XXII ASSEMBLEA MaNGO MILANO

STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS

MILANO June 26th-29th, 2025

Responsabili Scientifici:
NICOLETTA COLOMBO, FRANCESCO RASPAGLIESI

MaNGO

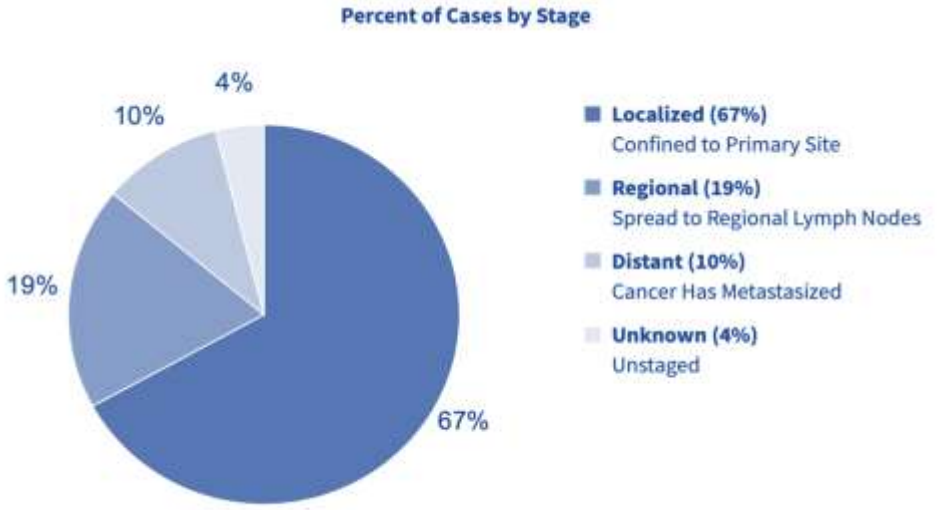
New endometrial cancer guidelines ESGO/ESTRO/ESP 2025: Surgeon perspective

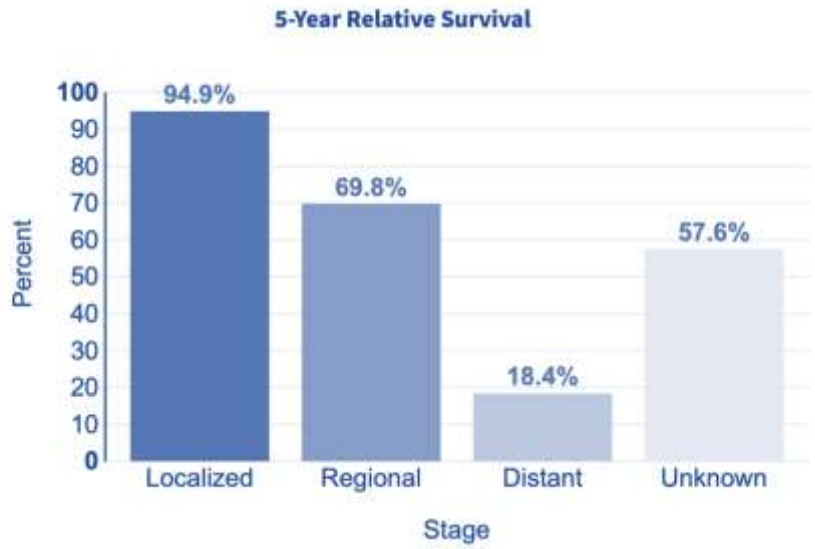
ALESSIA ALOISI, MD

IEO Istituto Europeo di Oncologia

I have no conflict of interest

Surgery in Endometrial Cancer





SURGERY

90%

Apparent Early-Stage

10%

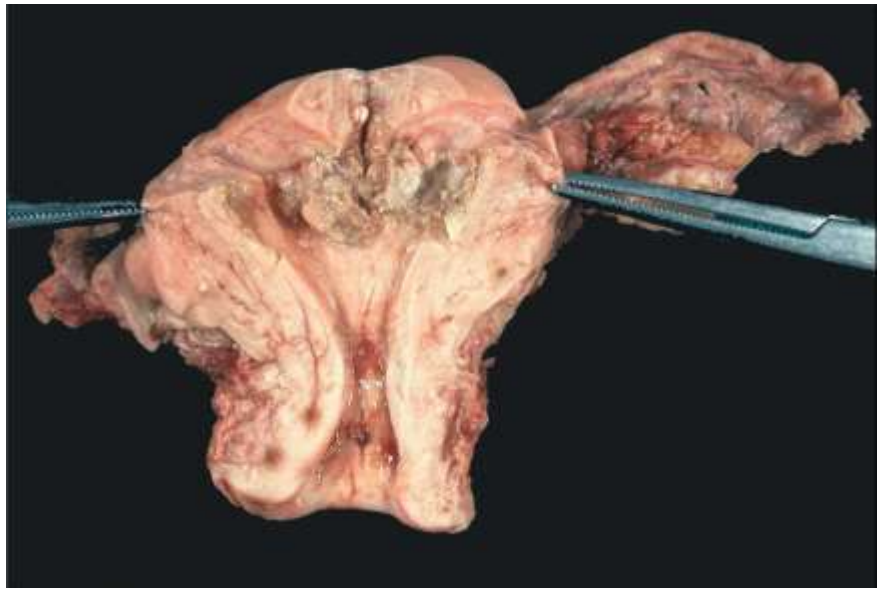
Advanced

(extrauterine disease)

SEER 22 (Excluding IL/MA) 2013–2019, All Races, Females

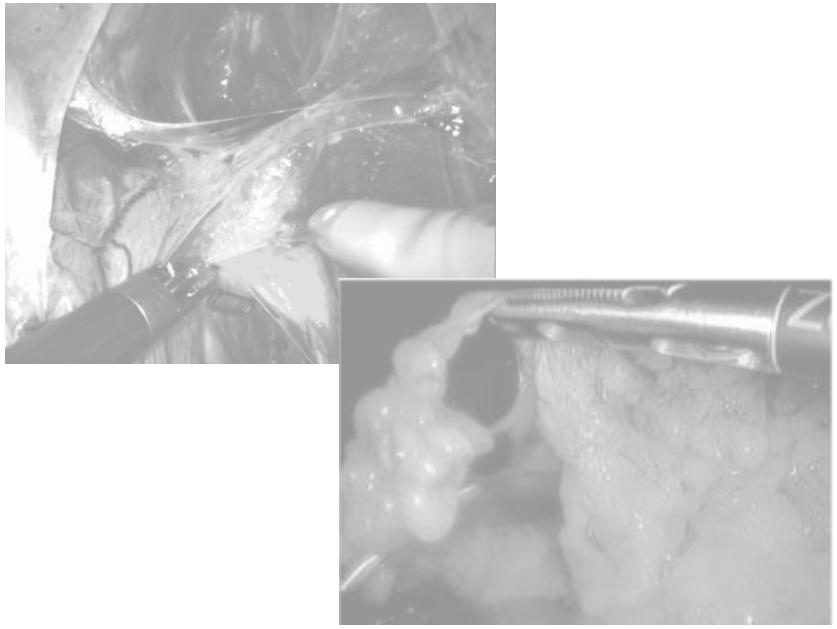
Surgery for apparent Early-Stage EC

THERAPEUTIC ROLE



Hysterectomy + BSO

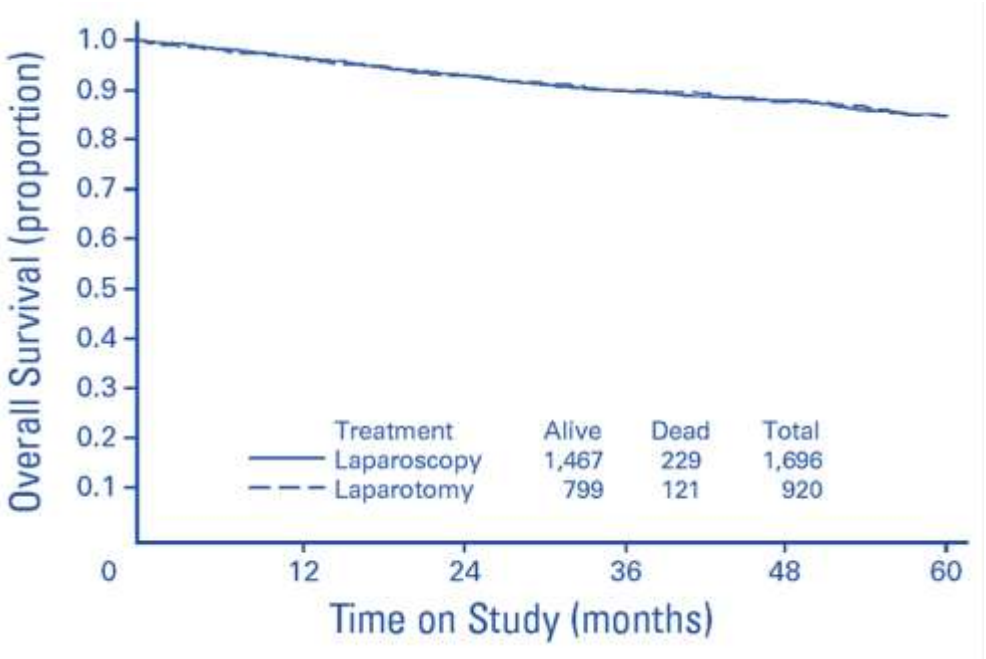
STAGING ROLE



Peritoneum and retroperitoneum evaluation

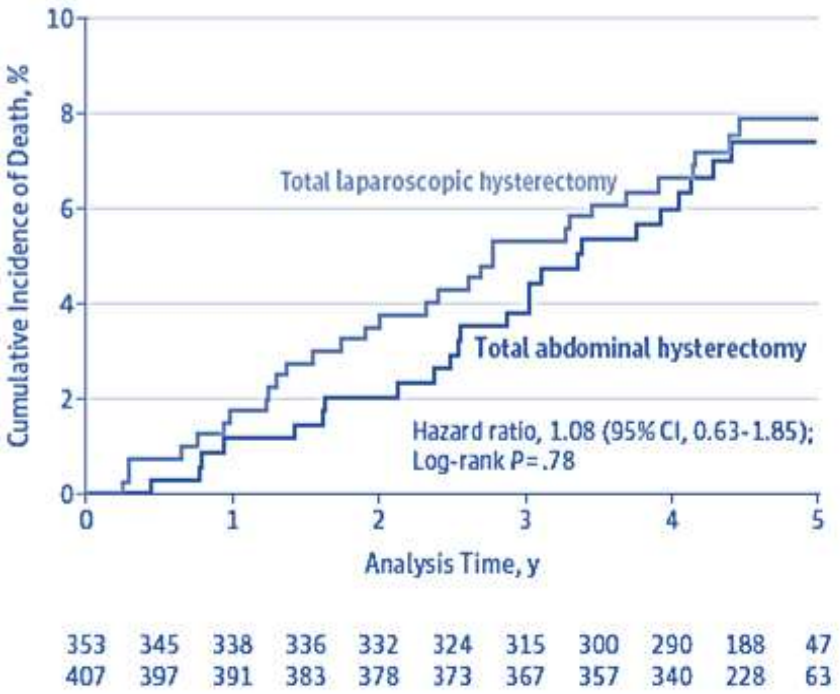
Surgery for apparent Early-Stage EC: therapeutic role

GOG group LAP2 Study



Walker et al. JCO 2012

LACE trial



Janda et al. JAMA 2017

Surgery for apparent Early-Stage EC: therapeutic role

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up†

2016

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

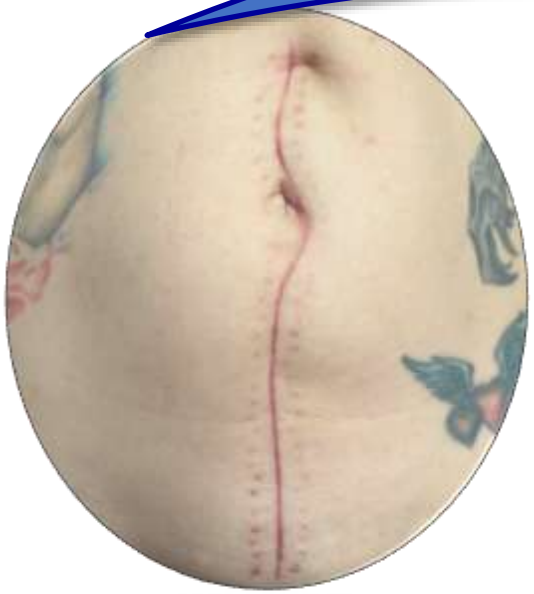
ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

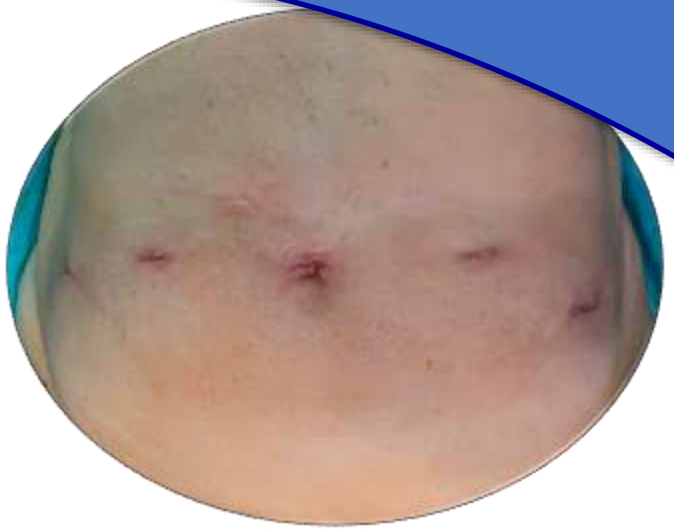
NOW

ESGO-ESTRO-ESP Guidelines NOW

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

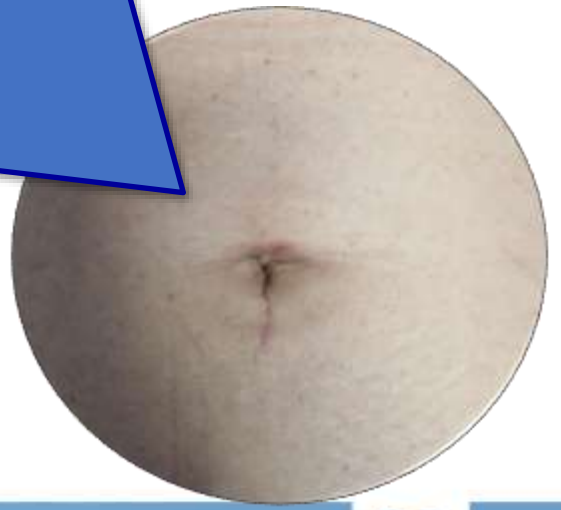
De-escalating surgery for apparent Early-Stage EC



