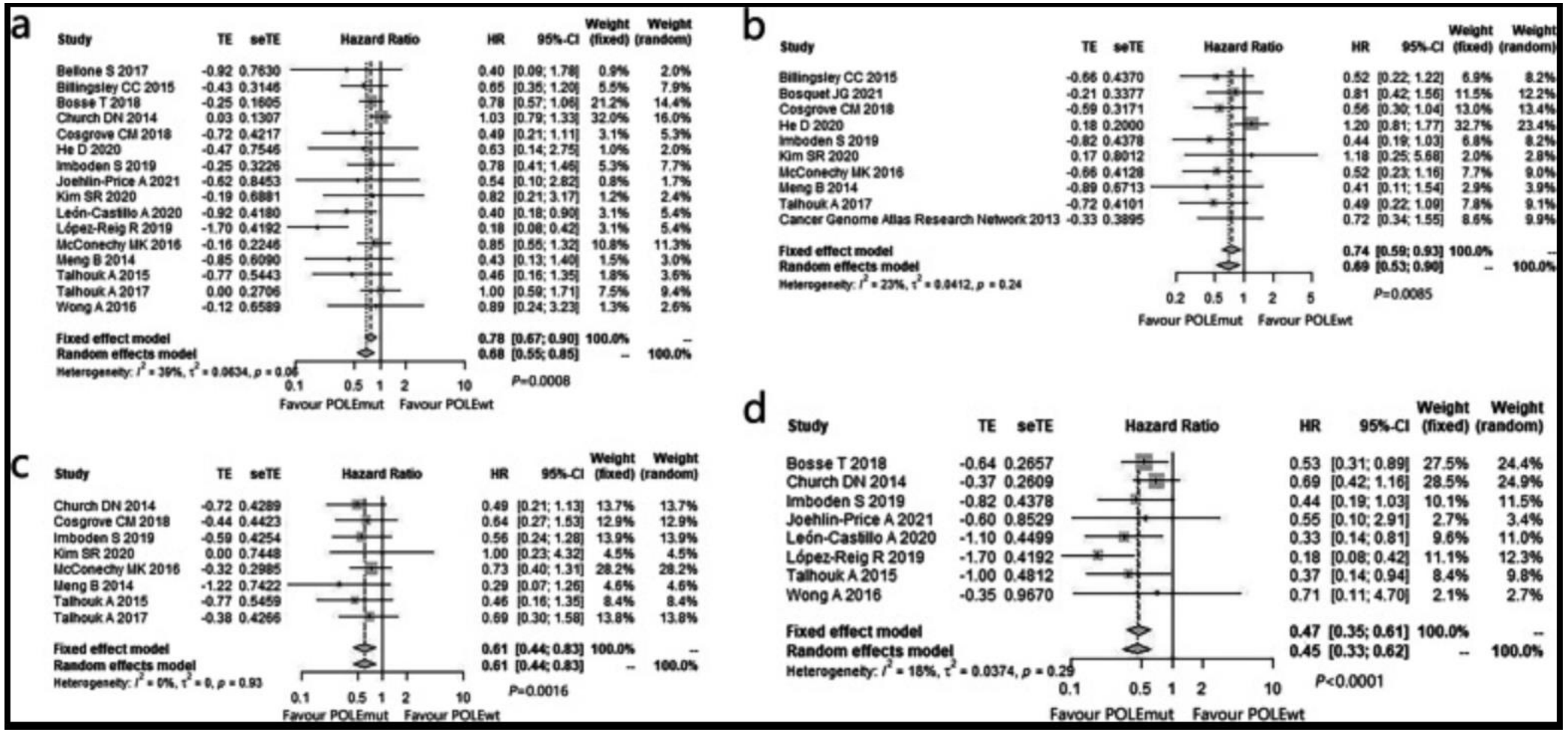
11 cohort studies comprising 5508 EC patients (442 POLE mut)



Jumaah AS et al., PLOSone 2022

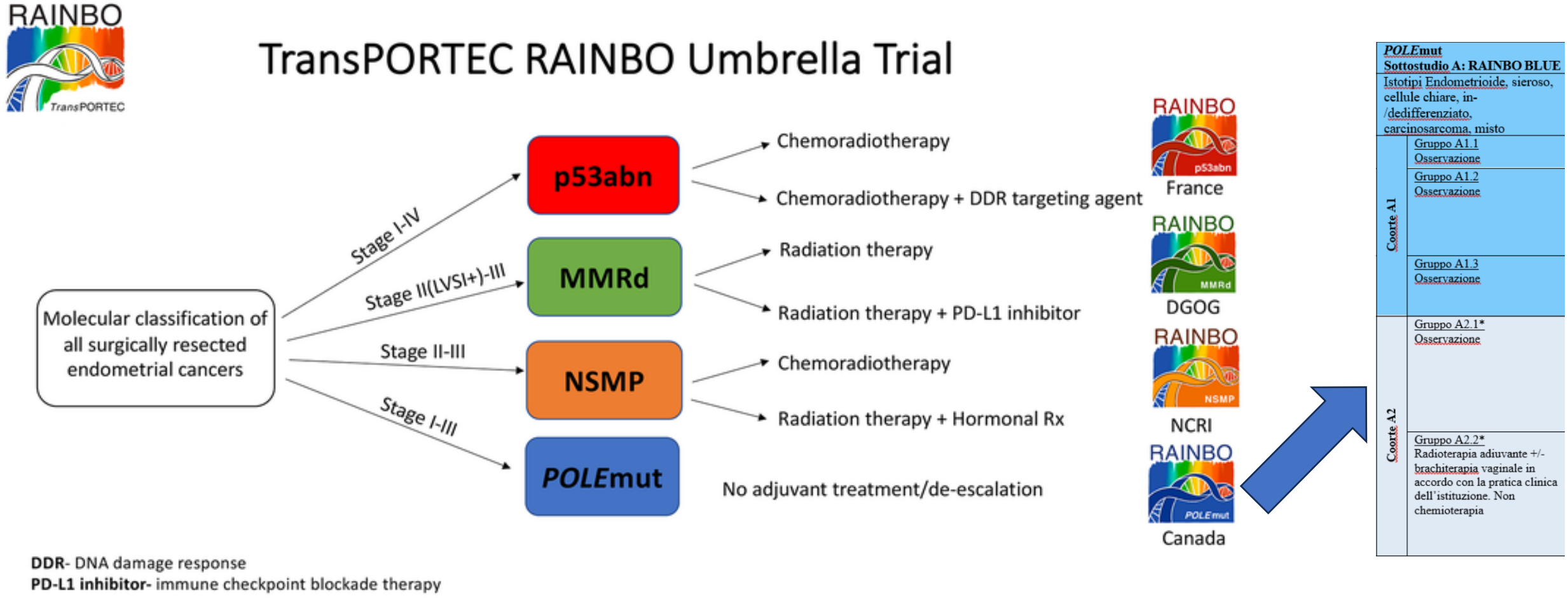
The clinicopathological characteristics of POLE-mutated/ultramutated endometrial carcinoma and prognostic value of POLE status: a meta-analysis based on 49 articles incorporating 12,120 patients

POLE 8%



Qing Wu et al., BMC cancer 2022

More data…



DDR- DNA damage response
PD-L1 inhibitor- immune checkpoint blockade therapy

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, McAlpine, Talhouk Annals Onc 2018; Abdulfatahet al, Gyn Onc 2019; Leon-Castillo al, J Path 2019

Pathological classification doesn't really matter?

Gynecologic Oncology 148 (2018) 147–153

Contents lists available at ScienceDirect

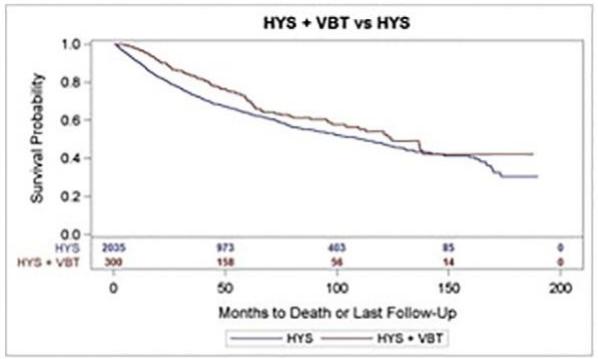
Gynecologic Oncology

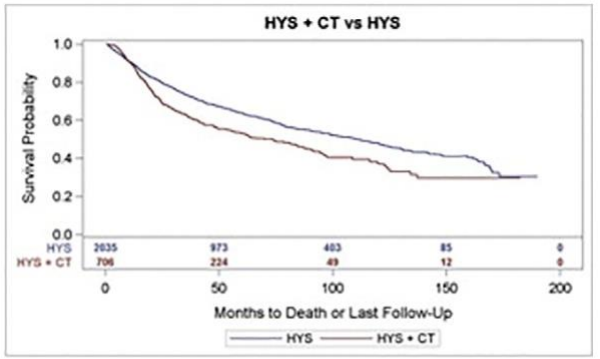
journal homepage: www.elsevier.com/locate/ygyno

