

Atypical Endometriosis의 적절한 처치

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A Case

- 19 yr-old woman with lower abd. pain
- GYN sono :
Rt ovary – 7.5 X 5.0 cm low echogenic,
homogenous cyst suggesting endometrioma

P/Lt ovary cystectomy

Histopathologic findings:

Endometriosis with nuclear atypia.

Close clinical f/up is recommended

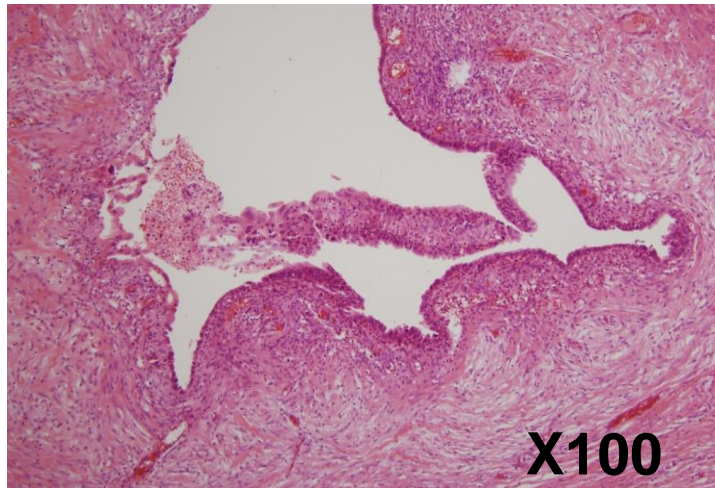
Endometriosis with atypia

P/Lt ovary cystectomy

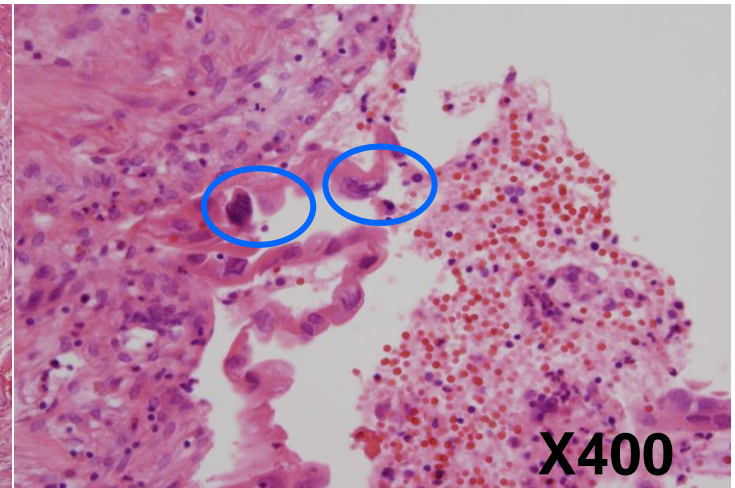
Histopathologic findings:

Endometriosis with nuclear atypia.

Close clinical f/up is recommended



X100



X400

EAOC : What is this ?

Endometriosis-associated ovarian cancer (EAOC)

- **Incidence of EAOC**

- : 1 % ~ of woman with endometriosis
- : EAOC affects women who are **10 ~ 20 yr.** younger than ovarian cancer patients without ES

Konincks, 1992, Herps J M , 1990

- Prevalence of ovarian cancer in women with ES
 - : higher than ovarian cancer in women without ES



Overview of common factors of both Endometriosis and Ovarian cancer

Protective factors	Risk factors	Common pathogenetic mechanisms
<ul style="list-style-type: none">▪ Oral contraceptives▪ Tubal ligation▪ Hysterectomy▪ Pregnancy	<ul style="list-style-type: none">▪ Early menarche▪ Late menopause	<ul style="list-style-type: none">▪ Familial predisposition▪ Immunological factors▪ Cell adhesion factors▪ Angiogenic factors

(Nezhat *al.*, 2008, F&S)

Ovarian cancer risk in Endometriosis patients

TABLE 2

Epidemiologic cohort studies assessing ovarian cancer risk in endometriosis patients.

Author	Study Type	Cohort Size	Mean Follow Up (Years)	Ovarian Malignancies Identified	Ovarian cancer in endometriosis patients SIR/OR	
Brinton et al., 1997	Cohort	20,686 endometriosis patients	11.4	29	Overall cancer risk	1.2
					Ovarian cancer	1.9
					Ovarian cancer with ≥ 10 yrs followup	2.5
					Ovarian cancer with Longstanding endometriosis	4.2
Brinton et al., 2004	Cohort	12,193 infertility patients		45	Ovarian cancer	2.5
Brinton et al., 2005	Cohort			2,491	2.53 (1.19-5.38)	
Ness et al., 2000	Case control			66	Ovarian cancer	1.7
Borgfeldt, Andolf, 2004	Nested case control	28,163		81	Ovarian cancer	1.3
Modugno et al., 2004	Case control			177	1.3 (1.1-1.6)	
Melin et al., 2006	Cohort	64,492	12.7	122	Overall cancer risk	1.04
					Ovarian cancer	1.43
					Ovarian cancer Early diagnosed endometriosis	2.0
					Ovarian cancer Long standing endometriosis	2.2
Olsen et al., 2002	Cohort	1,392	13	3	No increased risk for overall or ovarian cancer	
Kobayashi et al., 2007	Cohort	6,398	12.8	46	Ovarian cancer	8.95
					Ovarian cancer > 50 yrs old	13.2

Endometriosis & Ovarian carcinoma

- ❖ Incidence of Ov ca in ES: 3.4~52.6%
(Heidemann NL et al., 2014)
- ❖ No overall Ov ca risk increased but
Endometrioid & clear cell ca in Australian
cohort.
(Merritt et al., 2008)
- ❖ Endometrioid & clear cell ca risk was nearly
tripled with Hx. Of ES in Washington state
cohort.
(Rossing MA et al., 2008)

Cell types of EAOC

❖ Meta- analysis from 15 studies

Reference	Histological type			
	serous	mucinous	clear cell	endometrioid
Scully et al. (1966)	–	–	–	23.5% (4/17)
Aure et al. (1971)	0% (0/357)	0.5% (1/203)	23.7% (14/59)	9.4% (20/212)
Kurman et al. (1972)	1.7% (2/118)	0%	8.3% (1/12)	10.8% (4/37)
Russel (1979)	3.0% (7/233)	4.0% (3/69)	48.5% (16/33)	27.7% (20/72)
Brescia et al. (1989)	–	–	37.5% (9/24)	9.6% (5/52)
Crozier et al. (1989)	–	–	22.0% (13/59)	–
Jenison et al. (1989)	12.7% (7/55)	–	59.1% (26/44)	–
DePriest et al. (1992)	–	–	–	26.0% (11/42)
Vercellini et al. (1993)	3.6% (8/220)	6.4% (6/94)	21.1% (8/38)	26.3% (30/114)
McMeekin et al. (1995)	–	–	–	30.8% (28/91)
Cuesta et al. (1996)	–	–	41.2% (7/17)	39.1% (9/23)
Goff et al. (1996)	–	–	–	–
Jimbo et al. (1997)	8.7% (8/92)	2.9% (1/35)	40.6% (13/32)	23.1% (3/13)
Fukunaga et al. (1997)	9.5% (6/63)	5.7% (2/35)	54.0% (27/50)	41.9% (13/31)
Kernivama et al. (1999)	–	–	37.7% (20/53)	–
Total	3.3% (39/1,172)	3.0% (13/436)	39.2% (198/505)	21.2% (147/694)