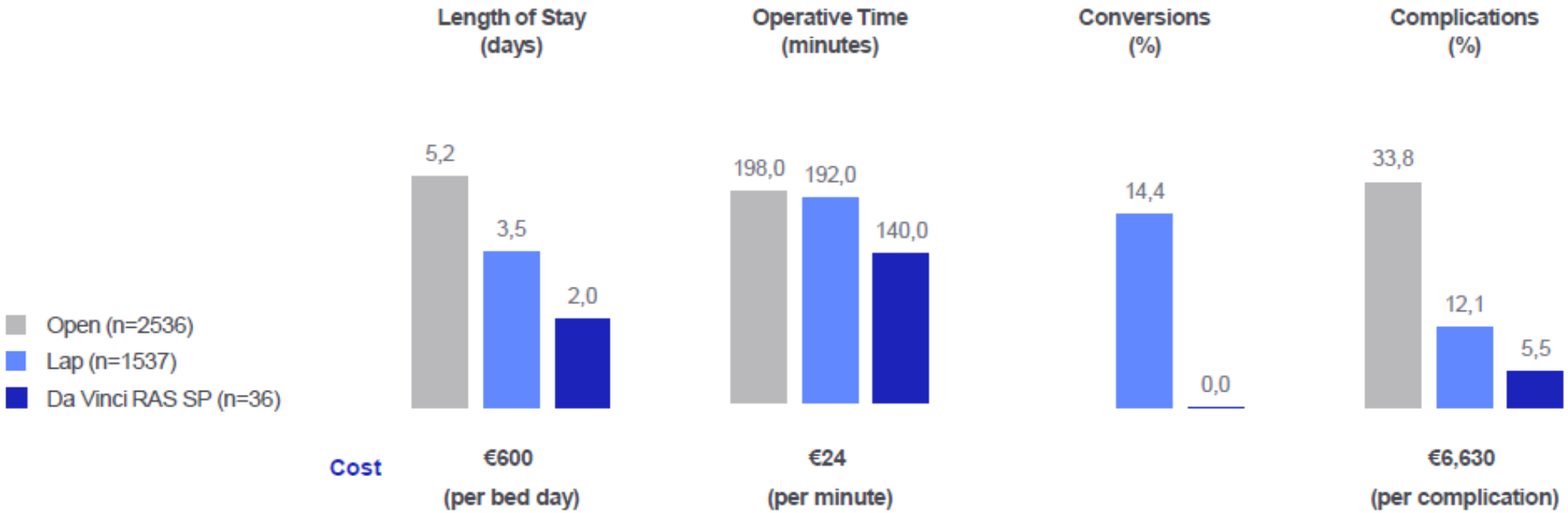


From
- Maximum
- Tolerated
- Treatment

To
- Minimal
- Effective
- Treatment



Single surgeon unpublished experience – clinical outcomes with estimated cost savings
Dr. Vanna Zanagnolo: Surgeon's own da Vinci data vs. published open and lap data
Hysterectomy - Malignant



Potential savings with da Vinci RAS per procedure: results from cost modeling

Estimated Cost Savings Per Procedure	Estimated Total Cost Savings
€5,185 vs. Open	€186,659 vs. Open
€2,586 vs. Lap	€93,081 vs. Lap

Matsuura et al J. Clin. Med. 2024

Minimally Invasive Surgery preferred surgical approach (I,A)

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

Any intra-peritoneal tumour spillage, including tumour rupture or morcellation (including in a bag), should be avoided

If vaginal extraction risks uterine rupture, other measures should be taken

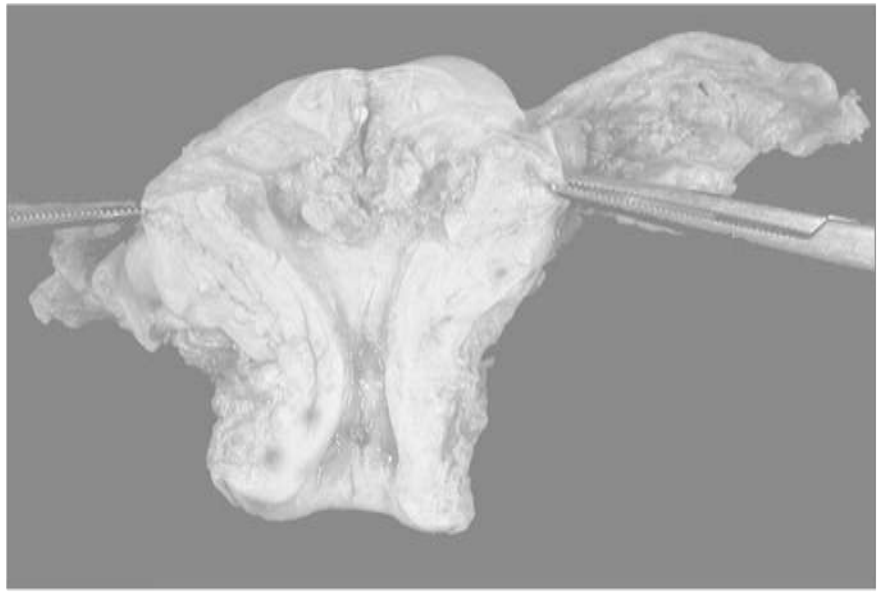
(eg. mini-laparotomy, use of endobag [III, B]

pre-/intra-operative finding of metastatic spread outside the uterus (excluding lymph node metastases) is a relative contra-indication

ESGO Accredited Centre in Endometrial Cancer Surgery

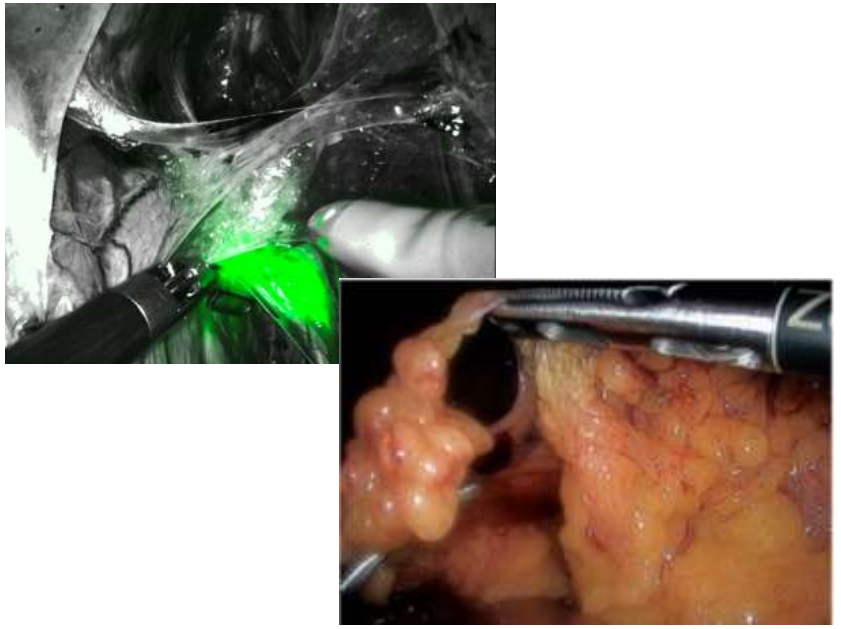
Surgery for apparent Early-Stage EC

THERAPEUTIC ROLE



Hysterectomy + BSO

STAGING ROLE

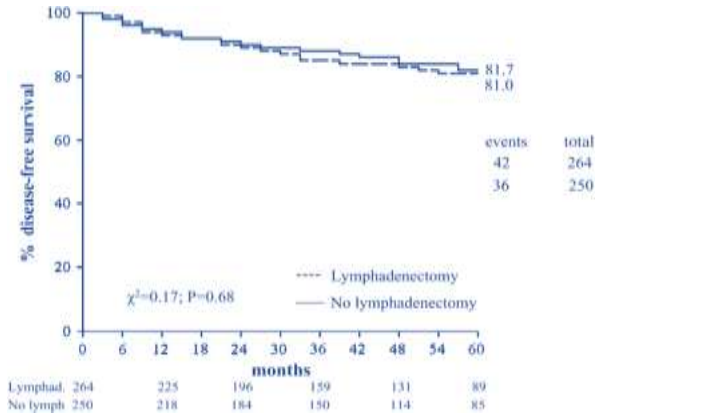


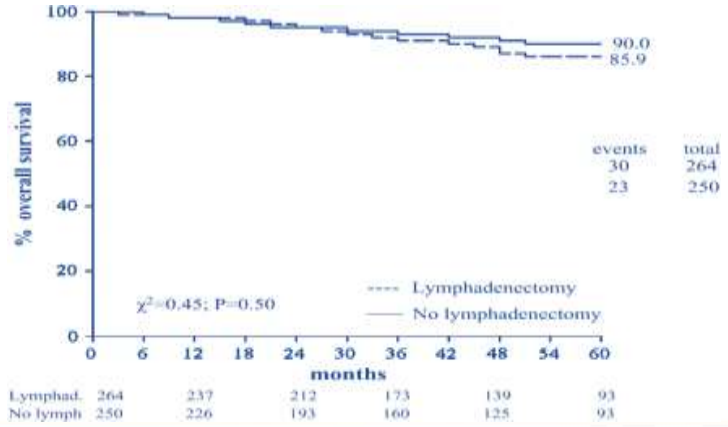
Peritoneum and retroperitoneum evaluation

Surgery for apparent Early-Stage EC: staging role

Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial

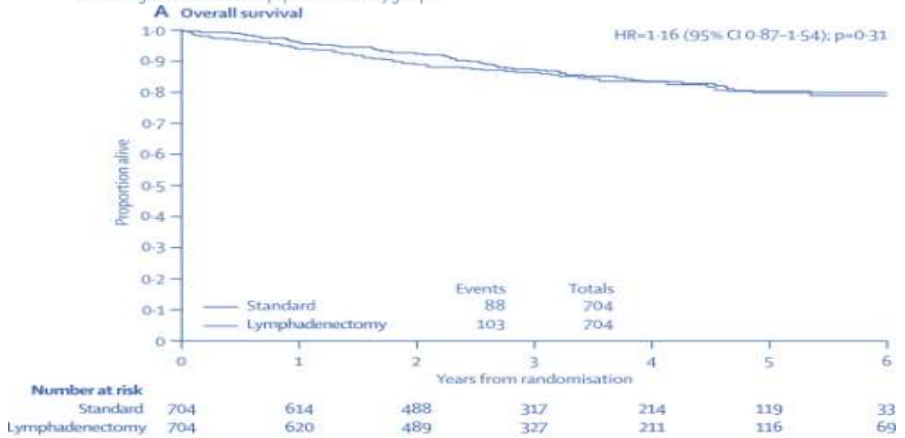
Pierluigi Benedetti Panici, Stefano Basile, Francesco Maneschi, Andrea Alberto Lissoni, Mauro Signorelli, Giovanni Scambia, Roberto Angioli, Saverio Tateo, Giorgio Mangili, Dionyssios Katsaros, Gaetano Garozzo, Elio Campagnutta, Nicoletta Donadello, Stefano Greggi, Mauro Melpignano, Francesco Raspagliesi, Nicola Ragni, Gennaro Cormio, Roberto Grassi, Massimo Franchi, Diana Giannarelli, Roldano Fossati, Valter Torri, Mariangela Amoroso, Clara Crocè, Costantino Mangioni

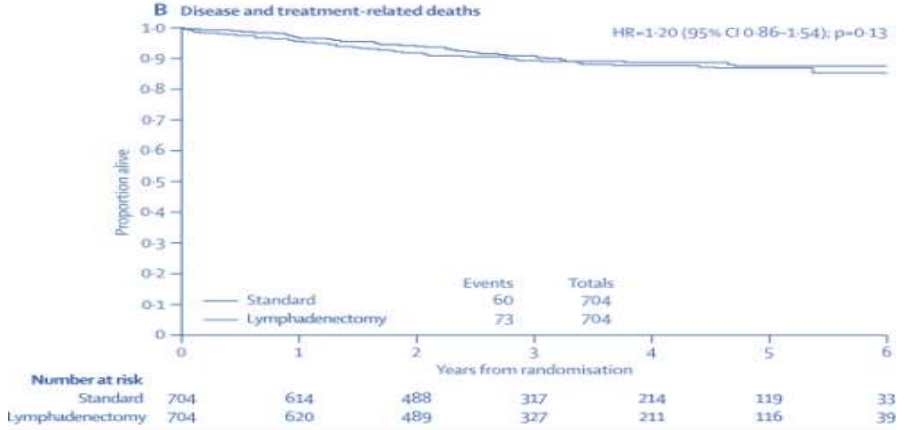




Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study

The writing committee on behalf of the ASTEC study group*





Can we pre/intra op identify patients that would benefit from LN evaluation?

PRE-OPERATIVE PREDICTION OF NODAL STATUS

	SENSITIVITY	SPECIFICITY
CT SCAN	41%	98 %
PET	79 %	98%
MRI	91%	95%

INTRA-OPERATIVE PREDICTION OF NODAL STATUS

	SENSITIVITY	SPECIFICITY
INTRA-OPERATIVE PALPATION	72%	81 %
GROSS INSPECTION	79 %	96%
FROZEN SECTION	81%	98%

UP TO 16% OF PATIENT ARE UPSTAGED AFTER SURGERY. THERE IS NO MODEL TO PREDICT NODE METASTASIS ON PREOP

Arango 2000 Obstet Gynecol.95(4):553-6.
KiLoubeyre 2011 Surg Oncol.20(2):e102-8
Turan 2011 Eur J Obstet Gynecol Reprod Biol.158(2):274-90
Choi 2007 Radiology. 242(1):137-43.
Kitajima 2011 Ann Nucl Med. 25(7):511-9
Chang 2012 Eur J Radiol 81:3511–7
Leitao Jr MM, et al. Gynecol Oncol 2008;111:24-2481
Koh WJ, et al. (Univ Washington) Women's Oncol Rev 2001.

.

Who should benefit from lymph node assessment?

Pelvic nodal metastasis

Myoinvasion	Grade 1	Grade 2	Grade 3
Endomet only	0%	3%	0%
Inner 1/3	3%	5%	9%
Middle 1/3	0%	9%	4%
Outer 1/3	11%	19%	34%

Para-aortic nodal metastasis

Myoinvasion	Grade 1	Grade 2	Grade 3
Endomet only	0%	3%	0%
Inner 1/3	1%	4%	4%
Middle 1/3	5%	0%	0%
Outer 1/3	6%	14%	23%

	LVS Neg	LVS Pos	*p*
POSITIVE NODES	3.6 %	35 %	< 0.001
RECURRENCE	2.9 %	11%	< 0.001

LYMPHONODAL STATUS	
HISTOTYPE	POSITIVE NODES (%)
ENDOMETRIOID	4
ADENOSQUAMOUS	7
MUCINOUS	14
PAPILLARY	11
CLEAR CELL	12

NODAL METASTASIS RISK IS DIFFERENT ACCORDING TO MYOMETRIAL INVASION, GRADE, HYSTOTYPE AND LVI

Creasman WT, et al. Cancer 1987;60:2035-2041. *Annual Report FIGO 2006. Hahn et al. ANZJOG. 2013;53:29*

Who should benefit from lymph node assessment?

Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

N. Colombo[1], E. Preti[1], F. Landoni[1], S. Carinelli[2], A. Colombo[3], C. Marini[4] & C. Sessa[5,6]

On behalf of the ESMO Guidelines Working Group*

LOW RISK	**- Stage IA (G1 & G2) with Endometrioid type**
INTERMEDIATE RISK	**- Stage IA G3 with Endometrioid type** **- Stage IB (G1 & G2) with Endometrioid type**
HIGH RISK	**- Stage IB G3 with Endometrioid type** **- All stages with Non-Endometrioid type**

MAYO CLINIC - CRITERIA

Low risk of nodal mets:

- **FIGO grade 1 and 2**
- **Endometrioid histology**
- **Tumor size**
  - **≤ 2 cm**
- **0/59 pelvic nodal mets**
  - **> 2 cm**
- **8/107 (7%) pelvic nodal mets**
- **Myoinvasion ≤ 50%**
- **No extrauterine disease**
- **Negative peritoneal cytology**

Colombo et al. Ann Oncol. 2011;22(S&):vi35-39. Mariani A, et al. Am J Obstet Gynecol 2000;182:1506-1519

Who should benefit from lymph node assessment?

CTS ABOUT POSITIVE NODES IN ENDOMETRIOID CANCER: LAP 2

"Low-Risk Endometrial Cancer "is a **retrospective diagnosis**"
Ronnie Alvarez, MD
ABS meeting Chicago July 2014

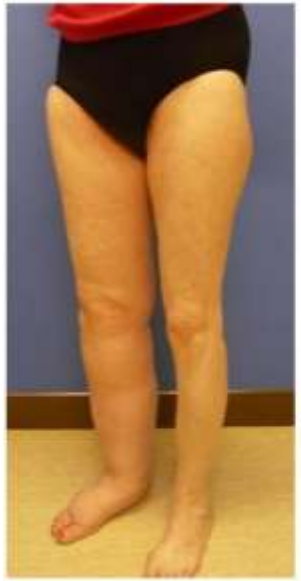
Endometrioid ca
odes

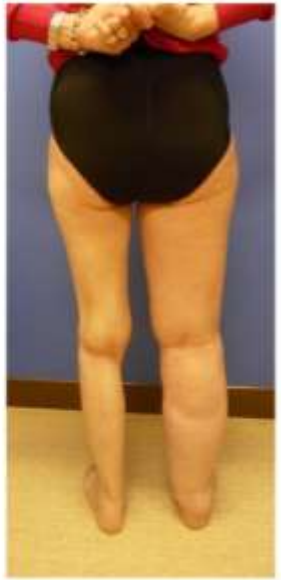
Characteristics of

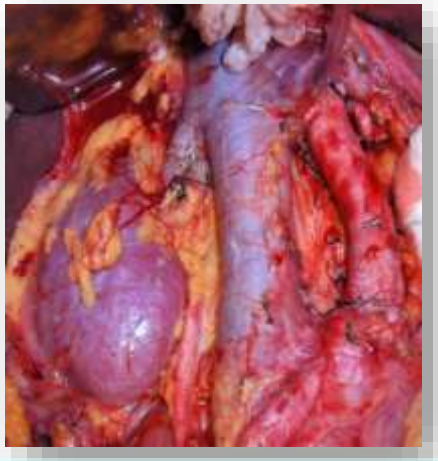
- ✓ 60% of node positive cases
- ✓ 48% had < 50% myoinvasion
- ✓ 23% had tumor size < 2cm

Milam M, et al. Obstetrics & Gynecology, February 2012

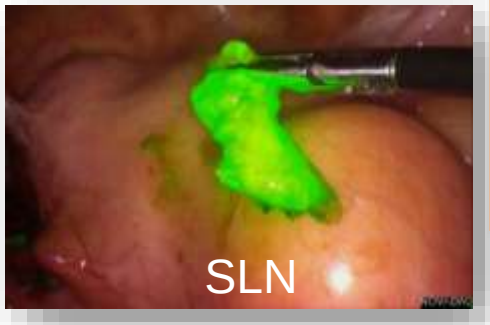
Who should benefit from lymph node assessment?



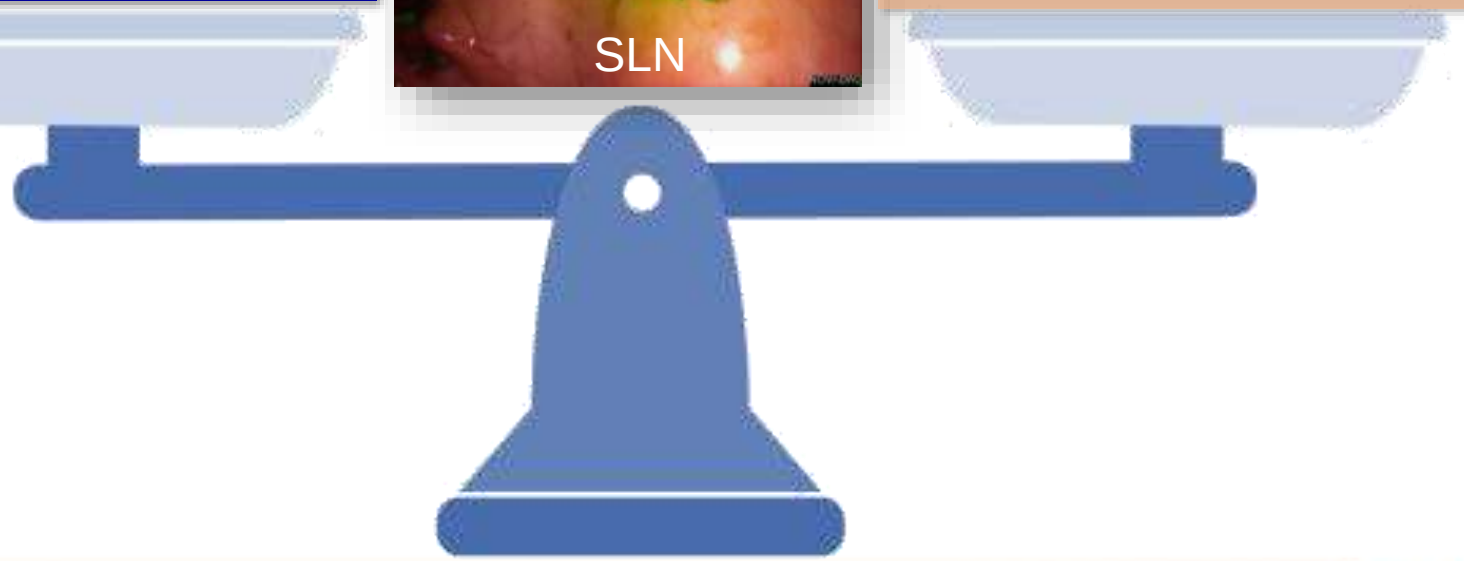




FULL LYMPHADENECTOMY:
- PROGNOSIS
- GUIDE APPROPRIATE ADJUVANT

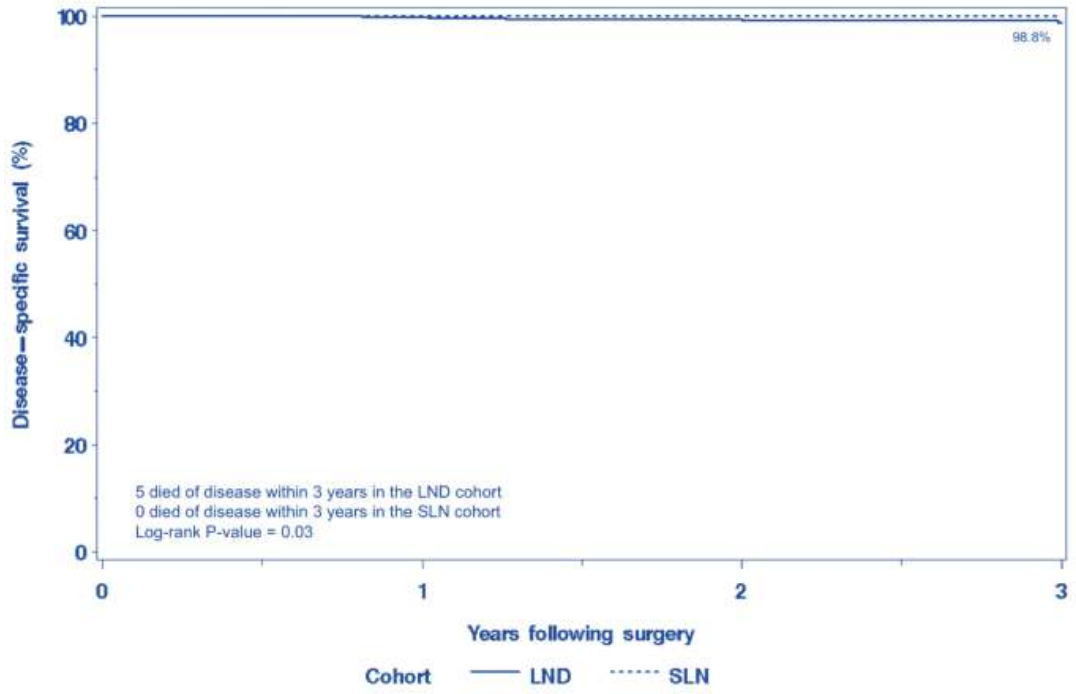


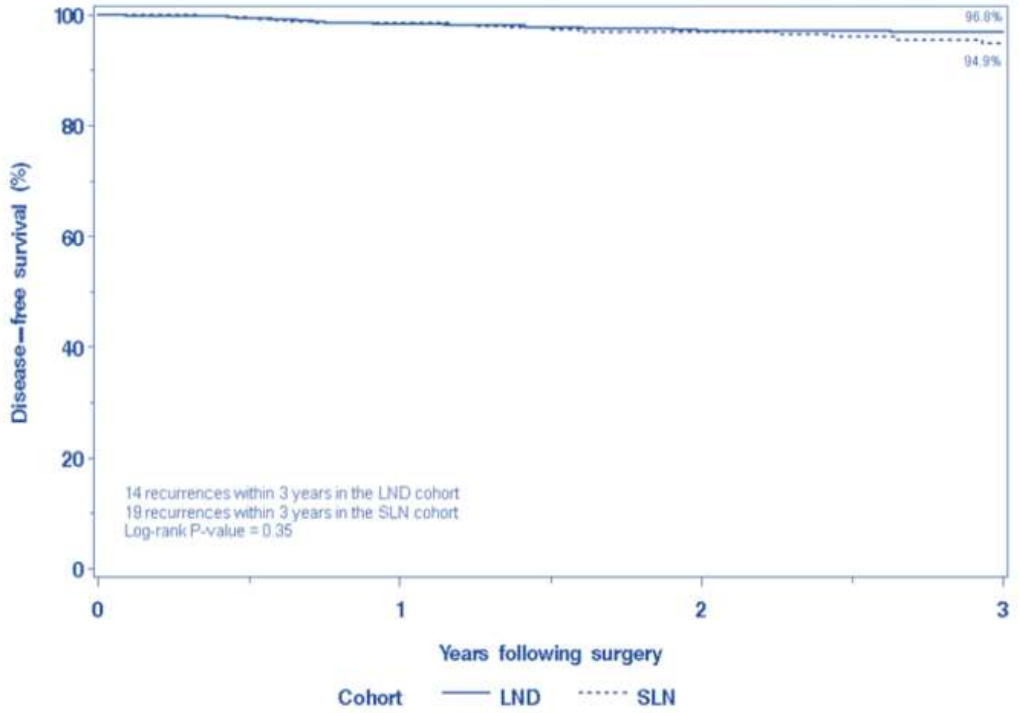
NO LYMPHADENECTOMY:
- NO LYMPHDEMA OR LYMPHCYSTS
- SHORTER OPERATIVE TIMES
- NO VASCULAR OR NERVE INJURIES
-RISK OF UNDERSTAGE



Who should benefit from lymph node assessment?

Comparison of a Sentinel Lymph Node and a Selective Lymphadenectomy Algorithm in Patients with Endometrioid Endometrial Carcinoma and Limited Myometrial Invasion





Eriksson AG, et al. Gynecol Oncol 2016

Who should benefit from lymph node assessment?

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up†

2021

Sentinel lymph node biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease.

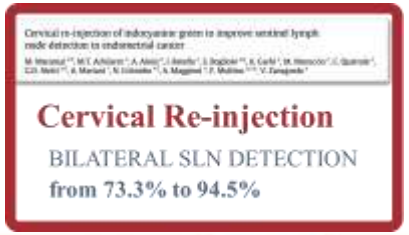
Surgical lymph node staging should be performed in patients with high–intermediate-risk/high-risk disease. Sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy for lymph node staging in stage I/II

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

NOW

Sentinel lymph node (SLN) biopsy **should be performed for staging purposes in all patients with presumed uterus confined disease**

Tracer re-injection is an option if sentinel biopsy is not visualized. If sentinel lymph node is not detected, side-specific systematic lymphadenectomy should be performed in high-intermediate/high risk patients, and can be considered in presumed intermediate risk patients



Surgical management in stage I & II disease

STAGE I & II ENDOMETRIAL CARCINOMA

Minimally invasive surgery

Hysterectomy①② + BSO③ [IV, A for stage I; IV, B for stage II]

+ SLN④ [II, A]

+ Infracolic (total or partial) omentectomy in [IV, B]:
Serous carcinoma
Carcinosarcoma
Undifferentiated carcinoma

①Intra-operative frozen section of the uterus is not encouraged for myometrial invasion assessment because of poor reproducibility and interference with adequate pathologic processing.
②For stage II cases, more extensive procedures should only be performed if required to achieve free surgical margins. This includes vaginal cuff and parametria resection.
③For ovarian preservation, see corresponding algorithm.
④If sentinel lymph node is not detected: side specific systematic lymphadenectomy should be performed in high-intermediate/high risk patients and can be considered in presumed intermediate risk patients.
BSO bilateral salpingo-oophorectomy; SLN sentinel lymph node.

Can we use the molecular profile to further de-escalate surgery?

IMPORTANCE OF APPROPRIATE STAGING

- **10-15% recurrences in low-intermediate disease** (Creasman 1987, Ballester 2008, Ballester 2011, Todo 2007)
- **Not all high-risk patients present with metastases at diagnosis, and ~50% of the high-risk patients do not recur.**
- **No or suboptimal staging results in**
  -important over- and undertreatment (Visser 2017, Hoang 2013)
- **11% pos SN in low risk disease** (Abu-Rustum, 2009)
- **50% of lymph node metastasis are detected in EC patients considered as intermediate risk** (Kommos, 2018)

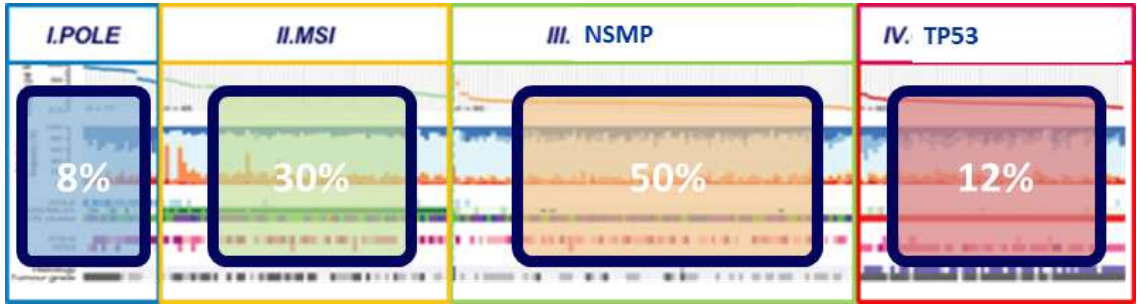
Type and frequency of metastatic spread for each molecular subtype and the associated prognosis?

