

UPDATE ON BORDERLINE OVARIAN TUMOR MANAGEMENT

Confusing, Controversial, Inadequate vs Overtreatment

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Flowchart

- Background
 - Molecular pathways
 - WHO 2014 classification
 - Prognostic factors
- Cystectomy vs USO?
- Is hysterectomy, lymphadenectomy necessary?
- MIS vs Open?
- Appendectomy in MBOT?

Flowchart

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Introduction

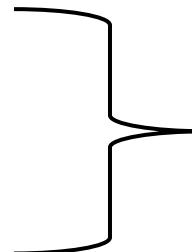
Up-regulated cellular proliferation
Slight nuclear atypia
No destructive stromal invasion

- 1929 Taylor “Semi-malignant”
 - Peritoneal involvement but surprisingly good prognosis
- 1971 FIGO “Low malignant potential”
- 2014 WHO Classification of Tumours of the Female Genital Organs
 - **Borderline = “atypical proliferative tumor”**

Histologic subtypes

- Serous (55%)
- Mucinous (40%)
- Rest (5%) endometrioid, clear cell, seromucinous, Brenner tumor

- Microinvasion
- Lymph node involvement
- Non invasive peritoneal implants

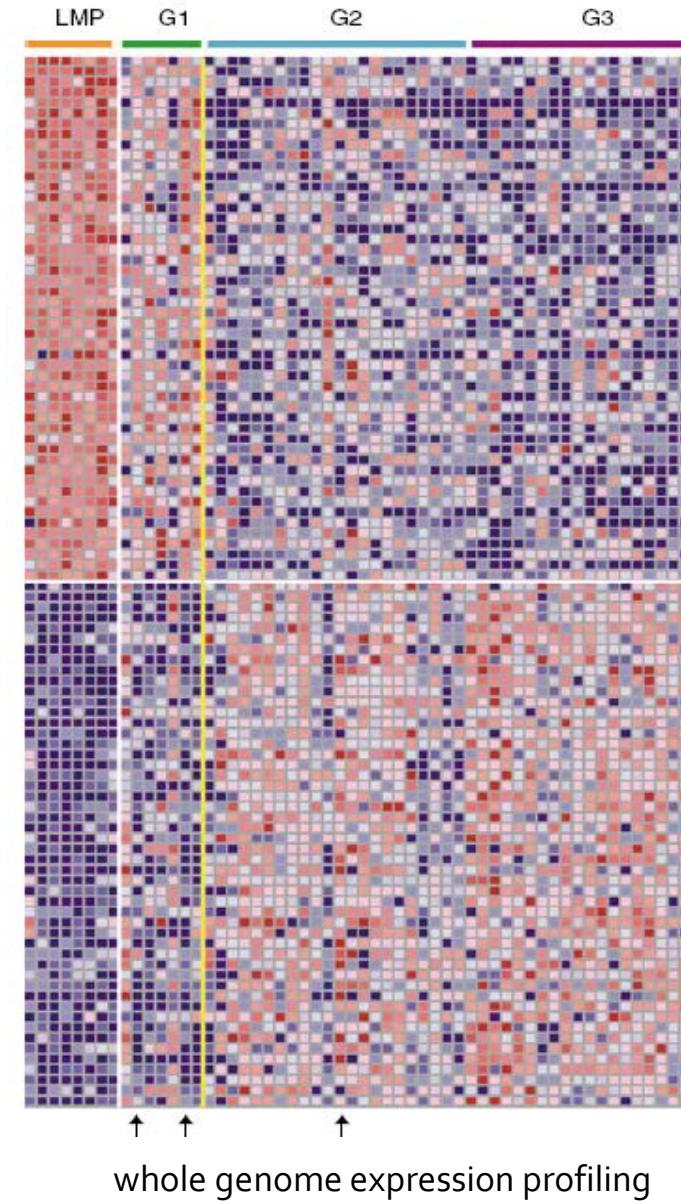


Diagnosis
challenging

- 75% - FIGO stage I (limited to the ovaries)
- Excellent prognosis
 - 97% - 10-year survival (for all stages combined)
- **Standard treatment**
 - Complete surgical resection
 - Surgical staging: omentectomy, peritoneal biopsies, cytology, and appendectomy (mucinous BOT)
 - Adjuvant chemotherapy - not indicated

