

# Some Thoughts (and Data) on Surgery in Primary Epithelial Ovarian Cancer

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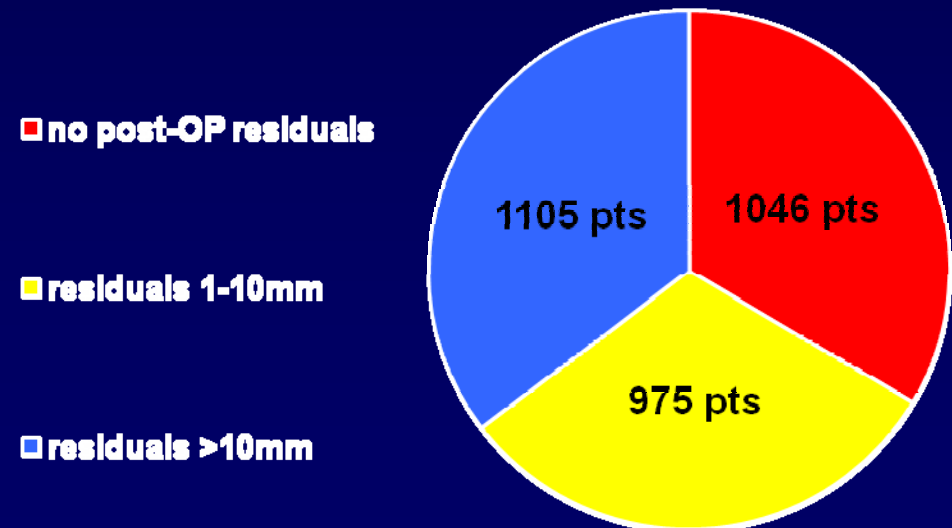


# Population:

- **3 randomized studies in FIGO IIB-IV ovarian cancer patients receiving 6 courses platinum-paclitaxel ± third drug after initial surgery:**
  - **AGO-OVAR 3** (Cisplatin/Paclitaxel vs Carboplatin/Paclitaxel) - du Bois A, et al. *J Natl Cancer Inst.* 2003;95(17):1320-29.
  - **AGO-OVAR 5/GINECO** (Carboplatin/Paclitaxel±Epirubicin) – du Bois A, et al. *J Clin Oncol.* 2006;24(7):1127-35.
  - **AGO-OVAR 7/GINECO** (Carboplatin/Paclitaxel±Topotecan) – Pfisterer J, et al. *J Natl Cancer Inst.* 2006;98(15):1036-45.
- **3126 of 3388 randomized patients (92.3%) included of whom 1837 (58.8%) had died within a median observation period of 53.9 months.**
- **Patients characteristics:**

Age, median (range)		58.9 (19.6-83.6) years	
PS	ECOG 0	1190	38.1
	ECOG 1	1592	50.9
	ECOG 2	326	10.4
Stage	FIGO IIB-IIIA	448	14.4
	FIGO IIIB	366	11.7
	FIGO IIIC	1779	56.9
	FIGO IV	530	17.0
Grading	G1	244	7.8
	G2	998	31.9
	G3	1702	54.4
Histology	Serous	2296	73.4
	Endometrioid	272	8.7
	Mucinous	147	4.7

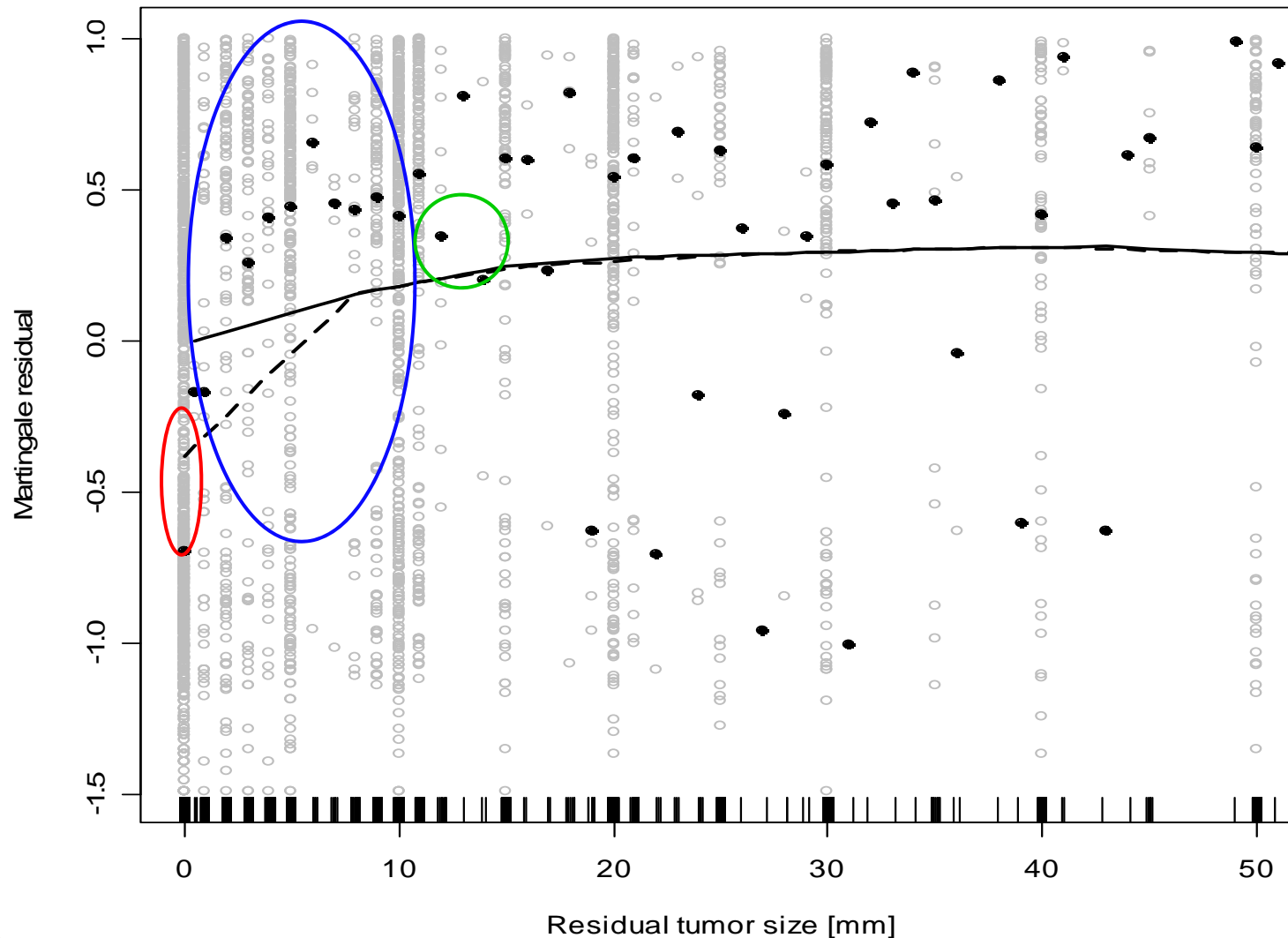
## Surgical outcome:



# Questions:

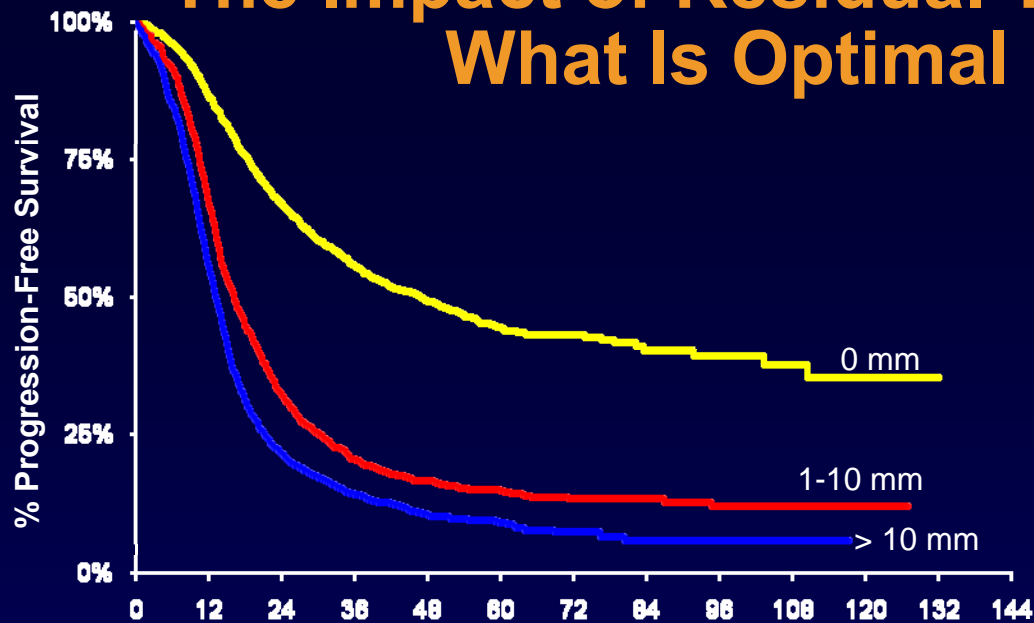
- **What means “optimal” – and should be the goal of debulking surgery?**
- **Which impact has initial tumor burden (ie, FIGO stage)?**
  - **Is debulking efficient in any FIGO stage?**
  - **Can debulking correct for initial tumor burden?**
- **Which impact has tumor biology (histo types)?**
  - **Is debulking efficient in any histo type (incl. high risk mucinous)?**
- **Is there any interaction between residual tumor and other prognosticators?**
- **How could we improve outcome for those patients who end up with tumor residuals >1 cm (and probably do not benefit from upfront surgery)?**
  - **Improve resection rates by pre-OP chemotherapy?**
    - **If so, does this result in better outcome?**
  - **Improve surgical skills and techniques?**

