ESMO-ESGO-ESTRO CONSENSUS CONFERENCE ON ENDOMETRİAL CANCER

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INTRODUCTION

Endometrial cancer is the most common gynecologic cancer in developed countries.

More than %90 of cases occur in women >50 years of age while a median age at diagnosis 63 years.

%4 of women with endometrial cancer are <40 years old.

Type-1 and Type-2 endometrial cancer

Genetic (molecular) classification of endometrial cancer

- POLE(ultra-mutated) tumours
- microsatellite unstable tumours
- copy number high tumours(p53 mutation)
- others

Hereditary endometrial cancer

FIGO ENDOMETRIAL CANCER STAGE

Table 1: 2009 FIGO staging system for carcinoma of the endometrium

Stage I[a]	Tumor contained to the corpus uteri		
	IA	No or less than half myometrial invasion	
	IB	Invasion equal to or more than half of the myometrium	
Stage II		Tumor invades the cervical stroma but does not extend beyond the uterus[b]	
Stage III[a]		Local and/or regional spread of tumor[c]	
	IIIA	Tumor invades the serosa of the corpus uteri and/or adnexas	
	IIIB	Vaginal and/or parametrial involvement	
	IIIC	Metastases to pelvis and/or para-aortic lymph nodes	
		IIIC1	Positive pelvic nodes
		IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV[a]			Tumor invades bladder and/or bowel mucosa and/or distant metastases
	IVA		Tumor invasion of bladder and/or bowel mucosa
	IVB		Disant metastases, including intra-abdominal metastases and or inguinal lymph nodes

FIGO = International Federation of Gynecology and Obstetrics
[a] Includes grades 1, 2, or 3
[b] Endocervical glandular involvement only should be considered as stage I and no longer as stage II.
[c] Positive cytology has to be reported separately without changing the stage.

LEVELS OF EVIDENCE & 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

QUESTIONS???

Which surveillance should be used for asymptomatic women?

What is the management scheme in patients who want to preserve fertility with atipical hyperplasia/EIN or grade-1 endometrioid endometrial cancer?

Which molecular markers can help to distinguish (pre)cancerous lesions from benign lesions?

How does the medical condition influence surgical management?

What are the indications for lymphadenectomy? Extent of lymphadenectomy?

How radical should the surgery be in different stages and histological subtypes?

Currently new definition of risk groups for adjuvant therapy?

What are the best adjuvant treatment for patients with low , intermediate and high risk groups?

Does the surgery or radiotherapy have a role in advanced and recurrent disease?

Optimal systemic therapy for advance and recurrent disease?

What are the most promising targeted agents and which study designs should be used to evaluate their clinical benefit?

SURVEILLANCE IN ASYMPTOMATIC WOMEN

A- There is no evidence for endometrial cancer screening in general population.(LoE:II)

A-Anopposed oestrogen treatment should not be started or should be stopped in women with uterus in situ.(LoE:III)

B-Asymptomatic women with obesity, diabetes, infertility, nulliparity, and late menapouse should not be screened routinely.(LoE:III)

B-For women who have adult granulosa cell tumour; if hysterectomy has not been performed, endometrial sampling is recommended.(LoE:IV)

B-In patients with ovarian cancer who undergoing fertility-sparing surgery, endometrial sampling is recommended.(LoE:IV)

B-Routine screening is not recommended for asymptomatic tamoxifen users.(LoE:IV)

B-In LS mutantion carriers; annual screnning is recommended to start at 35 years old with examination, TVUSG, and biopsy until hysterectomy is performed.(LoE:IV)

B-Proflactic surgery(hysterectomy and bilaterally salpingooferectomy) should be discussed at 40 years old for LS mutation carriers.(LoE:IV)

FERTILITY PRESERVATION – EIN/ GRADE-1 END CANCER

A-This patients must be referred to specialised centers.(LoE:V)

A-D&C or hysterescopy must be performed for diagnosis.(LoE:IV)

A-AH/EIN must be diagnosed or confirmed by a specialised pathologist.(LoE:IV)

B-Pelvic MRI should be performed for deep myometrial invasion or adnexal involvement. Expert ultrasound examination is an alternative method.(LoE:III)

A-Giving information to patients about fertility sparing treatments is not a standart treatment. Pros and cons must be discussed.(LoE:IV)

B-For patients undergoing fertility preserving therapy; MPA (400-600 mg/d) or MA (160-320 mg/d) is recommended. LND-IUD treatment can be considered.(LoE:IV)

B- In order to assess response; D&C, hysteroscopy, and imaging must be performed at 6 months. If no response is achieved, standart surgical procedure should be performed.(LoE:IV)

B- If complete response is achieved, patient should be referred to infertility clinic immediately.(LoE:IV)

B- If hysterectomy is not performed, every 6 months patients should reevaluated for recurrences.(LoE:IV)

B- After completion of childbearing, hysterectomy and salpingo-ooferectomy should be recommeded.Preservation of ovaries can be considered as a genetic risk factors and age.(LoE:IV)

MOLECULAR MARKERS (PRECANCEROUS OR BENIGN?)