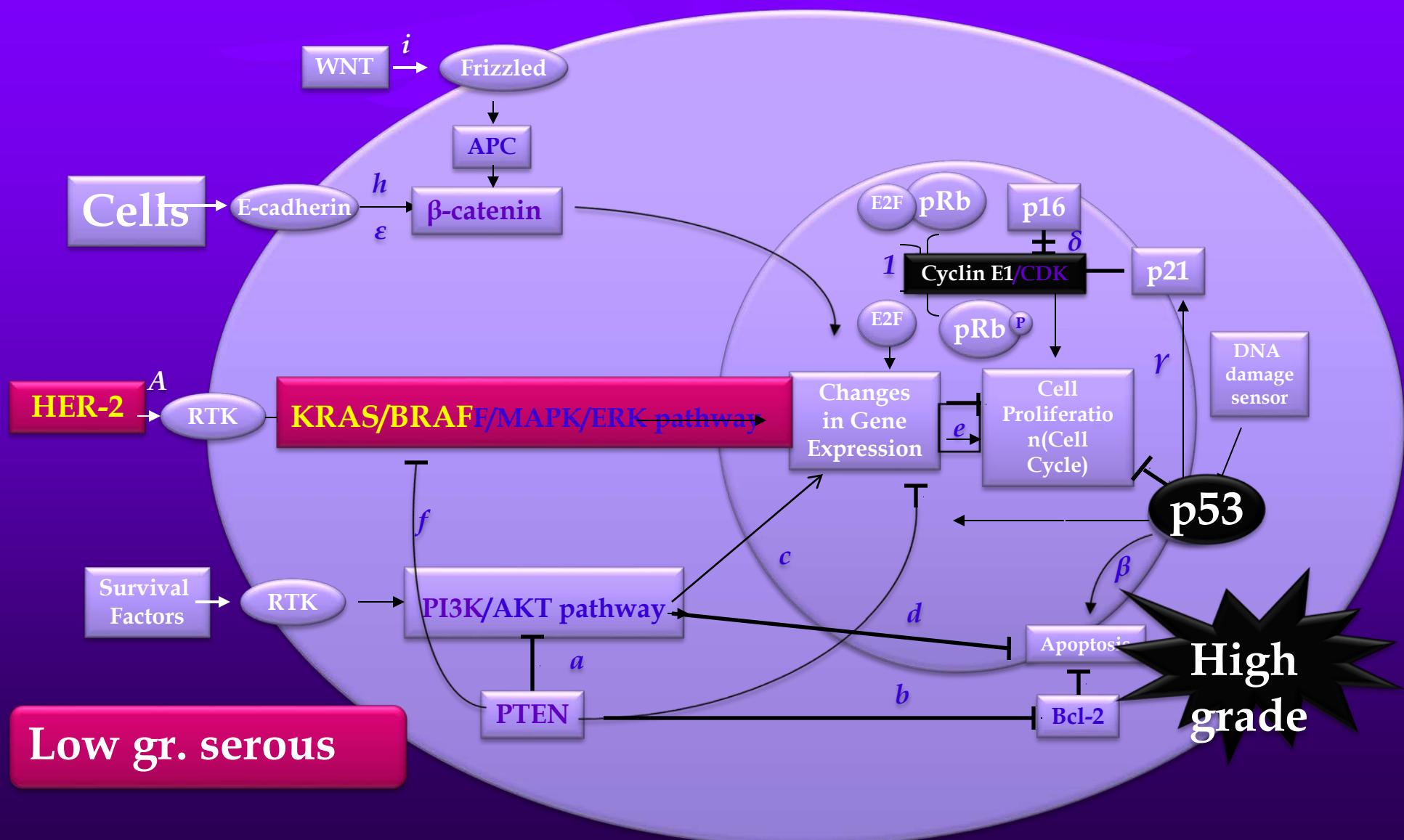
Molecular pathways

- Similar molecular, genetic alterations as low-grade serous carcinomas





OVARIAN LMP/CANCER



Pathologic examination

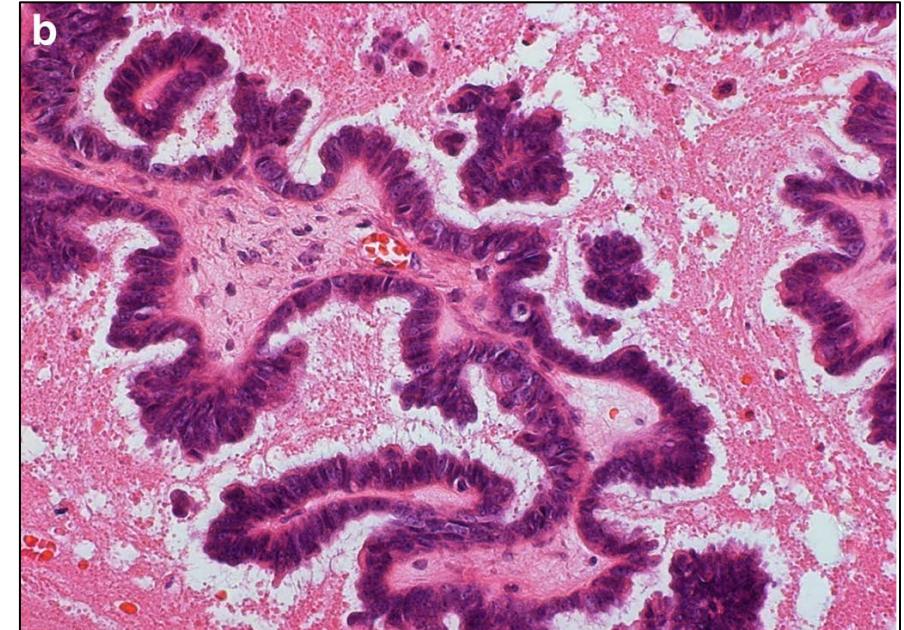
- **MACROSCOPIC**

- Unilocular or multilocular
- Bilateral (1/3 cases)

- **MICROSCOPIC**

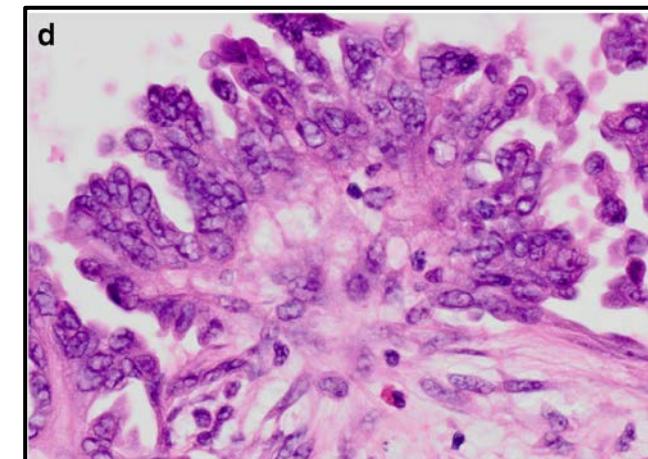
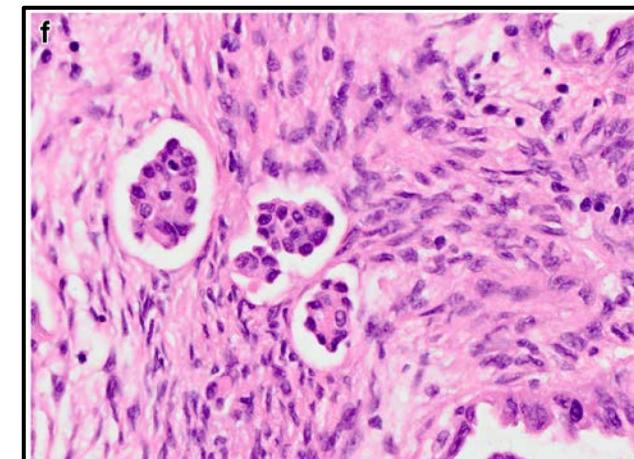
- Hierarchically branching papillae
- Epithelial cells columnar, ciliated
- Mild - moderate nuclear atypia

- IHC: WT1, PAX8, Bcl-2, estrogen and progesterone receptor



WHO 2014 classification

- BOT > 10% borderline histology within a cystadenoma
 - Cystadenoma with focal epithelial proliferation <10% borderline histology
- **Microinvasion:** isolated rounded eosinophilic cells/cell clusters within the stroma up to 5 mm in the largest dimension
- **SBT—micropapillary variant = “non-invasive LGSC”**
 - 5–15% of SBT
 - Lack of hierarchically branching papillae
 - Rounded cells with lack of cilia
 - Greater nuclear atypia