3.3 % in serous

3.0 % in mucinous

39.2 % in clear cell

21.2 % in endometrioid

- Clear cell & Endometrioid type: related to endometriosis

Endometriosis malignant transformation

■ In 1925, Sampson criteria

Three criteria:

- (i) Co-existence of carcinoma and endometriosis of the same ovary
- (ii) Histology is compatible with an endometrial origin
- (iii) No other primary tumor sites

+

- (iv) *Dysplastic phase* between benign ES and carcinoma
: Most convincing feature

Scott, Obstet & Gynecol, 1953

Atypical Endometriosis

- ❖ Earliest step in the malignant transformation of ES.
- ❖ Cytologic atypia, eosinophilic cytoplasm, large hyperchromatic or pale nuclei with moderate to marked pleomorphism etc...

(LaGrenade A et al., 1988)

CLINICAL SIGNIFICANCE OF ATYPICAL ENDOMETRIOSIS

“Atypia” in Endometriosis - not risk factor -

- ❖ Almost always found in the epithelial lining of endometriotic cysts, as focal or multifocal.
- ⇒ Reactive or degenerative change in most cases
- ⇒ No realistic risk in clinical management.

Seidman, 1996, Clement et al., 2007

“Atypia” in ES

- precursor of malignancy -

1. **Atypia** - more frequently found in endometriosis accompanied by malignant tumors.
: 6.1 % (ES with malignant tumors) **vs.** 1.7% (Only ES)

Ogawa., 2000, Fukunaga, 1997

2. Pathological reports

: continuous transition from benign ES to carcinoma in these areas, atypia is frequently described.

3. In molecular analyses,
: Mutation of tumor suppressor gene...

Transitional phenotype

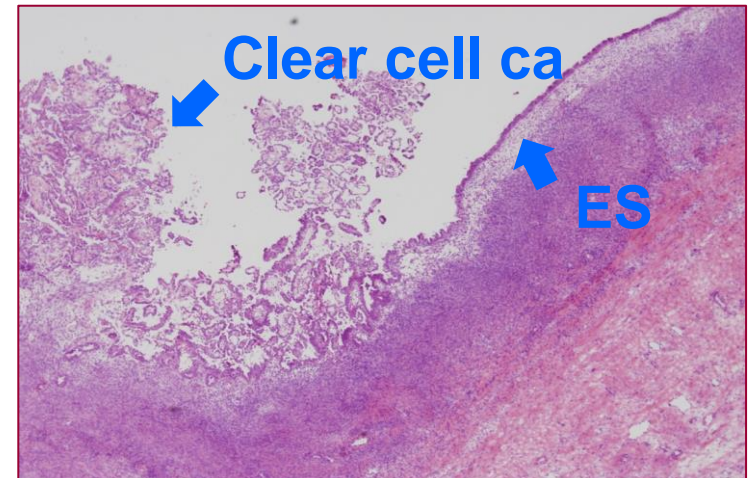
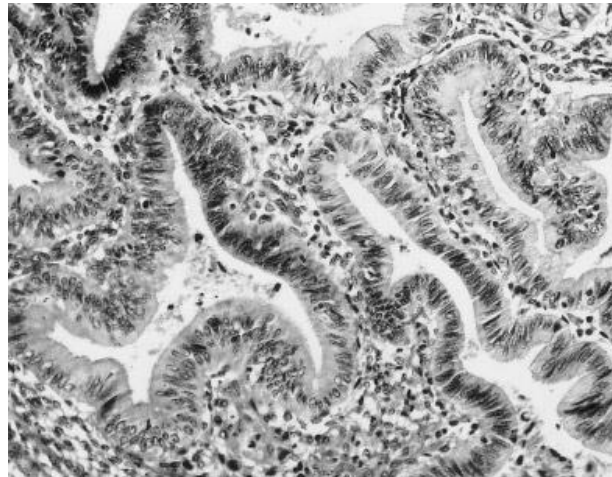
Benign endometriosis



Malignant
progression

Clear cell or
endometrioid carcinoma

- Histologic evidence of direct transition from endometriosis gland to atypia to carcinoma



ES with atypia

- ❖ About 60~80% of EAOC arise from atypical lesion in ES
 - Endometrioid ov ca: up to 60%
 - Clear cell ov ca: up to 15%
 - A case of a clear cell ca were reported after 3 yrs in ES with atypia.

(Moll et al, 1990)

Pathogeneisis of EAOC

- **GENOMIC INSTABILITY & MUTATION**
- **MICROENVIRONMENT**
- **ENDOCRINE FACTORS**

1. Genomic instability & mutations

❖ Tumor suppressor gene

<i>p53</i>	Mutated in as many as 50% of solid tumor
<i>Rb</i>	Deletions and mutations predispose to retinoblastoma
<i>PTEN</i>	Dual specific phosphatase that represses PI3-kinase/Akt pathway activation with negative effect on cell growth
<i>P16^{INK4a}</i>	Binds to cyclin-CDK4 complex inhibiting cell cycle progression
<i>FHIT</i>	Fragile histidine triad gene with tumor suppressor function via unknown mechanisms
<i>WT1</i>	Mutations are correlated with Wilm's tumor
<i>NF1</i>	Neurofibromatosis gene
<i>APC</i>	Associated with colon cancer development in patients with familial adenomatous

PTEN & hMLH-1 in EAOc

- *PTEN*: tumor suppressor gene
- *hMLH-1* gene: corrects error in DNA replication

Abnormal gene expression of *PTEN (inactivation)* and DNA mismatch repair gene *hMLH-1(hypermethylation)*

: identified in endometrial and ovarian cancers

: similarly recognized in advanced-stage endometriosis

Original Article

The Role of *p53* Mutation in the Carcinomas
Arising from Endometriosis

- 13 cases with OCCA (ovarian clear cell carcinoma) + EMsis
9 cases with OEC (ovarian epithelial cancer) + EMsis

