

**Neoadjuvant chemotherapy in  
Stage IIIc and IV ovarian carcinoma**

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**EGAM 2011**



**EORTC**  
European Organisation for Research  
and Treatment of Cancer



National  
Cancer Institute  
of Canada

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**The NEW ENGLAND  
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**RANDOMIZED CONTROLLED TRIAL  
PRIMARY SURGERY (PDS) WITH  
NEOADJUVANT CHEMOTHERAPY (NACT) FOLLOWED  
BY DEBULKING (IDS) IN  
ADVANCED EPITHELIAL OVARIAN, FALLOPIAN TUBE AND  
PERITONEAL CANCER.**

# RANDOMISED EORTC-GCG/NCIC-CTG TRIAL ON NACT + IDS VERSUS PDS

Ovarian, tuba or peritoneal cancer  
FIGO stage IIIc-IV (n = 718)

Randomisation

48 patients excluded from  
1 center -> n = 670

Primary Debulking Surgery

3 x Platinum based CT

Interval debulking  
(not obligatory)

≥ 3 x Platinum based CT

Neoadjuvant chemotherapy

3 x Platinum based CT

Interval debulking if no PD

≥ 3 x Platinum based CT

Primary Endpoint: Overall survival

Secondary endpoints: Progression Free Survival, Quality of Life, Complications

# Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS

## Eligibility

- **Biopsy** proven ovarian, fallopian tube or peritoneal carcinoma (OVCA)
- **Fine needle** aspiration suggesting the presence of OVCA, in combination with a pelvic mass, presence of **metastases of  $\geq 2$  cm** outside the pelvis (or proof of stage IV) and a **CA125/CEA** ratio  $> 25$ .

# Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS

## Baseline Characteristics (ITT)

	PDS	NACT -> IDS
Method of biopsy/fnac		
<i>FNAC</i>	42%	46%
<i>Laparoscopy</i>	31%	35%
<i>Image guided biopsy</i>	23%	16%
<i>Laparotomy</i>	4%	4%
Primary		
<i>Ovary</i>	87%	85%
<i>Fallopian tube</i>	0%	1%
<i>Peritoneum</i>	7%	8%
Diagnosis different after PDS/IDS	3%	2%

# Randomised EORTC-GCG/NCIC-CTG trial on NACT+ IDS versus PDS Protocol Compliance (PP1)

	PDS (n = 310)	NACT -> IDS (n = 322)
Primary debulking	100 %	0%
Interval debulking	17%	88%
Second look surgery	3%	2%
At least 6 courses CT	82%	86%

# Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS

## Surgical findings and results (PP1)

	PDS (n = 310)	NACT -> IDS (n = 322)
Metastases before > 2 cm	95%	69%
Metastases before > 10 cm	62%	24%
No residual after surgery	19%	51%*
≤ 1 cm after surgery	42%	80%*

\* % calculated on the 295 patients who underwent IDS.

# Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS

≤ 1cm residual per country (PP1)

	PDS (n = 329)	NACT -> IDS (n = 339)*	Difference PDS-IDS
Belgium (n=133)	71%	92%	21%
Spain (n=62)	43%	71%	28%
Italy (n=38)	38%	67%	29%
The Netherlands (n=104)	37%	75%	38%
Norway (n=82)	32%	80%	48%
UK (n=101)	31%	79%	48%
Canada (n=84)	31%	71%	40%

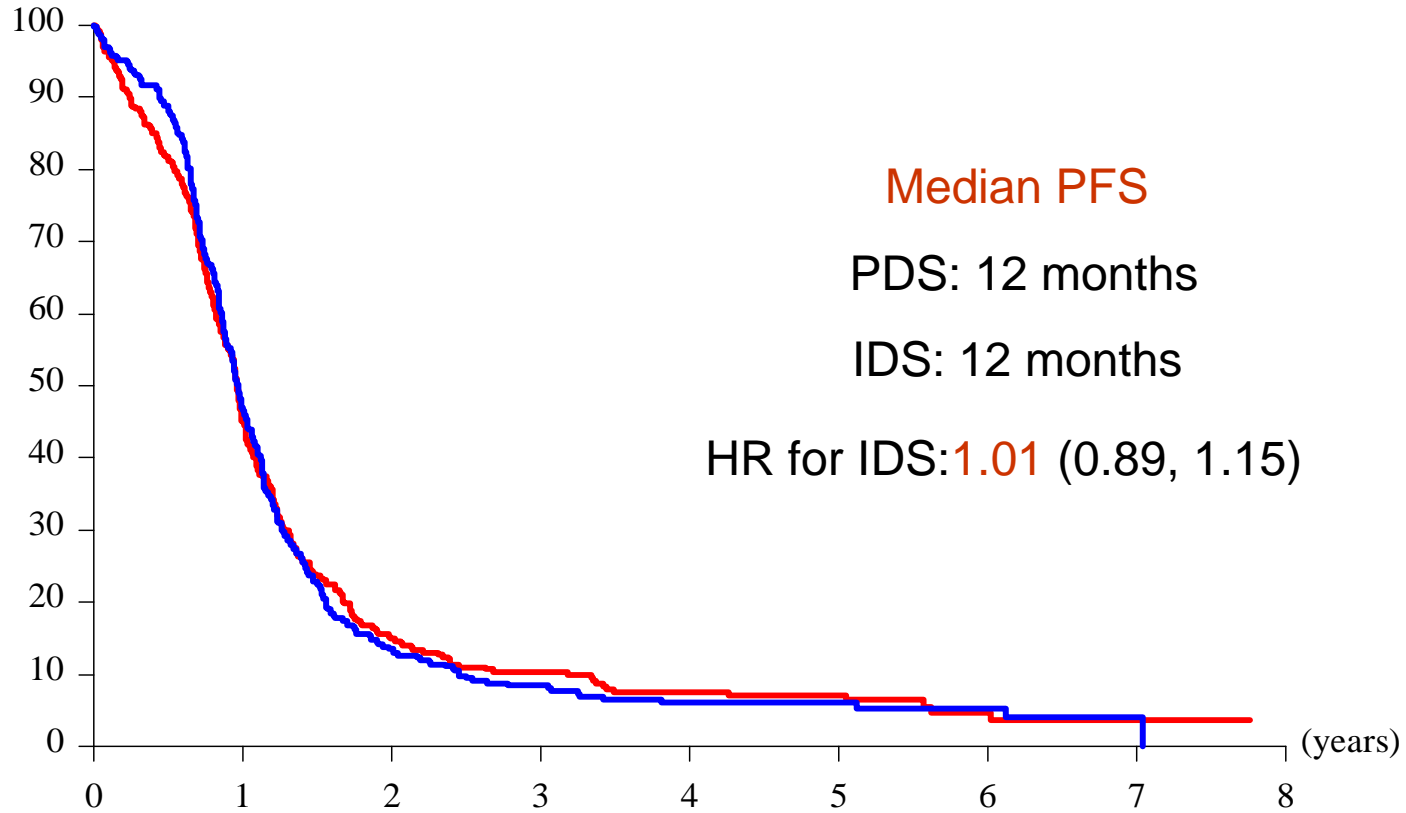
# Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS

## Surgical characteristics (PP1)

	PDS (n = 329)	NACT -> IDS (n = 339)*
Postoperative mortality ( $< 28$ days)	2,5%	0,7%
Postoperative fever G3-4	8%	2%
Fistula (bowel/GU)	1,0% / 0,3%	0,3% / 0,3%
Median operative time (min) 0/1-10mm/> 10 mm	165 312/190/120	180 194/179/120
Red blood cell transfusion	52%	52%
Hemorrhage Grade 3/4	7%	4%
Venous Gr 3/4	2,5%	0%