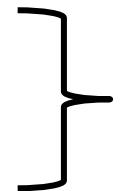
WHO 2014 classification

- **Implants**
 - 1/3 of SBOT
 - Non-invasive VS. invasive implants - NO MORE
 - Invasive – “foci of peritoneal LGSC”
 - Non-invasive (epithelial or desmoplastic) – “IMPLANTS”
 - No infiltration to the underlying sub-peritoneal fat

Prognostic factors

- **Microinvasion**

- Not consistently associated with an adverse prognostic effect
- McKenney et al. 60 SBT (FIGO I-III)
 - Size of largest invasive aggregate (1–12 mm max dimension)
 - Number of micro-invasive foci



No correlation with outcome

- Du Bois et al. Meta-analysis
- 17 series

- Microinvasion and Micropapillary pattern
- Higher recurrence rates: **23% (47/203) 36% (92/255)**
- Not documented - invasive peritoneal disease LGSC, “invasive implants”

McKenney et al. (2006) Patterns of stromal invasion in ovarian serous tumors of low malignant potential (borderline tumors): a reevaluation of the concept of stromal microinvasion. Am J Surg Pathol 30(10):1209–1221

Du Bois A, Ewald-Riegler N, Du Bois O, Harter P (2009) Borderlinetumoren des Ovars—eine systematische Übersicht. **Borderline tumors of the ovary—a systematic review.** Geburtshilfe Frauenheilkd 69:1–27 German

Prognostic factors

- SBT—micropapillary variant

- 1487 women, Denmark (1978–2002)
- SBT or “micropapillary variant”
- FIGO stage I – OS same as general population
- Serous carcinoma risk significantly higher
 - “micropapillary variant” vs SBT
 - stage I patients/patients without implants
 - (**HR = 5.3; 95% CI: 1.7–16.3**)
- Micropapillary variant advanced stages compared to SBT (27 versus 13%)

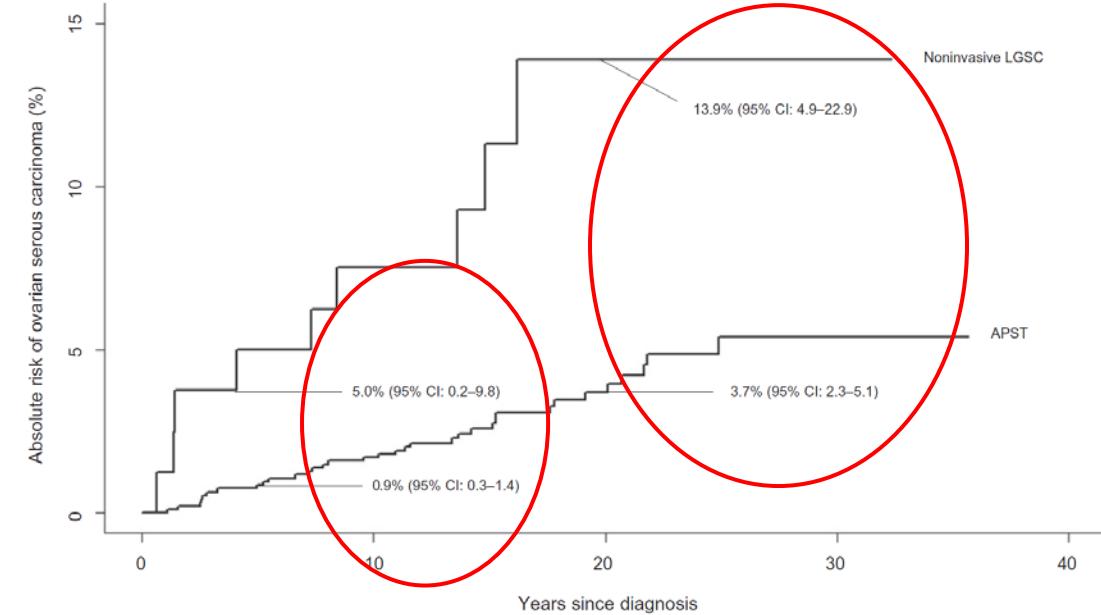


Fig. 2. Absolute risk of developing ovarian serous carcinoma.

Hannibal CG et al (2014) A nationwide study of serous “borderline” ovarian tumors in Denmark 1978–2002: centralized pathology review and overall survival compared with the general population. Gynecol Oncol 134(2):267–273

Prognostic factors

- **Micropapillary variant - No association with recurrence risk**

du Bois A, Ewald-Riegler N, de Gregorio N, Reuss A, Mahner S, Fotopoulos C et al (2013) **Borderline tumours of the ovary: a cohort study of the Arbeitsgemeinschaft Gynakologische Onkologie (AGO) Study Group.** Eur J Cancer 49(8):1905–1914

Prat J, De Nictolis M (2002) **Serous borderline tumors of the ovary: a long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion.** Am J Surg Pathol 26(9):1111–1128

Park JY, Kim DY, Kim JH, Kim YM, Kim KR, Kim YT et al (2011) **Micropapillary pattern in serous borderline ovarian tumors: does it matter?** Gynecol Oncol 123(3):511–516

Prognostic factors

- **Implants**
 - Non-invasive - no adverse prognosis
 - Invasive peritoneal disease (LGSC) - shorter OS
- Seidman et al. Meta-analysis
- 97 studies, 4129 patients, 6.5 y mean FU
- Stage I tumors OS - 100%
- Advanced stage tumors with (non-invasive) implants - OS 95.3%
- Invasive peritoneal disease (LGSC) - OS 66%
 - “Micropapillary variant” strong predictor for concurrent invasive peritoneal disease (LGSC)

Seidman JD, Kurman RJ (2000) Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. Hum Pathol 31(5):539–557

Prognostic factors

**Only known prognostic factors
for progression to IOC:**

- Residual disease after up-front surgery
- Invasive implants

Controversial factors

- Micropapillary pattern
- Stromal micro-invasion

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- **Cystectomy vs USO? (Low and advanced stage)**
 - Is hysterectomy, lymphadenectomy necessary?
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AGO ROBOT