***p53* mutation (+)** in specimens of **EMsis + OCCA**

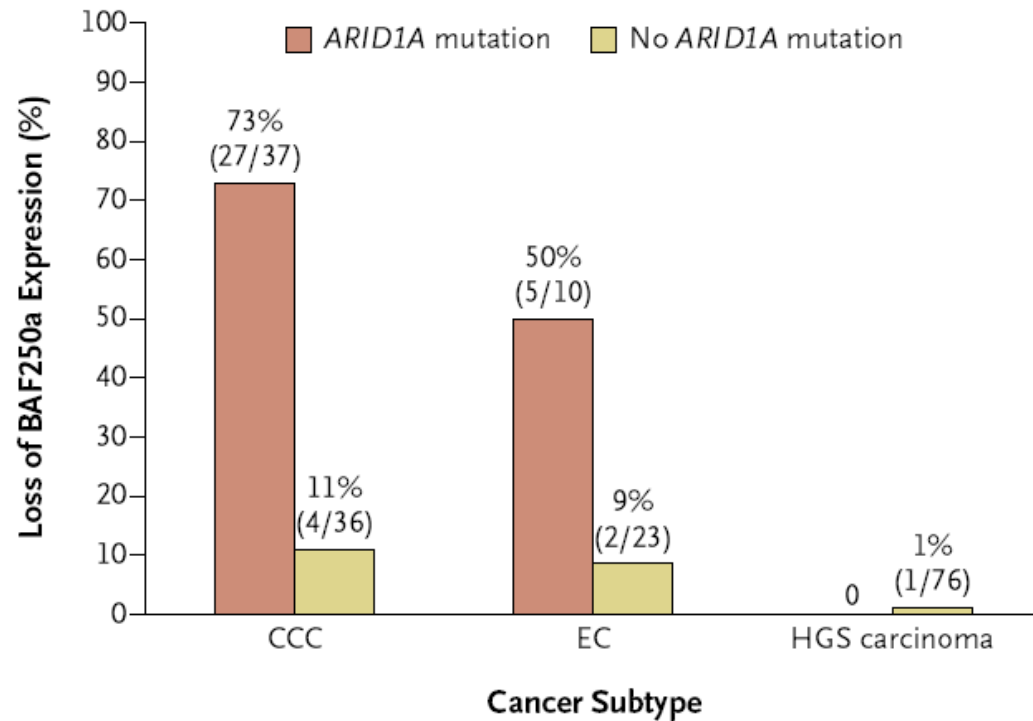
No mutation in solitary EMsis or EMsis with OEC

- ➡ Genetic alterations inducing *p53* mutations in EMsis
affect malignant transformation of EMsis into OCCA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ARID1A Mutations in Endometriosis-Associated Ovarian Carcinomas



Biologic & Molecular profile in EAOC

Table 2. Biological and molecular profile in ovarian endometrioid carcinoma.

Molecular profile	
CTNNB1 mutations	23.8% (Catasùs et al. [42]) 16–38% (Cho et al. [43]) 53.3% (McConechy et al. [44])
PTEN mutations	14% (Catasùs et al. [42]) 14% (Cho et al. [43]) 16.6% (McConechy et al. [44]) 20% (Sato et al. [45])
ARID1A mutations	30% (Wiegand et al. [46]) 55% (Ayhan et al. [47])
MSI	17.5% (Catasùs et al. [42]) 20% (Liu et al. [51])

MSI, microsatellite instability.

Table 3. Biological and molecular profile in ovarian clear cell carcinoma.

Molecular profile	
PIK3CA mutations	20–25% (Cho et al. [43]) 33% (Kuo et al. [52]) 40% (Jones et al. [53]) 40% (Yamamoto et al. [54])
ARID1A mutations	46% (Wiegand et al. [46]) 75% (Ayhan et al. [47]) 57% (Jones et al. [53]) 55% (Yamamoto et al. [54]) 57.7% (Xiao et al. [55]) 15% (Katagiri et al. [56])
HNF-1b overexpression	92.3% (Xiao et al. [55]) 100% (Kato et al. [59])
MET amplification	25–30.8% (Yamashita et al. [62])

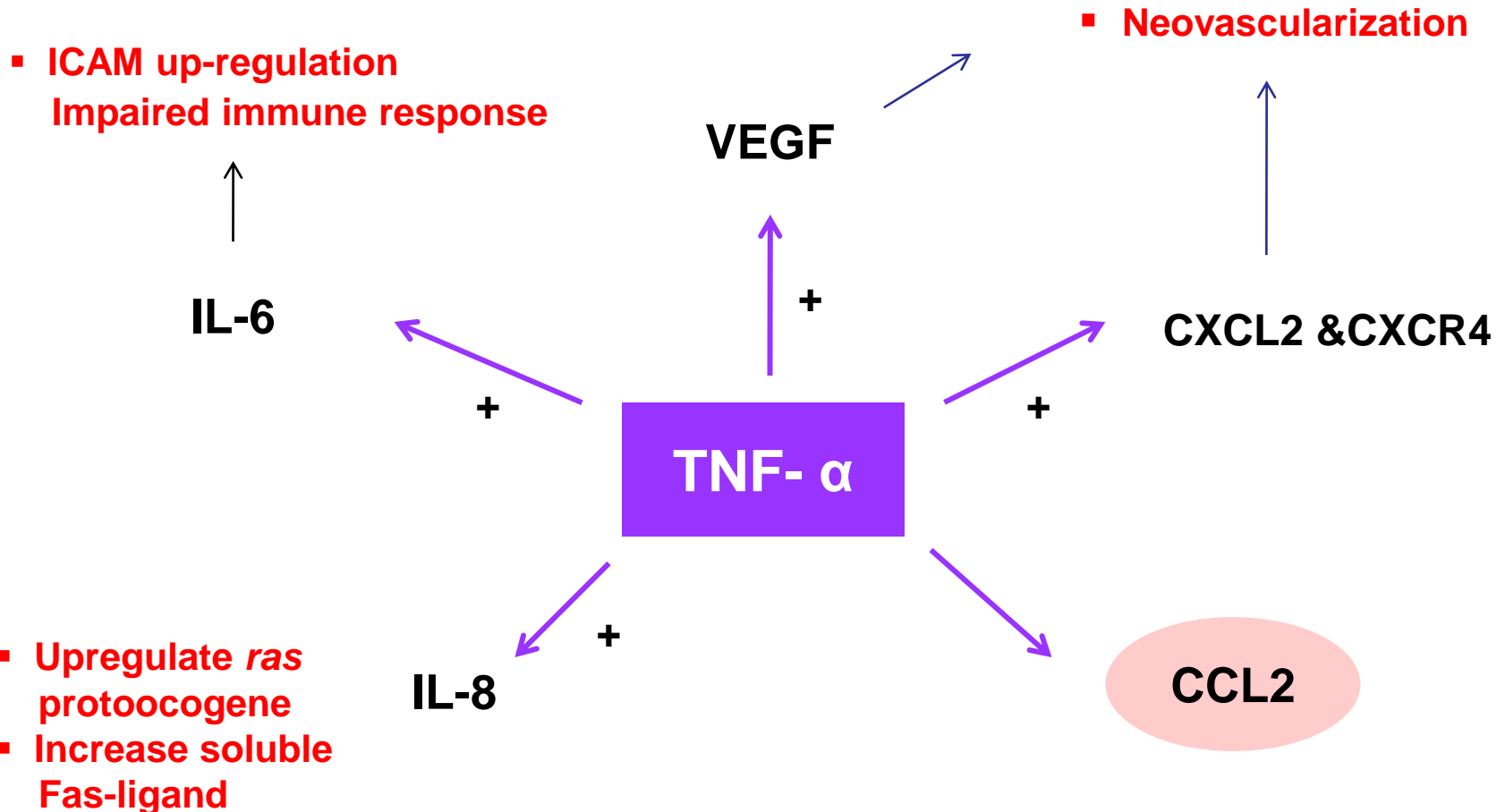
HNF-1b, hepatocyte nuclear factor-1 beta.

