

# Ovarian Cancer

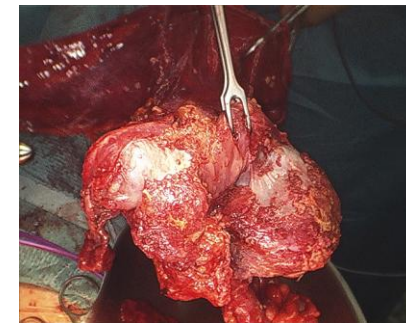


## Role of Neoadjuvant chemotherapy in advanced ovarian cancer



PD Dr. O. Camara

Bad Langensalza, Germany



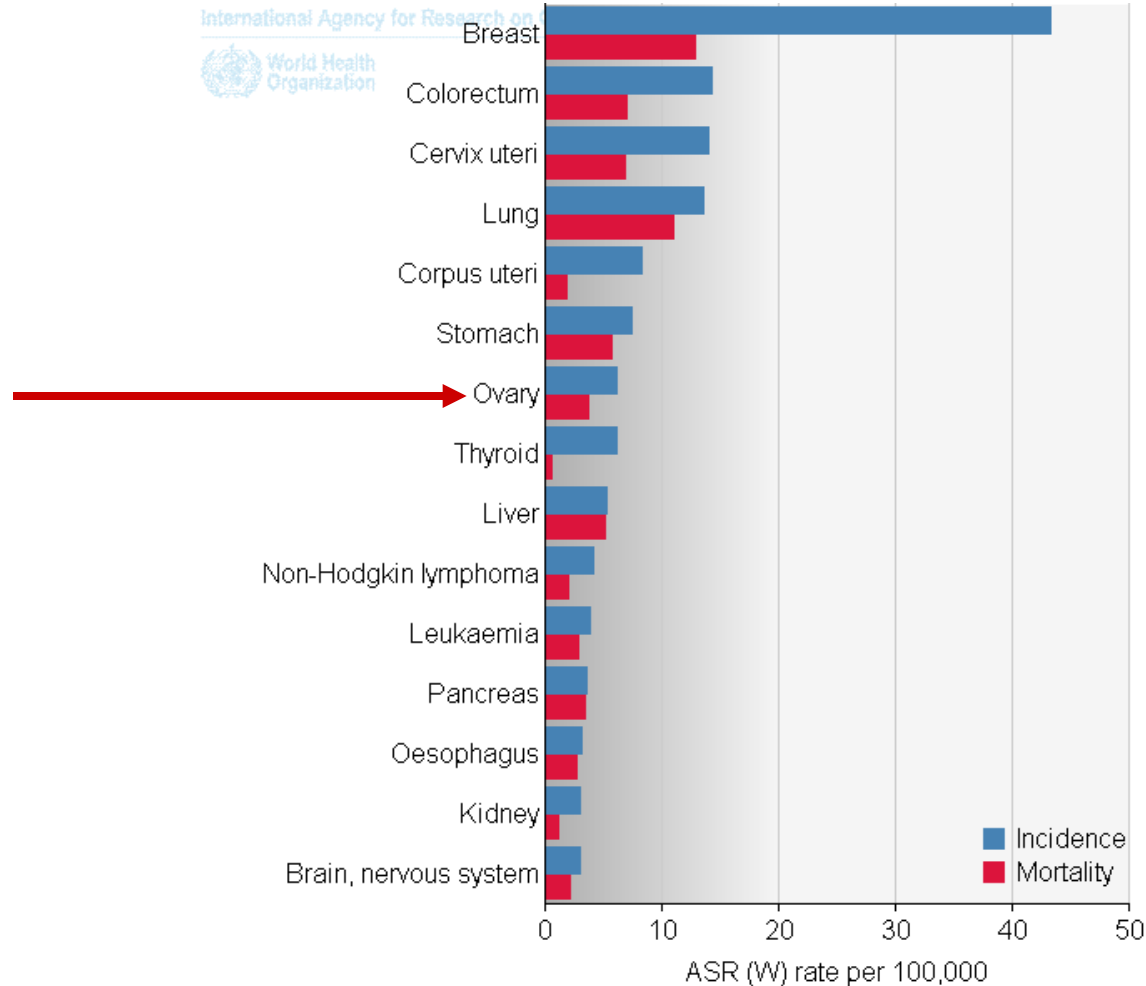
# Disclosures

No conflict of interest