24 ctr 1998-2008: **280/950 <40**; 149 fertil preserv; 32 cystectomy

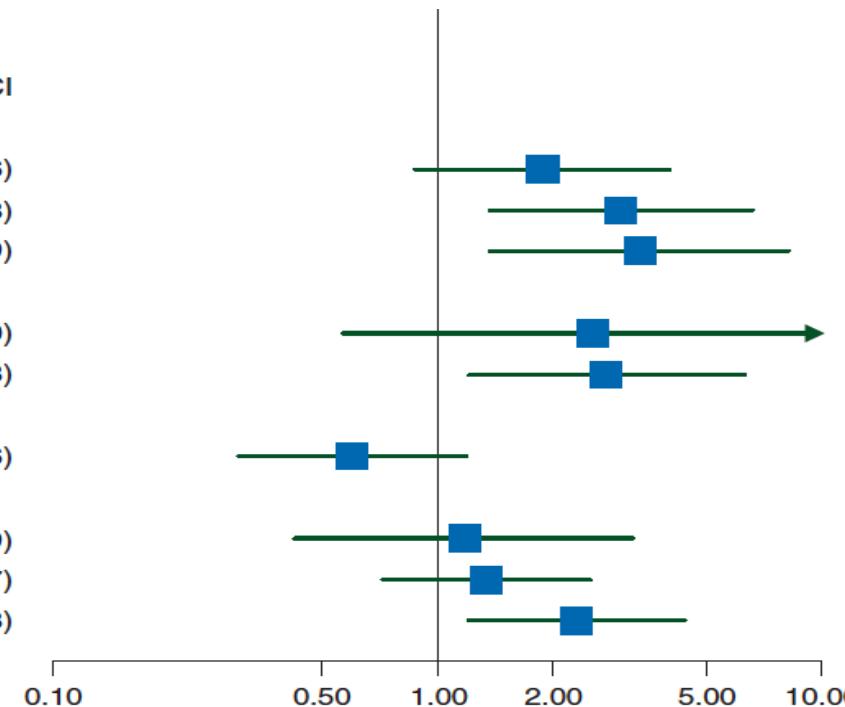
More frequent relapses **18 vs 4%**

Malignant transformation: **12% 6/50<40yo vs 66% 16/24 >40yo**

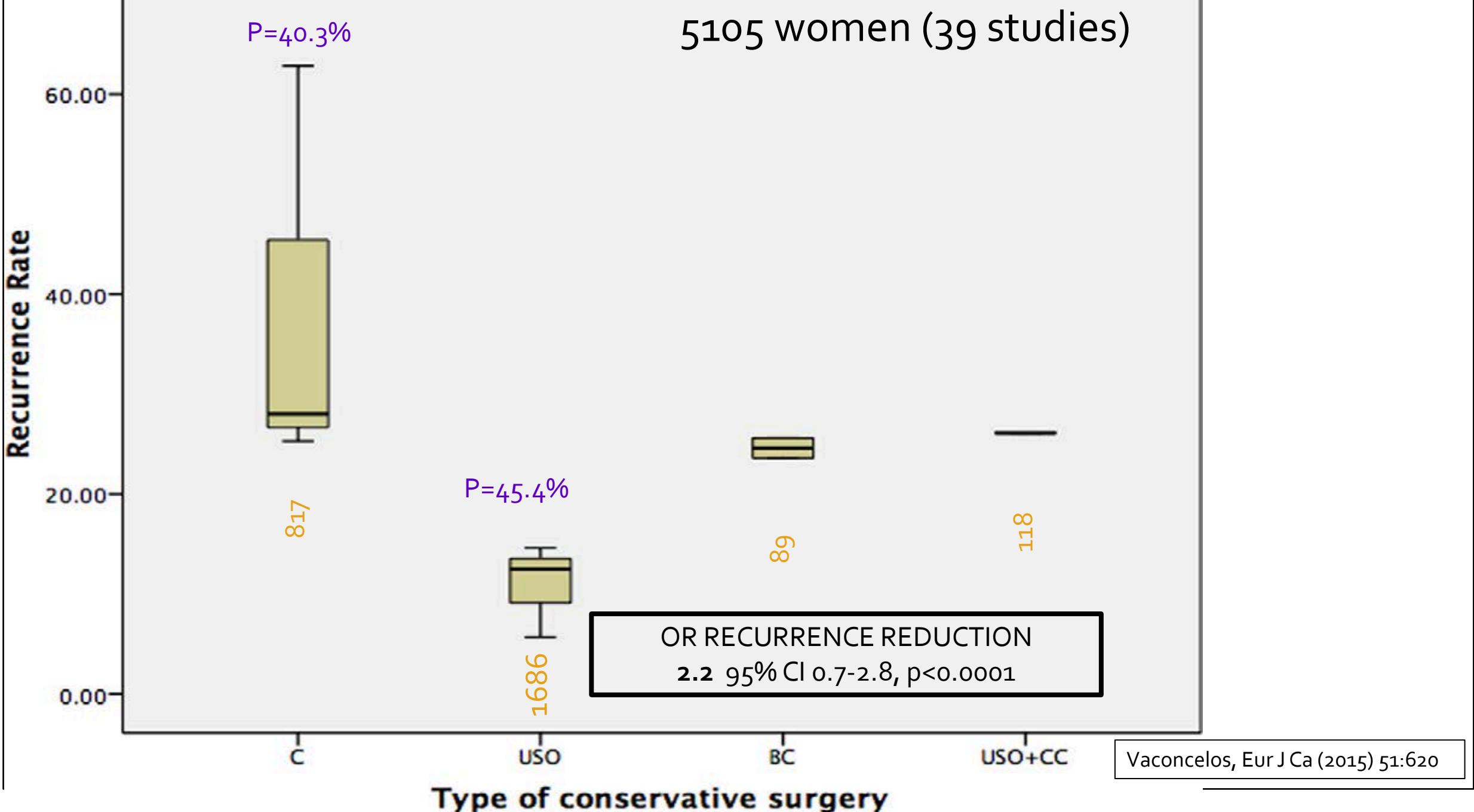
2 /3 ovary

B

Parameter	HR	95% CI
FIGO stage		
IC vs IA/B	1.88	(0.89, 3.96)
IIA-C vs IA/B	3.00	(1.39, 6.48)
IIIA-C vs IA/B	3.38	(1.42, 8.09)
Post-OP residual tumor		
macroscopic vs. microscopic	2.53	(0.57, 11.20)
unknown vs. microscopic	2.74	(1.22, 6.18)
Staging quality		
adequate vs. incomplete	0.60	(0.31, 1.16)
Surgical approach		
LSC → LAP vs. LAP	1.18	(0.43, 3.19)
LSC vs. LAP	1.34	(0.73, 2.47)
Fertility-sparing surgery	2.31	(1.23, 4.33)



< 40 yo



Cystectomy only

- Perform if:
 - Bilateral tumor:
 - Recurrence after BC = USO+CC
 - Vaconcelos meta analysis (26.1 vs 25.6%)
 - Only one ovary

Lim-Tan et al. Ob Gyn (1988) 72: 775
Yinon Y (Gotlieb) Fertil Steril (2007) 88:479
Koskas et al. Ann Surg Oncol (2010)
Palomba et al. Hum Reprod (2010)

Advanced stage: conservative?

