

Fertility Preservation in Ovarian Cancer

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Ovarian cancer

- the highest fatality-to-case ratio of all gynecologic cancers
- less than 40% of cases are diagnosed in early-stage disease

Ovarian cancer

- Agreed fertility preservation in all young patients who want childbearing (<40 years) as:
 1. Germ cell tumors : very chemosensitive
 2. Borderline tumors : rarely relapse
 3. Early stage ovarian cancer

Expected number of cases for FSS

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How many ovarian cancer patients are eligible for fertility-sparing surgery?



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Expected number of cases for FSS

ABSTRACT

Objective: To assess how many epithelial ovarian cancer (EOC) patients are eligible for fertility-sparing surgery (FSS) in a population-based study.

Study design: Using data from the Geneva Cancer Registry, we conducted a retrospective review of all women diagnosed with epithelial ovarian cancer (EOC) between January 1979 and December 2008. Patients were classified into two age groups ("young group" ≤ 45 years and "old group" > 45 years) and as "eligible for FSS" (FIGO IA, G1-G2 or unilateral ICG1) and "non-eligible for FSS" (FIGO IA, G3; IC G2-G3; IB or II-IV). Patients and tumor characteristics were tested with the chi-square test. Estimates of survival were calculated using the Kaplan-Meier method and differences between groups were analyzed by the log-rank test.

Results: A total of 888 EOC patients were analyzed. The young group included 87 patients (9.8%); eleven (1.2%) were identified as eligible for FSS and 6 (0.6%) were nulliparous. The annual incidence of EOC women eligible for FSS in Geneva was 0.48/100,000 (0.5 women/year) and the expected annual incidence rate for Switzerland (8 million inhabitants) is 6.5 women/year.

Conclusion: Only a very small proportion of EOC patients are eligible for FSS. These results highlight the need to centralize FSS data in dedicated European units, in order to maintain expertise and quality of care for these patients.

Surgery

- The standard surgical treatment of patients with FIGO stage I - II epithelial ovarian cancer :
 - TAH+BSO, peritoneal sampling (washing and directed biopsies), omentectomy, and pelvic and paraaortic lymphadenectomy
- Fertility sparing surgery :
 - USO, complete staging including peritoneal sampling, pelvic and para-aortic lymph node dissection and omentectomy
 - Biopsy of the remaining ovary and an appendectomy : optional

Fertility sparing surgery

- considerations in technique

- If the macroscopic **appearance** of the contralateral ovary is **normal**
→ the rate of microscopic tumor : **0 - 2.5%**
- A biopsy of the remaining ovary
→ potential cause of adhesions → reduce fertility
- Cystectomy for benign-appearing contralateral ovarian cysts
→ must be done
two bilateral cancers out of nine cystectomies (Park et al, 2008)
- **Appendectomy** : recommended as part of the surgical staging in **mucinous** tumors (same as borderline ovarian tumors)
- Uterine **curettage** : to rule out concomitant uterine cancer

Borderline tumor

- Fertility-preserving procedures in cases of borderline ovarian tumor is now **well-established**
- The standard of care in young women
 - : USO, omentectomy, peritoneal washing, careful examination of the peritoneal surface and contralateral ovary
- Appendectomy, in cases of mucinous borderline tumors
- Key to diagnosis
 - : pathology to avoid any **infiltrative micropapillary** pattern

Clinical outcomes and fertility after conservative treatment of ovarian borderline tumors

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Objective: To assess clinical outcome and fertility in patients treated conservatively for a low malignant potential (LMP) ovarian tumor.

Design: Retrospective study.

Setting: Gynecologic oncology department of a cancer care center in France.

Patient(s): Forty-four patients treated with conservative management for a stage I (n = 32) or stage II or III (n = 12) LMP tumor.

Intervention(s): Thirty-three patients had unilateral adnexectomy and 11 had cystectomy. Cystectomy was bilateral in 1 patient and was done in conjunction with contralateral adnexectomy in 5 patients.

Main Outcome Measure(s): Tumor recurrence and pregnancy rates.

TABLE 1

Patient characteristics.