W Glenn McCluggage, ESMO 2023

	Total	MMR-D	POLE EDM	p53 wt	p53 abn	*P*-value
Number of patients	452 (100%)	127 (28.1%)	42 (9.3%)	228 (50.4%)	55 (12.2%)	
Clinicopathological parameters						
Age at diagnosis (years)						
Mean (±SD)	65.0 (±11.5)	67.3 (±9.9)	60.7 (±10.7)	63.2 (±12.4)	70.3 (±9.3)	0.000
Median	65.3	67.7	58.8	63.4	71.7	
BMI						
Mean (±SD)	29 (±7.7)	28.8 (±7.4)	28.2 (±6.6)	29.8 (±8.3)	27.4 (±5.9)	0.102
Median	27.7	27.8	27.1	27.9	27.4	
Missing	*20*	*6*	*1*	*12*	*1*	
Stage (FIGO 2009)						
I	365 (80.8%)	99 (78%)	39 (92.9%)	198 (86.8%)	29 (52.7%)	0.000
II–IV	87 (19.2%)	28 (22%)	3 (7.1%)	30 (13.2%)	26 (47.3%)	
Tumour grade						
Grade 1/2	357 (79%)	102 (80.3%)	36 (85.7%)	211 (92.5%)	8 (14.5%)	0.000
Grade 3	95 (21%)	25 (19.7%)	6 (14.3%)	17 (7.5%)	47 (85.5%)	
Histology						
Endometrioid	397 (87.8%)	118 (92.9%)	38 (90.5%)	226 (99.1%)	15 (27.3%)	0.000
Non-endometrioid	55 (12.2%)	9 (7.1%)	4 (9.5%)	2 (0.9%)	40 (72.7%)	
LVSI						
Negative	388 (86.6%)	100 (80%)	37 (88.1%)	213 (93.4%)	38 (71.7%)	0.000
Positive	60 (13.4%)	25 (20%)	5 (11.9%)	15 (6.6%)	15 (28.3%)	
Missing	*4*	*2*	*0*	*0*	*2*	
Myometrial invasion						
None	127 (28.1%)	25 (19.7%)	18 (42.9%)	70 (30.7%)	14 (25.5%)	0.002
<50%	172 (38.1%)	44 (34.6%)	15 (35.7%)	96 (42.1%)	17 (30.9%)	
>50%	153 (33.8%)	58 (45.7%)	9 (21.4%)	62 (27.2%)	24 (43.6%)	
Lymph Node Status						
Negative	346 (76.7%)	100 (78.7%)	40 (95.2%)	178 (78.4%)	28 (50.9%)	0.000
Positive	41 (9.1%)	12 (9.4%)	0 (0%)	10 (4.4%)	19 (34.5%)	
Not tested	64 (14.2%)	15 (11.8%)	2 (4.8%)	39 (17.2%)	8 (14.5%)	
Missing	1	0	0	1	0	
Post-surgical treatment						
None	171 (37.8%)	39 (30.7%)	20 (47.6%)	97 (42.5%)	15 (27.3%)	0.027
Any	281 (62.2%)	88 (69.3%)	22 (52.4%)	131 (57.5%)	40 (72.7%)	
ESMO (2013)						
Low	241 (53.3%)	58 (45.7%)	31 (73.8%)	146 (64%)	6 (10.9%)	0.000
Intermediate	80 (17.7%)	26 (20.5%)	4 (9.5%)	49 (21.5%)	1 (1.8%)	
High	131 (29%)	43 (33.9%)	7 (16.7%)	33 (14.5%)	48 (87.3%)	
ESMO (2016)						
Low	230 (50.9%)	55 (43.3%)	28 (66.7%)	141 (61.8%)	6 (10.9%)	0.000
Intermediate	64 (14.2%)	18 (14.2%)	4 (9.5%)	42 (18.4%)	0 (0%)	
High–intermediate	27 (6%)	11 (8.7%)	3 (7.1%)	12 (5.3%)	1 (1.8%)	
High	131 (29%)	43 (33.9%)	7 (16.7%)	33 (14.5%)	48 (87.3%)	

S. Kommoss, Ann Oncol 2018

Can we use the molecular profile to further de-escalate surgery: OPEN QUESTIONS



Postoperative treatments

- Will we need a retroperitoneal staging in rN0 (POLEmut/p53 abn)?

Fertility sparing treatments

- Will the molecular profile affect fertility sparing options?

Can we use the molecular profile to further de-escalate surgery: OPEN QUESTIONS

The unfa… …of early-stage p53abn EC is not due … …tastasis, and the indole… …of

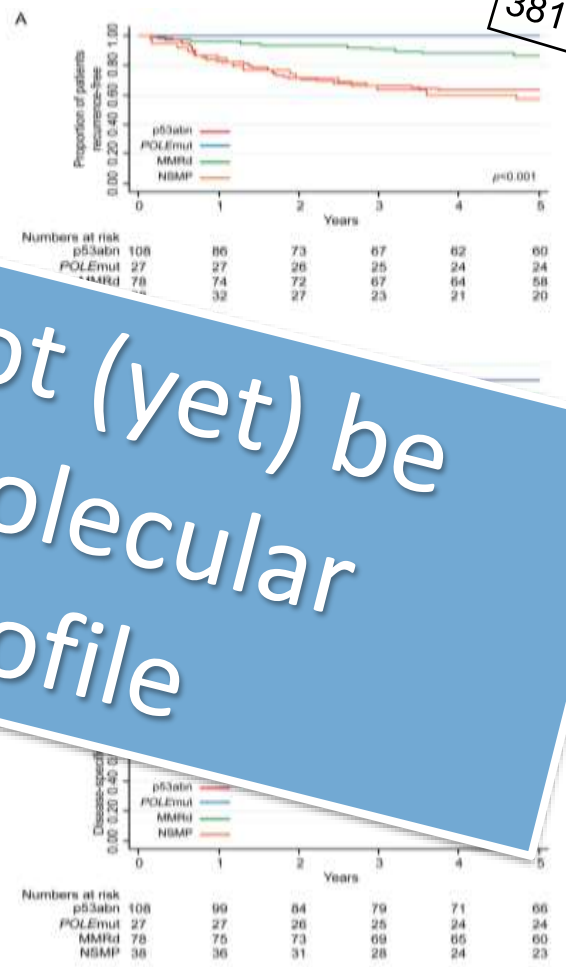
17% of pts with POLE mut (23 pts) develop recurrences after a median f/u of 30 months

Stasenko M, Gynecol Oncol 2020

Surgical staging should not (yet) be adapted based on the molecular endometrial cancer profile

Prognostic relevance of the molecular classification in high-grade endometrial cancer for patients staged by lymphadenectomy and without adjuvant treatment

381 pts



Leon-Castillo , Ann Oncol 2018

Can we use the molecular profile to further de-escalate surgery?

Ongoing trials

UZ LEUVEN

EUGENIE
Study

ASSOCIATION OF EACH MOLECULAR SUBGROUP WITH **THE SPREAD OF THE DISEASE TO THE EXTRA-UTERINE SITES**

	Adnexa	Lymph nodes	Peritoneum	Omentum	Systemic
NSMP	3 (2.5)	16 (13.2)	5 (4.1)	3 (2.5)	2 (1.7)
MMRd	8 (8.5)	18 (19.1)	8 (8.5)	0	2 (2.1)
p53abn	7 (16.3)	10 (23.3)	9 (20.9)	8 (18.6)	2 (4.7)
POLE	1 (4.5)	1 (4.5)	0	0	0
TOTAL	19 (6.8)	45 (16.1)	22 (7.9)	11 (3.9)	6 (2.14)

- Lymph nodal metastases are present in all 4 molecular subgroups
- Only one POLE patients (4.5%) had positive pelvic lymph nodes.

- Transperitoneal and systemic spread was observed in MMRd, p53abn, and NSMP EC

- Highest incidence of transperitoneal spread in the p53abn group

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Data managment, sample collection and registration of patients						
Definition of molecular subgroups						
Association between disease stage and molecoular subgroups						
Assess if combinig disease stage and MC can improve the prognosis prediction						

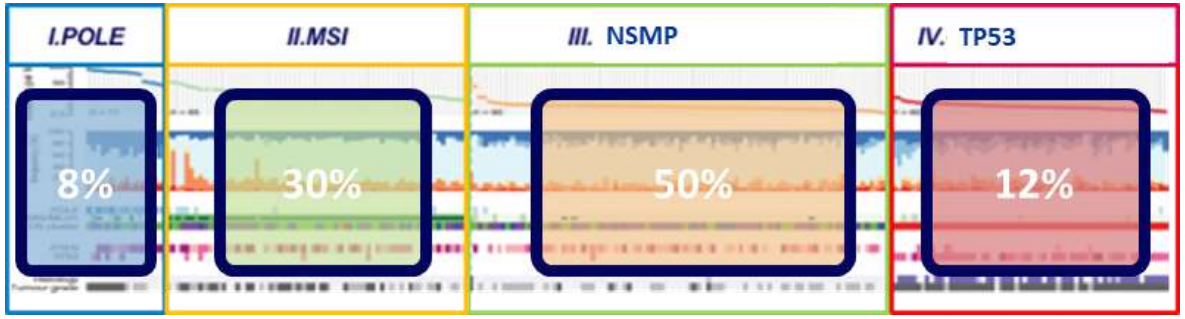
Mature data /Publication

2028!

Can we use the molecular profile to further de-escalate surgery: OPEN QUESTIONS

Postoperative treatments

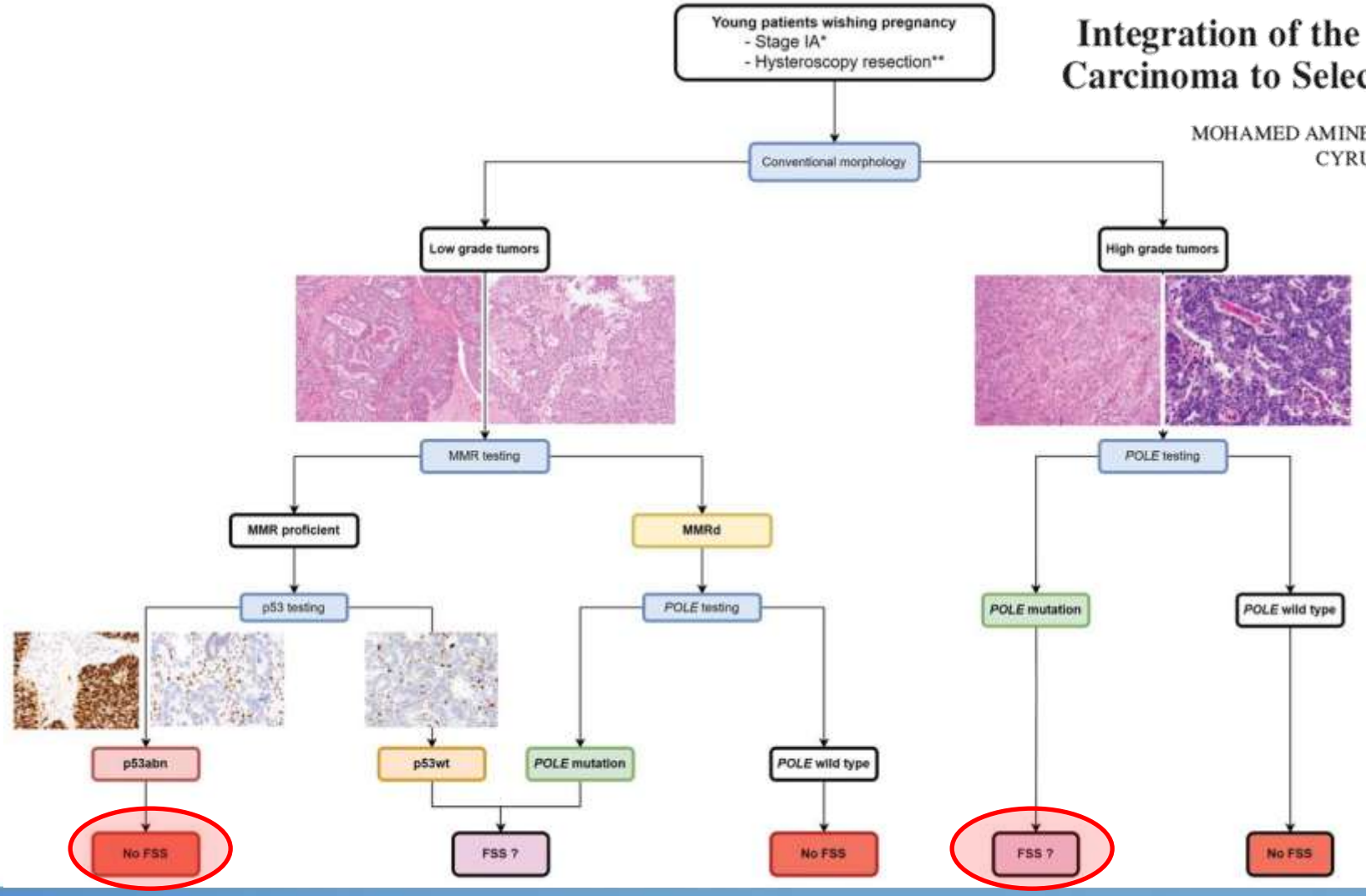
- Will we need a retroperitoneal staging in rN0 (POLEmut/p53 abn)?



Fertility sparing treatments/ovarian preservation

- Will the molecular profile affect fertility sparing options?

Can we use the molecular profile to further de-escalate surgery: OPEN QUESTIONS



Integration of the Molecular Classification of Endometrial Carcinoma to Select Patients for Fertility Sparing Strategies

MOHAMED AMINE BANI[1,2], AMANDINE MAULARD[3], PHILIPPE MORICE[3,4], CYRUS CHARGARI[5] and CATHERINE GENESTIE[1]

NSMP: FS should be discussed considering histology, grade and stage.

Bani et al. ANTICANCER RESEARCH, 2024

Can we use the molecular profile to further de-escalate surgery: OPEN QUESTIONS

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up†

2021

- Ovarian preservation can be considered in pre-menopausal patients aged <45 years with low-grade endometrioid endometrial carcinoma with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease (IV, A).

