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Lyon France

Systemic treatment for early stage

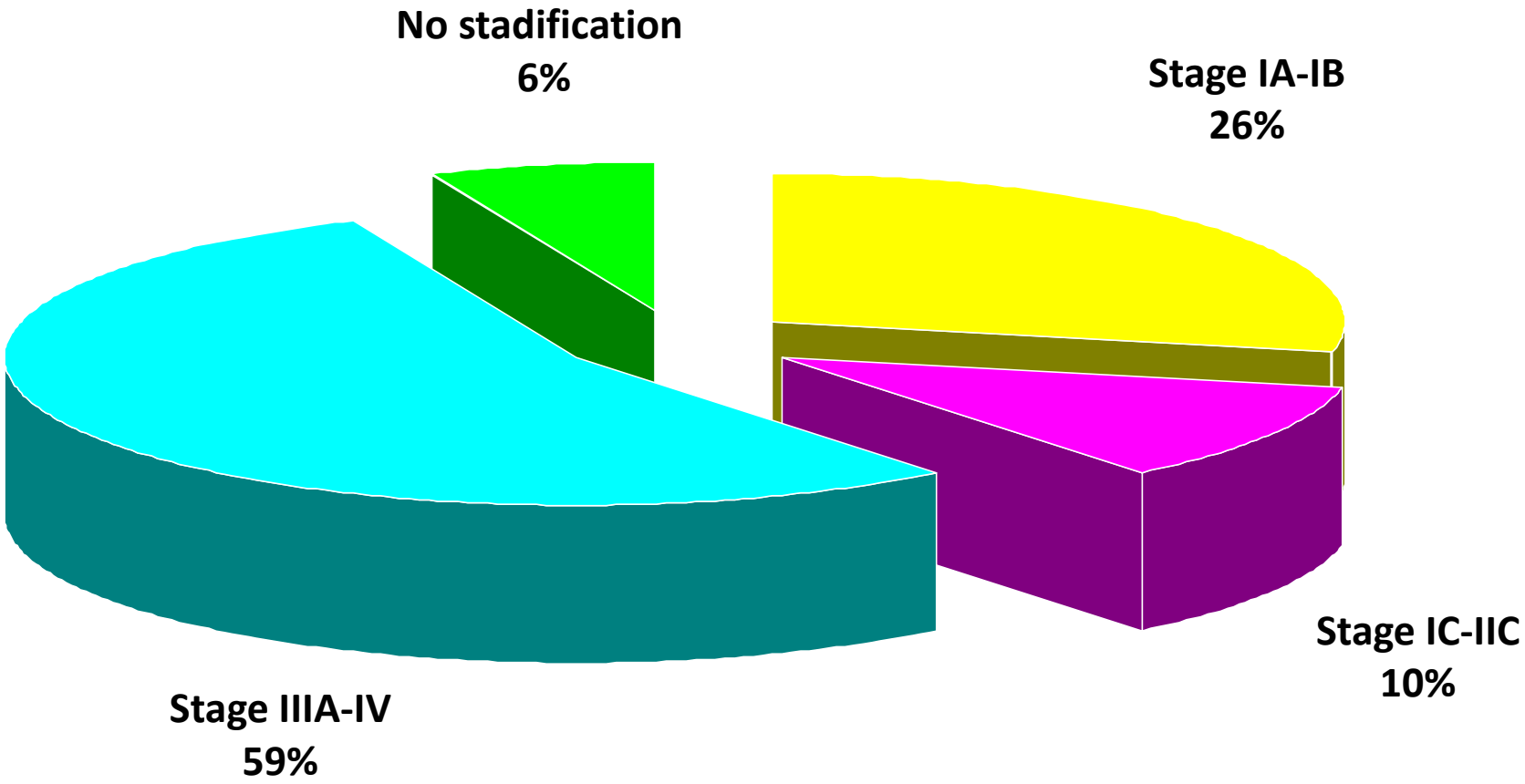
DISCLOSURE SLIDE

- Honoraria
  - Astra Zeneca,
  - Roche,
  - Novartis-GSK,
  - Pfizer,
  - Pharmamar,
  - Lilly,
  - Merck,
  - Bayer,
  - Amgen
  - Tesaro

Early stages (Ia-Ic) challenges

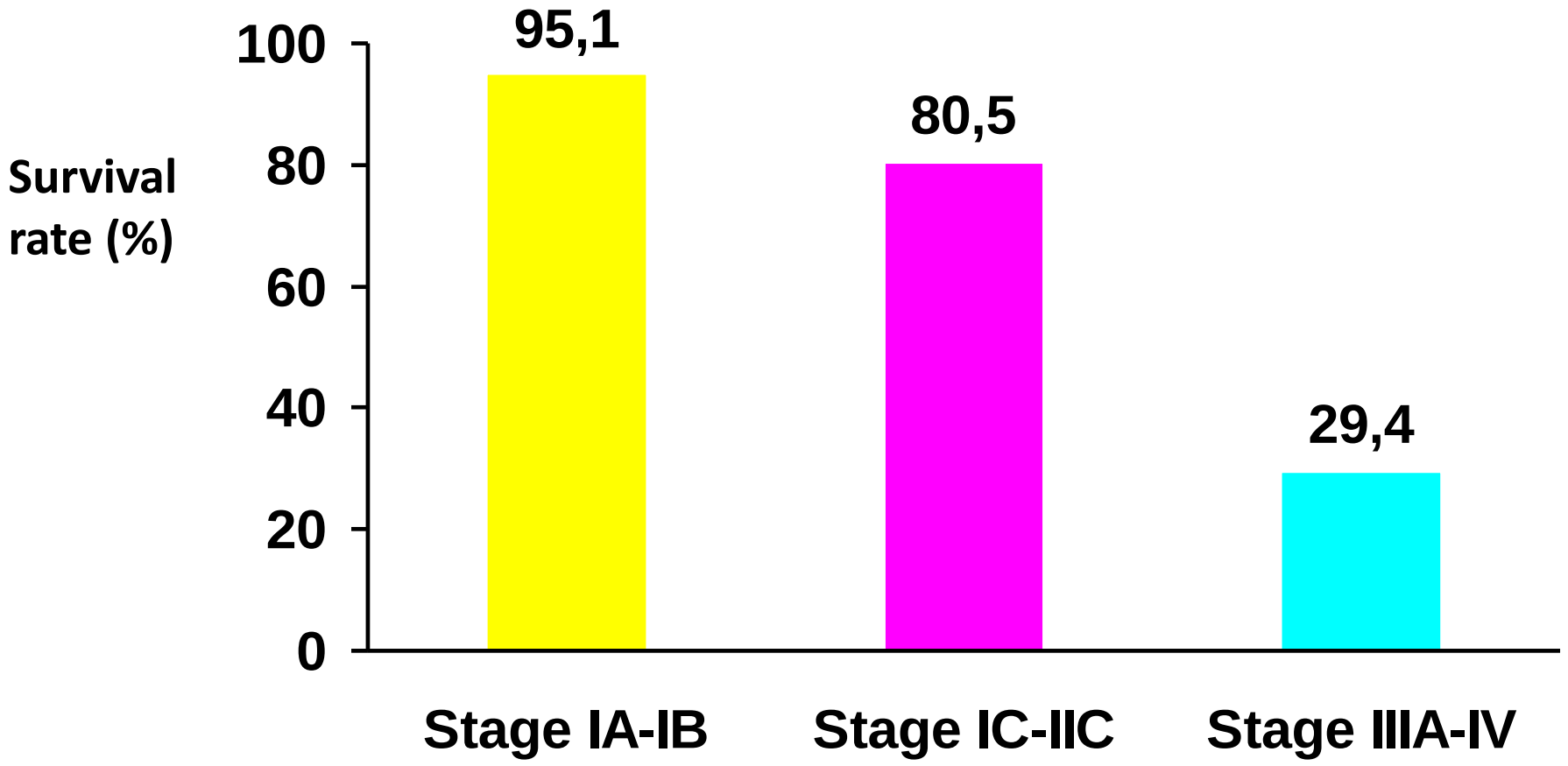
- Definition for early stages: st IA-IC, IA-IIB, IA-IIIA?
- Diagnosis at early stage = screening
- ✓ Indications for conservative surgery (C Marth)
- Indications for adjuvant therapies
  - For who? Duration ?
- Particular histology : clear cell carcinoma, mucinous, low grade serous
- Very few patients less than 35% and < 20% «high risk of relapse»

EOC and stage at diagnosis (US 1992-1997)



SEER data: Ries et al, 2001

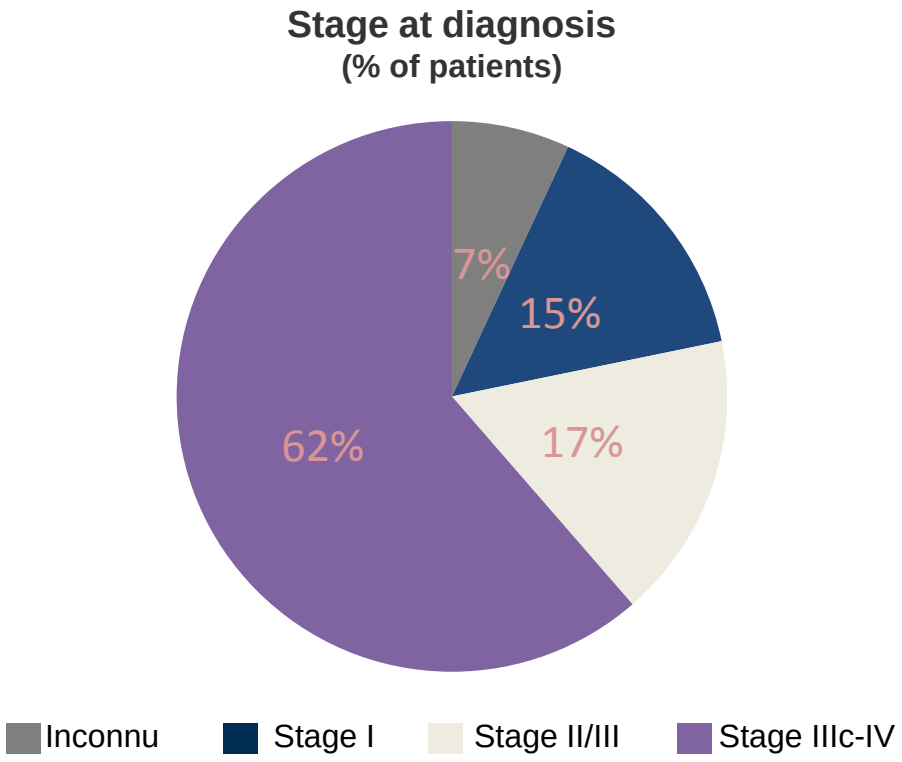
Survival @ 5 years according to stage US (1992-97)

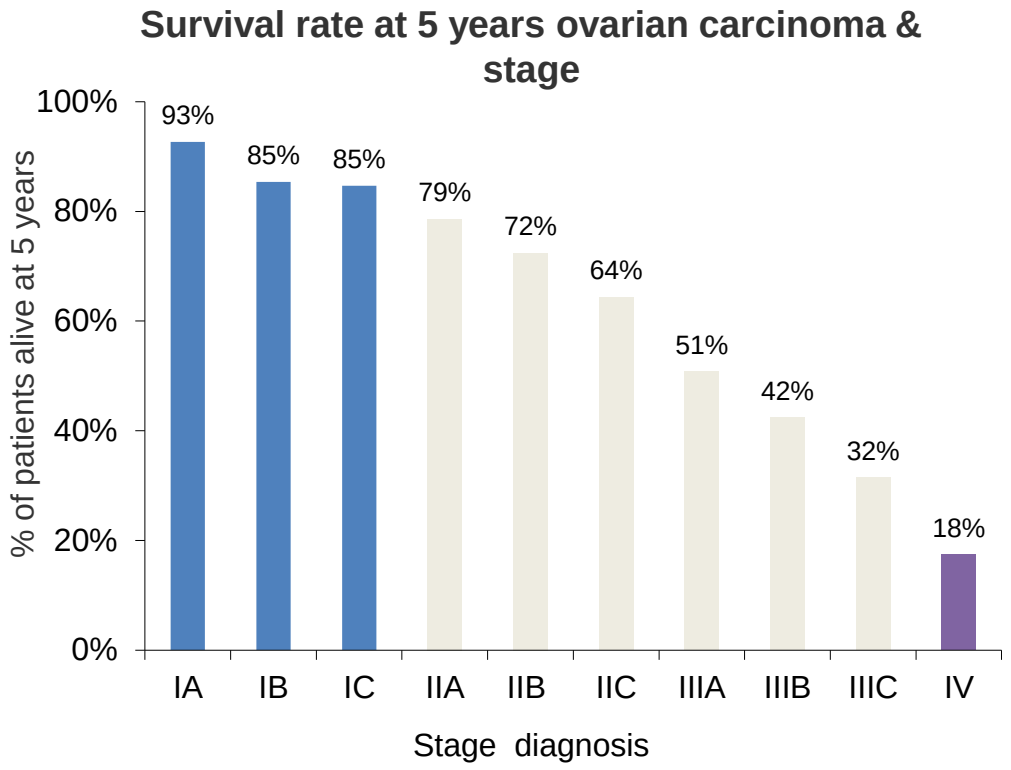


SEER data: Ries et al 2001

Stage and Prognosis (1)

