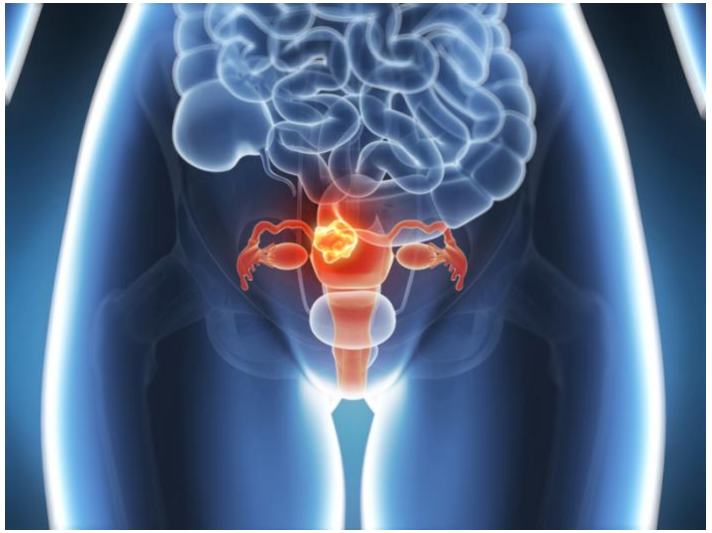
TREATMENT OF EARLY STAGE ENDOMETRIAL CANCER

Dr Shunit Armon

SZMC, Jerusalem



ENDOMETRIAL CANCER

- Introduction
- Surgical Staging
- Sentinel lymph node biopsy
- Adjuvant treatment
- Conservative treatment – fertility preservation

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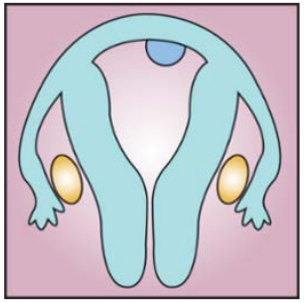
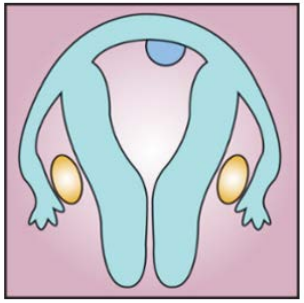
INTRODUCTION



- Endometrial cancer is the most common gynecological cancer in developed countries.
- The number of newly diagnosed cases in Europe was nearly 100,000 in 2012
  - 13.6 per 100,000 women.
  - Cumulative risk of a diagnosis of endometrial cancer is 1.71%.
- More than 90% of cases of endometrial cancer occur in women >50 years of age
  - Median age at diagnosis of 63 years.
- 4% of women with endometrial cancer are younger than 40 years old many of whom still wish to retain their fertility.

INTRODUCTION



- The majority of endometrial cancers are diagnosed early
  - 80% in stage I
  - Good prognosis- 5-year survival rates > 95%.

- Approximately 10% -15% of these patients will have metastatic nodal disease.

- Nearly 15% will be deemed to have grade 1 tumors preoperatively on office biopsy or D&C will actually have higher-grade disease on final pathologic review after hysterectomy

CLINICO-PATHOLOGIC SUBTYPES

TYPE I

- Endometrioid
- Estrogen related
- Associated with obesity
- More likely to die of cardiovascular disease than cancer and lifestyle issues need to be addressed when treating these women
- 70% are confined to the corpus at the time of diagnosis.
- 5-year survival 83%

TYPE II

- Non-endometrioid
- Non-estrogen related
- More likely to be older, nonwhite, multiparous, current smokers, non-obese.
- at least 1/2 have already spread beyond the corpus at the time of diagnosis.
- 5-year survival –
  - 62% for clear cell carcinomas
  - 53% for serous cancers

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- Sentinel lymph node biopsy
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- Conservative treatment – fertility preservation

ESMO–ESGO–ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up ☆

Nicoletta Colombo [a,*], Carien Creutzberg [b], Frederic Amant [c,d], Tjalling Bosse [e], Antonio González-Martín [f,g], Jonathan Ledermann [h], Christian Marth [i], Remi Nout [j], Denis Querleu [k,l], Mansoor Raza Mirza [m], Cristiana Sessa [n], The ESMO–ESGO–ESTRO Endometrial Consensus Conference Working Group [1]

Table 1
Levels of evidence and grades of recommendation.

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised 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 recommendation	
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

By permission of the Infectious Diseases Society of America-United States Public Health Service Grading System [9].

ESGO European Society of Gynaecological Oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

PRE-OPERATIVE WORK UP

MANDATORY

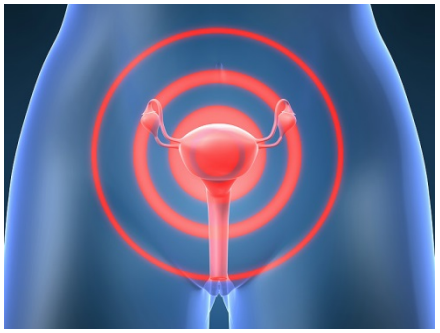
- Family history
- General assessment and inventory of comorbidities
  (Geriatric assessment)
- Clinical examination, pelvic examination
- TV/TR ultrasound
- Pathology assessment-
  - histotype and grade

OPTIONAL

- Additional imaging is considered according to the clinical situation.
- In clinically advanced endometrial cancer:
  - CT scan and/or PET-CT
- In apparent stage I endometrial cancer
  - MRI may be useful to complete information regarding myometrial invasion

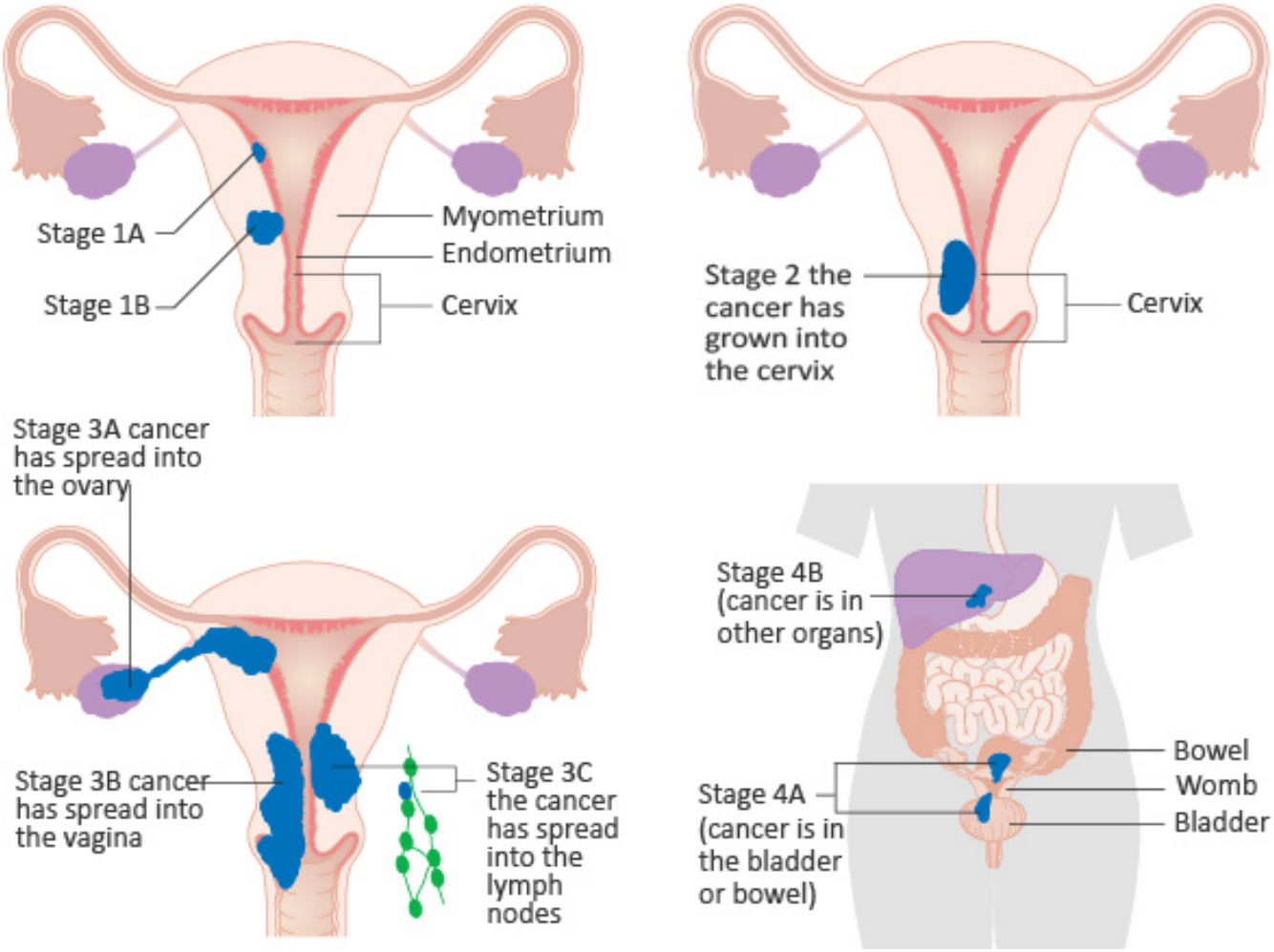
Level of evidence: V
Strength of recommendation: A

SURGICAL STAGING

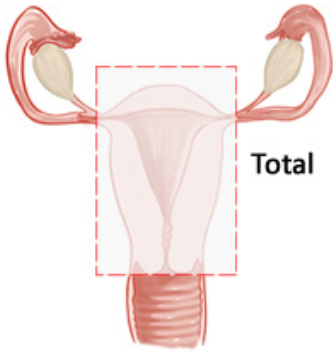


- Total hysterectomy with bilateral salpingo-oophorectomy and complete surgical staging by lymph node dissection has been the recommended standard of care for endometrial cancer.