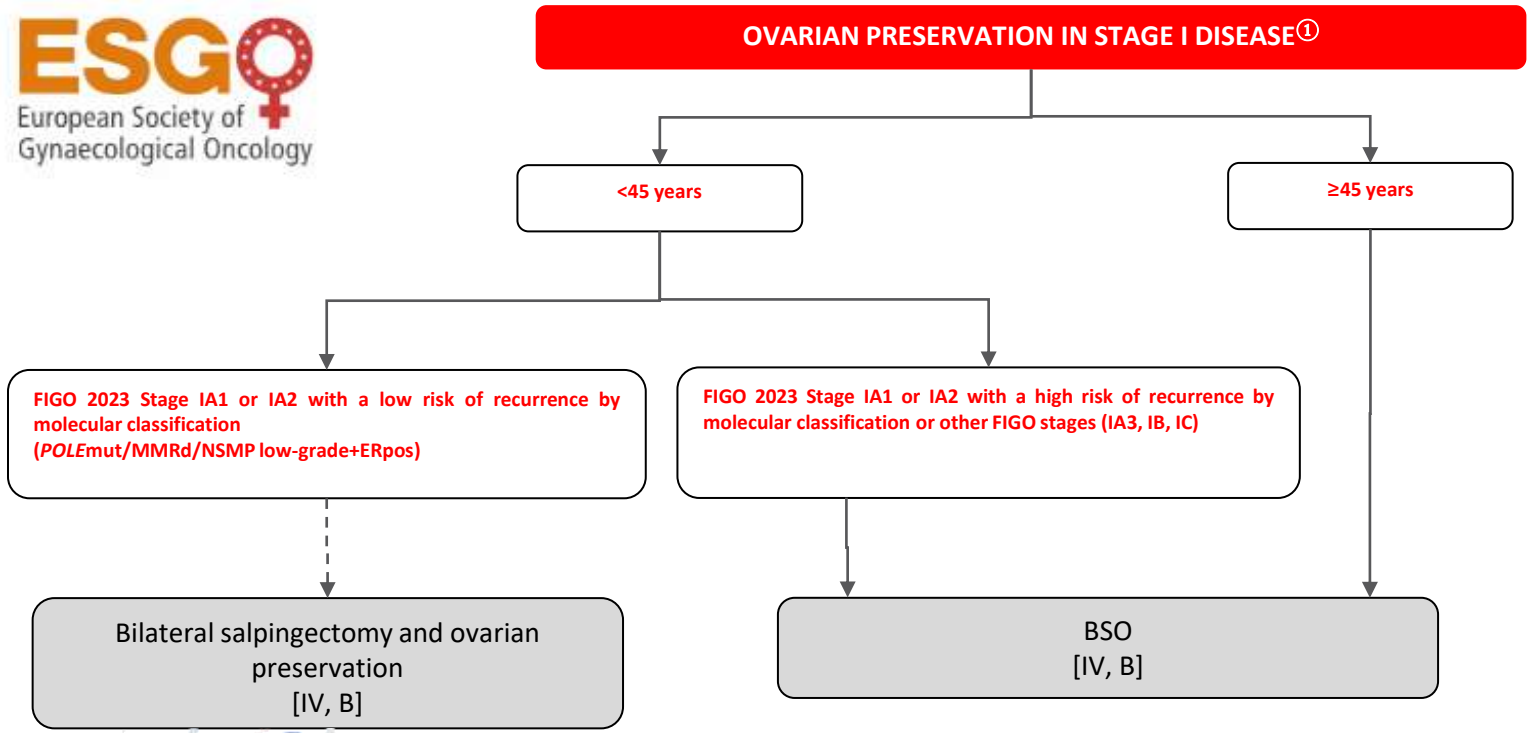
ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma

NOW

Ovarian preservation can be considered in premenopausal patients aged <45 years with FIGO 2023 IA1 or IA2 that have a low risk of recurrence by molecular classification [IV, B].

			*POLE*mut	MMRd	NSMP ERpos	NSMP ERneg	p53abn
I	Confined to the uterine corpus						
IA	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)	IAm *POLE*mut				
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI	IAm *POLE*mut				IICm p53abn

Ovarian preservation in stage I disease

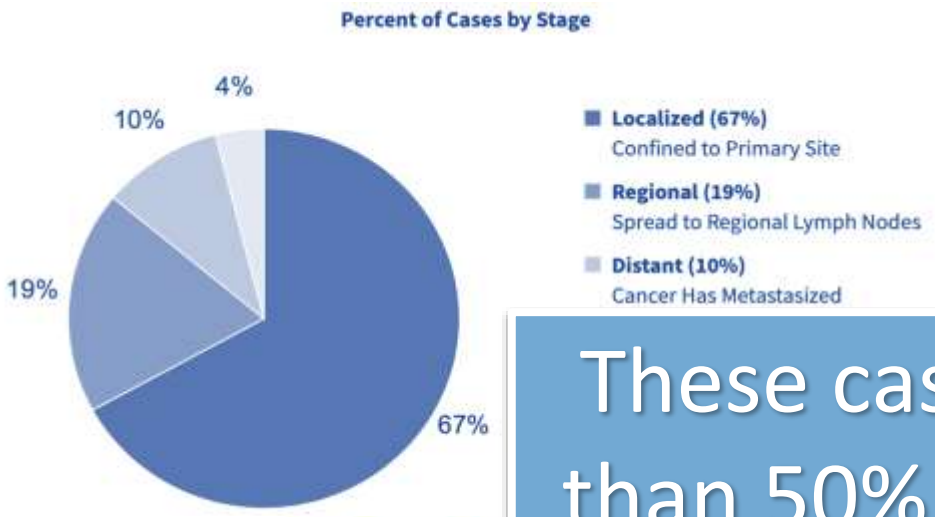


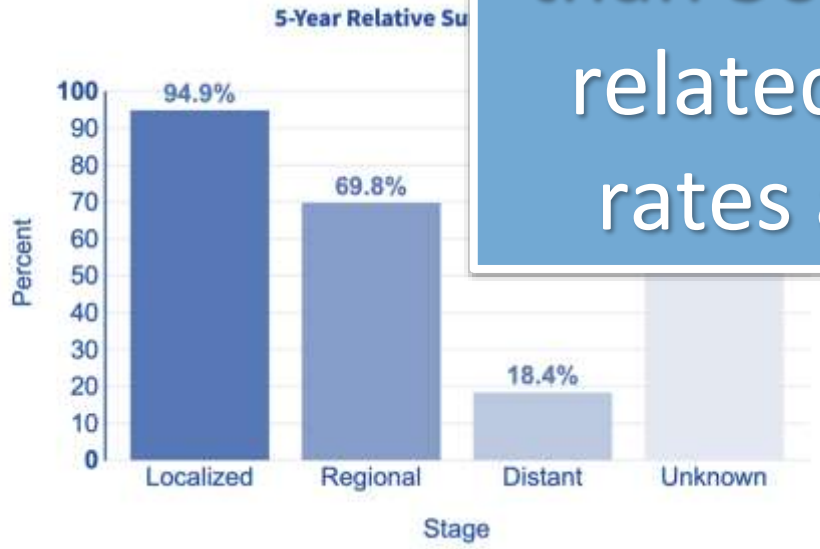
①Ovaries should not be preserved in patients at hereditary risk of ovarian cancer such as carriers of germline *BRCA* mutations or *MLH1/MSH2/MSH6* mutations (Lynch syndrome), and ovarian preservation should be carefully discussed in patients with ovarian or breast cancer family history.
BSO bilateral salpingo-oophorectomy; ERpos oestrogen receptor positive; MMRd mismatch repair deficient; NSMP no specific molecular profile.

Conclusions – Early stges

- Minimally invasive surgery (laparoscopic or robotic) should be the intended approach in case of apparent early-stage disease
- Sentinel Lymph Node (SLN) algorithm should be followed, also in high-risk patients.
- Side specific lymphadenectomy should be performed in case of unsuccessful mapping (even after reinjection) (at least in intermediate-high / high risk cases)
- Surgical staging should not (yet) be adapted based on the molecular endometrial cancer profile

Surgery in Endometrial Cancer





These cases account for more than 50% of all uterine cancer-related deaths, with survival rates as low as 15% to 40%

GERY

Early-Stage

10%

Advanced

(extrauterine disease)

SEER 22 (Excluding IL/MA) 2013–2019, All Races, Females

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Cytoreductive surgery for advanced or recurrent endometrial cancer: A meta-analysis

672 pts
No RCTs

Author	Year	Patients (n)	Median age	% Primary	% Recurrent	% UPSC	% Clear cell	% UPSC or clear cell	% Grade 3	% Stage IV
Chi	1997	55	67	100	0	22	2	24	49	100
Scarabelli	1998	20	(59 mean)	0	100	15	20	35	NA	(40 stages III–IV)
Bristow	2000	65	65	100	0	32	6	38	42	100
Bristow	2001	31	65	100	0	100	0	100	100	100
Ayhan	2002	37	62	100	0	8	5	13	38	100
Memarzadeh	2002	35	70	100	0	100	0	100	100	54
Lambrou	2004	58	63	100	0	0	0	0	44	16
Moller	2004	49	67	100	0	100	0	100	100	100
Campagnutta	2004	75	62	0	100	20	16	36	NA	(31 stages III–IV)
van Wijk	2006	67	63	100	0	5	NA	5	31	28
Awtrey	2006	27	62	0	100	19	4	23	48	15
Bristow	2006	35	63	0	100	25	7	32	30	10
Thomas	2007	70	68	100	0	100	0	100	100	46
Gardner	2009	48	69	100	0	100	0	100	100	100

Author	Year	Optimal	% Optimal	% Complete	% Chemo	% Platinum	% Radiation	Optimal OS	Complete OS	Total OS	Reference
Chi	1997	≤2	53	18	71	NA	25	31	NA	15	20
Scarabelli	1998	No gross	65	65	50	NA	10	12	12	9	30
Bristow	2000	≤1	55	40	63	63	38	34	41	15	21
Bristow	2001	≤1	52	19	87	71	3	26	30	14	25
Ayhan	2002	≤1	59	32	54	54	54	25	48	15	22
Memarzadeh	2002	No gross	57	57	66	37	34	40	40	26	26
Lambrou	2004	≤2	72	NA	27	NA	45	18	NA	17	23
Moller	2004	≤1	53	NA	73	71	16	15	NA	12	29
Campagnutta	2004	≤1	75	64	57	11	20	53	NA	19	31
van Wijk	2006	No gross	75	75	16	15	73	108 (66% 5-year survival)	(66% 5-year survival)	104	24
Awtrey	2006	≤2	67	56	NA	NA	NA	43	NA	35	32
Bristow	2006	No gross	66	66	57	NA	43	39	39	24	33
Thomas	2007	≤1	60	37	64	61	20	20	51	18	27
Gardner	2009	≤1	58	NA	NA	NA	NA	51	NA	32	28

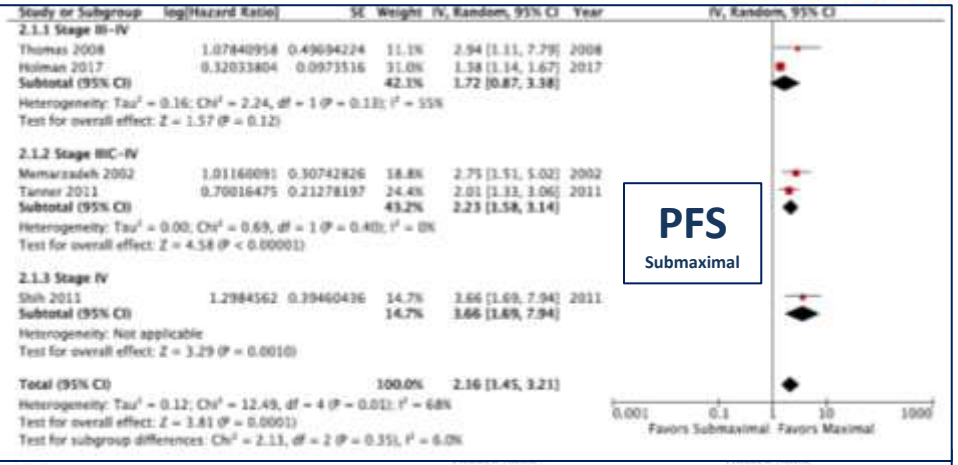
UPSC = uterine papillary serous cancer, OS = overall survival, NA = not applicable.

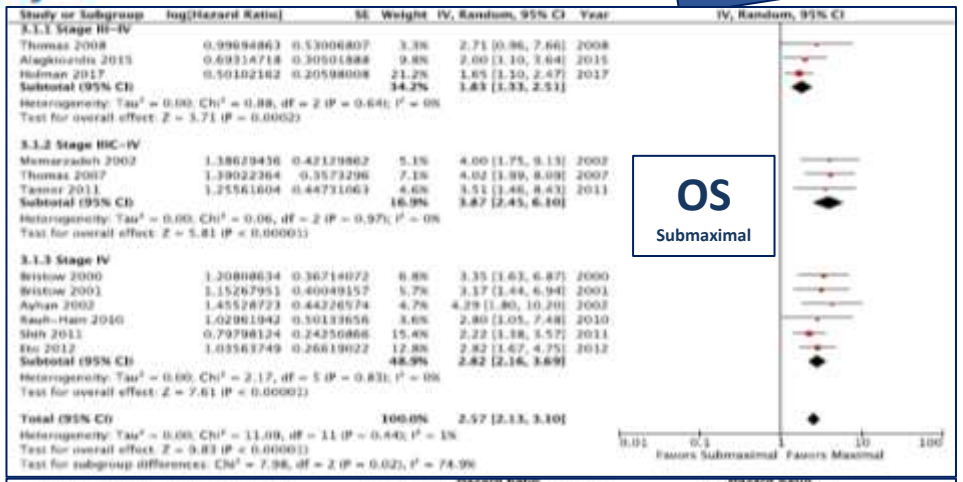
Cohort median OS was positively associated with increasing proportion of patients undergoing complete surgical cytoreduction (each 10% increase improving survival by 9.3 months, p=0.04)

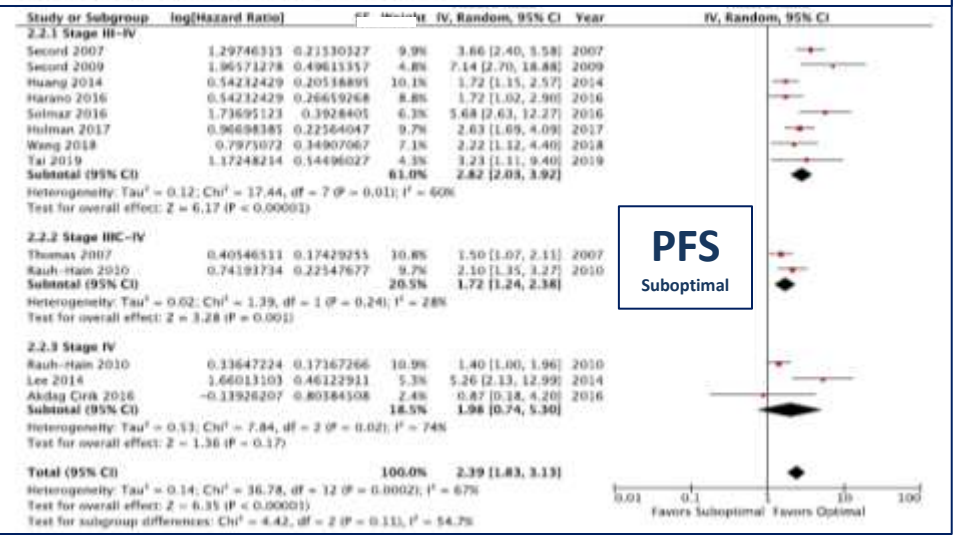
J.N. Barlin et al. Gynecologic Oncology 118 (2010) 14–18

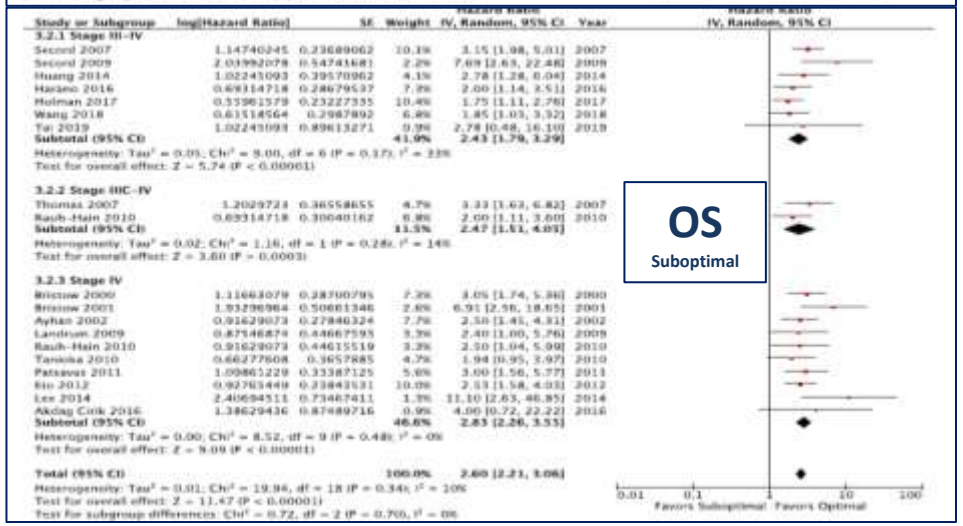
Primary cytoreductive surgery for advanced stage endometrial cancer: a systematic review and meta-analysis

2920 pts over 6-24 years









Patients who met the maximal or optimal cytoreduction thresholds had a statistically significant improvements in both **PFS** and **OS** with HR estimates around 2.6 (range 1.7-4.1),regardless of histology

Median survival for pts who had <1 cm residual disease was 15 months vs 40 months among those who had RT=0

Albright et al. Am J Obstet Gynecol 2021

Surgery in advanced Endometrial Cancer

ESGO
European Society of Gynaecological Oncology

SURGERY FOR CLINICALLY OVERT STAGE III & IV DISEASE

Full pre-operative staging and discussion by specialist multidisciplinary team

Complete macroscopic resection feasible with acceptable morbidity and quality of life?