Characteristics	Conservative treatment	Radical treatment	Total
Mean age (\pm SD) (y)	32 \pm 11.4	46 \pm 15.7	42.3 \pm 15.8
Disease stage			
IA	30	39	69
IB	2	6	8
IC	5	18	23
Total	37	63	100
IIA	0	5	5
IIB	1	7	8
IIC	3	8	11
II unknown	0	1	1
Total	4	21	25
IIIA			
IIIB			
IIIC			
Total	8	41	49
Surgical procedure			
Omentectomy			
Peritoneal biopsy			
Pelvic lymphadenectomy			
Paraortic lymphadenectomy			
Peritoneal implants			
Noninvasive			
Invasive			
Adjuvant treatment			
No	45	72	117
Yes	4	53	57
Total	49	125	174

TABLE 2

Recurrence rates by type of surgery.

Type of surgery	No. with recurrence (%)	No. with progressive invasive disease (%)	Total
Radical	6 (5.7)	3 (2.8)	105
Conservative	9 (20.5)	0	44
Unilateral adnexectomy	5 (15.1)	0	33
Cystectomy:	4 (36.3)	0	5
Unilateral adnexectomy plus contralateral cystectomy	1	0	5
Unilateral cystectomy	2	0	5
Bilateral cystectomy	1	0	1

None of these 9 patients died of progression of their disease. All recurrences were detected during follow-up procedures.

Conclusion:

Conservative management of LMP tumor significantly increases the risk of recurrence but **does not affect overall survival**.

Conservative management might be proposed in young patients who wish to preserve their fertility, but careful follow-up will be required to detect tumor recurrence.

Borderline tumor

- Prognosis of borderline tumor is excellent, with overall survival rates for early stage as high as 97%.
- Rates of recurrence are higher in cases of conservative surgery than with radical surgery
- Even if conservative surgery increases the risk for recurrence, disease is often amenable to surgical management, and patient survival is not affected by the conservative approach

Conservative treatment in epithelial ovarian cancer: results of a multicentre study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer) and SFOG (Société Française d'Oncologie Gynécologique)

Philippe Morice^{1,8}, Eric Leblanc², Annie Rey¹, Marc Baron³, Denis Querleu⁴, Jérôme Blanchot⁵, Pierre Duvillard¹, Catherine Lhommé¹, Damienne Castaigne¹, Jean Marc Classe⁶, Pascal Bonnier⁷ and GCCLCC⁶ and SFOG⁷

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A multi center retrospective study

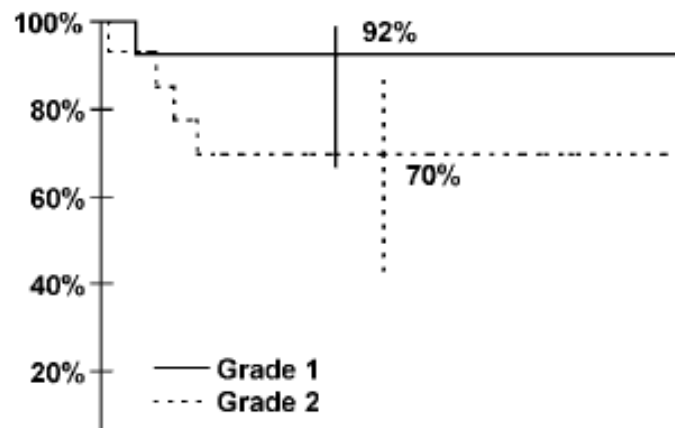
Inclusion criteria :

- (i) Histological review by the same pathologist
- (ii) age ≤ 40 years
- (iii) conservative management with complete peritoneal staging
- (iv) delivery of a platinum-based chemotherapy in stage \geq IC
- (v) follow-up >1 year

Conservative treatment in epithelial ovarian cancer: results of a multicentre study of the GCCLCC (Groupe des Chirurgiens de Centre de Lutte Contre le Cancer) and SFOG (Société Française d'Oncologie Gynécologique)

RESULTS:

34 patients had conservative surgery (Stage 1A: 30, Stage 1B: 4).
11 patients had recurrent disease (10 invasive diseases, 1 non-invasive).
Among 10 patients with recurrent disease (Stage 1A G1:1, Stage 1B:1, Stage 2:1, Stage 3:1, Stage 4:1, Stage 5:1, Stage 6:1, Stage 7:1, Stage 8:1, Stage 9:1).



All patients Conclusion:

10 pre-operative patients with EOC could be considered in young patients with stage IA G1 disease.

This procedure **should not be performed in patients with FIGO stage > IA.**

grade in patients with stage IA disease.