2. Microenvironment

- Extraperitoneal Endometrium
 - its **pluripotency**, producing **cytokines, hormones**
- **Inflammation** – “central” to tumorigenesis

- **IL-1, 6, 8, TNF- α , TGF- β**
 - : Cause unregulated **mitotic division, differentiation, and apoptosis** similar to malignant mechanisms.

Microenvironment



IGF-1 in Endometriosis

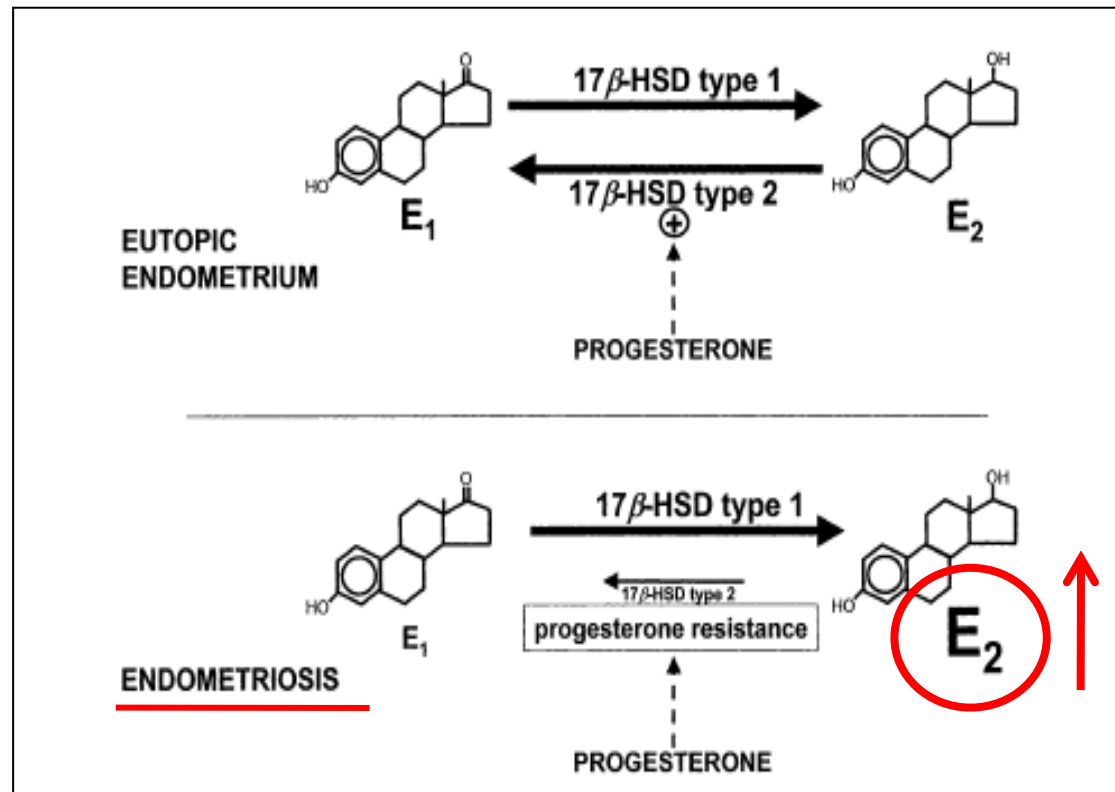
- Higher levels of IGF-1 in plasma and peritoneal fluid of women with ES
- Up-regulation of IGF-1
: inhibit apoptosis in normal ov surface epithelial cells

Kuroda, 2001, Druckmann et al., 2002 & Kim et al., 2000

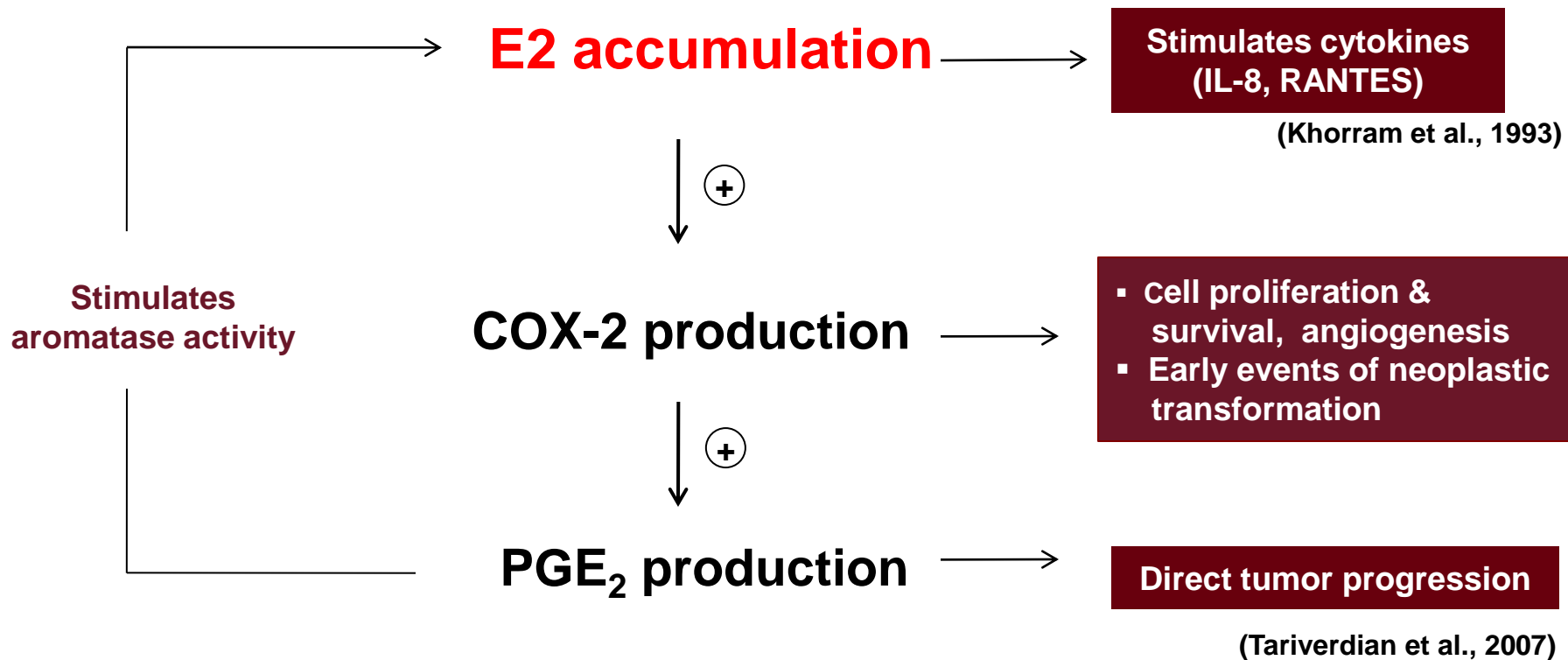
Dysregulation of IGF-1-mediated signaling