# Structure

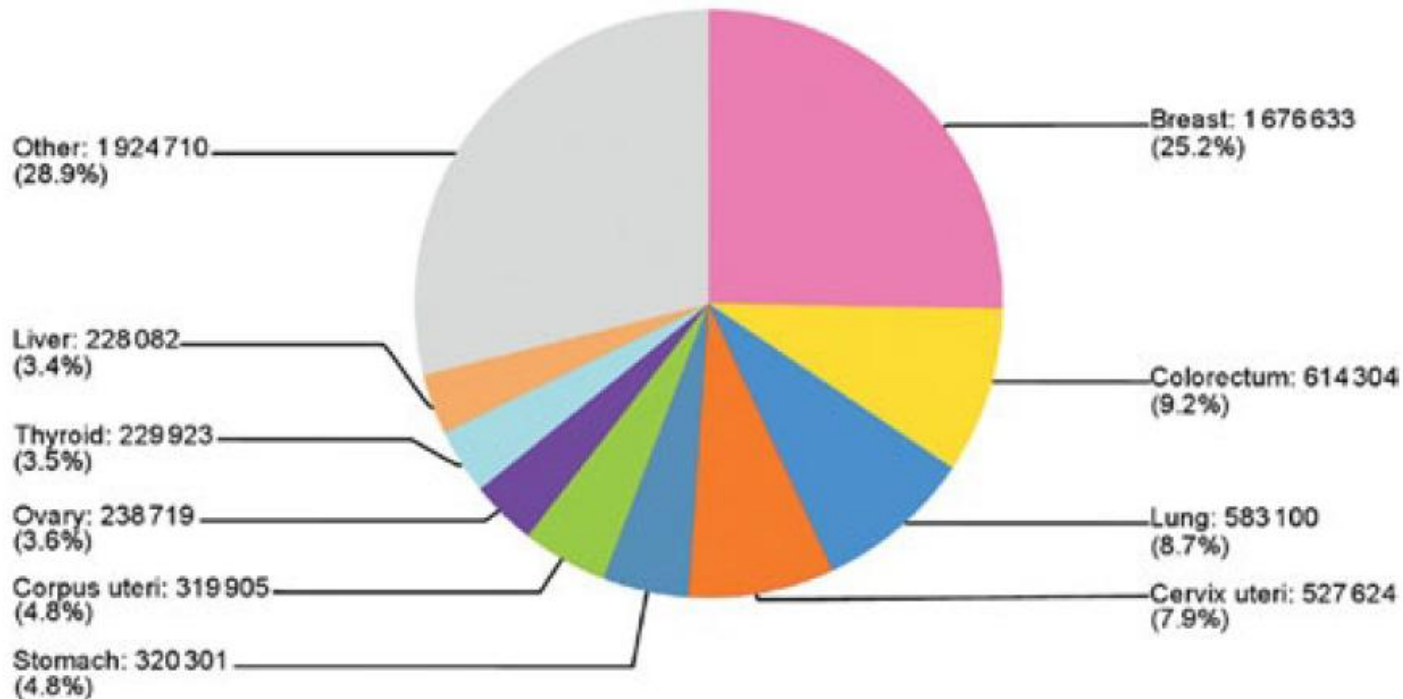
- ▶ Introduction
- ▶ Factors influencing Survival in advanced ovarian cancer
- ▶ Phase 3 trials on neoadjuvans in advanced ovarian cancer
- ▶ Discussion of the data
- ▶ Role of neoadjuvant chemotherapy in this setting