- Majority of cancers diagnosed at advanced disease
- More than 70-80% of patients will relapsed





Sources: Goff et al 2007; Mattson Jack Cancer Impact data 2007; Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. Semin Surg Oncol 2000;19:3-10. http://seer.cancer.gov/statfacts/index.html

Natural History : early ovarian cancer

SEER database, Chan et al, BJC 2008

	Total	1988–1992	1993–1997	1998–2001	P-value
Overall	8372	2511	3294	2567	
Age at diagnosis (years)					
Median (range)	57 (12–99)	58 (12–99)	57 (15–99)	55 (14–97)	
Age <50	2799 (33.4%)	836 (33.2%)	1110 (33.7%)	853 (33.2%)	0.917
Age ⩾50	5573 (66.6%)	1675 (66.8%)	2184 (66.3%)	1714 (66.8%)	
Race					
Caucasian	6564 (78.4%)	2125 (84.6%)	2530 (76.8%)	1909 (74.4%)	<0.001
Hispanic	587 (7.0%)	120 (4.8%)	250 (7.6%)	217 (8.5%)	
African American	401 (4.8%)	105 (4.2%)	174 (5.3%)	122 (4.7%)	
Asian	605 (7.2%)	118 (4.7%)	257 (7.8%)	230 (8.9%)	
Other	215 (2.6%)	43 (1.7%)	83 (2.5%)	89 (3.5%)	
Surgery					
Yes	7945 (94.9%)	2406 (95.8%)	3102 (94.2%)	2437 (94.9%)	0.018
No	427 (5.1%)	105 (4.2%)	192 (5.8%)	130 (5.1%)	
Lymphadenectomy					
Yes	3327 (39.7%)	659 (26.2%)	1276 (38.7%)	1392 (54.2%)	<0.001
No	4360 (52.1%)	1648 (65.6%)	1713 (52.0%)	999 (38.9%)	
Unknown	685 (8.2%)	204 (8.1%)	305 (9.3%)	176 (6.9%)	
Stage					
Stage I	6152 (73.4%)	1853 (73.8%)	2443 (74.2%)	1856 (72.3%)	0.253
Lymphadenectomy	2506 (29.9%)	510 (20.3%)	964 (29.3%)	1032 (40.2%)	<0.001
No lymphadenectomy	3120 (37.3%)	1188 (47.3%)	1237 (37.6%)	695 (27.1%)	
Stage II	2220 (26.5%)	658 (26.2%)	851 (25.8%)	711 (27.7%)	
Lymphadenectomy	821 (9.8%)	149 (5.9%)	312 (9.5%)	360 (14.0%)	<0.001
No lymphadenectomy	1240 (14.8%)	460 (18.3%)	476 (14.4%)	304 (11.8%)	
Histology					
Serous	2214 (26.4%)	671 (26.7%)	847 (25.7%)	696 (27.1%)	<0.001
Endometrioid	2230 (26.6%)	574 (22.9%)	875 (26.6%)	781 (30.4%)	
Mucinous	1601 (19.1%)	552 (22.0%)	641 (19.5%)	408 (15.9%)	
Clear cell	940 (11.2%)	256 (10.2%)	380 (11.5%)	304 (11.8%)	
Other	1387 (16.6%)	458 (18.2%)	551 (16.7%)	378 (14.7%)	
Grade					
Grade 1	1703 (20.3%)	474 (18.9%)	717 (21.8%)	512 (19.9%)	0.010
Grade 2	2163 (25.8%)	635 (25.3%)	834 (25.3%)	694 (27.0%)	
Grade 3	2219 (26.5%)	566 (22.5%)	902 (27.4%)	751 (29.3%)	
Unknown	2287 (27.3%)	836 (33.3%)	841 (25.5%)	610 (23.8%)	

3 years survival

	Total (%)	1988–1992 (%)	1993–1997 (%)	1998–2001 (%)	Log-rank
Overall	87.2 (±0.4)	86.1 (±0.7)	87.2 (±0.6)	88.8 (±0.8)	$P = 0.076$
Age at diagnosis (years)					$P < 0.001^{\Delta}$
<50	93.1 (±0.5)	93.8 (±0.8)	92.2 (±0.8)	94.0 (±1.1)	$P = 0.259^{*}$
⩾50	84.2 (±0.5)	82.2 (±1.0)	84.5 (±0.8)	86.3 (±1.1)	$P = 0.048^{*}$
Race					$P = 0.005^{\Delta}$
Caucasian	87.1 (±0.4)	86.2 (±0.8)	86.7 (±0.7)	88.2 (±1.0)	$P = 0.374^{*}$
Hispanic	88.8 (±1.5)	90.3 (±2.8)	86.7 (±2.2)	91.1 (±2.8)	$P = 0.395^{*}$
African American	84.5 (±2.0)	80.9 (±4.0)	86.3 (±2.7)	85.1 (±4.2)	$P = 0.213^{*}$
Asian	89.4 (±1.4)	84.7 (±3.4)	90.7 (±1.9)	91.0 (±2.6)	$P = 0.495^{*}$
Surgery					$P < 0.001^{\Delta}$
Yes	90.1 (±0.4)	88.4 (±0.7)	90.7 (±0.5)	91.5 (±0.8)	$P = 0.678^{*}$
No	24.8 (±2.6)	22.2 (±4.9)	22.3 (±3.5)	34.1 (±5.2)	$P = 0.022^{*}$
Lymphadenectomy					$P < 0.001^{\Delta}$
Yes	93.3 (±0.5)	93.2 (±1.0)	93.5 (±0.7)	93.1 (±0.9)	$P = 0.978^{*}$
No	82.0 (±0.6)	82.8 (±1.0)	81.2 (±1.0)	82.0 (±1.6)	$P = 0.211^{*}$
Stage					$P < 0.001^{\Delta}$
Stage I	91.8 (±0.4)	91.4 (±0.7)	91.5 (±0.6)	93.4 (±0.8)	$P = 0.202^{*}$
					$P < 0.001^{\Delta}$
Lymphadenectomy	95.2 (±0.5)	95.0 (±1.0)	94.7 (±0.7)	96.3 (±0.8)	$P = 0.468^{*}$
No lymphadenectomy	89.0 (±0.6)	90.0 (±0.9)	88.4 (±0.9)	88.6 (±1.6)	$P = 0.295^{*}$
Stage II	74.2 (±1.0)	70.7 (±1.8)	74.5 (±1.5)	77.3 (±2.1)	$P = 0.057^{*}$
					$P < 0.001^{\Delta}$
Lymphadenectomy	87.4 (±1.3)	87.0 (±2.8)	89.5 (±1.8)	84.3 (±2.7)	$P = 0.425^{*}$
No lymphadenectomy	63.4 (±1.5)	63.2 (±2.4)	62.1 (±2.3)	67.0 (±3.5)	$P = 0.410^{*}$
Histology					$P < 0.001^{\Delta}$
Serous	88.4 (±0.7)	86.6 (±1.3)	89.4 (±1.1)	88.9 (±1.7)	$P = 0.412^{*}$
Endometrioid	93.8 (±0.6)	92.1 (±1.1)	93.5 (±0.8)	96.7 (±0.8)	$P = 0.015^{*}$
Mucinous	92.5 (±0.7)	93.1 (±1.1)	92.9 (±1.0)	90.2 (±1.9)	$P = 0.460^{*}$
Clear cell	85.8 (±1.2)	84.4 (±2.3)	84.9 (±1.9)	87.2 (±3.0)	$P = 0.863^{*}$
Grade					$P < 0.001^{\Delta}$
1	96.4 (±0.5)	96.5 (±0.9)	96.1 (±0.7)	96.6 (±1.1)	$P = 0.875^{*}$
2	92.4 (±0.6)	92.2 (±1.1)	92.1 (±0.9)	93.3 (±1.2)	$P = 0.676^{*}$
3	82.0 (±0.9)	75.9 (±1.9)	83.3 (±1.3)	86.7 (±1.7)	$P < 0.001^{*}$

Pronostic factors in early stage disease

- 5 independent prognostic factors
  - Age over 50-60 years old
  - Spontaneous or surgical capsule rupt.
    - IC1 vs IC2
  - Histological grade
  - Histology as clear cell carcinoma
  - Complete surgical staging or not
    - Better OS & PFS for restaging +/- CT vs CT alone!

Multivariate Analysis of Prognostic Factors for Recurrence-free Survival (RFS) and Overall Survival (OS) (N = 506)

	Disease recurrence			Death		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, y						
< 60	1.0			1.0		
≥60	1.57	1.12–2.19	.009	1.96	1.41–2.71	<.001
Stage						
IA or IB	1.0			1.0		
IC	1.74	0.91–3.33	.003	1.54	0.85–2.79	.005
II	2.70	1.41–5.16		2.36	1.30–4.27	
Tumor grade*						
1	1.0			1.0		
2	1.84	1.04–3.27		1.23	0.72–2.09	
3	2.47	1.39–4.37	.02	1.86	1.10–3.15	.09
Not graded, clear cell	1.66	0.91–3.04		1.46	0.85–2.50	
Cytology						
Negative	1.0			1.0		
Positive	1.72	1.21–2.45	.003	1.53	1.09–2.16	.02

HR indicates hazard ratio; CI, confidence interval.

* Hazard ratio estimated by Cox model adjusted for age group, stage, tumor grade, and cytology, as well as stratified with type of treatment.

FY Ahmed, J Clin Oncol 1996
H TU et al, Int J of Gyn Cancer 2016
Chan et al, Cancer 2008

ADJUVANT CHEMOTHERAPY FOR EARLY STAGE

Randomized Studies before ACTION / ICON1

- In total 15 trials
- 2 489 patients randomized
- Wide range of
  - inclusion criteria
  - treatment
  - type of chemotherapy

Randomized Studies before ACTION / ICON1

Conclusion

- No unequivocal support for a survival benefit from any form of adjuvant therapy
- Studies are too small and lack power to detect treatment effects
- Suggest a possible interest from adjuvant chemotherapy

Randomized Phase III (evidence)

- Eligibility criteria
  - **ICON1**: all patients where CT is indicated

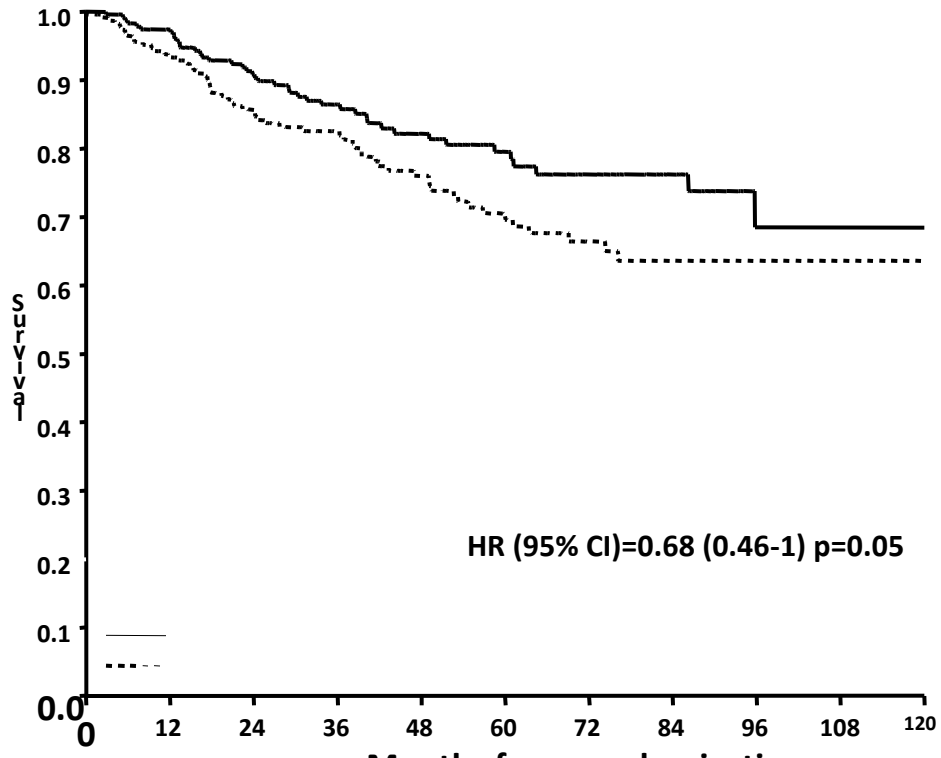
    treatment: carboplatine monotherapy (82%) or CAP (x6)
  - **ACTION**: stages IA-B gr 2-3, IC, IIA or clear cell carcinoma

    treatment (x4): Cisplatine-Cyclophosphamide : 47%
    Carboplatine monotherapy : 33%
  - Primary Endpoints OS
  - Combined data from the ICON1 (MRC) and ACTION (EORTC)