2009 FIGO Surgical Staging for Carcinoma of the Endometrium



HYSTERECTOMY



- Standard surgery is total hysterectomy with BSO without vaginal cuff.

- Minimally invasive surgery is recommended in the surgical management of low-and intermediate risk endometrial cancer

Level of evidence: I

Strength of recommendation: A

- No significant adverse effect of a laparoscopic approach on:
  - Overall survival
  - disease-free survival
  - cancer-related survival

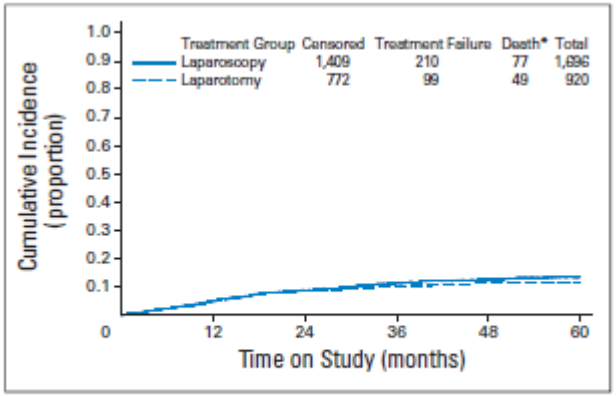


Fig 2. Cumulative incidence of recurrence by randomly assigned treatment group. (*) Deaths prior to recurrence.

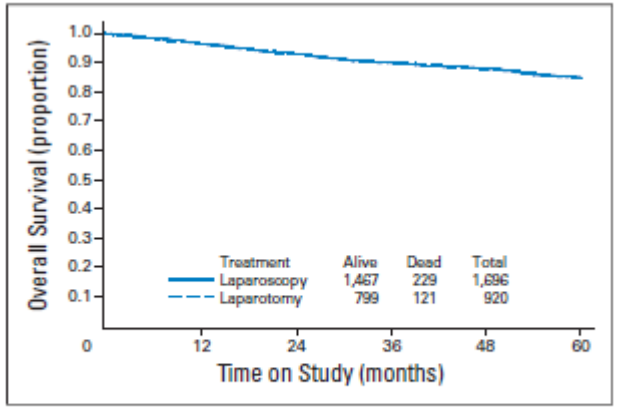
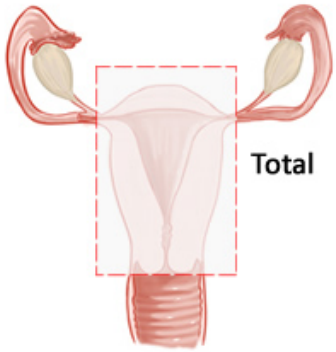


Fig 3. Overall survival by randomly assigned treatment group.

Recurrence and Survival After Random Assignment to Laparoscopy Versus Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group. LAP2 Study 2012.

HYSTERECTOMY



Minimally invasive surgery can be considered in the management of high-risk endometrial cancer.

Level of evidence: IV

Strength of recommendation: C

Consensus: 100% yes (37 voters)

- Retrospective, multi-institutional trial of patients with high grade endometrial cancer
- Women staged by minimally invasive techniques:
  - Fewer complications
  - Similar survival outcomes compared with those staged by laparotomy.

- Vaginal hysterectomy

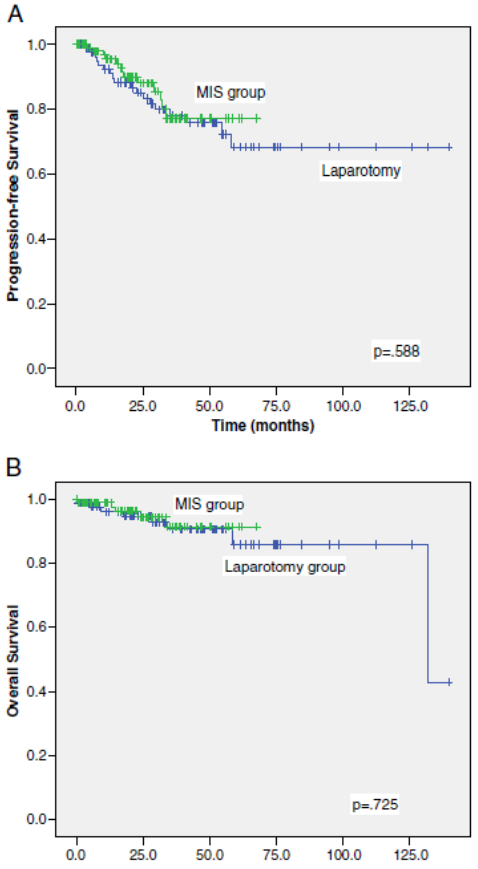
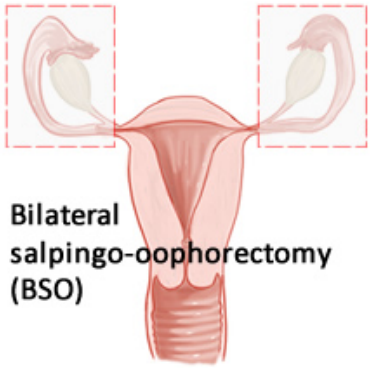


Fig. 1. A: Progression free survival in stage I/II patients. B. Overall survival in stage I/II patients.

BSO



- Rationale:
  - To rule out ovarian metastases
  - To prevent ovarian cancer

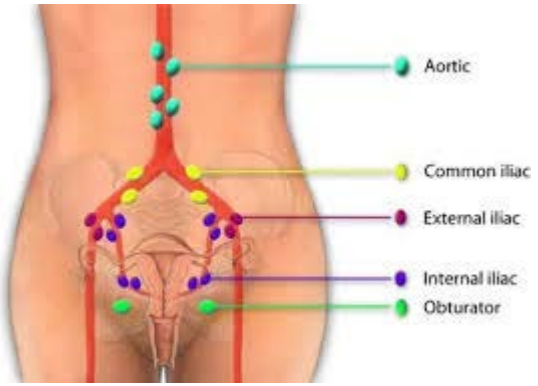
- Ovarian preservation can be considered:
  - Patients younger than 45 years old
  - G1 Endometrioid adenocarcinoma
  - Myometrial invasion <50%
  - No obvious ovarian or other extra-uterine disease

- Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk (e.g. BRCA mutation, LS, etc.).

Level of evidence: IV
Strength of recommendation: B
Consensus: 100% yes (37 voters)

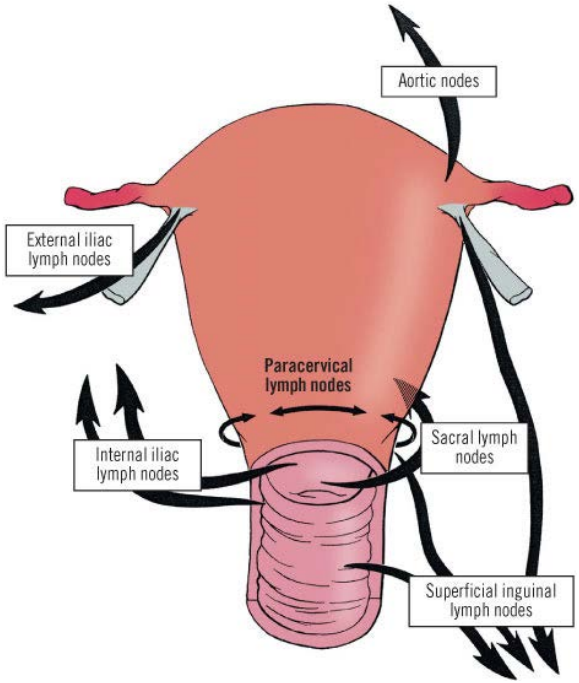
LYMPHADENECTOMY

- The purpose of lymphadenectomy:



1. To assign a surgical stage, and provide prognostic information
2. To treat patients with positive nodes
3. To direct adjuvant radiation

- Controversy-
  - The role of lymphadenectomy in early endometrial cancer is unclear
  - Indications
  - Anatomic extent
  - Therapeutic value



RISK OF LYMPH NODE METASTASIS

Table 9.9 Grade, Depth of Invasion, and Pelvic Nodal Metastasis of Endometrial Carcinoma

	Histologic Grade		
Depth of Myometrial Invasion	G1 (n = 180)	G2 (n = 288)	G3 (n = 153)
Endometrium only (n = 86)	0/44 (0%)	1/31 (3%)	0/11 (0%)
Inner third (n = 281)	3/96 (3%)	7/131 (5%)	5/54 (9%)
Middle third (n = 115)	0/22 (0%)	6/69 (9%)	1/24 (4%)
Outer third (n = 139)	2/18 (11%)	11/57 (19%)	22/64 (34%)

Reproduced from **Creasman WT, Morrow CP, Bundy BN, et al**. Surgical pathologic spread patterns of endometrial cancer: A Gynecologic Oncology Group study. *Cancer*. 1987;60:2035–2041, with permission.

- Extent of LND:
  - The clinicopathologic factor most strongly related to the existence of para-aortic lymph node metastasis was positive pelvic lymph node metastasis.
  - 96.2% (101/105 cases) had negative para-aortic nodes when the pelvic nodes were negative.
  - When the pelvic nodes were positive, 48% also had positive para-aortic nodes.

Nomura H; Int J Gynecol Cancer. 2006.
Mariani A; Gynecol Oncol. 2006.