# Cancer Incidence and Mortality Worldwide



# Introduction

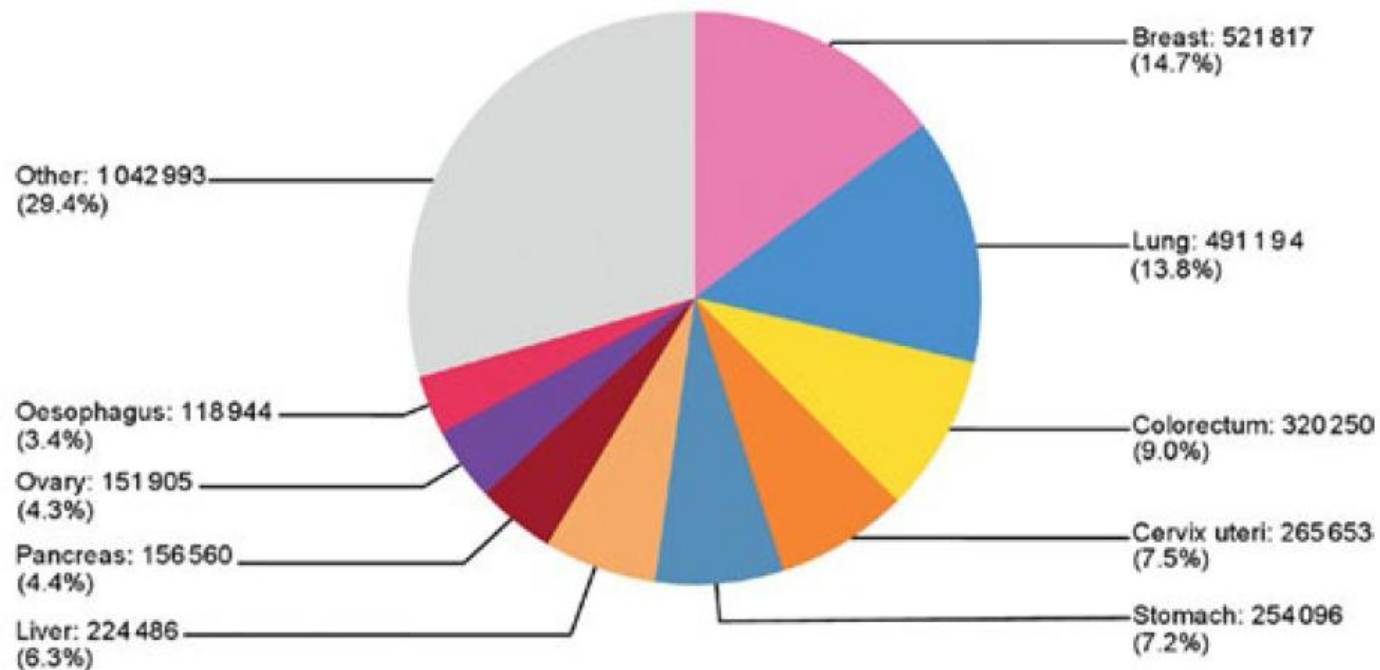
**Women**  
Estimated number of cancer cases, all ages (total:6663001)