: induction of proliferative activity of
ovarian surface epithelium

3. Endocrine factors



Excess E2 production in Ectopic endometrial cell



CLINICAL IMPLICATION OF EAOC

- *Special considerations* -

Monitoring & Early diagnosis

- ❖ No definite guideline for the management of ES with special attention to malignant transformation.

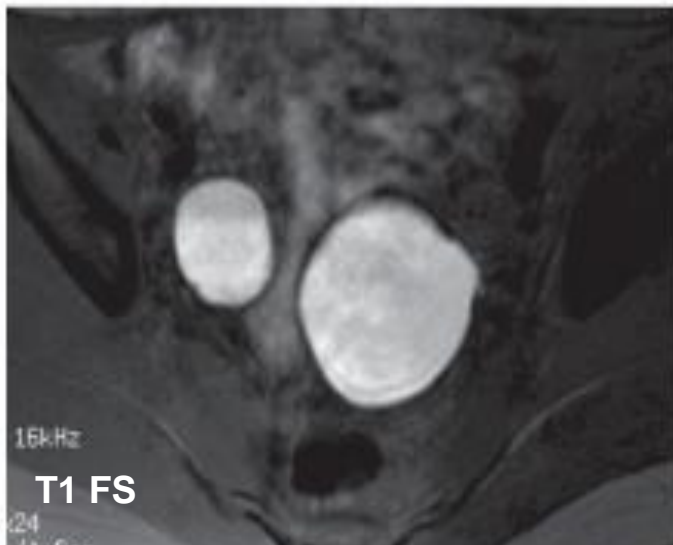
Ultrasound & CA 125



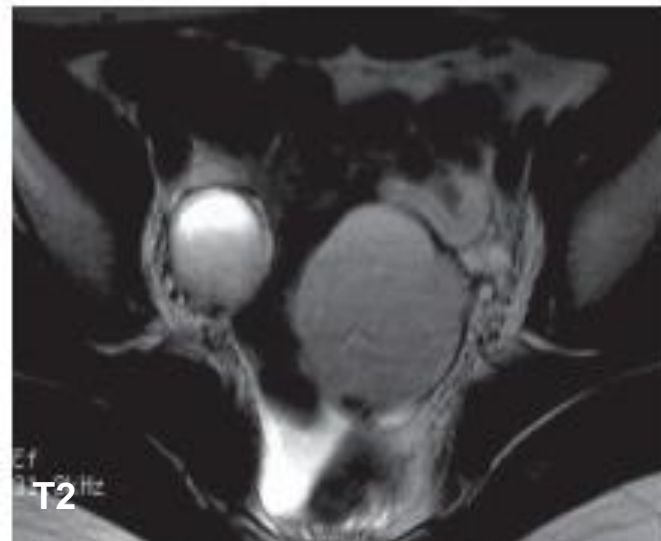
Pelvis MRI !!