- 1969 -2006, 41 pts conservative trt, (\geq Ic)
 - 20 USO
 - 18 C
 - 2 BC
 - 3 INVASIVE IMPLANTS
 - mF/U 57m (range 4-235)

**High
recurrence rate
56%**

Excellent OS
100% at 5 years
92% at 10 years

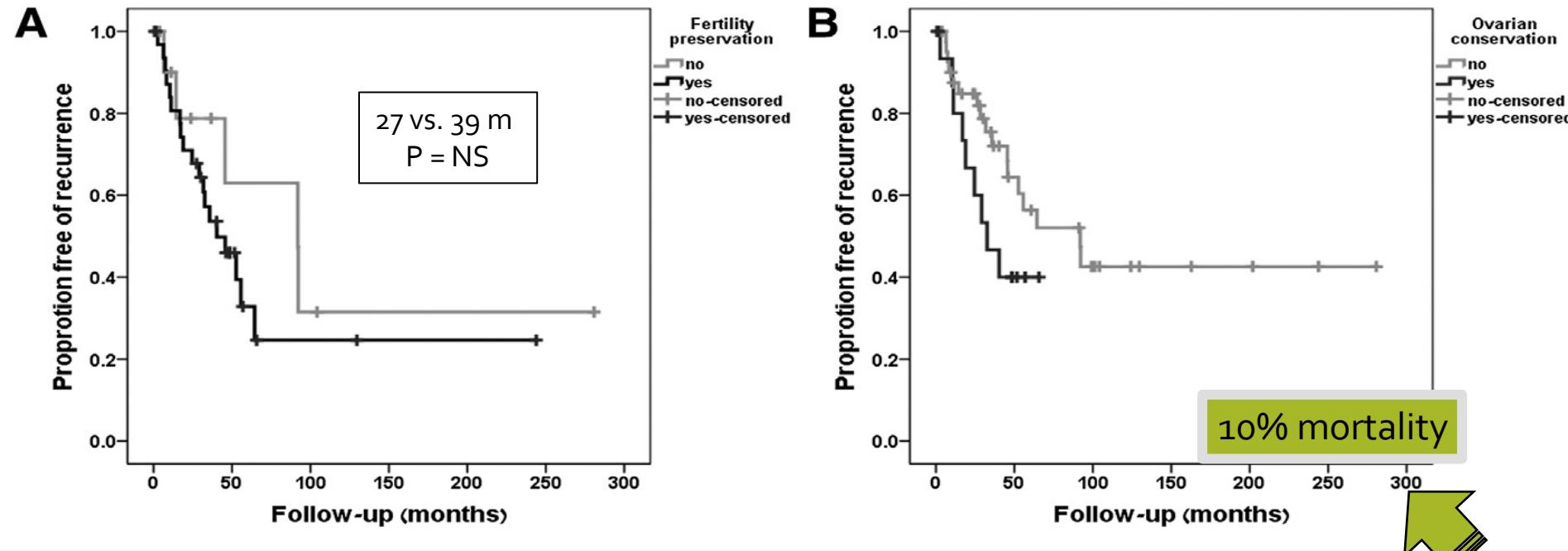
CONCLUSIONS:

Conservative surgery can be proposed
Non-invasive peritoneal implants
Spontaneous pregnancies can be achieved
IVF?

18 pregnancies, 9 spontaneous
(14 patients)

Advanced stage

246 BOT 1981-2011 , 33/59 fertility sparing (17 40% cystectomy), 26 live births in 21 pts



Six cases of deaths in patients with recurrent borderline ovarian tumor.

Histology	Stage	Implants	Fertility preservation	Time to recurrence (mo)	Histology of recurrence	Treatment of recurrence	2nd recurrence (mo)	Time to death (mo)
Mucinous	1C	None	No	14	Invasive implants	Surgical	13	28
Mucinous	1C	None	Yes	17	Noninvasive implants	Surgical	17	70
Serous	1C	None	Yes	10	Local	Surgical	13	31
Serous	3a	Invasive	No	92	Unknown	Chemotherapy	165	
Serous	3b	Invasive	No	26	Invasive implants	Surgical	9	38
Serous	3b	NONINVASIVE	Yes	40	Local	Surgical	15	75

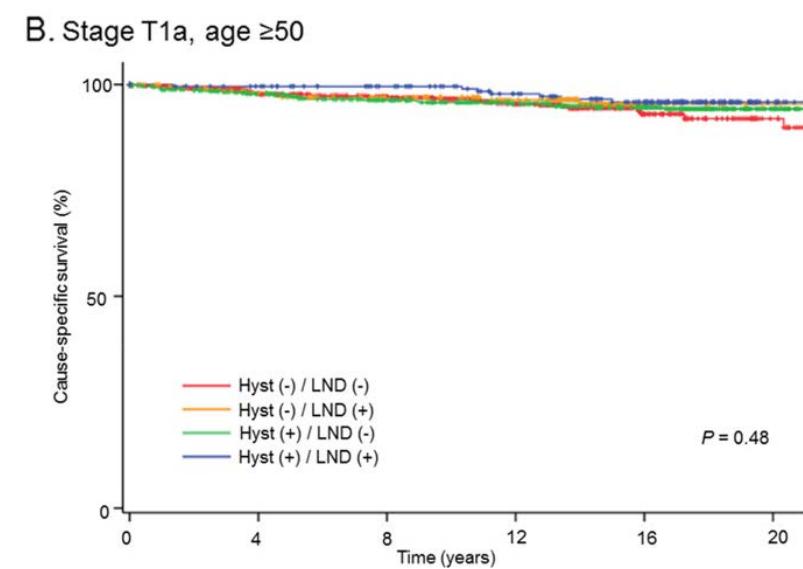
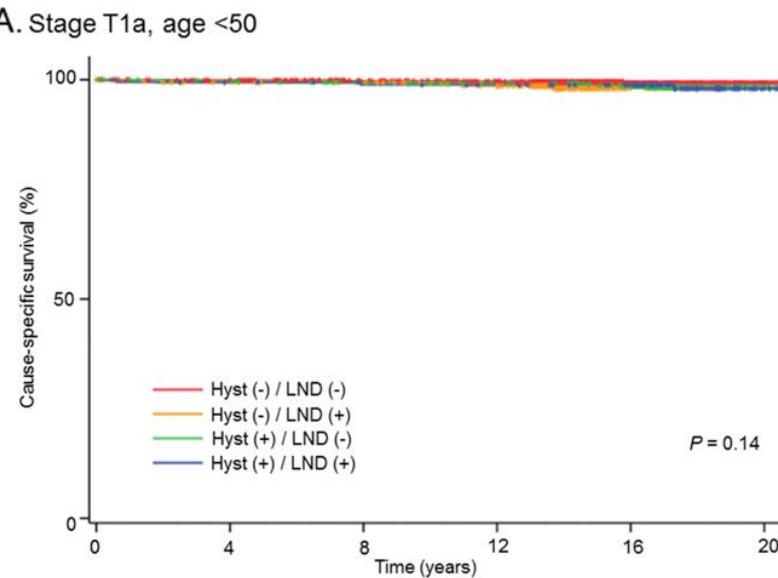
Helpman. Advanced borderline tumors: sparing fertility. Fertil Steril 2015.