A- PTEN and PAX-2 staining is recommended to distinguish AH/EIN from benign lesions.(LoE:IV)

B- p53 staining can be distinguish serous intraepithelial carcinoma from its mimics.(LoE:IV)

B- A panel of markers (ER, CEA, p16, vimentin,…) should be used where endoservical cancer is suspected.(LoE:IV)

A- WT-1 is recommended to determine the origin of the serous cancer.(LoE:IV)

WHAT ARE THE INDICATIONS AND EXTENTION OF LYMPHADENECTOMY IN ENDOMETRIAL CANCER?

D- Sentinel lymph nod dissection is still experimental. SLND increases the detection rate of small metastases and isolated tumour cells but its importance is still unclear.(LoE:IV)

B- If lymphadenectomy is perfomed, the extent of dissection should be up to renal veins.(LoE:IV)

A- Patients with low risk endometrial cancer (grade1-2, < %50 invasion) have a low risk of lymph nod involvement. It is not recommended lymphadenectomy.(LoE:II)

C- Patients with intermediate risk(grade-3 or deep myometrial invasion), data cannot be shown survival benefit, lymphadenectomy can be considered as a part of staging.(LoE:II)

B- In a high risk group(grade-3 and deep invasion) lymphadenectomy should be recommended.(LoE:IV)

C- In incomplete operated high risk patients; lymphadenectomy should be completed for adjuvant treatment planning.(LoE:V)

the lack of central pathology review, subspecialty of surgeons, and adequacy of statistical power.

Decisions about whether to perform lymphadenectomy, and, if done, to what extent (eg, pelvic nodes only or both pelvic and para-aortic nodes), can be made based on preoperative and intraoperative findings. Criteria have been suggested as indicative of low risk for nodal metastases: 1) less than 50% myometrial invasion; 2) tumor less than 2 cm; and 3) well or moderately differentiated histology.[72,73] However, this may be difficult to accurately determine before final pathology results are available.

Another associated benefit of lymphadenectomy is the diagnosis of those with nodal metastases to guide appropriate adjuvant treatment to improve survival or decrease toxicity. However, o
designed to address this question.[65] Therefore, th
standardization of adjuvant treatment after stagin
lymphadenectomy. In fact, the use of lymphadenectomy did not translate into an increased use of adjuvant therapy. This may have contributed to the lack of difference in recurrence and survival in the two groups.

The question of whether to add para-aortic lymphadenectomy to pelvic node dissection has been debated. Prior studies have shown conflicting information regarding the risk of para-aortic nodal metastases in patients without disease in the pelvic nodes.[49,72,74,75] There was a high rate of lymphatic metastasis above the inferior mesenteric artery, suggesting a need for systematic pelvic and para-aortic lymphadenectomy. Hence, para-aortic lymphadenectomy up to the renal vessels may be considered for selective high-risk situations, including those with pelvic lymphadenectomy or high-risk histologic features. Many surgeons do not do a full lymphadenectomy in patients with grade 1 early-stage endometrial cancer.[60]

In summary, lymph node dissection identifies patients requiring adjuvant treatment with RT and/or systemic therapy.[76] A subset of patients may not benefit from lymphadenectomy; however, it is difficult to preoperatively identify these patients because of the uncontrollable variables of change in grade and depth of invasion on final pathology. The NCCN panel recommends that lymphadenectomy should be done for selected patients with endometrial cancer with para-aortic lymphadenectomy done as indicated for high-risk patients (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[6] Lymphadenectomy is contraindicated for patients with uterine sarcoma. SLN mapping can be considered as an alternative to full lymphadenectomy in the setting of apparent uterine-

Sentinel Lymph Node Mapping

The section on surgical staging (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma) includes recommendations about SLN mapping. SLN mapping may be considered for patients with apparent uterine-confined endometrial cancer to assess whether they have metastatic pelvic lymph nodes.[77-81] In SLN mapping, dye is injected into the cervix, which travels to the sentinel nodes (see Figures 1–3 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).

