Carcinoma ovarico stadio I-II e terapia adiuvante: quando e quale?

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AIGOM

ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

2025: NOVITÀ NEL TRATTAMENTO DELLE NEOPLASIE GINECOLOGICHE

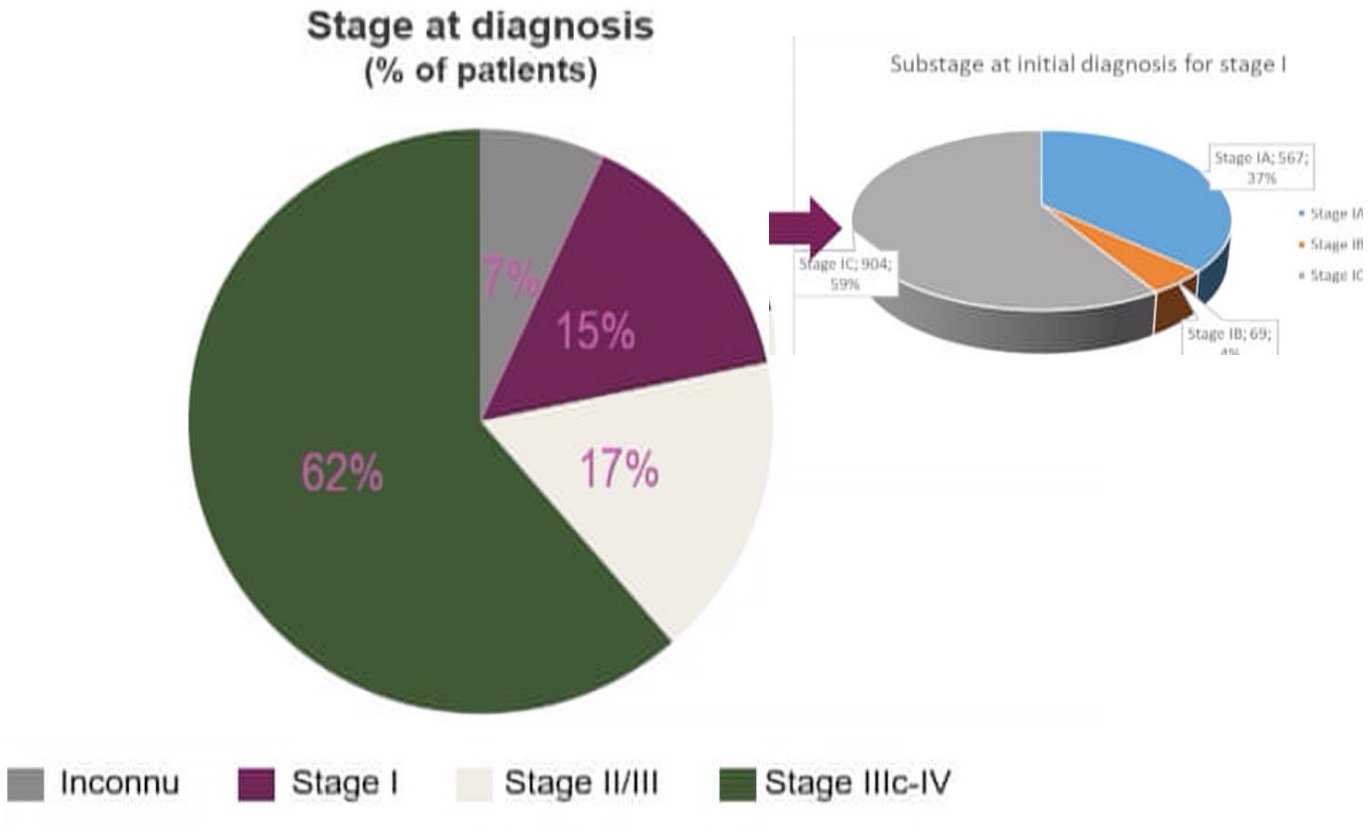
SCARCITY OF LITERATURE !!!!

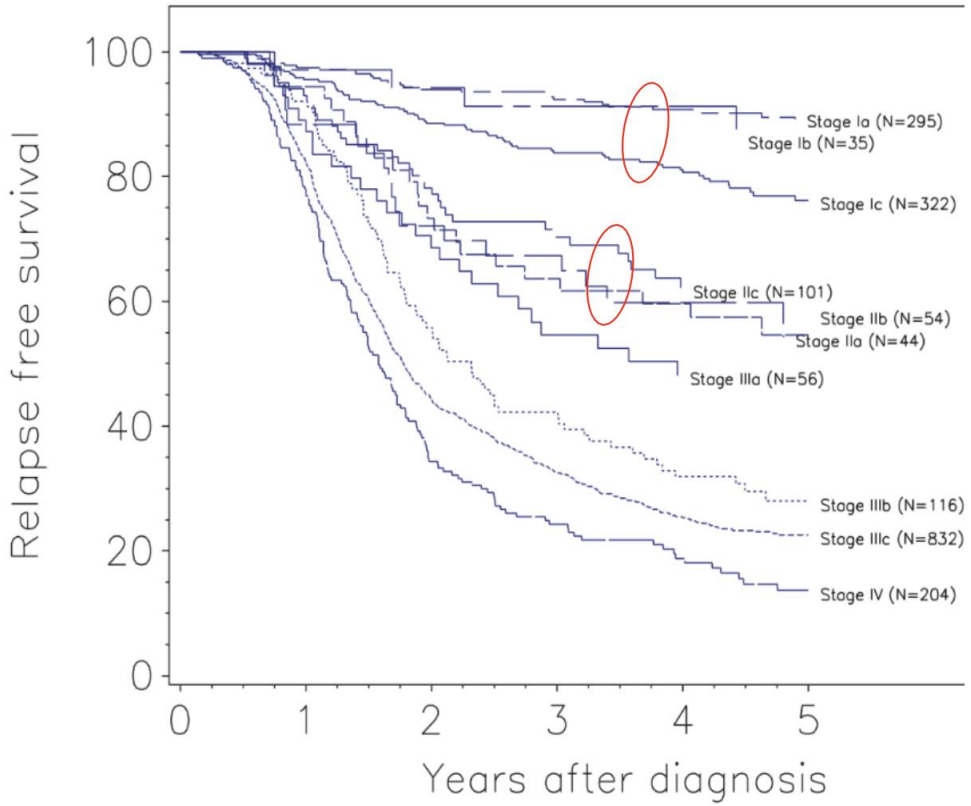
Outline

- Definition for early stages: stage IA-IC, IA-IIB, IA-IIIA?
- Indications for adjuvant therapies: Define risk of recurrence !!!
- For who? Duration ?
- Alternative to chemotherapy?
- Particularities (by hystology)

Epidemiology & Prognosis

- Majority of cancers diagnosed at advanced disease
- More than 70-80% of patients will relapse
- Outcome for early stage is very good: 5y survival in the range of 80 % to 93 %

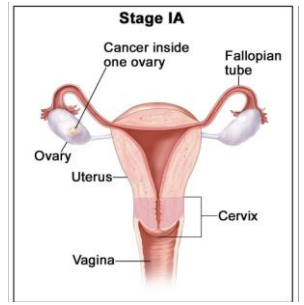


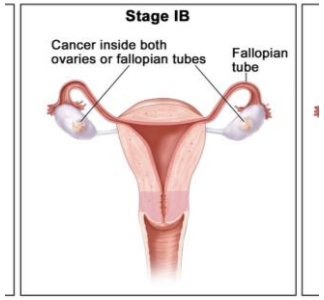


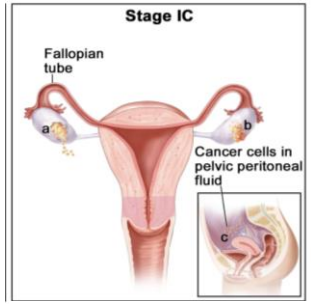
Heintz et al., Int J Gyn & Obst 2006, FIGO annual report

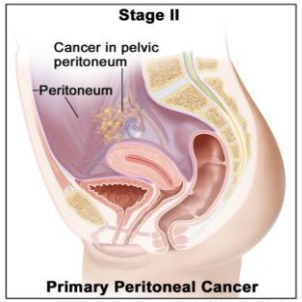
Ovarian cancer early stage (FIGO 2014)

Stage I Tumor confined to ovaries	IA		Tumor involving 1 ovary Capsule intact No tumor present on external surface No malignant cells in ascites or peritoneal washings
	IB		Tumor involving both ovaries Capsule intact No tumor present on external surface No malignant cells in ascites or peritoneal washings
	IC		Tumor limited to 1 or both ovaries
		IC1	Surgical spill
		IC2	Capsule rupture before surgery or tumor on ovarian surface
		IC3	Malignant cells in ascites or peritoneal washings
Stage II Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer	IIA		Extension and/or implant on uterus and/or fallopian tubes
	IIB		Extension to other pelvic intraperitoneal tissues









What is early stage ovarian cancer?

- Definition of early stage (IA-IC; IA-IIB?)
- ESMO clinical practice guideline 2023: Figo I-IIA
- NCCN recommends same treatment algorithm for stage II as for stage III/IV

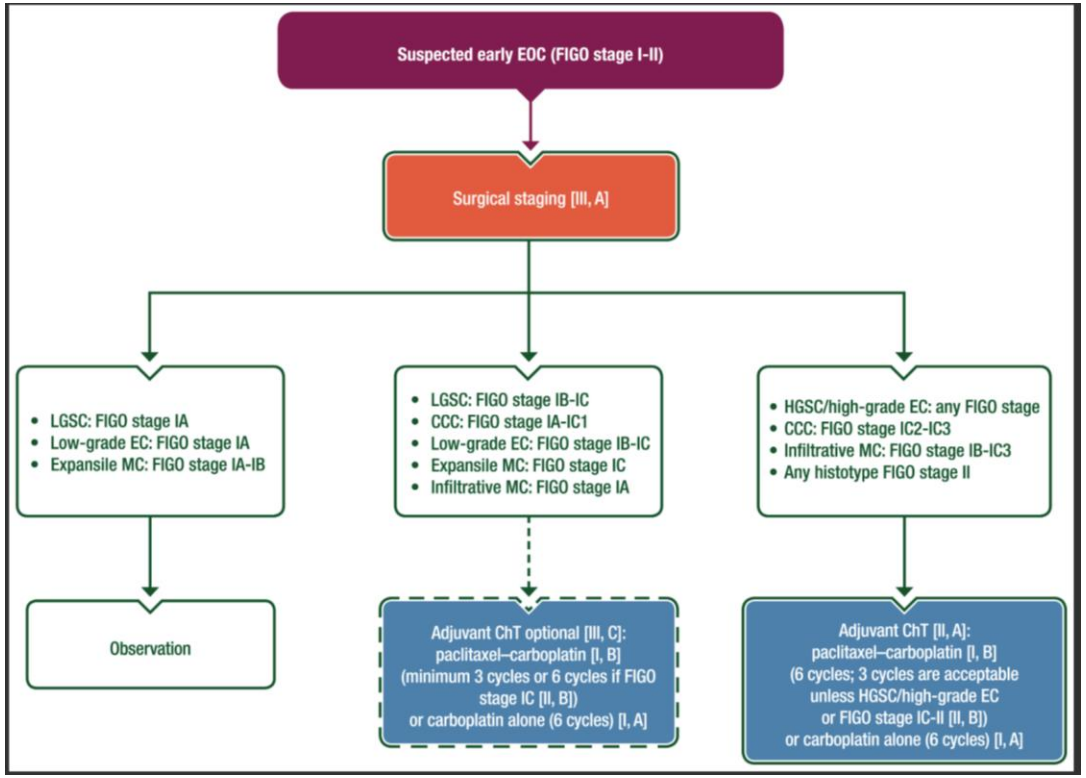
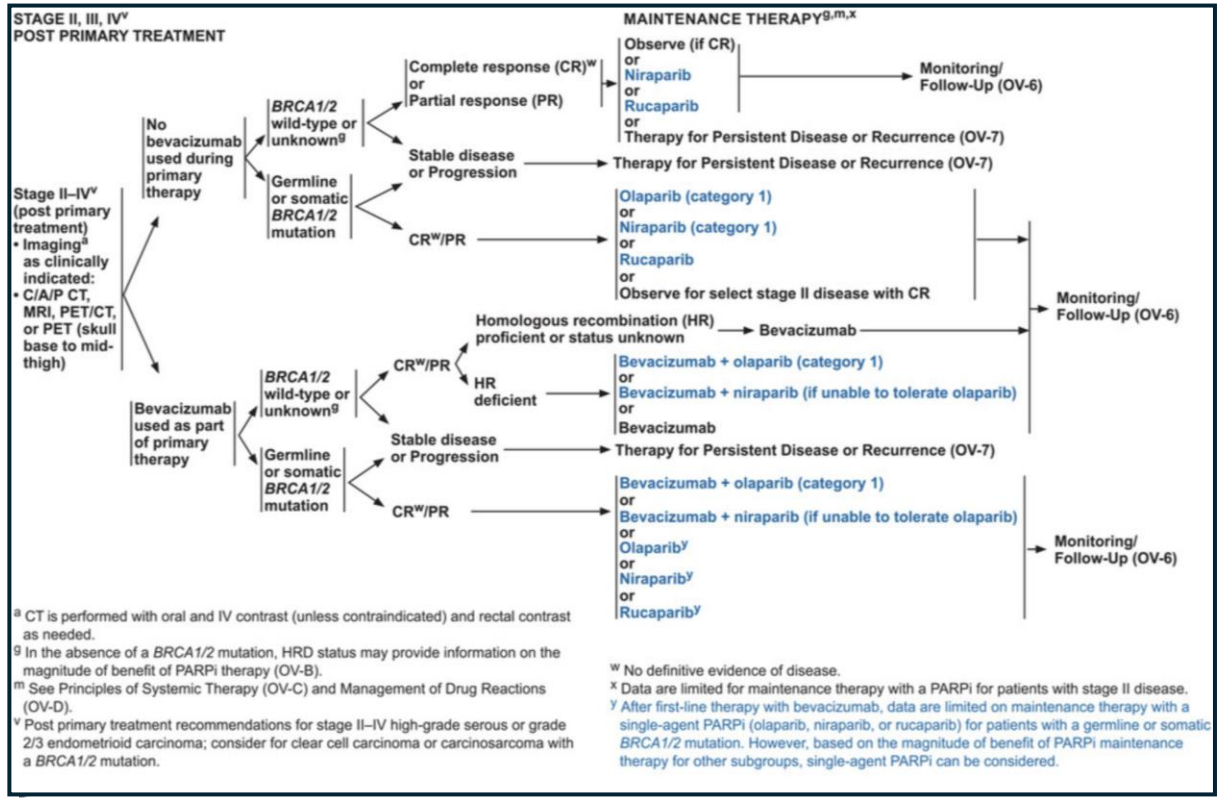


Figure 1. Management of early EOC (FIGO stage I-II).



NCCN Guidelines Version 3.2024

PROGNOSTIC FACTORS IN EARLY OC

Independent prognostic factors

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

Prognostic Factors for High-Risk Early-Stage Epithelial Ovarian Cancer

A Gynecologic Oncology Group Study

TABLE 3
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.

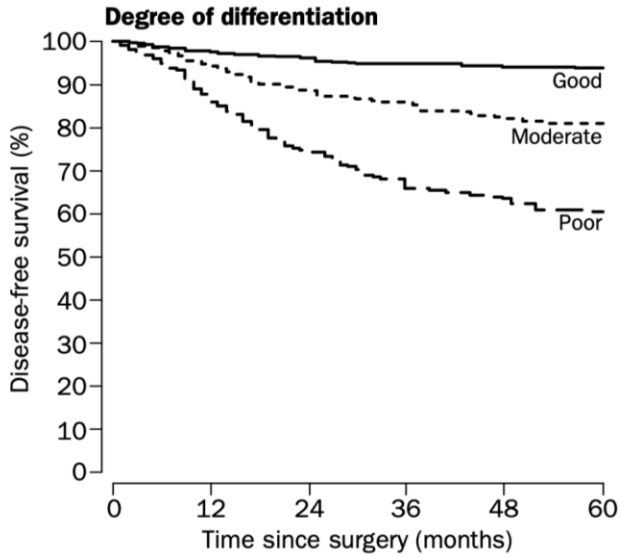
FY Ahmed, J Clin Oncol 1996; H TU et al, Int J of Gyn Cancer 2016 Chan et al, Cancer 2008

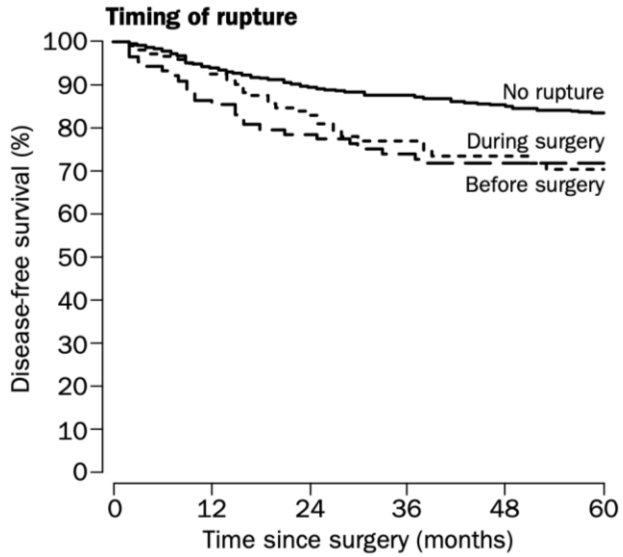
Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma

Characteristic	Hazard ratio (95% CI) on multivariate analysis	p
Degree of differentiation		
Good*	1·00	..
Moderate	3·13 (1·68–5·85)	0·0003
Poor	8·89 (4·96–15·9)	0·0001
Rupture before surgery		
No*	1·00	..
Yes	2·65 (1·53–4·56)	0·0005
Rupture during surgery		
No*	1·00	..
Yes	1·64 (1·07–2·51)	0·022
FIGO stage 1973		
Ia*	1·00	..
Ib	1·70 (1·01–2·85)	0·046
Age (per year	1·02 (1·00–1·03)	0·053

*Reference category.

Table 3: **Significant variables for actuarial disease-free survival in final multivariate model**





Degree of differentiation: the most powerful prognostic indicator of DFS, followed by rupture before and during surgery

Vergote et al, The Lancet Vol 357 • January 20, 2001

ADJUVANT TREATMENT in EARLY STAGE

SURGERY !!!

To remove the disease and for accurate staging

+/- CHEMOTHERAPY

- FSS for young women – low risk
- Important role of trained gynaecologist oncologist
- Lymphadenectomy?