# The Impact of Residual Tumor on Outcome: What Is Optimal Debulking?



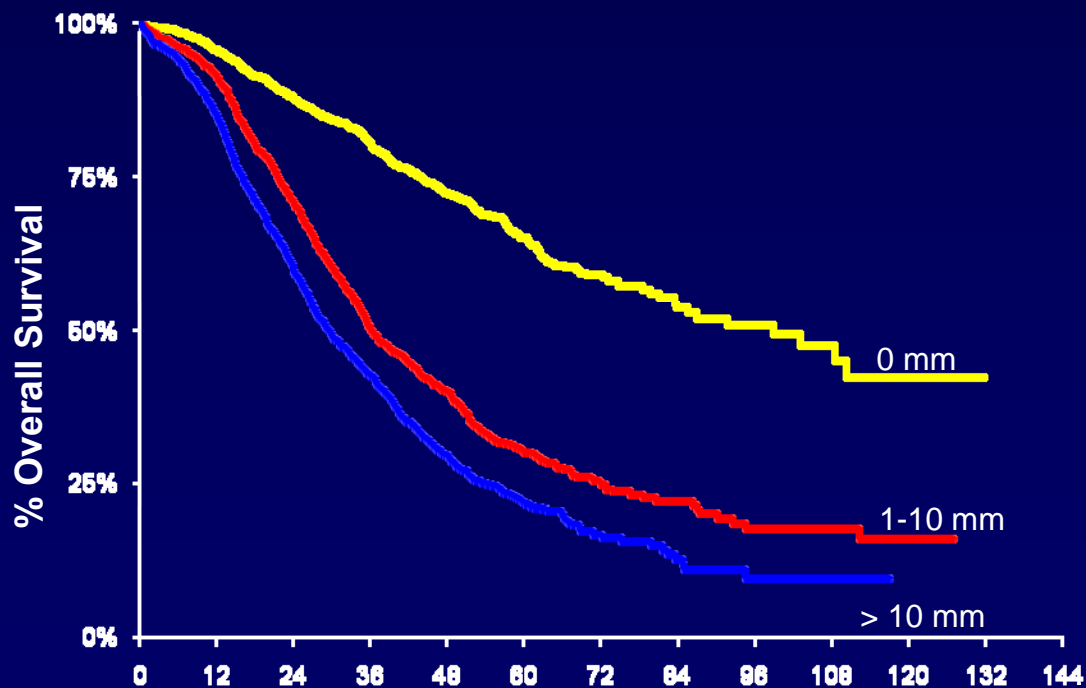
Plot of martingale residuals for null model of survival against residual tumor size after primary surgery with smoothed regression lines to assess functional form of residual tumor size as a covariate. The grey circles show the patient-wise martingale residuals. Black dots are medians of martingale residuals for given residual tumor sizes. The solid line is a smoothed loess regression curve taking into account only patients with macroscopic residual tumor, while the dashed line accounts for all patients.

# The Impact of Residual Tumor on Outcome: What Is Optimal Debulking?



	<u>HR</u>	<u>(95%CI)</u>
1-10 mm vs 0 mm:	2.52	(2.26;2.81)
>10 mm vs 1-10 mm:	1.36	(1.24;1.50)

log-rank:  $P < .0001$



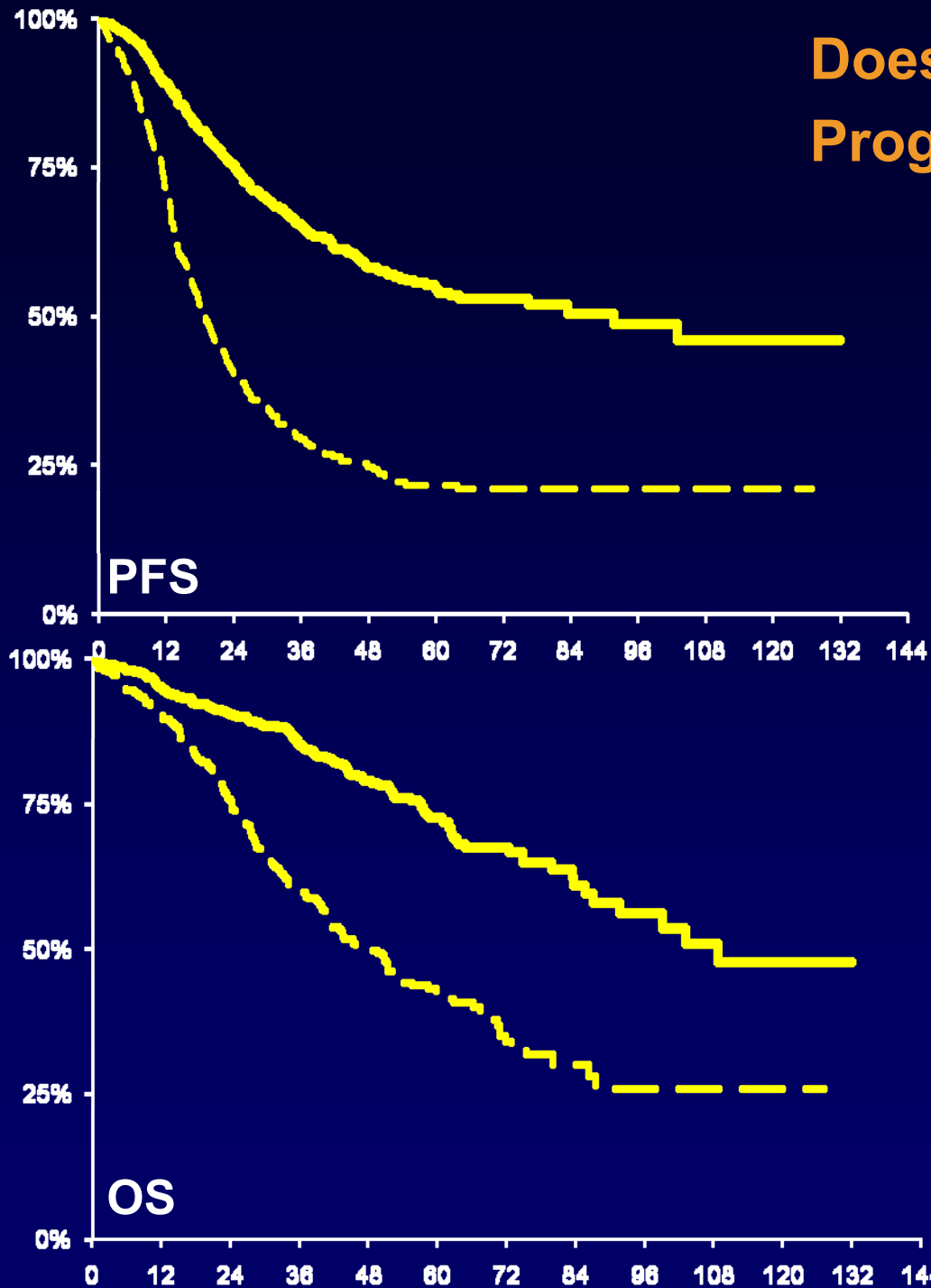
	<u>HR</u>	<u>(95%CI)</u>
1-10 mm vs 0 mm:	2.70	(2.37; 3.07)
>10 mm vs 1-10 mm:	1.34	(1.21; 1.49)

log-rank:  $P < .0001$

# Questions:

- What means “optimal” – and should be the goal of debulking surgery?
- Which impact has initial tumor burden (ie, FIGO stage)?
  - Is debulking efficient in any FIGO stage?
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# Does Surgery Improve Prognosis in Any FIGO Stage?