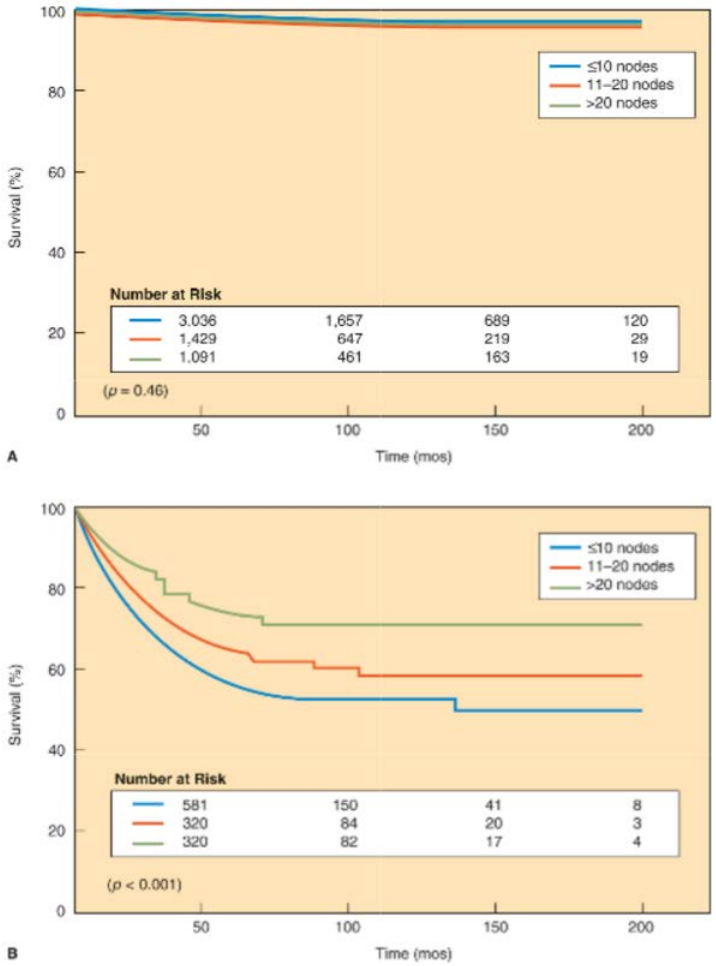
Predictive Models for Selective Staging

- The most commonly used- the "**Mayo algorithm**"
- This algorithm exempts from lymphadenectomy:
  - Patients with FIGO grade 1 to 2 tumors
  - Endometrioid histology
  - Greatest surface dimension of <2 cm
  - Myometrial invasion <50%
  - No intraoperative evidence of macroscopic disease
- 98.2% negative predictive value NPV

LYMPHADENECTOMY

- Retrospective studies showed a survival advantage in patients undergoing systematic LND compared with patients undergoing standard surgery
- The definition of an adequate lymphadenectomy has not been standardised.
- Lymph node counts have become a marker for adequacy of lymph node evaluation in a variety of solid tumour disease sites.
- Patients had improved survival when at least 10-12 lymph nodes were removed.
- Adequacy of a LND: >10 nodes.

Cragun JM. J Clin Oncol. 2005.
D.C Smith. Int J Gynecol Cancer 2008



Survival for patients with (A) low-risk endometrial cancer and (B) high-risk endometrial cancer versus extent of lymphadenectomy.
Chan J, *Therapeutic role of lymph node resection in endometrioid corpus cancer: A study of 12,333 patients. Cancer. 2006.*

INTERMEDIATE AND HIGH RISK

- Overall survival was significantly longer in the pelvic+para-aortic LND group than in the pelvic LND group in (p=0·0009)
- Overall survival was not related to lymphadenectomy type in low-risk patients.
- Analysis of 328 patients with intermediate/ high risk who were treated with adjuvant RTx or Chemotherapy showed that patient survival improved with pelvic and para-aortic lymphadenectomy and with adjuvant chemotherapy independently of one another.

SEPAL study; *Yukiharu Todo, Lancet 2010*

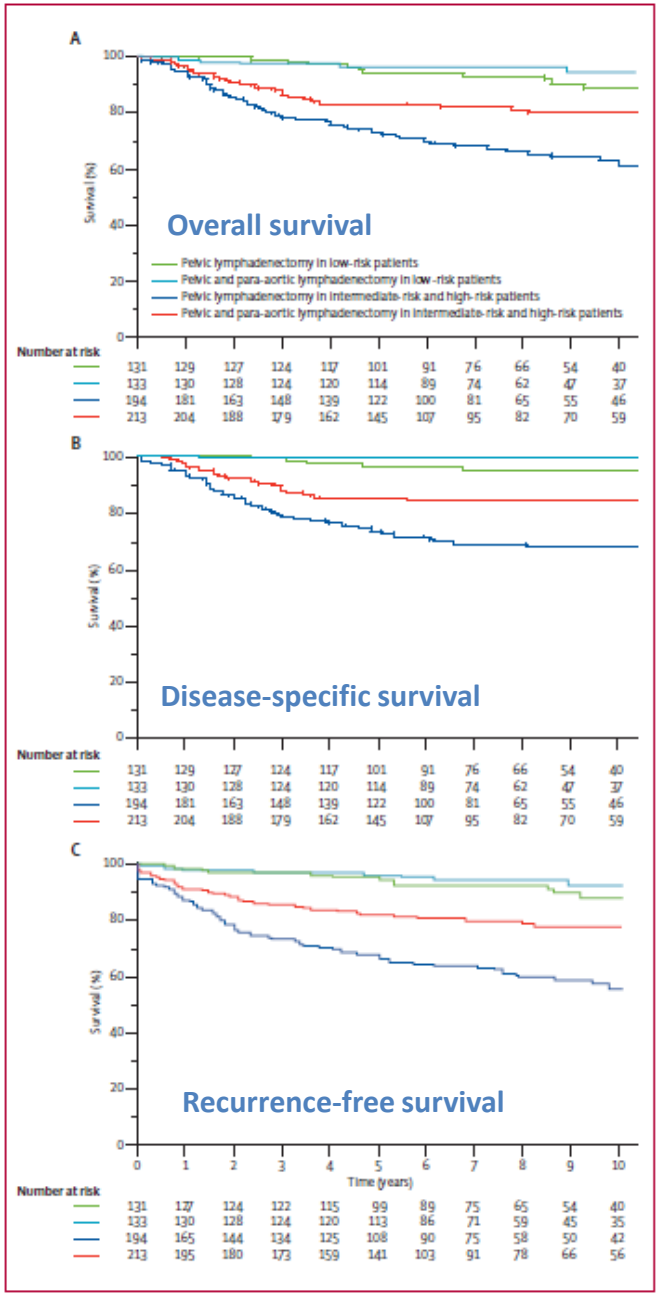


Figure 3: Kaplan-Meier analysis of overall (A), disease-specific (B), and recurrence-free (C) survival for patients with endometrial carcinoma according to type of lymphadenectomy and risk of recurrence

LYMPHADENECTOMY- morbidity

- Surgical related morbidity:
  - Increased mean operative time
  - Increased mean estimated blood loss
  - Longer postoperative hospitalization

- Postoperative morbidity- lymphedema.
- 13% incidence of lymphedema in 1243 patients treated for endometrial cancer
- lymphedema is common- 1:8 women following endometrial cancer

Incidence, risk factors and estimates of a woman's risk of developing secondary lower limb lymphedema and lymphedema-specific supportive care needs in women treated for endometrial cancer Vanessa L. Beesley 2015

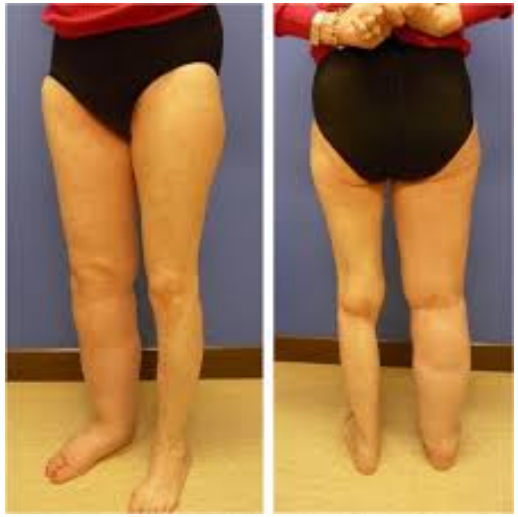


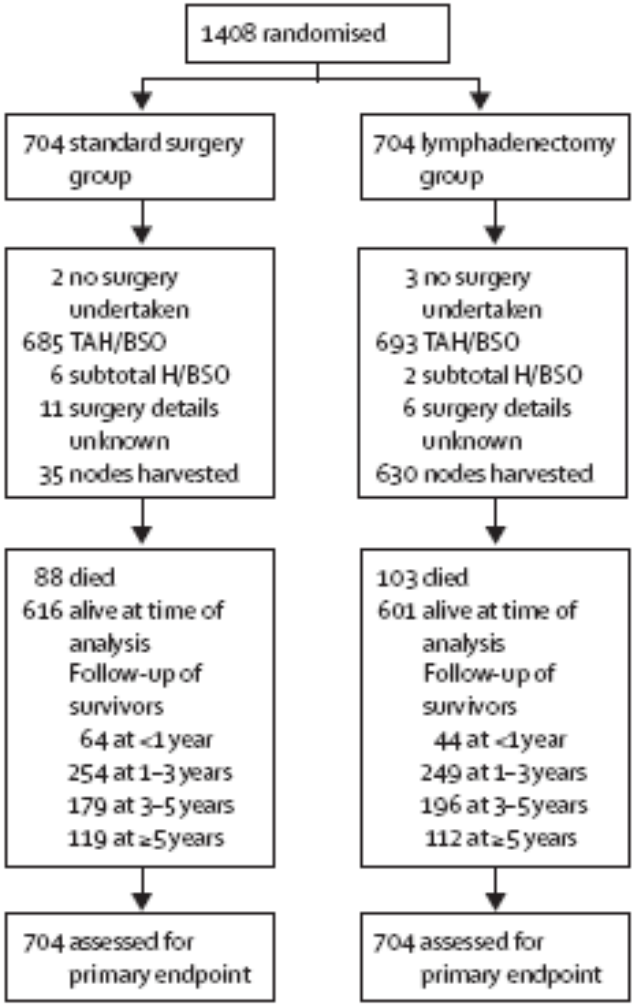
Table 3
Probability an individual woman will develop lower limb lymphedema for combinations of risk factors.