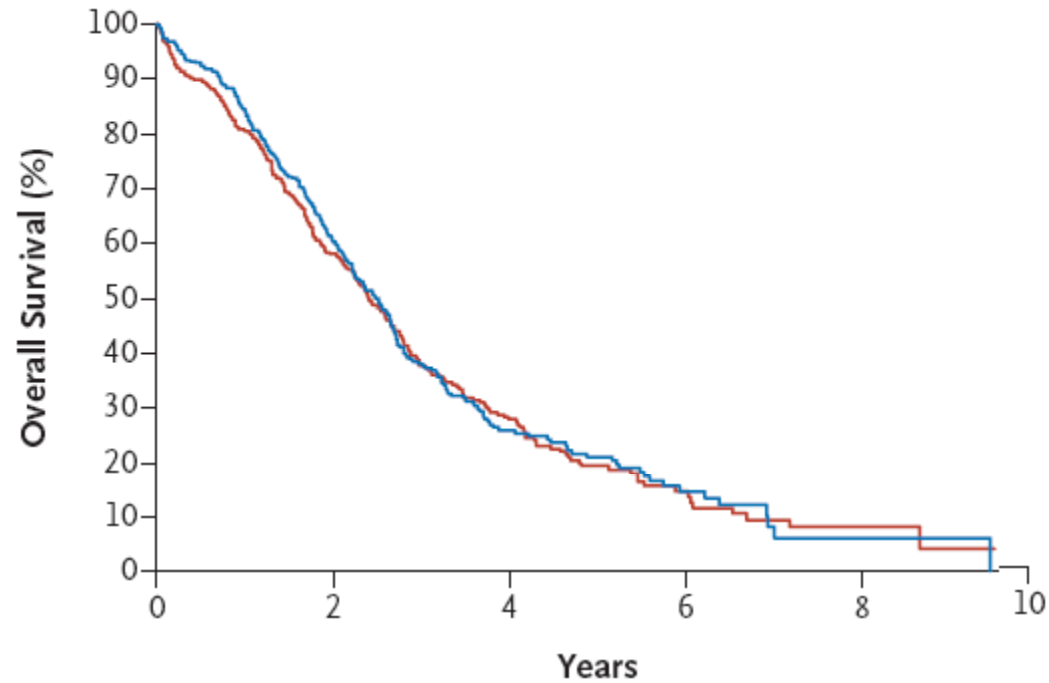
# NACT + IDS versus PDS: ITT

## Progression-free survival



O	N	Number of patients at risk :								Treatment
310	336	150	49	28	19	11	5	2	—	PDS
313	334	155	45	24	10	9	4	1	—	NACT

# NACT + IDS versus PDS: ITT



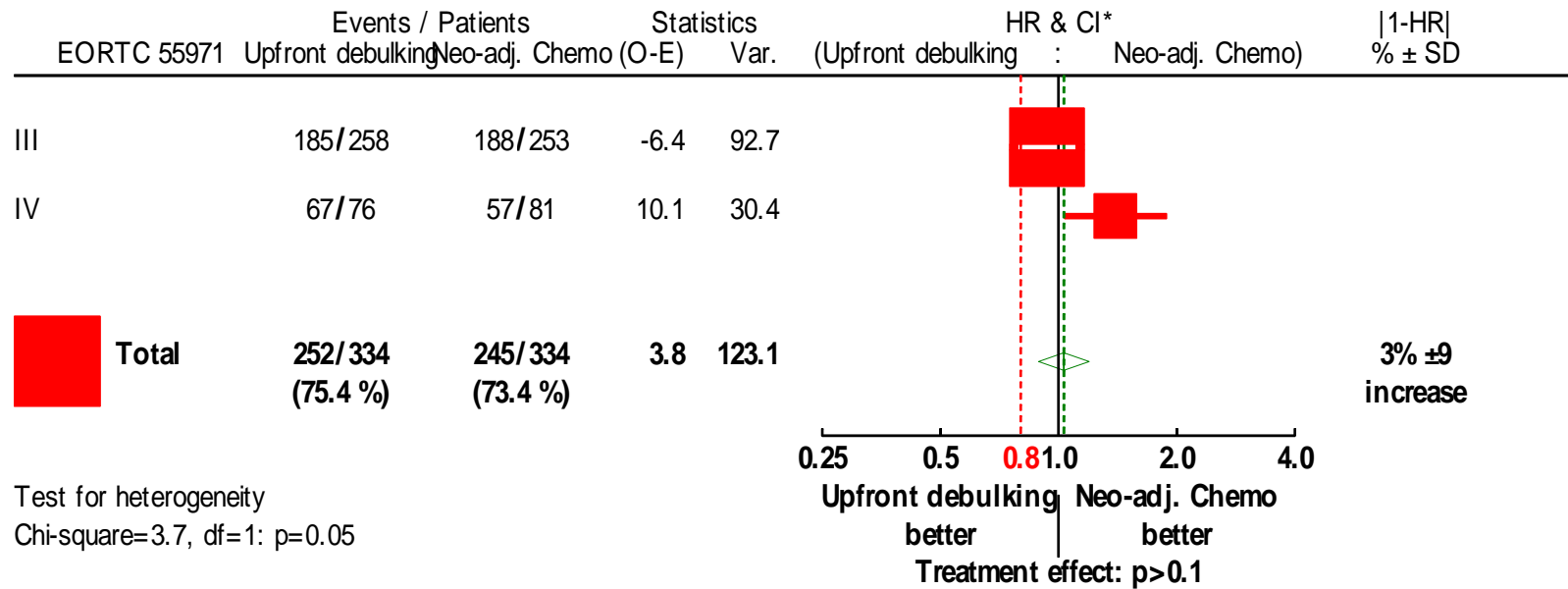
Median survival  
PDS: 29 months  
IDS: 30 months  
HR for IDS: 0.98  
(0.84, 1.13)

	No. of Events	No. of Patients at Risk				
		0	2	4	6	8
Primary Debulking Surgery (PDS)	253	336	189	62	14	2
Neoadjuvant Chemotherapy (NACT)	245	334	195	46	13	2