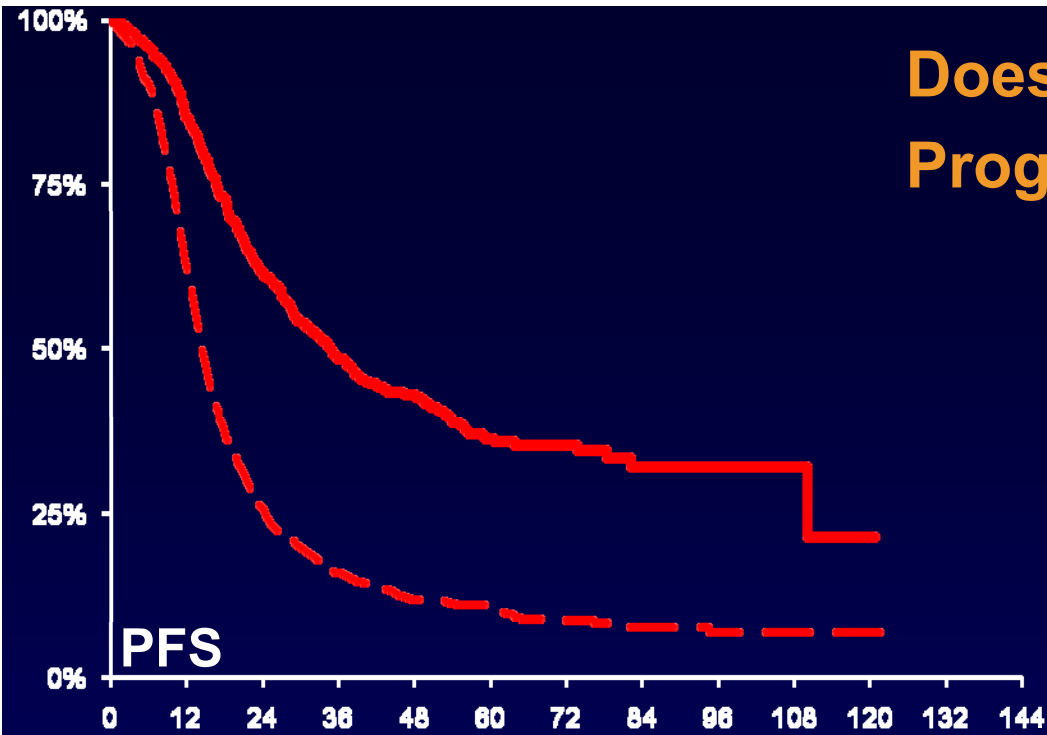
— res. tum. =0, FIGO IIB-III B

- - res. tum. >0, FIGO IIB-III B

log-rank:  $P < .0001$

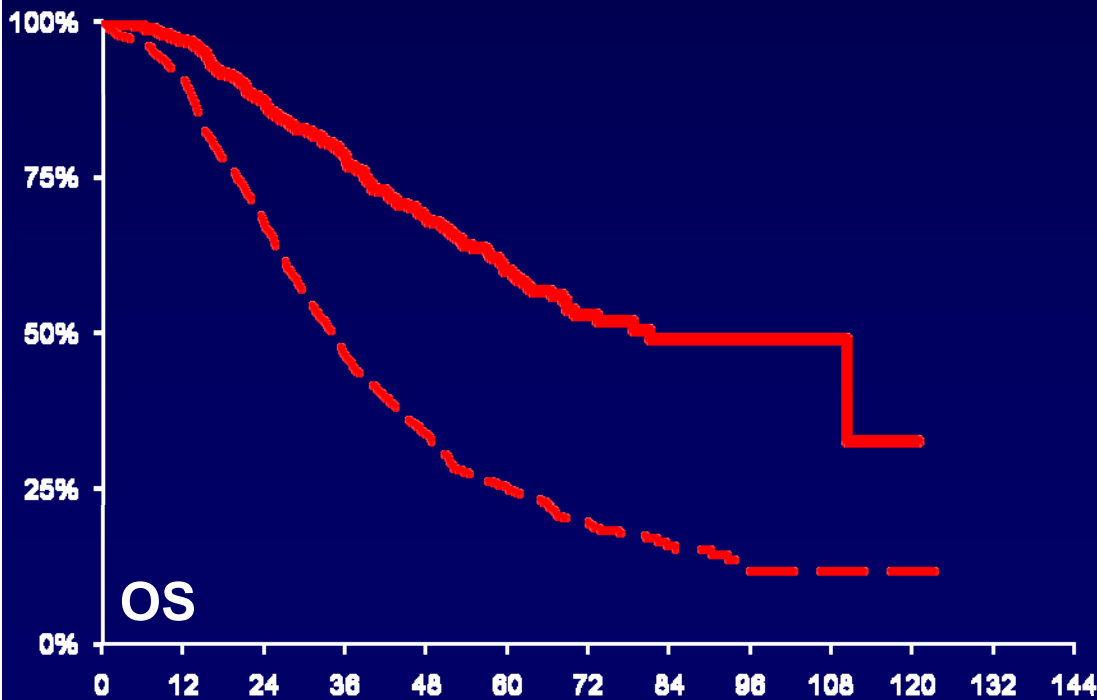
**YES**

# Does Surgery Improve Prognosis in Any FIGO Stage?



— res. tum. =0, FIGO IIB-III B  
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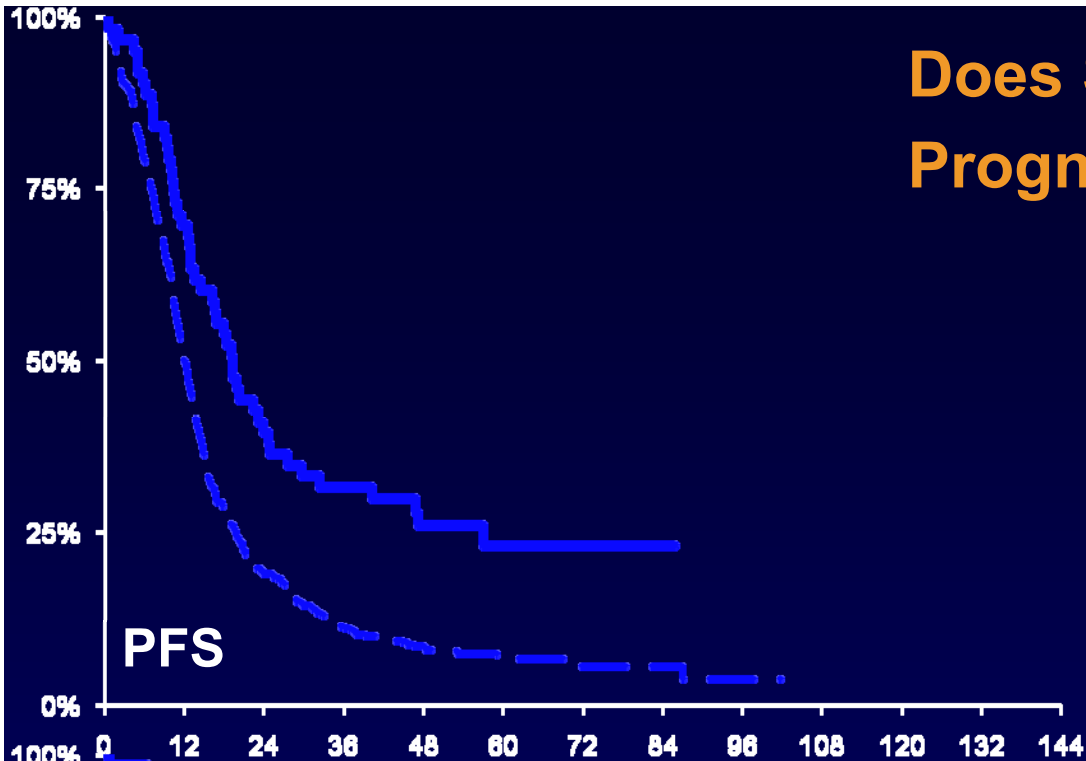
**YES**



— res. tum. =0, FIGO III C  
- - res. tum. >0, FIGO III C  
log-rank:  $P < .0001$

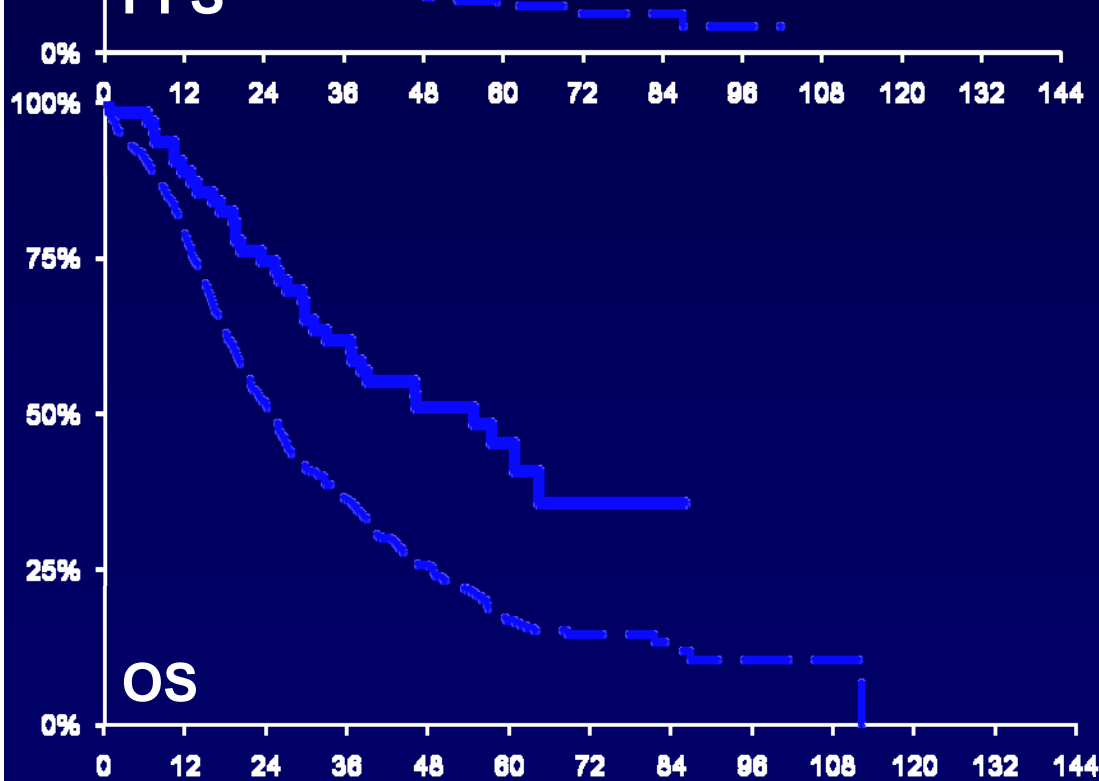
**YES**

# Does Surgery Improve Prognosis in Any FIGO Stage?



— res. tum. = 0, FIGO IIB-III B  
- - res. tum. > 0, FIGO IIB-III B  
log-rank:  $P < .0001$

**YES**



— res. tum. = 0, FIGO III C  
- - res. tum. > 0, FIGO III C  
log-rank:  $P < .0001$