Role of Lymphadenectomy

Table 2 Three-year disease-specific 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)	$P=0.076$
Lymphadenectomy						$P<0.001^{\Delta}$
Yes	93.3 (±0.5)	δ 11.3%	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)	δ 6.2%	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)	δ 24.0%	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)	$P=0.410$*

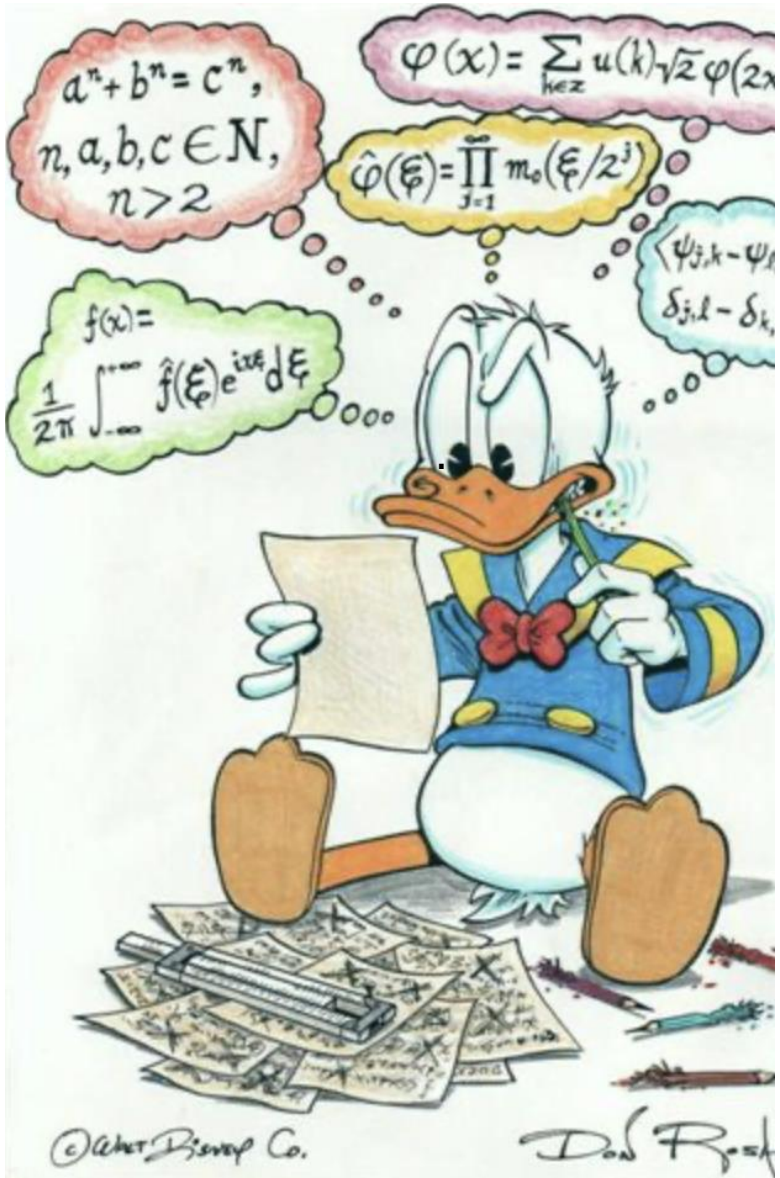
Chan KJ et al., BJC (2008) 98, 1191 – 1196

ADJUVANT CHEMOTHERAPY

Heterogeneous population

inadequate surgery

use of non standard chemotherapy drugs



survival benefit only in certain subsets

Varying number of chemotherapy cycles

ADJUVANT CHEMOTHERAPY

RANDOMIZED PHASE III TRIALS

Adjuvant chemotherapy versus observation

ICON-1 (n=477)

- Histol. confirmed EOC
- Clinician uncertain if CHT needed
- Surgery: all visible tumour removed
  - Radical hysterectomy, bilat. adnexectomy, omentectomy as minimum
  - Lymphadenectomy not mandated
- Primary endpoint: overall survival

ACTION (=448)

- Histol. confirmed EOC
  - **FIGO IA/B & G2/3**
  - **FIGO IC–IIA all grades**
  - **FIGO I–IIA clear cell**
- Surgery: strict guidelines for comprehensive surgical staging
  - hysterectomy, bilat. Adnexectomy + surgical staging:
  - Omentectomy, peritoneal washings; blind biopsies (pelvic peritoneum, paracolic gutters; right hemidiaphragm) iliac & periaortic lymph nodes sampling **(all met = staging optimal)**
- Primary endpoint: overall survival

ICON Collaborators., JNCI, Vol. 95, No. 2, January 15, 2003; pp. 125- Trimbos B et al., JNCI, Vol. 95, No. 2, January 15, 2003; pp. 113

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Patient characteristica

- 93% stage I (40% IC)
- **32% serous; 23% mucinous; 23% endometrioid; 15% CCC**
- 27% G3; 41% G2; 32% G1
- Chemoptherapy received (6 cylcles recommended):
  - **86% carboplatin mono**
  - 10% cisplatin combo
  - 2% other (platinum based)
  - 2% not received
  - **85% received 6 cycles**

ACTION (=448)

- Histol. confirmed EOC
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- Primary endpoint: overall survival

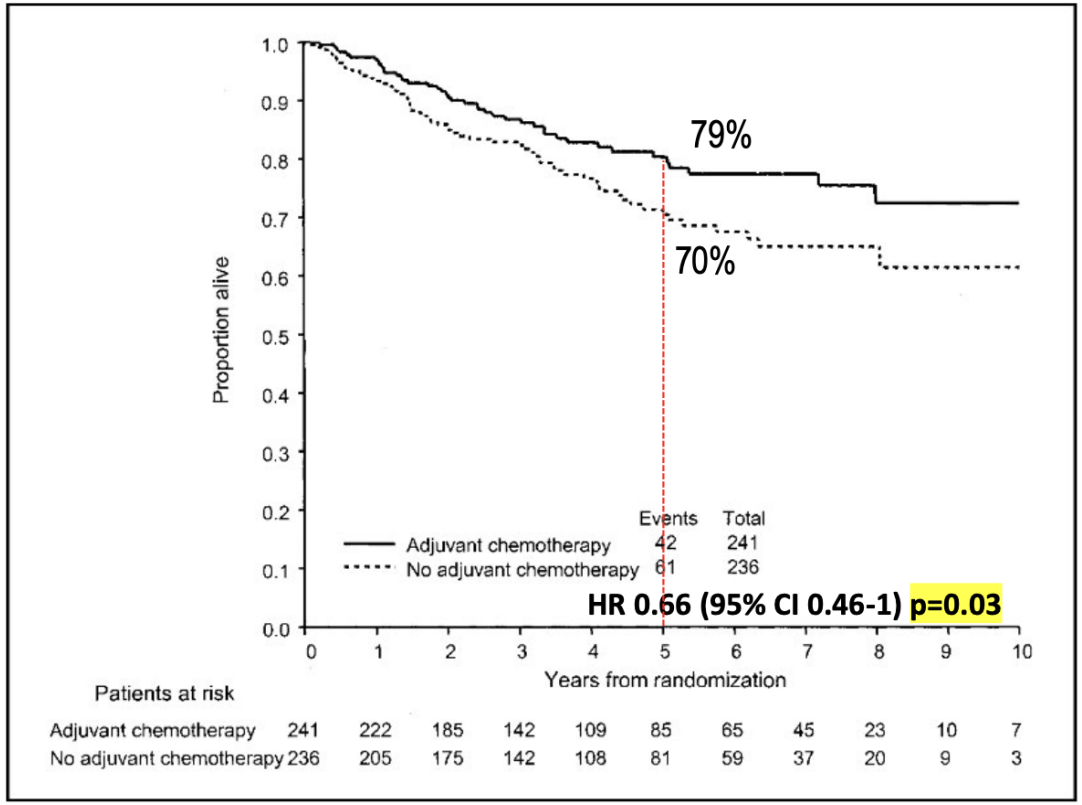
Patient characteristica

- 93% stage I (50% IC)
- **35% serous; 17% mucinous; 27% endometrioid; 14% CCC**
- 35% G3; 51% G2; 12% G1
- Surgical staging:
  - optimal: 34%
  - minimal/inadequate: 35%
- Chemoptherapy received (6 cylcles recommended):
  - **47% Cisplatin/Cyclophosphamid**
  - **33% carboplatin mono**

ICON Collaborators., JNCI, Vol. 95, No. 2, January 15, 2003; pp. 125- Trimbos B et al., JNCI, Vol. 95, No. 2, January 15, 2003; pp. 113

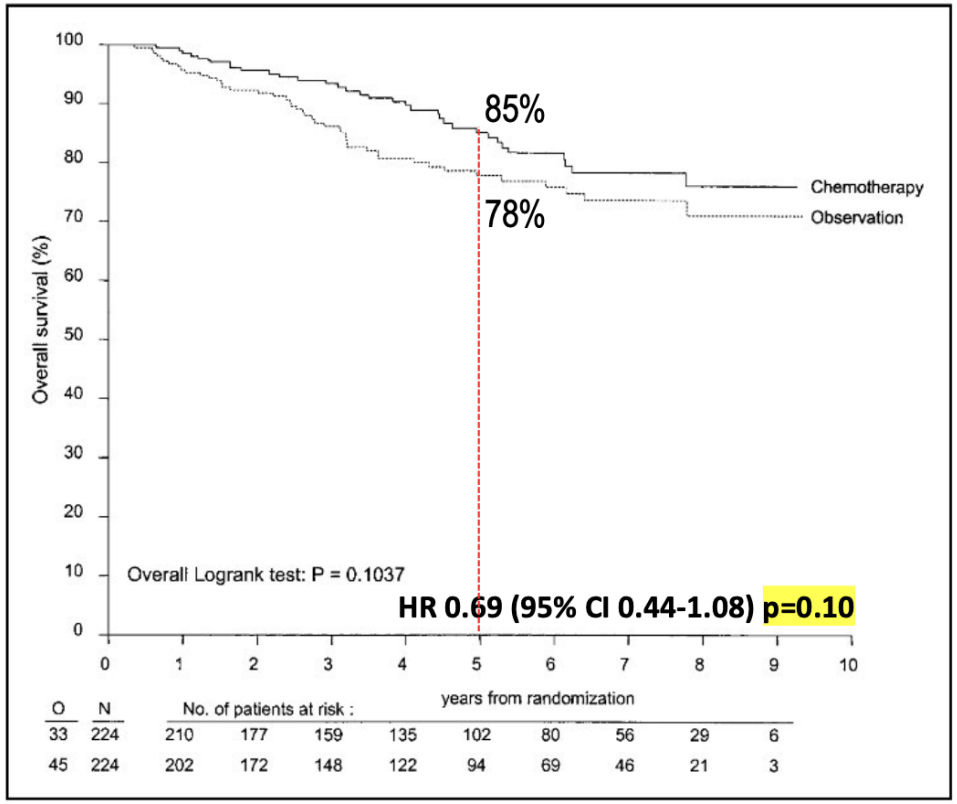
PRIMARY ENDPOINT: OS

ICON1



ICON Collaborators., JNCI, Vol. 95, No. 2, January 15, 2003; pp. 125

ACTION



Trimbos B et al., JNCI, Vol. 95, No. 2, January 15, 2003; pp. 113

Combined ICON1 and ACTION:
POOLED ANALYSIS (N=925)

JOURNAL ARTICLE

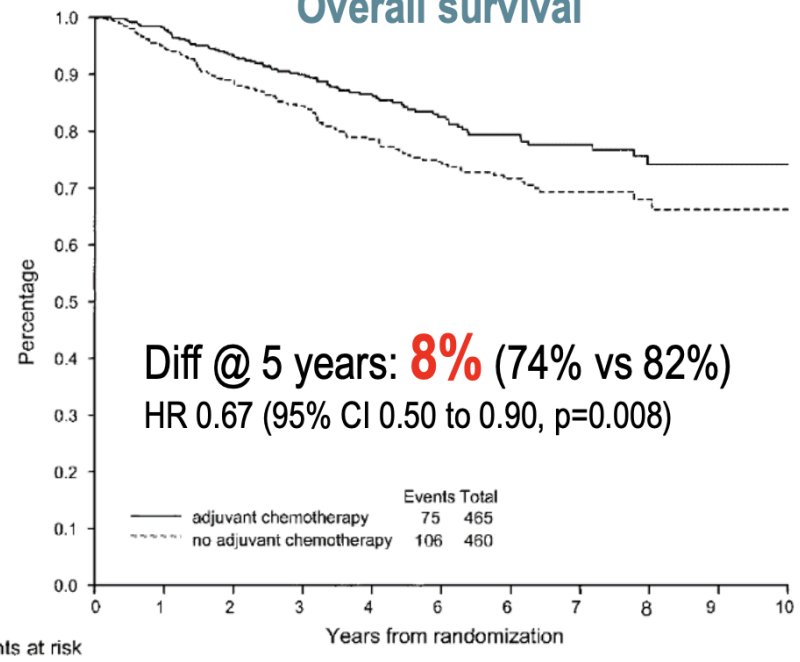
International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm Trial: Two Parallel Randomized Phase III Trials of Adjuvant Chemotherapy in Patients With Early-Stage Ovarian Carcinoma Get access ›

International Collaborative Ovarian Neoplasm 1 (ICON1),
European Organisation for Research and Treatment of Cancer Collaborators–Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC–ACTION)

JNCI: Journal of the National Cancer Institute, Volume 95, Issue 2, 15 January 2003, Pages

Adjuvant chemotherapy versus observation

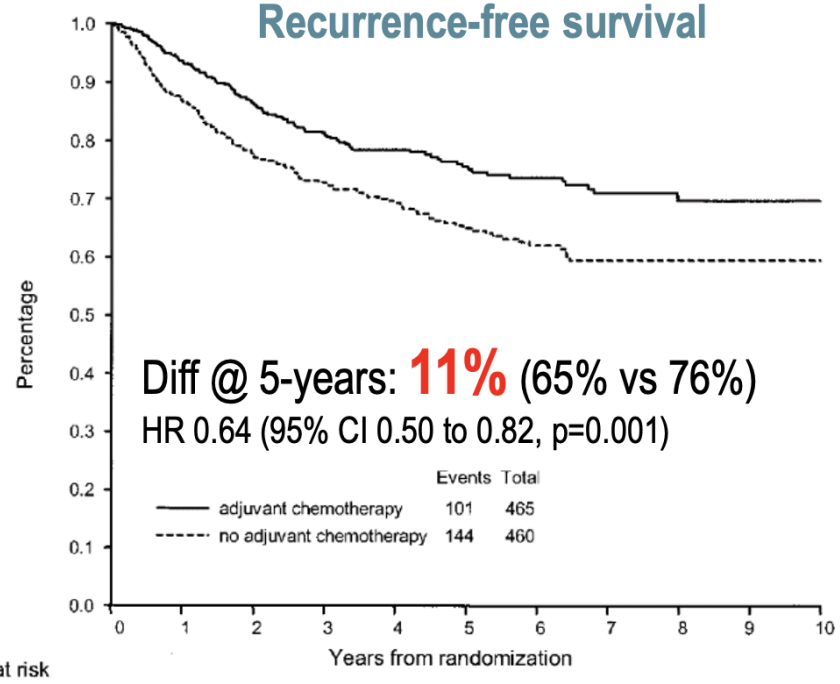
Overall survival



Diff @ 5 years: **8%** (74% vs 82%)

HR 0.67 (95% CI 0.50 to 0.90, p=0.008)

Recurrence-free survival



Diff @ 5-years: **11%** (65% vs 76%)

HR 0.64 (95% CI 0.50 to 0.82, p=0.001)

93% stage I

60% single agent platin
35% platin combo

33% serous
20% mucinous
24% endometrioid
14% clear cell

21% G1
45% G2
30% G3

Median FU:
ACTION: 59 months
ICON1: 51 months

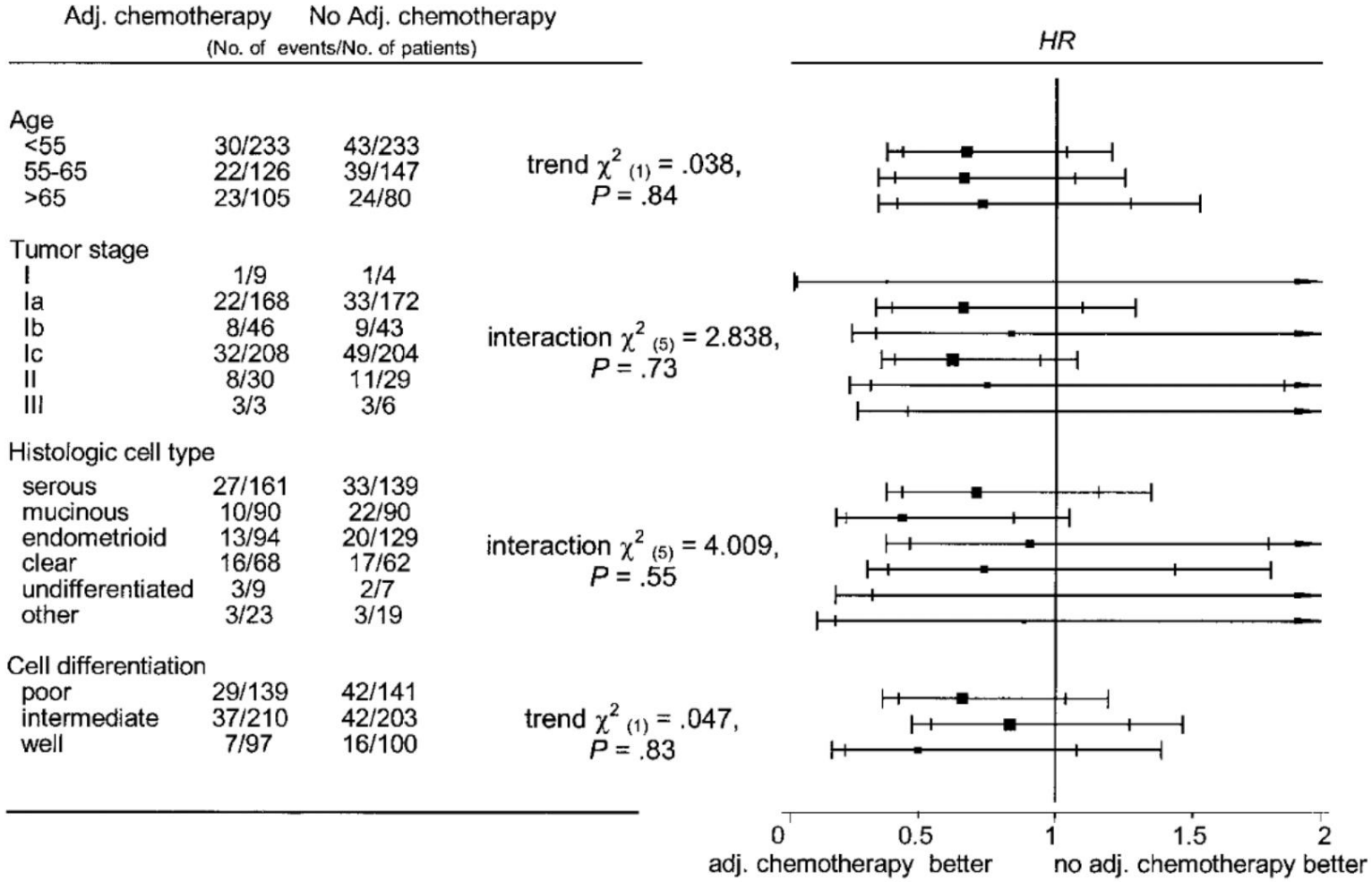
Trimbos / Vergote et al., JNCI, Vol. 95, No. 2, January 15, 2003; pp. 105

ICON1 and ACTION POOLED ANALYSIS (N=925)

Subgroup analysis

No subgroup identified, that benefited less or more from adjuvant chemotherapy
(age, grade, histotype, stage)

A separate subgroup analysis of staging completeness was not done because information about surgical staging was not collected in the ICON1 trial



Trimbos / Vergote et al., JNCI, Vol. 95, No. 2, January 15, 2003; pp. 105

UPDATED ICON1 RESULTS (median FU 10ys)

Annals of Oncology 25: 1165–1171, 2014
doi:10.1093/annonc/mdu116
Published online 14 March 2014

Optimal treatment of early-stage ovarian cancer

F. Collinson[1†], W. Qian[2†], R. Fossati[3], A. Lissoni[4], C. Williams[5], M. Parmar[6*], J. Ledermann[7], N. Colombo[8] & A. Swart[9] on behalf of the ICON1 collaborators

Table 1. Classification of stage 1 patients by risk of recurrence

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Stage 1A	13	20	10
Stage 1B	3	4	4
Stage 1C	15	17	12

Figures represent the proportion of patients in ICON1 (2% unknown). Light grey represents low risk (13%); medium grey represents intermediate risk (38%); dark grey represents high risk (47%).

High-risk: 47%
Intermediate: 38%
Low-risk: 13%

Extended FU from ICON1 confirms that adjuvant chemotherapy should be offered to women with early-stage OC, particularly those with high-risk disease.