# Introduction

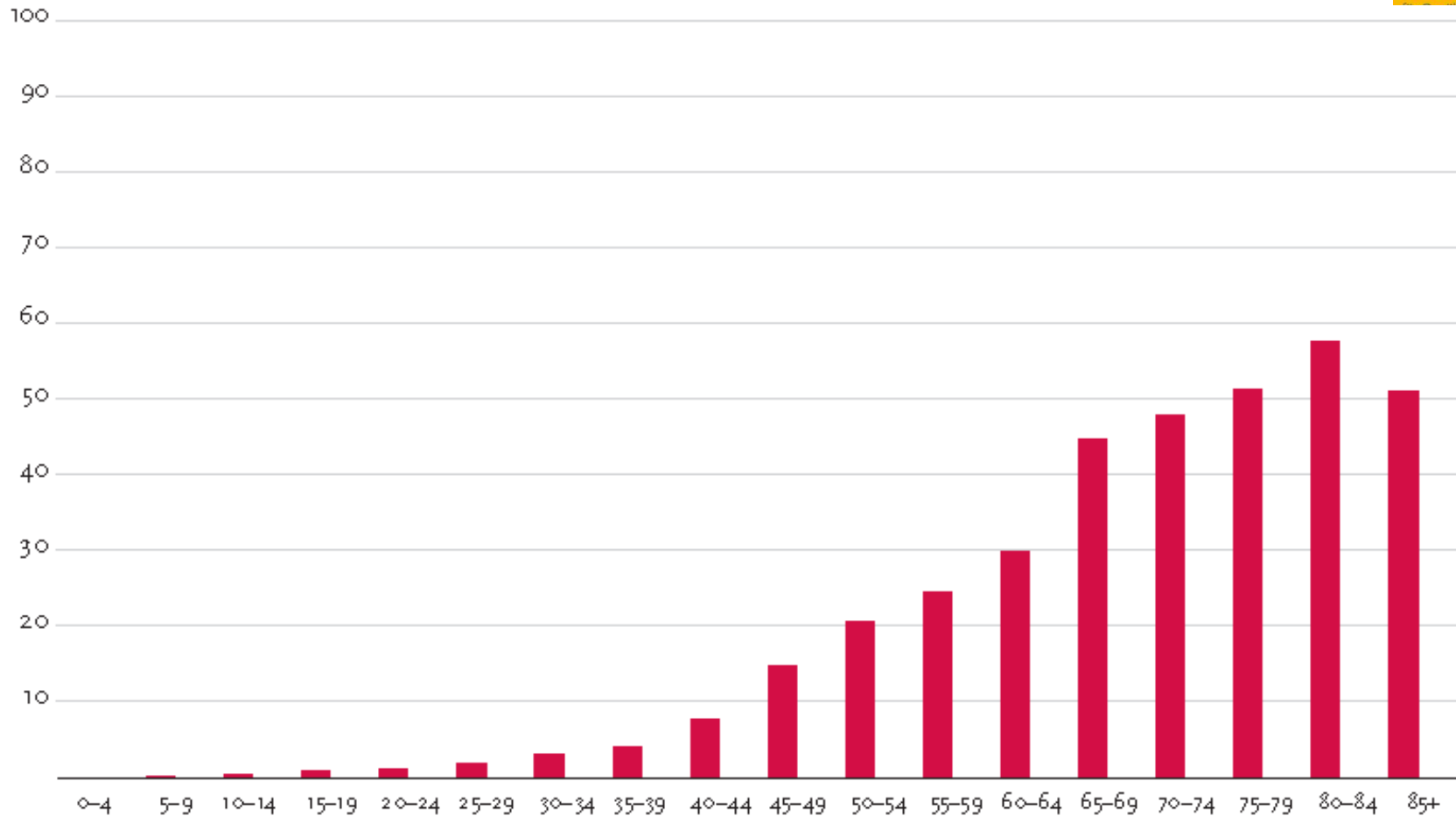
## Women

Estimated number of cancer deaths, all ages (total: 3 547 898)