**YES**

— res. tum. = 0, FIGO IV  
- - res. tum. > 0, FIGO IV  
log-rank:  $P < .0001$

**YES**

## Which Kind of Surgery Does Improve Prognosis in Which FIGO Stage?

Initial FIGO stage	No Macroscopic Residual Tumor		Any Residual Tumor		HR (95% CI)	No Residual Tumor		Any Residual Tumor		HR (95% CI)
	Patients, n	PFS, mos	Patients, n	PFS, mos		Median OS, mos				
<b>FIGO IIB-IIIB</b>	497	91.7	317	19.1	<b>0.37 (0.31; 0.45)</b>	108.6	48.3	<b>0.37 (0.30; 0.47)</b>		
<b>FIGO IIIC</b>	486	35.0	1293	14.5	<b>0.39 (0.35; 0.45)</b>	81.1	34.2	<b>0.36 (0.31; 0.42)</b>		
<b>FIGO IV</b>	63	19.2	467	12.1	<b>0.53 (0.39; 0.72)</b>	54.6	24.6	<b>0.49 (0.34; 0.70)</b>		

HR = Hazard Ratio, reference class for HR is "Any residual tumor"

Initial FIGO stage	Residual Tumor 1-10 mm		Residual Tumor >10 mm		HR (95% CI)	Residuals 1-10 mm		Residuals > 10 mm		HR (95% CI)
	Patients, n	PFS, mos	Patients, n	PFS, mos		Median OS, mos				
<b>FIGO IIB-IIIB</b>	205	22.2	112	16.7	<b>0.73 (0.56; 0.95)</b>	52.3	41.0	0.75 (0.55; 1.01)		
<b>FIGO IIIC</b>	613	15.9	680	13.7	<b>0.78 (0.70; 0.88)</b>	35.6	30.7	<b>0.80 (0.70; 0.91)</b>		
<b>FIGO IV</b>	156	13.5	311	11.5	0.84 (0.69; 1.03)	26.2	23.9	0.86 (0.69; 1.07)		

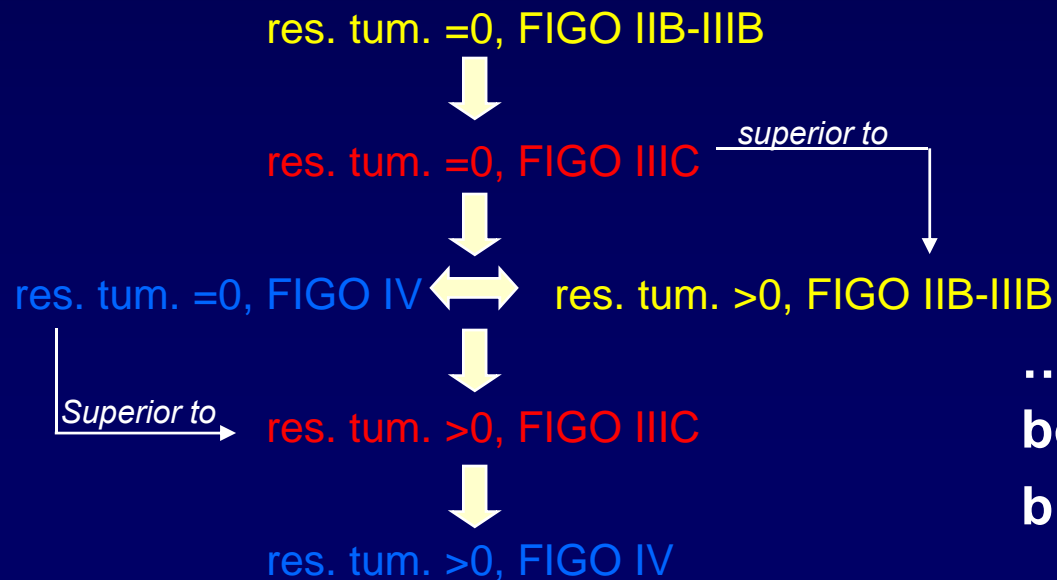
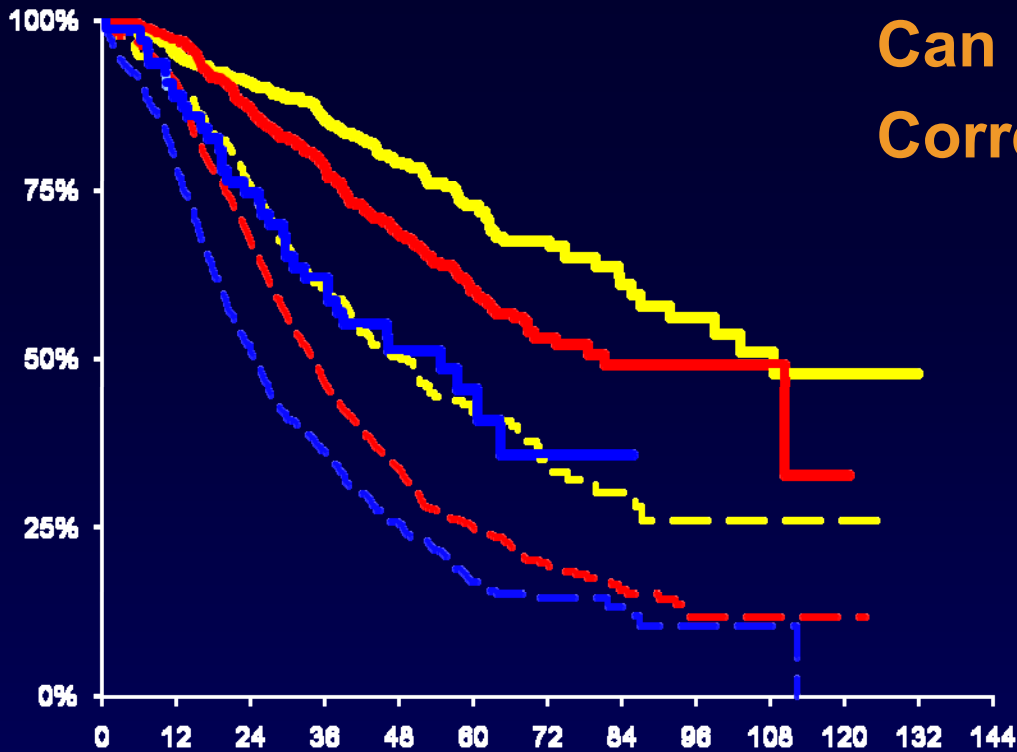
HR = Hazard Ratio, reference class for HR is "residual tumor > 10 mm"

# Which Kind of Surgery Does Improve Prognosis in Which FIGO Stage?

Initial FIGO stage	No Macroscopic Residual Tumor		Any Residual Tumor		HR (95% CI)	Median OS, mos	HR (95% CI)	
	Patients, n	PFS, mos	Patients, n	PFS, mos	<b>Gain in med. Survival (OS)</b>			
<b>FIGO IIB-IIIB</b>	497	91.7	317	19.2	<b>+ 60.3 mos</b>	108.6	<b>0.37 (0.30; 0.47)</b>	
<b>FIGO IIIC</b>	486	35.0	1293	14.1	<b>+ 46.9 mos</b>	81.1	<b>0.36 (0.31; 0.42)</b>	
<b>FIGO IV</b>	63	19.2	467	12.1	<b>+ 30.0 mos</b>	54.6	<b>0.49 (0.34; 0.70)</b>	
HR = Hazard Ratio, reference class for HR is "Any residual tumor"								
Initial FIGO stage	Residual Tumor 1-10 mm		Residual Tumor >10 mm		HR (95% CI)	Residuals 1-10 mm	Residuals > 10 mm	HR (95% CI)
	Patients, n	PFS, mos	Patients, n	PFS, mos	<b>Gain in med. Survival (OS)</b>			
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<b>FIGO IIIC</b>	613	15.9	680	13.1	<b>+ 4.9 mos</b>	35.6	30.7	<b>0.80 (0.70; 0.91)</b>
<b>FIGO IV</b>	156	13.5	311	11.1	<b>+ 2.3 mos</b>	26.2	23.9	0.86 (0.69; 1.07)

HR = Hazard Ratio, reference class for HR is "residual tumor > 10 mm"

# Can Surgical Resection Correct for Initial Tumor Burden?



... only partially...  
 both initial and post-op tumor  
 burden have a prognostic impact

# Questions:

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## Uni- and Multivariate Cox Regression Models for Overall (A) and Progression-free-survival (B)

Parameter	Univariate Analysis			Multivariate Analysis		
	HR	95%-CI	P value	HR	95%-CI	P value
Age [10 yrs]	1.23	(1.17; 1.29)	<.0001	1.13	(1.08, 1.18)	<.0001
ECOG 2 vs 0-1	1.76	(1.54, 2.01)	<.0001	1.36	(1.18, 1.56)	<.0001
FIGO IIIC-IV vs IIB-IIIB	2.24	(1.99, 2.53)	<.0001	1.45	(1.28, 1.65)	<.0001
Grading G2/3 vs G1	2.50	(1.99, 3.13)	<.0001	1.74	(1.37, 2.21)	<.0001
Endometroid vs serous histology	0.77	(0.64, 0.91)	.0029	0.94	(0.79, 1.13)	.5030
Mucinous vs serous histology	1.76	(1.43, 2.15)	<.0001	<b>2.38</b>	<b>(1.94, 2.93)</b>	<.0001
Residuals 1-10 mm vs 0 mm	2.70	(2.37; 3.07)	<.0001	<b>2.12</b>	<b>(1.85, 2.43)</b>	<.0001
Residuals > 10 mm vs 1-10 mm	1.34	(1.21; 1.49)	<.0001	1.20	<b>(1.08, 1.33)</b>	.0006
Ascites > 500 mL yes vs no	1.95	(1.76, 2.16)	<.0001	1.36	(1.22, 1.51)	<.0001