Trimbos / Vergote JNCI 2003

Overall Survival

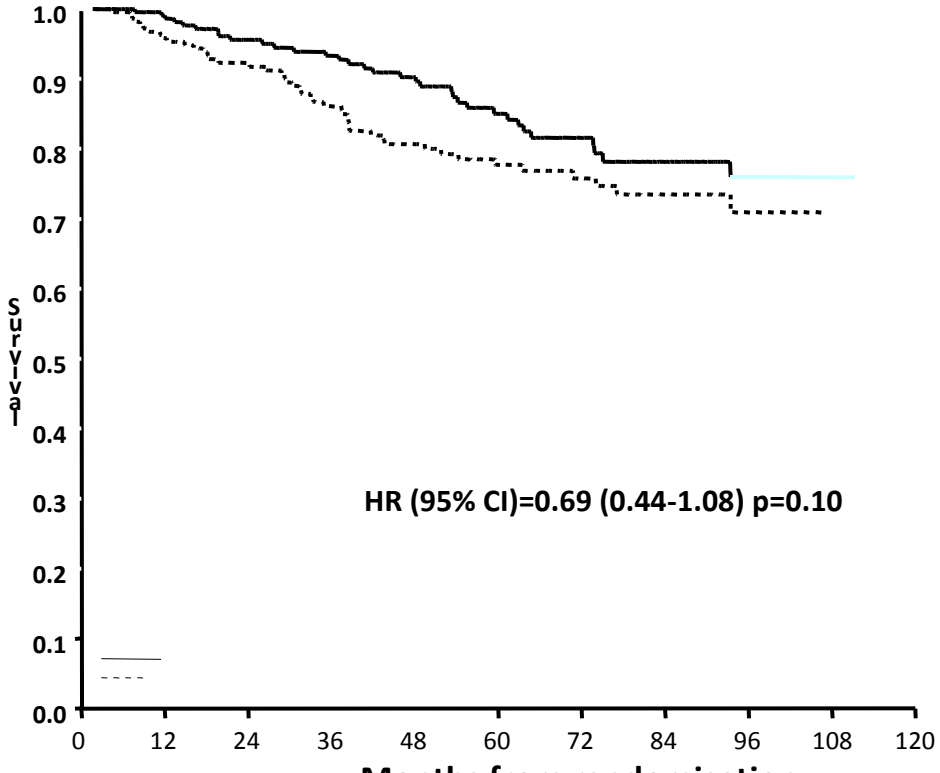
ICON1



Patients at risk

immediate	241	219	179	135	104	76	55	37	12	7	4
defer	236	203	170	135	104	77	51	27	12	5	1

ACTION



Patients at risk

immediate	224	210	177	159	135	102	80	56	29	6	0
defer	224	202	172	148	122	94	69	46	21	3	0

Trimbos / Vergote JNCI 2003

Early stages

Population: 925 patients

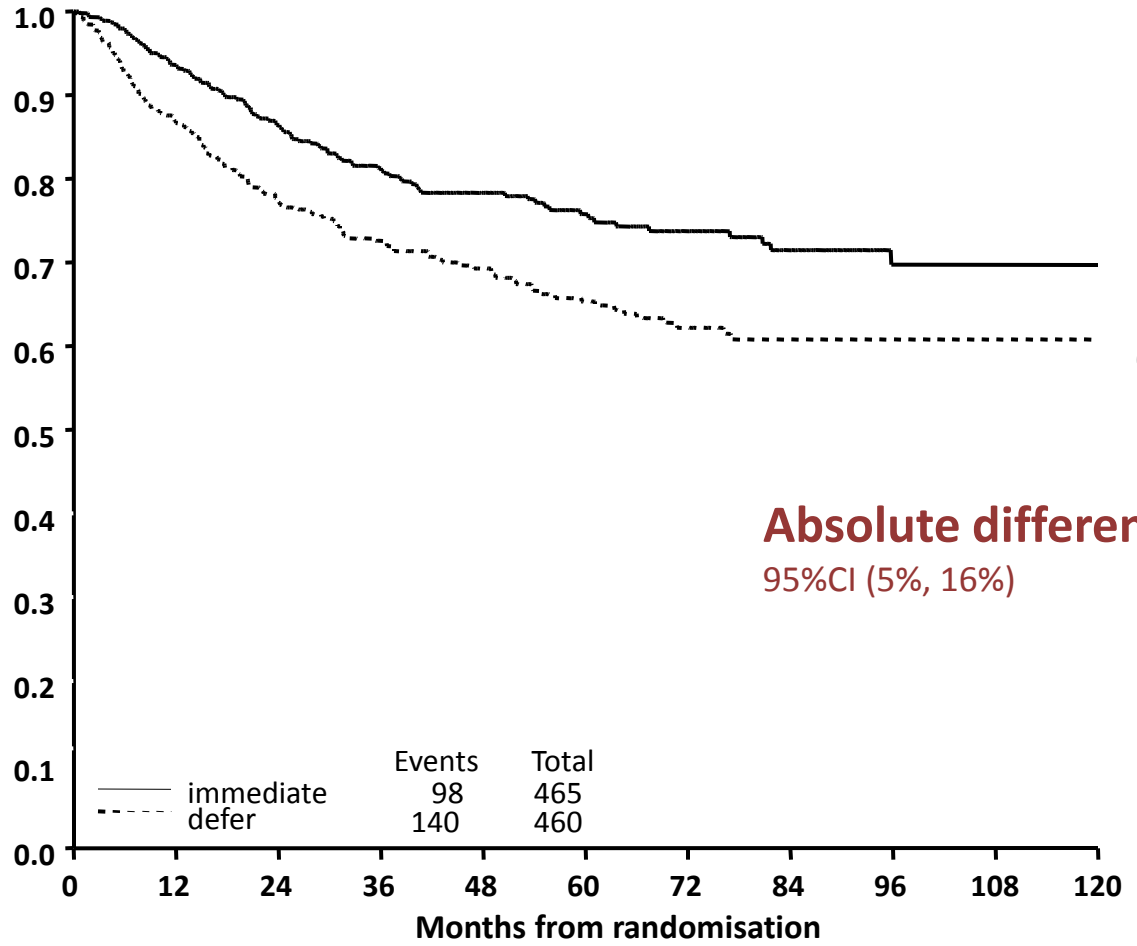
ICON1 (n=477 pts) +ACTION (n=448 pts)

Chemotherapy	Risk	Absolute Difference	% @ 5 years	p
PFS	0.64	11%	76%	0.001
OS	0.67	8%	82%	0.01

Trimbos / Vergote JNCI 2003

Recurrence free survival

RR = 0.64 p = 0.001



76%

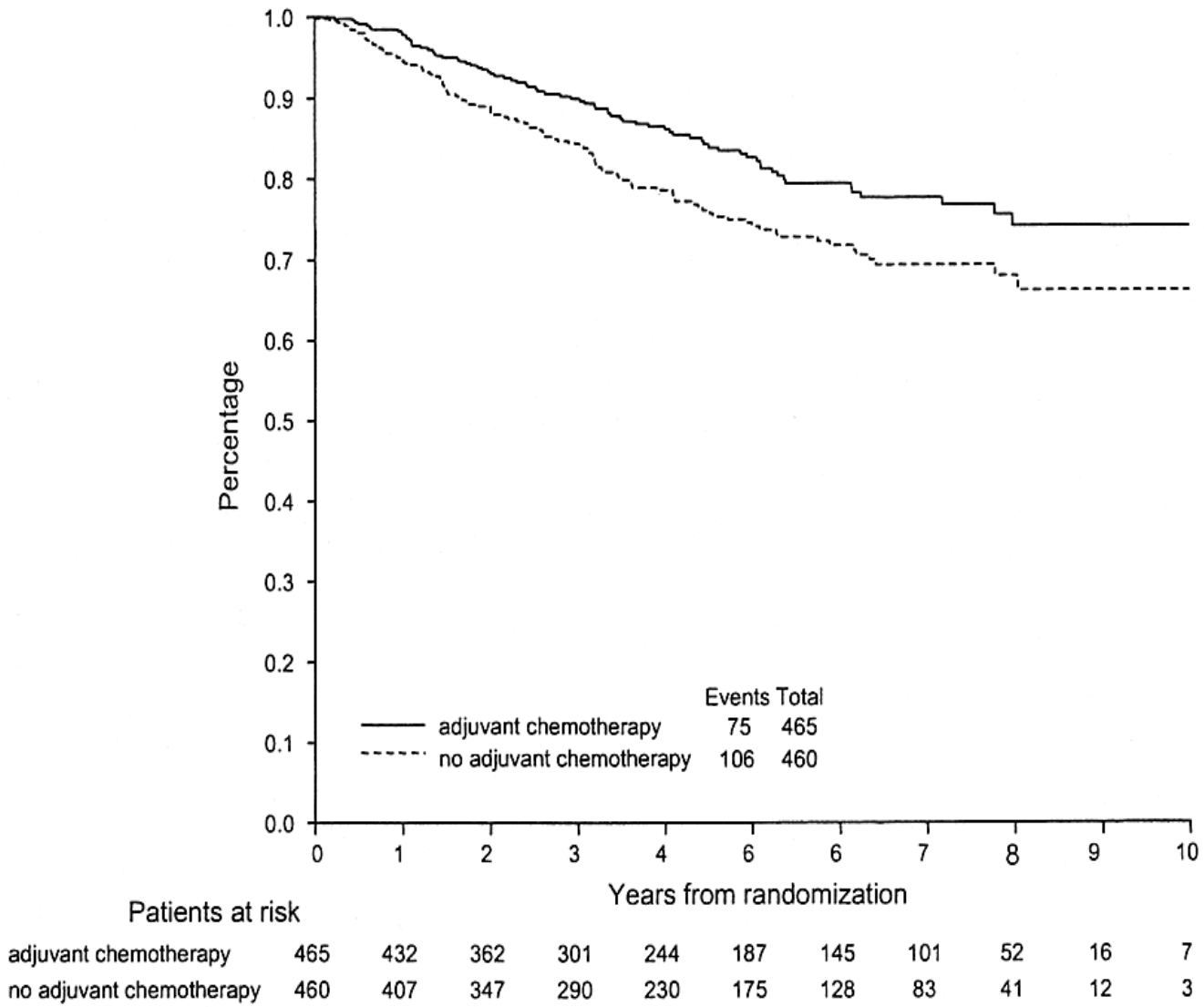
65%

Absolute difference at 5-year = 11%

95%CI (5%, 16%)

Trimbos / Vergote JNCI 2003

Overall survival (ICON1 + ACTION)