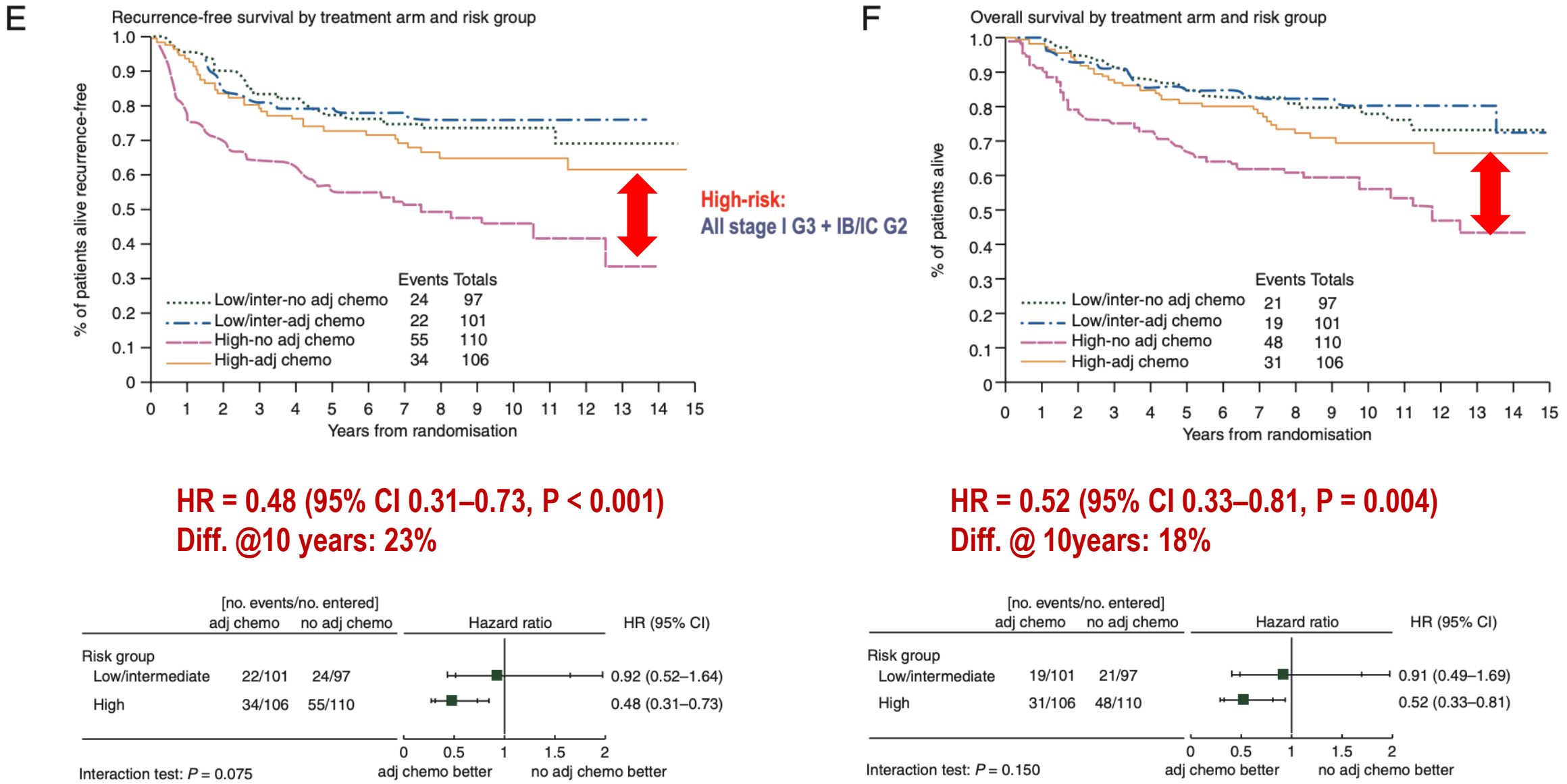
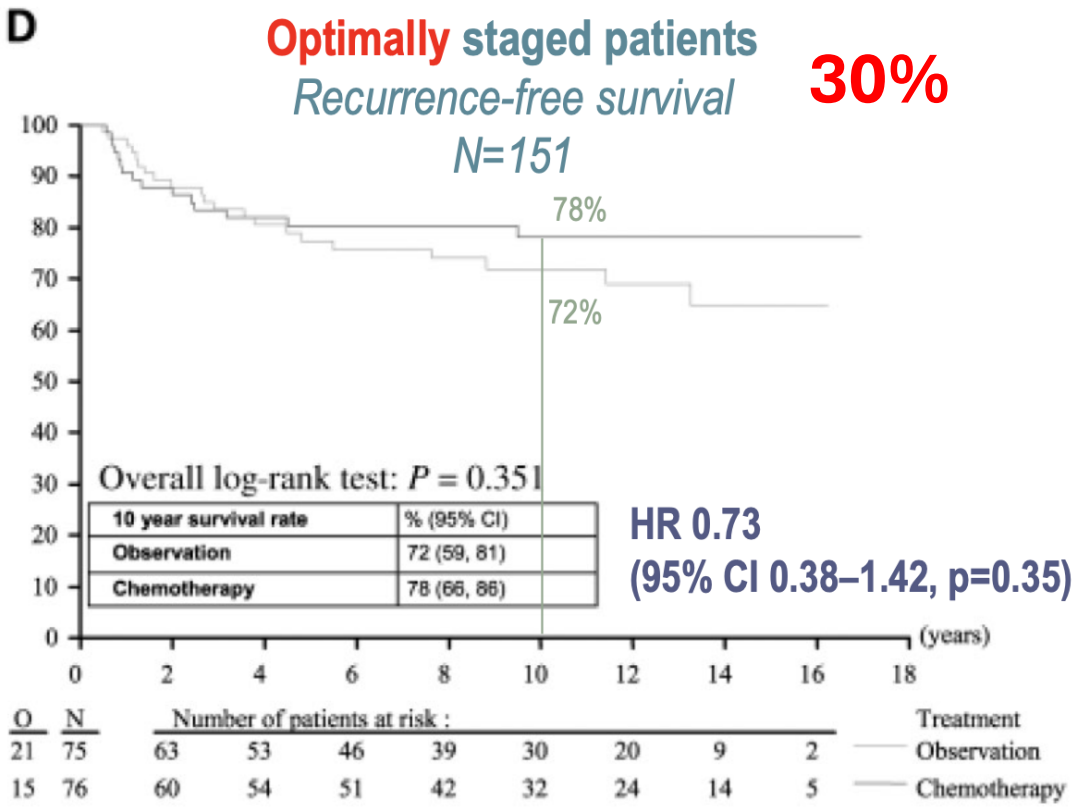
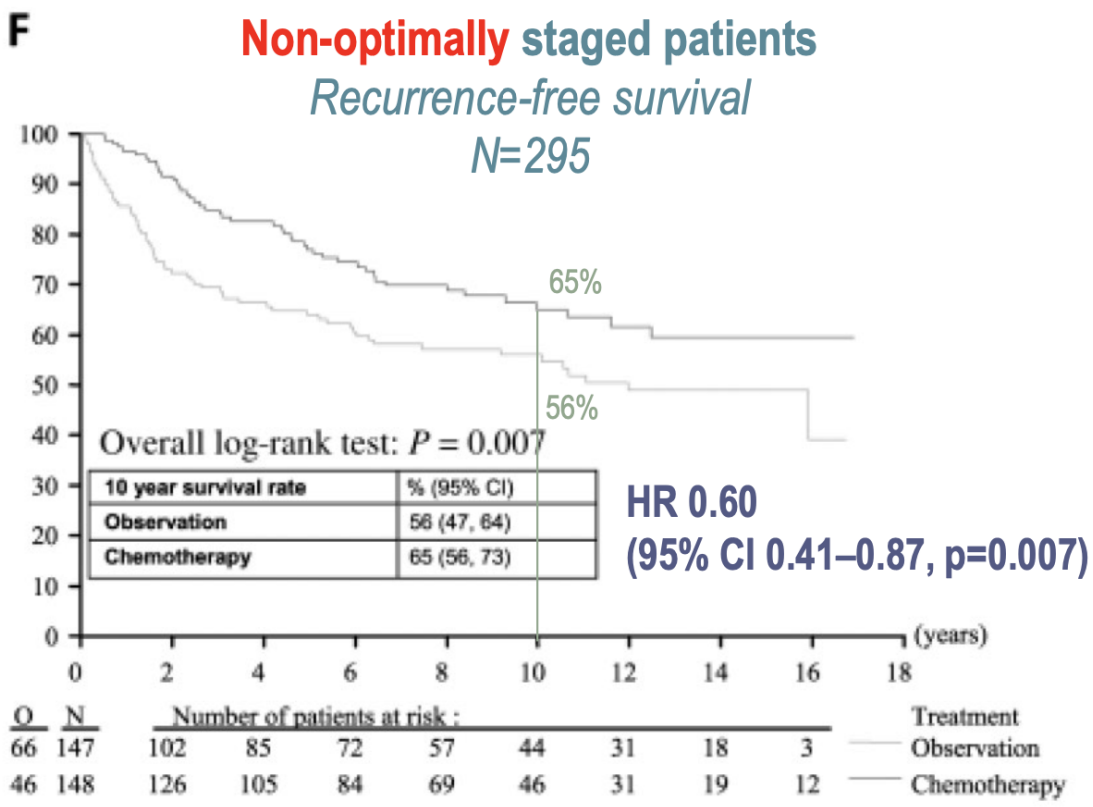


Figure 2. Updated ICON1 results with median follow-up 10 years.

Impact of surgery on Adjuvant CT
ACTION – 10 ys FU





Importance of complete staging!

Trimbos B et al., J Natl Cancer Inst 2010;102:982–987

ESMO CLINICAL PRACTICE GUIDELINE 2023

Management of early stage ovarian cancer (FIGO I-II)

Recommendations

- Surgical staging is recommended in presumed early-stage ovarian cancer for classification and recommendation of optimal systemic therapy [III, A].
- Adjuvant ChT in early-stage ovarian cancer is generally recommended for FIGO stage I-IIB (see exceptions below) [II, A], either paclitaxel—carboplatin [I, B] or carboplatin (six cycles) alone [I, A].

Histologies	Stage IA	Stage IB/C1	Stage IC2-3	Stage IIA
HGSOC	Yes	Yes	Yes	Yes
high-grade Endometrioid (G3)	Yes	Yes	Yes	Yes
LGSOC	No	Option*	Option*	Yes
Low-grade Endometrioid (G1/2)	No	Option*	Yes	Yes
Expansile Mucinous (G1/2)	No	Option*	Option*	Yes
Infiltrative Mucinous (G3)	No	Yes	Yes	Yes
Clear cell	Option*	Option*	Yes	Yes

Gonzalez-Martin A et al., Ann Oncol . 2023 Oct;34(10):833-848

ADJUVANT CHEMOTHERAPY

- Both regimens, **Carboplatin** mono and **Carboplatin + Paclitaxel** are used
- The addition of Paclitaxel leads to significantly more toxicity, including long term toxicity like PNP
- NO answer by data from ICON1 & ACTION
  - ✓ Non-randomized for this question
  - ✓ Single agent platin most frequently used in ICON1 & the pooled analysis of ICON1 & ACTION

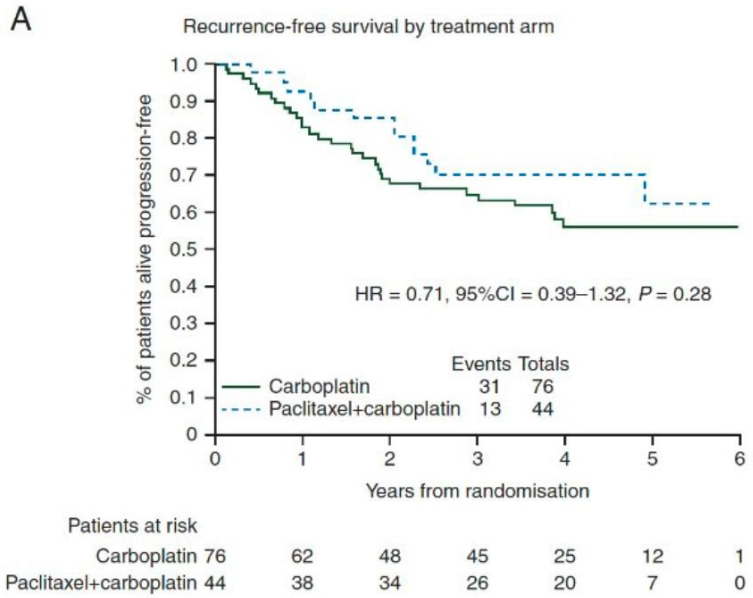
Choice of optimal adj CT regimen & duration of treatment in early stage EOC remains a subject of continuing debate

Only limited data available

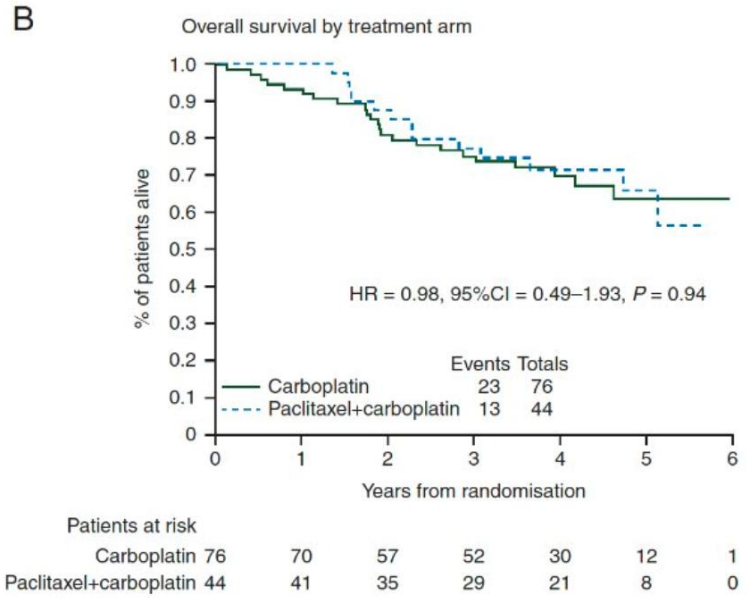
ICON3 – STAGE I PATIENTS (N=120; 6%)

6x Carboplatin vs 6x Carboplatin/Paclitaxel

A



B



	Carboplatin (N=76)	Carboplatin/paclitaxel (N=44)
Number	n (%)	**n (%)**
Age		
<55	27 (36)	**21 (48)**
55-65	29 (38)	**10 (23)**
>65	20 (26)	**13 (30)**
Histology		
Serous	30 (39)	**20 (45)**
Mucinous	8 (11)	**3 (7)**
Endometroid	18 (24)	**9 (20)**
Clear cell	14 (18)	**8 (18)**
Undifferentiated	2 (3)	**0**
Other	4 (5)	**4 (9)**
Grade		
Poor	**26 (34)**	**15 (34)**
Moderate	**35 (46)**	**12 (27)**
Well	**12 (16)**	**15 (34)**
Unknown	**3 (4)**	**2 (5)**

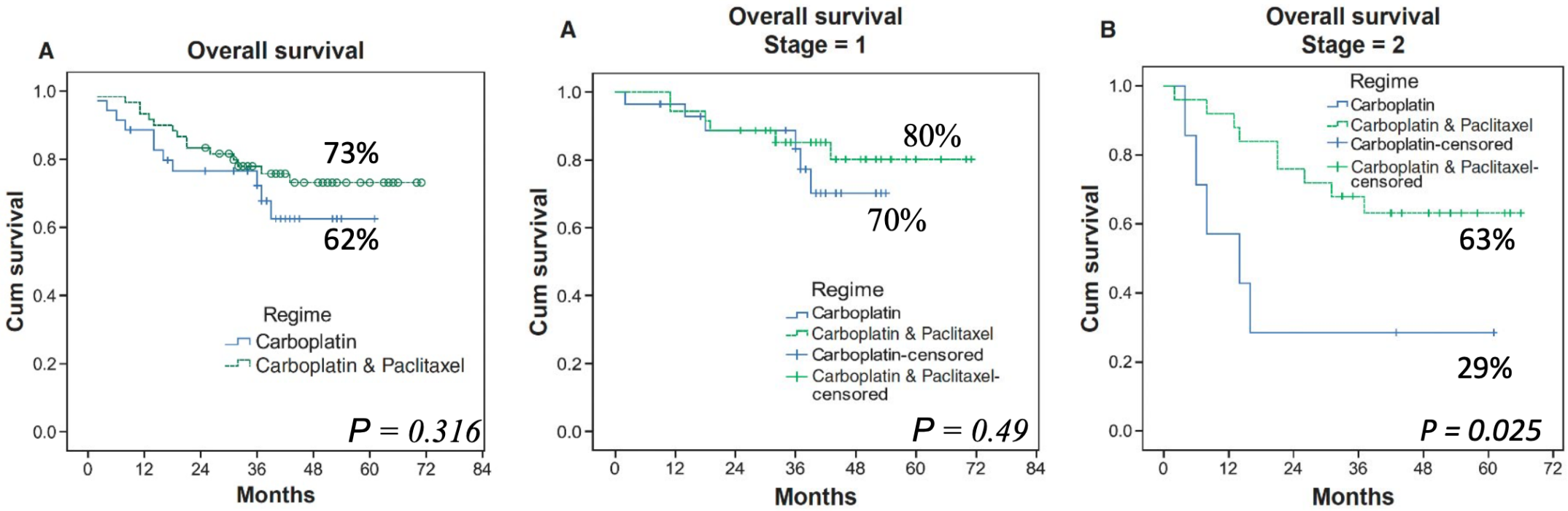
- Small samples seize
- Exploratory subgroup analysis
- HR_{RFS} of 0.71 supports combination
- Wide confidence intervals & lack of signal for OS argue against it

➜ the optimal chemotherapy regimen for early stage EOC remains an open question (in clinical practice both are used)

Collinson F et al., Annals of Oncology 25: 1165–1171, 2014

Retrospective single center experience (n=95, non-randomized)

Serous 39%, endometrioid 30%, clear cell 23% and mucinous 8%



Conclusions Combination therapy is administered more often than carboplatin; especially in those with younger age, better PS and nonmucinous histology. Recurrence and death rates were similar with both treatments. Well-designed trials are needed to identify the optimum chemotherapy regimen in this group.

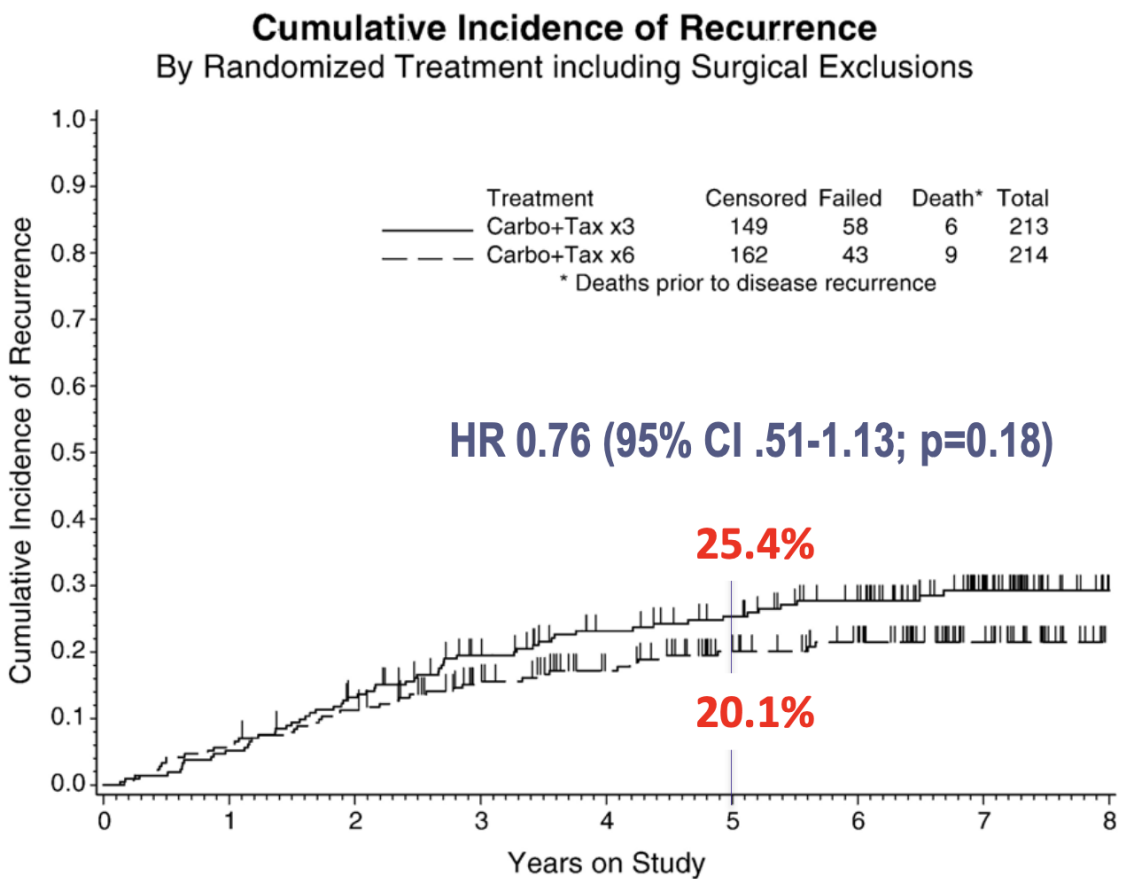
Adam G et al., BJOG 2010;117:1459–1467

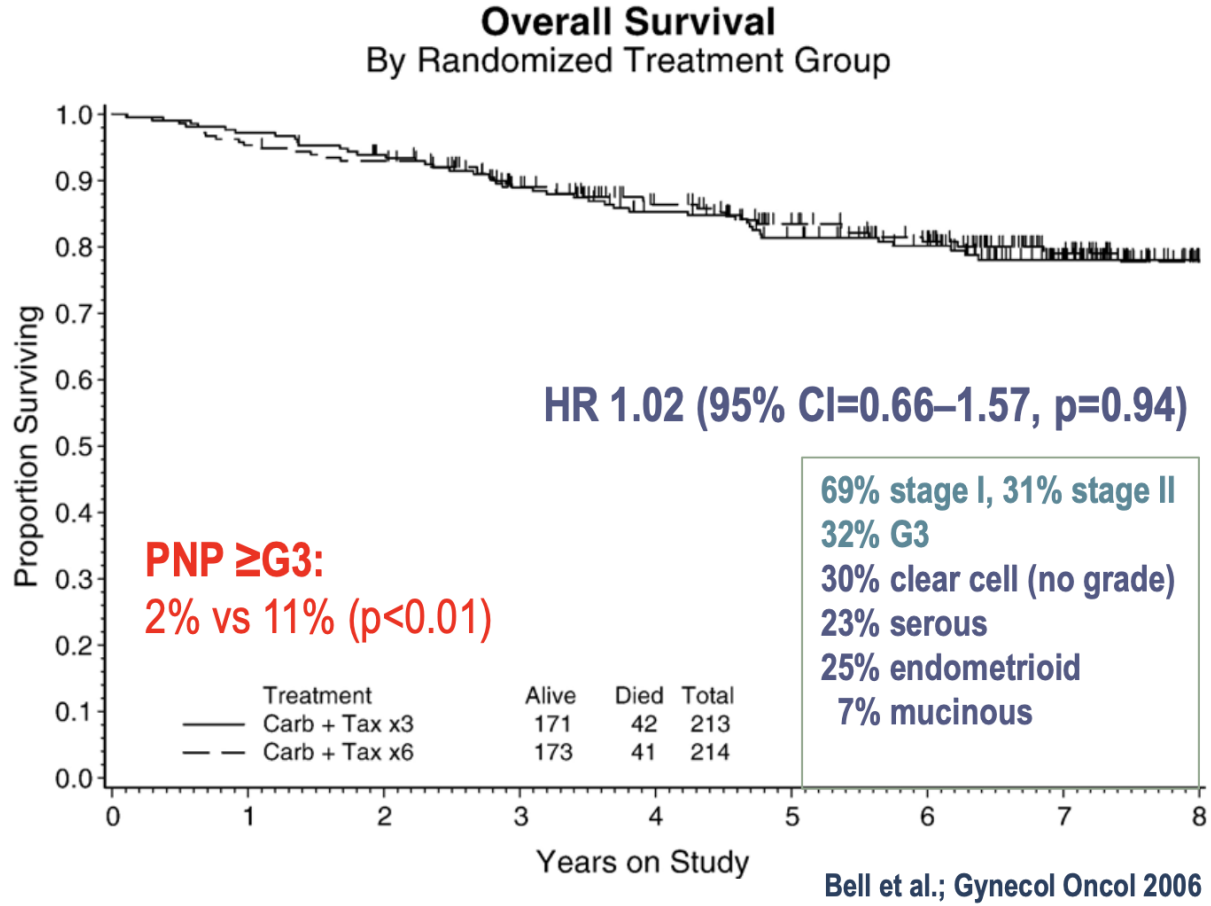
ADJUVANT CHEMOTHERAPY

GOG 157: DURATION OF ADJUVANT CHEMOTHERAPY (N=427)