## Does Surgery Improve Prognosis in Any Histo Type?

A= OS	Serous Histology			Mucinous Histology		
	HR	95%-CI	p-value	HR	95%-CI	P value
Age [10 yrs]	<b>1.15</b>	(1.09, 1.22)	<b>&lt;.0001</b>	1.18	(0.98, 1.43)	.0773
ECOG 2 vs 0-1	<b>1.22</b>	(1.05, 1.43)	<b>.0117</b>	<b>1.98</b>	(1.01, 3.87)	<b>.0456</b>
FIGO IIIC-IV vs IIB-IIIB	<b>1.50</b>	(1.29, 1.75)	<b>&lt;.0001</b>	1.10	(0.65, 1.88)	.7131
Grading G2/3 vs G1	<b>1.67</b>	(1.26, 2.21)	<b>.0004</b>	1.95	(0.99, 3.84)	.0523
<b>Residual tumor 1-10 mm vs 0 mm</b>	<b>2.16</b>	(1.84, 2.54)	<b>&lt;.0001</b>	<b>2.40</b>	(1.35, 4.29)	<b>.0031</b>
Residual tumor > 10 mm vs 1-10 mm	<b>1.16</b>	(1.03, 1.31)	<b>.0141</b>	1.01	(0.62, 1.65)	.9559
Ascites yes vs no	<b>1.36</b>	(1.20, 1.55)	<b>&lt;.0001</b>	1.43	(0.85, 2.40)	.1801

- **Mucinous histo type overrules most other prognostic factors**
- **Complete resection is almost the only remaining prognosticator in mucinous OC**
- **Tumor reduction to 1-10 mm was beneficial in serous OC only**

## Does Residual Tumor Overrule Other Prognostic Factors?

PFS Analysis	No Residual Post-OP Tumor			Residual Tumor 1-10 mm			Residual Tumor > 10 mm		
	HR	95%-CI	<i>P</i> value	HR	95%-CI	<i>P</i> value	HR	95%-CI	<i>P</i> value
Age [10 yrs]	1.17	(1.08, 1.27)	<b>.0002</b>	1.02	(0.95, 1.09)	.5969	1.06	(0.99, 1.13)	.0912
ECOG 2 vs 0-1	1.53	(1.11, 2.11)	<b>.0091</b>	1.14	(0.91, 1.42)	.2567	1.09	(0.91, 1.30)	.3486
FIGO IIIC-IV vs IIB-IIIB	1.52	(1.28, 1.81)	<b>&lt;.0001</b>	1.47	(1.22, 1.77)	<b>&lt;.0001</b>	1.41	(1.13, 1.75)	<b>.0022</b>
Grading G2/3 vs G1	2.13	(1.56, 2.91)	<b>&lt;.0001</b>	1.26	(0.89, 1.79)	.1910	1.38	(0.97, 1.96)	.0693
Mucinous vs serous	1.53	(1.05, 2.25)	<b>.0282</b>	2.17	(1.52, 3.11)	<b>&lt;.0001</b>	2.16	(1.62, 2.87)	<b>&lt;.0001</b>
Ascites yes vs no	1.70	(1.39, 2.07)	<b>&lt;.0001</b>	1.19	(1.00, 1.43)	.0515	1.19	(1.02, 1.40)	<b>.0273</b>

**Significant loss of prognostic factors with increasing tumor residuals**

**Postoperative residual tumor overrules patient characteristics' and tumor biology associated factors (except mucinous histo type)**

**Consequences for study designs evaluating biologicals?**

# Questions:

- What means “optimal” – and should be the goal of debulking surgery?
- Which impact has initial tumor burden (ie, FIGO stage)?
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- Is there any interaction between residual tumor and other prognosticators?
- How could we improve outcome for those patients who end up with tumor residuals >1 cm (and probably do not benefit from upfront surgery)?  
*[Improvement for patients optimally debulked is also mandatory → systemic therapy!]*
  - Improve resection rates by pre-OP chemotherapy?
    - If so, does this result in better outcome?
  - Improve surgical skills and techniques?

# Hypothesis:

At least secondary resistance is a function of tumor volume

- Significant debulking reduces tumor burden → fewer resistant cells → better prognosis
- Large tumor burden → more mutations/resistance → poor prognosis
- Strategy of neoadjuvant chemotherapy implies:
  - Higher initial tumor volume → higher risk for secondary resistance → poor prognosis

*but also:*

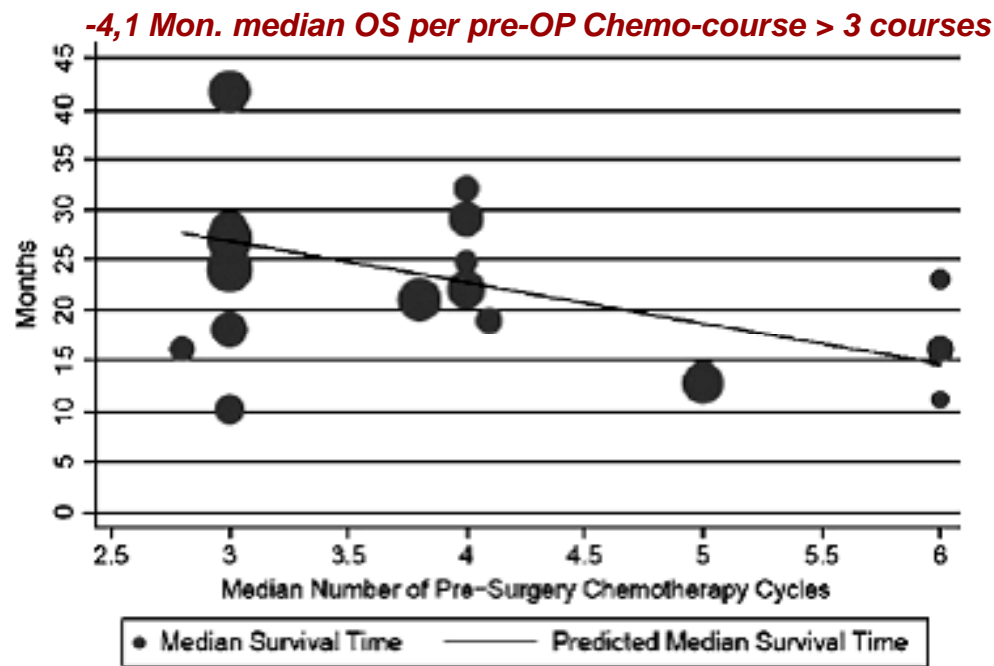
- Higher rate of tumor debulking → better prognosis
- *How does improved resection rate balance for higher mutation risk?*
- *Might this strategy result in a net benefit ?*

**Hypothesis Supported if Outcome Becomes Inferior with Longer Duration  
Of Pre-OP Chemotherapy  
(= Longer Time with Significant Tumor Volume → Higher Risk for Resitance)**

# Hypothesis Supported if Outcome Becomes Inferior with Longer Duration Of Pre-OP Chemotherapy (= Longer Time with Significant Tumor Volume → Higher Risk for Resitance)

## Meta-Analysis publications 1989-2005

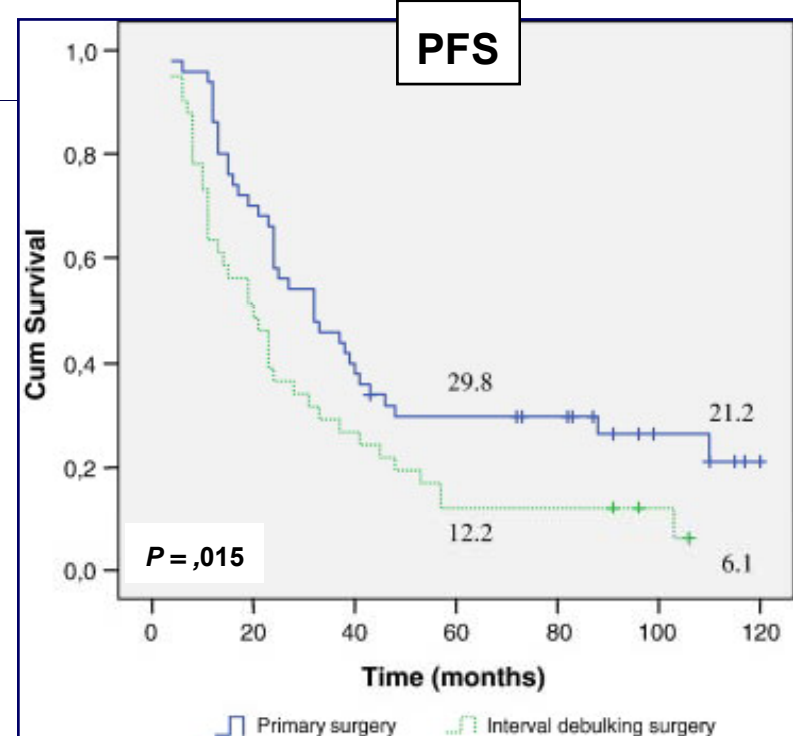
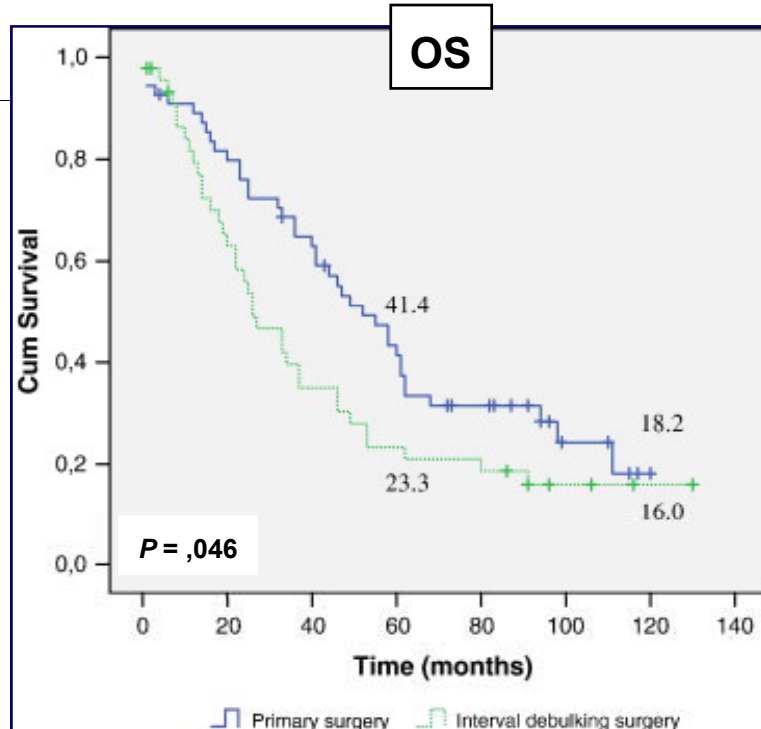
- 22 cohorts / 835 patients with FIGO III/IV ovarian cancer
- All patients had pre-OP platunim-based chemotherapy followed by interval-OP
- Prognostic factors: Year, % FIGO IV, % “optimal debulking,” chemotherapy +/- taxane and number of pre-OP chemotherapy courses > 3 → negative impact!