Yes

Upfront surgery in a specialised centre [IV, B]:

- Complete macroscopic resection
- No systematic lymphadenectomy indicated, only removal of suspicious lymph nodes

No

Due to local extent of the disease

Refer to the corresponding algorithm

Due to unresectable disseminated stage III, IV disease

Refer to the corresponding algorithm

UNRESECTABLE STAGE III OR IV DUE TO LOCAL EXTENT OF DISEASE

Consider molecular subtype in decision making on treatment modality

Primary systemic therapy [IV, C]

Refer to the corresponding

Definitive radiotherapy (EBRT and IGBT) [IV, C]

Good response to primary systemic therapy?

Yes

Delayed surgery depending on [IV, C]:

- Suitability of the patient for surgery
- Feasibility for complete macroscopic resection
- Patient wishes

Further systemic therapy [IV, C]

Radiotherapy [IV, C]

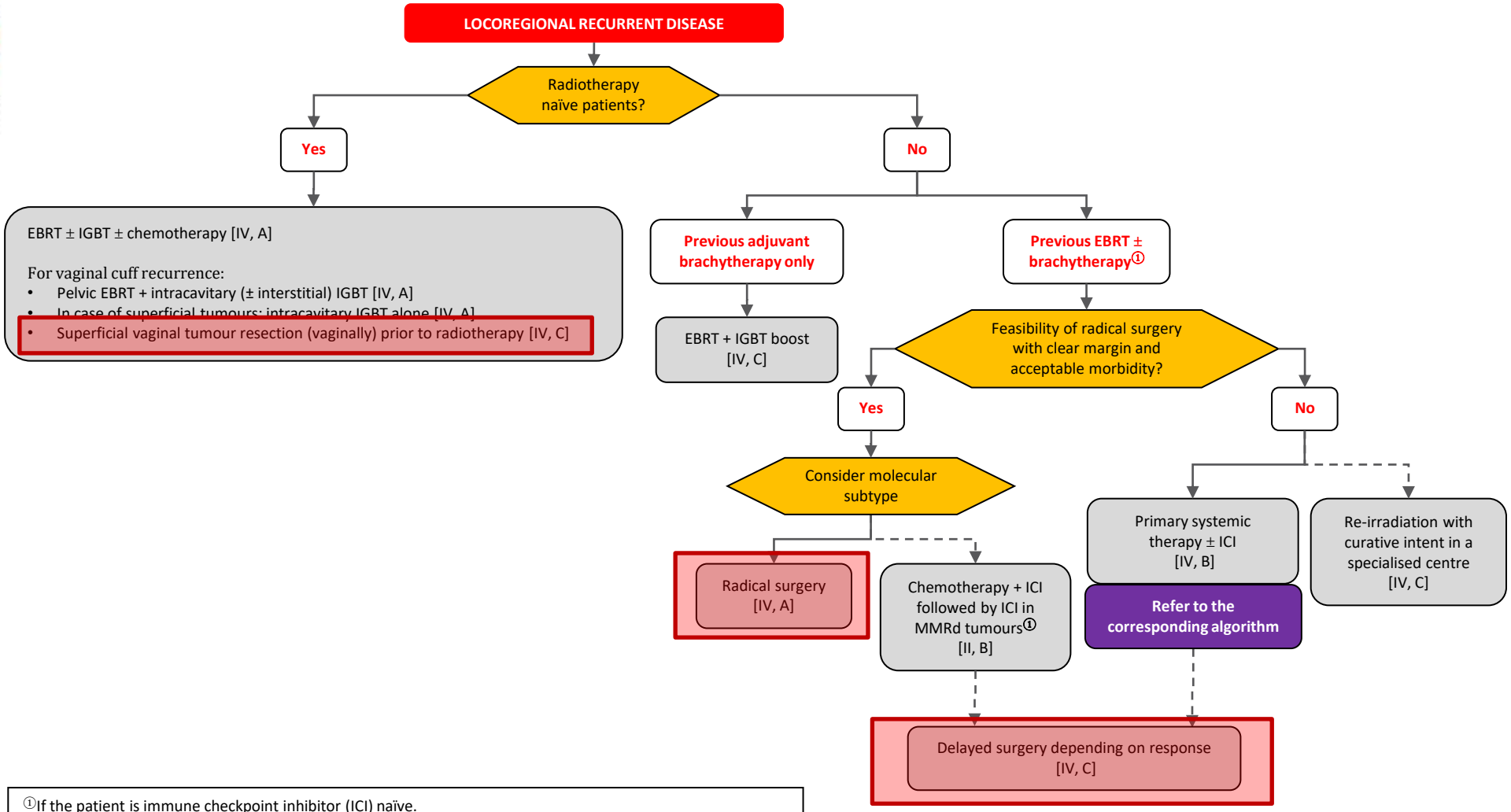
No

Further systemic therapy [IV, C]

Definitive radiotherapy (EBRT and IGBT) [IV, C]

Systemic therapy [IV, C]

Surgery in recurrent Endometrial Cancer

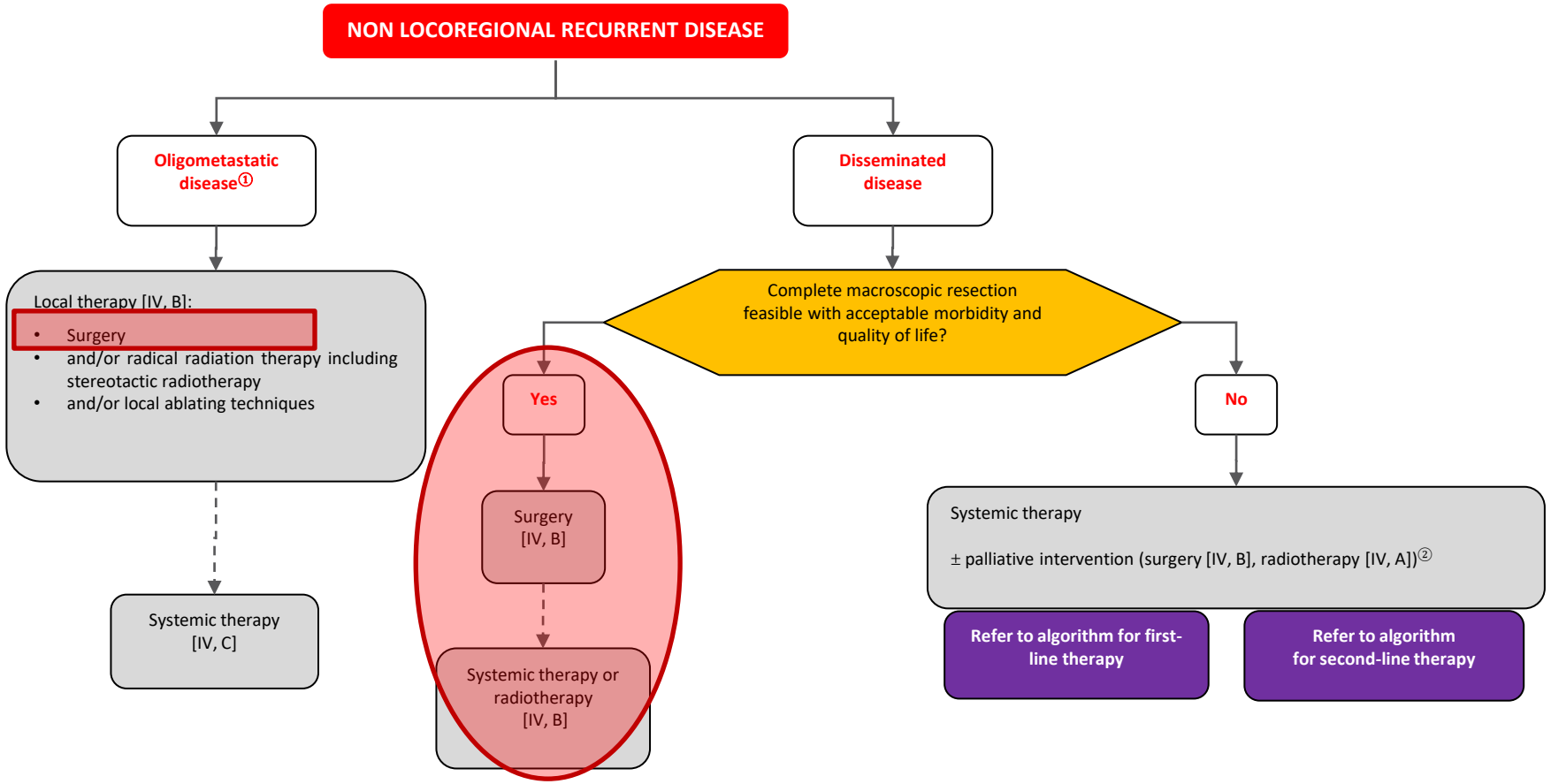


①If the patient is immune checkpoint inhibitor (ICI) naïve.

EBRT External beam radiotherapy; MMRd mismatch repair deficiency; IGBT image-guided brachytherapy.

Surgery in recurrent Endometrial Cancer

ESGO European Society of Gynaecological Oncology



①1-5 metastases/up to 3 regions.
②Palliative surgery can be performed in selected cases to alleviate symptoms (e.g. bleeding, fistula, bowel obstruction). Palliative radiotherapy is indicated for symptoms related to pelvic or systemic disease.

Conclusions – advanced/recurrent disease

- **Surgery** is considered the primary option in resectable/operable patients with metastatic disease
- **Neo-adjuvant treatment** followed by surgery is the best alternative in patients with non-resectable disease/ non operable/high risk of complications
- The molecular profile (**MMR status in particular**) is an integrated tool in defining the best systemic approach

Bright future ahead!

RISK GROUPS

2023 FIGO staging𝕋			Molecular classification*				
			*POLE*mut	MMRd	NSMP low-grade+ERpos	NSMP high-grade/ERneg**	p53abn
I	**Confined to the uterine corpus**						
IA	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)	IAm *POLE*mut			**	
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#	IAm *POLE*mut			**	
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
IC		High-grade histologies^, limited to polyp/endometrium	IAm *POLE*mut		n.a.		
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm *POLE*mut			**	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI***	IAm *POLE*mut			**	IICm p53abn
IIC		High-grade histologies^, myoinvasion	IAm *POLE*mut	Myoinvasion <50%, no/focal LVSI	n.a.		IICm p53abn
			IAm *POLE*mut	Myoinvasion ≥50%, no/focal LVSI			
			IAm *POLE*mut	Cervical stromal invasion, no/focal LVSI			
			IAm *POLE*mut	Substantial LVSI**			
III	**Local and/or regional spread**						
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)					
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa					
IIIB	IIIB1	Metastasis or direct spread to the vagina and/or the parametria					
	IIIB2	Metastasis to the pelvic peritoneum					
IIIC	IIIC1	Pelvic lymph node metastasis					
	IIIC1i	Micrometastasis					
	IIIC1ii	Macrometastasis					
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)					
	IIIC2i	Micrometastasis					
	IIIC2ii	Macrometastasis					
IV	**Locally advanced and/or metastatic disease**						
IVA		Invasion of the mucosa and/or the intestinal mucosa					
	Metastatic disease or residual disease after surgery						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

Green denotes low risk for recurrence; yellow denotes intermediate risk; orange denotes high-intermediate risk and red denotes high risk; grey denotes uncertain risk classification because of lack of data.

𝕋 2023 FIGO staging: when molecular classification is known, the FIGO stage should be reported with an annotation of m (for molecular) followed by the specific molecular subtype. There are two specific molecularly defined FIGO stages, namely stage IAm *POLE*mut (stages I and II disease with a pathogenic *POLE* mutation) and stage IICm p53abn (stages I and II disease with a p53 abnormality and myometrial invasion). (these two molecularly defined FIGO stages are indicated in the table's cells)

*Details on determining the molecular classification, including allocation for double classifiers, are detailed in figure 2 and the webappendix, pp 18-20.