3 *versus* 6 cycles of Carboplatin (AUC7.5)/Paclitaxel (175) q3w

Stage IA/B G3, IC & II

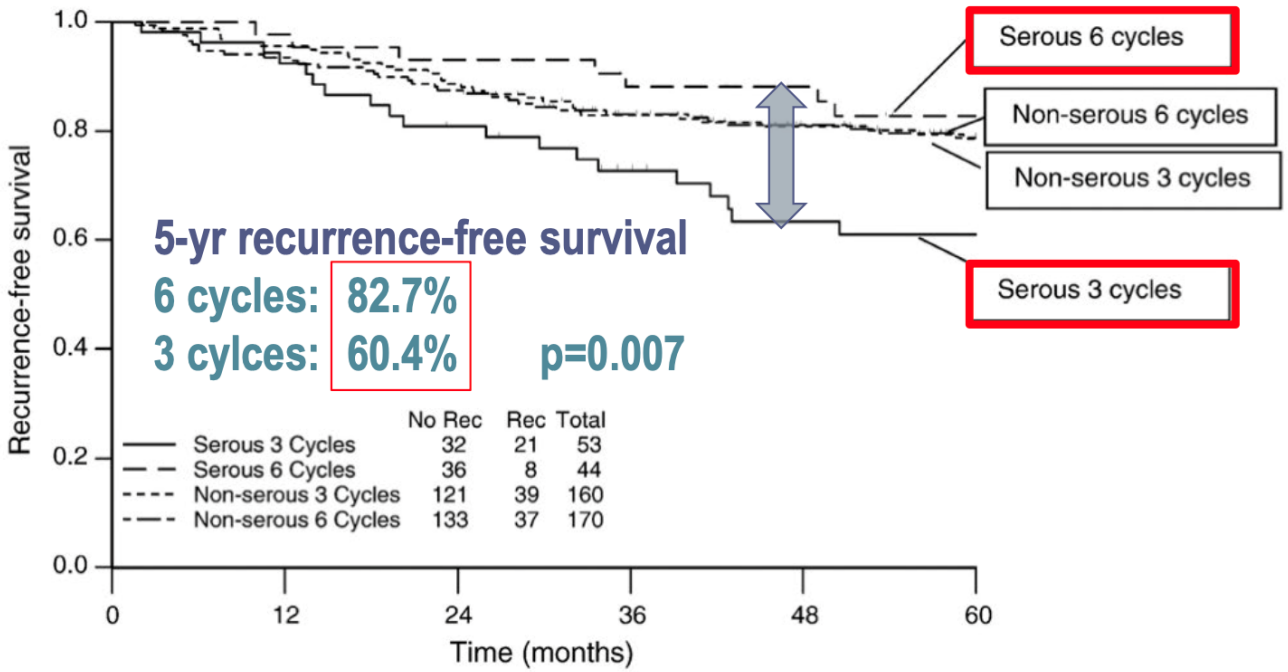


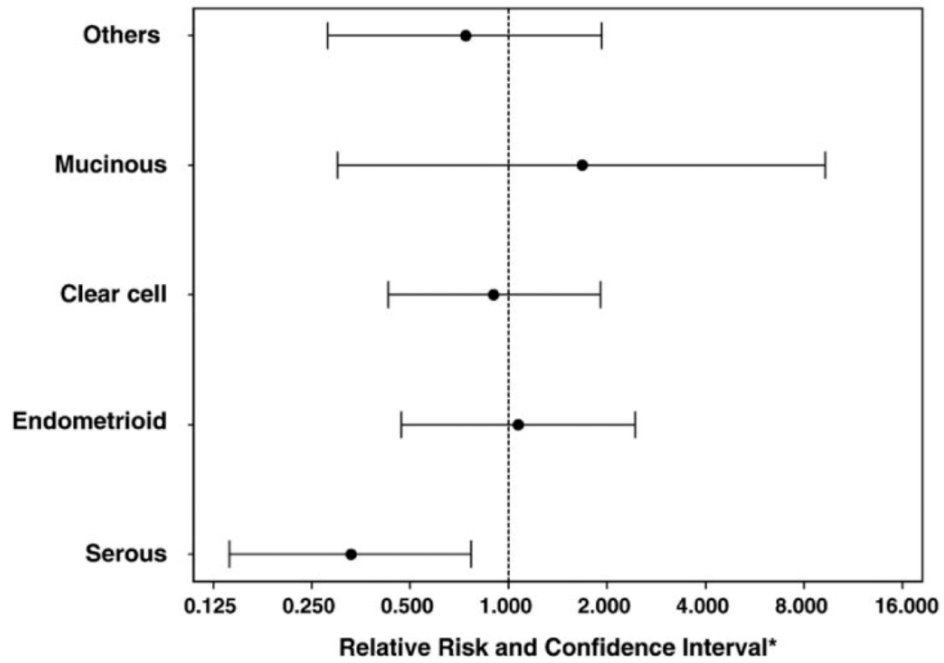


Bell et al.; Gynecol Oncol 2006

GOG 157: DURATION OF ADJUVANT CHEMOTHERAPY (N=427)

Outcomes by histotype





J.K. Chan et al., Gynecologic Oncology 116 (2010) 301–306

ESMO CLINICAL PRACTICE GUIDELINE 2023

Management of early stage ovarian cancer (FIGO I-II)

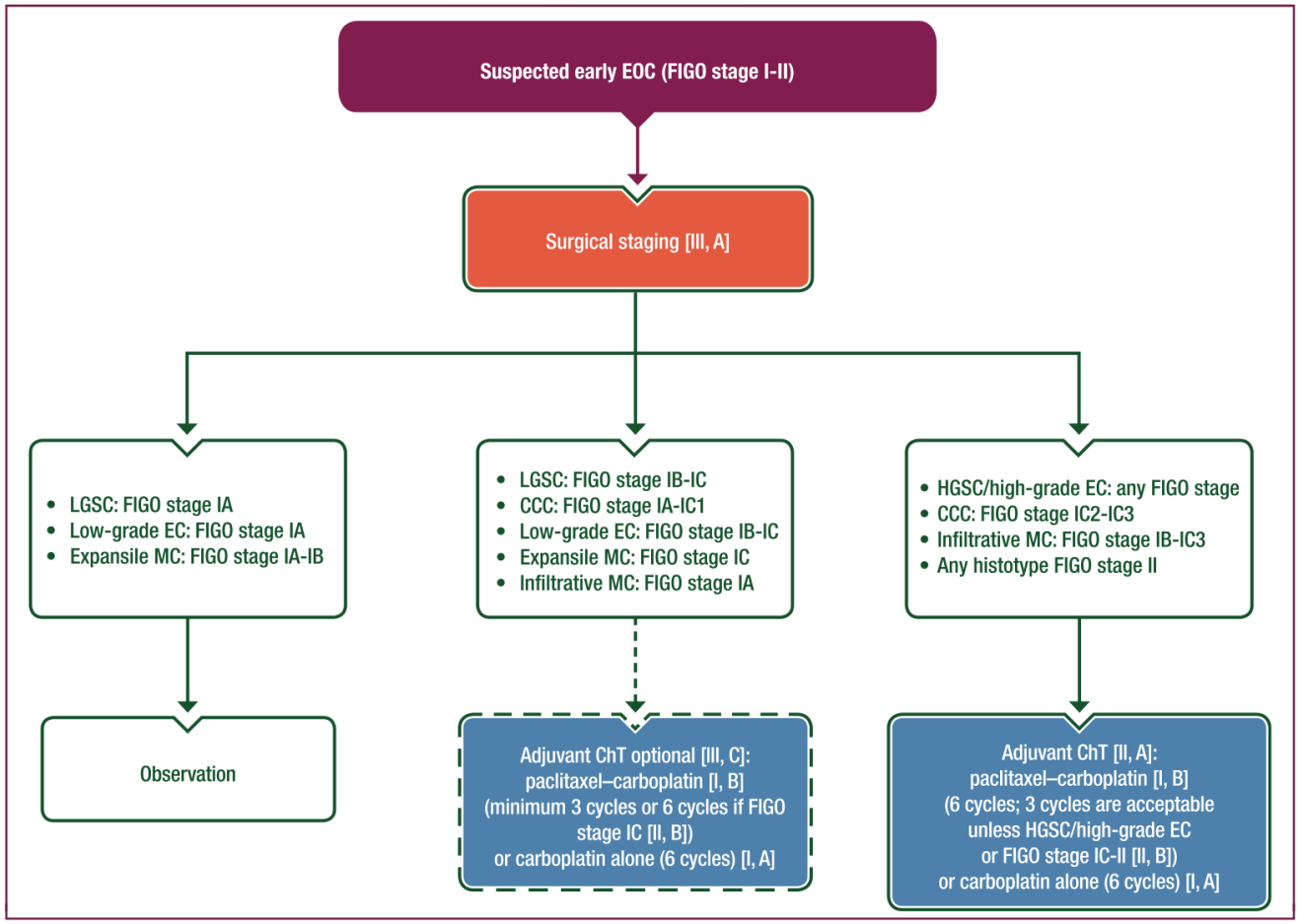


Figure 1. Management of early EOC (FIGO stage I-II).

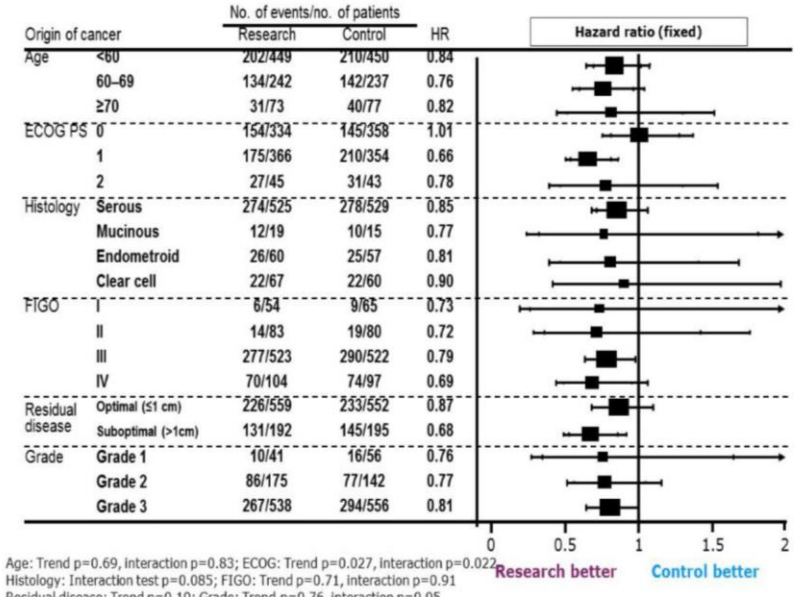
Recommendations

- Surgical staging is recommended in presumed early-stage ovarian cancer for classification and recommendation of optimal systemic therapy [III, A].
- Adjuvant ChT in early-stage ovarian cancer is generally recommended for FIGO stage I-IIB (see exceptions below) [II, A], either paclitaxel—carboplatin [I, B] or carboplatin (six cycles) alone [I, A].
- For patients receiving paclitaxel—carboplatin, a minimum of three cycles are recommended except for HGSC/high-grade EC or any stage IC-II regardless of histotype, for which six cycles are suggested [II, B].
- The benefit of adjuvant ChT is uncertain and can be considered as optional [III, C] for:
  - o LGSC stage IB-IC
  - o CCC stage IA-IC1
  - o Low-grade EC stage IB-IC
  - o Expansile MC stage IC
  - o Infiltrative MC stage IA
- Adjuvant ChT is not recommended in completely staged patients with LGSC stage IA, low-grade EC stage IA or expansile MC stage IA-IB [II, E].

Gonzalez-Martin A et al., Ann Oncol . 2023 Oct;34(10):833-848

ALTERNATIVE TO CT ALONE?

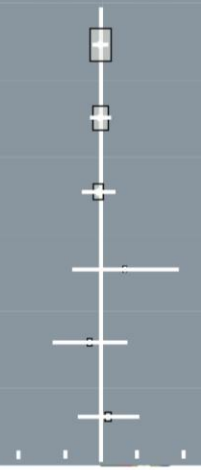
Subgroup analysis of PFS



ICON7
Bevacizumab in Ovarian Cancer

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



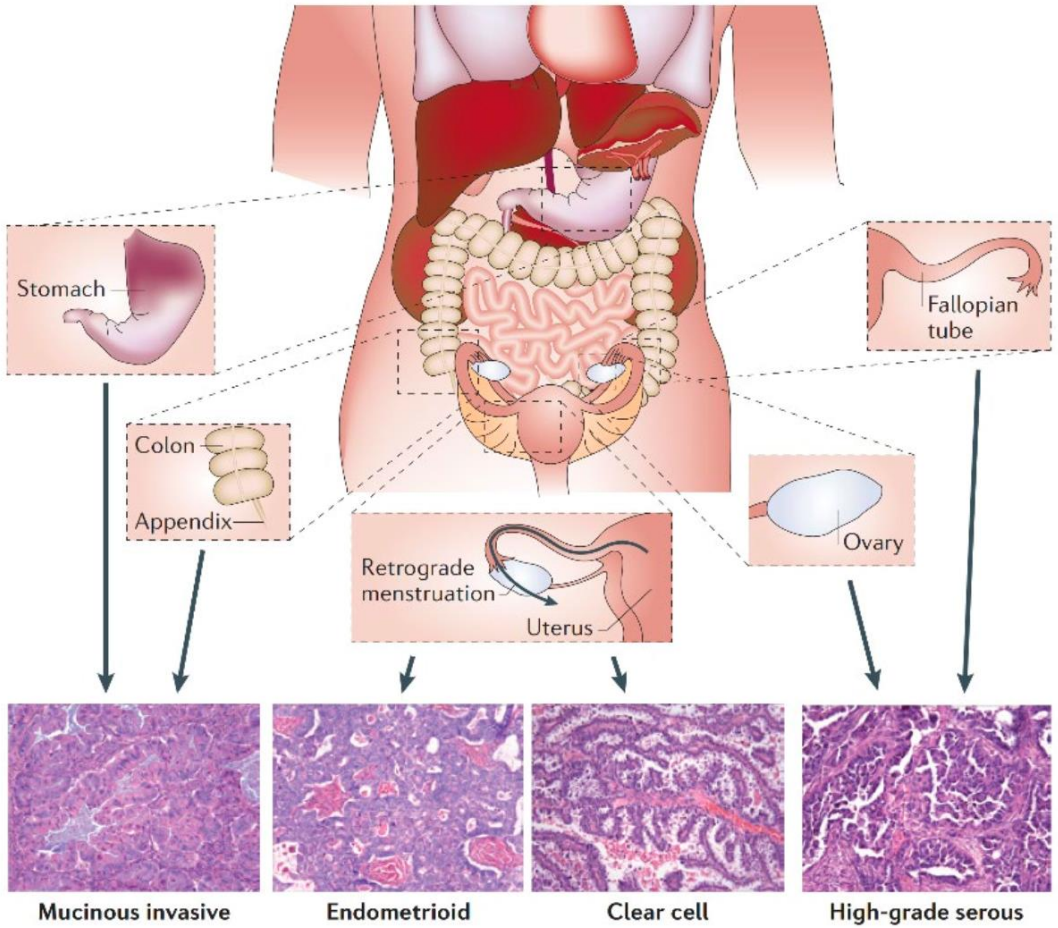
Place for parp inhibitors?

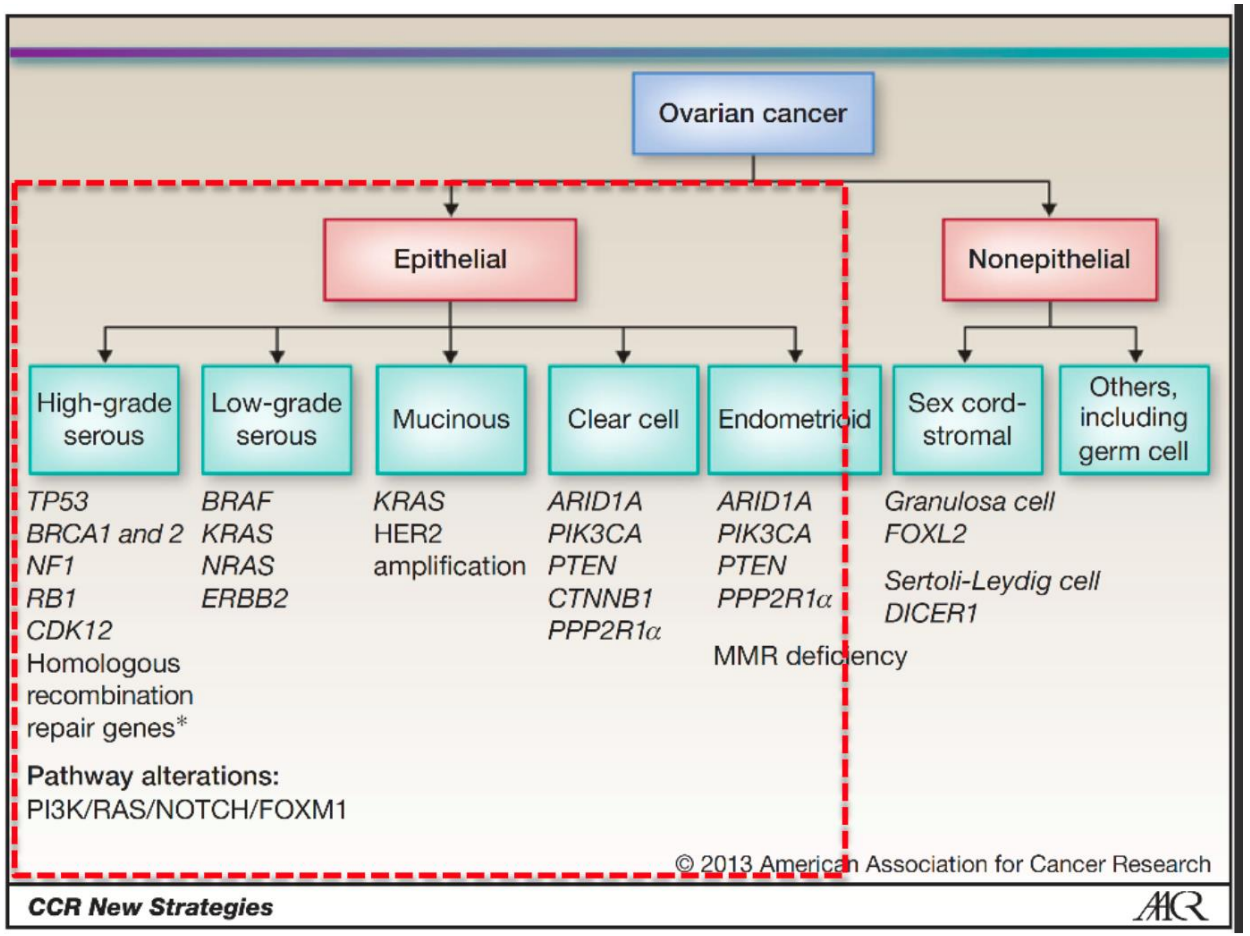
- Challenges
- Efficacy versus safety compared to CT
- Duration of therapy
- Alternative to CT versus maintenance
- Standard CT?

Impact of Histology?