— PDS  
— NACT

# NACT + IDS versus PDS: ITT

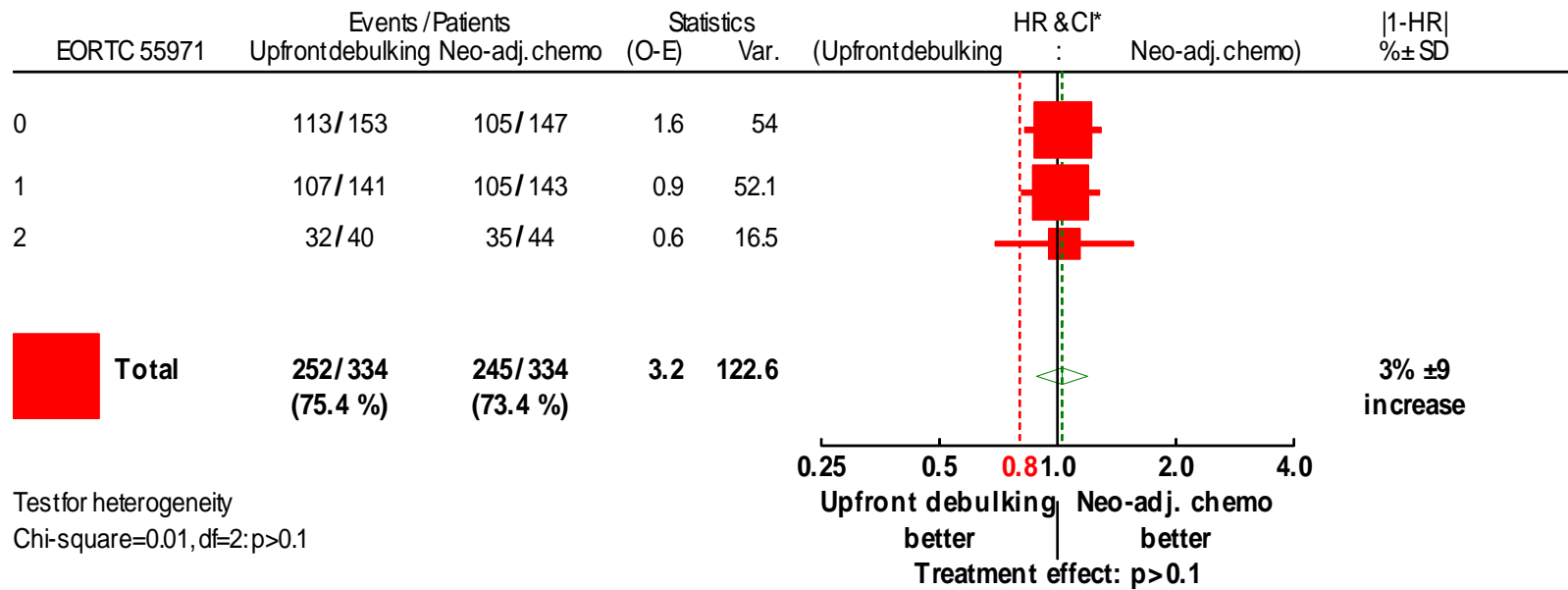
## Survival time: Figo stage



\*90% CI everywhere

# NACT + IDS versus PDS: ITT

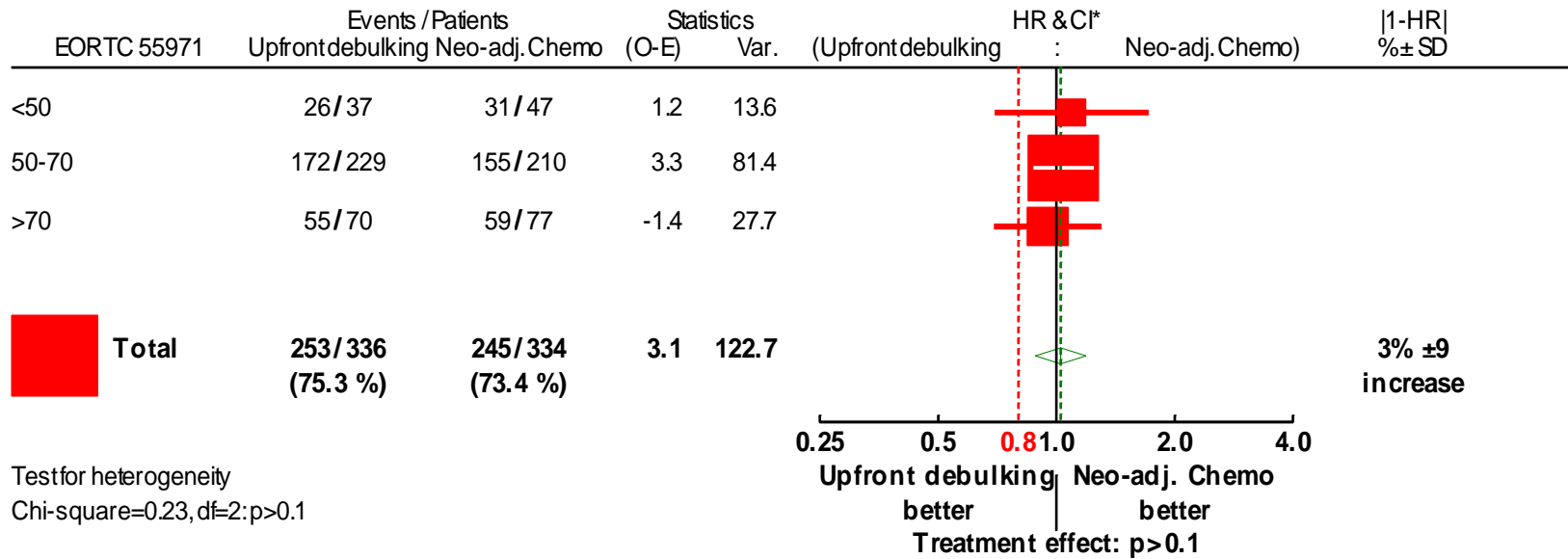
## Survival time: WHO PS



\*90%CI everywhere

# NACT + IDS versus PDS: ITT

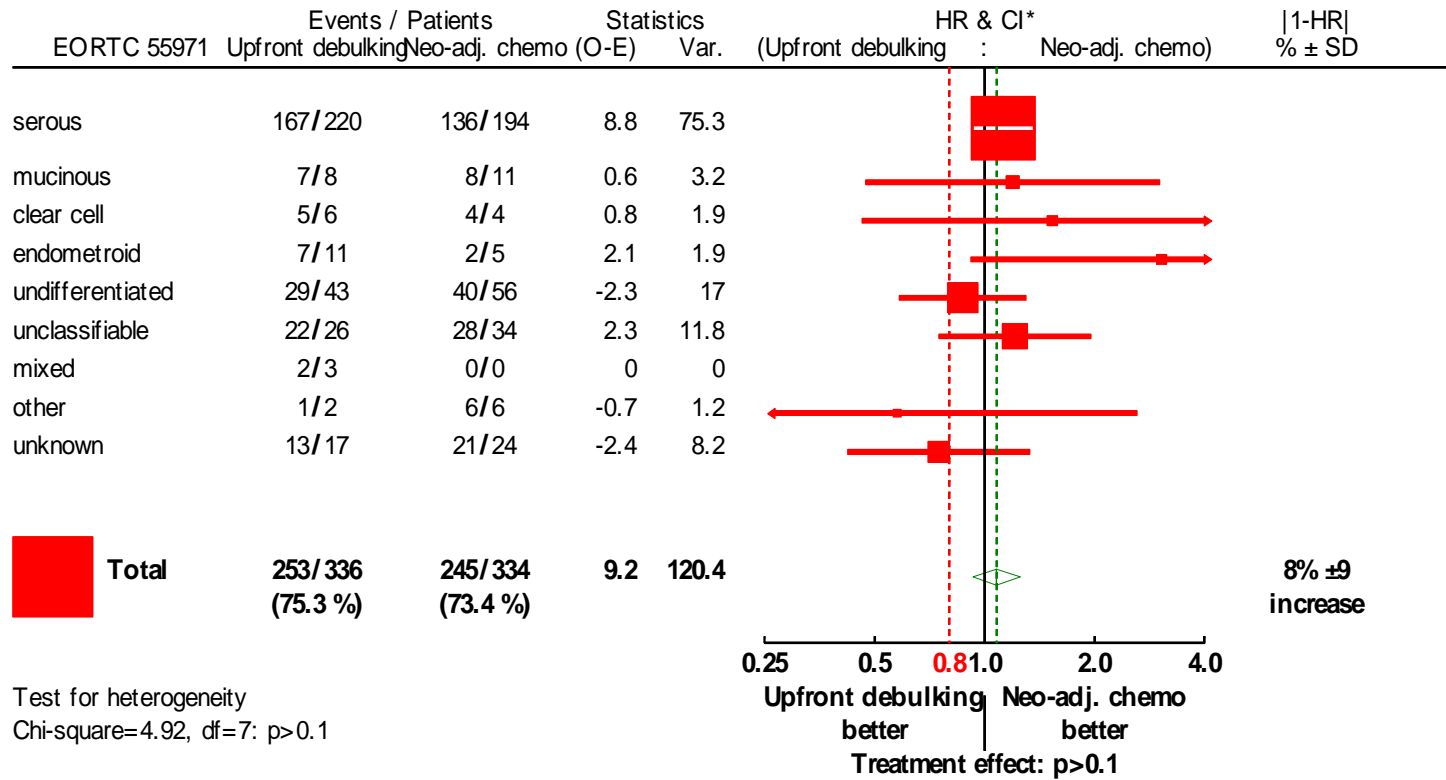
## Survival time: Age



\*90%CI everywhere

# NACT + IDS versus PDS: ITT

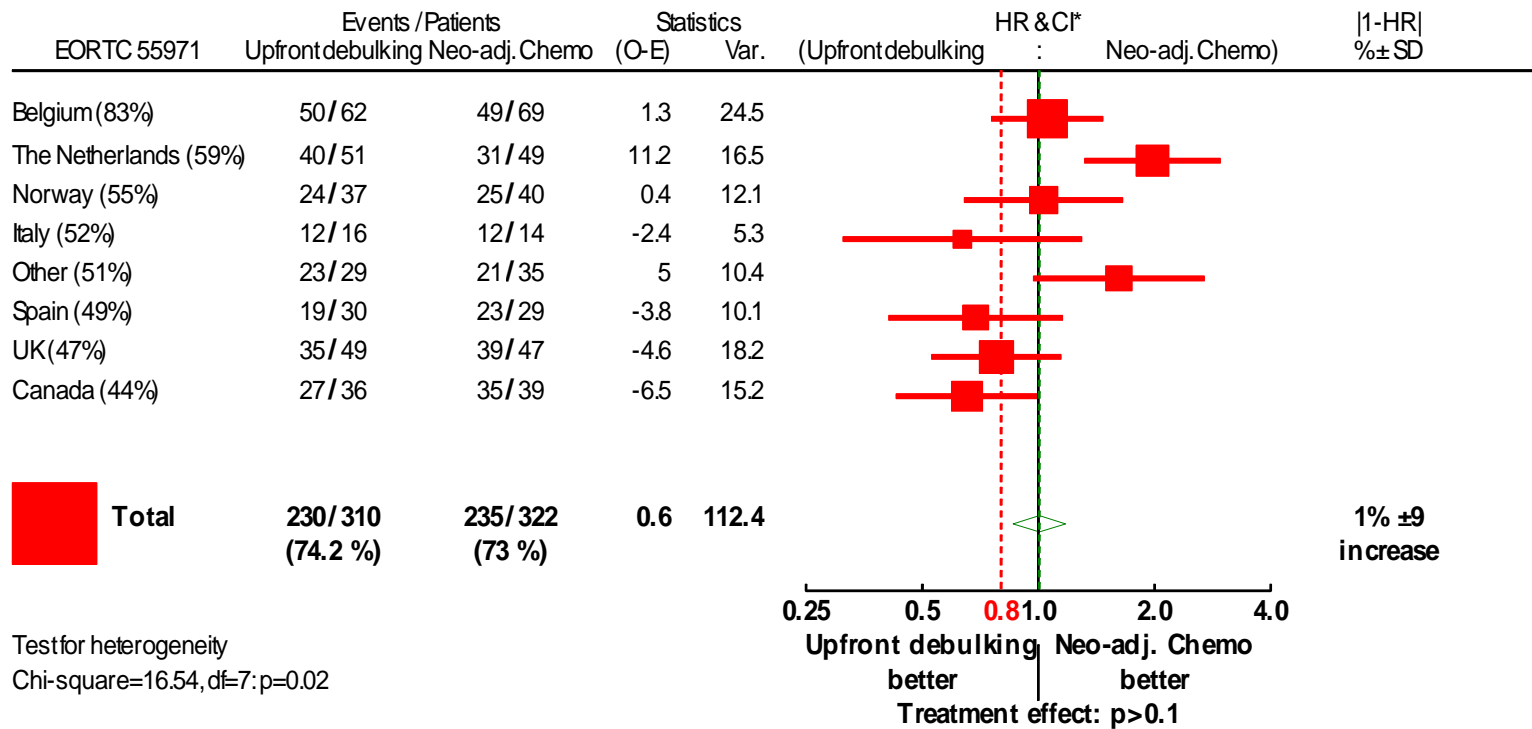
## Survival time: Histology



\*90% CI everywhere

# NACT + IDS versus PDS: PP1

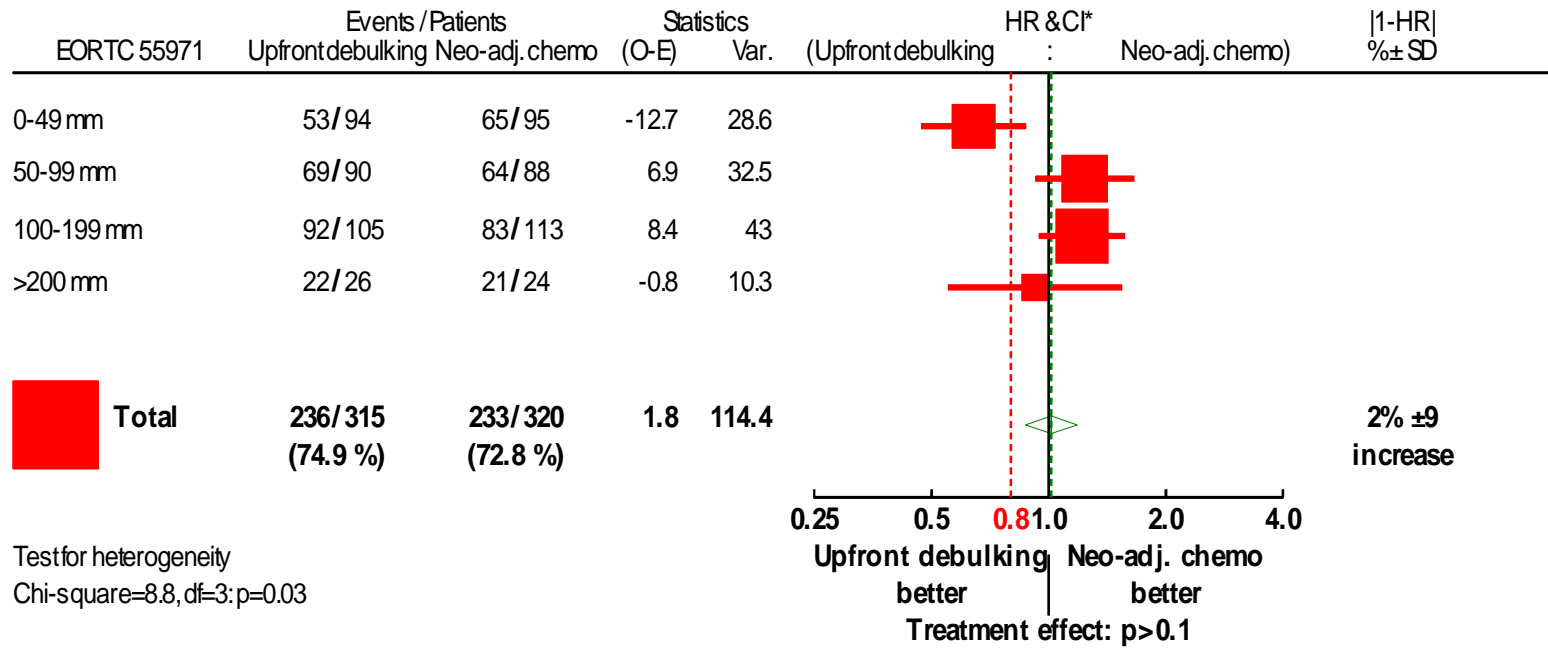
## Survival time: Country



\*90%CI everywhere

# NACT + IDS versus PDS: PP1

## OS: Largest metastatic tumor size



\*90% CI everywhere

< 5 cm : hazard ratio: 0.64; 95% confidence intervals 0.45-0.93

# Multivariate analysis for OS(PP1)

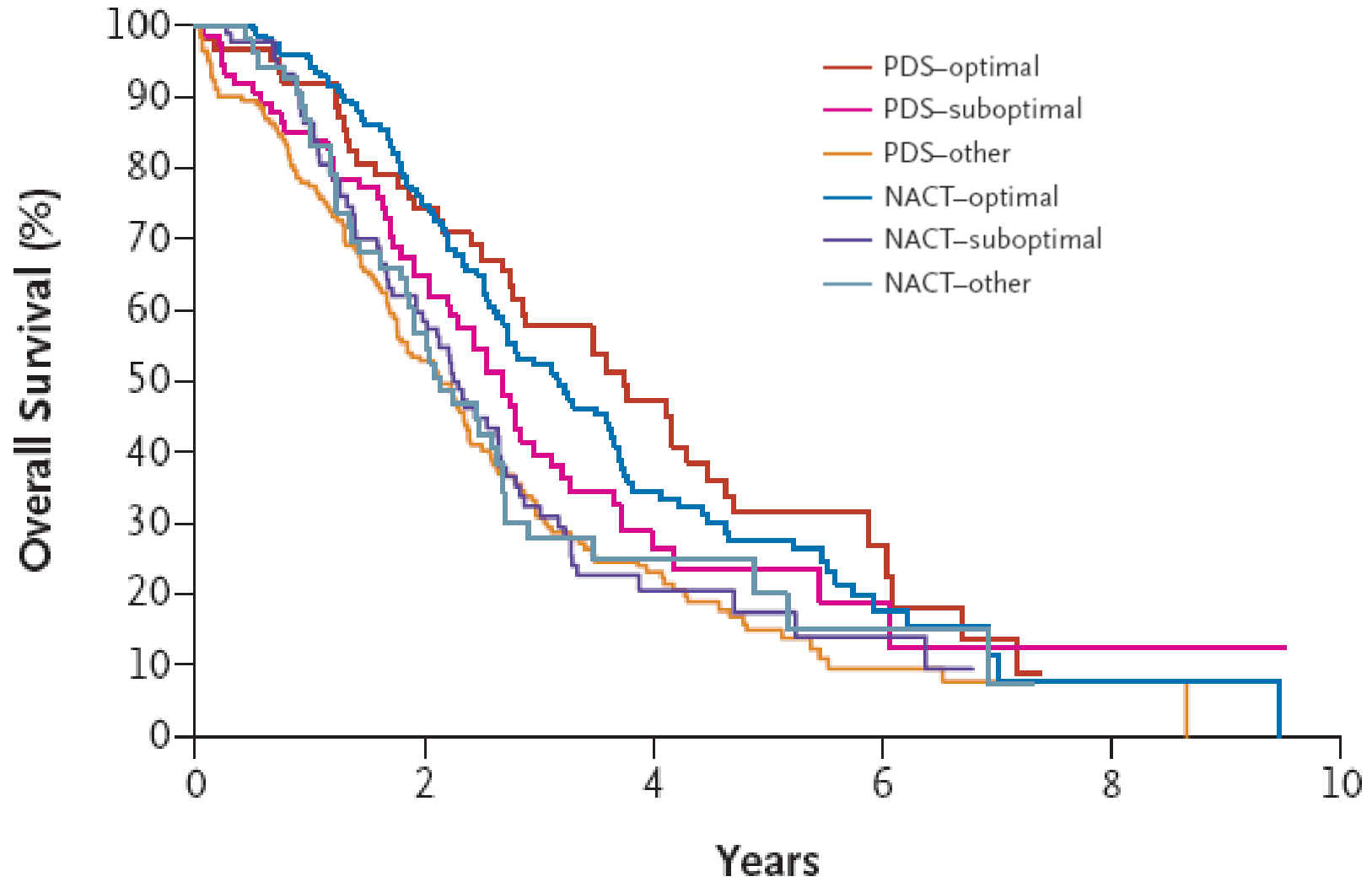
	P values
Optimal (no residual) debulking	< 0.0001
Largest tumor size at randomisation	0.0008
Figo Stage (IIIc vs IV)	0.0008
Histological type (9 categories)	0.0048
Country (7 categories)	NS
Age	NS
WHO PS	NS
Differentiation Grade	NS
Treatment arm	NS

# Neoadjuvant or primary debulking in Stage IIIc or IV ovarian carcinoma?

## EORTC study

1. The EORTC-GCG NCIC-CTG 55971 study was performed in patients with **very advanced** Stage IIIc-IV disease on CT (62% > 10cm met's at PDS).
2. In such cases neoadjuvant chemotherapy followed by interval debulking has the **same survival** as primary debulking. There are **no subgroups** with significantly better survival (except for a tendency for better survival with PDS if metastases < 5 cm).
3. The goal of (primary/interval) debulking surgery should be obtaining **NO residual tumor with an acceptable morbidity**.