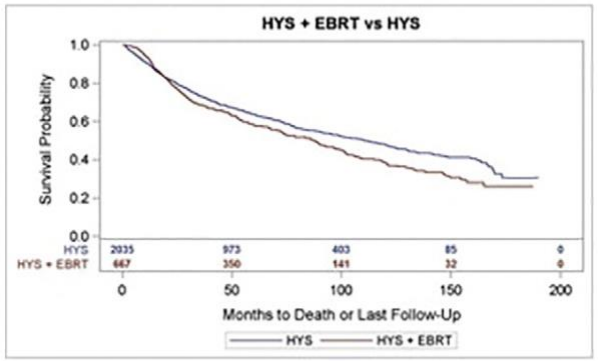
Adjuvant therapy in patients with clear cell endometrial carcinoma: An analysis of the National Cancer Database☆

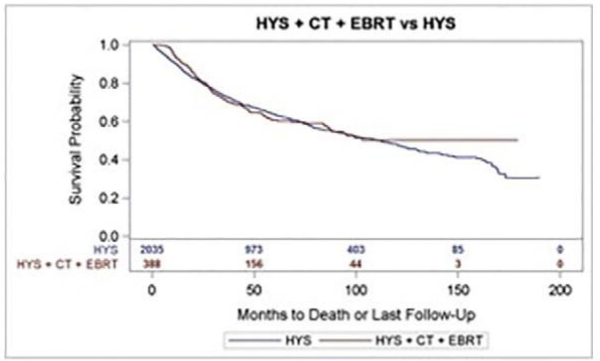
Karina Nieto [a], William Adams [b], Nghia Pham [c], Alec M. Block [e], Surbhi Grover [d], William Small Jr [e], Matthew M. Harkenrider [e,*]

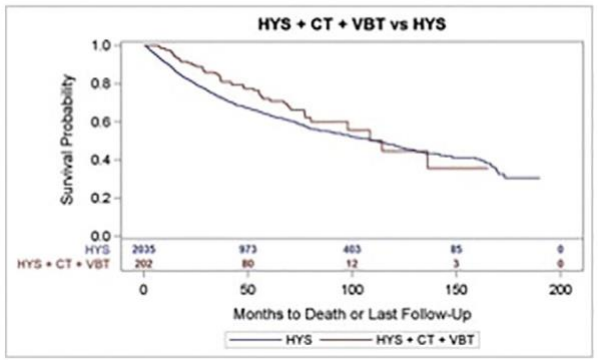
4298 patients treated from 1998 to 2011 with Stage I–IVA CCC were identified within the National Cancer Database.

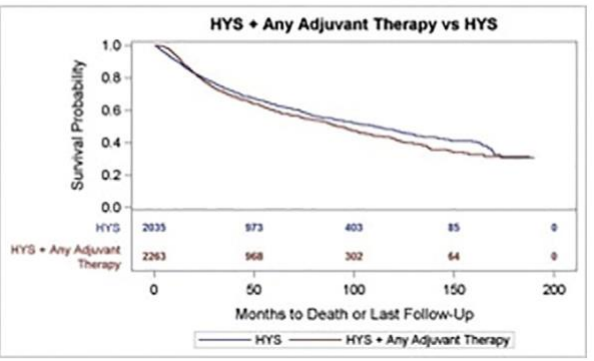






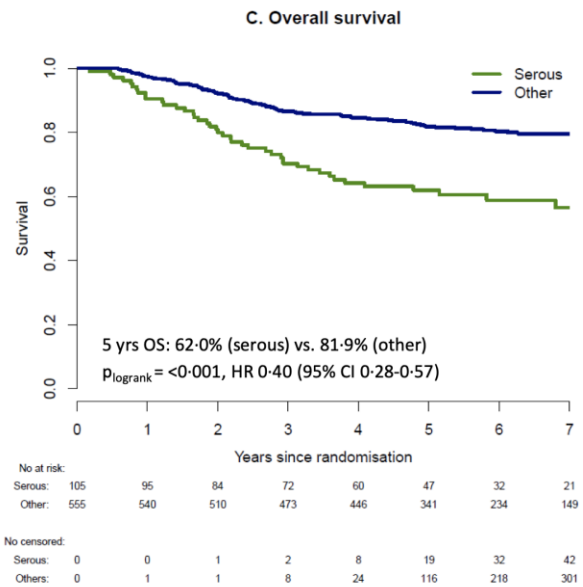


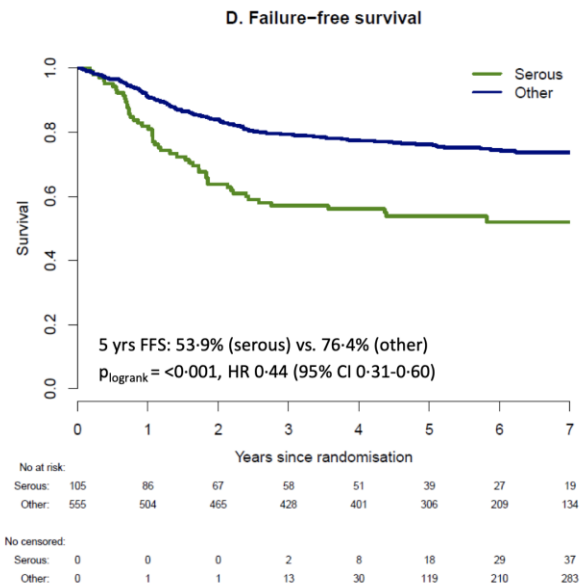


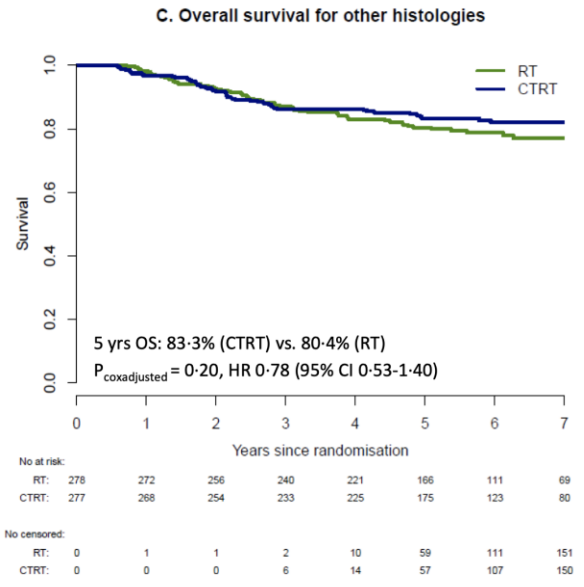


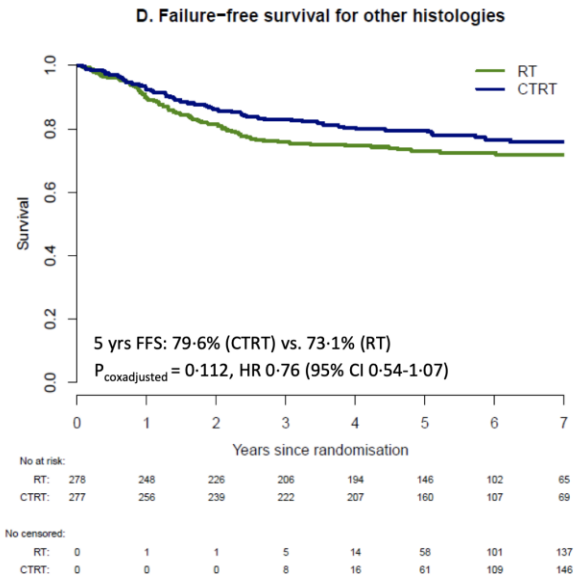
Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial

*Stephanie M de Boer, Melanie E Powell, Linda Mileshkin, Dionyssios Katsaros, Paul Bessette, Christine Haie-Meder, Petronella B Ottevanger, Jonathan A Ledermann, Pearly Khaw, Romerai D'Amico, Anthony Fyles, Marie-Helene Baron, Ina M Jürgenliemk-Schulz, Henry C Kitchener, Hans W Nijman, Godfrey Wilson, Susan Brooks, Sergio Gribaudo, Diane Provencher, Chantal Hanzen, Roy F Kruitwagen, Vincent T H B M Smit, Naveena Singh, Viet Do, Andrea Lissoni, Remi A Nout, Amanda Feeney, Karen W Verhoeven-Adema, Hein Putter, Carien L Creutzberg, on behalf of the PORTEC Study Group**









686 women were enrolled, of whom 660 were eligible and evaluable

With data in other tumors being controversial!!!!