HETEROGENEITY OF OVARIAN CANCER: HISTOLOGY

EOC is a heterogenous group of tumours with distinctly different underlying biology, behaviour, patterns of spread, prognosis & therapeutic targets





Vaughan S et al., Nat Rev Cancer. 2011 Sep 23;11(10):719-25
Banerjee S et al. Clin Cancer Res. 2013 Mar 1;19(5):961-8

- ICON1 & ACTION are a **mixed bag of heterogenous tumors**
- **Rarer histologies have higher representation** compared to trials in advanced stages
- as they are more frequently diagnosed in earlier stages
- Information of histology limited by **lack of central review** & changes of the classification over time
- No distinction made here between low-grade & high-grade serous EOC

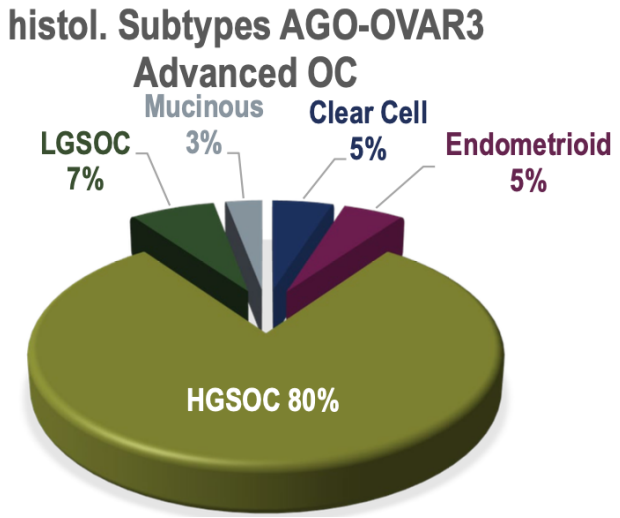
Baseline Characteristics of the pooled analysis of ICON1 & ACTION

93% stage I

33% serous
20% mucinous
24% endometrioid
14% clear cell

21% G1
45% G2
30% G3

Only ~ 1/3 serous
Only ~ 1/3 high-grade

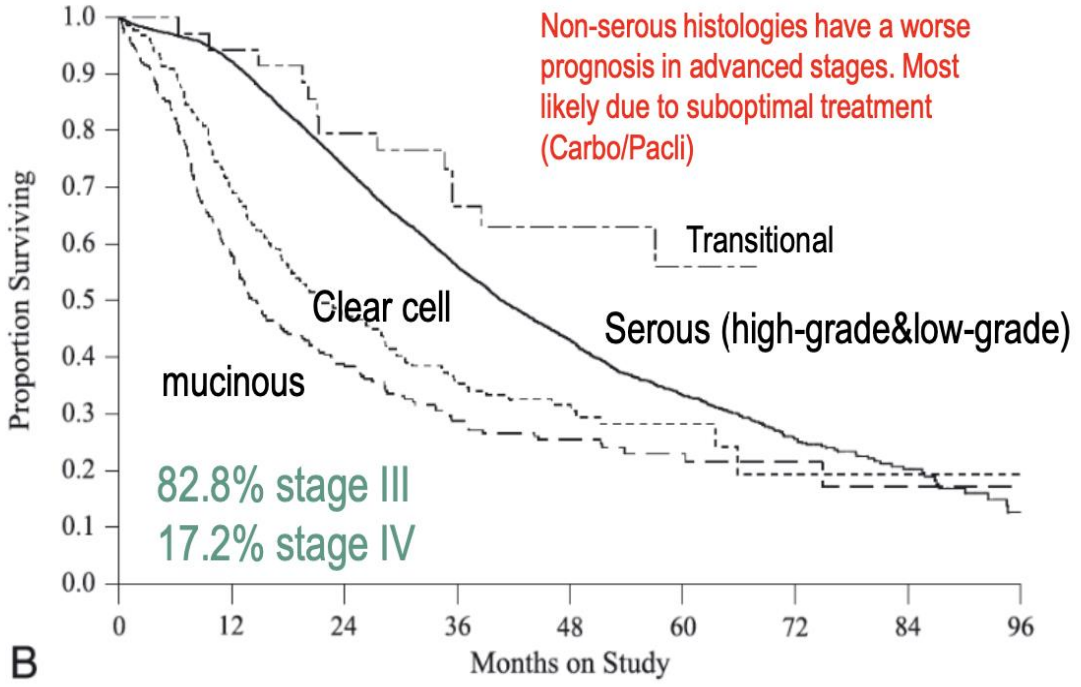


Kommoss S et al., Br J Cancer. 2016 Oct 11;115(8):993-999

Survival by Histotype: advanced versus early stage EOC

Advanced stage EOC FIGO III-IV

overall survival by histology

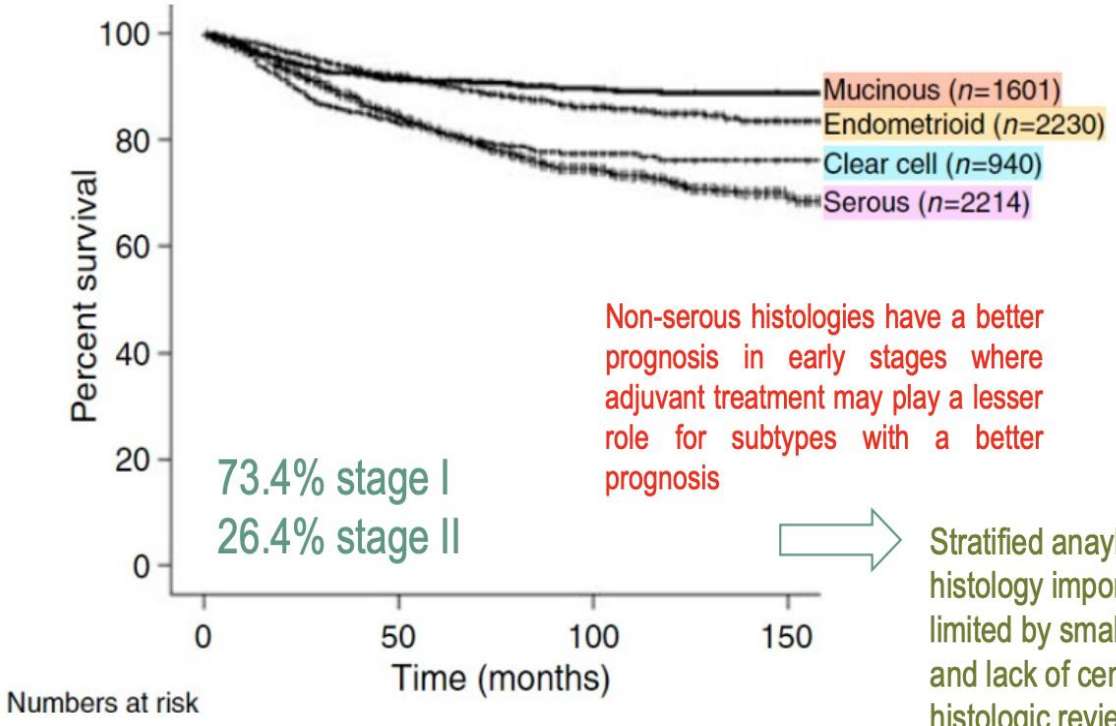


Data on 8704 women with **stage III/IV** EOC from 7 randomized trials

Mackay HE et al., Int J Gynecol Cancer. 2010 Aug;20(6):945-52

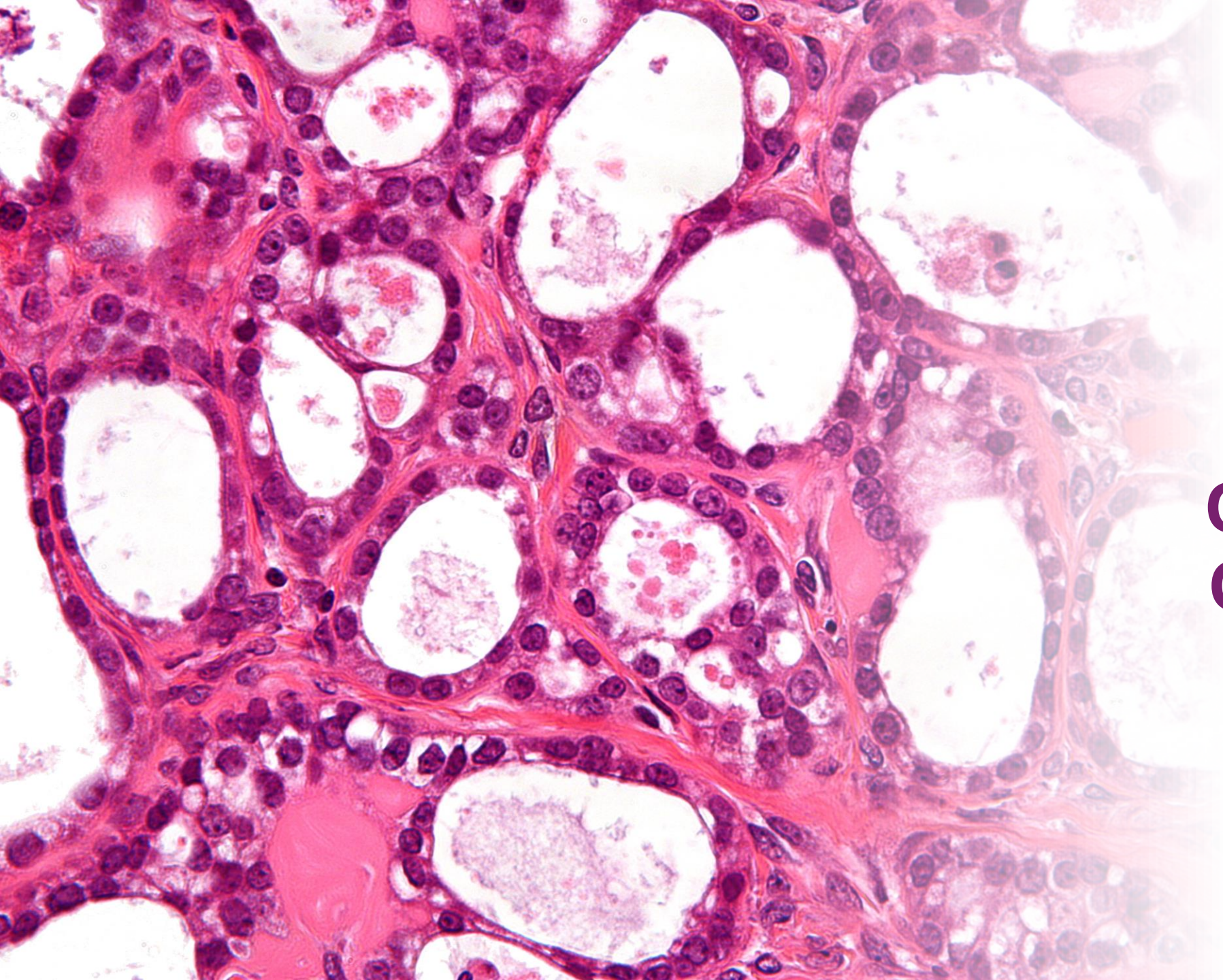
Early stage EOC FIGO IA-II

Disease-specific survival by histology



Stratified anaylsis by histology important but limited by small numbers and lack of central histologic review

Chan KJ et al., BJC (2008) 98, 1191 – 1196

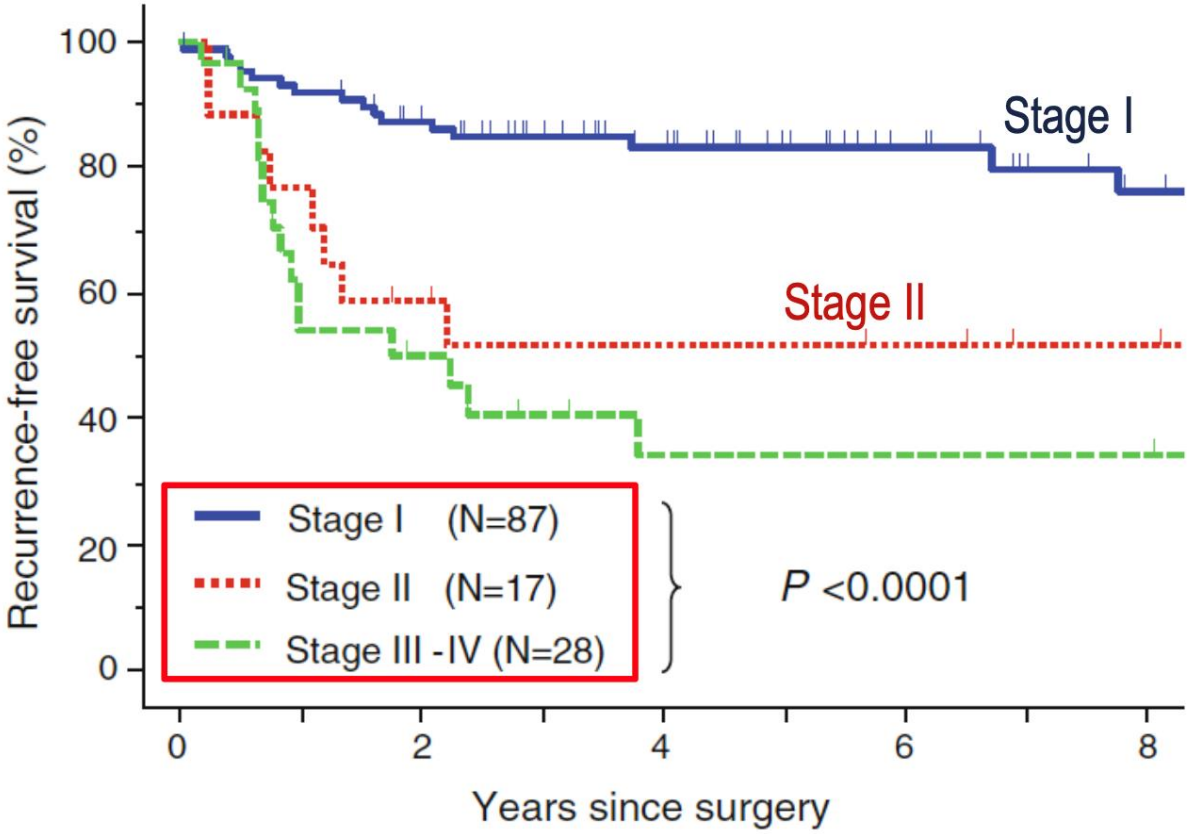


OVARIAN CLEAR CELL CARCINOMA

OCCC

PROGNOSIS: Population-based regional study 1986-2011 (n=132)

No chemo: 7.6%; platinum: 34.1%; platinum + taxane 58.3



- Multivariate only stage IC2/3 prognostic

Table 2 Multivariable analyses of clinicopathological parameters in relation to recurrence-free survival of stage I patients

	Recurrence-free survival	
	Hazard ratio (95 % CI)	*P*
Total		
Age		
<40	1	
≥40	0.903 (0.272–3.001)	0.8677
FIGO stage		
IA	1	
IC(r)	0.948 (0.139–6.448)	0.9565
IC(non-r)	9.394 (1.445–61.070)	0.0190
Preoperative CA125 value (U/ml)		
≤35 or unknown	1	
>35	3.892 (0.835–18.145)	0.0836
Surgery		
Radical	1	
Conservative	1.046 (0.258–4.235)	0.9498
Chemotherapy		
Taxane plus platinum	1	
Conventional platinum-based	1.184 (0.385–3.636)	0.7684
None	1.633 (0.133–20.044)	0.7014

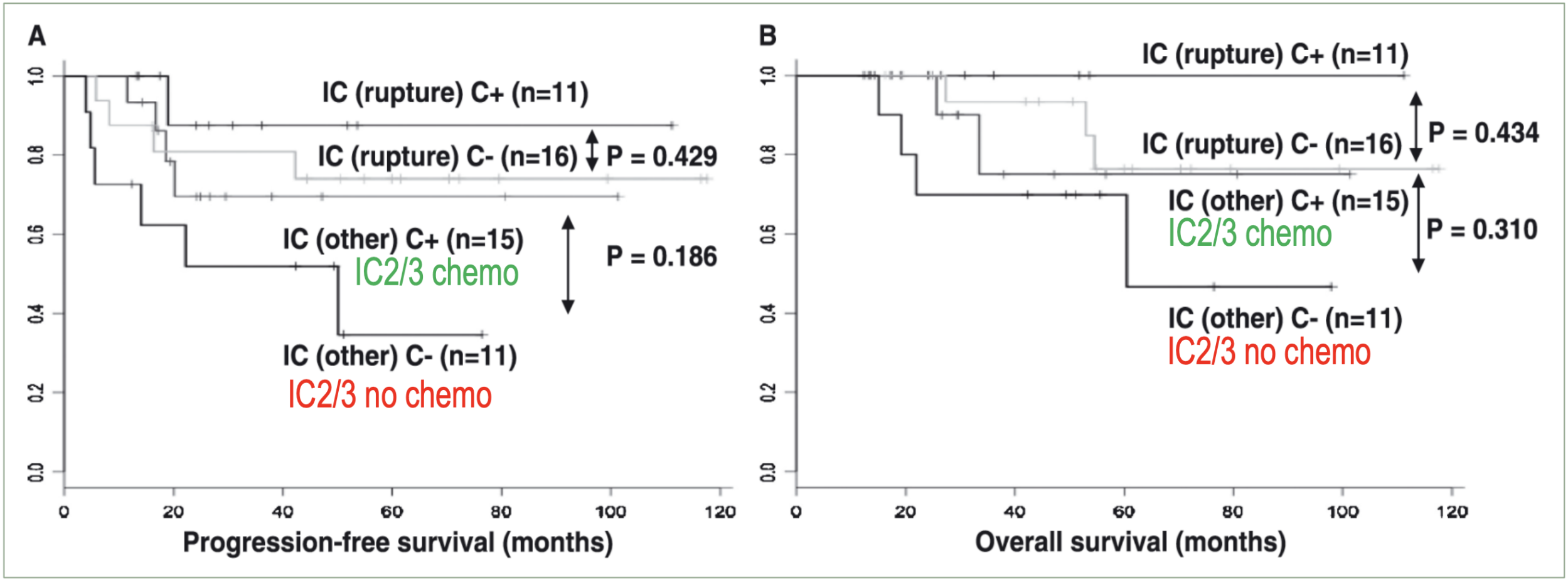
IC(r) patients who had only intraoperative capsule rupture (no surface involvement and negative cytology); *IC(non-r)* as IC excluding IC(r), including patients with preoperative capsule rupture, or surface involvement irrespective of cytological washings/ascites

Kajiyama H et al., Int J Clin Oncol (2014) 19:921–927

OCCC stage I

Role of Adjuvant Chemotherapy (n=73)

no chemo: n= 43; chemo: n=30



Very, very, very small numbers….

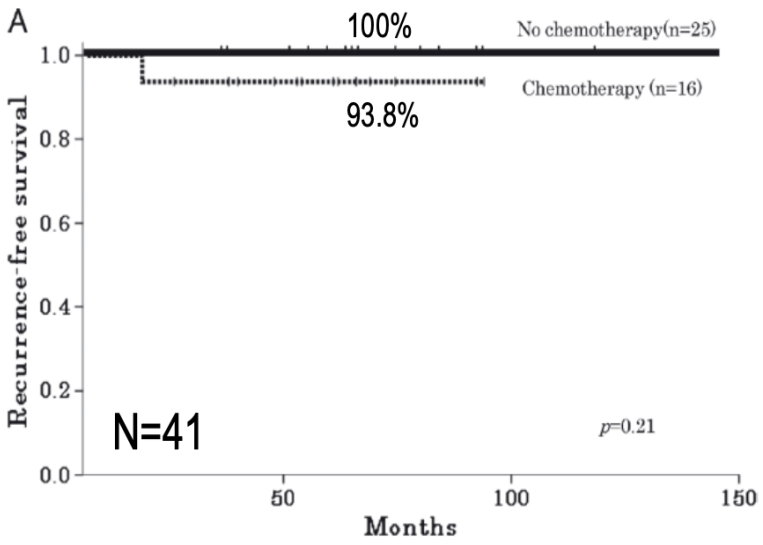
Takada T et al., IJGC Volume 22, Number 4, May 2012

OCCC stage I

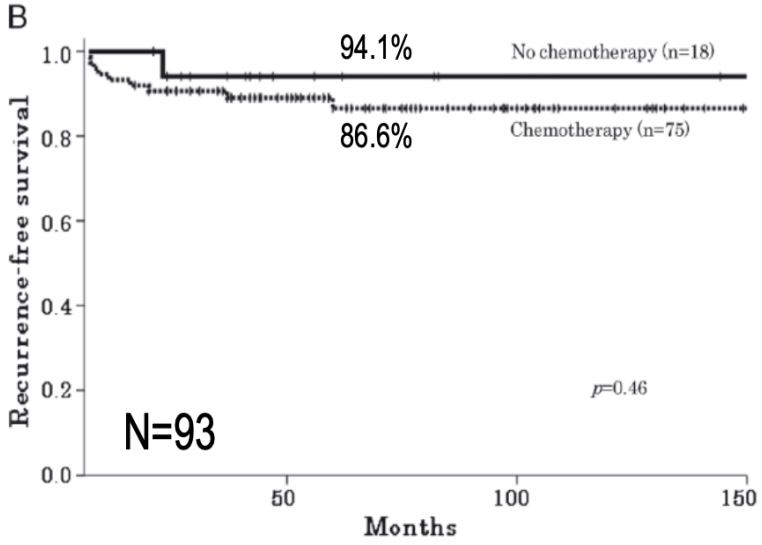
Role of Adjuvant Chemotherapy; 1991-2007 (n=185)

Stage IA & IC1: no chemo: n= 43; chemo: n=91

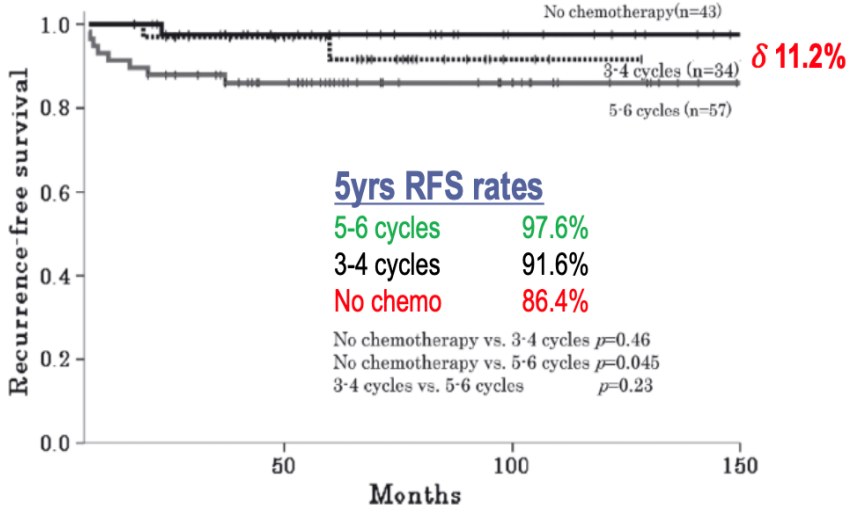
Stage IA



Stage IC1 (rupture)



All Stage I (IA&IC1)



Completely staged OCCC with stage IA/IC1 has an excellent prognosis,
➔regardless of chemotherapy

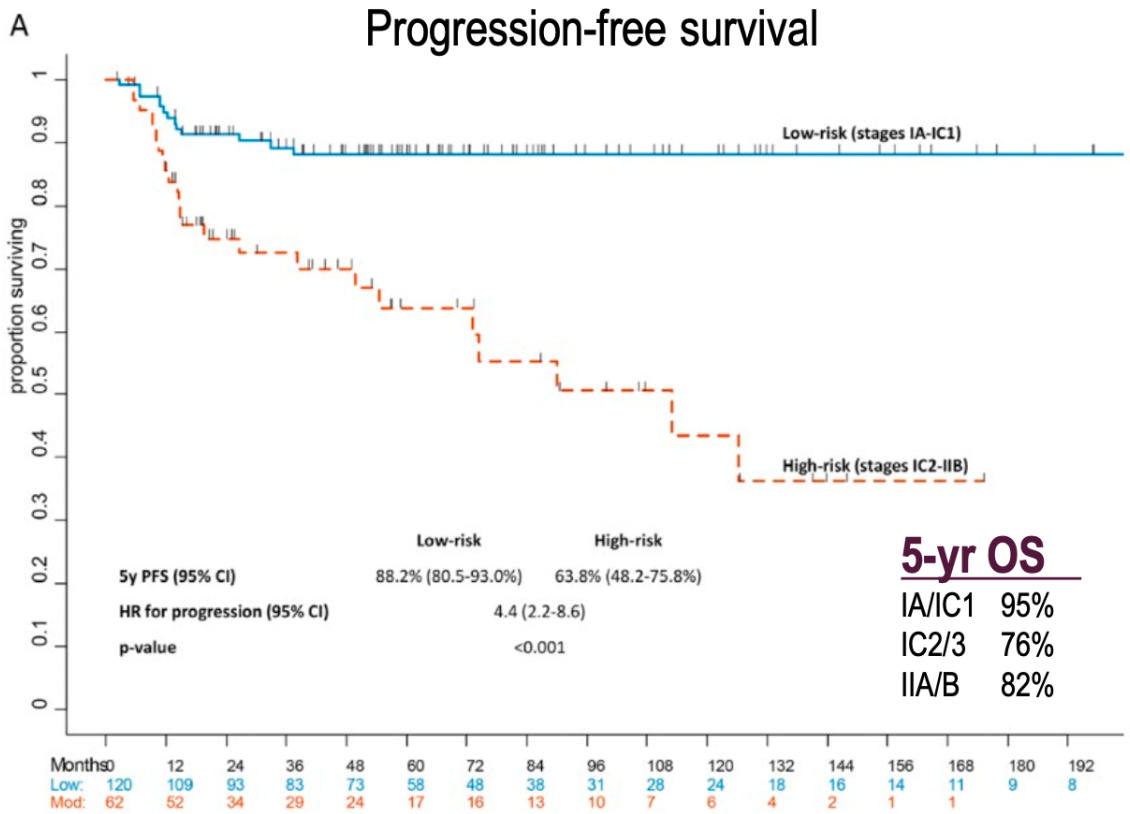
Mizuno Met al., IJGC Volume 22, Number 7, September 2012

OCCC Early stage

Risk Stratification

Retrospective MSKCC 1996 – 2020 (n=182)

MMR & TP53 etc.