	Number of lymph nodes removed			
Number of other risk factors[a]	0	1–5	6–14	≥15
None	2%	7%	13%	30%
One only	4%	11%	19%	41%
Two only	5%	15%	25%	52%
All three	8%	22%	36%	62%

Note: Greyscale indicates level of risk: darker equals higher risk.
[a] Includes adjuvant chemotherapy, adjuvant radiation and nonsteroidal anti-inflammatory drug use (pre-diagnosis).

Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study Lancet 2009

Clinical stage 1 disease



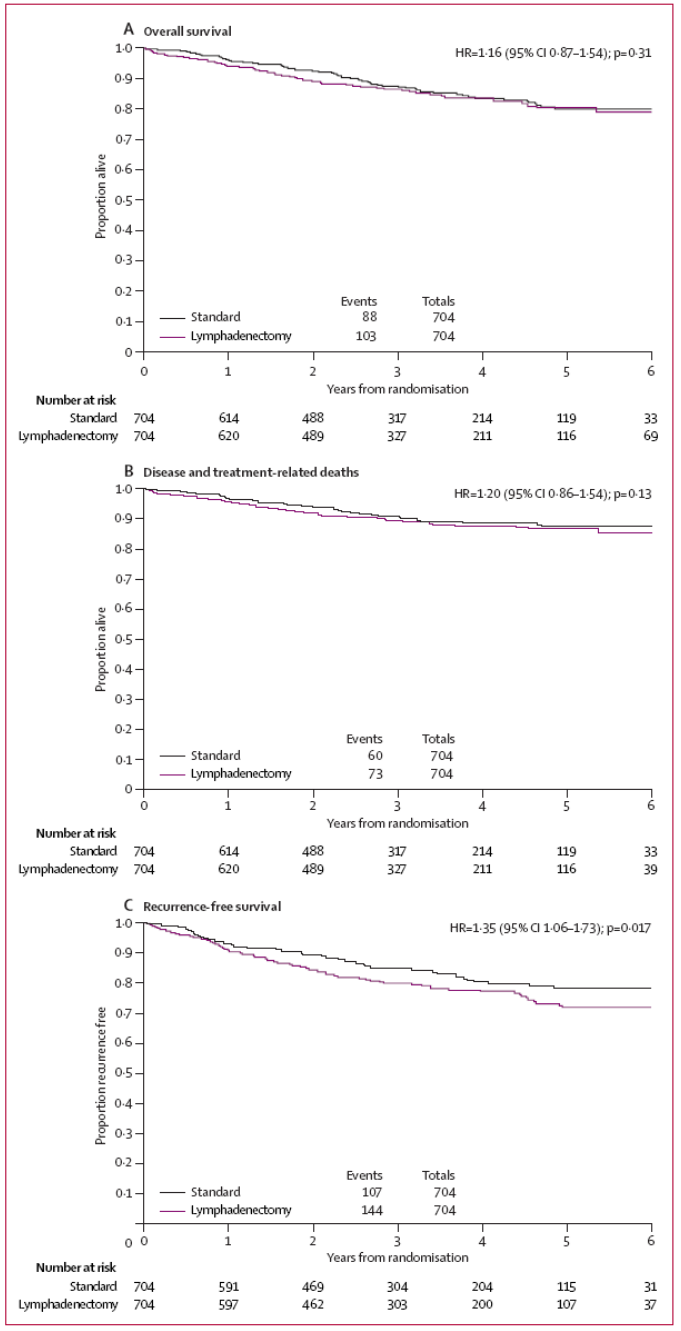


Figure 3: Overall survival (A), disease and treatment-related deaths (B), and recurrence-free survival (C) by treatment group

Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial
J Natl Cancer Inst 2008

Table 6. Univariate and multivariable analysis of disease-free survival and overall survival data by different prognostic factors*

	Univariate				Multivariable			
	Disease-free survival		Overall survival		Disease-free survival		Overall survival	
Prognostic factor	**HR (95% CI)**	***P*†**	**HR (95% CI)**	***P*†**	**HR (95% CI)**	***P*†**	**HR (95% CI)**	***P*†**
Treatment arm								
No lymphadenectomy	1.0 (referent)	.68	1.0 (referent)	.50	1.0 (referent)	.41	1.0 (referent)	.59
Lymphadenectomy	1.10 (0.70 to 1.71)		1.20 (0.70 to 2.07)		1.20 (0.75 to 1.91)		1.16 (0.67 to 2.02)	
Age, y								
≤65	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
>65	1.74 (1.12 to 2.73)	.02	2.69 (1.57 to 4.63)	<.001	1.49 (0.93 to 2.38)	.09	2.85 (1.65 to 4.92)	<.001
Tumor grade								
1–2	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
3	1.75 (1.12 to 2.73)	.01	2.04 (1.19 to 3.50)	.01	1.44 (0.90 to 2.31)	.13	2.03 (1.17 to 3.52)	.01
Myometrial invasion, %								
≤50	1.0 (referent)		1.0 (referent)		1.0 (referent)			
>50	1.66 (1.03 to 2.68)	.03	1.31 (0.74 to 2.34)	.36	1.35 (0.82 to 2.22)	.24	Not included	
Tumor stage								
I–II	1.0 (referent)		1.0 (referent)		1.0 (referent)		1.0 (referent)	
III–IV	2.56 (1.56 to 4.19)	<.001	2.44 (1.34 to 4.45)	.007	2.03 (1.18 to 3.50)	.01	2.14 (1.17 to 3.93)	.01

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- Adjuvant treatment
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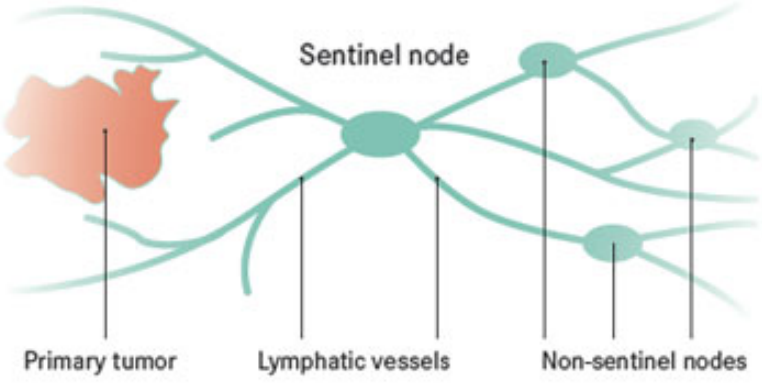
- Based on the current standard of treatment, surgeons are faced with the dilemma of "understaging" versus "overtreating."

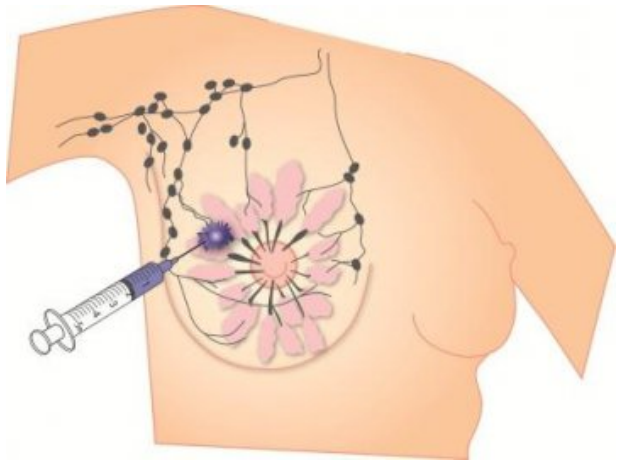
- The appeal of SLN mapping lies in the possible avoidance of "overstaging" via lymph node dissection of normal/negative nodes.

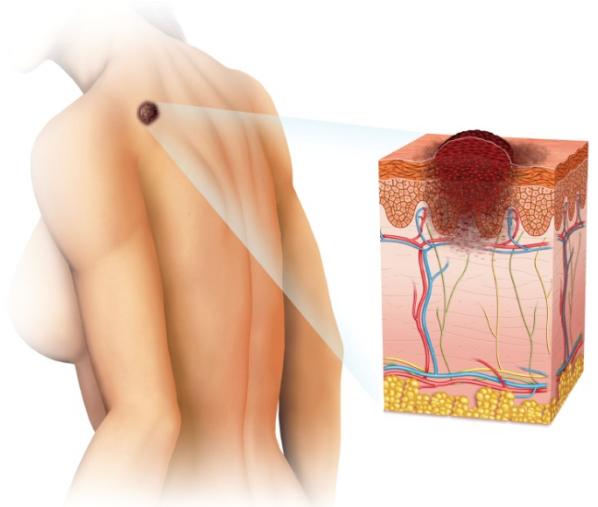
- Enhanced precision in finding micrometastasis with pathologic ultrastaging of SLNs.

SENTINEL NODE



- Sentinel lymph node mapping is an image guided procedure that is well established in the treatment of cancers, such as melanoma and breast cancer.
- This approach is based on the concept that lymph drains in an orderly pattern away from the tumor through the lymphatic system.
- If the SLN, or first node, is negative for metastasis, then the ensuing nodes should also be negative.
- Gould et al coined the term *sentinel node* in 1960 with his observations of carcinoma of the parotid gland.