5 years

82%

74%

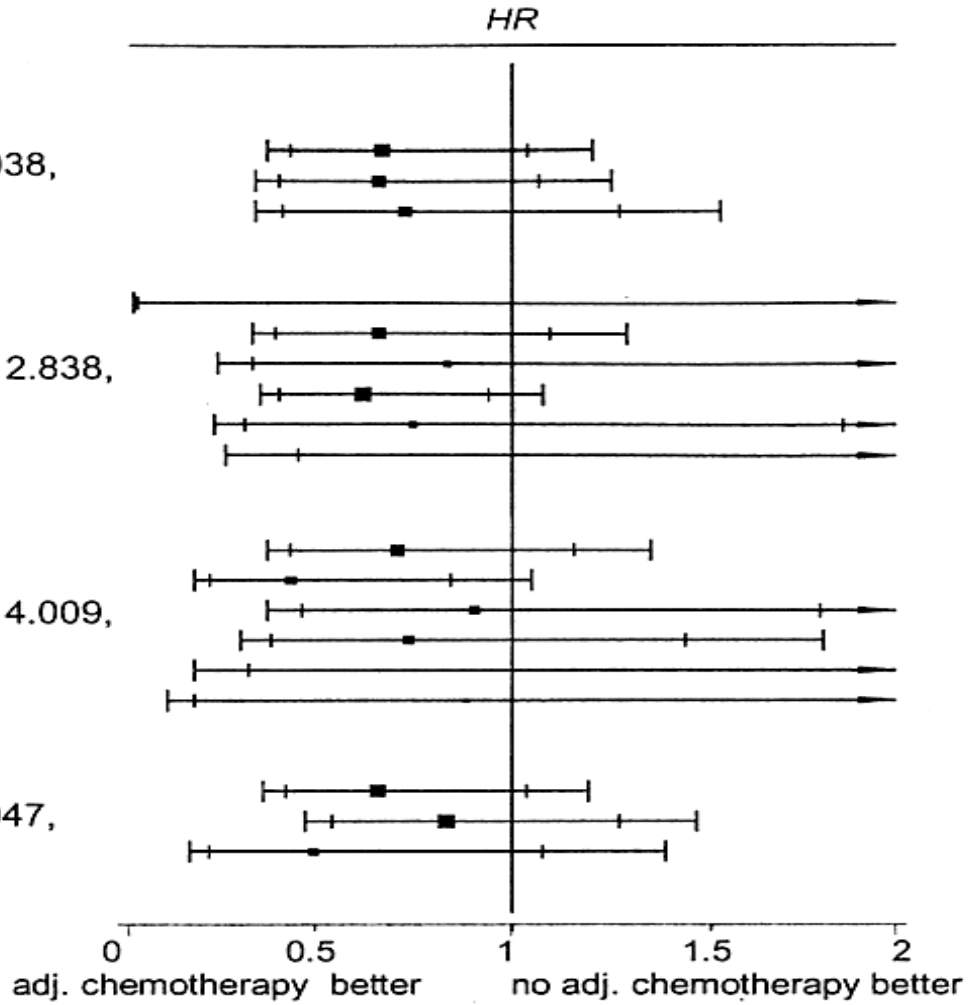
RR = 0.68

p = 0.01

Trimbos / Vergote JNCI 2003

ICON1 + ACTION, Subgroup analysis

	Adj. chemotherapy (No. of events)	No Adj. chemotherapy (No. of patients)	
Age			
<55	30/233	43/233	trend $\chi^2_{(1)} = .038$, $P = .84$
55-65	22/126	39/147	
>65	23/105	24/80	
Tumor stage			
I	1/9	1/4	interaction $\chi^2_{(5)} = 2.838$, $P = .73$
Ia	22/168	33/172	
Ib	8/46	9/43	
Ic	32/208	49/204	
II	8/30	11/29	
III	3/3	3/6	
Histologic cell type			
serous	27/161	33/139	interaction $\chi^2_{(5)} = 4.009$, $P = .55$
mucinous	10/90	22/90	
endometrioid	13/94	20/129	
clear	16/68	17/62	
undifferentiated	3/9	2/7	
other	3/23	3/19	
Cell differentiation			
poor	29/139	42/141	trend $\chi^2_{(1)} = .047$, $P = .83$
intermediate	37/210	42/203	
well	7/97	16/100	



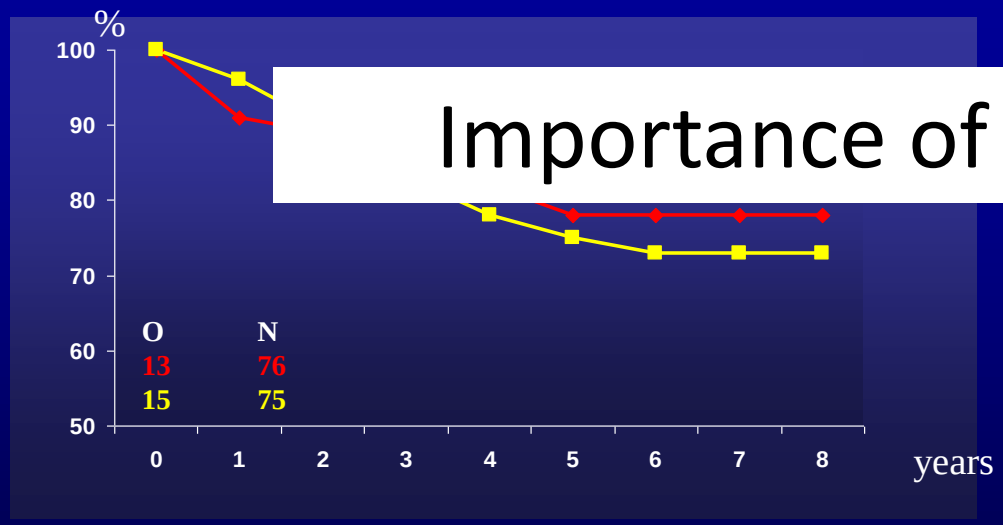
No evidence that the effect of adjuvant chemotherapy is smaller or larger in any of the tested subgroups (age, differentiation, histological type, FIGO substage)

Impact of surgery on Adjuvant CT

ACTION trial only

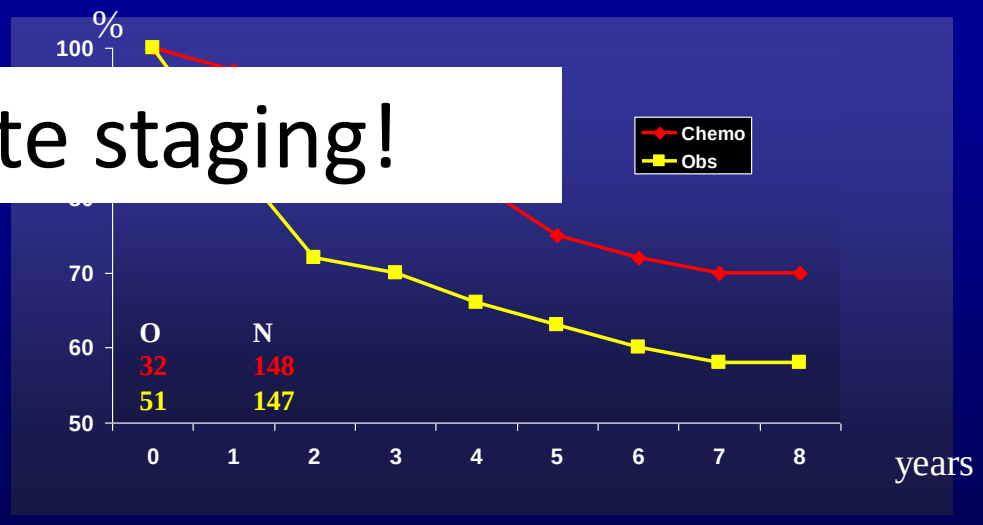
Disease free survival

Optimal staging (30%)



Overall logrank test: p=0.7319
Overall Wilcoxon test: p=0.9757

Non optimal staging



Overall logrank test: p=0.0086
Overall Wilcoxon test: p=0.0007

Importance of complete staging!

Cochrane Library

Cochrane Database of Systematic Reviews

Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer (Review)

Lawrie TA, Winter-Roach BA, Heus P, Kitchener HC

Analysis 1.5. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 5 Progression-free survival (5 yr).

Review: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer

Comparison: 1 Adjuvant chemotherapy versus observation

Outcome: 5 Progression-free survival (5 yr)

Study or subgroup	Chemotherapy N	Observation N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
ACTION 2003	224	224	-0.462 (0.194)		35.7 %	0.63 [0.43, 0.92]
Bolis 1995	41	42	-0.6931 (0.4425)		6.9 %	0.50 [0.21, 1.19]
ICON1 2003	241	236	-0.4308 (0.174)		44.4 %	0.65 [0.46, 0.91]
Trop 2000	81	81	-0.0202 (0.321)		13.0 %	0.98 [0.52, 1.84]
Total (95% CI)	**587**	**583**			**100.0 %**	**0.67 [0.53, 0.84]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.97$, df = 3 ($P = 0.58$); $I^2 = 0.0\%$

Test for overall effect: $Z = 3.51$ ($P = 0.00046$)

Test for subgroup differences: Not applicable

Analysis 1.1. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 1 Overall survival (5 yr).

Review: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer

Comparison: 1 Adjuvant chemotherapy versus observation

Outcome: 1 Overall survival (5 yr)

Study or subgroup	Chemotherapy N	Observation N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI

Analysis 1.17. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 17 Subgroup analysis by risk: 10-yr OS.

Review: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer

Comparison: 1 Adjuvant chemotherapy versus observation

Outcome: 17 Subgroup analysis by risk: 10-yr OS

Study or subgroup	Favours chemo-therapy N	Observation N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Low/intermediate risk						
ICON1 2003	101	97	-0.0943 (0.3158)		42.2 %	0.91 [0.49, 1.69]
Subtotal (95% CI)	**101**	**97**			**42.2 %**	**0.91 [0.49, 1.69]**
Heterogeneity: not applicable						
Test for overall effect: $Z = 0.30$ ($P = 0.77$)						
2 High risk						
ICON1 2003	106	110	-0.6539 (0.2261)		57.8 %	0.52 [0.33, 0.81]
Subtotal (95% CI)	**106**	**110**			**57.8 %**	**0.52 [0.33, 0.81]**
Heterogeneity: not applicable						
Test for overall effect: $Z = 2.89$ ($P = 0.0038$)						
Total (95% CI)	**207**	**207**			**100.0 %**	**0.66 [0.38, 1.13]**

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 2.08$, df = 1 ($P = 0.15$); $I^2 = 52\%$

Test for overall effect: $Z = 1.51$ ($P = 0.13$)

Test for subgroup differences: $Chi^2 = 2.08$, df = 1 ($P = 0.15$), $I^2 = 52\%$

ESMO guidelines 2013, endorsed by JSMO

- Adjuvant chemotherapy should be offered to all high-risk patient (IB/C grade 2, any grade 3 or CCC)
- Intermediate risk (IAG2/IB-IC G1)?
- Optimal duration remains controversial

adjuvant chemotherapy for early-stage disease

A recent Cochrane meta-analyses of five large prospective clinical trials (4 of 10 with platinum-based chemotherapy) showed that chemotherapy is more beneficial than observation in patients with early-stage ovarian cancer [33]. Patients who received platinum-based adjuvant chemotherapy had better OS [hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.53–0.93] and PFS (HR 0.67; 95% CI 0.53–0.84) than patients who did not receive adjuvant treatment. Even though two-thirds of the patients included in the two major studies were suboptimally staged, some benefit for chemotherapy in optimally staged patients cannot be excluded. Long-term follow-up of the ICON 1 trial confirms the benefit of adjuvant chemotherapy, particularly in those patients at higher risk of recurrence (stage 1B/C grade 2/3, any grade 3 or clear-cell histology) [34]. Therefore, adjuvant chemotherapy should be offered not only to suboptimally staged patients but also to those optimally staged at higher risk of recurrence [I, A].

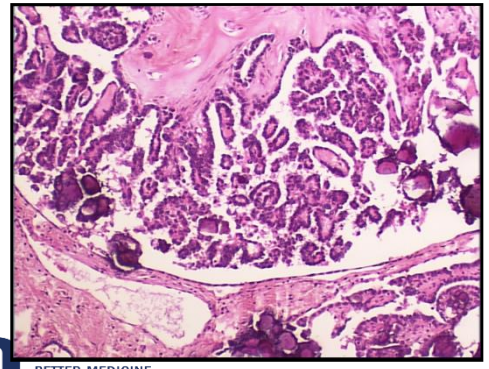
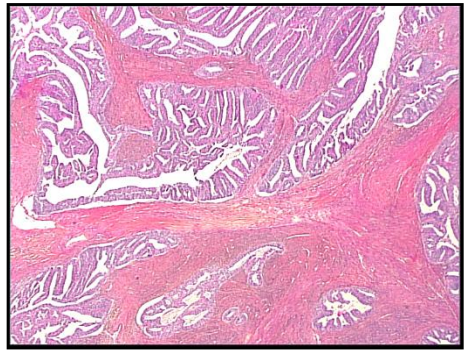
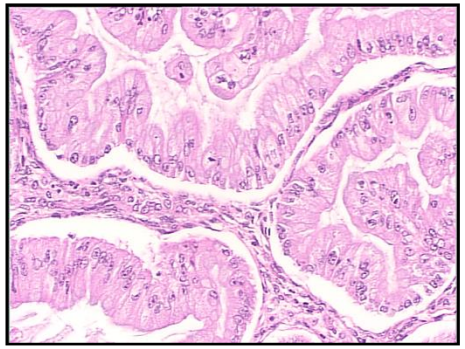
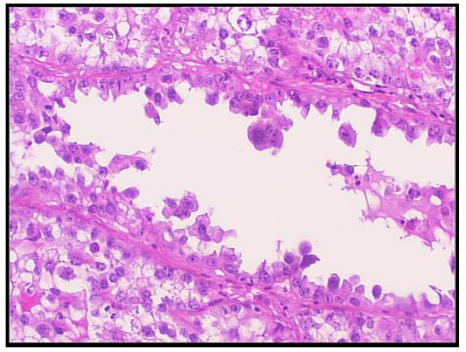
The optimal duration of treatment remains controversial; there has been only one randomised trial (GOG 157) which showed that six cycles of carboplatin and paclitaxel were not associated with longer PFS or OS, but with a significantly greater toxicity than with three cycles [35]. There are no data to demonstrate that the addition of paclitaxel to carboplatin is superior. Some clinicians feel that separating the choice of treatment between FIGO stage IC and stage II–IV is artificial, and therefore choose to offer combination chemotherapy to women with stage IC. However, evidence of a benefit of combination therapy in this group is lacking; therefore, it is reasonable to consider single-agent carboplatin to all women with intermediate and high-risk stage I disease.