Radiotherapy and Renal Cell Carcinoma: A Continuing Saga

DESPOINA SPYROPOULOU, PANAGIOTIS TSIGANOS, FOTEINOS-IOANNIS DIMITRAKOPOULOS, MARIA TOLIA, ANGELOS KOUTRAS, DIMITRIS VELISSARIS, MARIA LAGADINOU, NIKOLAOS PAPATHANASIOU, ARETI GKANTAIFI, HARALABOS KALOFONOS and DIMITRIOS KARDAMAKIS

In Vivo May 2021, 35 (3) 1365-1377; DOI: https://doi.org/10.21873/invivo.12389

Radiation Therapy for Recurrent Clear-Cell Cancer of the Ovary

Gina L Westhoff [1], Katherine C Fuh, Terry A Longacre, Jennifer Leah McNally, I-Chow Hsu, Daniel S Kapp, Nelson Teng, Lee-May Chen

Affiliations + expand

PMID: 27575628 DOI: 10.1097/IGC.0000000000000810

ESGO-ESTRO-ESP guidelines

A new FIGO staging in[illegible] classification has been first published on 20th June!!!

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
	[illegible] al LVSI[d]
	[illegible] gical types with
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

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

Original research

ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma

Alexandros Rodolakis [1], Giovanni Scambia [2], François Planchamp [3], Maribel Acien [4], Attilio Di Spiezio Sardo,[5] Martin Farrugia,[6] Michael Grynberg,[7,8,9] Maja Pakiz [10], Kitty Pavlakis,[11,12] Nathalie Vermeulen,[13] Gianfranco Zannoni [14], Ignacio Zapardiel [15], Kirsten Louise Tryde Macklon[16]

Differentiation of the Tumor

- Fertility-sparing treatment is considered for endometrioid patients with endometrial carcinoma with grade 1, stage IA without myometrial invasion and without risk factors (Level of evidence V, grade A).
- Evidence for grade 2 endometrioid endometrial carcinoma is limited. Therefore fertility-sparing treatment should be discussed on a case-by-case basis (Level of evidence IV, grade C).

Health Status, Obesity

- Following fertility-sparing therapy for endometrial carcinoma, weight loss in overweight and obese women or maintaining a healthy BMI is important for improving the chances of pregnancy (natural or after assisted reproductive technologies) and live birth. Therefore, weight loss in overweight and obese women or maintaining a healthy BMI after fertility-sparing treatment is strongly suggested as soon as possible (Level of evidence II, grade A).

Review of Initial Pathology by an Experienced Histopathologist

- A request for a second opinion by an experienced histopathologist is recommended if fertility-sparing treatment is considered (Level of evidence III, grade A).

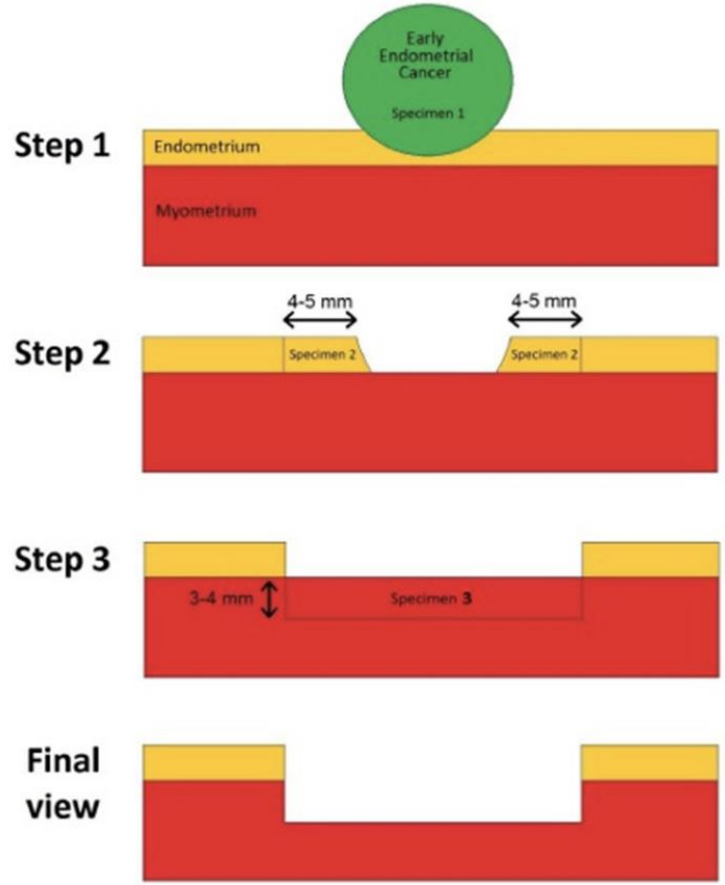
Rodolakis A, et al. Int J Gynecol Cancer 2023

Review of Initial Pathology by an Experienced Histopathologist

- A request for a second opinion by an experienced histopathologist is recommended if fertility-sparing treatment is considered (Level of evidence III, grade A).
- A combined approach consisting of hysteroscopic tumor resection, followed by oral progestins and/or levonorgestrel-intra-uterine device, is the most effective fertility-sparing treatment both for complete response rate and live birth rate compared with other treatment options (Level of evidence II, grade B).

Dose of Progestins

- Orally administered megestrol acetate at a dose of 160–320 mg/day or medroxyprogesterone acetate at a dose of 400–600 mg/day is recommended (Level of evidence III, grade B).
- A levonorgestrel-intra-uterine device at a dose of 52 mg, alone or in combination with oral progestins, is a safe and effective approach (Level of evidence III, grade B).



Duration of Treatment

- The recommended duration of therapy is 6–12 months, within which a complete response should be achieved (Level of evidence III, grade B).
- The maximum time to achieve complete response should not exceed 15 months (Level of evidence IV, grade C).
- In the absence of any kind of response at 6 months, multidisciplinary counseling is recommended for adapting the management on a case-by-case basis (Level of evidence IV, grade B).

Based on these evidences

Table 1. Oncological and Reproductive outcomes of fertility-sparing treatment of endometrial cancer.

First Author and Year	N. of Patient	Histology	Type of Treatment	Complete Response Rate	Recurrence Rate	Pregnancy Rate	Live Birth Rate
Ramirez 2004	81	EEC	OP	76%	24%	N.A.	N.A.
Gallos 2012	559	408 EEC 151 AEH	N.A.	76.2% 85.6%	40.6% 26%	N.A. N.A.	28% 26.3%
Falcone 2017	28	EEC	HR + OP/HR + LNG-IUS	96.3%	7.7%	93.3% [1]	86.6% [1]
Fan 2017	619	EEC	HR + OP	95.3%	14.1%	47.8%	N.A
			OP	76.3%	30.7%	52.1%	N.A.
			LNG-IUS	72.9%	11%	56%	N.A.
Wei 2017	1038	EEC/AEH	OP	71%	20%	34%	20%
			LNG-IUS	76%	9%	18%	14%
			OP + LNG-IUS	87%	N.A.	40%	35%
Giampaolino 2018	69	14 EEC 55 AEH	HR + LNG-IUS	78.6% 92.7%	18.2% 3.9%	0% 26.3% [1]	0% 26.3% [1]

Gallo A et al., JCM 2021

NEW EC GUIDELINES ARE EXPECTED WITHIN THE END OF 2024.

Integrating new data about the immunotherapy
New fertility sparing indications
Updated FIGO staging

Cervical cancer

FIRST CRITICISM: the STRUCTURE!!!

Comparing to the 2018 version the structure is similar, however…

ESGO EC guidelines

Joint statement

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

Different types of endometrial carcinoma have specific histological and molecular features, precursor lesions and natural histories. Conventional pathologic analysis remains an important tool for tumor stratification, but suffers from inter-observer variation. Different groups have applied a diagnostic algorithm using three immunohistochemical markers (p53, MSH6 and PMS2) and one molecular test (mutation analysis of the exonuclease domain of POLE) to identify prognostic groups analogous to the TCGA molecular-based classification.[17–21] The feasibility of this approach was confirmed by a large number of publications that have all consistently reported prognostic relevance particularly in high-grade and high-risk tumors in several independent cohorts and prospective clinical trials.[22] To apply this molecular classification, all these diagnostic tests need to be performed. Performing one of the surrogate marker tests in isolation is insufficient, as a combination of positive tests can occur in approximatively 5% of

There is still room for other biomarkers that may be potentially useful in the big group of low-grade endometrioid carcinoma with NSMP, such as L1CAM expression or mutations in *CTNNB1*.[29–32]

Recommendations

- ► Molecular classification is encouraged in all endometrial carcinomas, especially high-grade tumors (IV, B).
- ► POLE mutation analysis may be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology (IV, C).