**Hypothesis Supported if Outcome Is Better After Primary Surgery in Cohorts with Comparable Rates of Complete Resection (= Without Benefit of NACT Regarding Tumor Residuals)**

## Hypothesis Supported if Outcome Is Better After Primary Surgery in Cohorts with Comparable Rates of Complete Resection (= Without Benefit of NACT Regarding Tumor Residuals)

- Scholz et al., *Gynecol Oncol* 2007, 106: 591-5; Neumarkt 1995-1999 FIGO IIIC-IV OvCa
- 55 pts with primary OP and 46 pts with interval-OP after on average 4 courses platinum+
- No gross residuals in 82% after primary surgery and 85% following chemo and interval OP



- Outcome inferior after chemo + interval OP if complete resection rates do not differ !

**Hypothesis Supported if Outcome Is Better After Pre-OP Chemotherapy  
And Interval Surgery in Cohorts with Significant Higher Rates of Complete  
(or So-Called “Optimal”) Debulking  
(= Significant Benefit of NACT Regarding Tumor Residuals)**

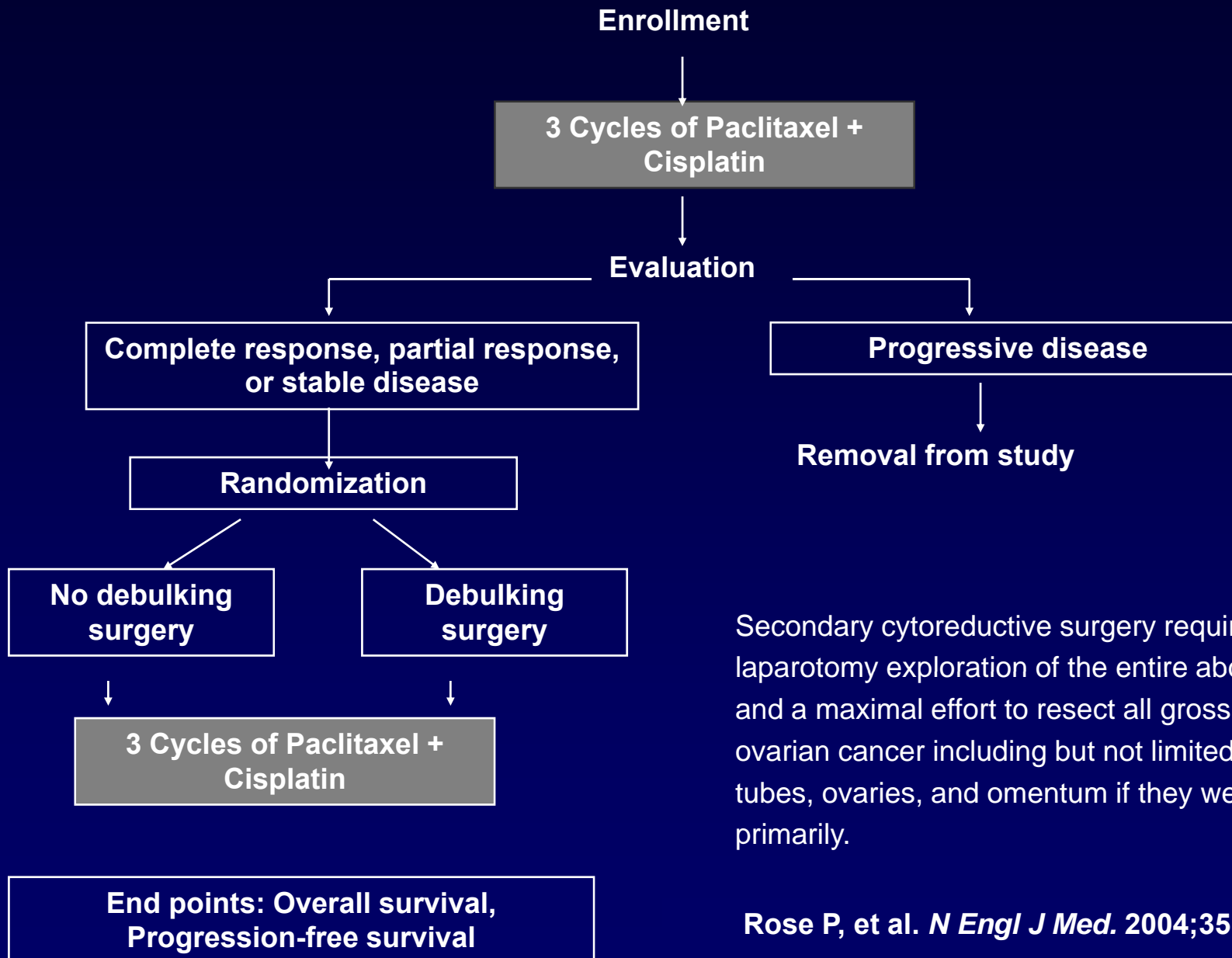
*but....*

**How much is “significant”?**

**Is a 20%, 30%, 40% ...higher optimal resection rate sufficient to compare  
for the negative impact of tumor volume over time?**

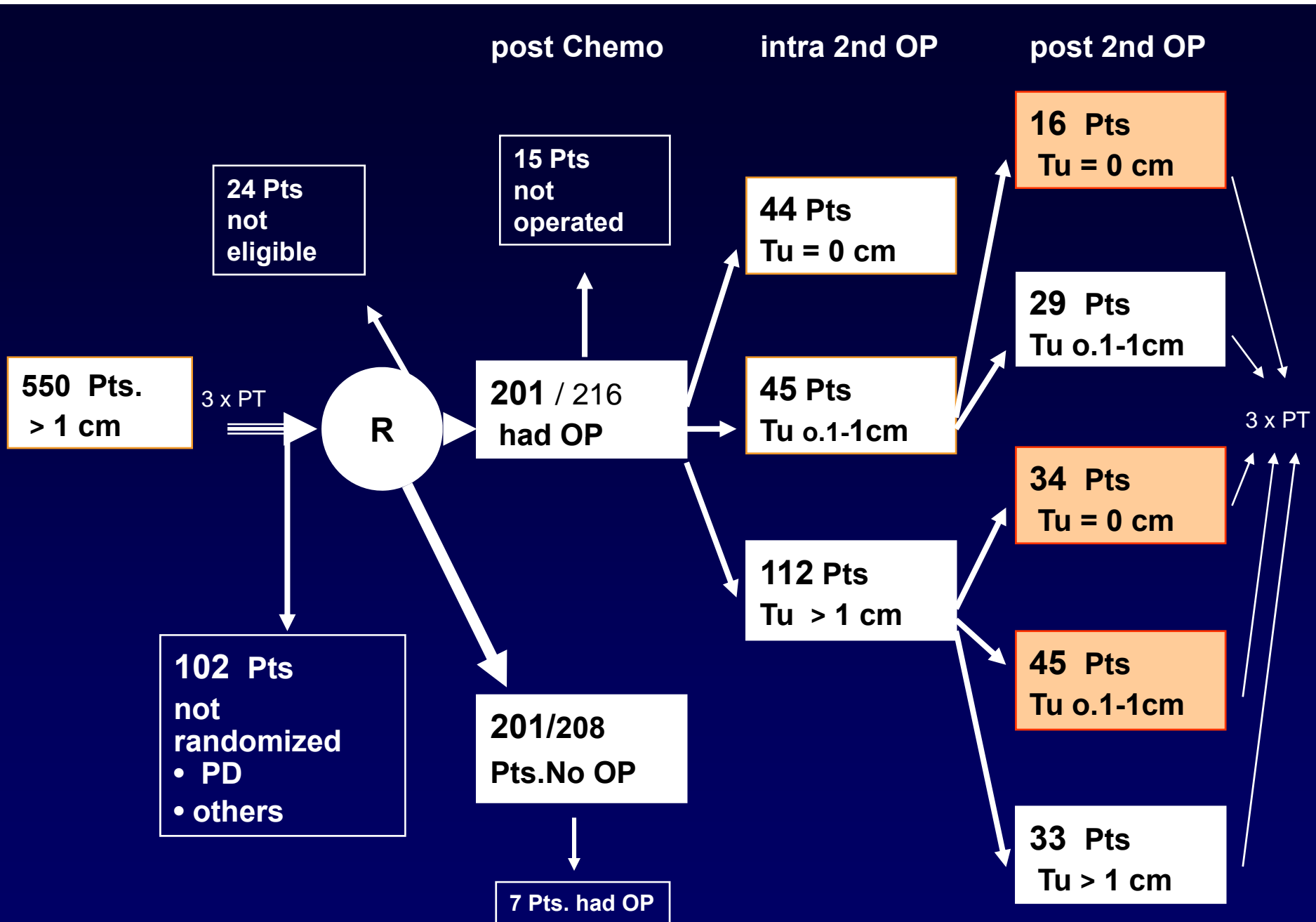
- **Data base:**
  - **GOG 152**
  - **EORTC NACT study**