J Ledermann et al, Ann of Oncol 2013

Tumor type

- EOC is a heterogeneous group of tumors
- different histological subtypes have different
  - biological behavior
  - patterns of spread
  - associated malignancies
  - or postulated precursors.

Need for a stratified analysis !

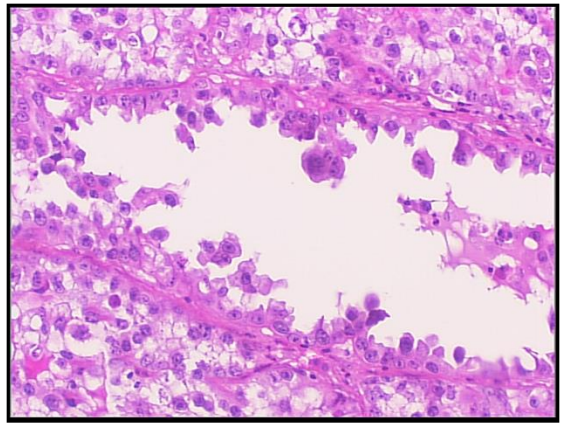
Tumor type

Two pathological types exhibit different behaviors

- Mucinous invasive carcinoma : excellent stage I prognosis

(~ 100% 5 year survival)

- Clear cell carcinomas : poor prognosis



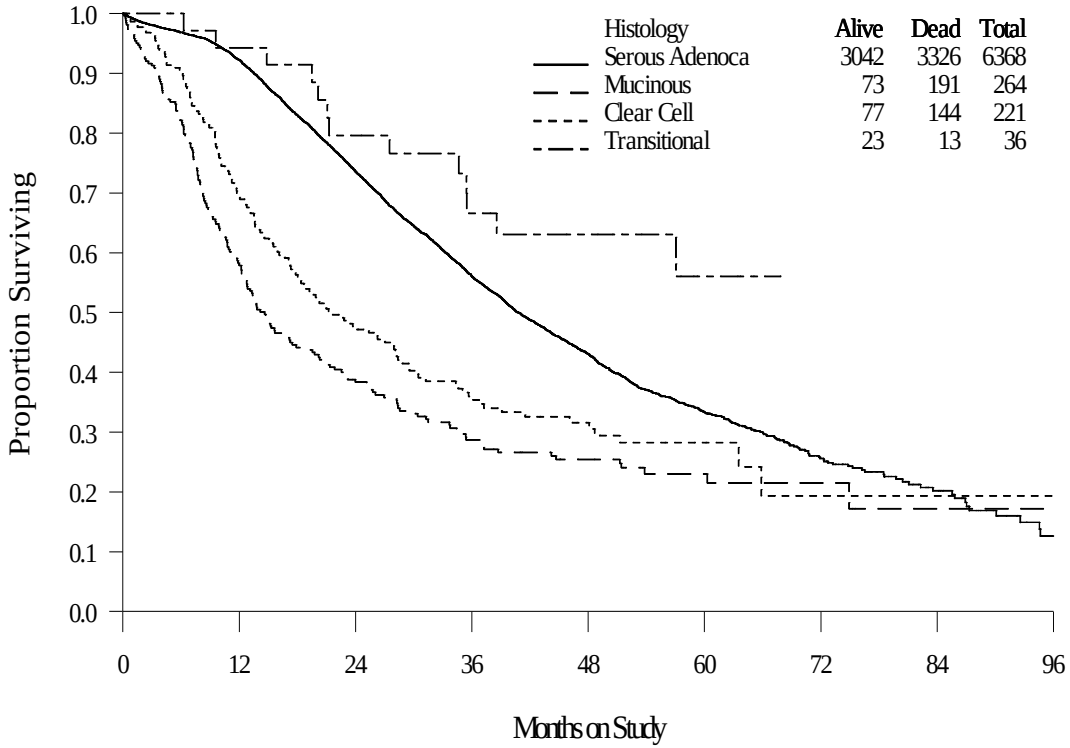
Chemotherapy for stage I tumor in most of the consensus conferences.

Survival analysis by histology

Advanced vs Early stage

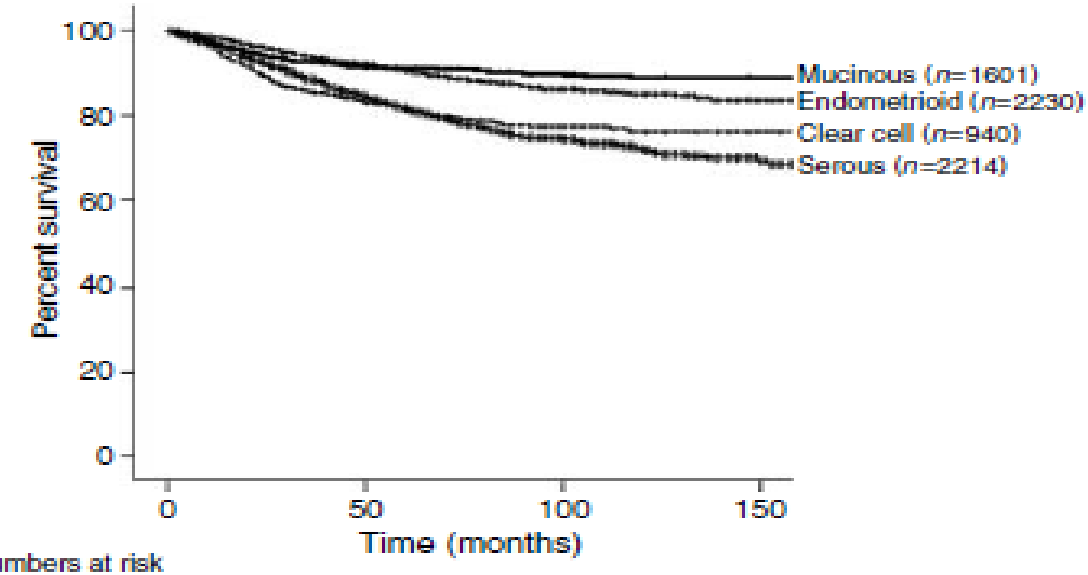
Clear Cell, Transitional, Mucinous, Serous

Overall survival in stage=(3,4) patients



AGO-GINECO, GOG-ANZGOG, MRC- MANGO

Disease specific Survival in early stage I/II, n = 8572 pts



Numbers at risk

Serous	2214	1116	440	95
Endometrioid	2230	1181	475	82
Mucinous	1601	957	468	82
Clear cell	940	480	194	33

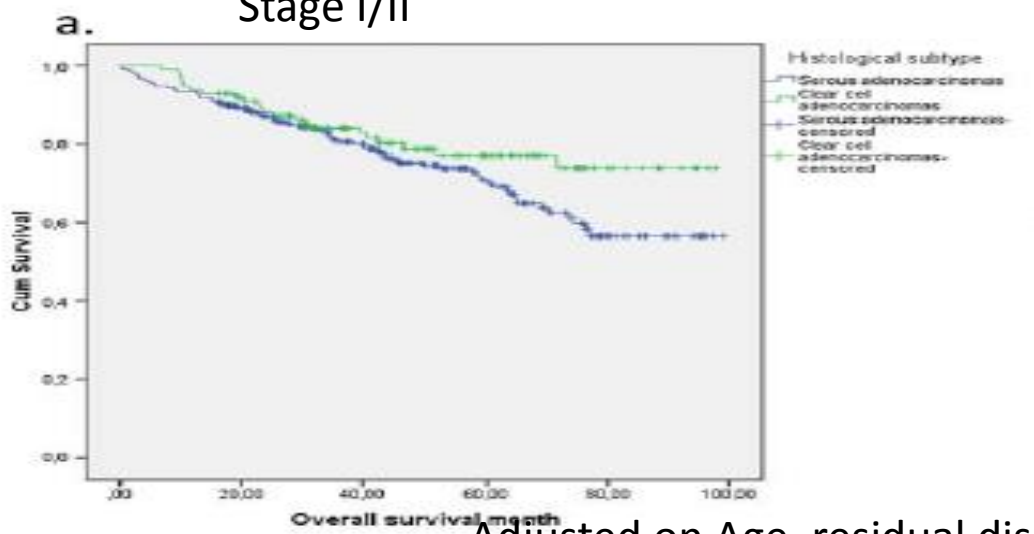
Figure 2 Kaplan–Meier disease-specific survival by histology ($P < 0.001$).

SEER database, Chan et al, BJC 2008

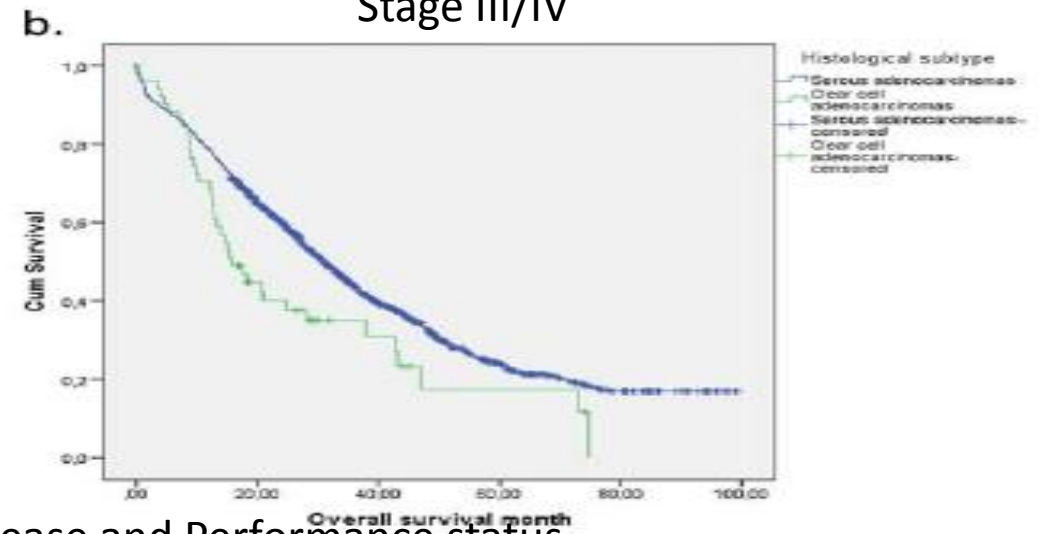
OCCC vs HGSC, early stage

International Journal of Gynecological Cancer • Volume 26, Number 1, January 2016 Clear Cell Carcinoma of the Ovary

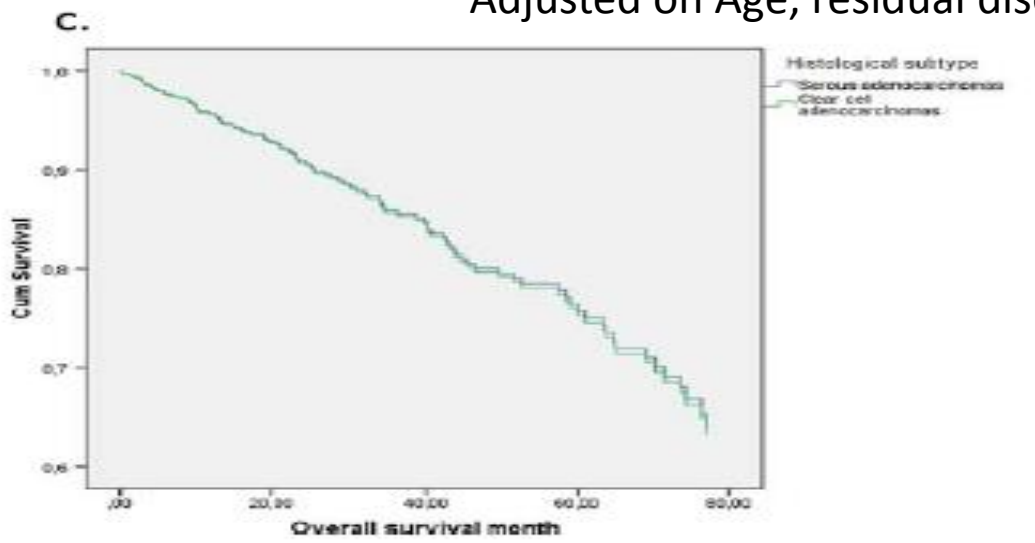
Stage I/II

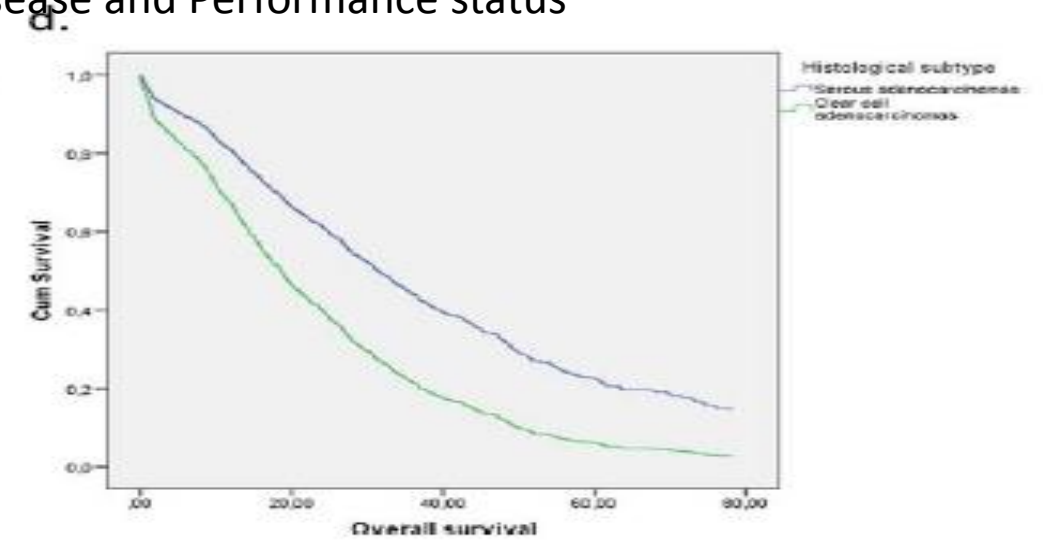


Stage III/IV



Adjusted on Age, residual disease and Performance status





European Society for Medical Oncology

Isabelle Ray-Coquard

(Danish database, T Schnack et al)