Long-term survival of young women receiving fertility-sparing surgery for ovarian cancer in comparison with those undergoing radical surgery

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After a central pathological review and search of the medical records from multiple institutions, a total of 572 patients with Stage I EOC were retrospectively evaluated.

All patients were divided into three groups:

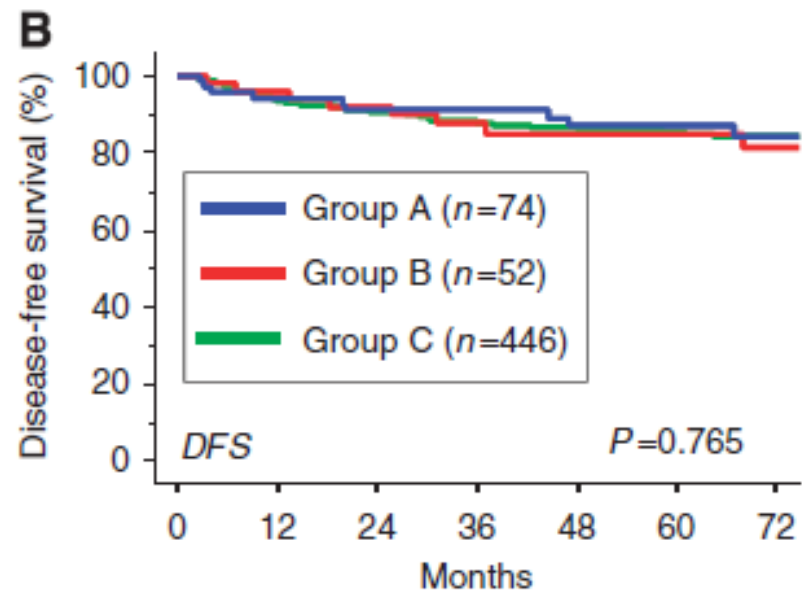
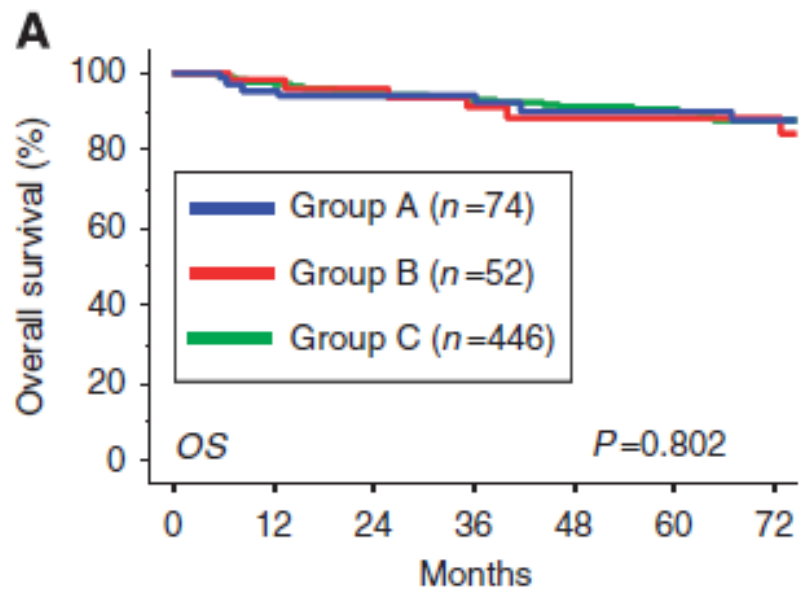
group A (n=74) : FSS, age \leq 40