**Useful for detecting malignant transformation
of endometrioma**

Typical MRI findings of Endometrioma



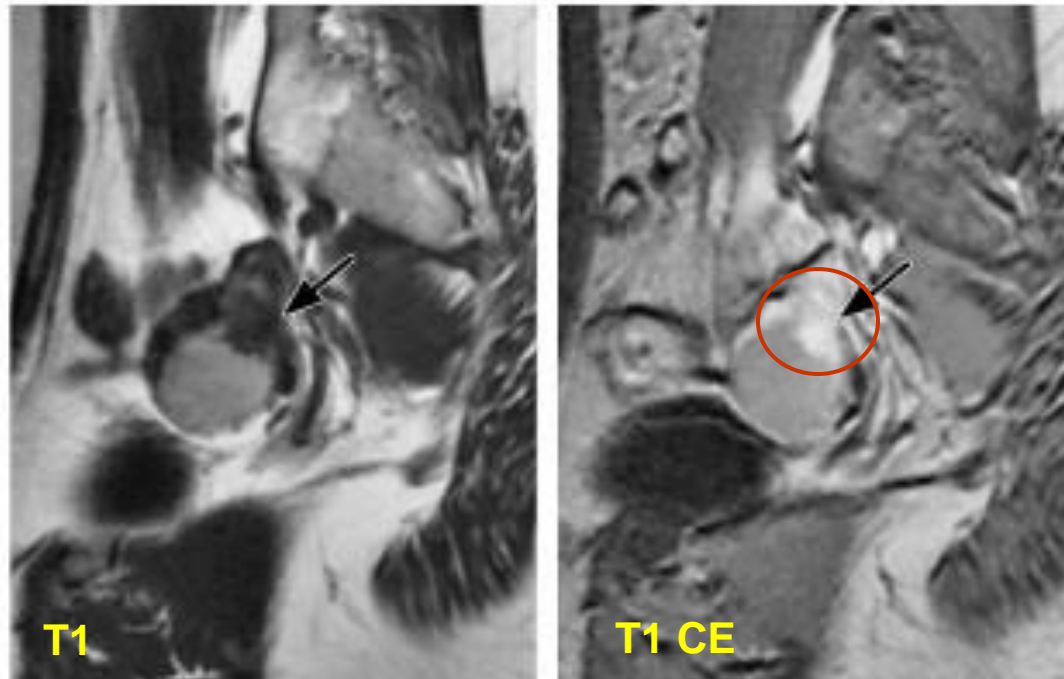
Hyperintense on T_1



Hypointense on T_2

Shading on T2

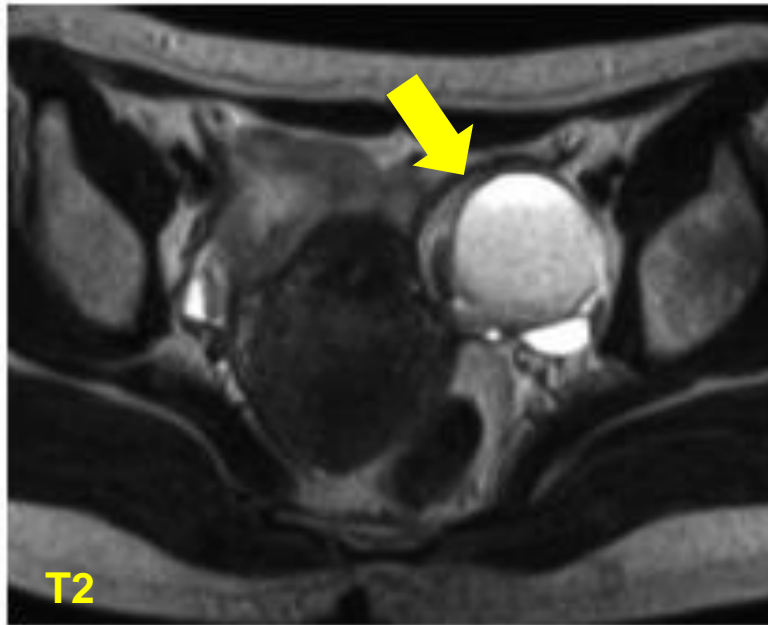
MR images of malignant transformation in endometrioma (1)



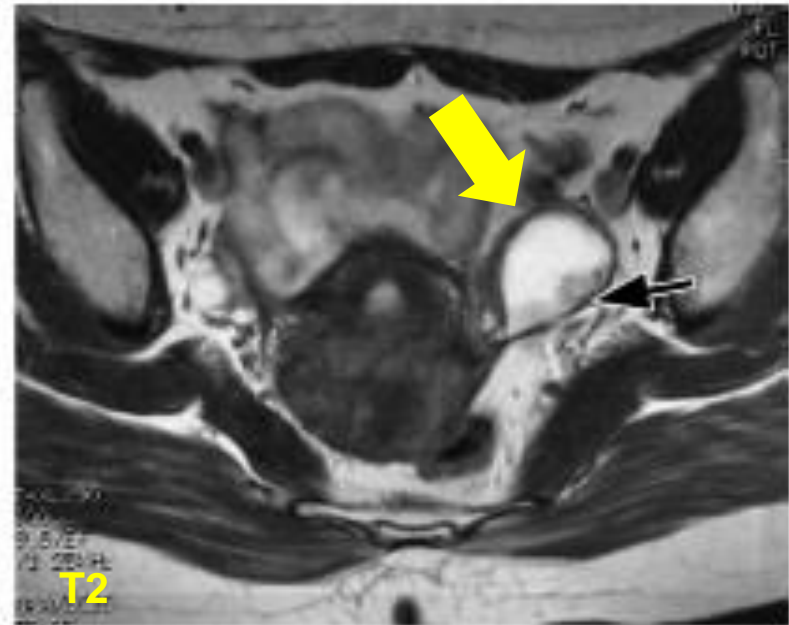
Contrast-enhanced mural nodules on T1

: Suggestive of EAO

MR images of malignant transformation in endometrioma (2)



Endometrioma

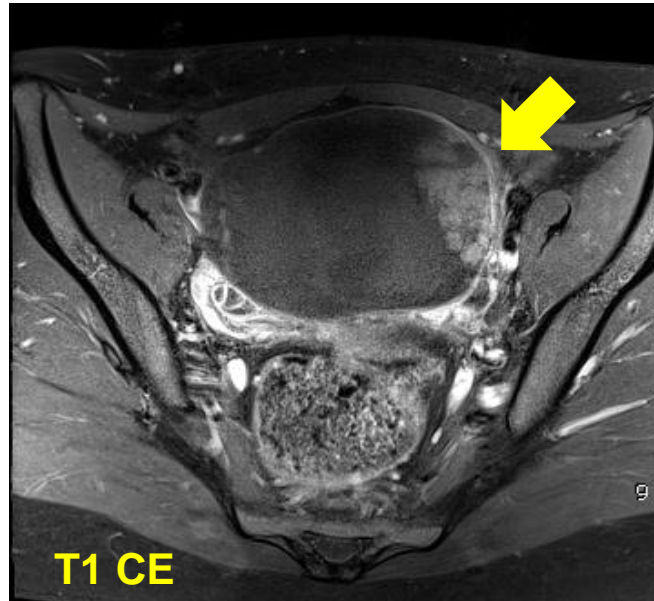


2년 후
Clear cell carcinoma

Loss of shading

MR images of malignant transformation in endometrioma (3)

❖ 30 yr-old woman with EAOC (clear cell)



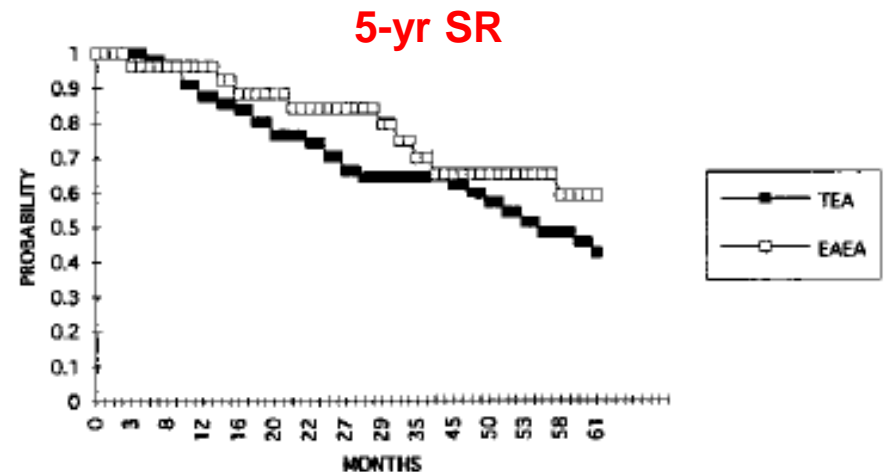
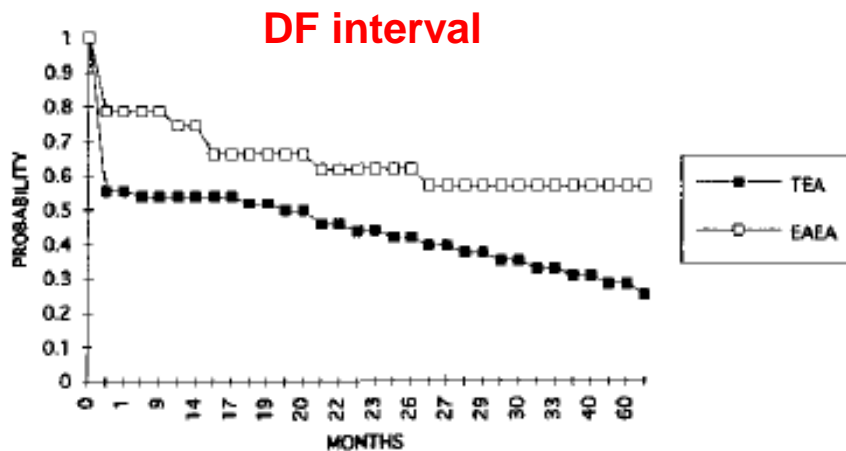
CE- Mural nodules in T1