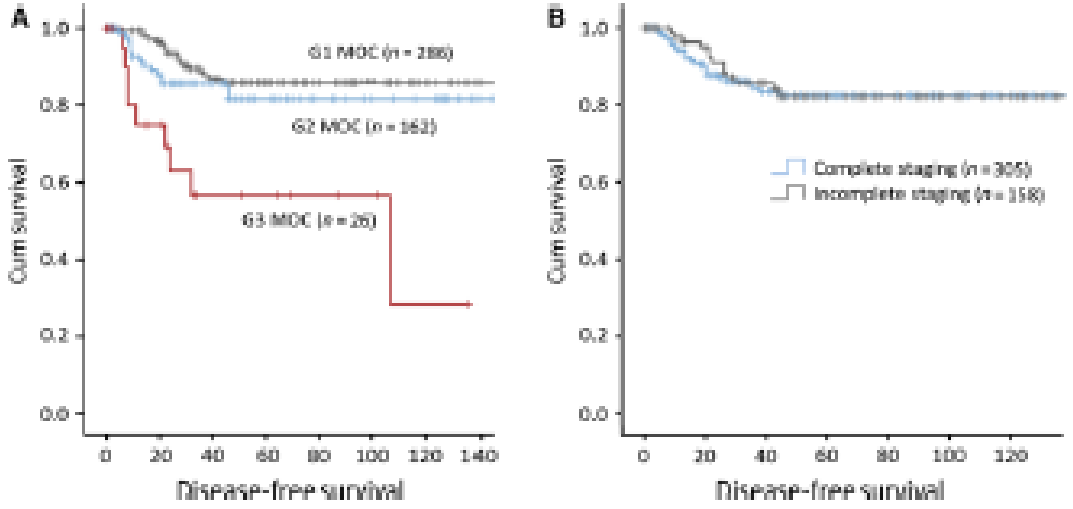
Mucinous EOC

Table 1. Characteristics of total group of 915 patients with MOC per tumour grade

Variable	All MOC *n* = 915 (%)	G1 MOC *n* = 369 (%)	G2 MOC *n* = 229 (%)	G3 MOC *n* = 88 (%)	Grade unspecified *n* = 229 (%)	P-value
Mean age (years ± SD)	55.7 ± 15.5	54.0 ± 15.6	55.4 ± 15.8	56.9 ± 15.4	58.1 ± 14.9	0.24*
FIGO stage						
I	623 (68.1)	286 (77.5)	162 (70.7)	26 (29.5)	149 (65.1)	<0.001**
II	46 (5.0)	17 (4.6)	8 (3.5)	14 (15.9)	7 (3.1)	
III	159 (17.4)	42 (11.4)	41 (17.9)	32 (36.4)	44 (19.2)	
IV	29 (3.2)	4 (1.1)	8 (3.5)	9 (10.2)	8 (3.5)	
Unknown	58 (6.3)	20 (5.4)	10 (4.4)	7 (8.0)	21 (9.2)	

Patients with unspecified histological tumour grade were excluded in statistical analyses.
*One-way analysis of variance test.
**Linear-by-Linear Association test, excluding patients with unknown FIGO stage.

- Dutch Registry
- Retrospective analysis
- 2002 to 2012
- n = 915 mucinous EOC
- No data on Adj CT!
- No central review



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

Von Baal et al, BJOG 2016

Low grade serous carcinoma

- Low-grade serous carcinoma (LGSC) is rare subtype that accounts for ~ 10% of serous carcinomas of the ovary/peritoneum
- May arise *de novo* or following diagnosis of serous borderline tumor
- Relative to high-grade serous carcinoma, LGSC characterized by:
  - Young age at diagnosis
  - Chemo resistance
  - Aberrations within the MAP kinase signaling pathway (BRAF/KRAS/NRAF)
  - Prolonged overall survival
- IA grade I (confirmed by central review) & complete staging, no adjuvant therapy (*Young et al, NEJM 1990*)
- Question for IC2 or IC3

Adjuvant chemotherapy

Which one?

Duration?

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

B2. What different control arms could be considered for trials of first-line therapy?

1. Intravenous 3-weekly carboplatin and paclitaxel remain the standard chemotherapy drugs for first-line therapy in advanced stage ovarian cancer
2. Acceptable additions or variations in dose, schedule, and route of delivery should be supported by at least one clinical trial demonstrating non-inferiority or superiority to a taxane/platinum. So far the following alternatives have been identified
   - Weekly intravenous paclitaxel with 3-weekly intravenous carboplatin.
   - Platinum/taxane and bevacizumab.
   - Intraperitoneal therapy after primary surgery with less than 1 cm residual disease. Both platinum and paclitaxel should be included using a validated schedule.
3. If more than one of the above regimens are included in the control arm of the same study then they should be stratified for.
4. Trials are needed to define the control arm for elderly and frail patients, defined on the basis of comprehensive geriatric assessment.
5. If chemotherapy is to be used in early stage disease platinum based chemotherapy should be the control arm.

C2. What should be investigated in rare eOC,

Rare epithelial ovarian cancer:

1. If indicated, platinum-based chemotherapy is a standard for high risk early or advanced stage rare eOC and should remain the control arm.
2. Rare eOC are a distinct entity and should be studied separately; dedicated rare eOC trials should be encouraged.
3. LGSOC and OCCC can continue to be included in ovarian cancer trials where the question is relevant but stratified on entry and analysed as distinct biological entities (well defined pathology/translational studies will allow analysis across trials).

Chemotherapy CP, 3 or 6 cycles?

Stage IA grade 3 or stage IC-II all grade
n = 457

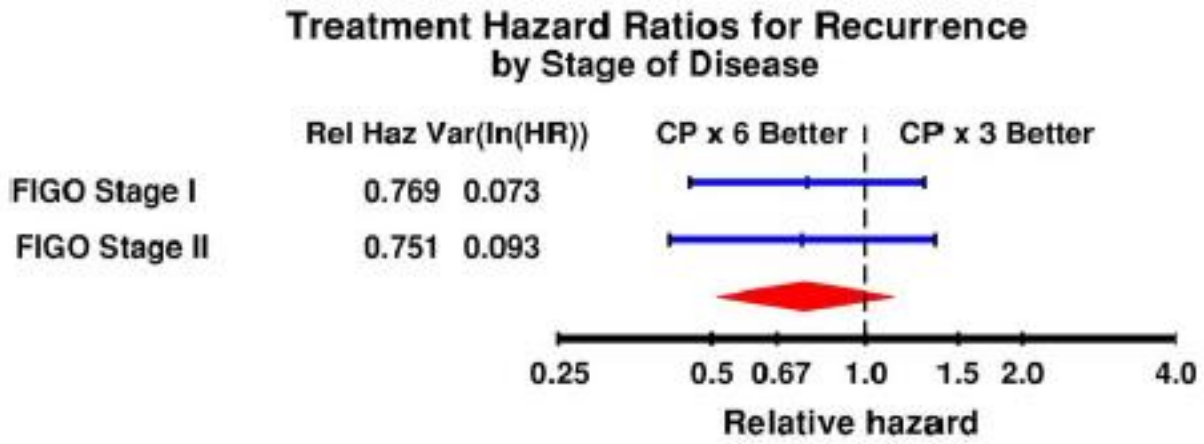
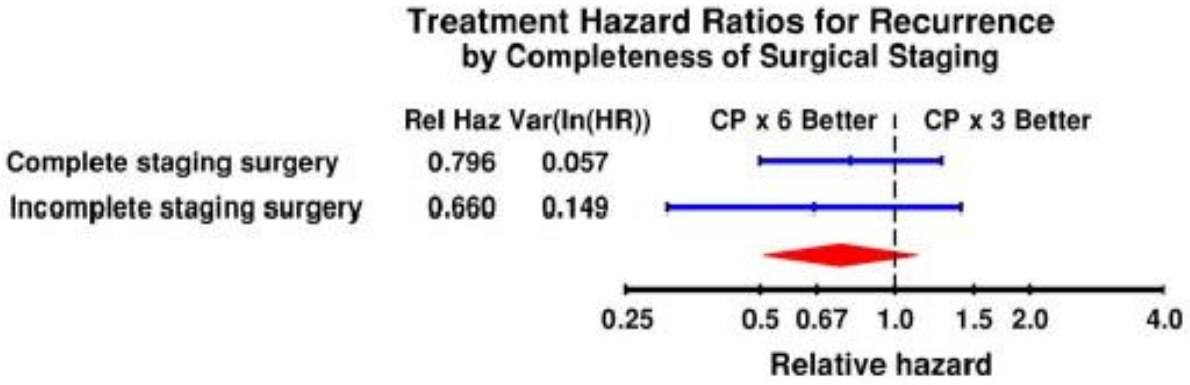


Fig. 2. Treatment hazard ratios for recurrence by disease stage.



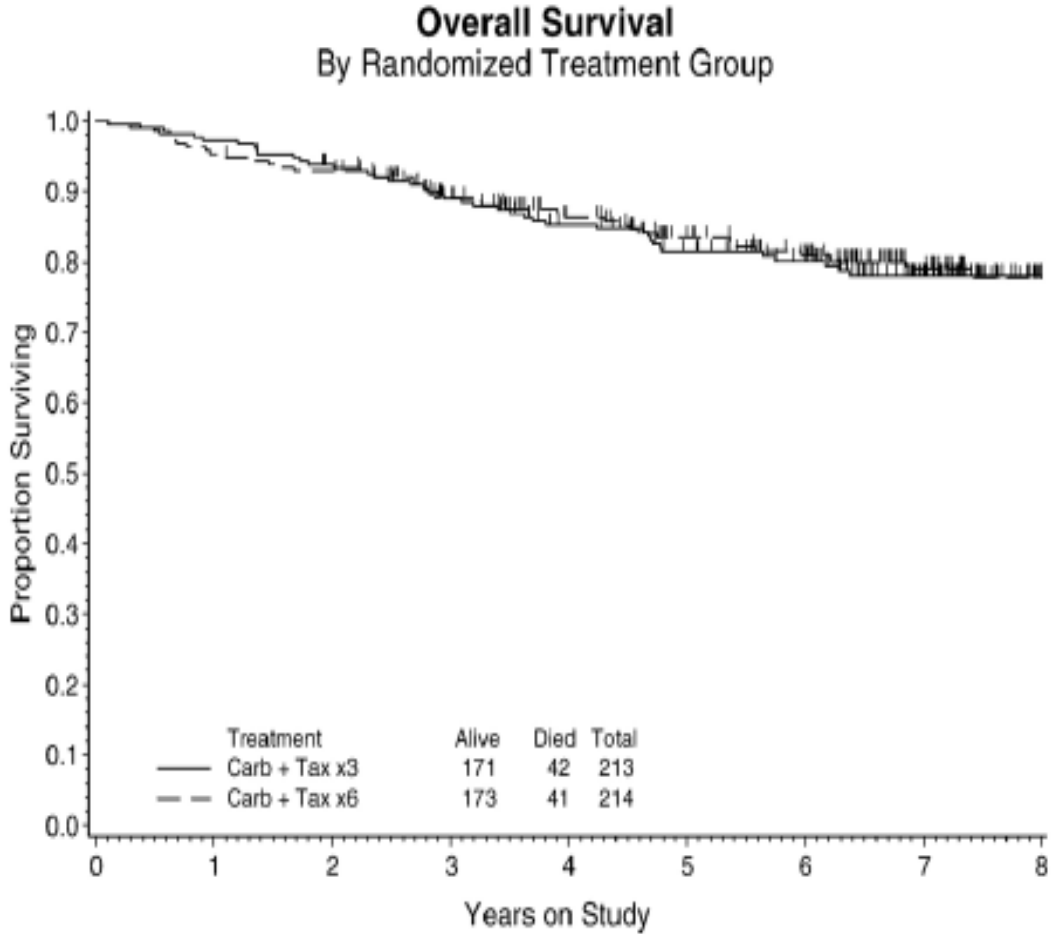


Fig. 3. Overall survival by randomized treatment.