# GOG Trial of Interval Secondary Debulking Surgery (#152)



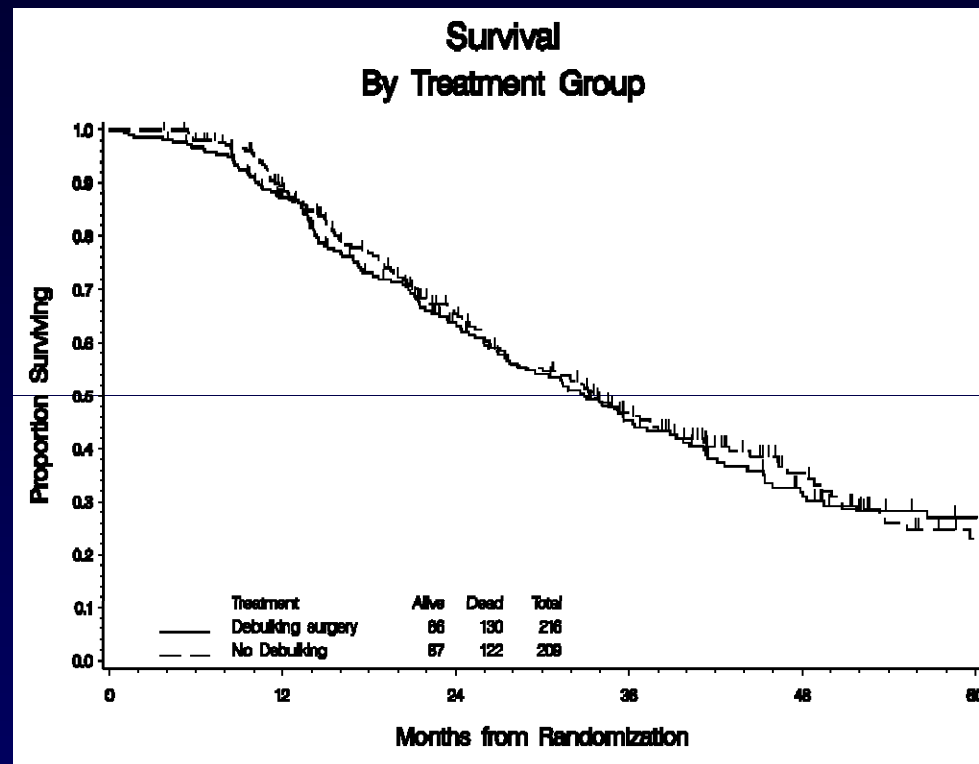
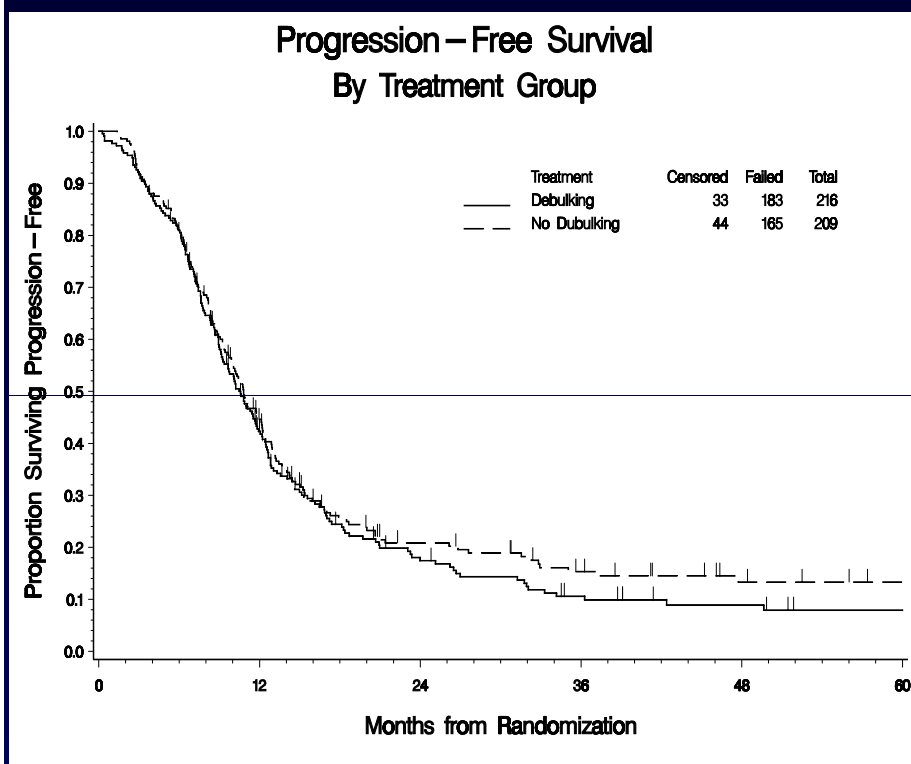
Secondary cytoreductive surgery required a laparotomy exploration of the entire abdominal cavity and a maximal effort to resect all gross residual ovarian cancer including but not limited to the uterus, tubes, ovaries, and omentum if they were not resected primarily.

Rose P, et al. *N Engl J Med.* 2004;351(24):2489-2497.



• Benefit:  $95 \times 2 / 550 = 34,5 \%$

# GOG #152: Results Were Negative



- ... although the secondary rate of complete and so-called optimal debulking was considerably high (34.5%)
- → 34.5% not enough to compensate for higher risk due to large tumor volume over time of pre-OP chemotherapy?

# EORTC/NCIC Study: NACT + Interval-OP vs Primary OP

FIGO IIIC/IV Ovarian-, Tubal-, Peritoneal-Carcinoma  
(40% FNA, 20% guided biopsy, 35% LSK, 5% L'tomie)

718 pts  
randomisation

9% noneligible  
329 pts → primary-OP

3% pts  
Diagnosis changed to non OC

19% pts  
Interval-OP

6 Courses platinum+  
83% pts with 6 courses

5% pts had SLO

5% ineligible  
339 ps → NACT 3 x platin+

10% pts. without  
Interval-OP (PD etc..)