A surgical SLN algorithm is proposed to decrease the false-negative rate (see Figure 4 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[77,82] For example, suspicious or grossly enlarged nodes should be removed regardless of SLN mapping results. In SLN mapping, the surgeon's expertise and attention to technical detail are critical. Patients may be able to avoid the morbidity of a standard lymphadenectomy with SLN mapping.[83,84] Because SLNs identify the primary lymphatic pathway, this increases

HOW RADICAL SHOULD THE SURGERY BE IN DIFFERENT STAGES AND HISTOLOGICAL SUBTYPES OF ENDOMETRIAL CANCER?

B-Radical hysterectomy is not recommended for stage-II cancer. But should be considered to achieve free margins if require.(LoE:IV)

B- In stage-II cancer(clinically or intraoperative); lymphadenectomy is recommended.(LoE:IV)

A- Completely macroscopic cytoreduction is recommended for advance stage cancer.(LoE:IV)

B- In non- endometrioid apperent stage-I cancer; lymphadenectomy is recommended.(LoE:IV)

C- Omentectomy should be considered in serous cancer.(LoE:IV)

RISK GROUPS FOR ADJUVAN TREATMENT

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

LOW & INTERMEDIATE RISK GROUPS

A- Patients with low risk group, no adjuvant treatment is recommended.(LoE:I)

B- In intermediate risk group , adjuvant brachytherapy is recommended to decrease vaginal recurrence.(LoE:I) Before 60 years, observation can be considered without adjuvant treatment.

In high-intermediate group;

- nodal staging+ and node- => brachytherapy or observe
- no nodal staging => LVSI+ => EBRT

  => grade-3 LVSI- => brachytherapy

HIGH-RISK GROUP (STAGE-I)

Nodal staging+ and node-

B- Limited field adjuvant EBRT(LoE:I)

B- Brachytherapy can be alternative(LoE:III)

C- Systemic therapy?

No nodal staging

B- External RT(LoE:III) for local relapses.

C- Sequential KT can be considered for increase PFS and CSS(LoE:II)

C- EBRT+ KT combination (LoE:II)

HIGH-RISK GROUP(STAGE-II)

Simple hysterectomy+ nodal staging+ node(-)

- grade 1-2 and LVSI- => vaginal brachytherapy
- grade-3 or LVSI+ => limited EBRT, brachytherapy?, KT?

Simple hysterectomy+ no nodal staging

- EBRT is recommended.
- grade-3 or LVSI+ => sequential KT should be considered.

STAGE-III- NO RESIDUAL DISEASE

There is more evidence to give KT and EBRT in combination than either alone.

HIGH RISK- NON ENDOMETRIOID TUMOR

Serous and clear cell tumors;

- stage IA and LVSI- => only brachytherapy is considered without KT.(C-IV)

- stage IB or more => EBRT can be considered in addition to KT, especially for node- positive patients.(C-III)

CARCINOSARCOMA AND UNDIFFERANTIATED TUMORS

Chemotherapy is recommended.(B-II)

EBRT can be considered.(C-III)

THE ROLE OF SURGERY OR RT IN ADVANCE STAGE OR RECURRENT ENDOMETRIAL CANCER

In these groups, surgery is recommended if complete cytoreduction can be achieved.(C-IV)

In selected cases palliative surgery is recommended to alleviate symptoms.

If technically comlete resection is possible, distant oligometastases and lymph nodes can be operated.(C-V)

Exenteration is considered, if clear surgical margins can be achieved in cases of locally-advance tumors and central pelvic relapses after RT.(C-IV)

Histological type should not influence the decision of surgery.(B-IV)

In isolated vaginal relapses, RT can be curative treatment after surgery.(A-III)

For vaginal and pelvic nodal recurrences, KT with RT can be considered in patients with high risk features for sysrtemic relapse. (C-IV)

Re-irradiation therapy can be considered highly selected patients and in specialized centers.(C-V)

If primary tumor is unresectable or surgery is contrendicated for medical reasons, RT may be indicated.(B-IV)

SYSTEMIC THERAPIES IN ADVANCE STAGE AND RECURRENT DISEASE

Hormone therapy is indicated for advance stage or recurrent EEC.(A-II)

Hormone therapy can be more effective in grade-1 and 2 endometrioid tumors than other histologic types.(B-IV)

Before the hormone therapy; hormone receptor status should be determined.(B-III)

Biopsy from metastic or recurrent tumor can be considered for hormone receptor status.(C-III)

In hormone receptor positive grade-1-2 tumors without rapidly progressive disease; hormone therapy is prefered front-line therapy.(A-V)

Progestogens 200 mg MPA or 160 mg MA is recommended.(A-III)

Other hormonal agents after progestins are tamoxifen, fulvestrant, aromatase inh.(C-III)

Standart KT is six cycle carboplatin- paclitaxel every 3 weeks.(A-I)