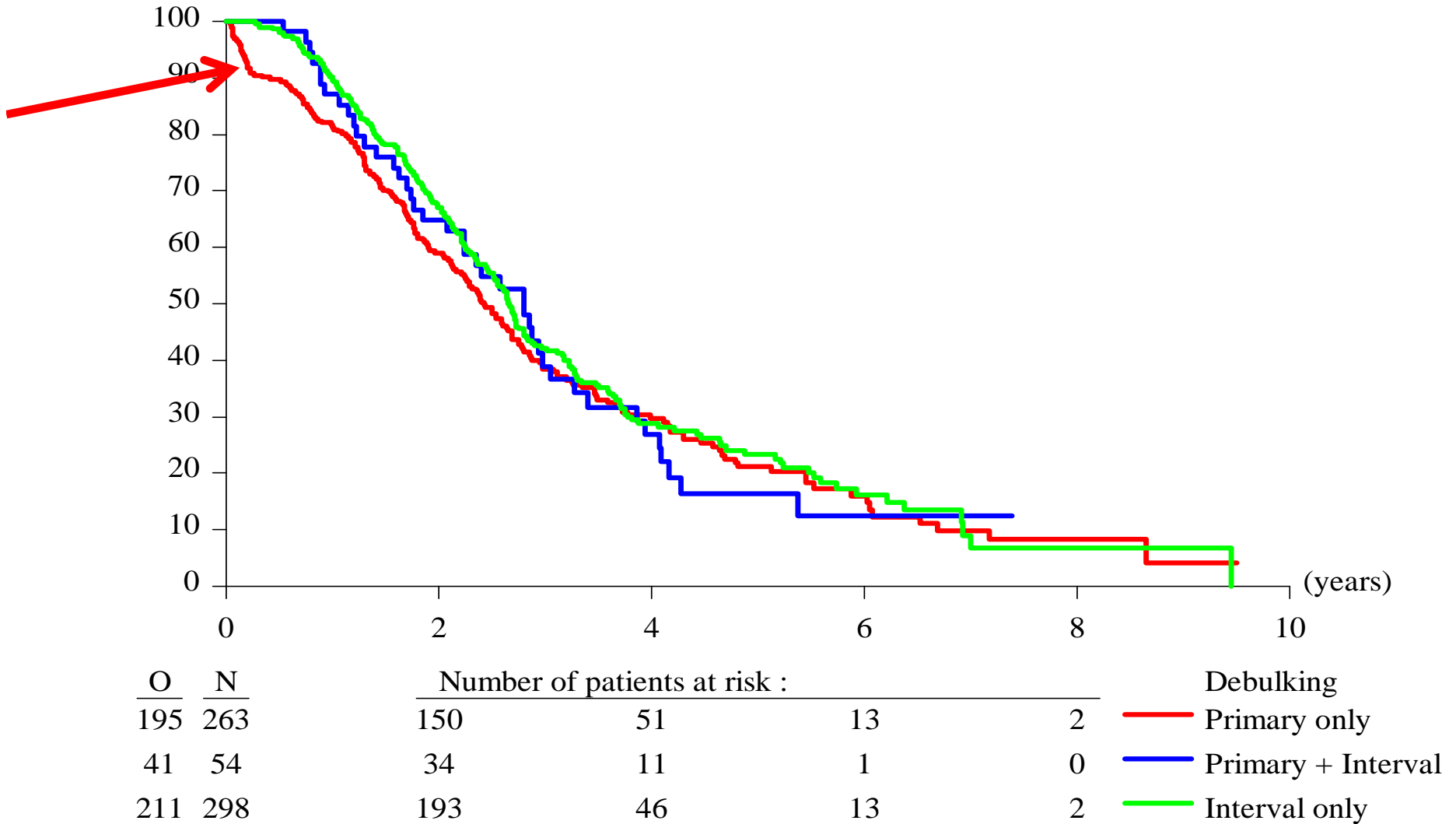
# Optimal Debulking and treatment arm: PP1



Optimal = no residual tumor  
Suboptimal = 1-10 mm residual  
Other > 10 mm

# PDS vs PDS+IDS vs IDS: ITT

## Overall survival



Ovarian carcinoma Stage II-IV  
Leuven Series 1993- 2003 (n = 288)  
Median survival 56 months

	< 1 cm	No residual tumor
Primary debulking (n = 192)	86%	78%
Interval debulking (n = 96)	86%	79%
<b>TOTAL</b>	<b>86%</b>	<b>78%</b>



## “Optimal” (< 1cm) Cytoreduction Rates: A Change in Surgical Approach

Variable	Group 1 (n=70)	Group 2 (n=70)	P-value
Extensive Procedure(s)	2 (3%)	19 (27%)	< 0.001
<b>Optimal (&lt; 1cm) Cytoreduction</b>	<b>35 (50%)</b>	<b>53 (76%)</b>	<b>&lt; 0.01</b>
Average Operative Time	174 min	<b>264 min</b>	< 0.001
Average EBL	460 ml	880 ml	< 0.001
Complication Rates	3 (4.3%)	4 (5.7%)	NS
Length of Stay	8 days	9 days	NS