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Role of hysterectomy and lymphadenectomy?

- SEER database (Surveillance, Epidemiology, and End Results)
- T₁ BOT (1988-2003), n = 4943
- T_{1a} 75.3%, mF/U 15.6 y, 159 (3.2%) DOD



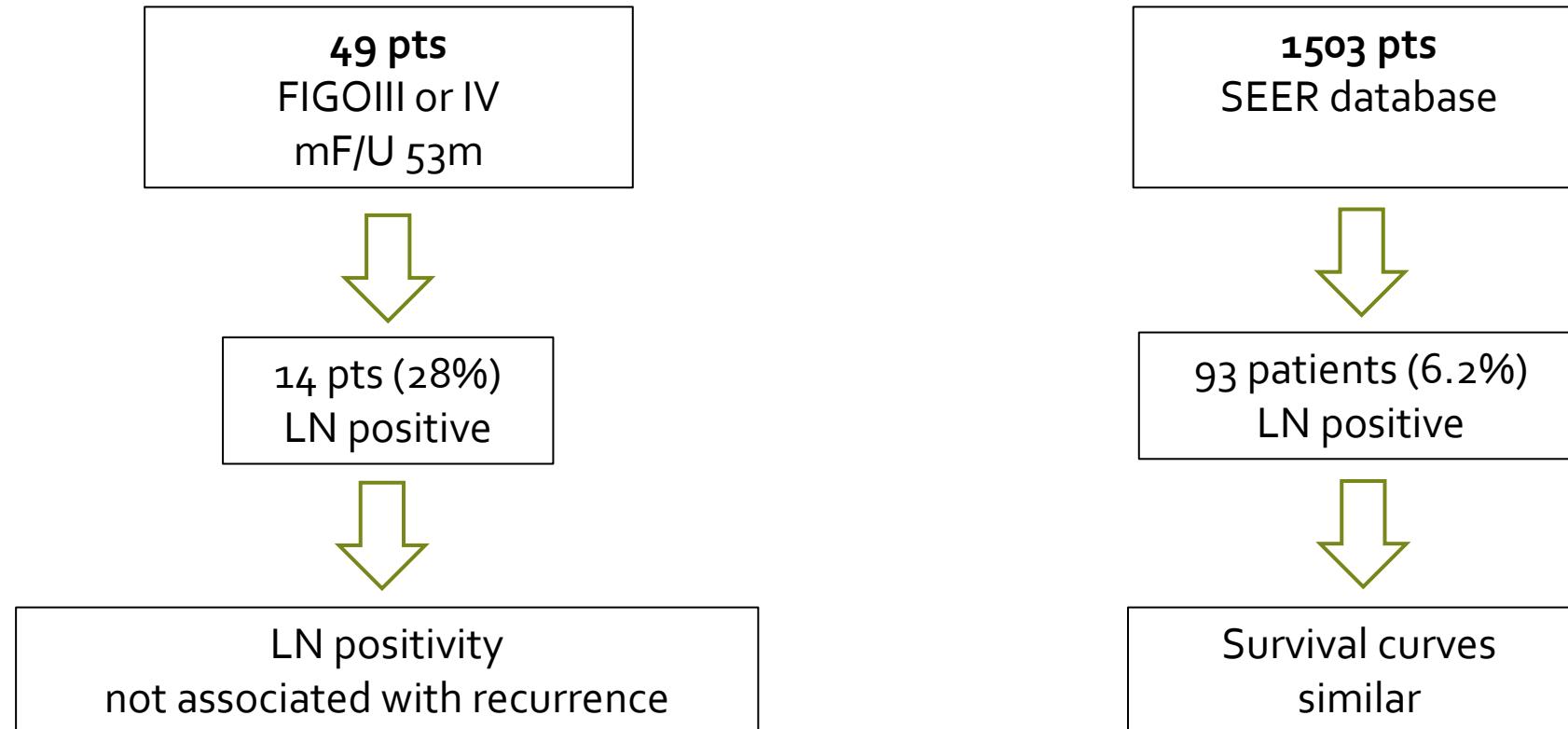
-- 46%
H - 27%
- L 15%
H L 11%

Lymph node metastasis
0.3%-1.1%

Black ethnicity
T_{1b-c} stages
Serous histology
Tumor > 5cm
Independent prognostic factors for + LN (all, P < 0.05)

Selective Lymphadenectomy

Lymphadenectomy – Advanced stage?