group B (n=52) : RS, age \leq 40

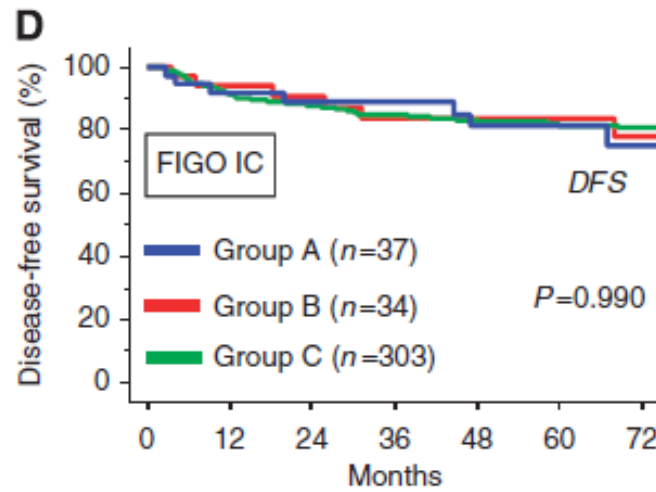
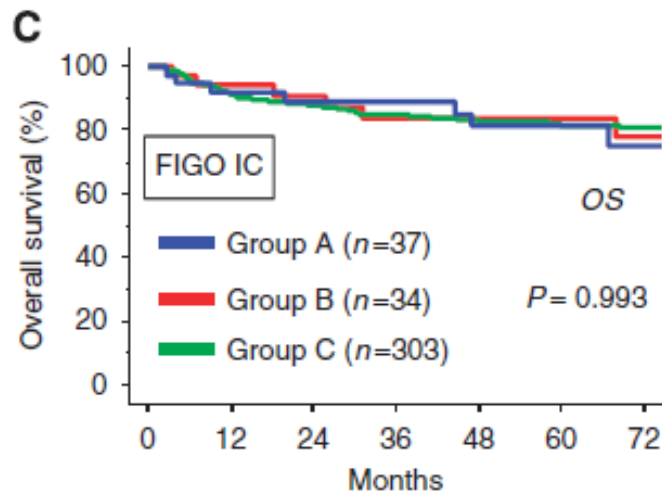
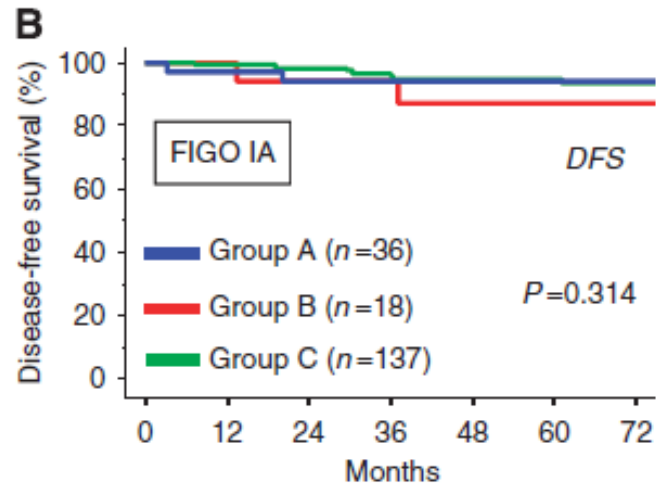
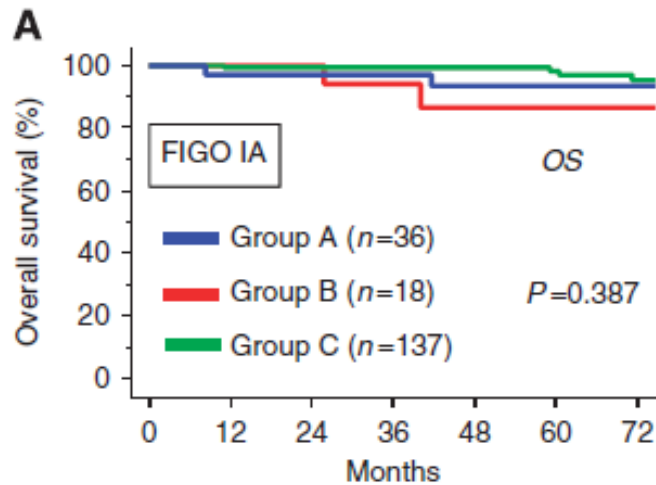
group C (n= 446); RS, age $>$ 40

Table I Patients' characteristics

	Total	FSS Group A	Radical surgery		P-value
			Group B	Group C	
Total	572	74	52	446	
Age					<0.0001
≤40	126	74	52	0	
>40	446	0	0	446	
FIGO stage					0.0291
IA	191	36	18	137	
IB	7	1	0	6	
IC	374	37	34	303	
IC(r) ^{*1}	213	21	21	171	
IC(non-r) ^{*2}	161	16	13	132	
Histological type					0.0002 ^{#1}
Serous	64	4	4	56	
Mucinous	150	43	18	89	
Clear-cell	212	13	17	182	
Endometrioid	128	14	11	103	
Others ^{*3}	18	0	2	16	
Grade					0.294 ^{#2}
G1/G2	323	57	33	233	
G3	37	4	2	31	
NC ^{*4}	212	13	17	182	