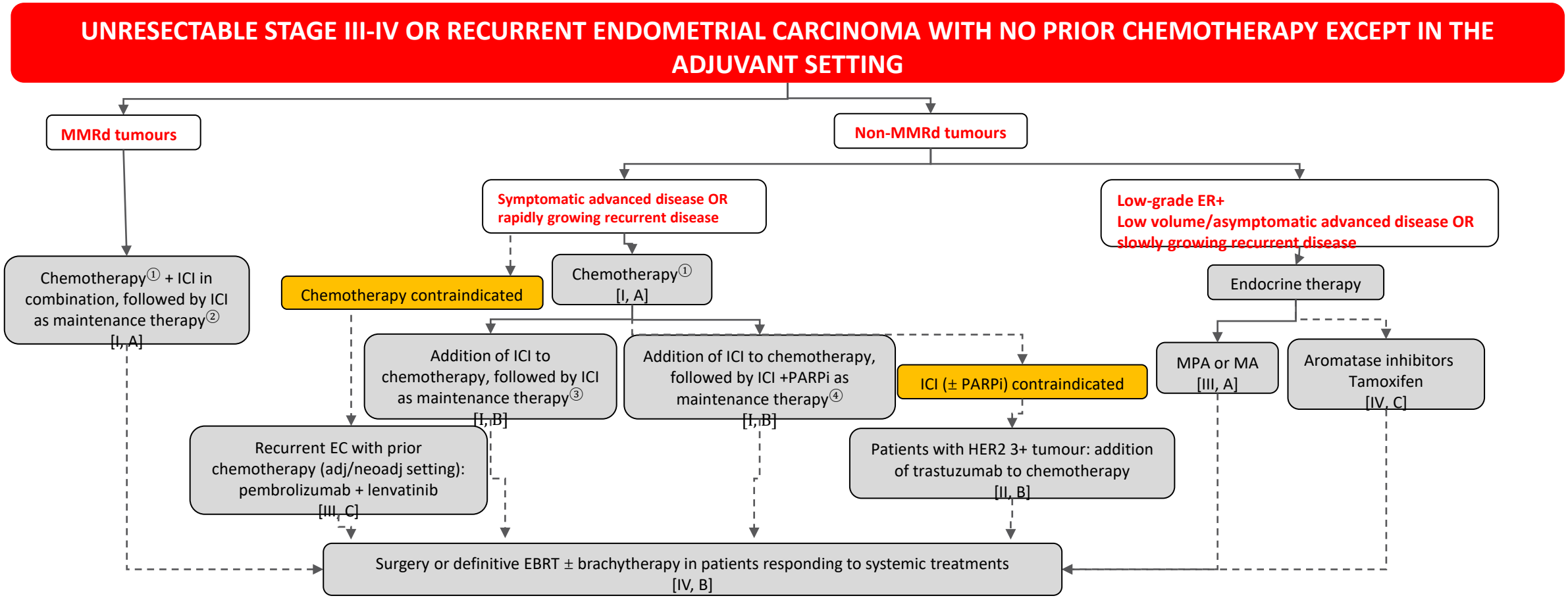
**The molecular subgroup NSMP high-grade/ERneg consists of either high-grade NSMP cases or ERneg NSMP cases. Thus, in FIGO stages referring to *low-grade* endometrioid carcinomas (i.e. IA1, IA2, IA3, IB, IIA and IIB) only to the ERneg cases of the molecular subgroup NSMP high-grade/ERneg apply.

***Substantial LVSI is defined according to WHO criteria by ≥4 vessels in at least one H&E slide (refer to appendix for information on LVSI, pp 18-20).

myoinvasion <50% + no/focal LVSI + ovarian tumour pT1a

^High-grade histologies are the FIGO 2023 aggressive histotypes that include high-grade endometrioid (grade 3), serous, clear cell carcinomas, carcinosarcomas, undifferentiated, mixed, mesonephric-like, and gastrointestinal mucinous type carcinoma.

Surgery in recurrent Endometrial Cancer



①The standard chemotherapy regimen is carboplatin + paclitaxel.

②Immune checkpoint inhibitor (ICI): dostarlimab or durvalumab or pembrolizumab (drugs in alphabetical order).

③ICI: dostarlimab or pembrolizumab.

④ICI + poly(ADP-ribose) polymerase inhibitor (PARPi): durvalumab + olaparib.

Adj/neoadj adjuvant/neoadjuvant; EBRT external beam radiotherapy; ER+ estrogen receptor positive; MA megestrol acetate; MMRd mismatch repair deficiency, MPA medroxyprogesterone acetate; non-MMRd non-mismatch repair deficiency; NSMP non-specific molecular profile.

Overview on spread pattern in different subtypes of endometrial cancer as reported in literature

Amant et al., Gynecol Oncol 2005;98:274-80

N (%)	Peritoneal cytology	Adnexal	Omental	Pelvic LN
Grade 3 E	86/668 (13)	41/721 (6)	3/25 (12)	78/734 (11)
Carcinosarcoma	72/373 (19)	75/512 (15)	15/96 (16)	80/423 (19)
Serous	17/57 (13)	27/125 (22)	47/202 (23)	72/244 (30)
Clear cell	7/20 (35)	3/32 (9)	3/6 (50)	9/20 (45)

INCOMPLETE PRIMARY SURGERY
NO RESIDUAL DISEASE

- In general, in presumed early-stage disease with no residual disease (based on the initial surgical report and on post-surgical imaging) re-surgery should be avoided in patients with low-risk disease as defined by uterine pathological and molecular factors [IV, B].

CERVIX RETAINED

If the patient is a candidate for surgery, the cervix should be removed. In case of no prior lymph node staging, SLN should be assessed by cervical injection. If the SLN cannot be detected, lymph node staging follows the standard principles used in primary surgery [IV, B].

INCOMPLETE PRIMARY SURGERY
NO RESIDUAL DISEASE
PERITONEAL STAGING NOT PERFORMED

- Re-surgery with infracolic (total or partial) omentectomy can be considered in serous EC, carcinosarcoma, and undifferentiated carcinoma confined to the uterus, if the outcome might have an implication for adjuvant treatment strategy and after careful assessment of the morbidity of the procedure [IV, B].

LYMPH NODE STAGING NOT PERFORMED

As SLN assessment cannot be performed in case of previous total hysterectomy, systematic pelvic lymphadenectomy should be considered only in non-low risk patients and if it can modify adjuvant treatment since its therapeutic role has not been established [IV, B].

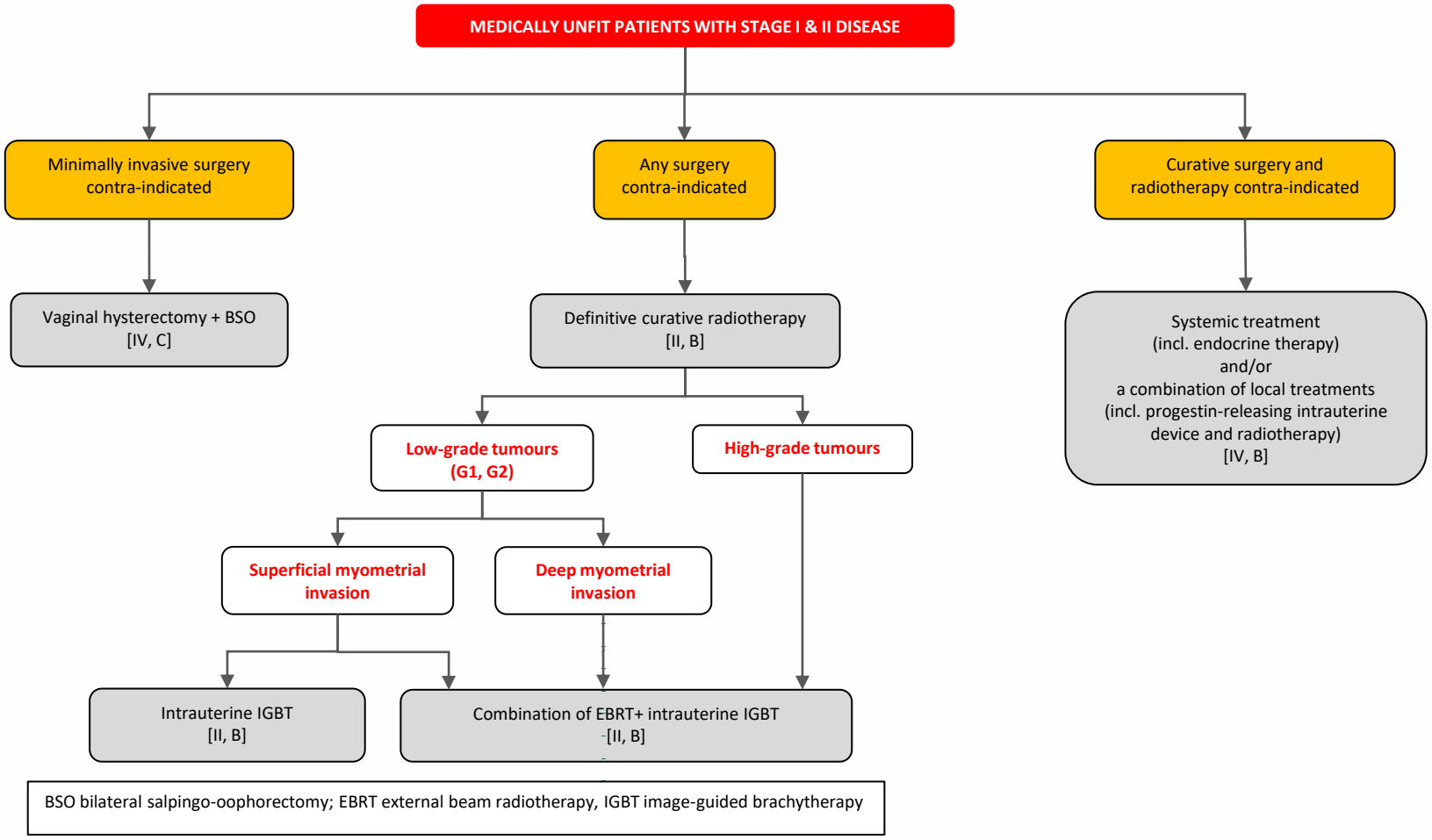
INCOMPLETE PRIMARY SURGERY
NO RESIDUAL DISEASE
ADNEXA RETAINED

- If the patient is undergoing re-surgery in order to complete staging (eg. peritoneal staging/lymph node staging/cervix removal), retained adnexa should also be removed (except in the scenario of ovarian preservation) [IV, B].
- The question of re-surgery for the sole reason of removal of adnexa rarely occurs and should be considered only in non-low risk patients and after careful assessment of morbidity of the procedure [IV, B].

RESIDUAL LYMPH NODE DISEASE IN PELVIC OR PARA-AORTIC REGION FOLLOWING SURGERY

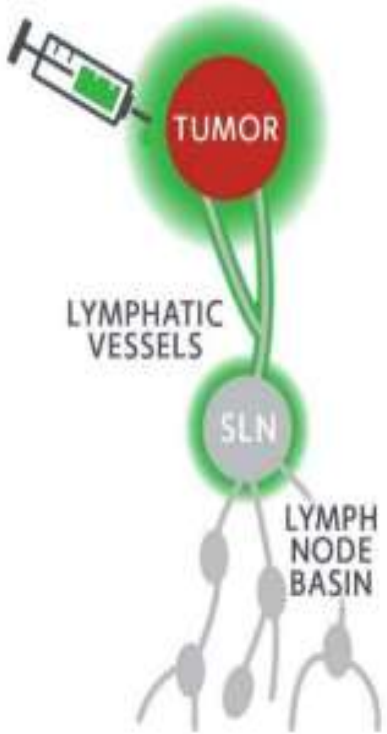
- Residual lymph node disease should be evaluated for resection if the initial resection did not occur within a specialist centre [V, A].
- If the residual lymph node disease is not resectable, primary systemic therapy taking into account the molecular profile and/or EBRT should be used [I, A].

Medically unfit patients with stage I & II disease



ENDO-3

A Phase III Randomised Clinical Trial Comparing Sentinel Node Biopsy with No Retroperitoneal Node Dissection in Apparent Early-Stage Endometrial Cancer



Oceania: 8 (3)
- Australia: 8 (3)

ASIA: 1 (1)
- Singapore: 1
- Hong Kong: (1)

USA: 1

Europe: (2)
- Italy: (2)

South America: (7)
- Brazil: (4)
- Colombia: (1)
- Argentina: (2)

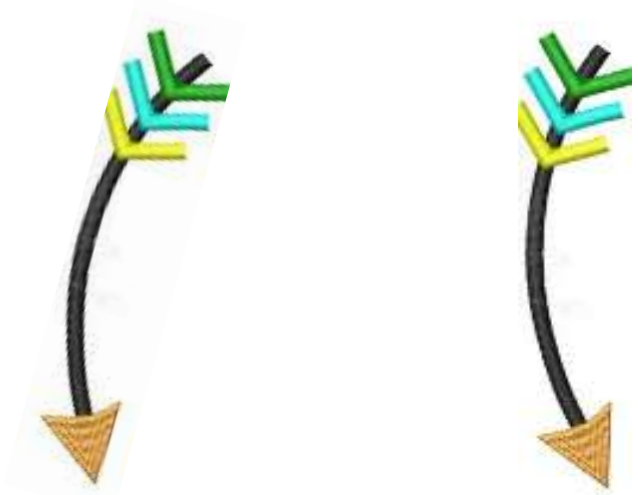
Study sponsor coordinator: University of Queensland
Study Chair: Prof. Andreas Obermair

AIM: to determine the value of ***sentinel node biopsy*** for ***patients, the healthcare system*** and to exclude detriment to patients.

- Plan to recruit 760 patients worldwide over 4 years.

Participants: females aged 18 years and over with **apparent early-stage endometrial cancer**.

RANDOMISATION 1:1



STANDARD TREATMENT
Total LPS/R-LPS Hysterectomy, BSO, without Retroperitoneal Node Dissection

INTERVENTION TREATMENT
Total LPS/R-LPS Hysterectomy, BSO, with Sentinel Node Biopsy

Primary Objectives:

- determine the recovery of participants and health care system of SNB for surgical treatment of endometrial cancer;
- compare disease-free survival at 4.5 years for participants with TH BSO without retroperitoneal node dissection.

INCLUSION CRITERIA

1) Females > 18yo with histologically confirmed primary epithelial cancer of the endometrium of any cell type or uterine carcinosarcoma (mixed malignant mullerian tumour);
2) Clinically stage I disease (confined to body of uterus);
3) ECOG 0-1;
4) Informed consent;
5) Eligibility of patients for LPS/R-LPS surgery according to discretion of the treating MD (e,g, suitable for TH BSO; toleration of Trendelenburg position);
6) No evidence of extrauterine disease at clinical-radiological findings;
7) Negative pregnancy test < 30 days of surgery in pre-menopausal women and in < 2 years from menopause

EXCLUSION CRITERIA

1) Extrauterine disease (involvement of cervix, vagina, parametria, adnexa, bladder, lymph nodes, bowel) by clinical exam and/or imaging;
2) Enlarged retroperitoneal pelvic and/or aortic lymph nodes on imaging;
3) Expentancy life < 6 months;
4) Absolute contraindication for RT or CHT;
5) Previous RT/CHT in pelvis;
6) Concomitant systemic disorders incompatible with study (discretion of treating MD);
7) Patient compliance and geographic promixity;
8) Allergy to Indiocianine Green;
9) Previous retroperitoneal surgery
10) ***Required retroperitoneal lymph nodal dissection***;
11) Prior malignancies in past 5 years excluding successfully treated keratinocyte skin cancers or ductal in situ;
12) Uterine perforation during EC sampling

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

The ENDOCancer-DATA: the surveillance, epidemiology, and end results database program on endometrial cancer in the Italian population

Responsabile Scientifico: Prof. Giovanni Scambia
Principal investigator: Prof. Francesco Fanfani
Sub-investigators: Dott. Emanuele Perrone

On the wake of the SEER Registry, a tool for National Health System requiring an optimization of the diagnosis and treatment strategies of this carcinoma.

Multi-center ambispective observational descriptive study

AIM of this study is to lay the bases for an ambitious project that reports and records all the epidemiological-clinical information of the cases of endometrial carcinoma diagnosed and treated in the reference oncology centers involved on the national territory, to create a process of analysis of the data collected, standardization and improvement of the therapeutic diagnostic procedures of endometrial carcinoma in Italy.

INCLUSION: all patients undergoing staging and cytoreduction surgery for tumor, database will make use of data collected retrospectively with information prognostics and clinical perspectives that are prospectively continuously updated.