DEFINITION OF PROGNOSTIC RISK GROUPS INTEGRATING MOLECULAR MARKERS

There is overwhelming evidence that traditional pathologic features, such as histopathologic type, grade, myometrial invasion, and lymphovascular space invasion (LVSI), are important in assessing prognosis, as recommended in the ISGyP guidelines.[9] Histopathologic typing should be performed according to the WHO Classification of Tumors (5th edition).[33] A binary International Federation of Gynecology and Obstetrics (FIGO) grading is recommended, which

ESGO CC guidelines

positive patients. Sentinel lymph node biopsy (without additional pelvic lymph node dissection) is an acceptable method of lymph node staging (grade B).

- Conization can be considered a definitive treatment as hysterectomy does not improve the outcome (grade C).
- Radical surgical approaches such as radical hysterectomy or parametrectomy represent overtreatment for patients with T1a1 disease (grade C).

Management of stage T1a2 disease

- In patients with stage T1a2 disease, conization alone or simple hysterectomy is an adequate treatment (grade C).
- Parametrial resection is not indicated (grade C).
- Lymph node staging can be considered in LVSI-negative patients but should be performed in LVSI-positive patients. Sentinel lymph node biopsy alone (without additional pelvic lymph node dissection) appears to be an acceptable method of LN staging (grade B).
- Routine completion of hysterectomy is not recommended after conservative management of stage T1a disease.

be recommended outside prospective clinical trials. Systematic lymph node dissection should include the removal of lymphatic tissue from regions with the most frequent occurrence of positive lymph nodes (sentinel nodes) including obturator fossa, external iliac regions, common iliac regions bilaterally, and presacral region. Distal external iliac lymph nodes (so-called circumflex iliac lymph nodes) should be spared if they are not macroscopically suspicious.

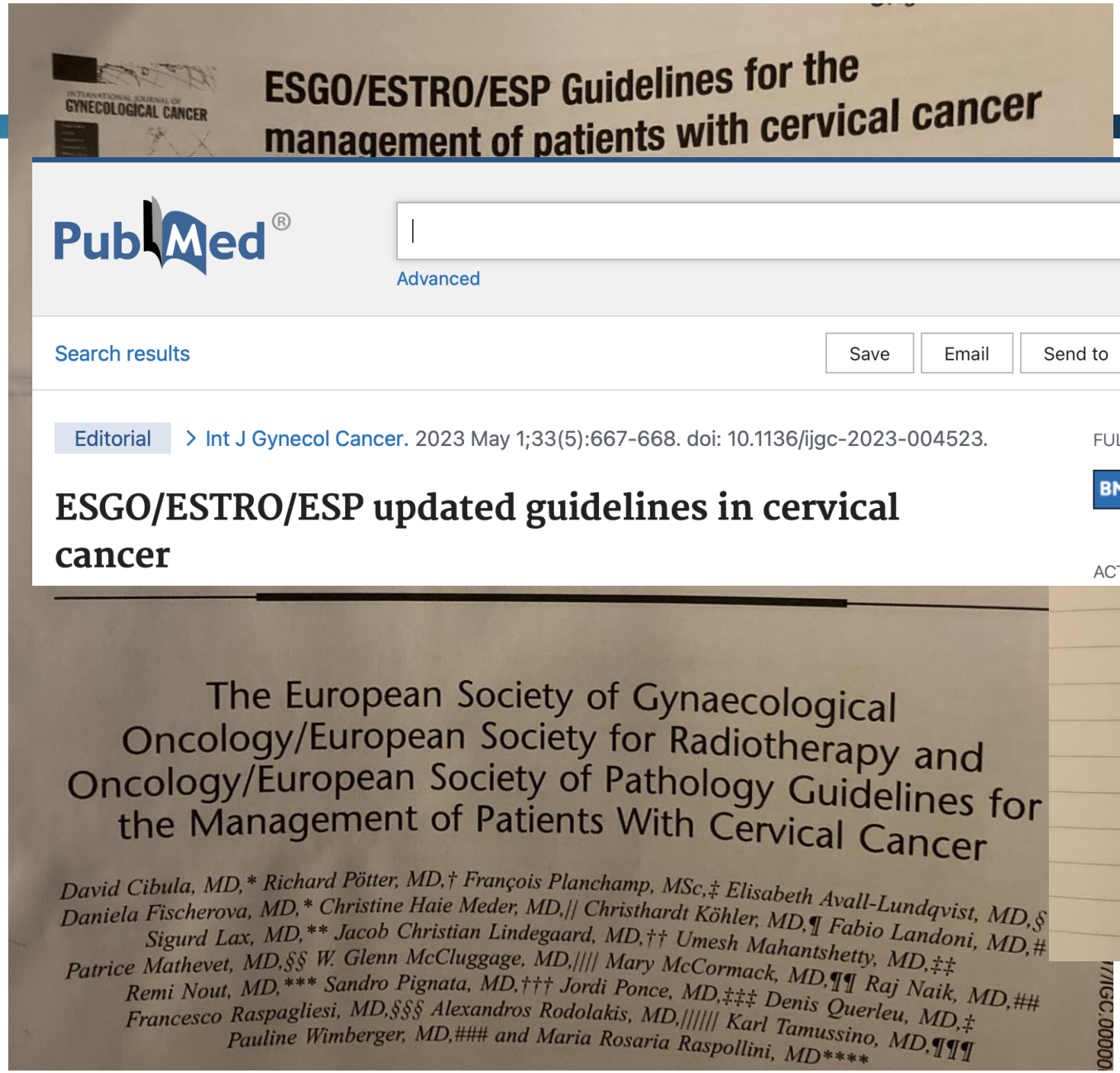
- The type of radical hysterectomy (extent of parametrial resection, type A-C2) should be based on the presence of prognostic risk factors identified preoperatively (Table 3). Major prognostic factors for oncological outcome as tumor size, maximum stromal invasion, and LVSI are used to categorize patients at high, intermediate, and low risk of treatment failure. Complete description of the template used for radical hysterectomy should be present in the surgical report. The 2017 modification of the Querleu-Morrow classification is recommended as a tool (Table 4).
- Ovarian preservation should be offered to premenopausal patients with squamous cell carcinoma and usual-type

Discussion of literature data----------Statements

Only statements

2018 → 2022

- Surgical management of stages T1b3 and T2a2 N0 — **UPDATED**
- Quality of life & palliative care — **NEW TOPIC**
- Rare tumors — **NEW TOPIC**


INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER
ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer
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Editorial
Int J Gynecol Cancer. 2023 May 1;33(5):667-668. doi: 10.1136/ijgc-2023-004523.
ESGO/ESTRO/ESP updated guidelines in cervical cancer
FULL TEXT LINKS
BMJ Full Text
ACTIONS
The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer
David Cibula, MD,* Richard Pötter, MD,† François Planchamp, MSc,‡ Elisabeth Avall-Lundqvist, MD,§
Daniela Fischerova, MD,* Christine Haie Meder, MD,|| Christhardt Köhler, MD,¶ Fabio Landoni, MD,#
Sigurd Lax, MD,** Jacob Christian Lindegaard, MD,†† Umesh Mahantshetty, MD,‡‡
Patrice Mathevet, MD,§§ W. Glenn McCluggage, MD,|||| Mary McCormack, MD,¶¶ Raj Naik, MD,##
Remi Nout, MD,*** Sandro Pignata, MD,††† Jordi Ponce, MD,‡‡‡ Denis Querleu, MD,‡
Francesco Raspagliesi, MD,§§§ Alexandros Rodolakis, MD,|||||| Karl Tamussino, MD,¶¶¶
Pauline Wimberger, MD,### and Maria Rosaria Raspollini, MD****
ESGO CC GUIDELINES
nvasive surgery
GADDUCCI
NACT
HPV related
Squamous vs non