There was no significant difference in OS among these groups



Even when they were stratified by sub-stage,
There were no significant differences in survival among the three groups

Table 2 Uni- and multivariate analyses of clinicopathologic parameters in relation to OS and DFS of patients

	No	OS				DFS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		5-Year OS (%)	P-value	Hazard ratio (95% CI)	P-value	5-Year DFS (%)	P-value	Hazard ratio (95% CI)	P-value
Total	572								
Age									
≤40	126	89.8	0.956	I	0.882 (0.430–1.811)	86.5	0.969	I	0.864 (0.440–1.697)
>40	446	90.6				85.3			
FIGO stage									
IA	191	96.1	0.0007	I	2.776 (1.314–5.866)	93.9	<0.0001	I	2.898(1.472–5.703)
IB/C	381	87.5				81.3			
Surgery									
Radical	498	90.4	0.663	I	0.877 (0.335–2.297)	85.2	0.592	I	0.874 (0.361–2.115)
FSS	74	90.8				87.9			

Long-term survival of young women receiving fertility-sparing surgery for ovarian cancer in comparison with those undergoing radical surgery

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Conclusion:

Stage I EOC patients treated with FSS showed an acceptable prognosis compared with those who underwent RS.

(Int J Gynecol Cancer 2009;19: 1199Y1204)

Long-Term Survival After Fertility-Sparing Surgery for Epithelial Ovarian Cancer

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Richard R. Barakat, MD, and Carol L. Brown, MD

TABLE 1. Patient demographic characteristics

	Fertility-Sparing Surgery	Standard Surgery
No patients	20	103
Median age	27	51
FIGO stage		
IA	11 (55%)	42 (41%)
IB	0	6 (6%)
IC	9 (45%)	55 (53%)
Histologic grade		
1	14 (70%)	36 (35%)
2	5 (25%)	36 (35%)
3	1 (5%)	20 (19%)
No data	—	11 (11%)
Histology		
Endometrioid	6 (30%)	37 (36%)
Serous	1 (5%)	21 (20%)
Mucinous	11 (55%)	21 (20%)
Clear cell	1 (5%)	23 (22%)
Mixed	0	1 (1%)
No data	1 (5%)	0

TABLE 2. Fertility-sparing surgery: procedures for staging (n = 20)

Procedure	No Patients	(%)
Cystectomy contralateral ovary	5	25
Biopsy of contralateral ovary	10	50
Gross appearance, contralateral ovary	5	25
Omentectomy	20	100
Pelvic and paraaortic lymph node sampling	18	90
Endometrial sampling	14	70

TABLE 3. Adjuvant therapy

	Fertility-Sparing Surgery (n = 20)	Standard Surgery (n = 103)
No patients treated	10 (50%)	85 (83%) $P < 0.05$
Radiation therapy	0	3 (3%)
Oral alkylating agent	2 (10%)	8 (8%)
Platinum-based chemotherapy	8 (40%)	74 (72%)

TABLE 4. Patient data and 5-year recurrence-free and overall survival*

	Fertility-Sparing Surgery	Standard Surgery Subgroup <45 y	Standard Surgery
No patients	20	25	103†
Median follow-up	122 months	111 months	113 months
RFS	84% (CI, 68–100%)	83% (CI, 70–100%)	78% (71–87%)
OS	84% (CI, 68–100%)	83% (CI, 70–100%)	82% (74–90%)

*Kaplan-Meier method.

†Five patients died of other causes.

RFS, recurrence-free survival; OS, overall survival; CI, confidence interval.



Outcomes of fertility-sparing surgery for invasive epithelial ovarian cancer: Oncologic safety and reproductive outcomes

Jeong-Yeol Park, Dae-Yeon Kim, Dae-Shik Suh, Jong-Hyeok Kim, Yong-Man Kim,
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Retrospective study with 62 invasive EOC patients who underwent fertility-sparing surgery, defined as the preservation of ovarian tissue in one or both adnexa and the uterus

Of the 62 EOCs

Stage : IA (n=36), IB(n=2), IC (n=21) , IIB(n=1), IIIA(n=1), and IIIC(n=1)

Grade :I (n=48), II(n=5), III (n=9)

48 patients received platinum-based adjuvant chemotherapy



Outcomes of fertility-sparing surgery for invasive epithelial ovarian cancer: Oncologic safety and reproductive outcomes

Jeong-Yeol Park, Dae-Yeon Kim, Dae-Shik Suh, Jong-Hyeok Kim, Yong-Man Kim,
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At a median follow-up of 56 months (range, 6–205 months)
11 patients recurred (6 died of disease, 2 were alive with disease, and 54
were alive without disease)
Patients with stage > IC ($p = 0.0014$) or grade III ($p = 0.0002$) tumors had
significantly poorer survival.