5-yr OS

IA/IC1	95%
IC2/3	76%
IIA/B	82%

MMRd **7.3%** not associated with PFS/OS
HR_{PFS} 0.75 (0.10 – 5.68, p=0.82)

TP53mut **4.5%** significantly associate with PFS/OS
HR_{PFS} 0.06 (0.02 – 0.25, p<0.001)
in favour of wildtype

Adj. CHT **91.2%** not associatedd with PFS/OS
HR_{PFS} 1.40 (0.34 – 5.86, p=0.69)
stage 1A/IC1 CHT vs observation: 94% vs 100% OS

Endometrioses 67% not associatedd with PFS/OS
HR_{PFS} 1.52 (0.73 – 3.14, p=0.26)
Fertility sparing in 9 pts. None had recurrence, 5 pregnancies

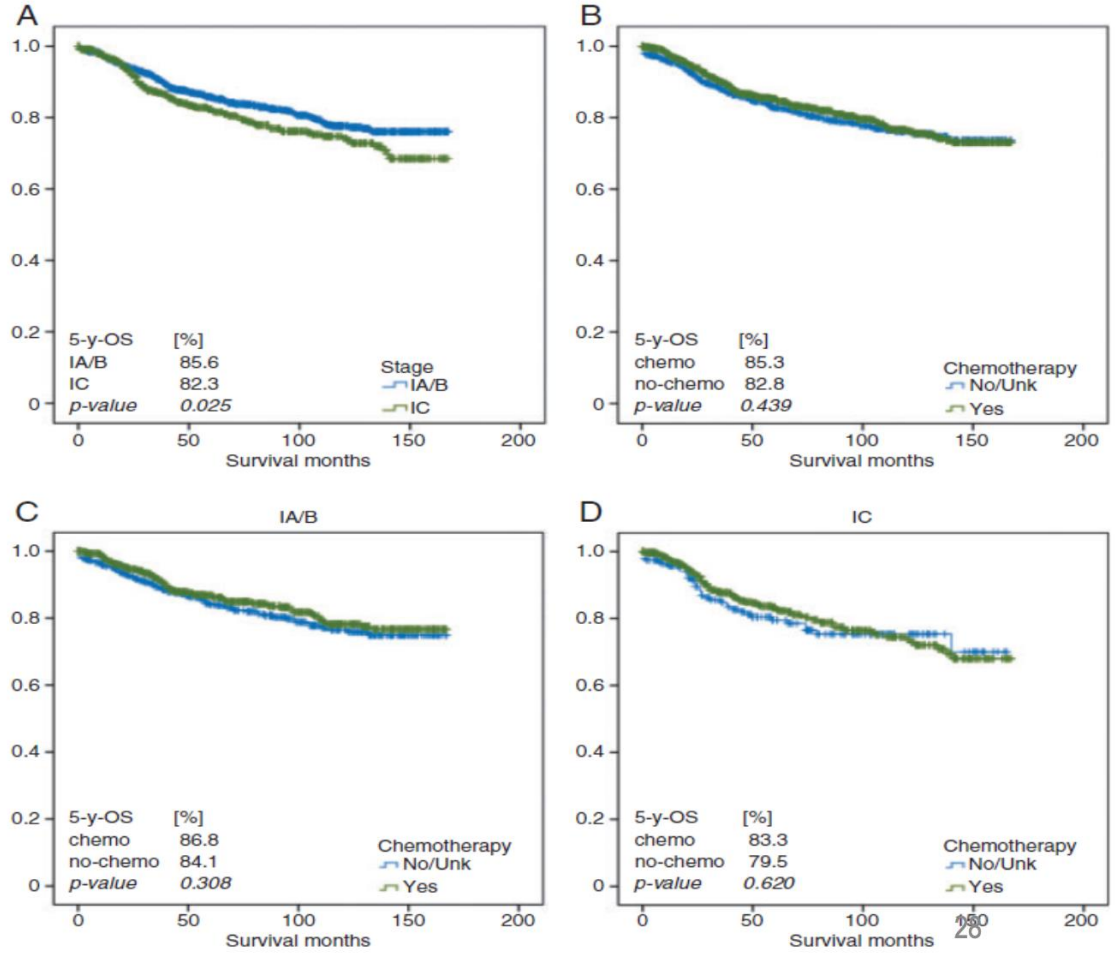
Abberant p53 expression may portend worse outcomes

Manning-Geist B, et al. Int J Gynecol Cancer 2022;32:1576–1582

OCCC Early stage
SEER database

- n=1995 stage I OCCC
- 69% adjuv. CHT
- Stage IA ≠ IC

NO IMPACT of CT on OS (all substages)!



No distinction between stage IC1 and IC2/3

Oseledchyk et al, Ann Oncol 2018

ESMO CLINICAL PRACTICE GUIDELINE 2023

Management of early stage ovarian cancer (FIGO I-II)

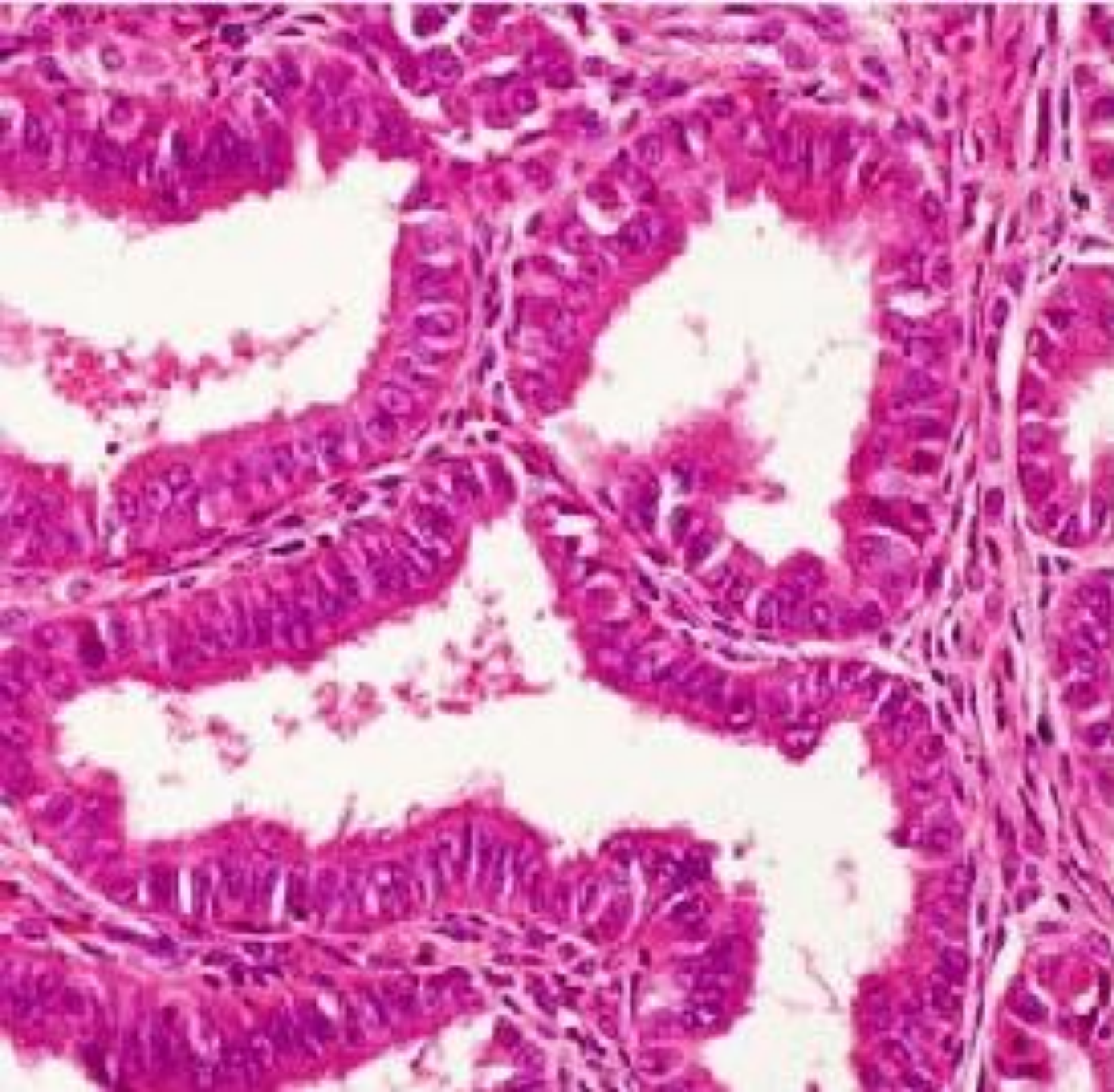
Recommendations

- The benefit of adjuvant ChT is uncertain and can be considered as optional [III, C] for:
  - o LGSC stage IB-IC
  - o CCC stage IA-IC1

Histologies	Stage IA	Stage IB/C1	Stage IC2-3	Stage IIA
Clear cell	Option*	Option*	Yes	Yes

*** Consider no adjuvant chemotherapy only for patients with complete surgical staging**

Gonzalez-Martin A et al., Ann Oncol . 2023 Oct;34(10):833-848



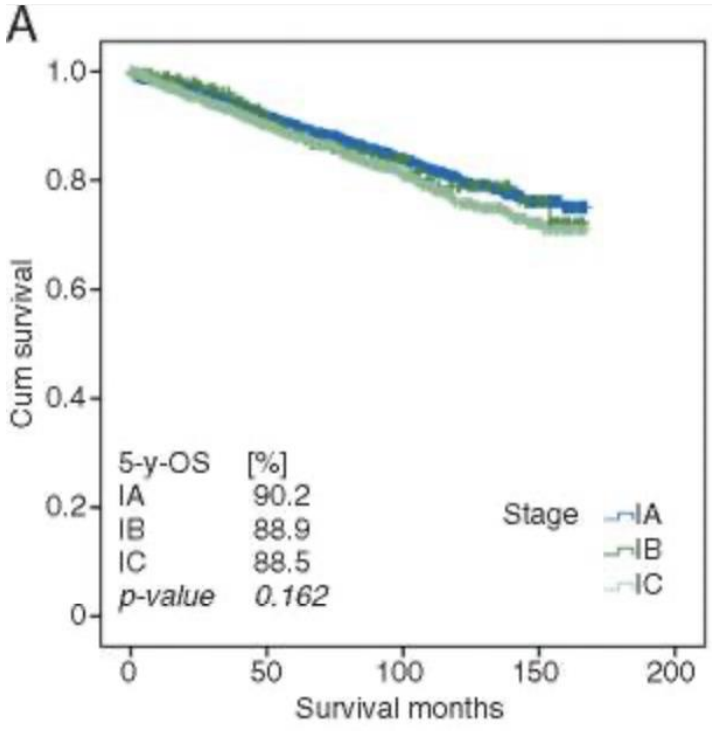
ENDOMETRIOID OVARIAN CANCER

EARLY STAGE ENDOMETRIOID OVARIAN CANCER: PROGNOSIS

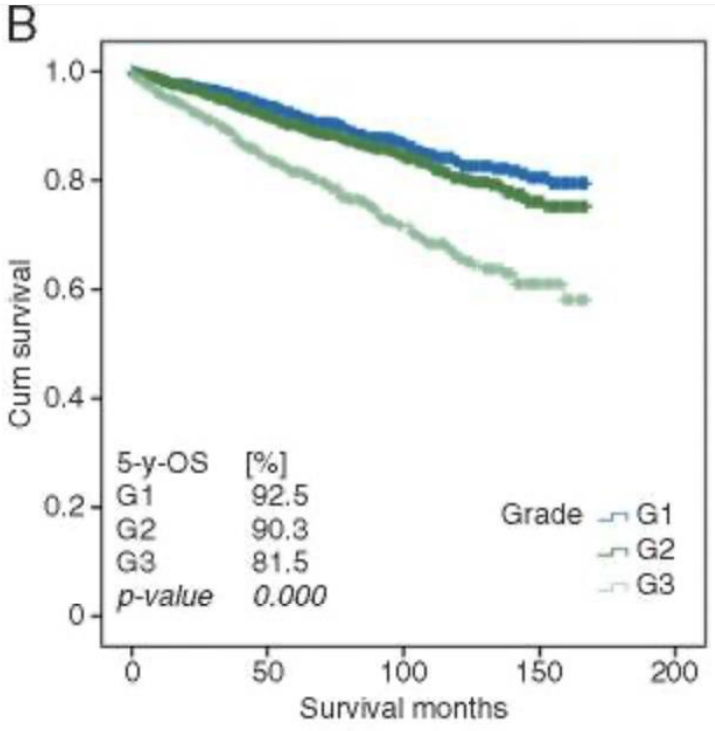
SEER database

- n = 3552 stage I EEOC
- 45% adjuv. CHT

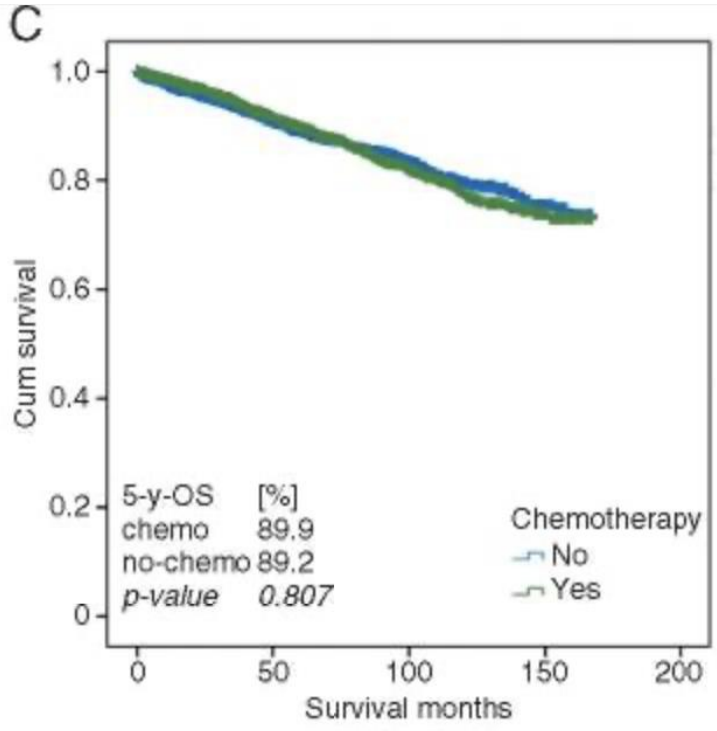
Overall Survival by Substage



Overall Survival by Grade



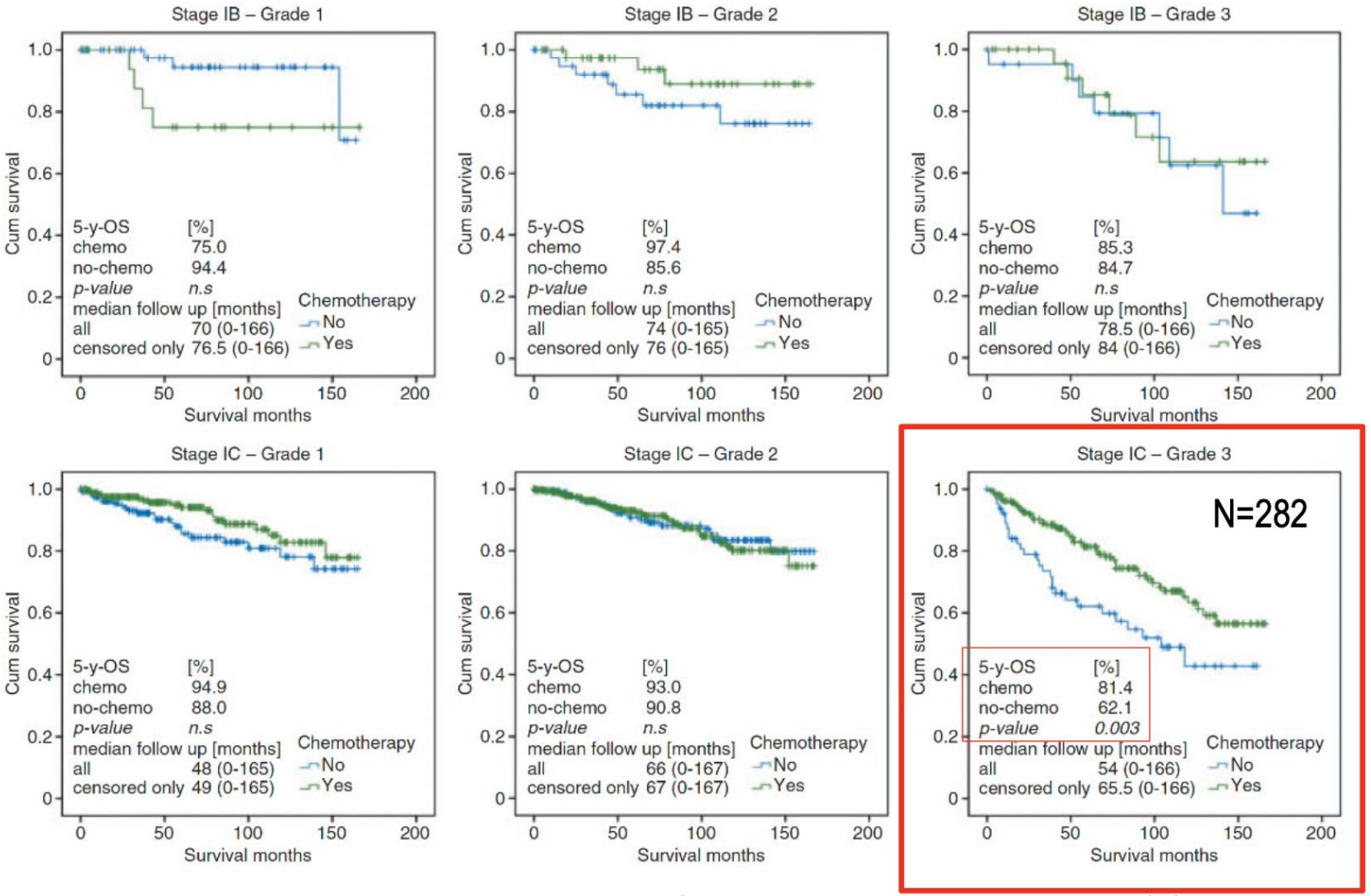
Overall Survival by CT



Oseledchyk A et al., Annals of Oncology 28: 2985–2993, 2017

EARLY STAGE ENDOMETRIOID OVARIAN CANCER

Role of Adjuvant Chemotherapy



ONLY IC G3 !!!

Oseledchyk A et al., Annals of Oncology 28: 2985–2993, 2017

Why might the genomics of endometrioid OC be relevant?