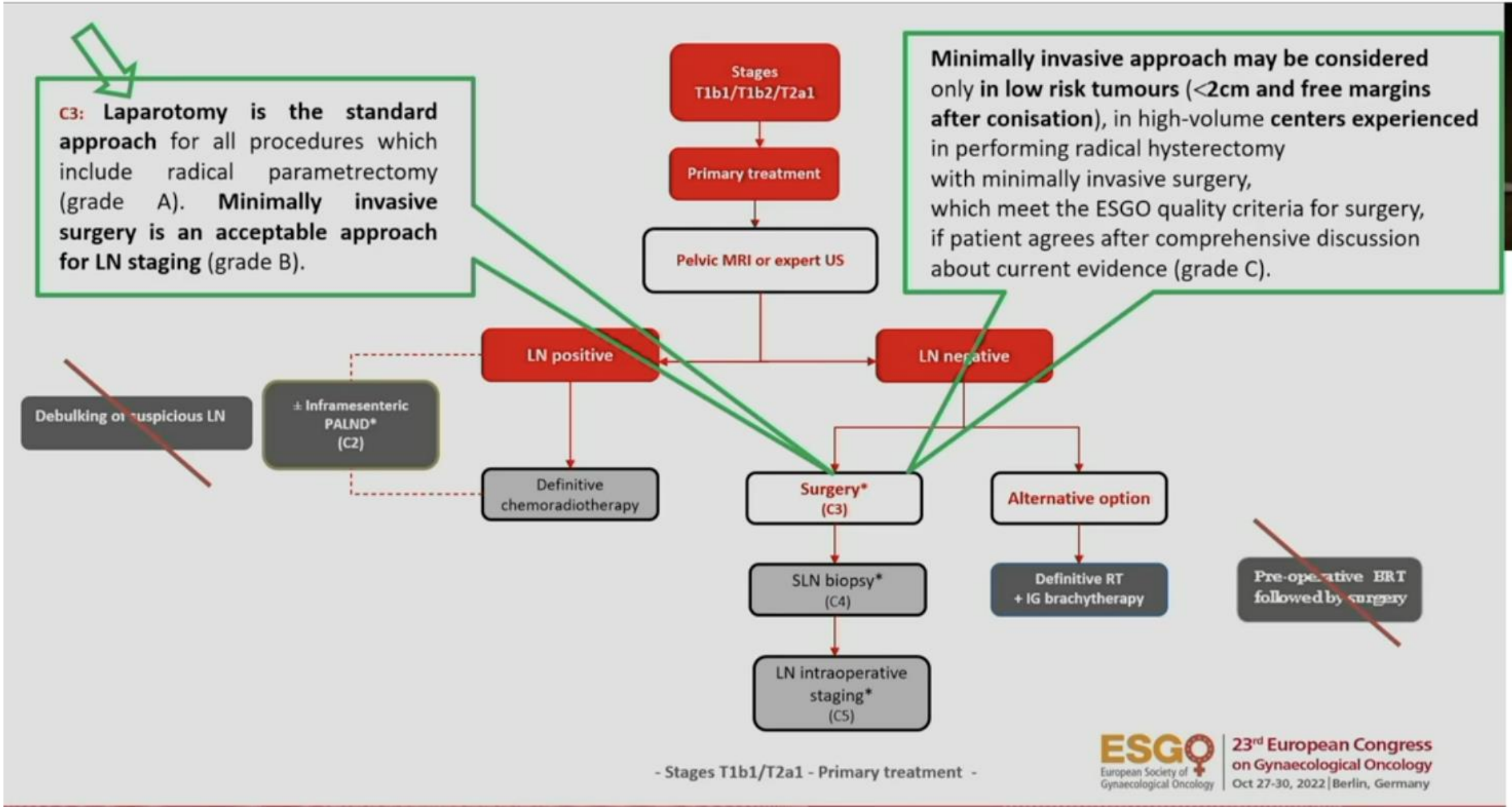
- .....
- .....
- .....

Editorial

ESGO/ESTRO/ESP updated guidelines in cervical cancer

Pedro T Ramirez

MINIMALLY INVASIVE SURGERY

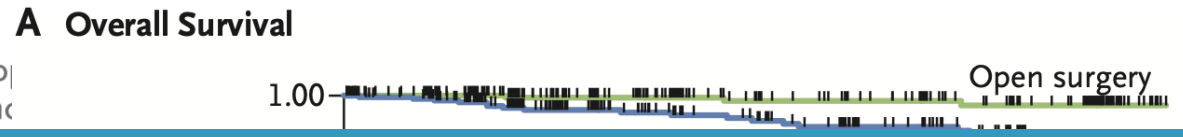


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2018 VOL. 379 NO. 20

Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

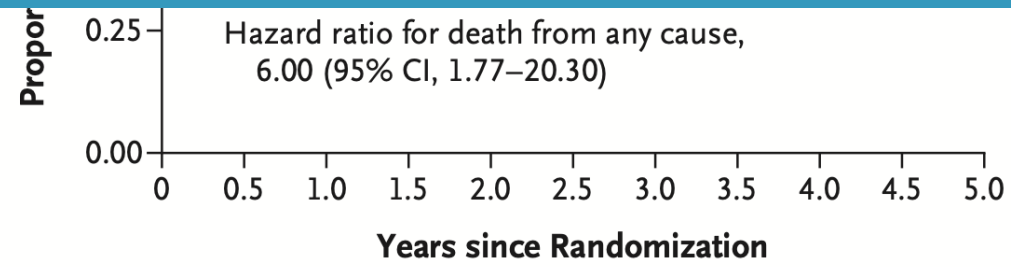
Pedro T. Ramirez, M.D., Michael Frumovitz, M.D., Rene Pareja, M.D., Aldo Lo
Reitan Ribeiro, M.D., Alessandro Buda, M.D., Xiaojian Yan, M.D., Yao Shuzh



REGARDING THE NEW GUIDELINES »The use of minimally invasive approach proposed in new guidelines as an option in patients with 'low risk' tumors should be interpreted with caution, as such a recommendation is not based on properly conducted prospective evaluation and patients should be informed of this fact".

Ramirez P et al., IJGC 2023

- stage of IA1 (lymphovascular invasion), IA2 (stromal invasion, 3 to 5 mm in depth and <7 mm in width), or IB1 (tumor size of ≤4 cm in the greatest dimension and no node involvement)
- 0-1 ECOG PS



No. at Risk

Open surgery	312	282	237	190	164	146	136	125	104	90	7
Minimally invasive surgery	319	297	249	198	174	163	150	133	113	87	5

RH vs SH

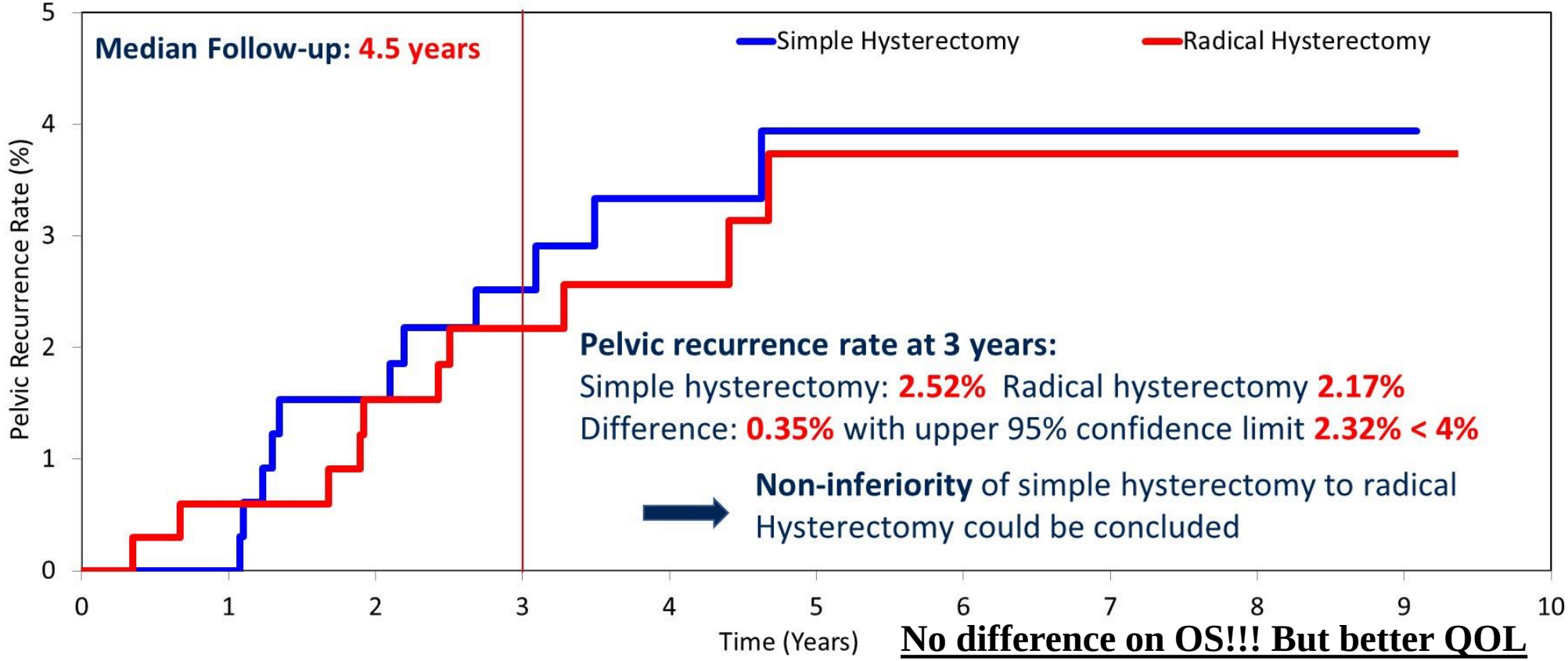
Minimally invasive surgery

80% in SH arm
69% in RH arm

Low-risk cervical cancer as defined by:

- Squamous cell, adenocarcinoma, adenosquamous carcinoma
- Stage IA2 and IB1
- < 10 mm stromal invasion on LEEP/cone
- < 50% stromal invasion on MRI
- Max dimension of ≤ 20 mm
- Grade 1-3 or not assessable

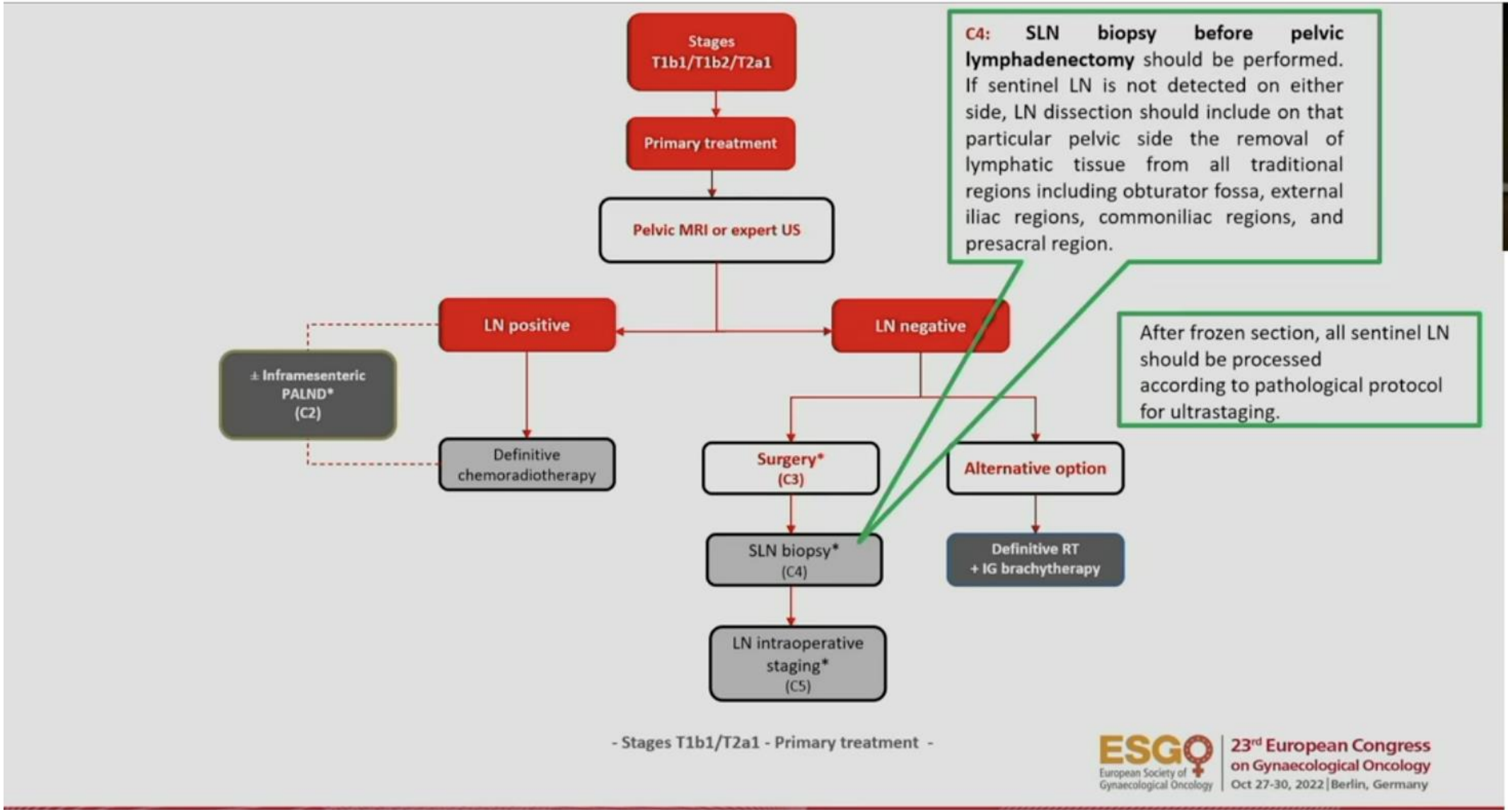
Pelvic Recurrence Rate (ITT)



No difference on OS!!! But better QOL

Simple	350	328	311	273	204	133	61	31	14	4	0
Radical	350	329	315	286	208	132	66	31	16	2	0

SLN biopsy before pelvic lymphadenectomy



SLN biopsy before pelvic lymphadenectomy

Gynecologic Oncology 129 (2013) 384–388

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Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

In order to benefit from the results of intra-operative FS examination adopting amore detailed intra-operative pathologic processing is essential. The alternative would be to wait for final pathology results and use two-step surgical management.

High false negative rate of frozen section examination of sentinel lymph nodes in patients with cervical cancer

J. Slama [a,*], P. Dundr [b], L. Dusek [c], D. Cibula [a]

[a] Gynaecologic Oncology Centre, General University Hospital and 1st School of Medicine, Charles University, Prague, Czech Republic
[b] Institute of Pathology, General University Hospital and 1st School of Medicine, Charles University, Prague, Czech Republic
[c] Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic

Table 3
Diagnostic value of SN frozen section (as compared with SN ultrastaging results).

FS	All metastases	LVD	Macrometastases
Sensitivity	0.56 (0.44; 0.68)	0.08 (0.01; 0.28)	0.81 (0.67; 0.91)
Specificity	1.00 (0.97; 1.00)	1.00 (0.96; 1.00)	1.00 (0.97; 1.00)
PPV	1.00 (0.89; 1.00)	1.00 (0.19; 1.00)	1.00 (0.89; 1.00)
NPV	0.83 (0.76; 0.88)	0.87 (0.81; 0.91)	0.94 (0.89; 0.97)

FS = frozen section; LVD = low volume disease (micrometastases and ITC); NPV = negative predictive value; PPV = positive predictive value.

SLN from 647 patients processed by an intensive ultrastaging protocol

Standard assessment ≈ frozen section

	FROZEN SECTION	ULTRASTAGING			TOTAL % of all patients
		1st level	2nd - 4th level		
MAC	36 (83.7%)	6 (14.0%)	1 (2.3%)	0 (0%)	43 (6.6%)
MIC	10 (25.6%)	14 (35.9%)	8 (20.5%)	6 (15.4%)	39 (6.0%)
ITC	2 (9.1%)	6 (27.3%)	10 (45.4%)	4 (18.2%)	22 (3.4%)
pN1 (MAC + MIC)	46 (56.1%)	20 (24.4%)	9 (11.0%)	6 (7.3%)	82 (12.7%)

ITC: isolated tumour cells … macrometastases; MIC: micrometastases

44% pN1 cases found by ultrastaging

ESGO European Society of Gynaecological Oncology 23rd Eur… on Gynae… Oct 27-30,

Is there a role for NACT?

T1b3-T4a

NACT in patients who otherwise are candidates for upfront definitive CTRT and IGBT is not recommended outside of clinical trials [II, D].

T1B3 and T2a2 (LN Negative)

NACT followed by radical surgery should not be performed outside clinical trials [I, E].

Figure 5. Forest plot of severe acute toxicity

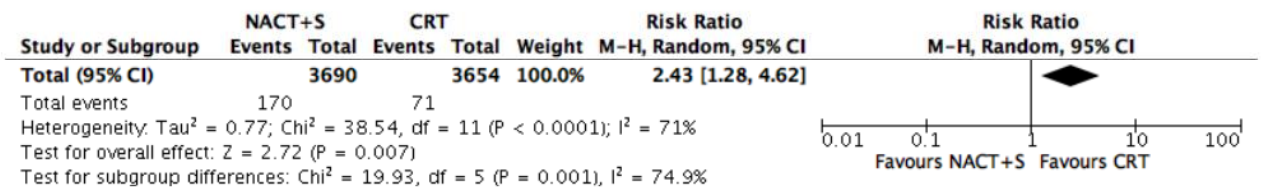
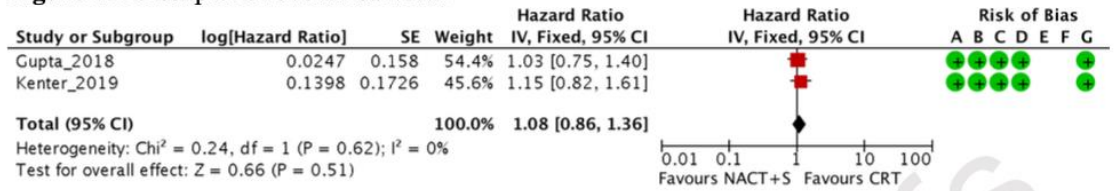
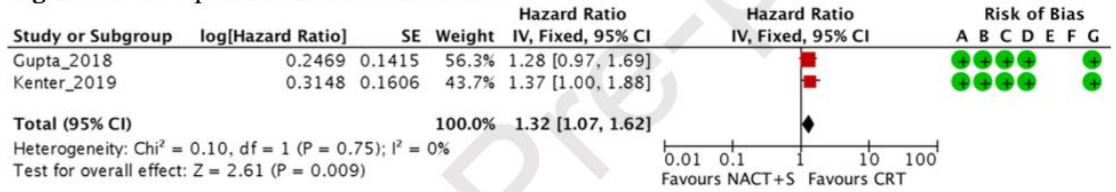