Conclusion:

Fertility-sparing surgery can be considered in young patients with **stages IA–C**
and **grades I–II** EOCs who desire to preserve their fertility.

Fertility Preservation in Young Women With Epithelial Ovarian Cancer

Jason D. Wright, MD^{1,2}; Monjri Shah, MD¹; Leny Mathew, MD³; William M. Burke, MD^{1,2,4}; Jennifer Culhane, MD³; Noah Goldman, MD⁴; Peter B. Schiff, MD^{2,5}; and Thomas J. Herzog, MD^{1,2}

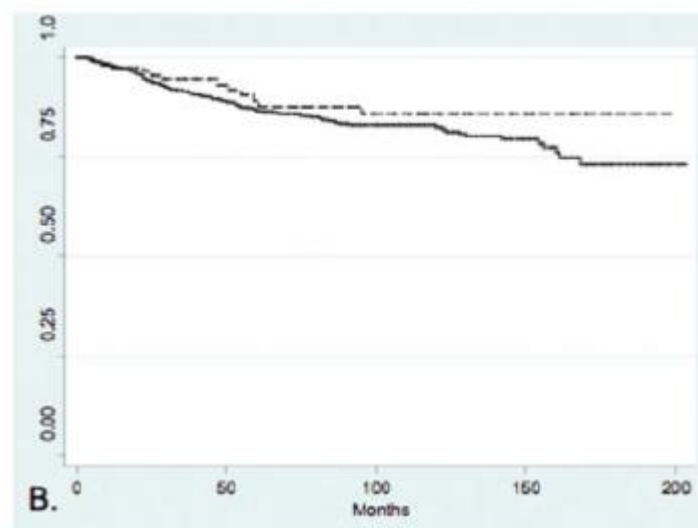
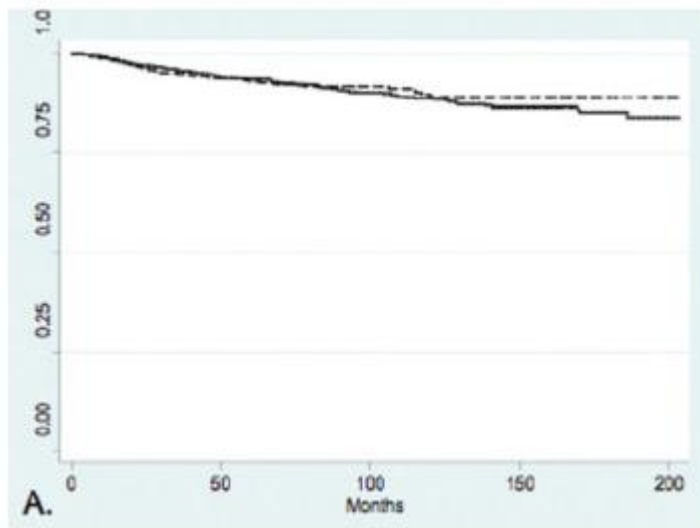
Cancer 2009;115:4118–26. © 2009 American Cancer Society.

- age ≤ 50 , stage IA or IC EOC patients in the SEER database
- bilateral oophorectomy vs ovarian conservation
- uterine conservation vs hysterectomy
- multivariate Poisson regression models, Cox proportional hazards models and the Kaplan-Meier method

Table 2. Poisson Regression Model of Factors Associated With Ovarian and Uterine Preservation