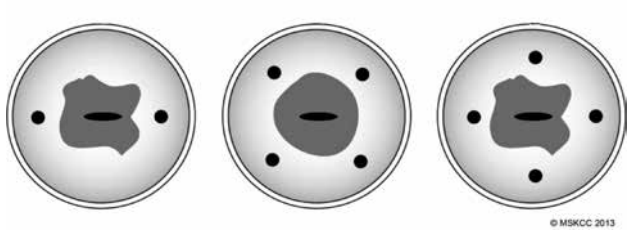


Gould EA, Winship T, Philbin PH, Kerr HH. Observations on a"sentinel node" in cancer of the parotid.
Cancer 1960;13:77-78

TECHNIQUE

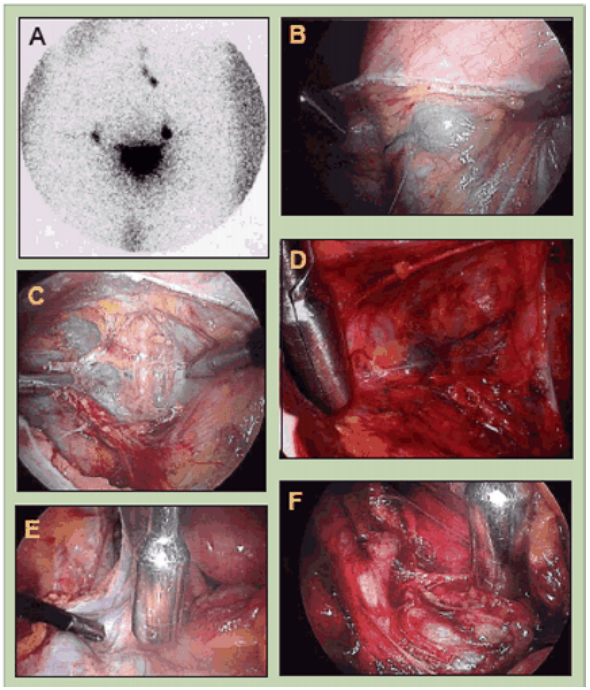
Injection site-

1) uterine subserosal
2) cervical
3) endometrial via hysteroscopy

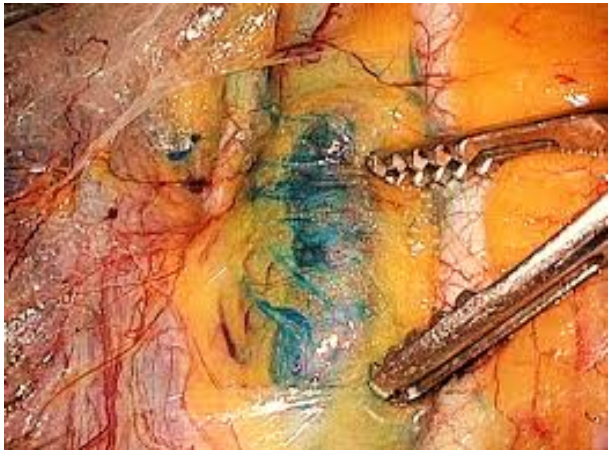


TECHNIQUE - TRACER

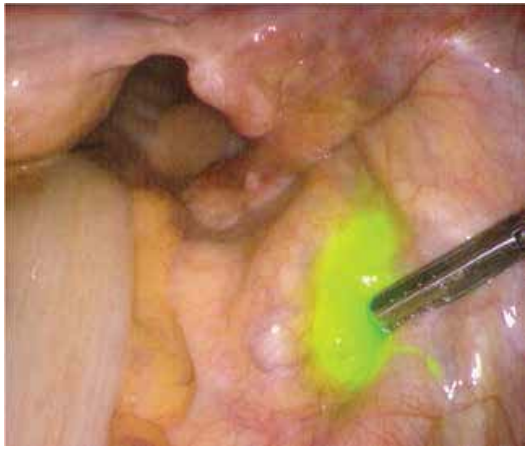
Lymphoscintigraphy-
radiolabeled colloid-
technetium-99

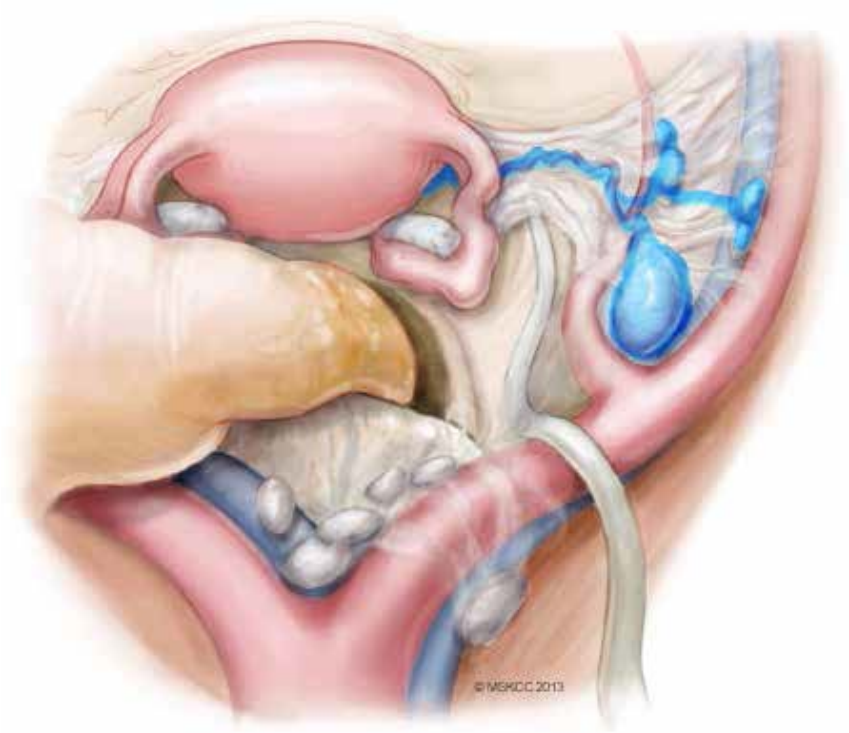


Colored Dye Injection-
Isosulfan blue 1%
Methylene blue 1%
Patent blue 2.5%



Fluorescent SLN Imaging With Indocyanine Green




© MSKCC 2013

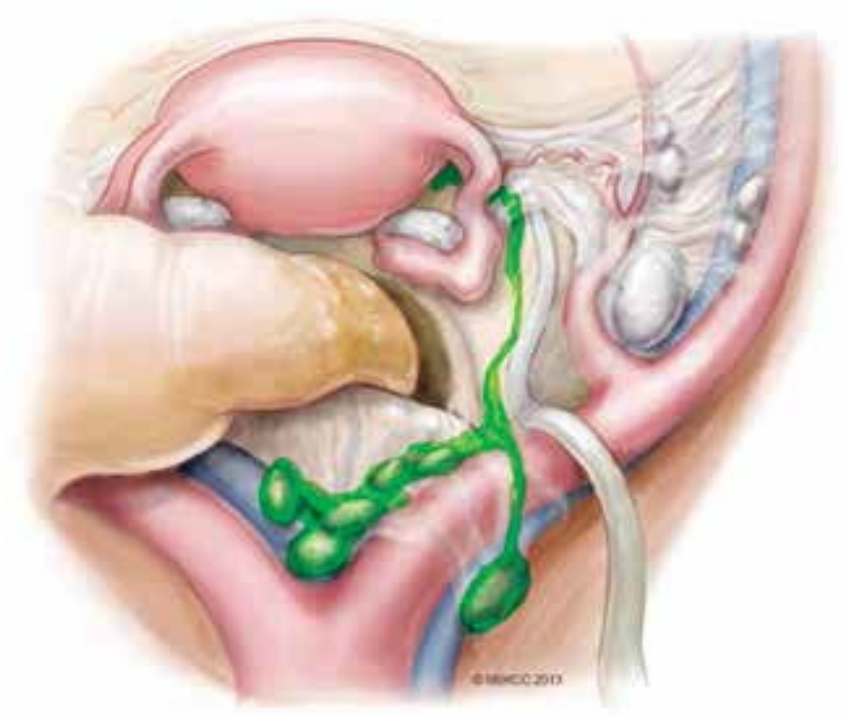


Table 1
Sentinel lymph node detection rates by injection method.

Author	N	Tracer used	Injection site	Overall detection rate (%)	Bilateral detection rate (%)
Ballester	125	Blue dye + technetium	Cervix	89	62
Bats	43			70	37
Niikura[a]	45			96	80
Robova	67		Corpus	73	NR
Delaloye	60			82	37
Niikura[a]	55			78	49
How	100		Cervix (deep)	92	66
Lopez-de la Manzanara	50			92	34
Mucke[b]	31			90	52
Sawicki	70		Cervix + Corpus	97	76
Barlin	498	Blue dye	Cervix	81	51
Desai	120			86	52
Vidal	66			62	35
Mais	34			62	NR
Lopes	40		Corpus	78	NR
Torné	74	Technetium	Corpus	74	19
Solima	59			95	NR
Holloway	35	Blue dye + indocyanine green	Cervix	100	100

Detection Rate:

Proportion of patients with at least one SLN detected

Sentinel lymph node procedure in endometrial cancer: A systematic review and proposal for standardization of future research. Beatrice Cormier et al. Communities of Practice (CoP) Group of the Society of Gynecologic Oncology of Canada (GOC) Gynecologic Oncology 2015

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Holloway	35	Blue dye + indocyanine green	Cervix	100	100

Detection Rate:

Proportion of patients with at least one SLN detected

- Cervical injection: 62%- 100%
- Corporeal injection: 73%- 95%.

- All studies with n ≥ 100 had overall detection rates of >80%.

Sentinel lymph node procedure in endometrial cancer: A systematic review and proposal for standardization of future research. Beatrice Cormier et al. Communities of Practice (CoP) Group of the Society of Gynecologic Oncology of Canada (GOC) Gynecologic Oncology 2015

Detection Rate- Indocyanine Green

Table 5
SLN mapping with ICG fluorescence imaging (intracervical injection).