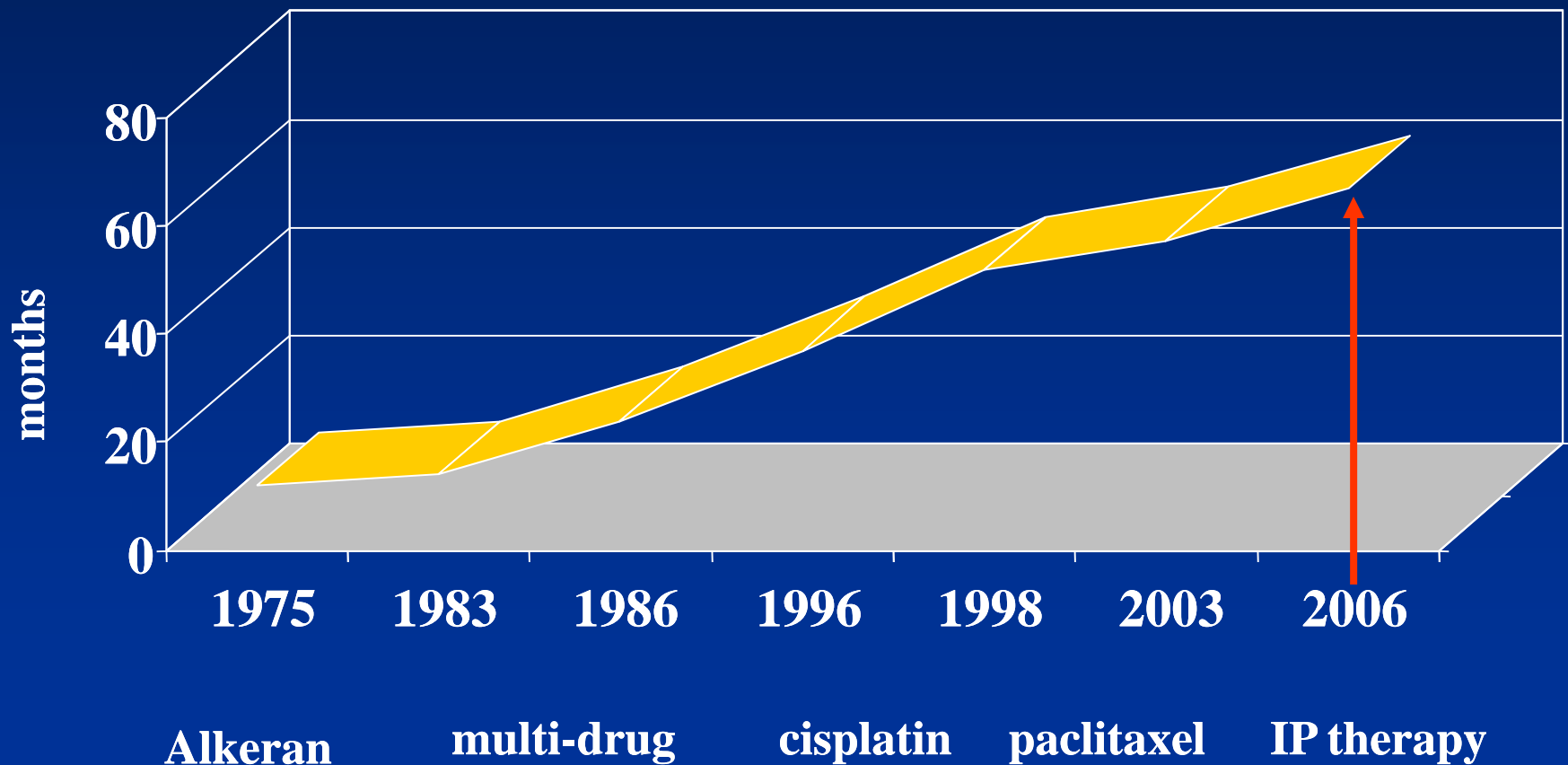
*Chi DS et al. Gynecol Oncol 2004*



# Advanced Ovarian Cancer

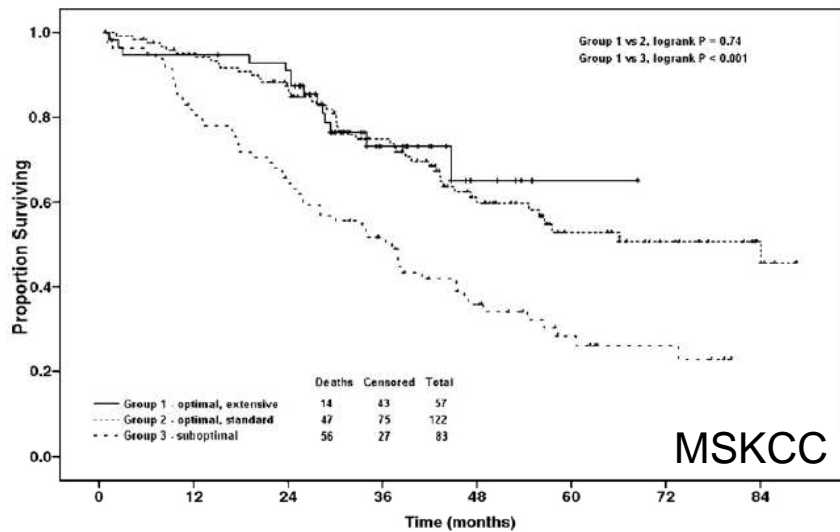
## Median Survival: 1975 - 2008

### Memorial Sloan Kettering Cancer Centre

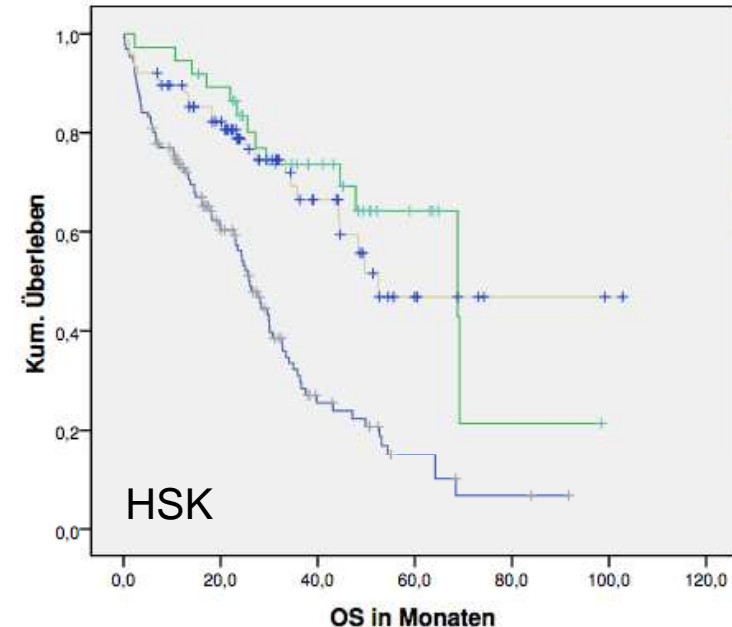


- Increase in radicality and complete resection rates showed improvement of outcome in single institution series (eg. Mayo, MSKCC, HSK Wiesbaden)

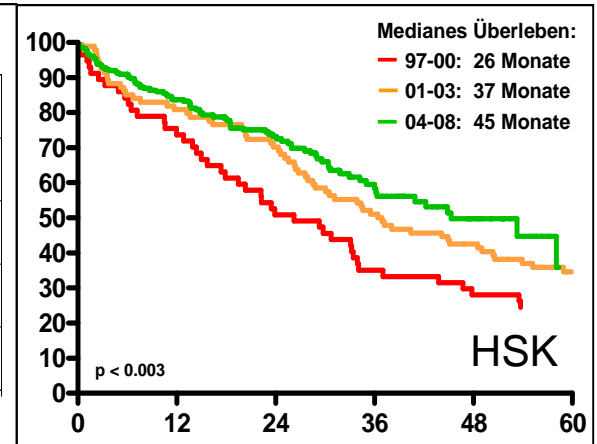
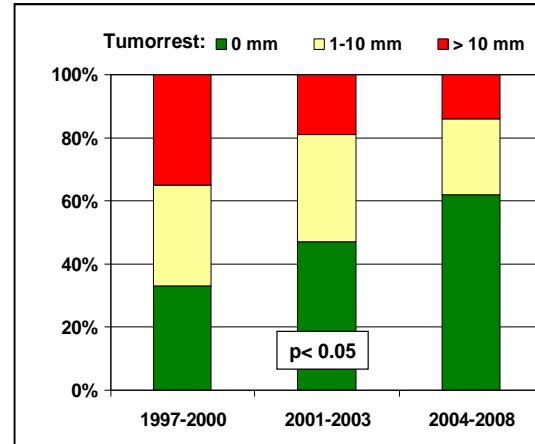
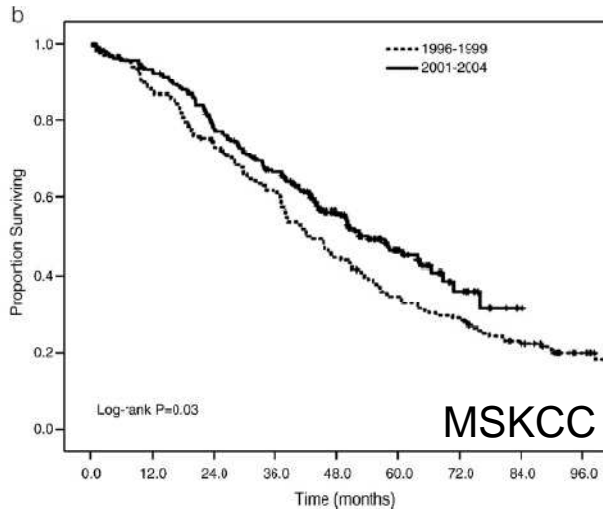
E.L. Eisenhauer et al. / *Gynecologic Oncology* 103 (2006) 1083–1090



S. Kommos et al. / *Ann Surg Oncol* 17 (2010) 279-286



Chi DS et al. *Gynecol Oncol* 114: 26-31, 2009



Debulking rate in EORTC-NCIC study should be compared with other multicenter studies, e.g.

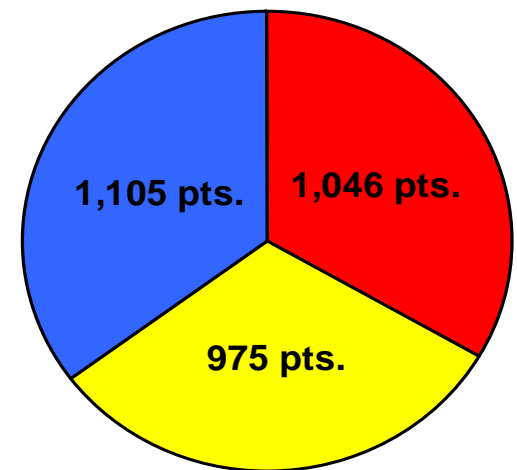
	Stage IIIc - IV		
	≤ 1 cm	No residual	1 – 10 mm
AGO (du Bois Cancer 2009)	57%	24%	33%
EORTC-NCIC	42%	19%	23%

Age [median; range]	58.9 (19.6-83.6) yrs		
PS	ECOG 0	1,190	38.1
	ECOG 1	1,592	50.9
	ECOG 2	326	10.4
Stage	FIGO IIB-IIIa	448	14.4
	FIGO IIIB	366	11.7
	FIGO IIIC	1,779	56.9
	FIGO IV	530	17.0
Grading	G1	244	7.8
	G2	998	31.9
	G3	1,702	54.4
Histology	Serous	2,296	73.4
	Endometrioid	272	8.7
	Mucinous	147	4.7