Variable	RR (95% CI)				
	Ovarian Preservation, n=1186	Uterine Preservation, n=2921			
Age, y			Histology		
<25	Referent	Referent	Mucinous	Referent	Referent
25-35	0.80 (0.71-0.89)	0.68 (0.59-0.76)	Serous	0.89 (0.75-1.06)	0.86 (0.73-1.00)
36-50	0.27 (0.23-0.32)	0.23 (0.19-0.27)	Endometrioid	0.74 (0.61-0.89)	0.81 (0.69-0.95)
			Clear cell	0.63 (0.46-0.86)	0.51 (0.38-0.68)
Race			Tumor grade		
White	Referent	Referent	1	Referent	Referent
Black	1.02 (0.78-1.31)	1.09 (0.85-1.38)	2	0.98 (0.82-1.17)	0.89 (0.76-1.03)
Other	1.03 (0.86-1.22)	1.07 (0.91-1.25)	3	0.99 (0.74-1.32)	0.76 (0.58-0.97)
Year of diagnosis			Unknown	1.15 (0.98-1.35)	1.17 (1.01-1.34)
1988-1996	Referent	Referent	Radiation		
1997-2004	1.17 (1.03-1.34)	1.15 (1.02-1.30)	No	Referent	Referent
SEER registry			Yes	0.53 (0.21-1.37)	0.10 (0.02-0.63)
Central	Referent	Referent	Unknown	0.83 (0.39-1.77)	0.80 (0.38-1.67)
Eastern	1.52 (1.23-1.86)	1.31 (1.09-1.57)	Lymphadenectomy		
Western	1.36 (1.12-1.64)	1.23 (1.05-1.45)	Performed	Referent	Referent
Marital status			Not performed	1.19 (1.03-1.38)	1.58 (1.39-1.79)
Married	Referent	Referent	Stage		
Single/unknown	0.91 (0.76-1.04)	1.16 (1.02-1.31)	IA	Referent	Referent
			IC	0.77 (0.62-0.95)	0.75 (0.63-0.88)

RR indicates relative risk; CI, confidence interval; SEER, the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.



Kaplan-Meier estimates of survival in patients

(A) stage IA

(B) stage IC

----- oophorectomy

———— ovarian preservation.

Table 3. Cox Proportional Hazards Model of Factors Associated With Overall Survival for Young Women With Stage IA and IC Ovarian Cancer With Ovarian and Uterine Conservation

Variable	Ovarian Preservation, n=1148	Uterine Preservation, n=2921			
Ovarian preservation					
Oophorectomy	Referent	—			
Ovarian preservation	0.69 (0.39-1.20)	—			
Uterine preservation					
Hysterectomy	—	Referent			
Uterine preservation	—	0.87 (0.62-1.22)			
			Histology		
			Mucinous	Referent	Referent
			Serous	0.76 (0.42-1.37)	0.75 (0.53-1.07)
			Endometrioid	0.66 (0.38-1.16)	0.67 (0.47-0.94)
			Clear cell	1.13 (0.58-2.18)	1.02 (0.69-1.49)
			Tumor grade		
			1	Referent	Referent
			2	0.77 (0.41-1.42)	1.24 (0.85-1.79)
			3	2.39 (1.29-4.45)	3.04 (2.07-4.44)
			Unknown	1.01 (0.57-1.77)	1.51 (1.05-2.18)
			Radiation		
			No	Referent	Referent
			Yes	1.77 (0.69-4.57)	1.17 (0.62-2.24)
			Unknown	3.53 (0.76-16.31)	0.89 (0.22-3.67)
			Lymphadenectomy		
			Performed	Referent	Referent
			Not performed	1.31 (0.82-2.07)	1.11 (0.86-1.43)
			Stage		
			IA	Referent	Referent
			IC	2.43 (1.55-3.80)	1.75 (1.35-2.26)

Fertility Preservation in Young Women With Epithelial Ovarian Cancer

Jason D. Wright, MD^{1,2}; Monjri Shah, MD¹; Leny Mathew, MD³; William M. Burke, MD^{1,2,4}; Jennifer Culhane, MD³; Noah Goldman, MD⁴; Peter B. Schiff, MD^{2,5}; and Thomas J. Herzog, MD^{1,2}

Cancer 2009;115:4118-26. © 2009 American Cancer Society.

Total of 1186 women; BSO ,754(64%) Ovarian preservation 432 (36%)
Younger age, later year of diagnosis, and residence in the eastern or western United States were associated with ovarian preservation
Women with endometrioid and clear cell histologies and stage IC disease

Conclusion:

Ovarian and uterine-conserving surgery were **safe** in young women who had **stage IA and IC** epithelial ovarian cancer.