ARTICLE

https://doi.org/10.1038/s41467-020-18819-5 OPEN

Check for updates

Molecular stratification of endometrioid ovarian carcinoma predicts clinical outcome

Robert L. Hollis[1,5], John P. Thomson[1,5], Barbara Stanley[1,5], Michael Churchman[1], Alison M. Meynert[2], Tzyvia Rye[1], Clare Bartos[1], Yasushi Iida[1,3], Ian Croy[1], Melanie Mackean[4], Fiona Nussey[4], Aikou Okamoto[3], Colin A. Semple[2], Charlie Gourley[1,6] & C. Simon Herrington[1,6]✉

Endometrial Cancer Molecular Risk Stratification is Equally Prognostic for Endometrioid Ovarian Carcinoma

Pauline Krämer; Aline Talhouk; Mary Anne Brett; Derek S. Chiu; Evan S. Cairns; Daniëlla A. Scheunhage;

ARTICLE

https://doi.org/10.1038/s41467-020-18819-5 OPEN

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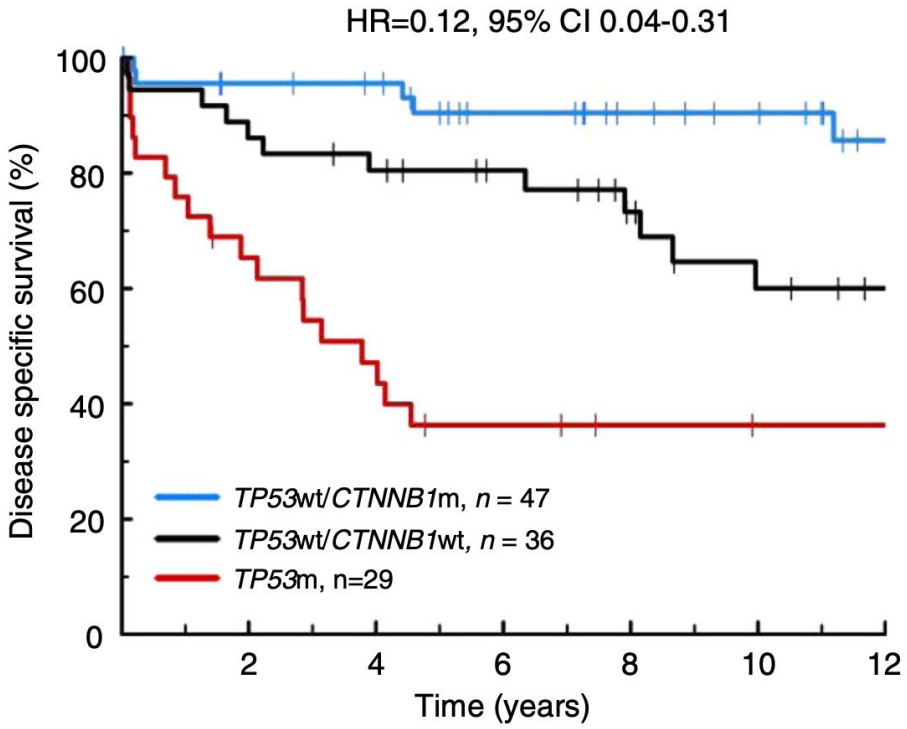


Endometrioid OC segregated into 3 groups based on CTNNB1 and TP53 mutational status

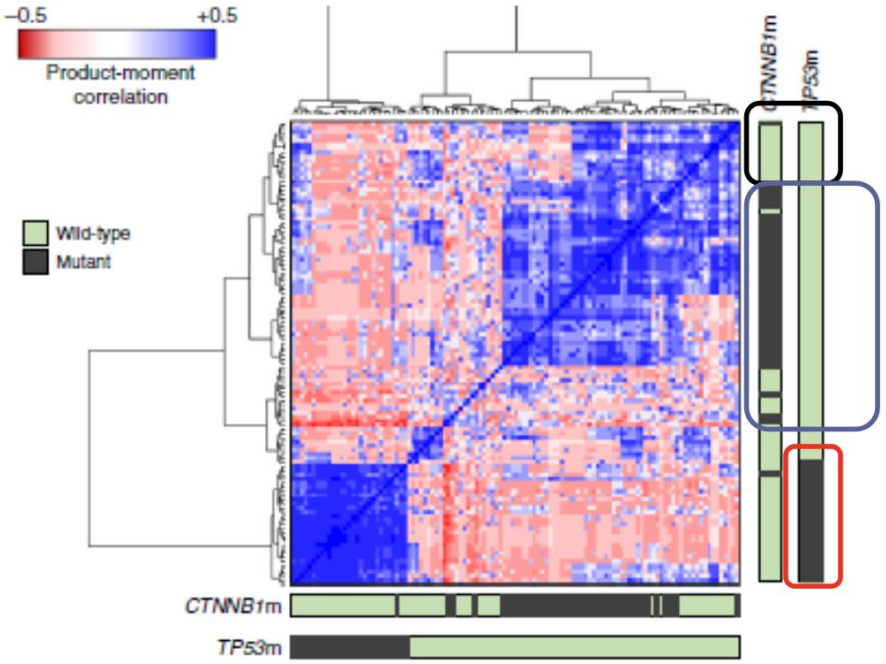
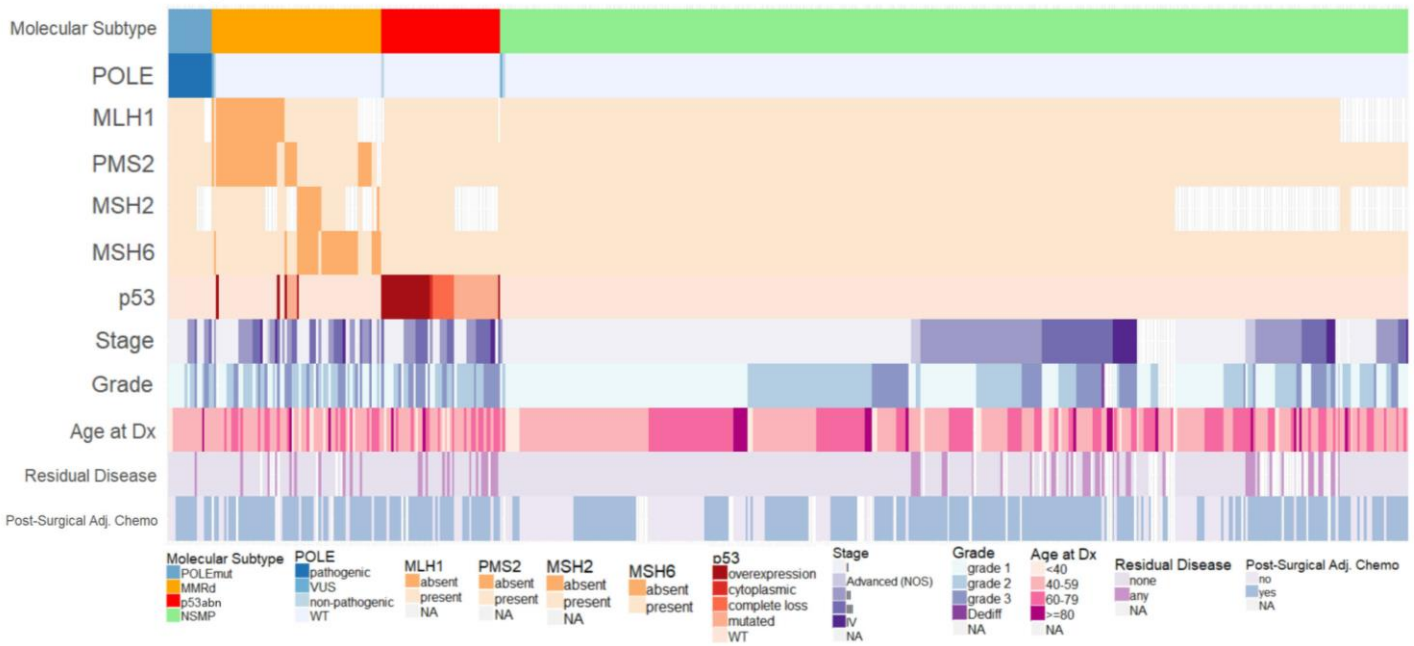


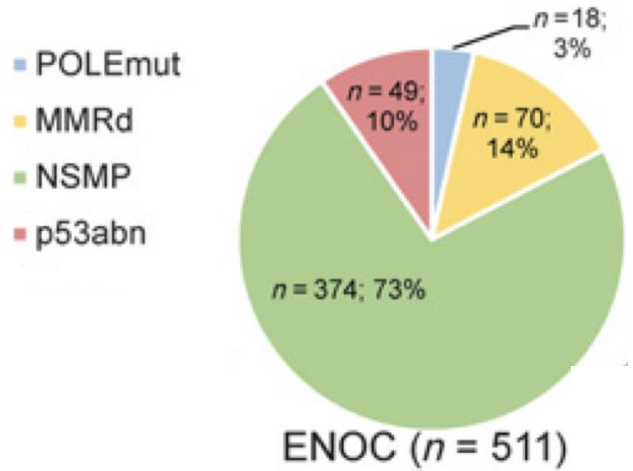
Fig. 2 Unsupervised clustering of endometrioid ovarian carcinomas by patterns of mutation. Product-moment correlation scores between

Endometrial Cancer Molecular Risk Stratification is Equally Prognostic for Endometrioid Ovarian Carcinoma

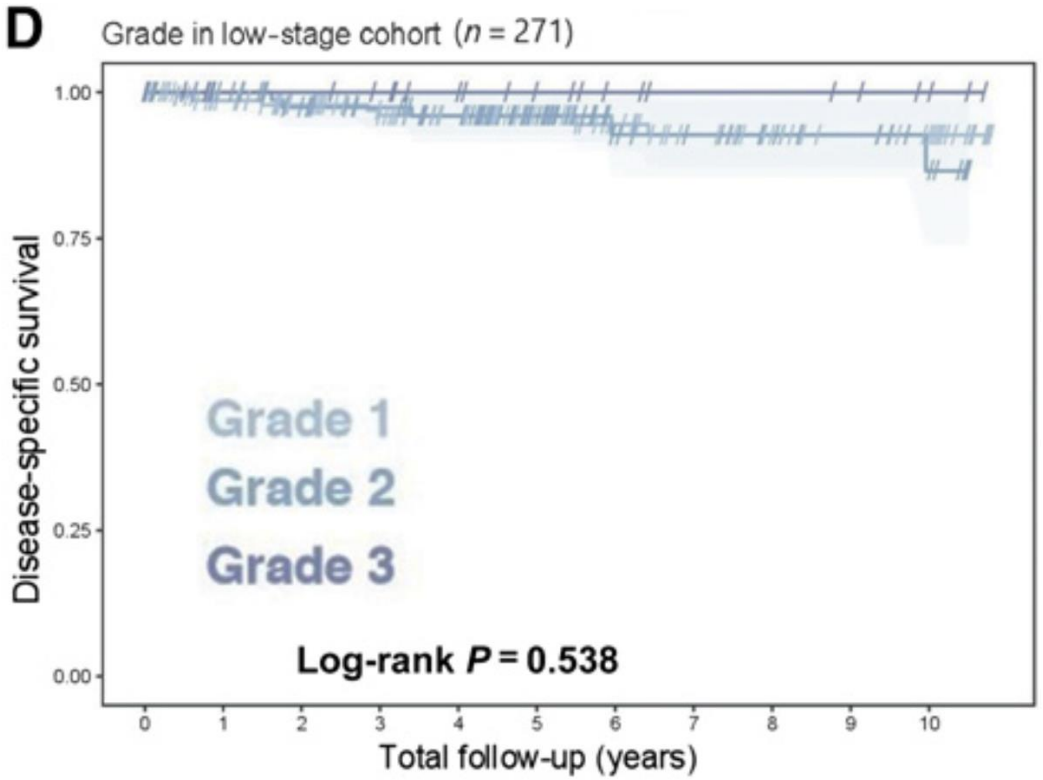
Pauline Krämer; Aline Talhouk; Mary Anne Brett; Derek S. Chiu; Evan S. Cairns; Daniëlla A. Scheunhage;

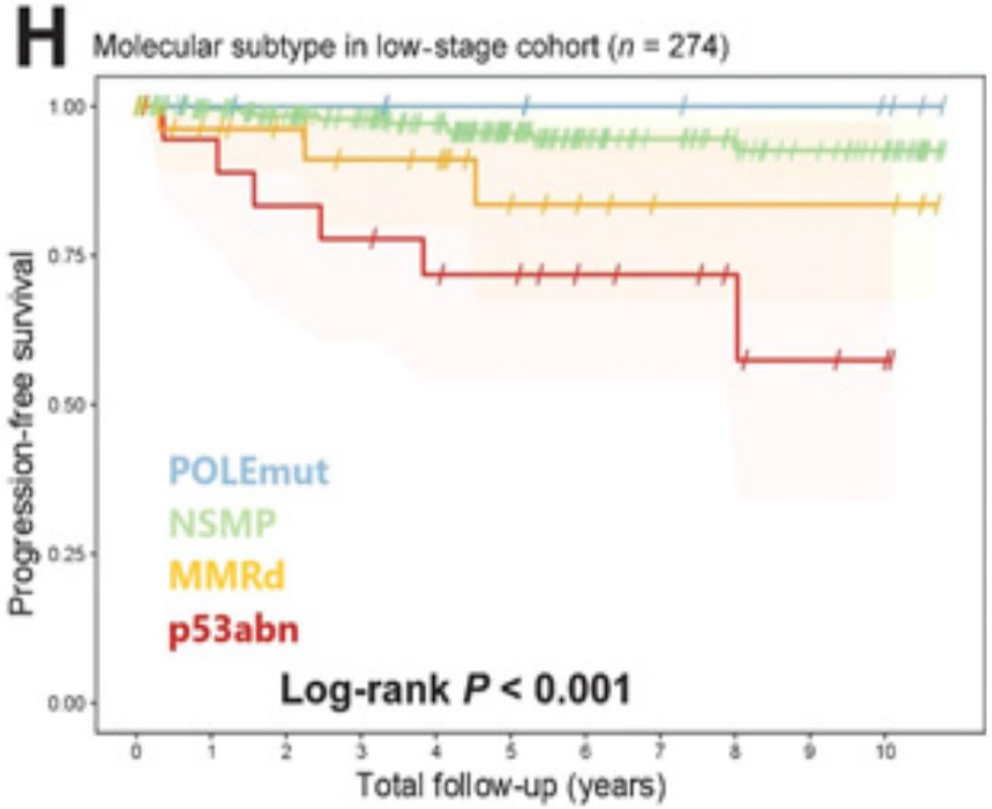
Molecular Classification of Endometrial Cancer Applied to Endometrioid Ovarian Cancer International Series (n=533)





Clin Cancer Res (2020) 26 (20): 5400–5410





Molecular classification might complement histopathology
➜ risk stratification
➜ Identification of targets & Lynch Syndrom

Clin Cancer Res (2020) 26 (20): 5400–5410

ESMO CLINICAL PRACTICE GUIDELINE 2023

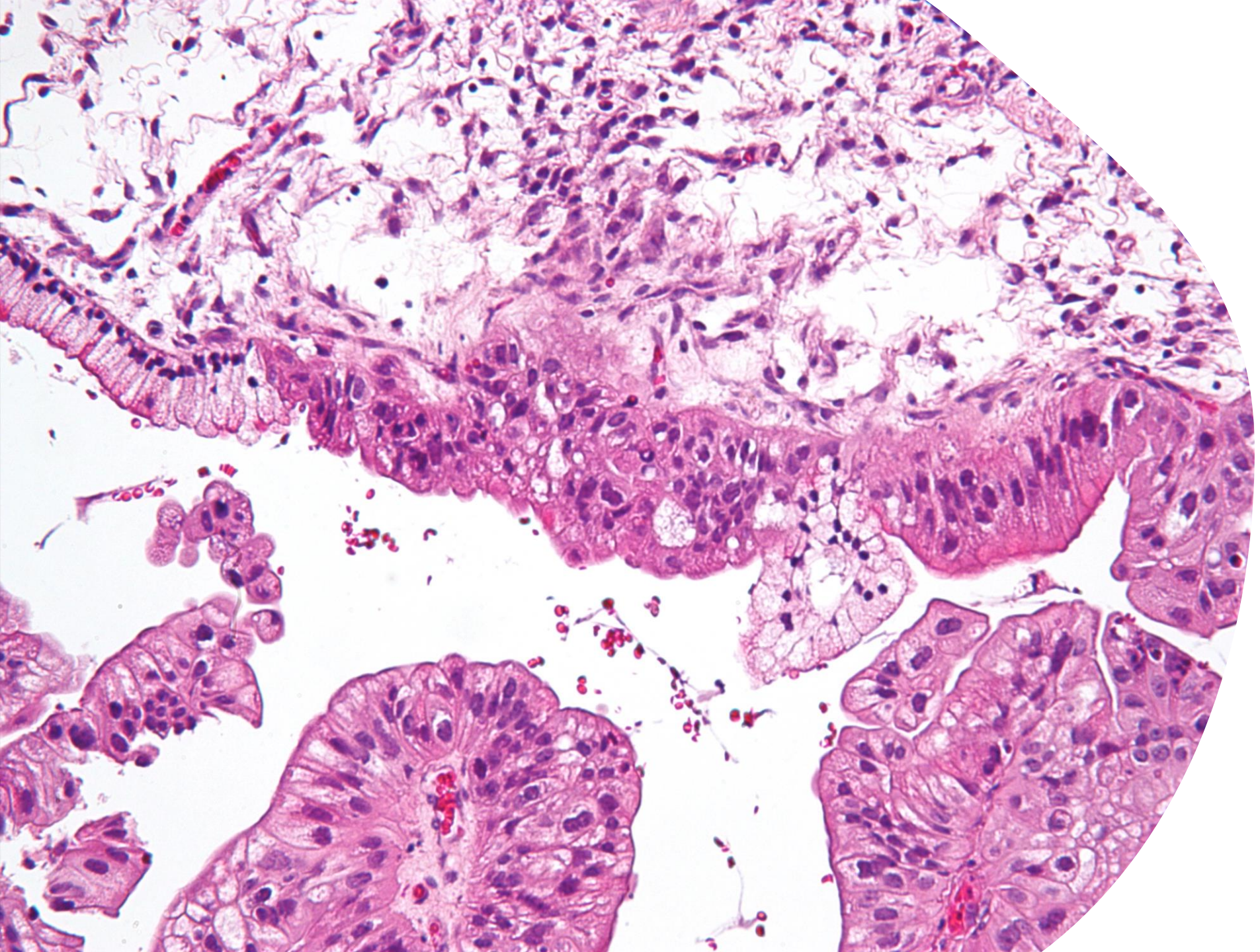
Management of early stage ovarian cancer (FIGO I-II)

Recommendations

- The benefit of adjuvant ChT is uncertain and can be considered as optional [III, C] for:
  - o LGSC stage IB-IC
  - o CCC stage IA-IC1
  - o Low-grade EC stage IB-IC
  - o Expansile MC stage IC
  - o Infiltrative MC stage IA
- Adjuvant ChT is not recommended in completely staged patients with LGSC stage IA, low-grade EC stage IA or expansile MC stage IA-IB [II, E].

Histologies	Stage IA	Stage IB/C1	Stage IC2-3	Stage IIA
high-grade Endometrioid (G3)	Yes	Yes	Yes	Yes
Low-grade Endometrioid (G1/2)	No	Option*	Yes	Yes

Gonzalez-Martin A et al., Ann Oncol . 2023 Oct;34(10):833-848



MUCINOUS OVARIAN CANCER

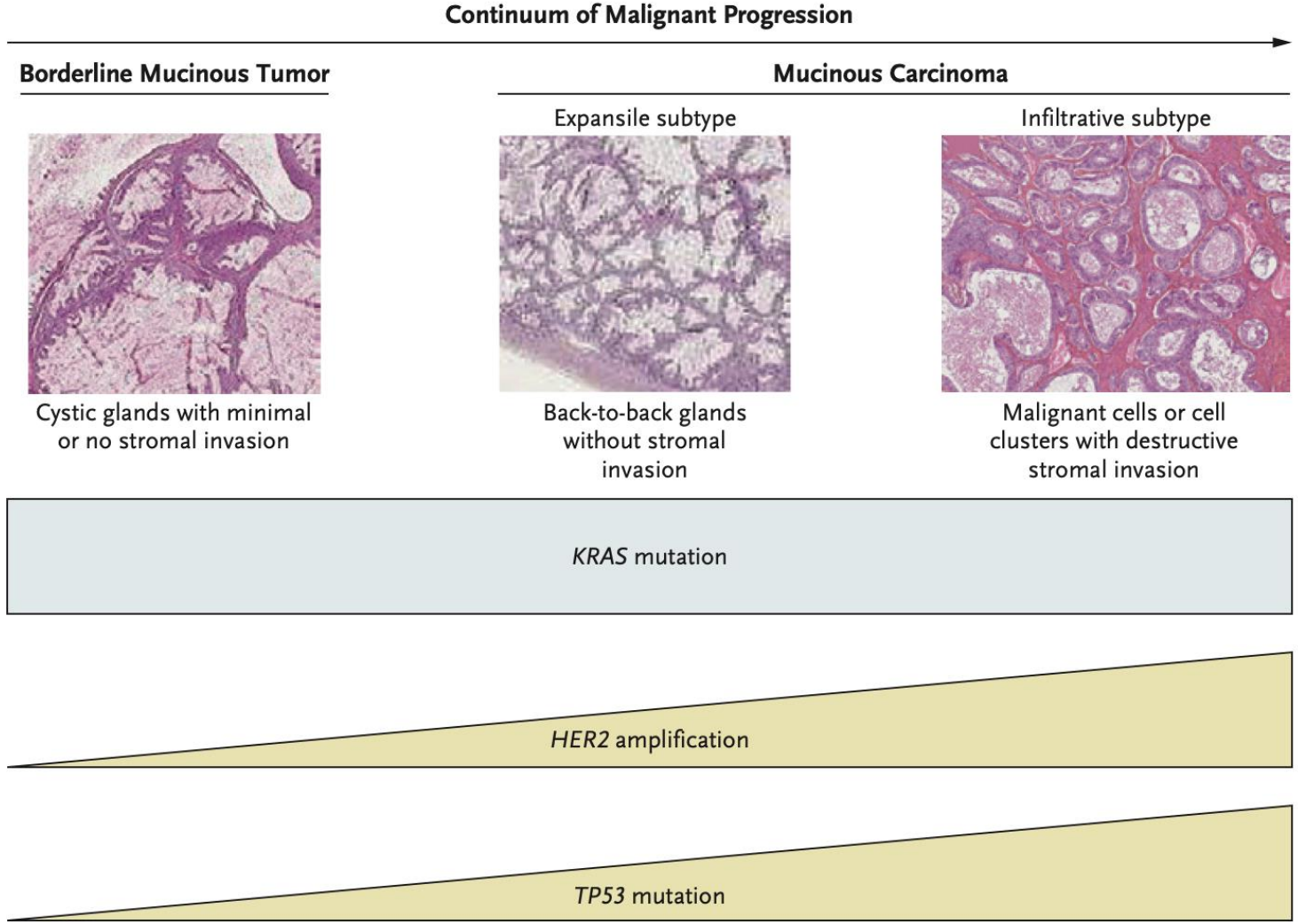


Figure 1. Stages in the Progression of Mucinous Ovarian Tumors.