The following data will be collected: clinical characteristics (age, BMI, ASA, previous tumors), histopathological data (histotype, grade, FIGO stage, etc.)

In addition, data related to chemotherapy treatment or adjuvant radiation therapy performed, out-come survival (DFS and OS), number of recurrences and deaths, type of recurrence, treatment at recurrence, cause of death

REDCap
Research Electronic Data Capture

DFS will be calculated from the date of surgery to the date of recurrence or last FU. OS will be calculated from the date of surgery to the date of death for any cause or last follow-up.

Starting from the study of known histopathological-clinical and molecular risk factors, Cancer risk classes will be created aimed at the elaboration of prognostic algorithms.

MULTIPLE COHORT LONGITUDINAL ANALYSIS

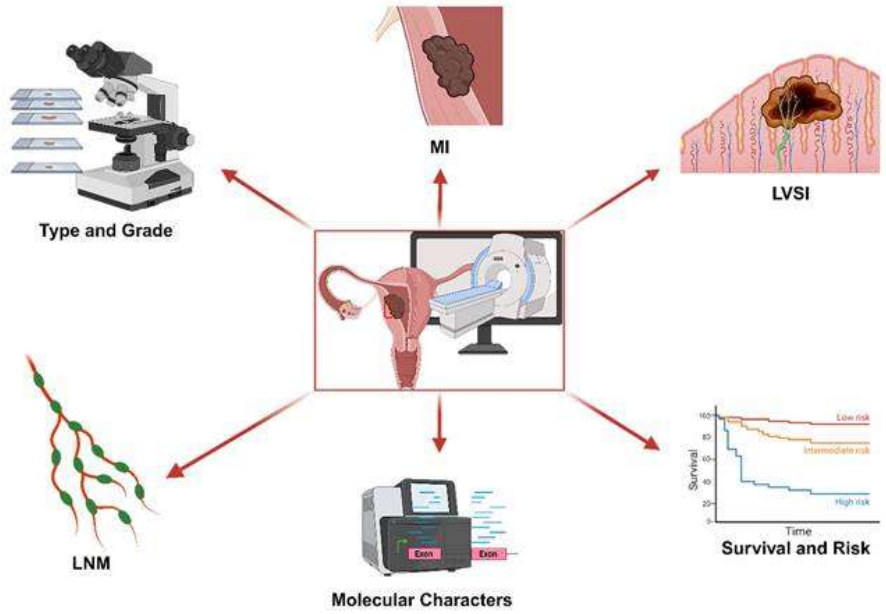
1. Risk classifications of EC;
2. Study of oncological and survival predictive models of molecular and histopathological factors;
3. Impact of various diagnostic, surgical and therapeutic approaches to EC;
4. Molecular alterations and genetic syndromes with increased risk of EC (S. Lynch, etc.)
5. Effectiveness of chemo and radiotherapy treatments based on information histopathological and molecular
6. In vitro and in vivo translational studies aimed at studying new molecular targets for potential innovative future approaches.
7. ***Radiogenomics*** study on the predictive potential of AI models that are use diagnostic imaging, histopathological and molecular data

INCLUSION CRITERIA

- diagnosis of endometrial cancer (stage I-IV, G1-3, and special histotypes)
- age > 18 years
- ASA score 1-3
- staging, cytoreduction or diagnostic surgery with acquisition of histological examination on which IHC and/or IHC study has been performed NGS for the molecular profile of carcinoma
- Signing of informed consent

EXCLUSION CRITERIA

- patients with information not present
- patients not treated in the participating centers of which there will only be Partial and fragmented information
- molecular profile not known and/or not recoverable and retrospectively analyzable



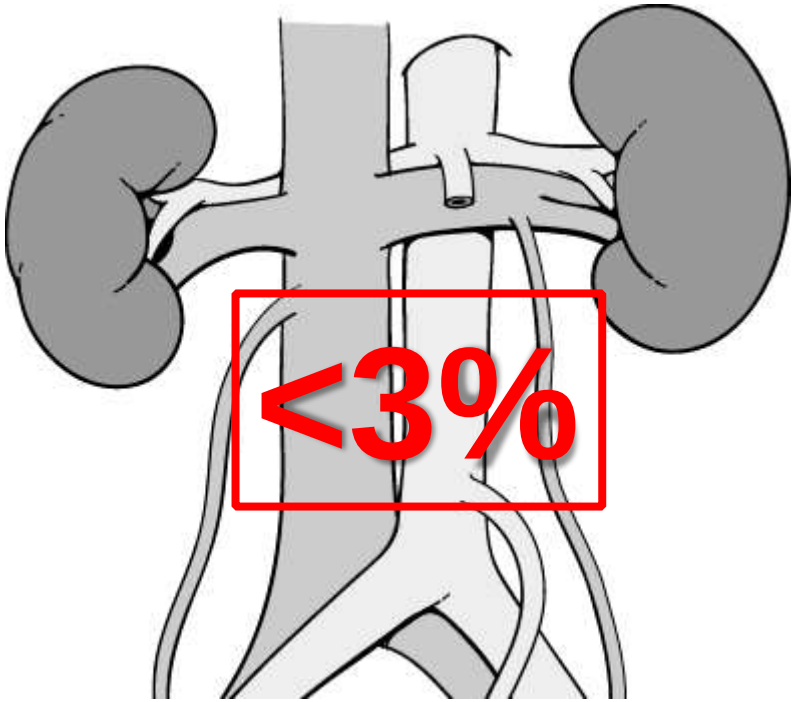
SLN vs PPAND comparison studies

	RISK GROUPS	Diagnostic	Oncology Outcomes
Zahl-Eriksson 2016	Endometrioid myo ≤ 50%		
Ducie 2017	Endometrioid myo > 50% Type II		NA
Schlappe 2018	Endometrioid myo > 50% Node negative	NA	
Multinu 2019	Stage IIIC No bulky nodes	NA	

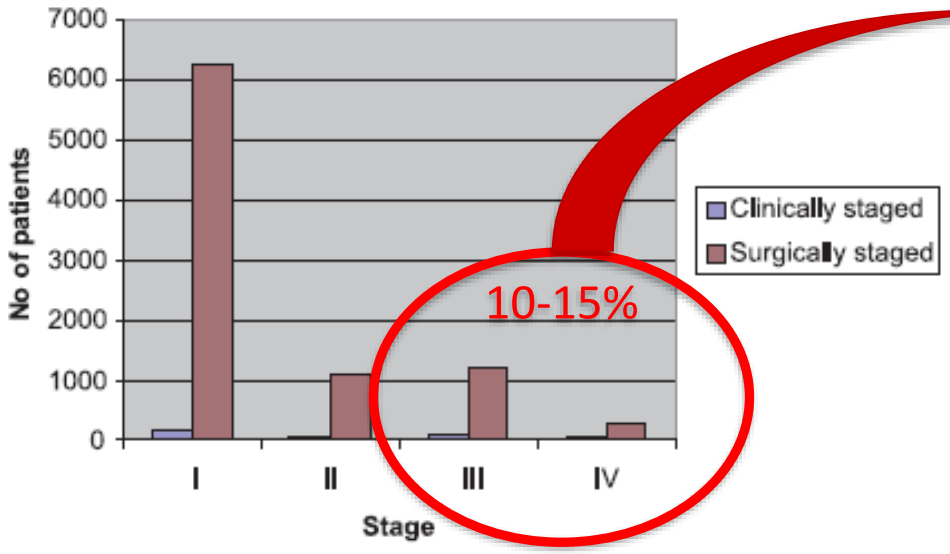
WHAT ABOUT AORTIC NODES?

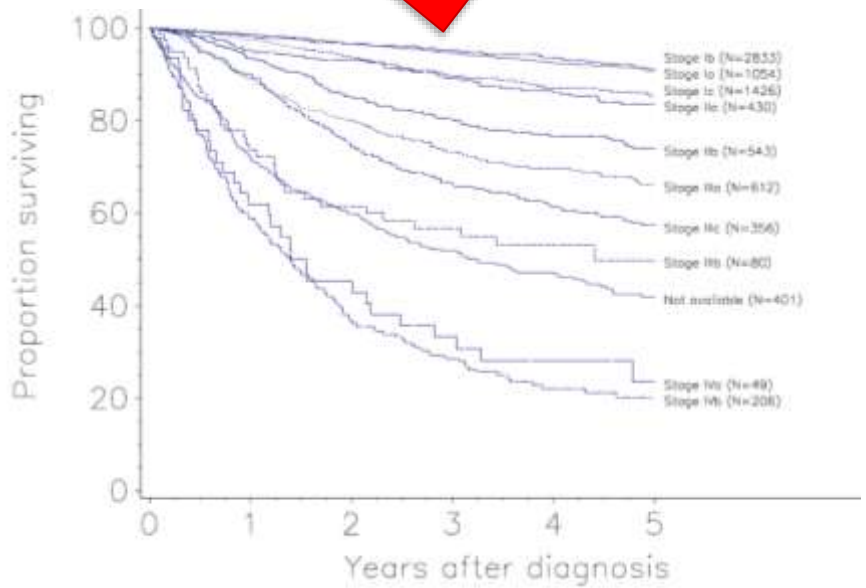
Authors	Year	N	P(−)/PA(+) when considering pelvic LNs (−) patients
Chen	1983	74	3/66 (4.5%)
Creasman	1987 GOG 33	621	12/563 (2.1%)
Morrow	1991	895	18/802 (2.2%)
Lanson	1993	50	0/48(0.0%)
Ayhan	1995	209	6/179(3.4%)
Fanning			
Yokoyam			
Onda			
Hirahata			
McMeekin	2001	607	8/568 (1.4%)
Mariani	2004	566	5/229 (2.2%)
Nomura	2006	155	4/105 (3.8%)
Mariani	2008	281	9/233 (3.4%)
Hoekstra	2009	1487	7/1409 (0.5%)
Lee	2009	349	7/264 (2.7%)
Fujimoto	2009	355	7/313 (2.2%)
Abu-Rustum	2009	847	12/734 (1.6%)
Chiang	2011	171	2/156 (1.3%)
Total		**7163**	**103/6024 (1.7%)**

103/6024 (1.7%)



DIMENSION OF THE PROBLEM





In approximately 10-15% of all new cases of endometrial cancer, disease is found outside the uterus. These cases account for more than 50% of all uterine cancer-related deaths, with survival rates as low as 15% to 40% .

Figo annual report 2006

IEO
European Institute of Oncology

DETERMINANTS OF SURVIVAL

Systematic Reviews

Primary cytoreductive surgery for advanced stage endometrial cancer: a systematic review and meta-analysis

2920 pts over 6-24 years

Meta-analysis summary estimates for association of suboptimal (≥1 cm) primary cytoreduction with increased hazard of progression or death in studies of advanced stage endometrial cancer

Group	Progression-free survival			Overall survival		
	Number of studies	HR (95% CI)	I^2 (%)	Number of studies	HR (95% CI)	I^2 (%)
Overall	12	2.55 (1.93–3.37)	63	18	2.62 (2.20–3.11)	15
Included stages						
Stage III–IV	8	2.82 (2.03–3.92)	60	7	2.43 (1.79–3.29)	33
Stage IIIC–IV	2	1.72 (1.24–2.38)	28	2	2.47 (1.51–4.05)	14
Stage IV	3	1.98 (0.74–5.30)	67	10	2.83 (2.26–3.55)	0
Included histology						
Endometrial with or without CS[a]	4	4.07 (2.29–7.24)	49	8	2.81 (2.25–3.51)	0
Serous	6	2.09 (1.59–2.73)	46	8	2.70 (1.93–3.79)	46
Study location						
United States	6	2.86 (1.90–4.32)	74	10	3.07 (2.29–4.12)	44
International	6	2.24 (1.49–3.35)	49	8	2.28 (1.81–2.89)	0
Sensitivity analyses						
Adjusted HRs only	8	2.74 (1.85–4.08)	64	7	2.68 (1.98–3.63)	14
No overlap[b]	10	2.27 (1.75–2.95)	57	15	2.41 (2.06–2.83)	0
High-quality studies[c]	10	2.61 (1.85–3.68)	70	11	2.79 (2.24–3.48)	5

CI, confidence interval; *CS*, carcinosarcoma; *HR*, hazard ratio; I^2, Higgins measure of study heterogeneity.

[a] Includes studies reporting collectively on endometrioid, serous, and clear cell carcinomas, with or without carcinosarcoma; [b] Excludes studies with potentially overlapping patient cohorts (Supplemental Table 1); [c] Excludes studies scoring <8/8 points on Newcastle-Ottawa scale (Supplemental Figure 1).

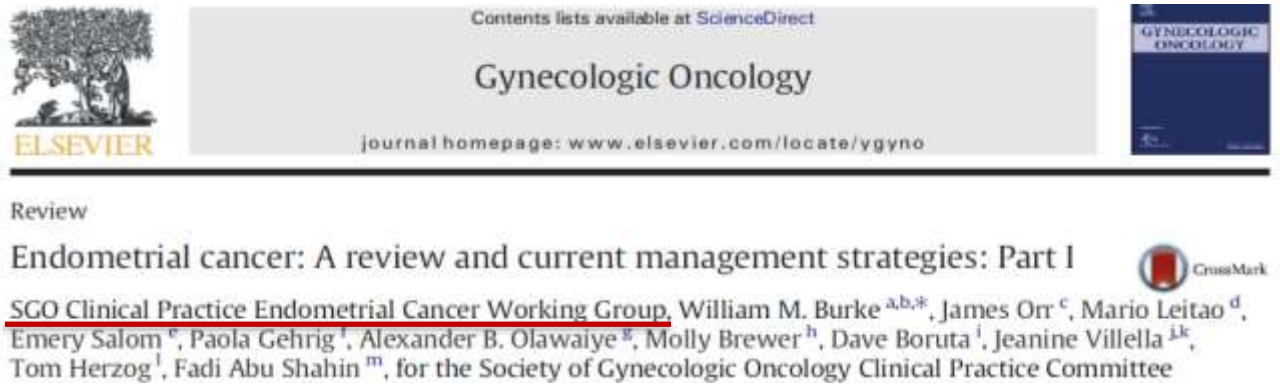
Albright. Primary cytoreductive surgery for advanced stage endometrial cancer. Am J Obstet Gynecol 2021.

The ability to achieve maximal or optimal cytoreduction had **no variation according to histology**

IEO European Institute of Oncology

Albright et al. Am J Obstet Gynecol 2021

A SHIFT OF TREATMENT ALGORITHM



Contents lists available at ScienceDirect

Gynecologic Oncology

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

Review

Endometrial cancer: A review and current management strategies: Part I

SGO Clinical Practice Endometrial Cancer Working Group, William M. Burke [a,b,*], James Orr [c], Mario Leitao [d], Emery Salom [e], Paola Gehrig [f], Alexander B. Olawaiye [g], Molly Brewer [h], Dave Boruta [i], Jeanine Villella [j,k], Tom Herzog [l], Fadi Abu Shahin [m], for the Society of Gynecologic Oncology Clinical Practice Committee

The treatment paradigm for advanced FIGO stage III and IV endometrial carcinoma has shifted in 2014 to a multimodality approach that includes surgery, chemotherapy, and radiation therapy, with cytoreduction being the most crucial aspect.

In all studies report cytoreduction resulted as an independent prognostic factor for Overall Survival

IEO
European Institute of Oncology