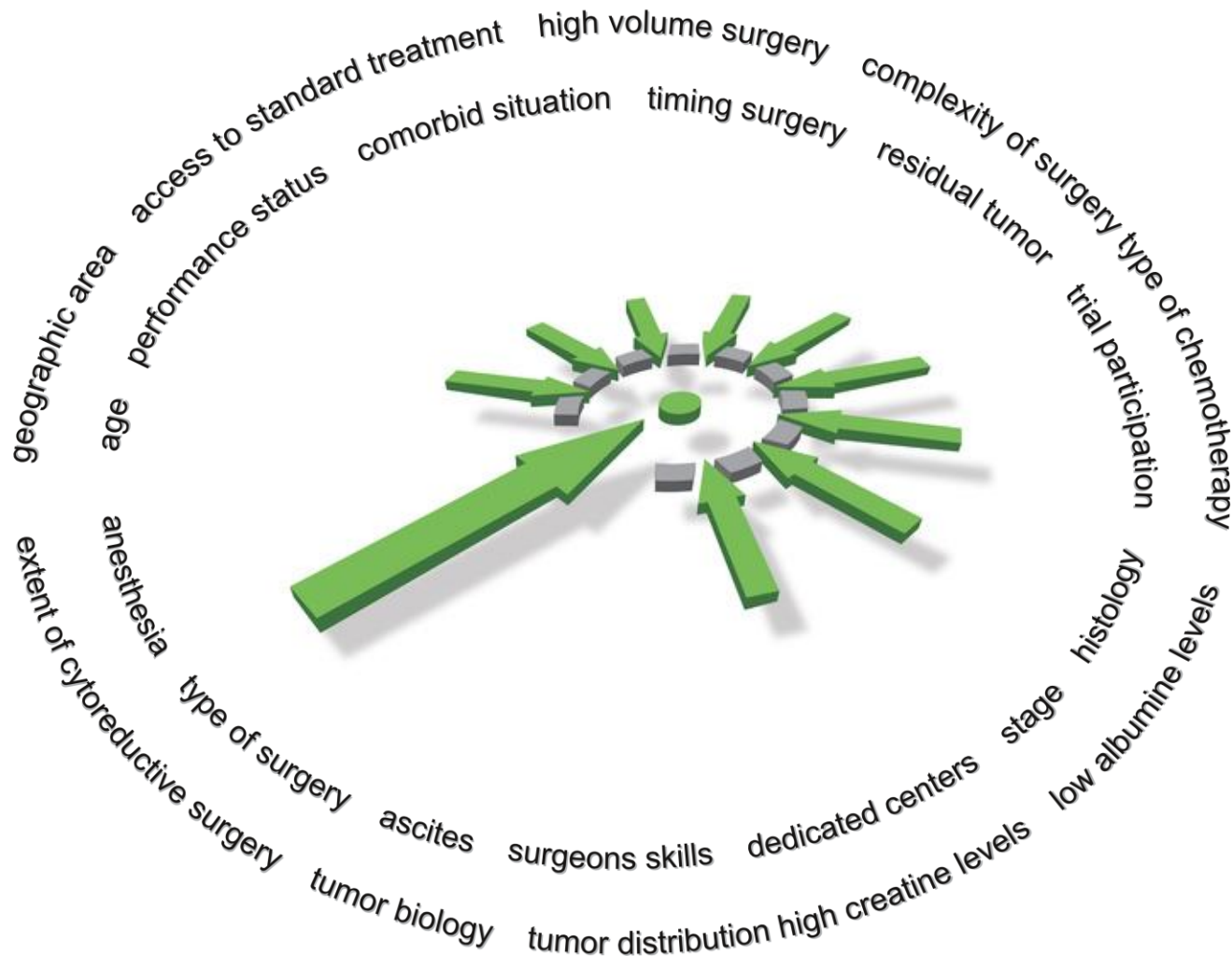


# Introduction

## Age distribution



# Factors influencing Survival





# Platinum-based neoadjuvant chemotherapy

Table 1  
Study characteristics

Author [reference]	Year of publication	n	Median age	Percent Stage IV	Residual tumor criteria	Number chemotherapy cycles	Percent taxane use	Percent maximum interval cytoreduction	Median overall survival (months)
Donadio [12] <sup>a</sup>	1989	24	54	29.2	>2 cm	4.1	0.0	53.3	18.9
Tummarello [13] <sup>b</sup>	1990	24	57	70.8	>2 cm	6	0.0	41.7	16
Jacob [14] <sup>c</sup>	1991	22	58.5	18.2	>2 cm	2.8	0.0	77.3	16
Lim [15] <sup>a</sup>	1993	30	56	33.3	>2 cm	3	0.0	30.0	10.2
Vergote [16] <sup>b</sup>	1998	75	64	41.3	>1.5 cm	3	20.0	36.0	24
Schwartz [17] <sup>b</sup>	1999	59	67	64.4	<1 cm	5	8.5	67.8	12.8
Lu [18] <sup>b</sup>	2001	45	58.5	53.3	>2 cm	3	68.9	75.6	18
Ansquer [19] <sup>b</sup>	2001	54	63	14.8	>2 cm	4	57.4	72.2	22
Kuhn [20] <sup>d</sup>	2001	31	61	0.0	>2 cm	3	100.0	83.9	42
Vrscaj [21] <sup>e</sup>	2002	20	65	15.0	>1 cm	4	0.0	60.0	24.7
Ushijima [22] <sup>b</sup>	2002	65	60.3	21.5	>1 cm	3.8	21.5	41.5	21
Shibata [23] <sup>e</sup>	2003	13	53.6	23.1	>2 cm	6	0.0	100.0	23
Shibata [23] <sup>e</sup>	2003	10	60	20.0	>2 cm	6	0.0	0.0	11.2
Chan [24] <sup>a</sup>	2003	17	57	76.5	>2 cm	3	100.0	58.8	22.9
Fanfani [25] <sup>b</sup>	2003	73	60	0.0	>2 cm	3	54.8	71.2	27
Morice [26] <sup>b</sup>	2003	48	57	17.2	>2 cm	3	100.0	100.0	28
Morice [27] <sup>e</sup>	2003	34	59	11.8	>2 cm	3	94.0	94.1	26
Mazzeo [28] <sup>b</sup>	2003	45	68	20.0	>2 cm	4	77.7	68.9	29
Loizzi [29] <sup>e</sup>	2005	25	64	23.3	>1 cm	4	60.0	76.0	32
Avril [30] <sup>a</sup>	2005	33	60	30.3	>1 cm	3	69.7	66.7	26.8
Hegazy [31] <sup>d</sup>	2005	27	58.7	59.3	>1 cm	3	0.0	48.1	25
Le [32] <sup>b</sup>	2005	61	63	3.3	>2 cm	3	100.0	80.0	41.7