Mucinous ovarian tumors develop on a continuum from benign epithelium to preinvasive (borderline) carcinoma to mucinous carcinoma. *KRAS* mutations are an early event, whereas other oncogenic alterations (*HER2* amplifications or *TP53* mutations) may be acquired later in the course of malignant transformation.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

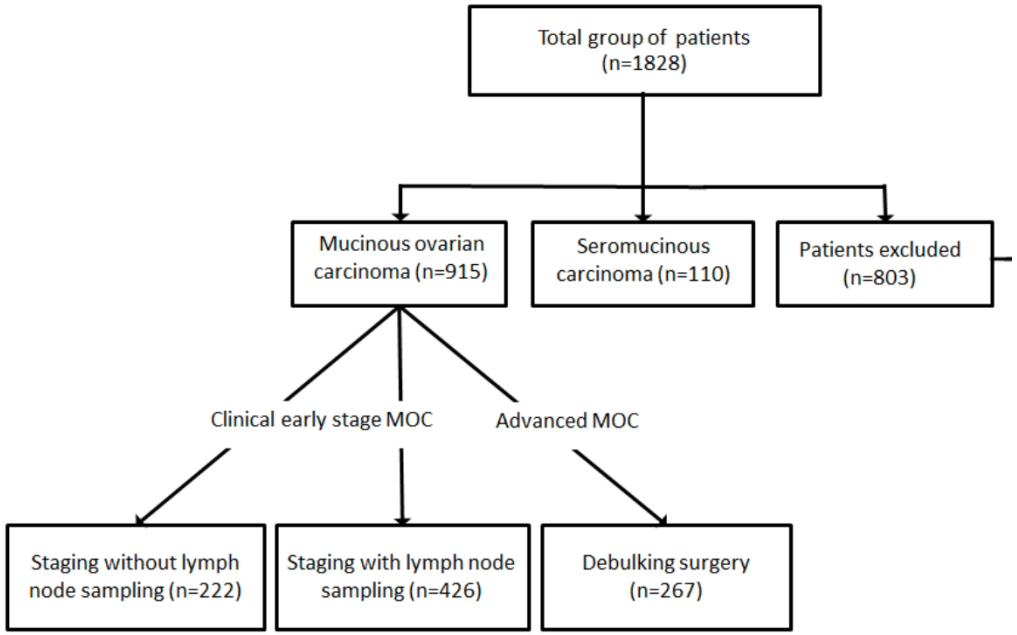
Dan L. Longo, M.D., *Editor*

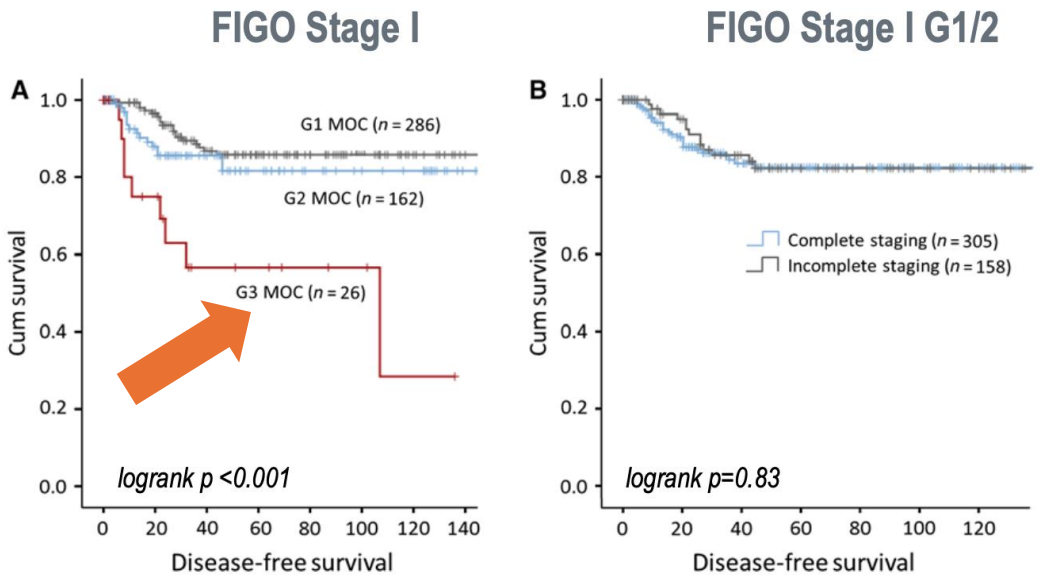
Mucinous Ovarian Carcinoma

Philippe Morice, M.D., Ph.D., Sebastien Gouy, M.D., Ph.D., and Alexandra Leary, M.D., Ph.D.

EARLY STAGE MUCINOUS OVARIAN CANCER

Netherland Cohort 2002-2012 (n=915)





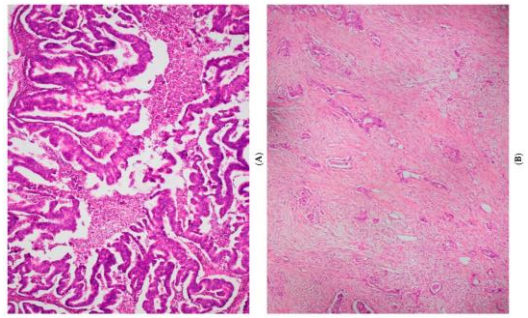
Variable	G1 MOC n (%)	G2 MOC n (%)	G3 MOC n (%)	MOC Grade unspecifie n (%)
Number of patients	190 (44.6)	115 (27.0)	22 (5.3)	99 (23.2)
LNM	4 (2.1)	1 (0.9)	3 (13.6)	0

van Baal et al., BJOG 2016

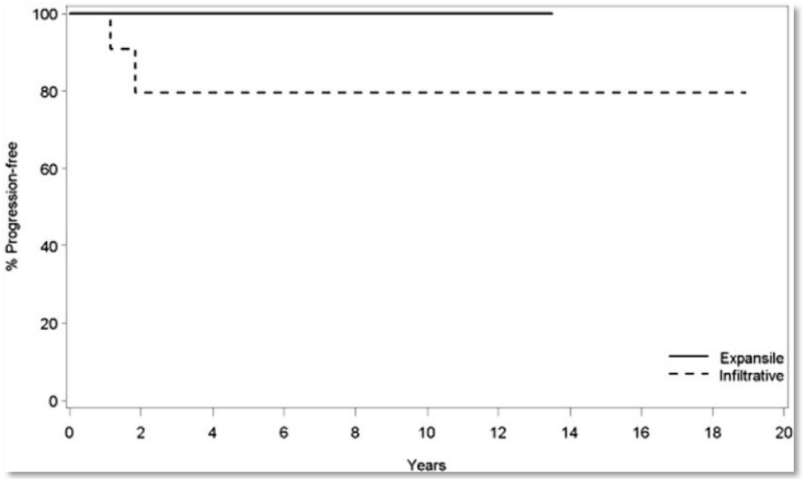
Expansile vs infiltrative

Primary invasive mucinous ovarian carcinoma of the intestinal type: Importance of the expansile versus infiltrative type in predicting recurrence and lymph node metastases

K. Muyldermans [a] · Ph. Moerman [b] · F. Amant [a] · K. Leunen [a] · P. Neven [a] · I. Vergote [a]



FIGO stage I only (n=45)



Overview of the literature comparing mucinous epithelial ovarian carcinoma (mEOC) of the expansile versus infiltrative type in relation to FIGO stage and recurrence*.

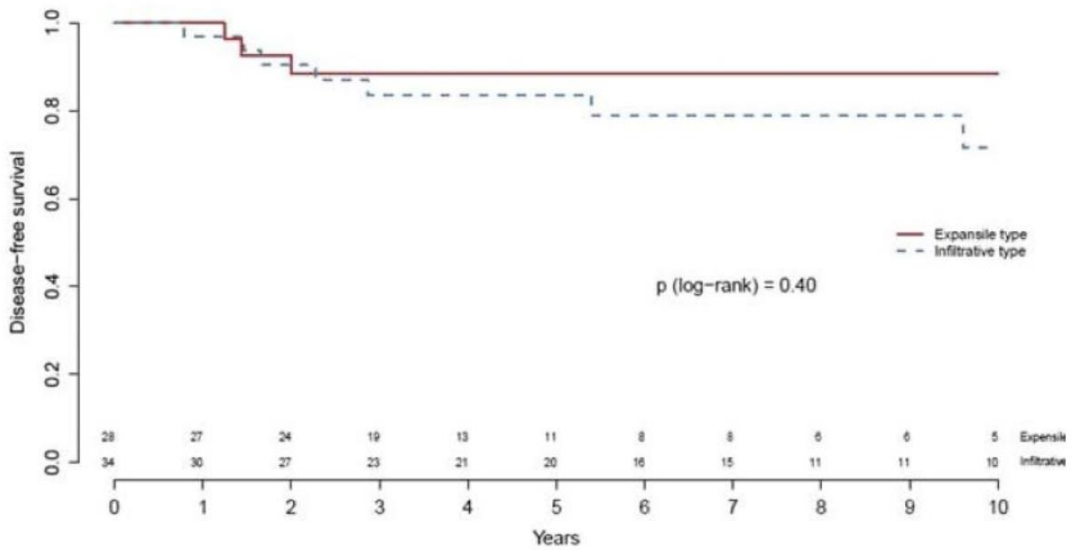
References	*n*	Median follow-up (years)	Expansile (recurrence)		Infiltrative (recurrence)	
			Stage I	Stage II–IV	Stage I	Stage II–IV
Hoerl and Hart[4]	18	10	–	–	14 (2)	4 (4)
Riopel et al.[6]	5	2.5	4 (0)	1 (1)	–	–
Lee and Scully[1]	21	5	10 (0)	–	5 (1)	6 (5)
Rodriguez and Prat[5]	26	5.6	11 (0)	–	9 (3)	6 (6)
Our series	44	5.4	21 (0)	2 (2)	12 (2)	9 (7)

K. Muyldermans et al. EJC (2013) 1600–1608

Characteristics and Prognosis of Stage I Ovarian Mucinous Tumors According to Expansile or Infiltrative Type

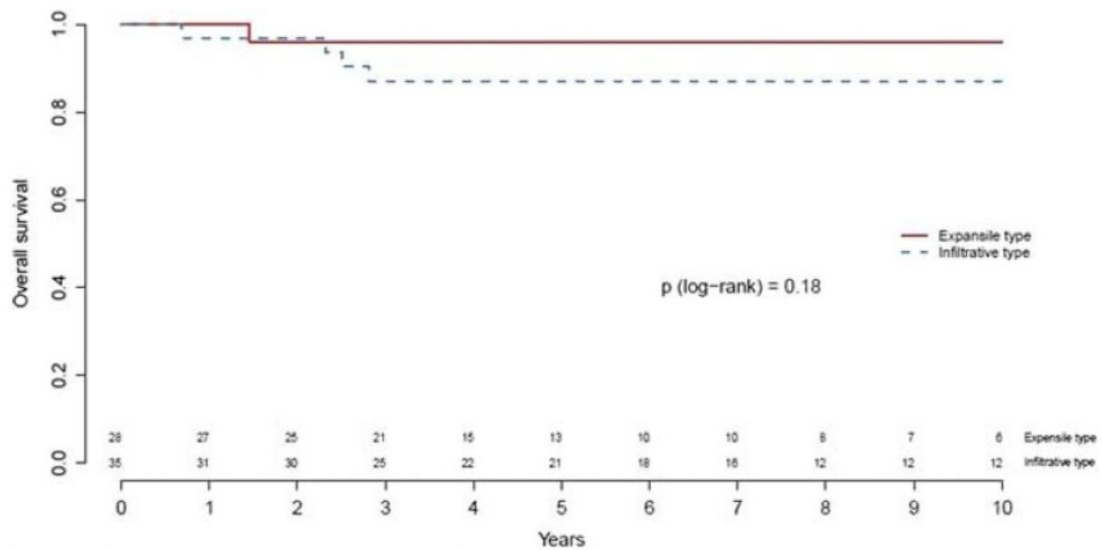
Sebastien Gouy, MD, PhD, Marine Saidani, MD,* Amandine Maulard, MD,* Slim Bach-Hamba, MD,†*

Disease-free survival



Disease-free survival in stage I mOC according to expansile or infiltrative type.

Overall survival



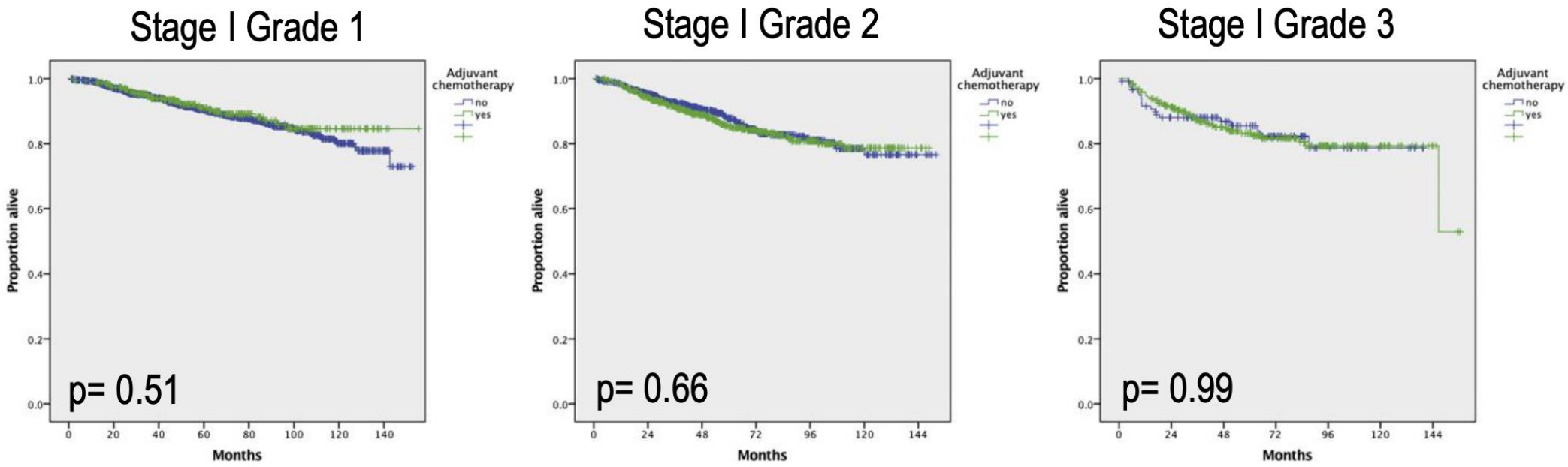
Overall survival in stage I mOC according to expansile or infiltrative type.

Gouy et al., IJGC Volume 28, Number 3, March 2018

Adjuvant chemotherapy is not associated with a survival benefit for patients with early stage mucinous ovarian carcinoma

Dimitrios Nasioudis · Ashley F. Haggerty · Robert L. Giuntoli, II · ... · Mark A. Morgan · Emily M. Ko · Nawar A. Latif

US National Cancer Database 2004 – 2014
N=4811
30.9% adjuvant chemotherapy
20.2% for stage IA/B
60.2% for stage IC



D. Nasioudis et al. / Gynecologic Oncology 154 (2019) 302–307

ESMO CLINICAL PRACTICE GUIDELINE 2023

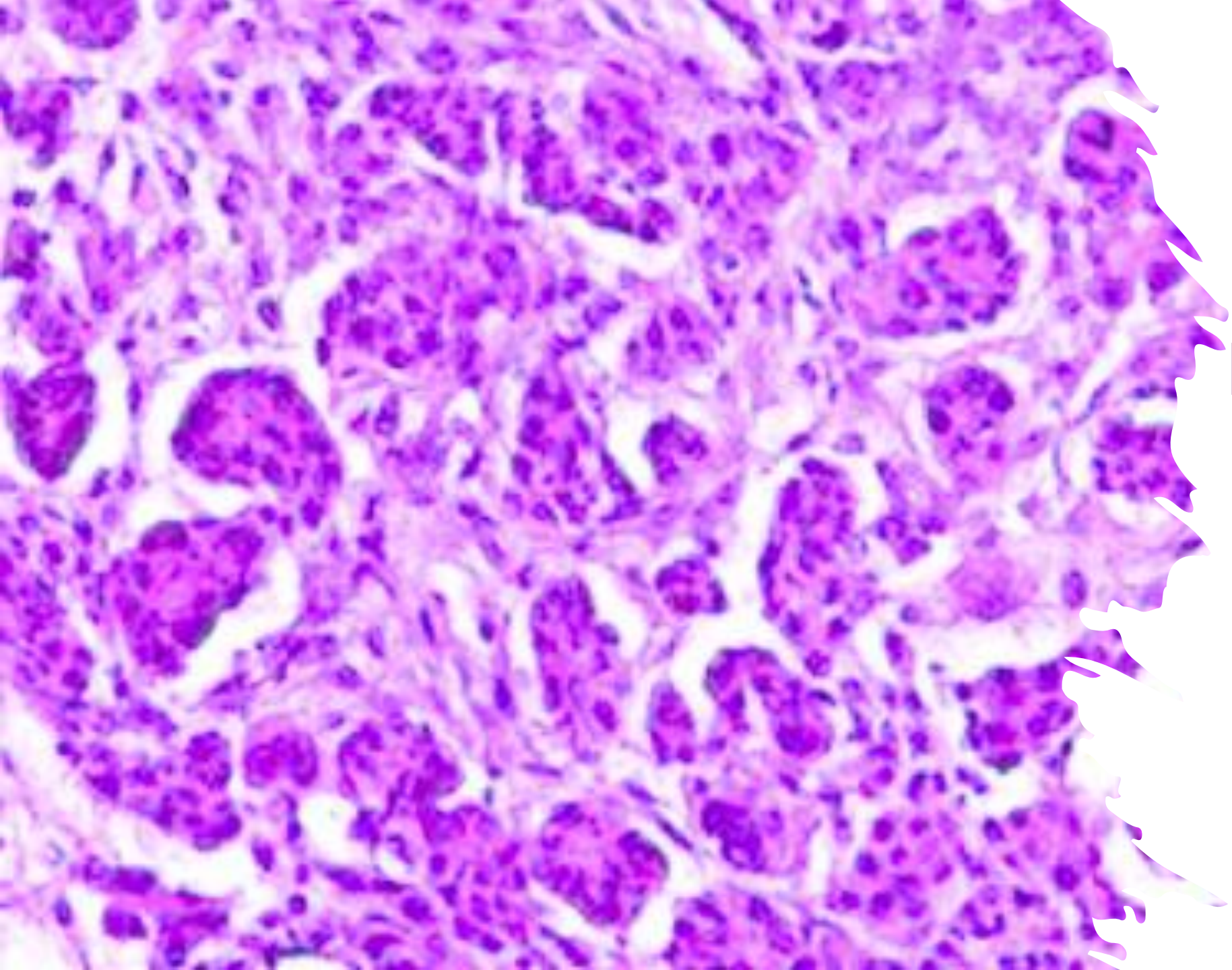
Management of early stage ovarian cancer (FIGO I-II)

Recommendations

- The benefit of adjuvant ChT is uncertain and can be considered as optional [III, C] for:
  - o LGSC stage IB-IC
  - o CCC stage IA-IC1
  - o Low-grade EC stage IB-IC
  - o Expansile MC stage IC
  - o Infiltrative MC stage IA
- Adjuvant ChT is not recommended in completely staged patients with LGSC stage IA, low-grade EC stage IA or expansile MC stage IA-IB [II, E].

Histologies	Stage IA	Stage IB/C1	Stage IC2-3	Stage IIA
Expansile Mucinous (G1/2)	No	Option*	Option*	Yes
Infiltrative Mucinous (G3)	Option*	Yes	Yes	Yes

Gonzalez-Martin A et al., Ann Oncol . 2023 Oct;34(10):833-848



LOW GRADE SEROUS OVARIAN CANCER

LOW GRADE SEROUS OVARIAN CANCER

- Low-grade serous carcinoma (LGSC) is rare subtype that accounts for ~ 10% of serous carcinomas of the ovary/peritoneum
- 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 but no enthusiasm for CT : a place for HT ?

ESMO CLINICAL PRACTICE GUIDELINE 2023

Management of early stage ovarian cancer (FIGO I-II)

Recommendations

- The benefit of adjuvant ChT is uncertain and can be considered as optional [III, C] for:
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Histologies	Stage IA	Stage IB/C1	Stage IC2-3	Stage IIA
LGSOC	No	Option*	Option*	Yes

Gonzalez-Martin A et al., Ann Oncol . 2023 Oct;34(10):833-848

Early Ovarian Cancer
TAKE HOME MESSAGES

Simple but not so easy

Attention to Grade

Optimal surgery!

Careful evaluation of
the risk/benefit balance

One size does not fit all

Attention to hystology

Urgent need
for clinical trials

Attention to
Stage and Substage

Need for more precise biological
and molecular classification


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Grazie