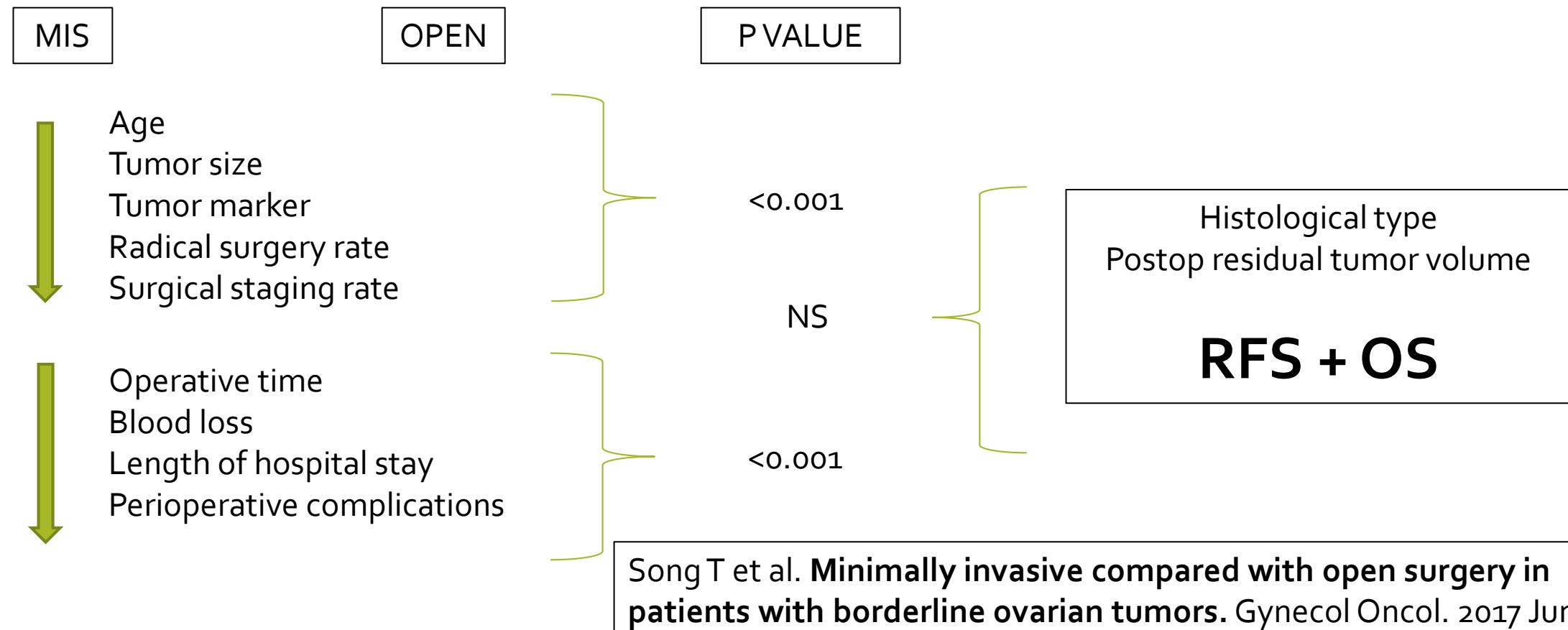
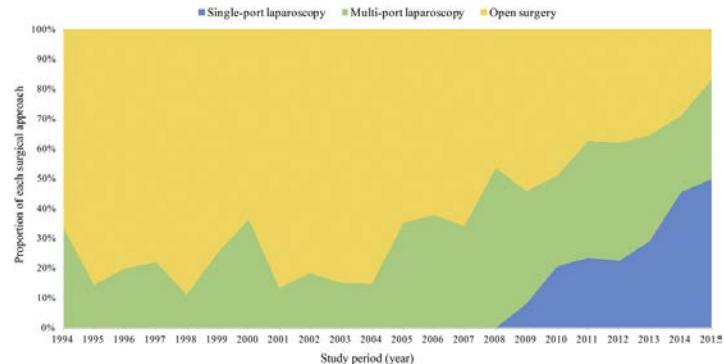
Lesieur B et al. Prognostic value of lymph node involvement in ovarian serous borderline tumors. Am J Obstet Gynecol. 2011

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MIS vs Open?

- 687 BOT pts, mF/U 41.8m
- Single-multi-port laparoscopy (n=89+223) VS. open surgery (n=375)



MIS vs Open?

- du Bois et al. Recurrence rate
 - Laparotomy 7.7%, VS. 14.9% laparoscopy
- Romagnolo el al. Multicenter study
 - Rupture/spilling greater in laparoscopy, statistically significant
 - Laparoscopy VS. open surgery - 13/113 (11.5%) NS

- A. du Bois, N. Ewald-Riegler, O. Du Bois, P. Harter, **Borderline tumors of the ovary-a systematic review**, Geburtshilfe Frauenheilkd. 69 (2009) 807–833.
- C. Romagnolo el al. **Management of borderline ovarian tumors: results of an Italian multicenter study**, Gynecol. Oncol. 101 (2006) 255–260.