MRI findings of EAOC

1. Contrast-enhanced **mural nodules** on **T1**-weighted images : **most important finding**
- 2 . Sudden **enlargement** of endometrioma
3. **Disappearance of shading** on T2

Prognosis of EAOC

- EAOC vs. Typical ov ca (both endometrioid type)



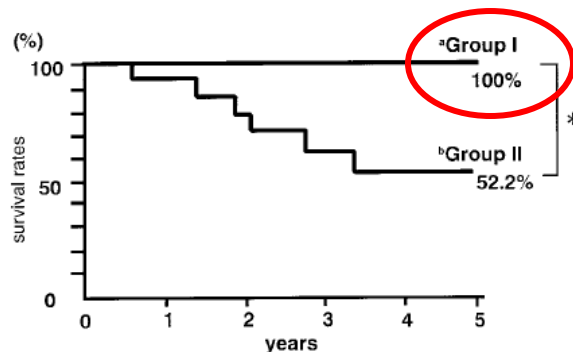
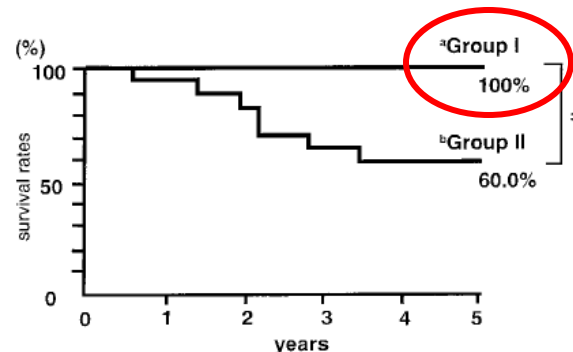
ES-associated endometrioid ca
: better 5-yr survival than typical
endometrioid ca (56% vs. 45%, $p < 0.17$)

Prognosis of Japanese Patients with Ovarian Clear Cell Carcinoma Associated with Pelvic Endometriosis: Clinicopathologic Evaluation

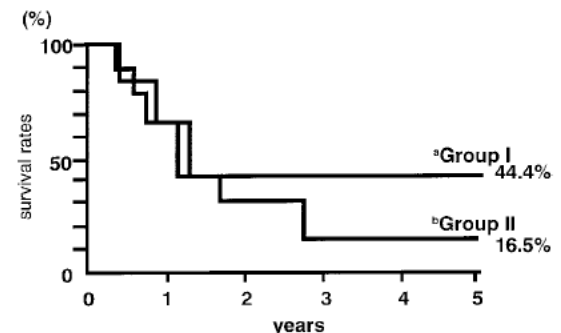
Shin-ichi Komiyama, M.D., Daisuke Aoki, M.D.,¹ Eiichiro Tominaga, M.D., Nobuyuki Susumu, M.D.,
Yasuhiro Udagawa, M.D., and Shiro Nozawa, M.D.

- Group 1: Clear cell carcinoma with ES (n = 20),
Group 2: Clear cell carcinoma without ES (n = 33)

Stage I



Stage Ic



Stage III

Better prognosis & early stage of EAOC than sporadic ovarian cancer

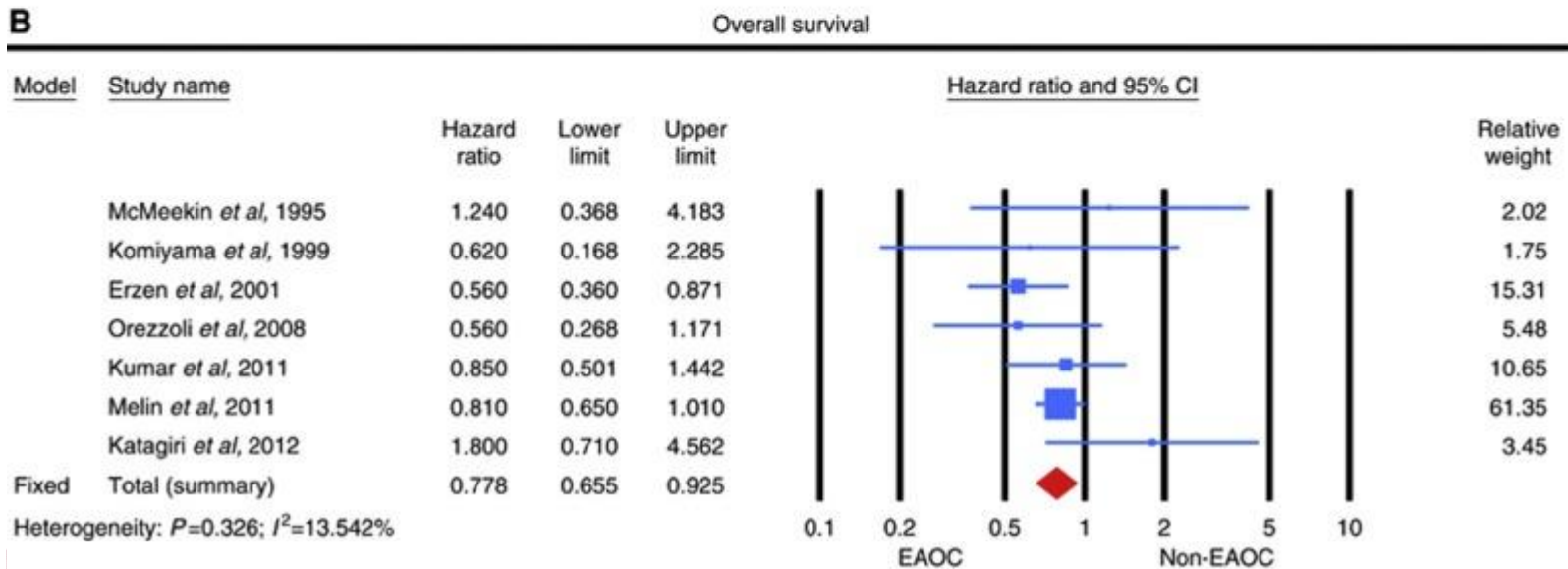
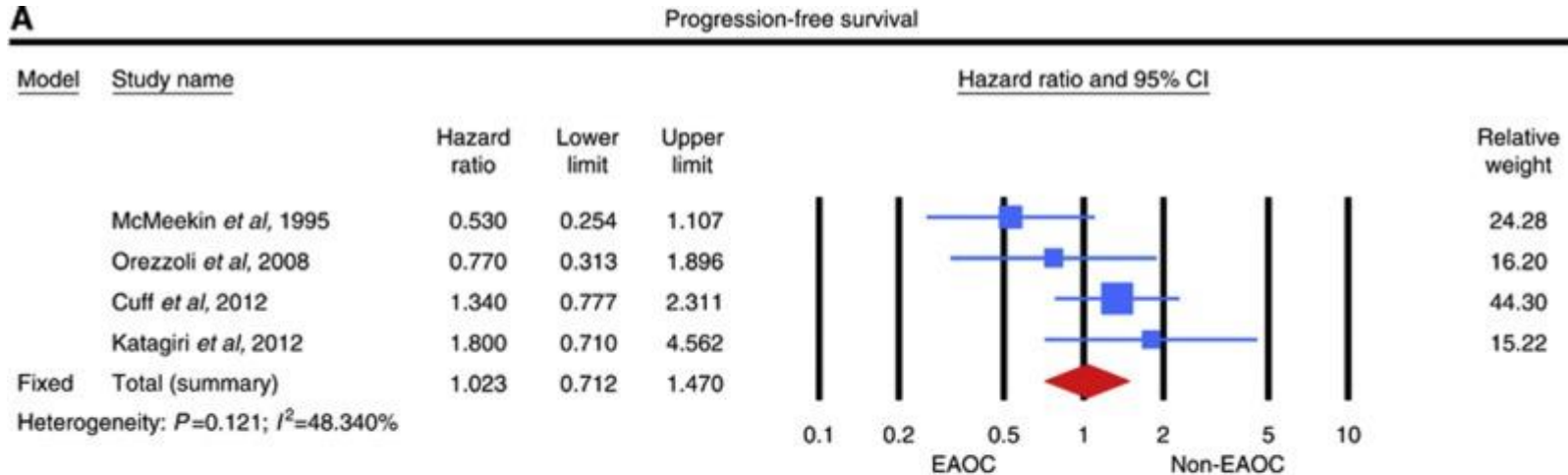
- ❖ Endometriosis patients – commonly **“Symptomatic”**