Germ Cell Tumours

<u>Ref</u>	<u>Cases</u>	<u>Chemo</u>	<u>Preg</u>	<u>Survival</u>
Perrin 1999	45	29	7 babies	2 deaths
Sagae 2003	26	23	4 pregnancies – no deaths	
Zanetta 2001	138	81	40 babies	95% 5 year

For Germ cell tumors – outcome excellent. Most problems were in the more advanced stage diseases.
Fertility can be retained.

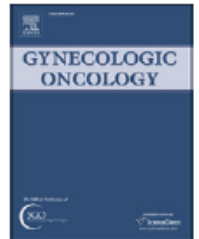
FSS for women with BRCA mutation



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Radical fimbriectomy: A reasonable temporary risk-reducing surgery for selected women with a germ line mutation of BRCA 1 or 2 genes? Rationale and preliminary development

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Possible candidate

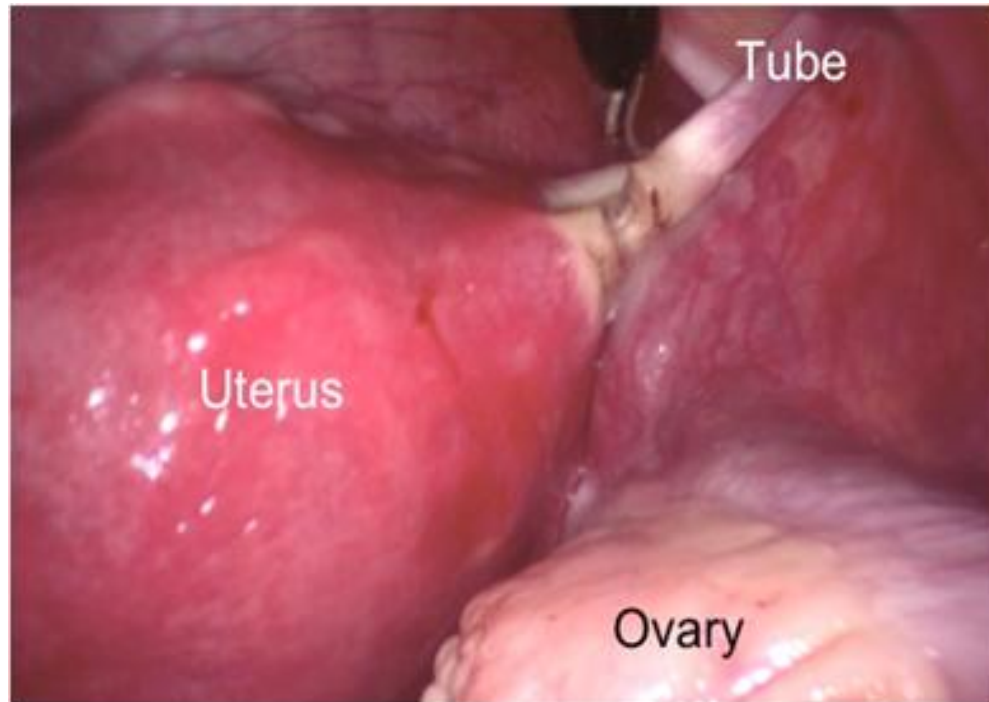
- young BRCA mutation carriers
- especially those with a history of breast cancer
- be reluctant to undergo prophylactic BSO

Radical fimbriectomy

- resecting the fallopian tube from the uterine level to the ovary
- resecting the totality of the terminal part of tube or fimbria along with its attachment to the underlying ovary
- bipolar coagulation and scissors are used to separate the tube from the uterine cornua
- dissecting tube free from mesosalpinx until the fimbria
- remove the portion of ovary tethered to the fimbria together
- at the most, 1/4 of the ovarian volume is removed along with the fimbria.

Radical fimbriectomy

Separation of fallopian tube from uterus after limited bipolar dessication (right side)



Radical fimbriectomy

The four methods of ovarian division

A: Sharp division with scissors ; B: Stapler: EndoGIA® 45mm vascular tape ;
C: Bipolar scalpel: 5mm LigaSure® blunt tip ; D: Harmonic scalpel: Ultracision®



Conclusions

- Fertility conservation is safe for Borderline tumor and germ cell tumor
- For invasive tumors – probably best to restrict fertility preservation surgery to properly staged, Stage 1 disease

Thank you for your attention