Bell et al, Gyn Oncol 2006

3 versus 6 by histological subtypes

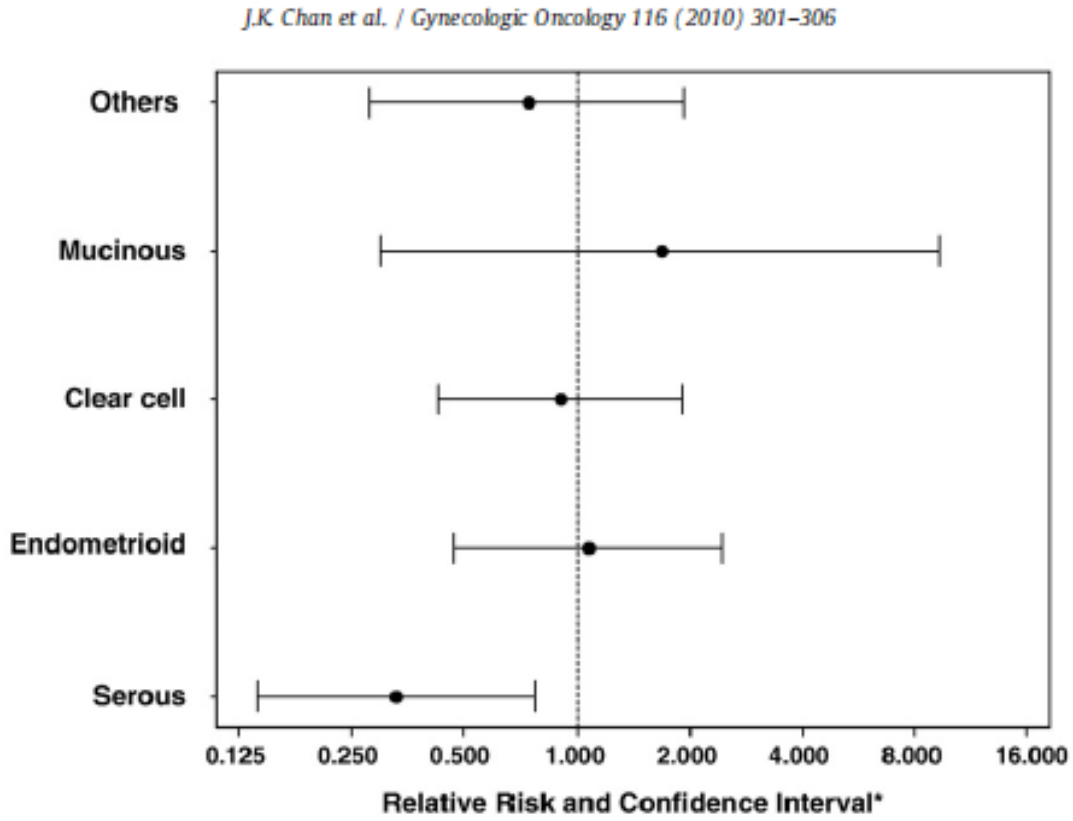


Fig. 1. Relative risk of recurrence for ovarian cancer patients receiving six versus three cycles of chemotherapy based on histology ($n = 427$).

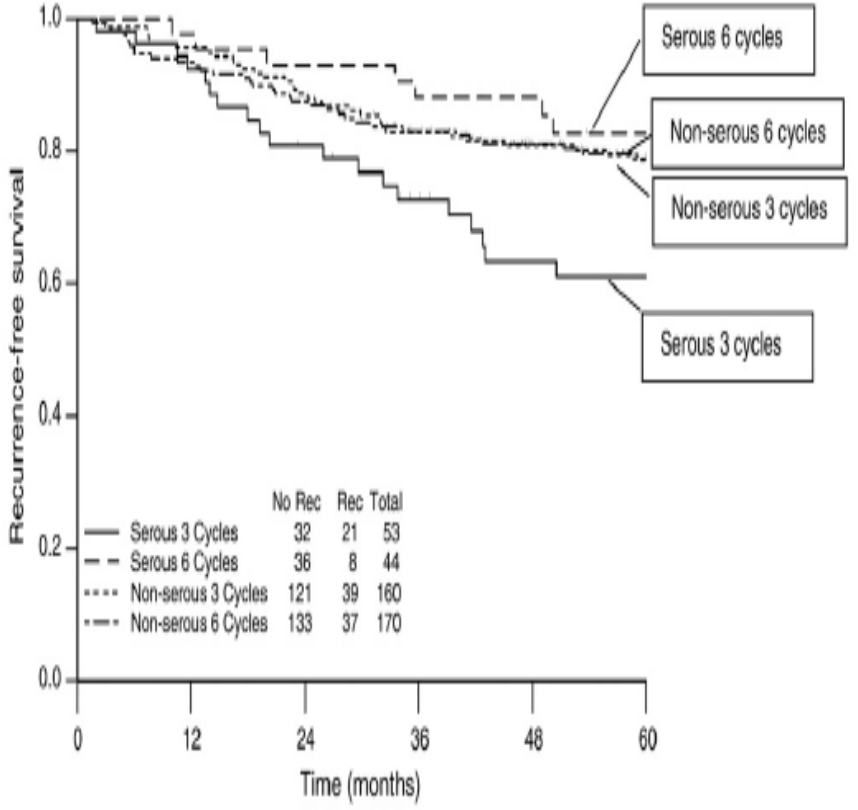
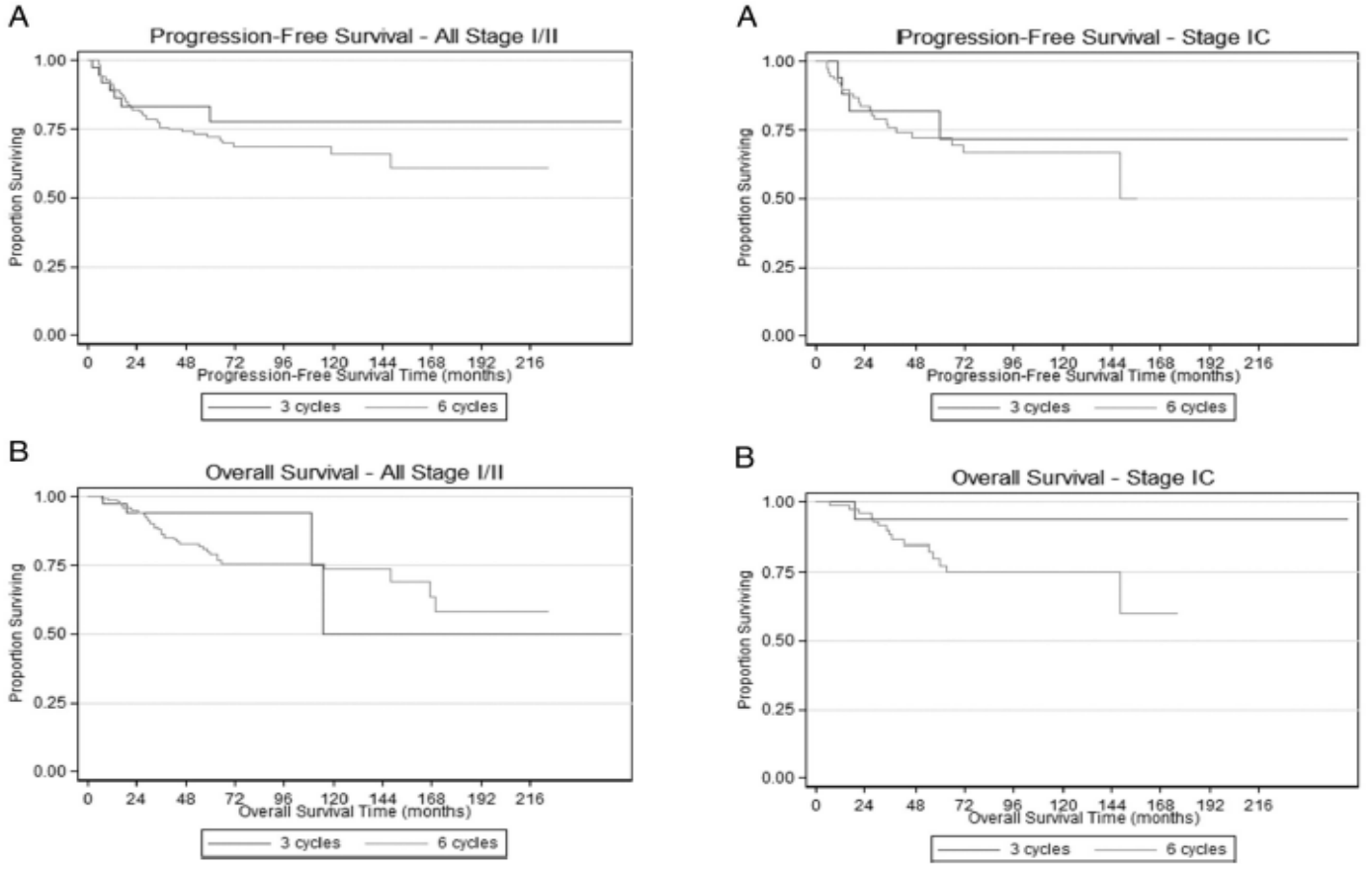


Fig. 2. Recurrence-free survival of serous and non-serous ovarian cancer patients treated with six versus three cycles of chemotherapy ($n = 427$).

Chan et al , Gynecol Oncol 2010

Clear cell carcinoma, 3 versus 6 cycles of CT

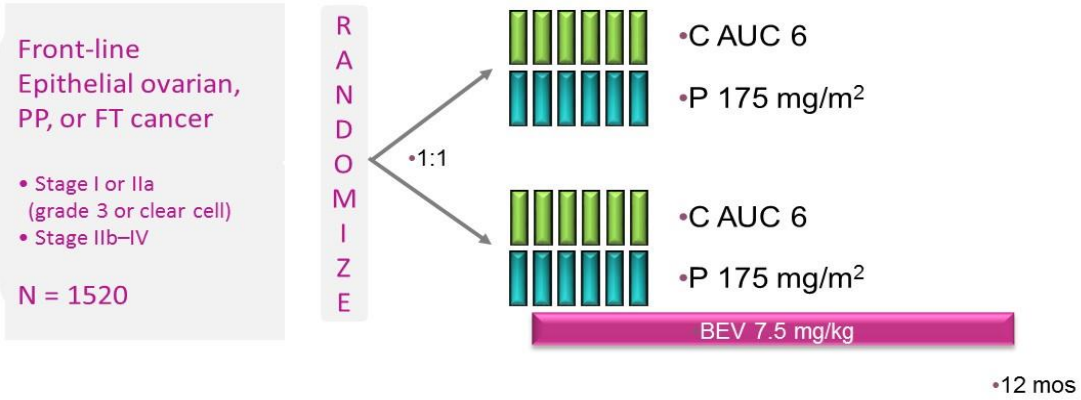
- Retrospective multicentric study
- N = 210
- 1994 to 2011
- Adj CT = CP 90%
- 18% 3 cycles
- 81% 6 cycles
- PFS & OS
- Cox model :
  - Stage IAB vs IC vs II HR 1,85 p 0,004
  - 3 vs 6 HR 1,70 p 0,3



Pendergast, et al Gyn Oncol 2016

ICON7
Bevacizumab in Ovarian Cancer

CP plus anti angiogenics?