(Sainz et al., 1995)

- ❖ **Under-estimated prevalence** of endometriosis in
advanced stage of ovarian cancer

(Yoshikawa, 2000)

EAOC survival



Surgery & Follow-up

- ❖ **Bilateral salpingo-oophorectomy** should be considered in women with ES & history of infertility, family history of ovarian cancer or breast cancer when hysterectomy near the menopause

Nezhat et al., 2008

- ❖ Even after surgical Tx, ES patients may have an **elevated ovarian cancer risk** compared with women without a history of ES.

→ 6 monthly follow-up with CA 125 and TVS

Van Gorp et al., 2004

Oral Contraceptives

❖ OC may reduce the risk of EAOOC

Variable	Endometriosis			No endometriosis		
	Control subjects (%)	Cases (%)	OR (95% CI)	Control subjects (%)	Cases (%)	OR (95% CI)
Births (M)						
0	18.6	42.6		14	27.3	
1-2	55.7	40.3	0.31 [‡] (0.18-0.54) [†]	45.5	41.9	0.48 [‡] (0.41-0.57) [†]
≥ 3	25.7	17	0.22 [‡] (0.11-0.45) [†] trend <i>P</i> < .001	40.5	30.8	0.38 [‡] (0.31-0.45) [†] trend <i>P</i> < .001
<i>P</i> interaction [#]						
OC duration						
Never	20.8	34.1		38.1	49.4	
< 10 Y	68.9	61.4	0.58 (0.33-1.03)	52.4	44.5	0.70 (0.60-0.80) [†]
≥ 10 Y	10.4	4.5	0.21 (0.08-0.58) [¶] trend <i>P</i> = .003	9.5	6.1	0.47 (0.37-0.61) [†] trend <i>P</i> < .001

Postmenopausal HT (1)

❖ Estrogen + **Progestin**

: recommended after hysterectomy & BSO due to ES

Hickman et al. & Reimnitz et al., 1988, Van Gorp., 2004, Nezhat et al., 2008

Case report: Endometrial adenocarcinoma arising during
estrogenic treatment 17 years after TAH BSO

Debus et al., 2001

Malignant transformation of residual endometriosis after
hysterectomy: three cases

Karanjgaokar et al., 2009, F&S

Postmenopausal HT (2) long term Progestin Tx is safe?

Clear cell carcinoma arising in endometriosis of
the rectum following **progestin therapy**

Pokieser et al., 2002

**... and
EPT has higher risk for breast cancer
than ET**

NICE guideline, 2017

Hysterectomy in combination with surgical management

- 1.10.8 If hysterectomy is indicated (for example, if the woman has adenomyosis or heavy menstrual bleeding that has not responded to other treatments), excise all visible endometriotic lesions at the time of the hysterectomy.
- 1.10.9 Perform hysterectomy (with or without oophorectomy) laparoscopically when combined with surgical treatment of endometriosis, unless there are contraindications.
- 1.10.10 For women thinking about having a hysterectomy, discuss:
 - what a hysterectomy involves and when it may be needed
 - the possible benefits and risks of hysterectomy
 - the possible benefits and risks of having oophorectomy at the same time

ESHRE guideline

Endometriosis and cancer

What information could be provided to women with endometriosis regarding the development of cancer?

The GDG recommends that clinicians inform women with endometriosis requesting information on their risk of developing cancer that:

GPP

there is no evidence that endometriosis causes cancer,

there is no increase in overall incidence of cancer in women with endometriosis,

some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.

The GDG recommends that clinicians explain the incidence of some cancers in women with endometriosis in absolute numbers.

GPP

The GDG recommends no change in the current overall management of endometriosis in relation to malignancies, since there are no clinical data on how to lower the slightly increased risk of ovarian cancer or non-Hodgkin's lymphoma in women with endometriosis.

GPP

Summary

- **Atypical Endometriosis is precancerous lesion.**
- **If EAOC is suspected, MRI could be recommended.**
- **Molecular works might help the risk assessment.**

Summary

- ES is an independent risk factor for ovarian cancer
: long term follow up, even after menopause, is required.

Reccurence

+

Ovarian ca. risk