90% pts  
Interval OP

2% pts  
Diagnosis changed to non OC

3 courses platinum+  
86% pts with 6 courses

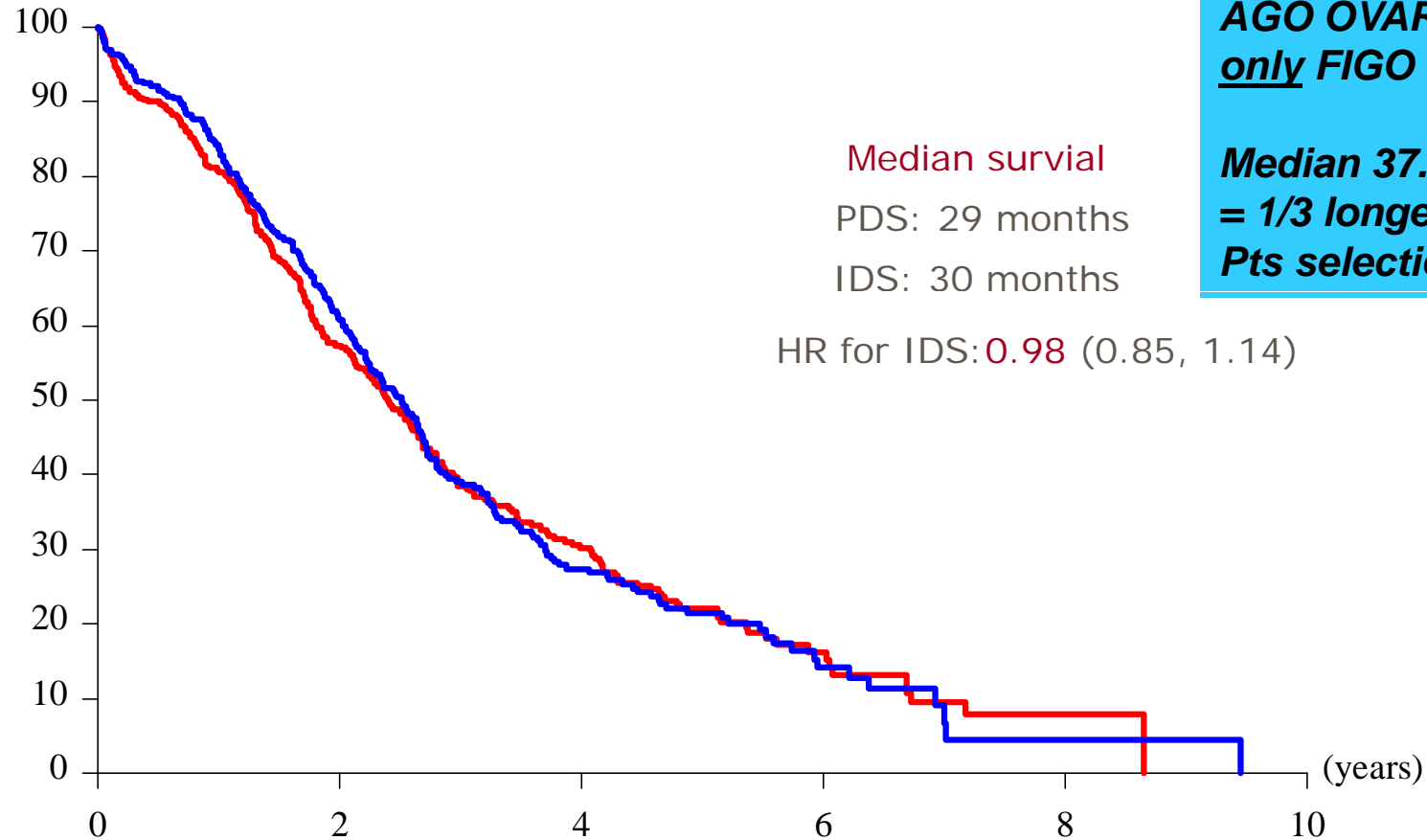
4% pts had SLO

## EORTC/NCIC Study: NACT + Interval-OP vs Primary OP

≤1cm Residual per Country (PP1)	Total	Primary-OP (n = 329)	NACT→IDS (n = 306/339)	Difference (%)
Belgium (n = 133)	83%	72%	94%	22
Argentina (n = 48)	71%	68%	74%	6
The Netherlands (n = 104)	59%	40%	77%	37
Sweden (n = 23)	59%	40%	75%	35
Norway (n = 82)	55%	35%	73%	38
Italy (n = 38)	52%	40%	64%	24
Spain (n = 62)	49%	44%	58%	14
UK (n = 101)	47%	37%	63%	26
Canada (n = 84)	44%	29%	59%	30
<b>No residual after surgery</b>		<b>21%</b>	<b>53%</b>	<b>32%</b>
<b>≤1 cm after surgery</b>		<b>46%</b>	<b>82%</b>	<b>36%</b>

# EORTC/NCIC Study: NACT + Interval-OP vs Primary OP

## Overall survival



**AGO OVAR 3+5+7  
only FIGO IIIc-IV:**

**Median 37.1 months  
= 1/3 longer  
Pts selection !?**

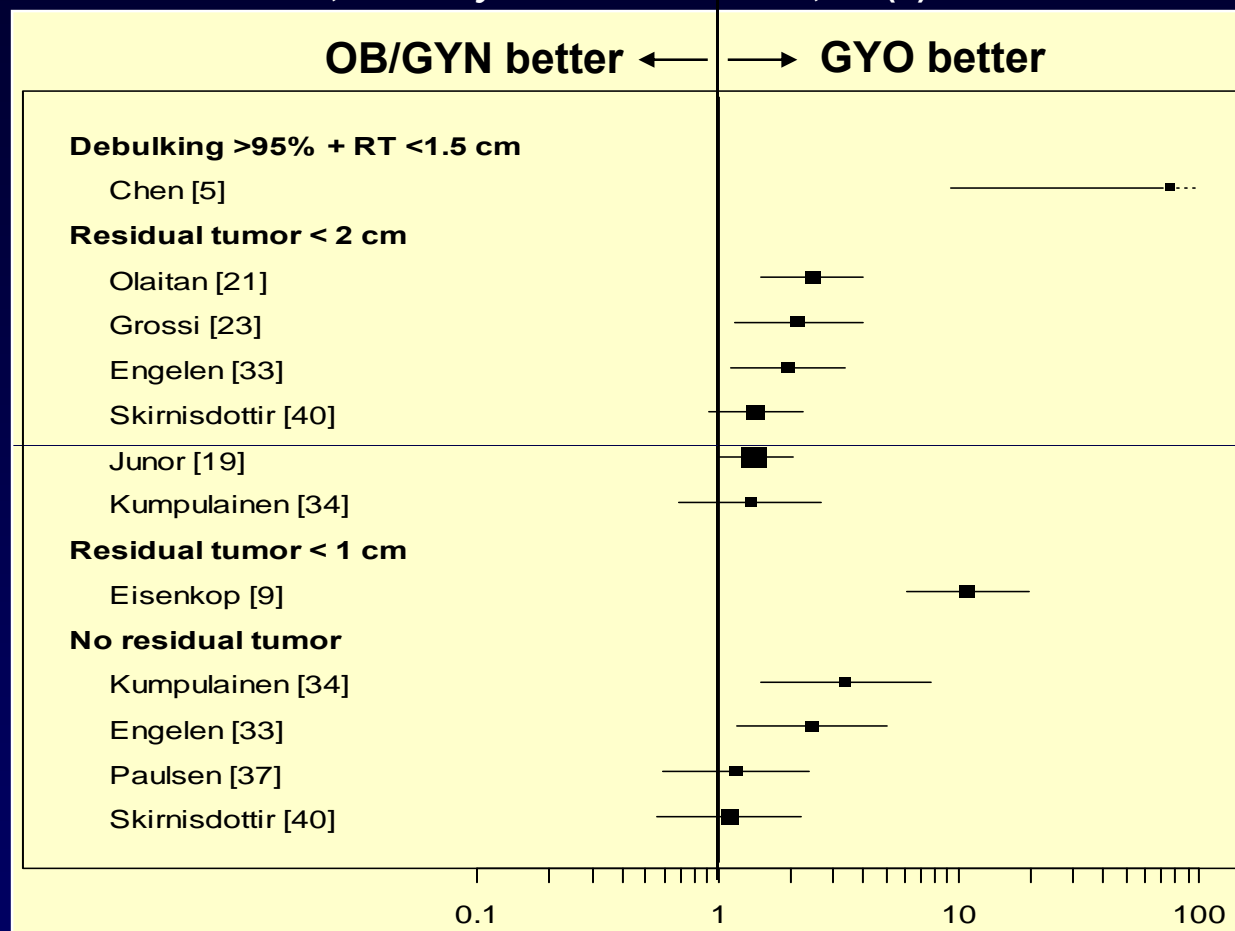
O	N	Number of patients at risk :				Treatment
259	361	183	68	16	2	— Upfront debulking
251	357	191	56	11	1	— Neoadjuvant chemotherapy

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  - Can debulking correct for initial tumor burden?
- Which impact has tumor biology (histo types)?
  - Is debulking efficient in any histo type (incl. high risk mucinous)?
- Is there any interaction between residual tumor and other prognosticators ?
- Is there an interaction between primary debulking and type of relapse?
- How could we improve outcome for those patients who end up with tumor residuals >1 cm (and probably do not benefit from upfront surgery)?  
*[Improvement for pts optimally debulked is also mandatory → systemic therapy !]*
  - Improve resection rates by pre-OP chemotherapy? **No !**
    - If so, does this result in better outcome?
  - Improve surgical skills and techniques?

# Improve Surgical Skills (Training), Techniques, and Infrastructure!

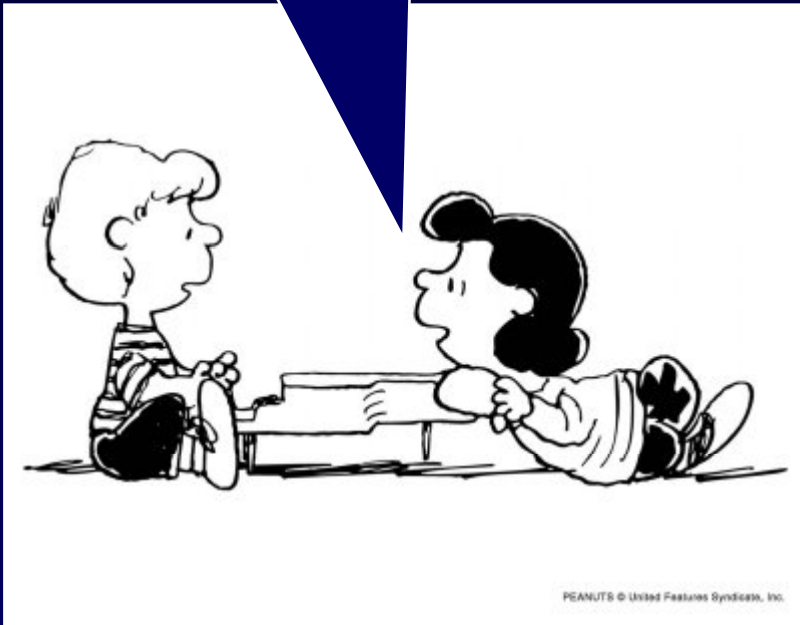
du Bois A, et al. *Gynecol Oncol.* 2009;112(2):422-436.



## Single centre experiences support this approach (eg. MSKC, C Mayo a.o.):

- Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Aletti GD, et al. *Obstet Gynecol.* 2006;107(1):77-85.
- The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Eisenhauer EL, et al. *Gynecol Oncol.* 2006;103(3):1083-1090.

„Wie schaffst du es nur, Beethoven Sonaten zu spielen, wenn die schwarzen Tasten bei deinem Kinderklavier nur aufgemalt sind?“



Üben,  
üben,  
üben !



*Surgery alone will not solve all problems (no matter how well performed), however, appropriate surgery may substantially contribute to better outcome in advanced ovarian cancer. Currently, quality of surgery has the biggest impact on outcome and improvements might and should be achieved.*