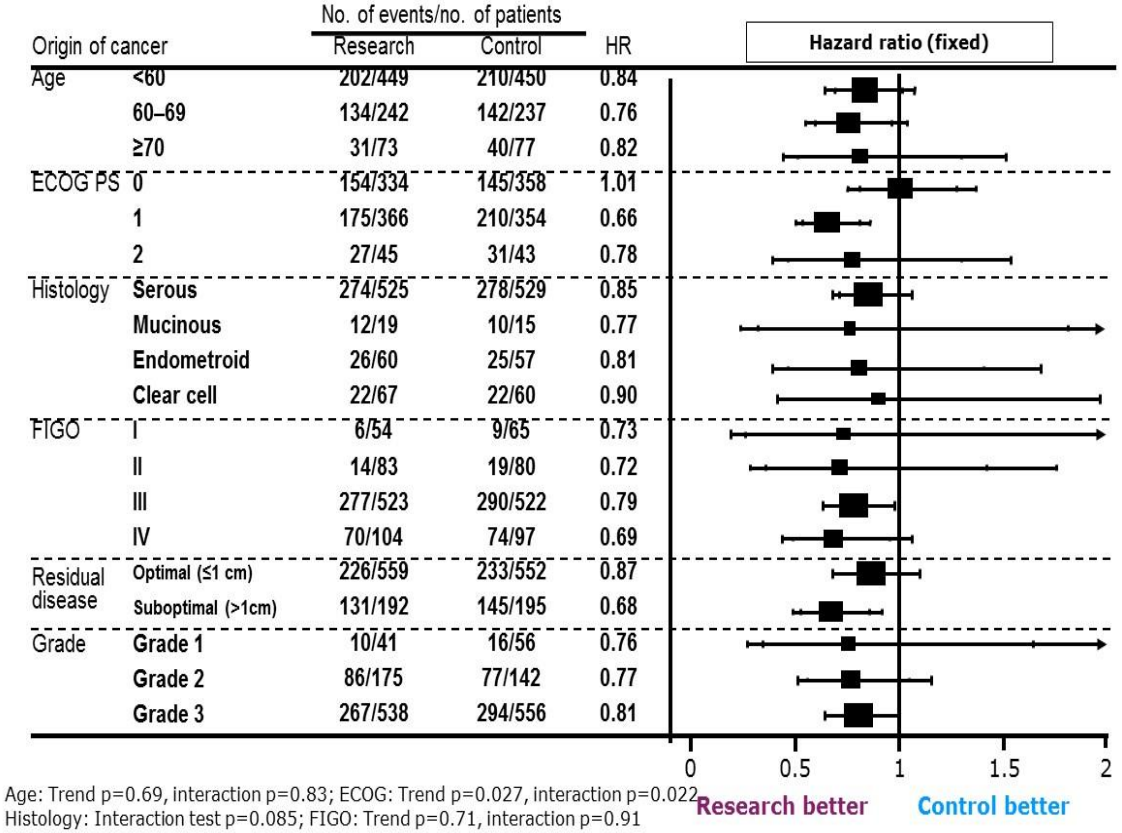
Baseline characteristics

Characteristic		Control (n=764)	Research (n=764)
Median age, years (range)		57 (18–81)	57 (24–82)
Origin of cancer, %	Ovary (epithelial)	87	88
Histology, %	Serous	69	69
	Clear cell	8	9
FIGO stage, %	I/IIA	10	9
	IIB–IIIB	21	20
	IIIC/IV	69	71
Debulking surgery/ residuum, %	≤1 cm	72	73
	>1 cm	25	25
	No surgery	2	2
Risk group, %	FIGO III >1 cm/FIGO IV debulking	31	30
	All the rest	69	70

ICON7
Bevacizumab in Ovarian Cancer

CP plus anti angiogenics?

Subgroup analysis of PFS

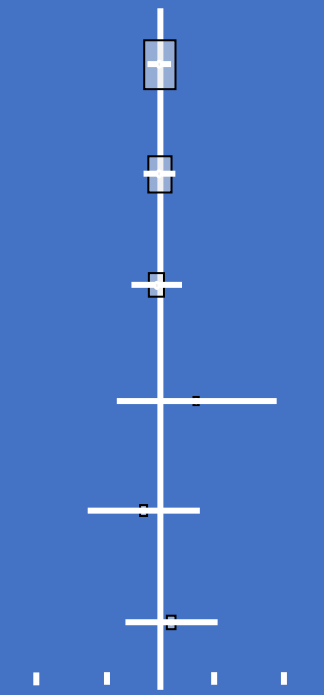


Origin of cancer		No. of events/no. of patients: Research	Control	HR
Age	<60	202/449	210/450	0.84
	60–69	134/242	142/237	0.76
	≥70	31/73	40/77	0.82
ECOG PS	0	154/334	145/358	1.01
	1	175/366	210/354	0.66
	2	27/45	31/43	0.78
Histology	Serous	274/525	278/529	0.85
	Mucinous	12/19	10/15	0.77
	Endometroid	26/60	25/57	0.81
	Clear cell	22/67	22/60	0.90
FIGO	I	6/54	9/65	0.73
	II	14/83	19/80	0.72
	III	277/523	290/522	0.79
	IV	70/104	74/97	0.69
Residual disease	Optimal (≤1 cm)	226/559	233/552	0.87
	Suboptimal (>1cm)	131/192	145/195	0.68
Grade	Grade 1	10/41	16/56	0.76
	Grade 2	86/175	77/142	0.77
	Grade 3	267/538	294/556	0.81

Age: Trend p=0.69, interaction p=0.83; ECOG: Trend p=0.027, interaction p=0.022
Histology: Interaction test p=0.085; FIGO: Trend p=0.71, interaction p=0.91
Residual disease: Trend p=0.10; Grade: Trend p=0.76, interaction p=0.95

Final OS by histology

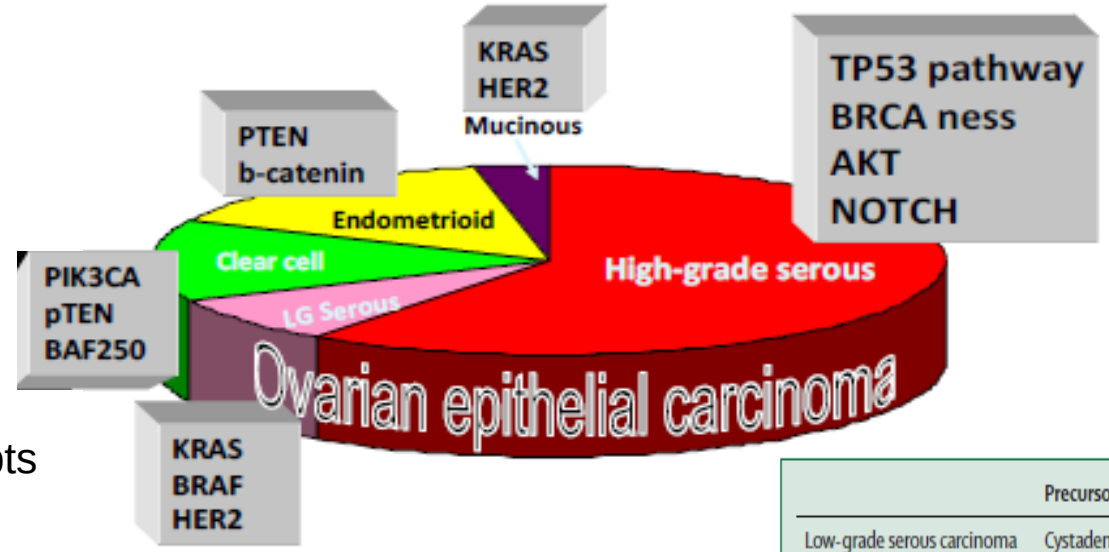
Subgroup	Restricted mean: Control	Restricted mean: Research	Median, months: Control	Median, months: Research	HR (95% CI)	Events/n
All patients	44.6	45.5	58.6	58.0	0.99 (0.85–1.14)	714/1528
High-grade serous	43.9	44.9	53.5	52.4	0.99 (0.81–1.21)	380/743
Low-grade serous	45.5	46.0	58.4	59.1	0.95 (0.69–1.31)	153/335
Clear cell stage I/II	53.9	53.7	NR	66.9	1.59 (0.57–4.48)	15/81
Clear cell stage III/IV	35.1	36.6	31.8	30.7	0.80 (0.39–1.66)	29/46
Clear cell	48.5	46.7	NR	66.9	1.15 (0.64–2.09)	44/127



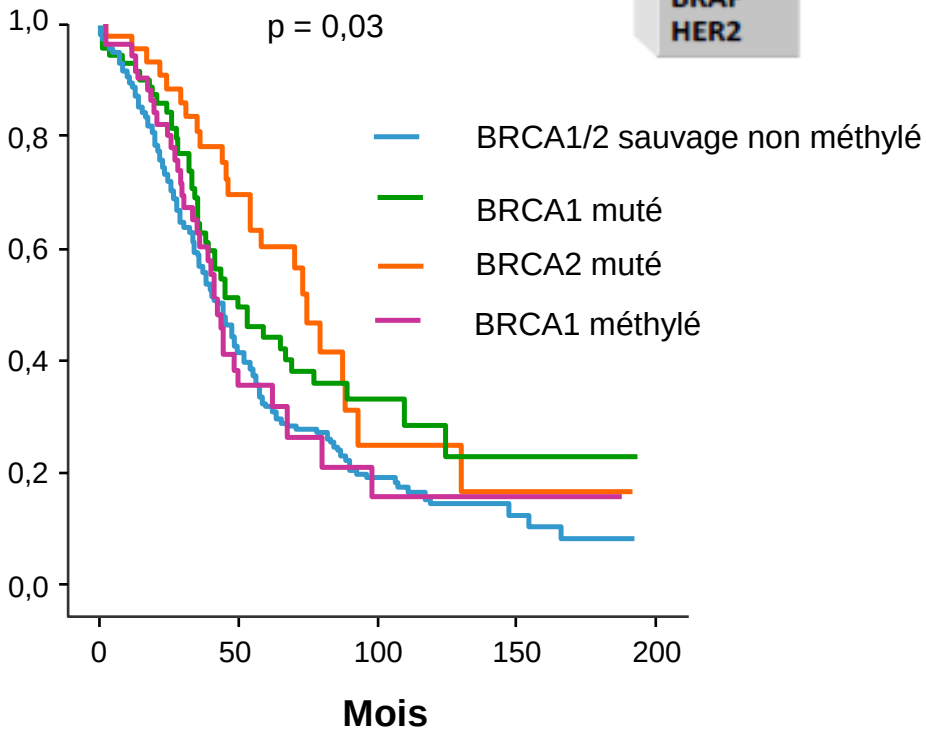
Take home message, early stage

- Complete surgical staging :
  - Stage IA/IB Gr 1, except clear cell carcinoma: surgery alone
  - Stage IA Gr 2 or IB-IC Gr 1: MTB discussion
  - Stage IA/IB Gr 3, clear cell carcinoma or stage $\geq$ IC : CP iv at least 3 cycles, 6 cycles for HGSC
- No complete surgical staging
  - Stage IA/IB Gr 1-2, except clear cell carcinoma, re staging then indication of CT in accordance to final staging
  - Stage IA/IB Gr 2-3, clear cell carcinoma or stage $\geq$ IC, re staging then CP at least 3 cycles (6 cycles for HGSC)
- Re staging not possible :
  - CP 6 cycles

Molecular Biology and Ovarian Cancer



Overall survival,
Pooled Analyse of 1 278 pts



	Precursor	Molecular features
Low-grade serous carcinoma	Cystadenoma-borderline tumour-carcinoma sequence	Mutations in *KRAS* or *BRAF*, or both
High-grade serous carcinoma	De novo in epithelial inclusion cysts	*TP53* mutation and *BRCA1* dysfunction; *PIK3CA* amplification (25–40%)
Low-grade endometrioid carcinoma	Endometriosis and endometrial-like hyperplasia*	Mutations in *CTNNB1* (B-catenin gene) and *PTEN* with microsatellite instability
High-grade endometrioid carcinoma	Epithelial inclusion glands or cysts	*TP53* mutation and *BRCA1* dysfunction; *PIK3CA* mutation
Mucinous carcinoma	Cystadenoma-borderline tumour-carcinoma sequence	Mutations in *KRAS*; possible *TP53* mutation associated with transition from borderline tumour to carcinoma
Clear-cell carcinoma	Possibly endometriosis	*PTEN* mutation/loss of heterozygosity; *PIK3CA* mutation

PIK3CA is the gene at chromosome 3q26 that specifically encodes the p110α subunit of the phosphatidylinositol-3-kinase (PI3K) protein. *Endometriosis and adjacent low-grade endometrioid carcinoma share common genetic events such as loss of heterozygosity at the same loci involving the same allele (eg, *PTEN*). By contrast, high-grade and poorly differentiated endometrioid carcinomas are similar to high-grade serous carcinomas.

Table 1: Origins and molecular pathology of epithelial ovarian cancer subtypes

Hennessy BT Jr, et al. Lancet. 2009; D'Angelo E, et al. Clin Transl Oncol. 2010.

Early stages conclusions

- Definition for early stages: st IA-IC (future C1 to C3), ~~IA-IIB, IA-IIIA~~
- Diagnosis at early stage = screening (next step, ctDNA?)
- Very few patients, 20% “high risk group” → molecular subgroups
- Indications for conservative surgery (see Christian Marth talk)
- Indications for adjuvant therapies (histology & grade)