<sup>a</sup> Phase I study.

<sup>b</sup> Retrospective analysis.

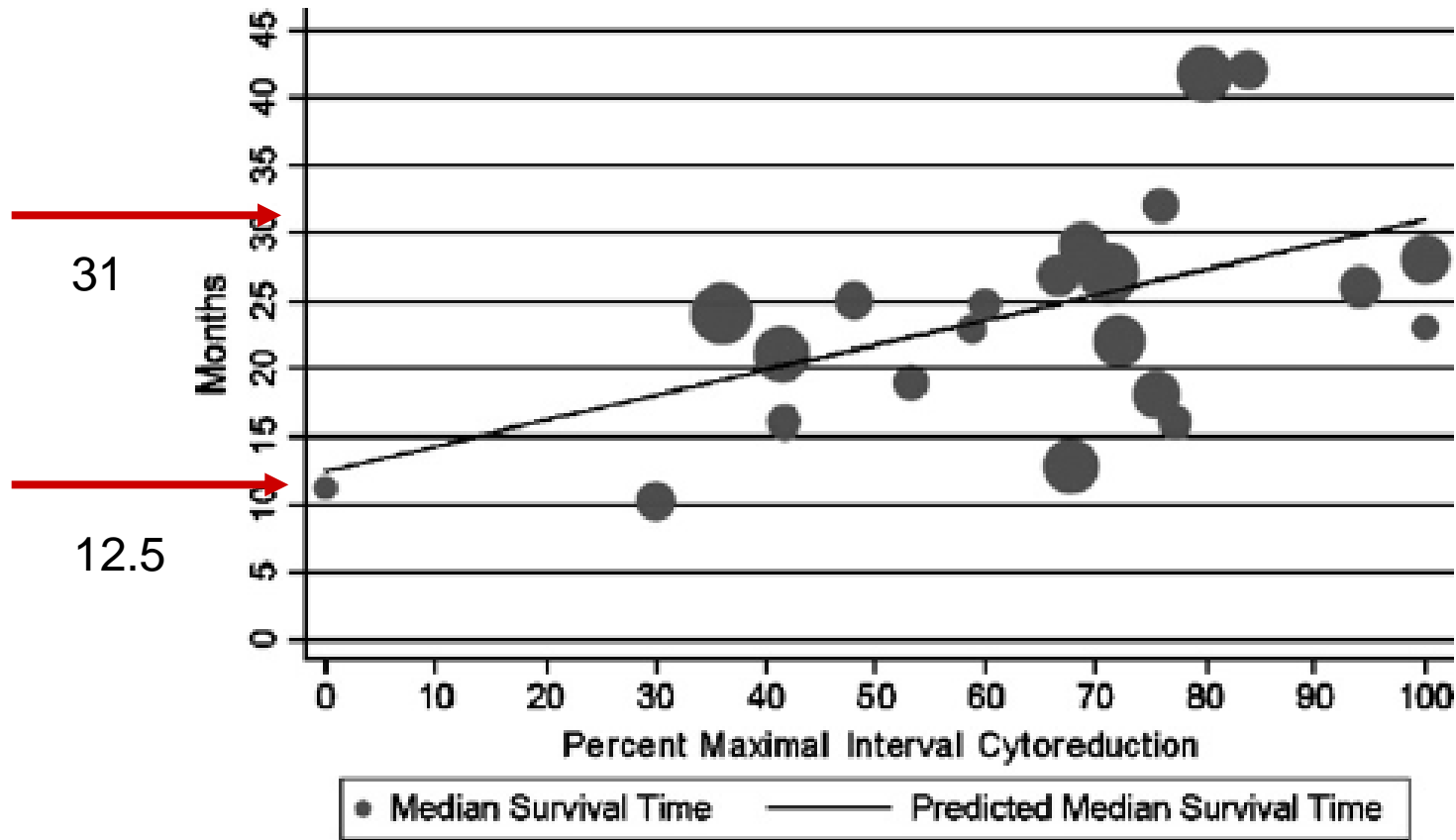
<sup>c</sup> Retrospective matched control study.