■ no post-OP residuals

■ residuals 1-10mm

■ residuals >10mm

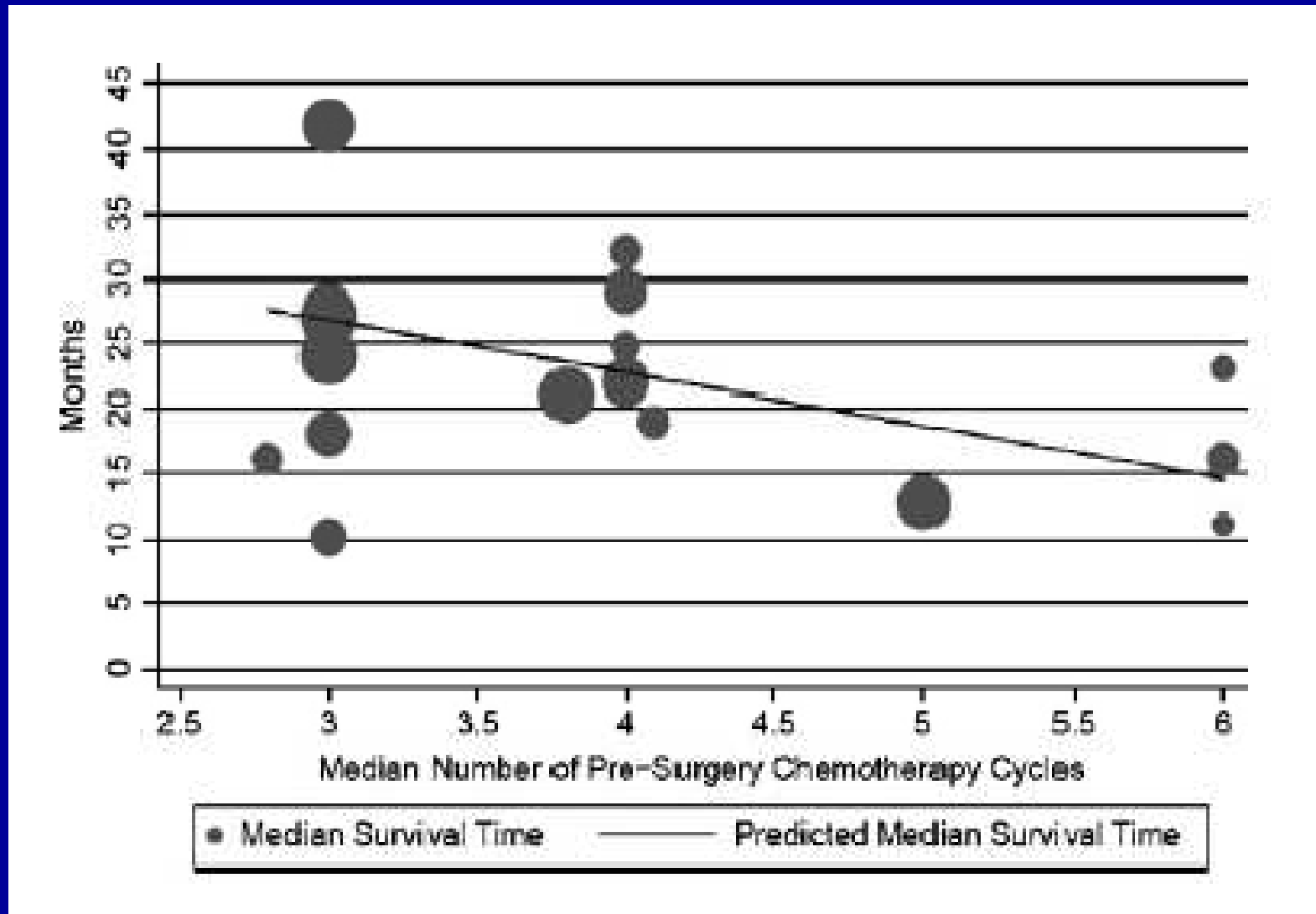


AGO primary debulking analysis compared  
with  
EORTC-NCIC 55971 PDS arm

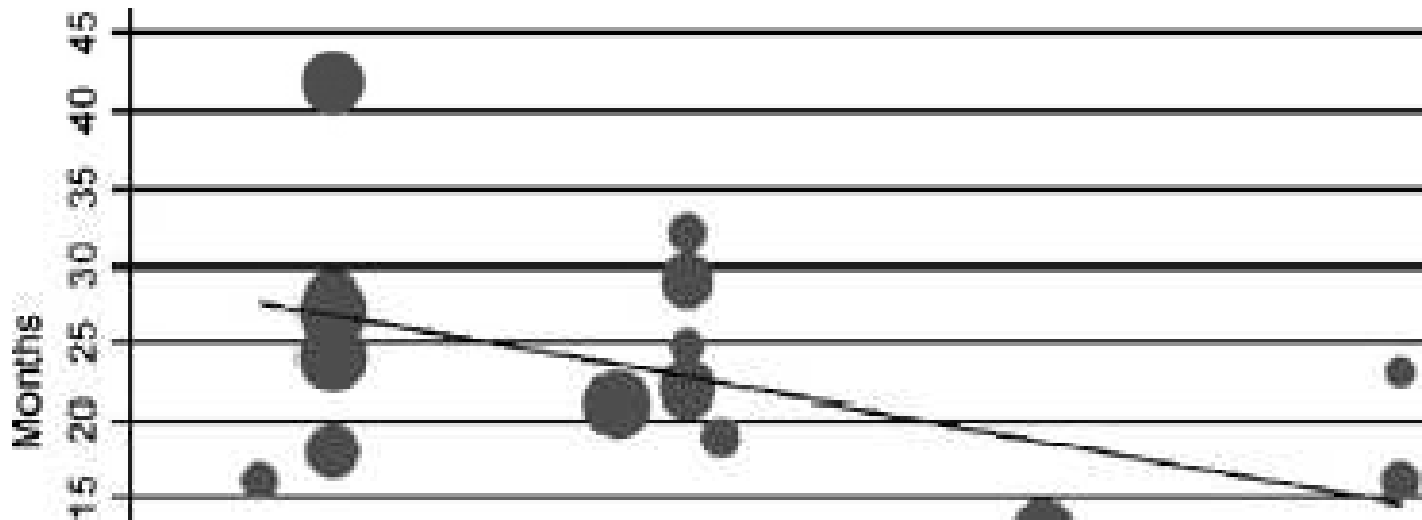
My interpretation:

The modest differences in debulking rates can be explained by the fact that in 55971 **small IIIc's are under represented** (diagnosis of IIIc-IV was already made on imaging, excluding small IIIc or IIIc with e.g. lymph node metastases as reason for being IIIc).

# Optimal timing of interval debulking surgery (*Bristow & Chi 2006*)



# Optimal timing of interval debulking surgery (*Bristow & Chi 2006*)



**Studies with late IDS had more Stage IV disease and less patients treated with paclitaxel (in addition to platin).**

Kang S, Nam BH.  
Meta-analysis of 21 studies.  
Ann Surg Oncol 2009;16:2315-20.

- Increased **optimal debulking rate** after neoadjuvant chemotherapy.
- **Same survival** as after primary debulking surgery.
- The number of chemotherapy **cycles** prior to IDS did not influence survival.