Figure 2. Forest plot of overall survival



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 3. Forest plot of disease-free survival



Marchetti C et al., Cancer Treat Rev 2020

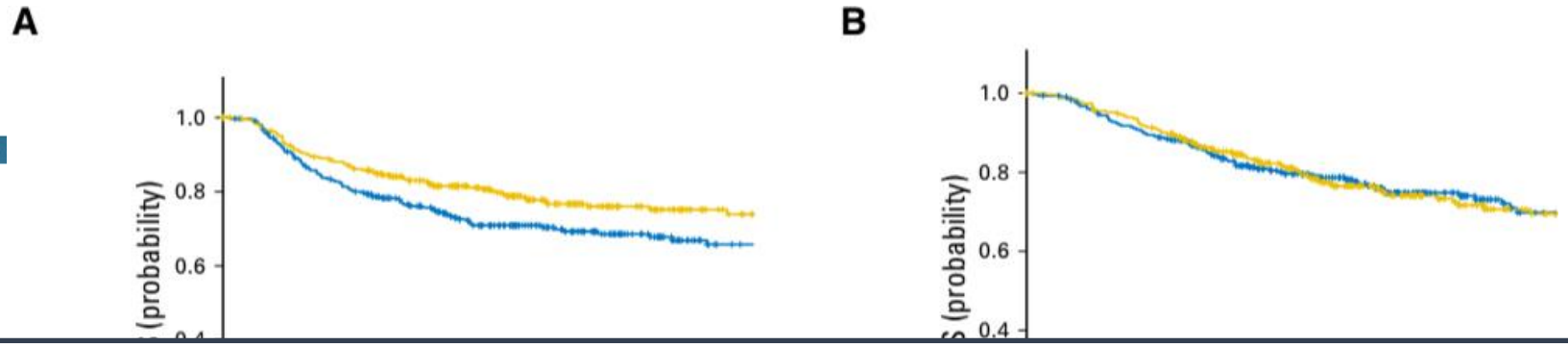


Table 4. Adverse Events of Any Grade Occurring or Persisting > 90 Days or > 24 Months After Completion of Treatment

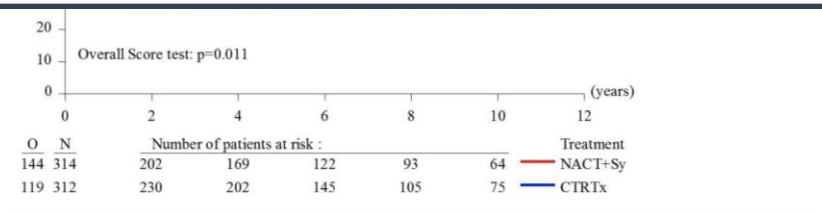
	> 90 Days			> 24 Months		
Site	NACT Plus Surgery, No. (%)	CTRT, No. (%)	*P*	NACT Plus Surgery, No. (%)	CTRT, No. (%)	*P*
Rectal	18 (5.7)	42 (13.3)	.002	7 (2.2)	11 (3.5)	.474
Bladder	9 (2.8)	23 (7.3)	.017	5 (1.6)	11 (3.5)	.204
Vaginal*	63 (19.9)	117 (36.9)	< .001	38 (12)	81 (25.6)	< .001
Other†	30 (9.5)	17 (5.4)	.068	17 (5.4)	11 (3.5)	.334

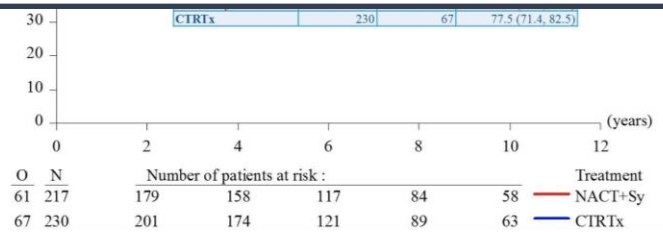
NOTE. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 2.0. Some patients had more than one adverse event.

Abbreviations: CTRT, concomitant chemotherapy and radiotherapy; NACT, neoadjuvant chemotherapy.

*Vaginal adverse events included synechiae, stenosis, and fibrosis.

†Other adverse events included lymphedema, hernia, and intestinal obstruction.





Gupta S et al., JCO 2018, Kenter G et al. JCO 2019

Criticisms

- **12 years accrual (SLOW)**
- Primary end point PFS (OS?)
- Statistical design: superiority NACT
- Final sample size 730 (635 enrolled! 87% accrual) (EARLIER STOPPED)
- 72% operability rate (LOW)
- **QoL not explored**

- **Study period: May 2002-June 2014**
- Patient enrolled=620
- Primary endpoint=5-yrs OS.
- Protocol treatment was completed in 459 (74%) patients (71% for NACTS; 82% for CCRT).
- (76%) patients underwent surgery. Main reasons for not having surgery as per protocol, were toxicity (25/74, 34%), progressive disease (18/74, 24%) and insufficient response to NACT (12/74, 16%).
- Short term severe adverse events (≥G3) occurred more frequently in arm 1 than in arm 2 (35% vs 21%, $p < 0.001$).
- **Heterogeneous chemotherapic treatment**

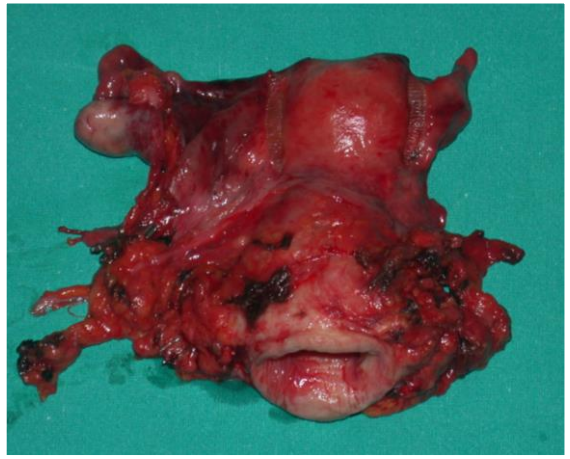
Surgical management of stages T1b3 and T2a2 N0

Role of Surgery in T1B3 and T2a2 (LN Negative) Tumors

- There is limited evidence to guide the choice between surgical treatment vs CTRT with IGBT in LN negative patients with T1b3 and T2a2 tumors. Histology, tumor size, completeness of the cervical rim, uterine corpus invasion, magnitude of vaginal invasion, age, comorbidity, menopausal status, body mass index, hemoglobin and experience with type C radical hysterectomy are some of the factors to consider [IV, B].
- For surgery, avoidance of the combination of radical surgery and post-operative external radiotherapy requires acceptance for modifications of the traditional selection criteria (tumor size, degree of invasion, LVSI) for adjuvant treatment [IV, B].
- The patient should be discussed in a multidisciplinary team and should be counseled for the advantages and disadvantages of both treatment options (surgery vs radiotherapy) in relation to the individual presence of prognostic factors [IV, A].
- Given the limited number of patients with T1b3 and T2a2 (<10%) tumors, referral to highly specialized centers for treatment is recommended [IV, A].
- Type C radical hysterectomy is recommended. LN staging should follow the same principles as in T1b1-2 tumors [IV, A].
- NACT followed by radical surgery should not be performed outside clinical trials [I, E].

NACT????