<sup>d</sup> Phase II study.

<sup>e</sup> Retrospective case-control study.

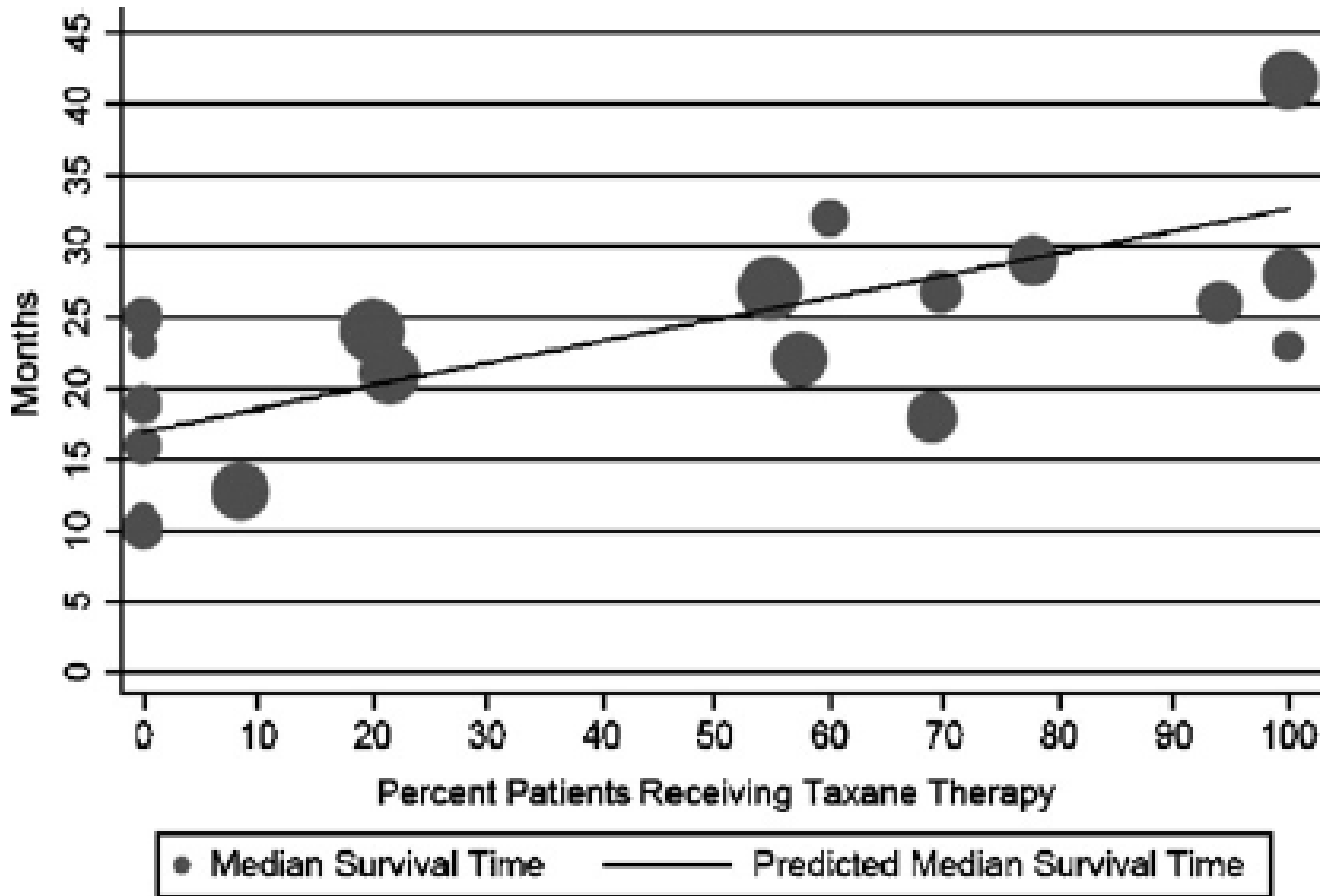
# Platinum-based neoadjuvant chemotherapy