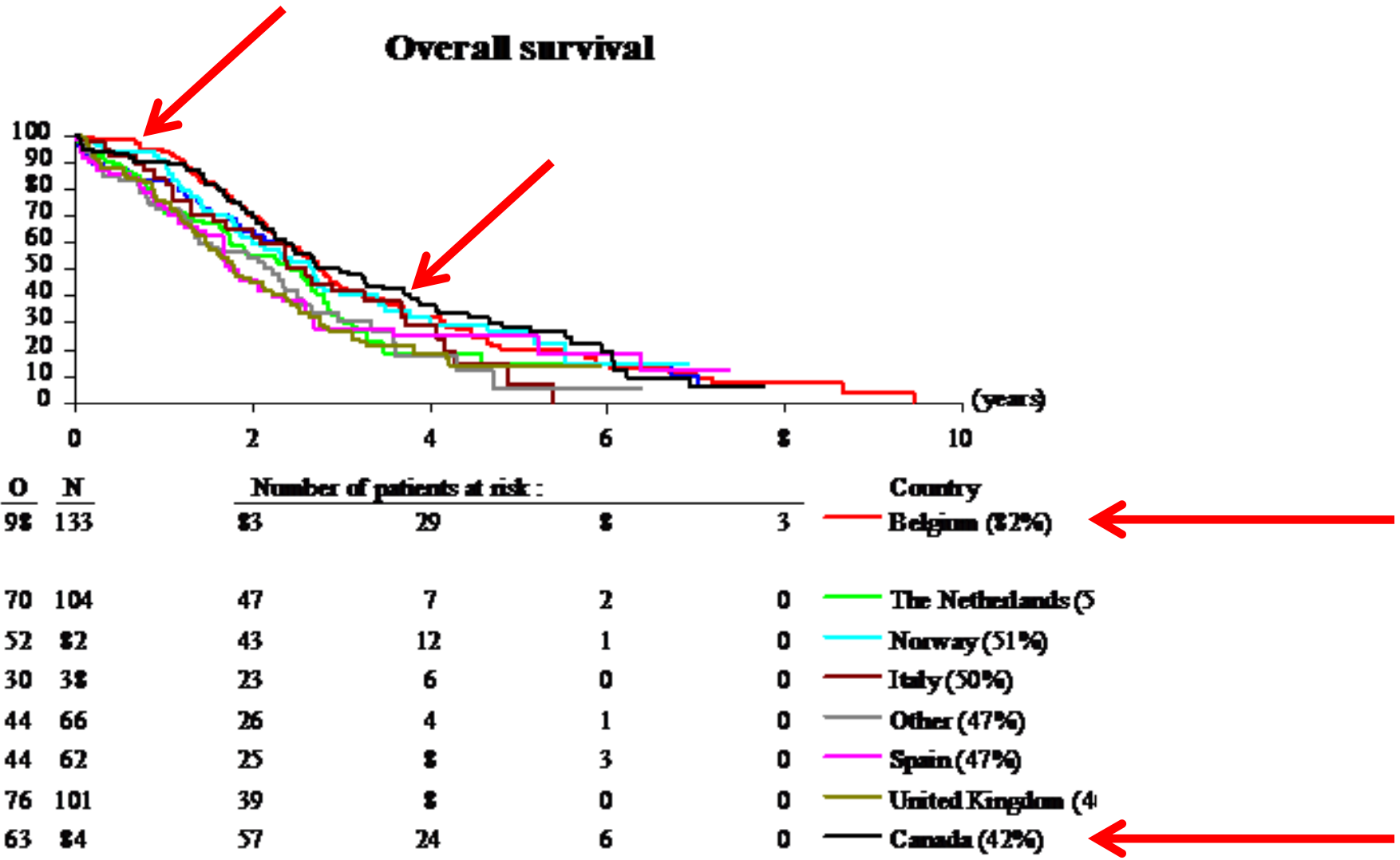
# EORTC/NCIC Study: NACT + Interval-OP vs. Primary OP

*I Vergote et al. NEJM 2010*

no residuals per country (PP analysis)	Primary-OP (n = 310)	NACT -> IDS (n = 322)	Difference (%)
Belgium	63%	87%	24
Argentina (n=48)	Excluded in NEJM		
Sweden (n=23)	Not shown in NEJM		
The Netherlands	4 %	28 %	24
Italy	6 %	39 %	33
Norway	8 %	50 %	42
Spain	10 %	42%	32
UK	10 %	43%	33
Canada	11%	41 %	30
No residual after surgery	19.4 %	51.2 %	<b>31.8%</b>
≤ 1 cm after surgery	41.6 %	80.7 %	39.1%

# Survival per country ITT

## Overall survival



# Leuven opinion on Surgery in stage IIb-IV ovarian carcinoma (1)

1. In stage **IIb – IIIb** ovarian carcinoma **primary** debulking is the standard of care.
2. Prior to surgery or neoadjuvant chemotherapy, all patients should undergo an evaluation by a **gynaecological oncologist to evaluate operability**.
3. **No residual** tumor is the only correct definition of optimal debulking in Stage IIb-IV disease.

# Leuven opinion on Surgery in stage IIb-IV ovarian carcinoma (2)

4. The EORTC-GCG NCIC-CTG 55971 study was performed in patients with **very advanced Stage IIIc-IV disease** on CT (62% > 10cm met's at PDS).
5. In such cases neoadjuvant chemotherapy followed by interval debulking **does not worsen the prognosis.**
6. Interval debulking should be performed **after 3 courses** of NACT.

# Leuven opinion on Surgery in stage IIb-IV ovarian carcinoma (3)

7. In cases considered for neoadjuvant chemotherapy, it is preferred to prove the diagnosis with **BIOPSY** (laparoscopy or tru cut).

*If **FNAC** is used, the other strict criteria as used in the EORTC-NCIC-CTG trial, should be used to exclude other primary tumors.*

# Leuven opinion on Surgery in stage IIb-IV ovarian carcinoma (4)

9. Sometimes it is technically more difficult to obtain a no residual tumor status at interval than at primary debulking surgery (manily due to fibrosis).
10. We prefer to perform primary debulking in Stage IIIc (IV) cases when an “easy debulking” is anticipated (e.g. metastases < 5 cm, limited disease on the serosa of the bowel, good performance status).

# Leuven opinion on Surgery in stage IIb-IV ovarian carcinoma (4)

10. It is important to **select** the patients for primary debulking or neoadjuvant chemotherapy with the **best possible information on histological diagnosis and operability**, and therefore we perform after imaging (including a PET-CT)

in most cases a diagnostic **laparoscopy**.

# Indications for neoadjuvant chemotherapy

Leuven Policy 2010: about 50% (?) IIc-IV

- 1. Tumors larger than 2 cm around the superior mesenteric artery or behind the porta hepatis, or*
- 2. Intrahepatic (multiple) metastases or several extraabdominal metastases (excluding resectable inguinal or supraclavicular lymph nodes) larger than 2 cm, or*
- 3. Poor general condition (e.g. > 80 years) making a “maximal surgical effort” to no residual tumor impossible, or*
- 4. Extensive serosal invasion (e.g. plaques) of the intestines necessitating bowel resections of > 1.5 m*
5. Patients that can **not be (easily) debulked to no residual** tumor (e.g. more than 1 bowel resection, expected operative time more than 4 hours, poor general condition, > 5cm met's ..).

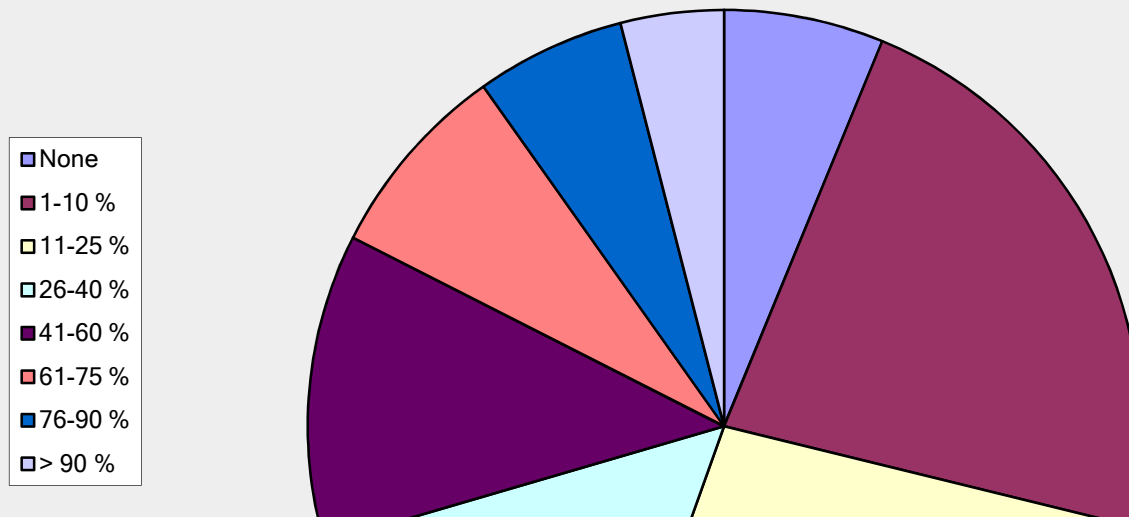
# SGO Survey (n = 339)

Dewdney SB Gynecol Oncol 2010

1. 60 % of the respondents use neoadjuvant chemotherapy in less than 10% of their patients with advanced stage ovarian cancer
2. 82% did not consider available evidence sufficient to justify neoadjuvant chemotherapy followed by interval debulking.

# ESGO survey (n = 315)

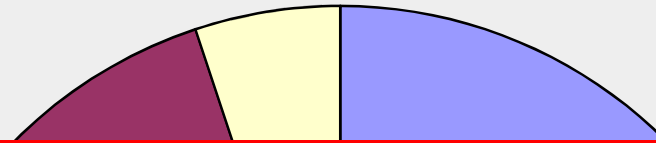
Percentage of patients with ovarian carcinoma stage IIIc or IV receiving neoadjuvant chemotherapy



**Only 26% uses neoadjuvant chemotherapy in less than 10 % of stage IIIc and IV ovarian cancer!**

## ESGO survey (n = 315)

Is there is sufficient evidence to use neoadjuvant chemotherapy followed by interval debulking as treatment for patients with stage IIIc/IV ovarian cancer?



**There is no debate  
needed!**

**The Europeans show once more the  
way to a balanced and correct  
treatment of advanced ovarian  
cancer based on  
level I evidence!**

know