NACT (Sapienza experience)



60 dati incompleti

250 pz

Campione di riferimento n=**167**

3 cicli di NACT Platino e Taxolo n=**167**

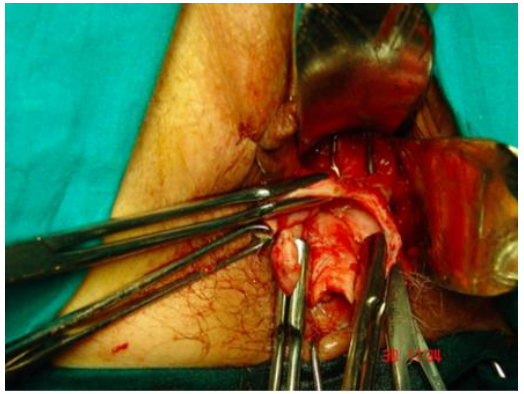
Isterectomia radicale e linfadenectomia n=**147**

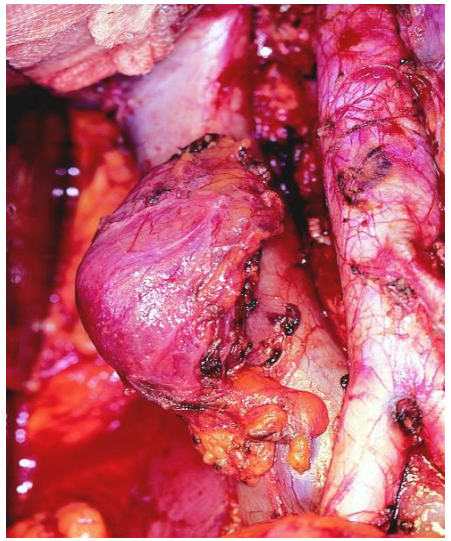
23 escluse
stadi iniziali=14
stadi avanzati= 9

PD=13
Non candidabili=7

20 RT

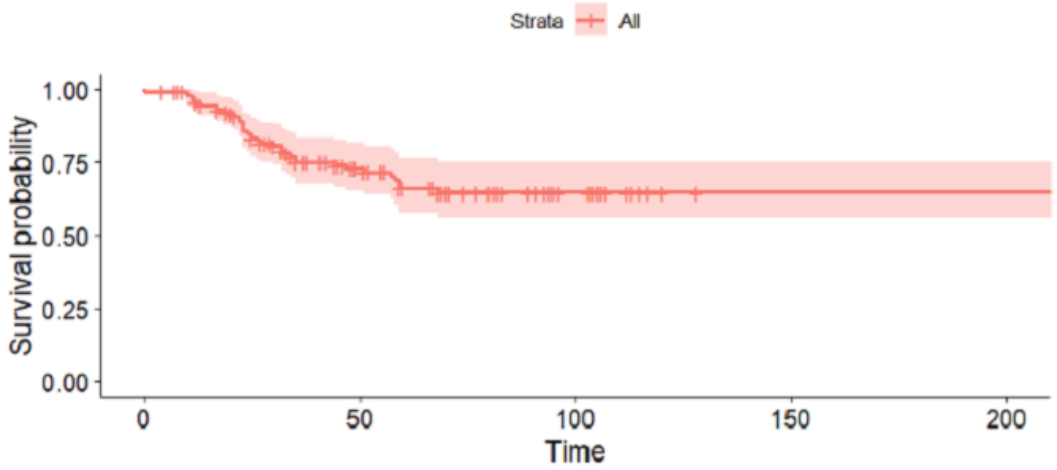
Results





Recurrence rate 34%

	IB2 n=2	IIA n=4	IIIB n=40	IIIA n=1	IIIB n=5	IIIC1 n=80	IIIC2 n=8	IVA n=5	TOT n=145
Vaginale	-	-	**1** (2,5%)	-	**1** (25%)	**4** (4,9%)	-	-	**6** (4,1%)
Linfonodale	-	-	**1** (2,5%)	-	-	**6** (7,4%)	**2** (25%)	**1** (20%)	**10** (7%)
Pelvica centrale	-	-	-	-	-	**3** (3,7%)	-	-	**3** (2,1%)
Isolate a distanza	-	-	-	-	**1** (25%)	**3** (3,7%)	-	-	**4** (2,8%)
A distanza + locale	-	-	**8** (20%)	-	-	**17** (21%)	**1** (12,5)	**1** (20%)	**27** (18,6%)



under submission

CC more than one!!!

HPVA	NHPVA
Usual-type	Endometrioid adenocarcinoma
Villoglandular	Gastric-type adenocarcinoma
Mucinous	Serous carcinoma
Mucinous, intestinal type	Clear cell adenocarcinoma
Mucinous, signet ring cell type	Mesonephric carcinoma
Invasive stratified mucin-producting carcinoma (iSMILE)	Invasive adenocarcinoma NOS

Rare Tumors

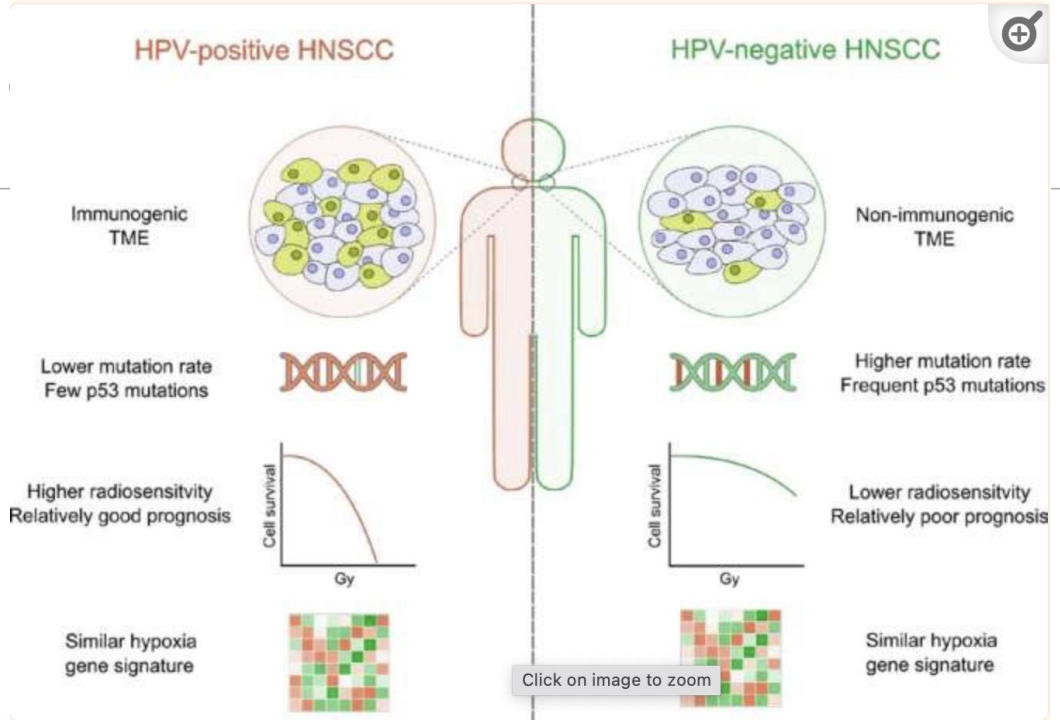
- Histopathological diagnosis of rare cervical tumors needs confirmation (second opinion) by an expert pathologist [IV, A].
- Treatment and care of rare cervical tumors needs to be centralized at referral centers and discussed in a multidisciplinary tumor board [IV, A].

Cibula D et al., IJGC 2023

Non HPV related cervical cancer

TABLE 3 | Studies of FIGO stage and prognosis of human papillomavirus (HPV)-negative cervical cancers.

Study (Reference)	Cases (HPV negative/ overall)	HPV testing	Advanced FIGO stage (HPV negative vs. HPV positive)	Lymphatic metastasis (HPV negative vs. HPV positive)	DFS (HPV negative vs. HPV positive)	OS (HPV negative vs. HPV positive)
Nicolas et al. (57)	21/214	PCR	91% vs. 57%, $p<0.01$	67% vs. 36%, $p<0.01$	59.8 m (95%CI 32.0–87.6 m) vs. 132.2 m (95%CI 118.6–145.8 m), $p<0.01$	77.0 m (95%CI 47.2–106.8 m) vs. 153.8 m (95%CI 142.0–165.6 m), $p=0.01$
Van der Marel et al. (58)	8/136	HC2™, PCR	87.5% vs. 52.3%, $p=0.053$	37.5% vs. 17.2%, $p=0.150$	51.9 m (95%CI 12.2–91.7 m) vs. 109.9 m (95%CI 98.2–121.5 m),	67.7 m (95%CI 20.0–106.9 m) vs. 108.9 m (95%CI 97.7–120.0 m), $p=0.225$
Feng et al. (59)	43/122					5 year: HR=1.250 (95%CI 0.562–2.784), $p=0.584$ 8 year: HR=1.530 (95%CI 0.697–3.362), $p=0.289$



5% of CC are HPV -

A **MANGO** proposal

MaNGO
Mario Negri Gynecologic Oncology

A **SURVEY** testing the adherence of MANGO centres to guidelines highlighting these and other cristicisms for each tumor.


#nhcollection
MILANO - PRESIDENTI
ENGOT
European Network of Gynaecological Oncological Trial groups
ENGOT MEETING
9-10 March, 2023
Milan, Italy


THANK YOU