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- **Appendectomy in MBOT?**

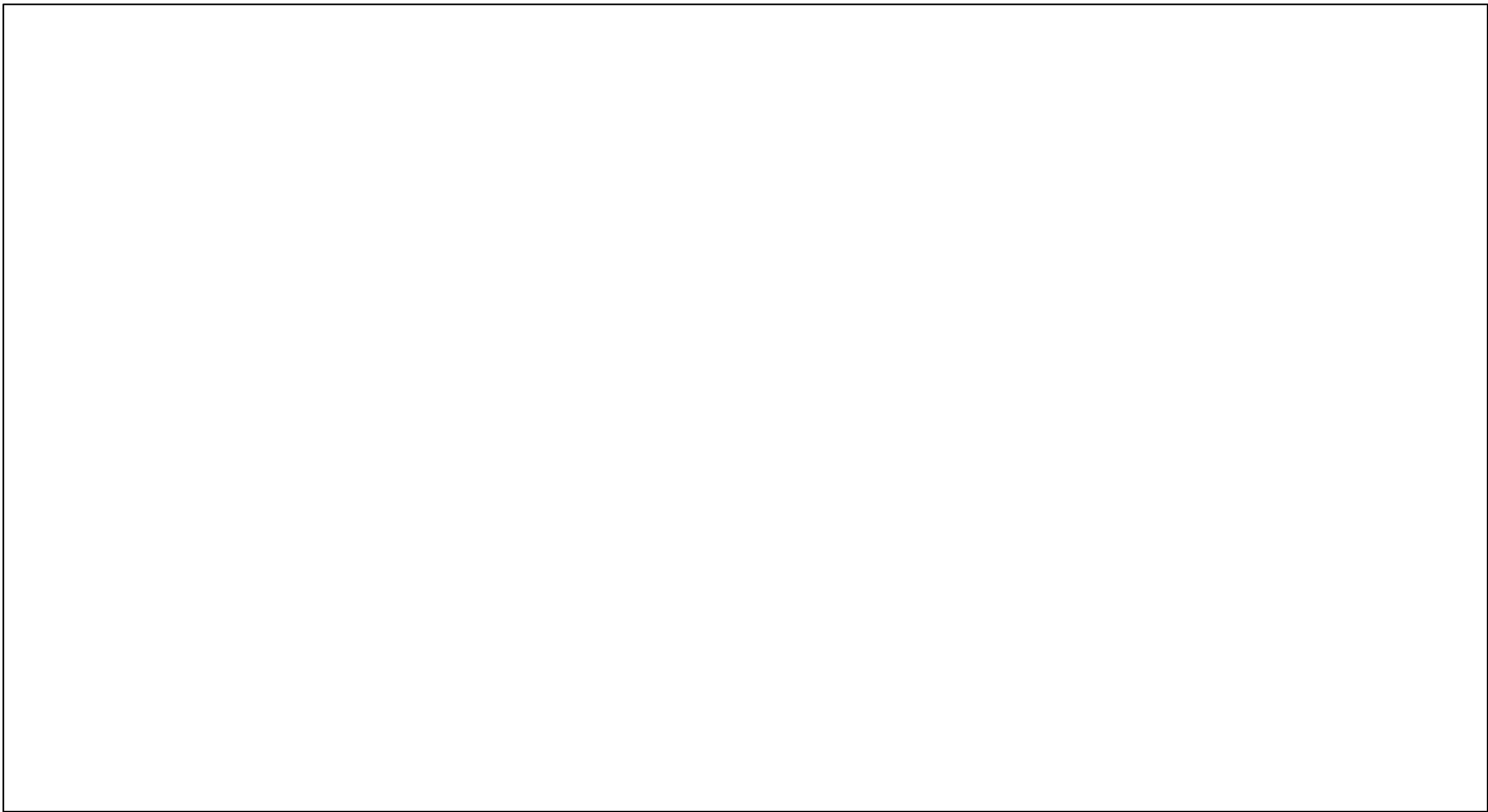
Table 3 Characteristics of studies specifying on appendectomies in mBOTs

Ref.	Author, year	No. mBOT	No. of appendectomies	No. of appendiceal mucinous malignancy	Remarks
Ten included studies specifying on appendectomy in mBOTs					
[10]	Camatte et al., 2004	2	14	0	
[12]	Fotopoulou et al., 2009	At least 1	At least 1	0	One appendix with tumor involvement by mucinous BOT
[14]	Timofeev et al., 2010	26	26	0	One appendiceal carcinoid tumor
[15]	Koskas et al., 2011	97	23	0	
[16]	Song et al., 2012	198	85	0	71 sBOT included but no information on appendectomy
[17]	Lin et al., 2013	68	41	0	One appendiceal carcinoid tumor
[18]	Feigenberg et al., 2013	30	30	2	Metastatic disease of appendiceal malignancy in two abnormal appendices and presence of PMP
[19]	Irving et al., 2014	5	3	0	
[8]	Kleppe et al., 2014	98	13	0	
[9]	Cosyns et al., 2015	27	8	0	
Total		552	232	2	Cosyns et al. Necessity of appendectomy for mucinous borderline ovarian tumors. Systematic review. Arch Gynecol Obstet. 2016 Nov

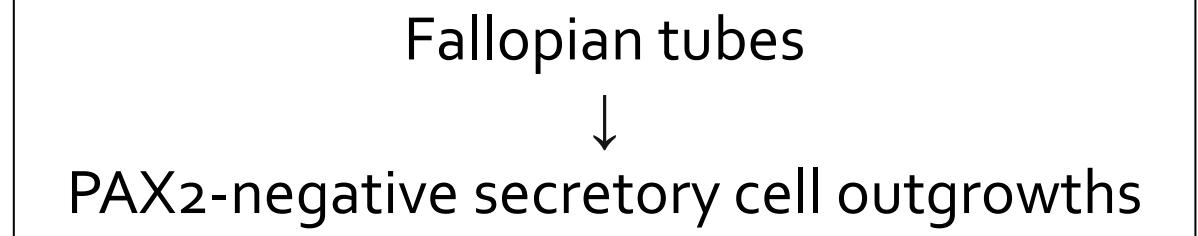
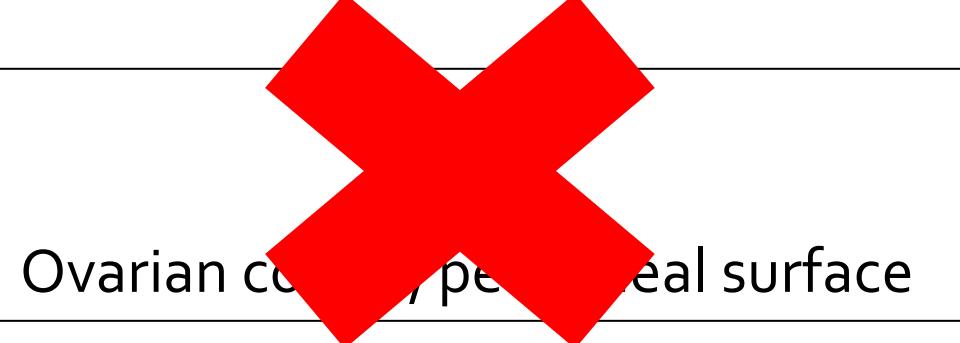
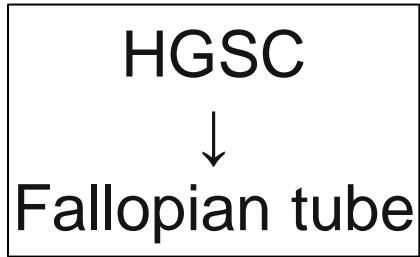
Take home pearls

- Cystectomy only if bilateral tumor or one ovary
- Lymphadenectomy – not necessary
- MIS possible if no residual disease
- MBOT, normal appendix - appendectomy not mandatory

THANK YOU!



Site of origin



Laury AR et al (2011) **Fallopian tube correlates of ovarian serous borderline tumors.** Am J Surg Pathol
35(12):1759–1765



Outcome: *non-Variables*

Microinvasion

No. of Series	Cases	1 recur., AWD	Survival 100%
15	101		

Lymph Node Involvement

25	63	1 DOD	Survival 98 %
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97 studies, 4000 patients, 6.5 yr mean FU

Seidman JD, Kurman RJ Hum Pathol 31:539-557, 2000