	N	Overall detection rate n (%)	Bilateral detection rate n (%)	Lymph node positivity rate n (%)
Rossi 2012 [23]	20*	17/20 (85%)	12/20 (60%)	3/20 (15%)
Rossi 2013 [25]	17	14/17 (82%)	8/17 (47%)	3/17 (18%)
Holloway 2012 [24]	35	35/35 (100%)	34/35 (97%)	10/35 (29%)
Sinno 2014 [26]	38	34/38 (89%)	30/38 (79%)	4/38 (11%)
Jewell 2014 [27]	197*	188/197 (95%)	156/197 (79%)	NR
Plante	50*	48/50 (96%)	44/50 (88%)	11/50 (22%)
Total	357	335/357 (94%)	284/357 (80%)	31/153 (20%)

NR: not reported.
* Studies including endometrial and cervical cancer.

Per side:

Sensitivity 93.3%

Specificity 100%

NPV 98.7%

Sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial cancer. A pilot study and review of the literature.
Marie Plante. Gynecologic Oncology 2015.

- Standard lymph node assessment during the surgical staging of endometrial cancer involves sectioning the node once along the longitudinal axis and staining it with H&E to determine if it contains metastatic tumor cells.

- For sentinel lymph nodes enhanced pathologic assessment is performed if the initial H&E stain is negative.

- Ultrastaging involves additional sectioning and staining of the SLN with H&E and immunohistochemistry to examine the SLN for low-volume metastatic disease.

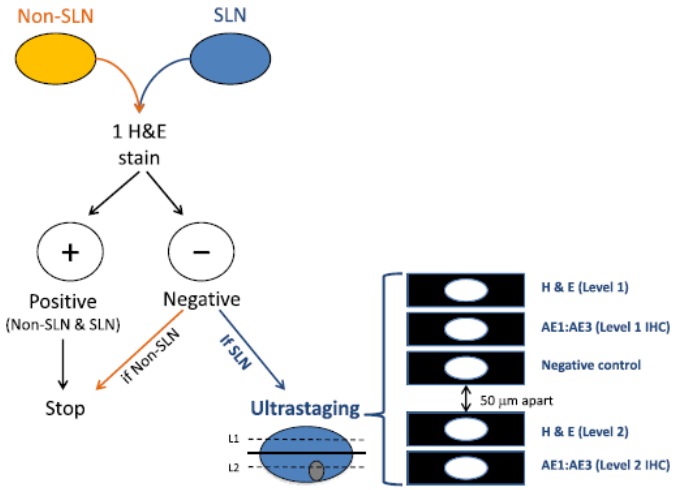


FIGURE 1. Memorial Sloan-Kettering Cancer Center's pathologic ultrastaging algorithm for sentinel lymph nodes

ULTRA-STAGING

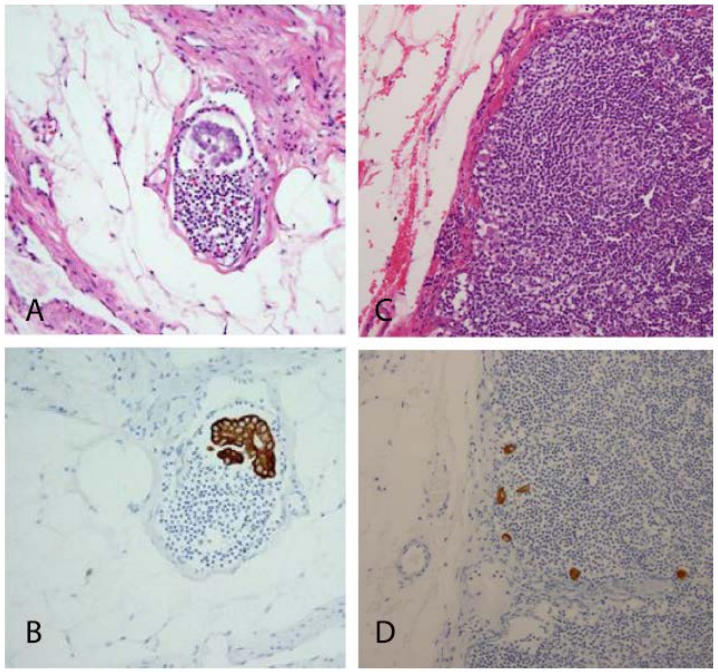
Lymph node metastases are classified according to their size:

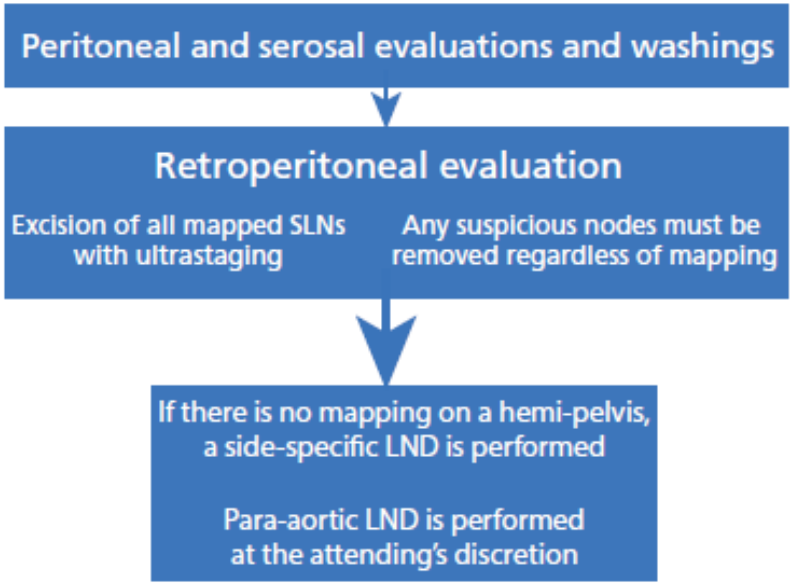
- Macrometastases are larger than 2 mm
- Micrometastases (MM) are 0.2–2 mm
- Isolated tumor cells (ITC) are <0.2 mm

} low-volume metastases

Consensus, Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast.

G.F. Schwartz, Cancer 2002.





- Satisfactory SLN mapping in endometrial cancer requires adherence to a surgical SLN algorithm and goes beyond just the removal of blue SLNs.
- Removal of any suspicious node along with side-specific lymphadenectomy for failed mapping are an integral part of this algorithm.

Table 3 Performance of SLN Mapping Alone Compared With the Algorithm for All Patients

	LN Positive	LN Negative	Total	SLN Alone	Calculation	Result
SLN positive	40	0	40	Sensitivity	40/47	85.1
SLN negative	7	354	361	Negative predictive value	354/361	98.1
	47	354	401	False-negative rate	7/47	14.9
	LN Positive	**LN Negative**	**Total**	**Algorithm**	**Calculation**	**Result**
Algorithm positive	53	0	53	Sensitivity	53/54	98.1
Algorithm negative	1	420	421	Negative predictive value	420/421	99.8
	54	420	474	False-negative rate	1/54	1.9

Barlin JN. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes.
Gynecol Oncol 2012

RECURRENCE SLN VS. LND

Table 4
Recurrences.

	SLN cohort N = 642	LND cohort N = 493	P
Disease progression/recurrence within 3 years, N (%)	19 (3.0)	14 (2.8)	0.35
3-year disease-free survival, % (95% CI)	94.9 (92.4–97.5)	96.8 (95.2–98.5)	
Route of first recurrence, N			
Hematogenous only	4	–	
Hematogenous and lymphatic	–	1	
Hematogenous and peritoneal	1	1	
Hematogenous, lymphatic and peritoneal	1	1	
Lymphatic only	2	2	
Lymphatic and peritoneal	1	–	
Vaginal only	9	4	
Vaginal and peritoneal	–	1	
Peritoneal only	1	4	

SLN, sentinel lymph node; LND, lymph node dissection.

Ane Gerda Zahl Eriksson; Gynecologic Oncology 2016
Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion.

LYMPHADENECTOMY- RECOMMENDATION

1. Lymphadenectomy is a staging procedure and allows tailoring of adjuvant therapy
Level of evidence: III
Strength of recommendation: B
Consensus: 100% yes (37 voters)

2. Patients with low-risk endometrioid carcinoma (grade 1 or 2 and superficial myometrial invasion <50%) have a low risk of lymph node involvement, therefore, lymphadenectomy is not recommended for these patients
Level of evidence: II
Strength of recommendation: A
Consensus: 100% yes (37 voters)

3. patients with intermediate risk (deep myometrial invasion >50% or grade 3 superficial myometrial invasion <50%), data have not shown a survival benefit.
Lymphadenectomy can be considered for staging purposes in these patients.
Level of evidence: II
Strength of recommendation: C
Consensus: 100% yes (37 voters)

4. For patients with high risk (grade 3 with deep myometrial invasion > 50%), lymphadenectomy should be recommended
Level of evidence: IV
Strength of recommendation: B
Consensus: 73.0% (27) yes, 8.1% (3) abstain, 18.9% (7) no (37 voters)

ENDOMETRIAL CANCER

- Introduction
- Surgical Staging
- Sentinel lymph node biopsy
- **Adjuvant treatment**
- Conservative treatment – fertility preservation

RECURRENCE

- Pattern of recurrence:
  - Localized vaginal recurrence
  - locoregional pelvic recurrence
  - Upper abdominal relapse
  - Distant metastases to the lung, bone, and brain.

- Adjuvant treatment modalities aimed at preventing recurrence include:

  Radiotherapy-
  - Pelvic EBRT is designed to irradiate sites of potential micrometastatic local cancer spread: the upper vagina (the cervix cuff excision margin, or vaginal vault), parametrial ligaments, and primary draining lymph nodes.
    - Treatments typically involve 25–28 EBRT treatments delivered over 5–6 weeks.
  - Vaginal vault brachytherapy is designed to treat only the upper vagina.
    - Treatment typically involves 1-5 internal vaginal radiotherapy treatments, irradiating a much smaller volume of the patient than with EBRT.

  Chemotherapy

- Although the 5-year survival rate for primary stage I disease is approximately 80%-90%, most patients with recurrent or metastatic disease unfortunately respond poorly to treatment.

ADJUVANT TREATMENT

- The majority of patients with endometrial cancer have a low risk of recurrence and are managed by surgery alone.

- Prognostic factors include:
  - Age
  - FIGO stage
  - Grade
  - Depth of myometrial invasion
  - Tumour type (endometrioid versus serous and clear cell)
  - LVSI

- Risk groups have been devised based on clinico-pathological prognostic factors to identify patients at risk of recurrence who may benefit from adjuvant therapy.

Uterine factors

- Histologic cell type
- Grade
- Depth of myometrial invasion
- Occult extension to the cervix
- Vascular space invasion

Extrauterine factors

- Adnexal metastases
- Other extrauterine intraperitoneal spread
- Positive peritoneal cytology,
- Pelvic lymph node metastases
- Para-aortic lymph node involvement

When surgical staging is inadequately performed, patients can be subjected to unnecessary adjuvant therapy, such as pelvic radiation therapy and its associated side effects.

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, grade 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.

LOW RISK

- Stage I
- Endometrioid, grade 1-2
- <50% myometrial invasion,
- LVSI negative

Local recurrence <5%

No adjuvant treatment is recommended

Level of evidence: I

Strength of recommendation: A

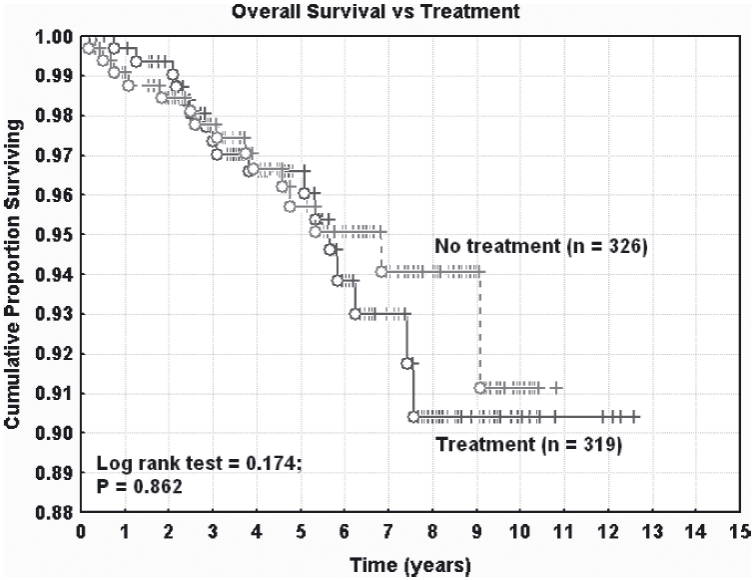


FIGURE 1. Overall survival rate of patients treated with surgery alone (control) and patients treated with surgery and postoperative vaginal irradiation (treatment). There was no significant difference between the 2 groups.

Sorbe.
Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study.
2009.

PORTEC 2000

- Stage 1 EAC
  - G1 + ≥ 50% myometrial invasion
  - G2 + any invasion
  - G3 +<50% invasion
- TAH BSO without lymphadenectomy
- 715 patients
- Randomised:
  - Pelvic RTx
  - No treatment.

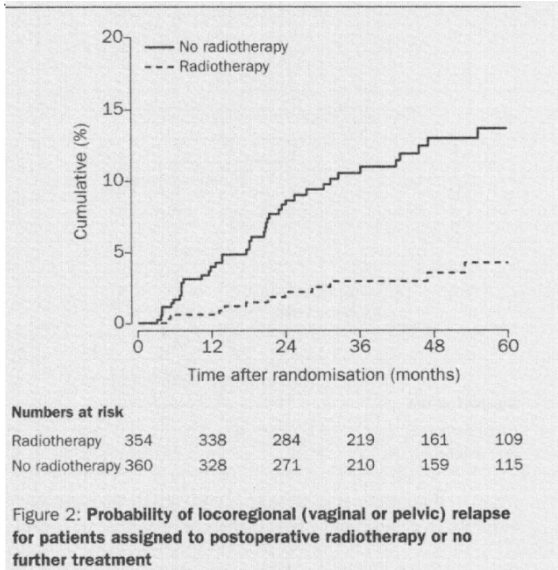


Figure 2: **Probability of locoregional (vaginal or pelvic) relapse for patients assigned to postoperative radiotherapy or no further treatment**

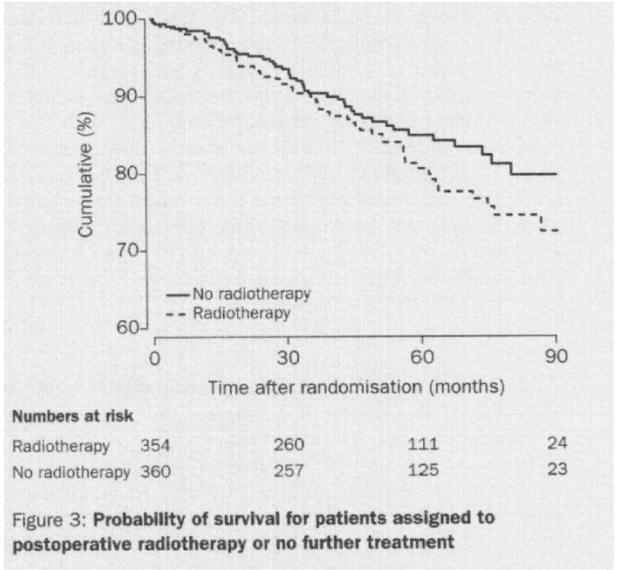


Figure 3: **Probability of survival for patients assigned to postoperative radiotherapy or no further treatment**

EBRT **reduced** the risk of pelvic **recurrence**

-- High-intermediate-risk patients- 2/3 risk factors.

No overall survival benefit

Increased risk of toxicity (predominantly gastrointestinal)

RECURRENCE		
	No Tx	RT
Entire group	14%	4%
HIR	20%	5%

GOG 99 2004

- 448 patients -"intermediate risk" EAC
- surgical staging lymphadenectomy was mandatory
- High intermediate risk (HIR) subgroup:
  - G2/3
  - LVSI
  - outer 1/3 myometrial invasion

≥50 2 risk factors
≥ 70 with any risk factor

- Low intermediate risk (LIR) subgroup- all other participants.

RECURRENCE			
	No Tx	RT	RH; P value
Entire group	12%	3%	0.42, 0.007
HIR	26%	6%	RH=0.42

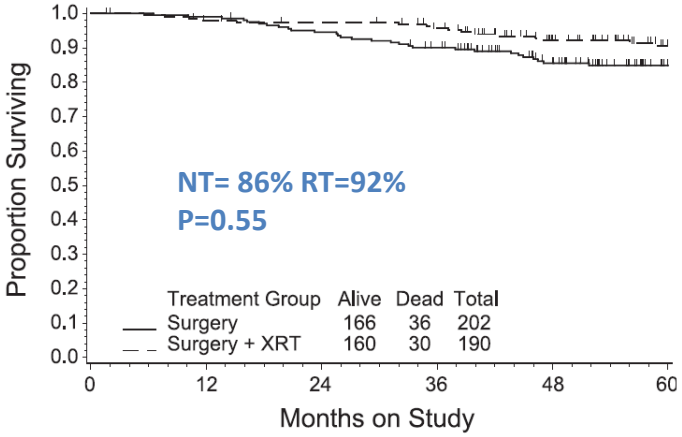


Fig. 2. Survival by randomized treatment group.

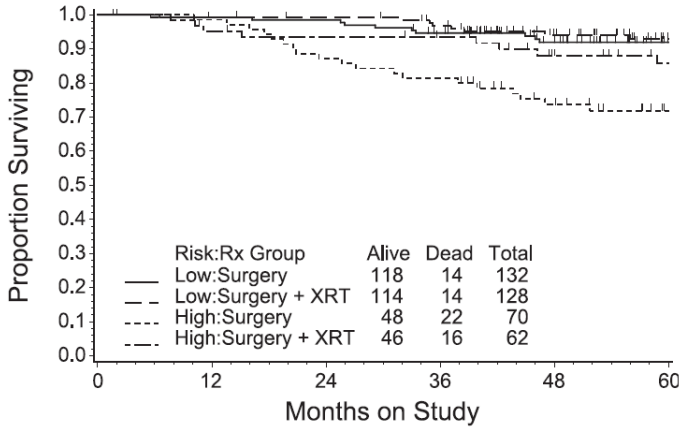
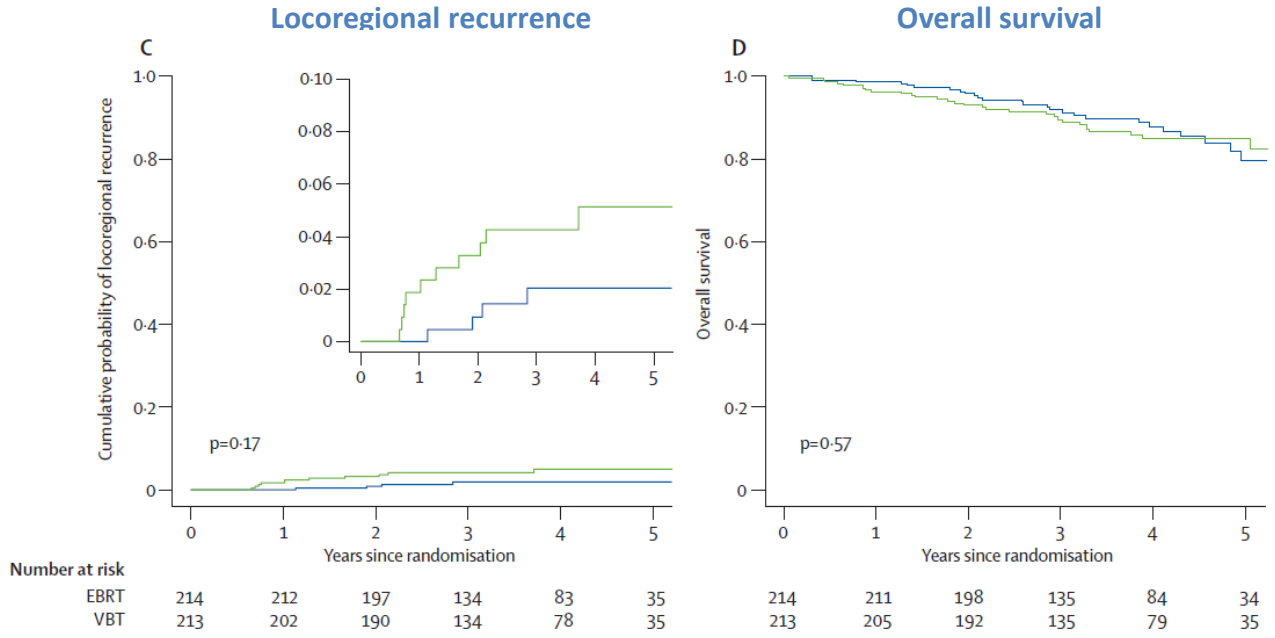


Fig. 4. Survival by randomized treatment group and risk group.

- Adjunctive RT in early stage **intermediate risk** endometrial carcinoma **decreases the risk of recurrence**
- Risk reduction was mainly caused by prevention of local (vaginal) recurrence
- **Limited** to patients whose risk factors fit a **high intermediate risk** definition.

PORTEC2 2010

- 427 patients with stage I or IIA EC with features of HIR
- Randomised:
  - Pelvic EBRT (46 Gy in 23 fractions)
  - Vaginal Brachytherapy



- VBT is effective in ensuring vaginal control, with fewer GI toxic effects than with EBRT.
- VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk

LVSI

Table 4
Multivariate Cox proportional hazard regression models for the three-tiered scoring system for LVSI.

	Vaginal Recurrence			Pelvic Regional Recurrence			Distant Recurrence			Overall Survival		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age												
<60	1			1			1			1		
>60	3.15	1.10–9.01	0.032	2.00	0.58–6.89	0.275	1.29	0.68–2.45	0.437	3.19	2.15–4.74	<0.001
Differentiation grade												
1	1			1			1			1		
2	1.68	0.75–3.76	0.212	2.13	0.82–5.55	0.120	1.89	1.05–3.42	0.035	1.19	0.87–1.62	0.285
3	2.31	1.01–5.26	0.046	2.75	1.02–7.43	0.045	3.72	2.12–6.53	<0.001	1.79	1.30–2.48	<0.001
Myometrial invasion												
<50%	1			1			1			1		
>50%	1.47	0.71–3.03	0.301	1.89	0.72–4.97	0.195	1.25	0.74–2.12	0.409	1.08	0.83–1.41	0.546
LVSI												
No LVSI	1			1			1			1		
Focal	1.86	0.65–5.35	0.251	1.10	0.26–4.74	0.900	2.42	1.31–4.45	0.005	1.36	0.93–2.00	0.111
Substantial	1.69	0.51–5.66	0.393	6.19	2.35–16.3	<0.001	3.61	1.90–6.84	<0.001	2.02	1.30–3.12	0.002
Treatment received												
NAT	1			1			1			1		
EBRT	0.17	0.08–0.37	<0.001	0.30	0.11–0.80	0.016	1.14	0.67–1.93	0.640	1.04	0.81–1.34	0.734
VBT	0.13	0.04–0.43	0.001	1.16	0.47–2.87	0.745	1.21	0.63–2.33	0.568	0.82	0.56–1.21	0.319

HR: hazard ratio; CI: confidence interval; LVSI: lymph vascular space invasion; NAT: no additional treatment; EBRT: external beam radiotherapy; VBT: vaginal brachytherapy.

Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer – A pooled analysis of PORTEC 1 and 2 trials.
Tjalling Bosse 2015

INTERMEDIATE RISK

Intermediate-risk endometrial cancer stage I endometrioid

- grade 1–2
- ≥50% myometrial invasion
- LVSI negative

Adjuvant brachytherapy

Decrease vaginal recurrence

(No adjuvant treatment is an option, especially for patients aged <60y)

Level of evidence: II
Strength of recommendation: C
Consensus: 100% yes (37 voters)

HIGH INTERMEDIATE RISK

High-intermediate-risk endometrial cancer stage I endometrioid

- grade 3 <50% myometrial invasion, regardless of LVSI status
- grade 1–2, LVSI unequivocally positive, regardless of depth of invasion

Surgical nodal staging performed; node negative:

Adjuvant brachytherapy

Level of evidence: III
Strength of recommendation: B

(No adjuvant therapy is an option)

No surgical nodal staging

- Adjuvant EBRT recommended for LVSI unequivocally positive
- Adjuvant brachytherapy alone is recommended for grade 3 and LVSI negative to decrease vaginal recurrence

Level of evidence: III
Strength of recommendation: B

HIGH RISK

- High-risk endometrial cancer is characterized by an increased risk of pelvic recurrence and distant metastases

- Non-endometrioid tumour types
  - 60–70% of patients with uterine serous cancer have disease outside the uterus at the time of presentation.
  - The 5-year OS rate for patients with uterine serous cancer is 20–25% versus 80% for all patients with endometrial cancer.

HIGH RISK

stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status

Surgical nodal staging performed; node negative:

Adjuvant EBRT with limited fields should be considered to decrease locoregional recurrence

Level of evidence: I

Strength of recommendation: B

(Adjuvant brachytherapy may be considered as an alternative to decrease vaginal recurrence)

Level of evidence: III

Strength of recommendation: B

No surgical nodal staging

Adjuvant EBRT is generally recommended for pelvic control and relapse-free survival

Level of evidence: III

Strength of recommendation: B

-- Sequential adjuvant chemotherapy may be considered to improve PFS and cancer specific survival

Level of evidence: II

Strength of recommendation: C

HIGH RISK- NON ENDOMETRIOID

Serous and clear cell after comprehensive staging:

1. Consider chemotherapy; clinical trials are encouraged
Level of evidence: III
Strength of recommendation: B

2. Stage IA, LVSI negative: Consider vaginal brachytherapy only without chemotherapy
Level of evidence: IV
Strength of recommendation: C

3. Stage ≥IB: EBRT may be considered in addition to chemotherapy, especially for node positive disease
Level of evidence: III
Strength of recommendation: C

ADJUVANT TREATMENT

- **Low-risk patients-**
  - Local recurrence <5%
  - adjuvant therapy is generally not indicated, with surgery alone considered curative.

- **High-intermediate risk** patients benefit from radiotherapy.
  - Vaginal brachytherapy and pelvic external beam radiotherapy
    - Reduce the rate of locoregional recurrence
    - No effect on overall survival

- **High-risk** patients may benefit from chemotherapy.

ENDOMETRIAL CANCER

- Introduction
- Surgical Staging
- Sentinel lymph node biopsy
- Adjuvant treatment
- **Conservative treatment – fertility preservation**

FERTILITY PRESERVING TREATMENT

- The diagnosis of endometrial carcinoma in young women of childbearing age is rare.
  - 4% of patients with endometrial carcinoma are <40 years of age.
- Younger women with endometrial carcinoma seem to have a better prognosis than older patients
  - Early stage
  - Low grade disease
- The standard approach for the management of endometrial cancer in young women of childbearing age is hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy.

- Although this is a highly effective approach, carrying a 5-year survival rate of 93%, it also results in a permanent loss of reproductive potential.

- Conservative management of endometrial carcinoma is based on medical treatment with oral progestins.

- The most important issues when considering a conservative management approach are the assessment of clinical and pathological characteristics of the tumour and selection of the appropriate medical intervention.

CONSERVATIVE MANAGMENT

- A conservative management approach is considered in:
  - Histological diagnosis of grade 1 endometrial carcinoma or premalignant disease such as CAH
- The histological diagnosis should be reviewed by an expert pathologist to improve the accuracy of histological assessment
- Imaging-
  - Pelvic MRI to exclude overt myometrial invasion, as well as adnexal or pelvic node involvement.
  - Pelvic US
- Patients should be informed:
  - Nonstandard approach and they should be willing to accept close follow-up during and after the treatment.
  - Need for future hysterectomy in case of failure of the treatment and/or after pregnancies.

CONSERVATIVE MANAGMENT

- Conservative medical treatment is based on progestins:
  - medroxyprogesterone acetate (MPA; 400– 600 mg/day)

    OR

    megestrol acetate (MA; 160–320 mg/day)
  - LNG-IUD?

- Assessment of response must be performed at 6 months with a new D&C and imaging.
  - Response rates: 75%
  - Recurrence rates: 30–40%

- Standard surgery with hysterectomy should be proposed to non-responders while maintenance treatment for a further 6 months can be considered in responders who wish to delay pregnancy.

CONSERVATIVE MANAGMENT

- Pregnancy is associated with a reduced risk for endometrial cancer recurrence
- Live birth rate:
  - 28%
  - 40% - with ART
- After completion of childbearing standard treatment with hysterectomy and salpingo-oophorectomy is recommended.
- Preservation of the ovaries can be considered in selected cases, depending on the patient's age and genetic risk factors.

- Minimal invasive surgery
- Lymphadenectomy
- Sentinel node
- Adjuvant treatment
- Fertility preserving treatment