## *Maximal intervall cytoreductive surgery*



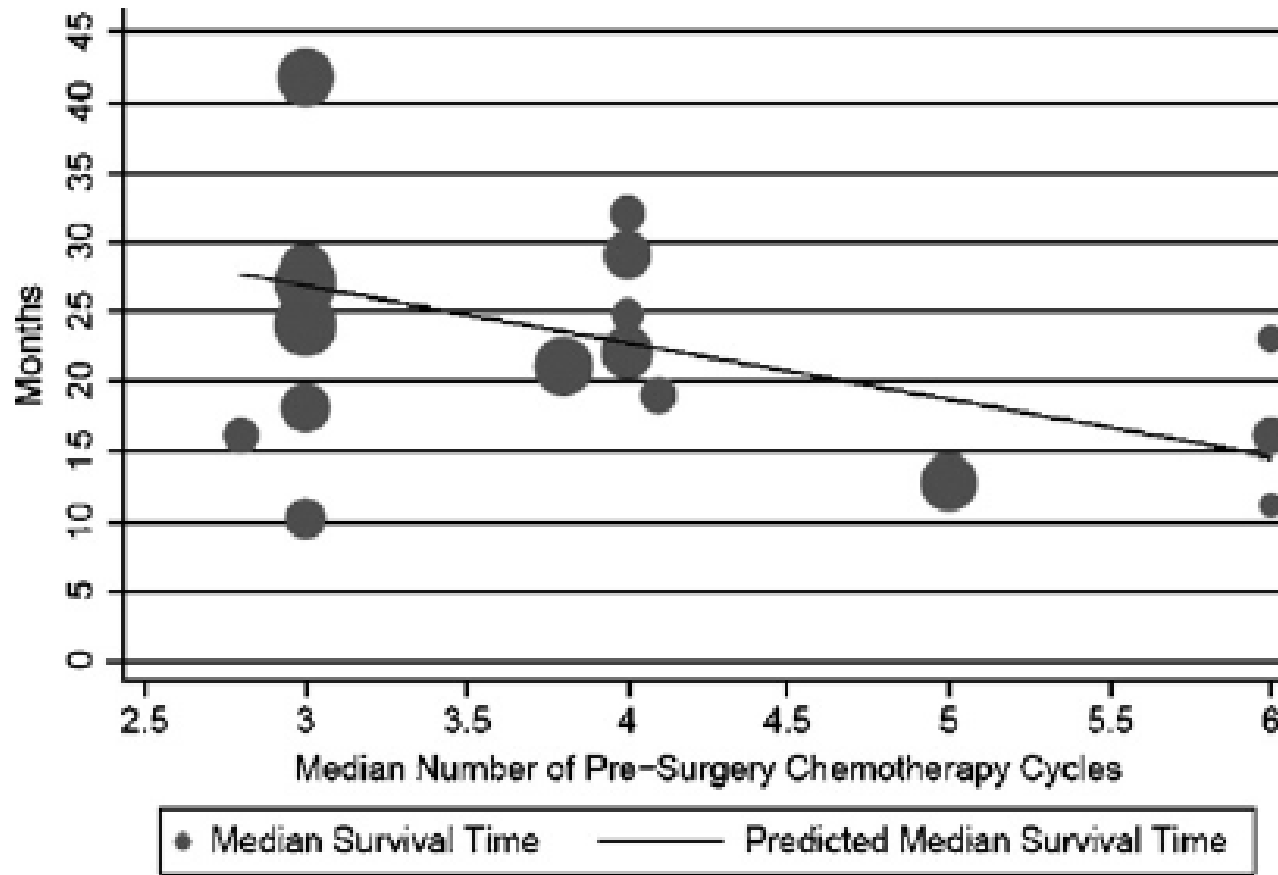
# Platinum-based neoadjuvant chemotherapy

*Number of patients receiving a taxane*



# Platinum-based neoadjuvant chemotherapy

*Number of pre-operative chemotherapy cycles*



# ADVANTAGES of neoadjuvant chemotherapy

- reduce the extent of disease
- improve patient performance status
- increase the rate of optimal residual tumor
- less extensive surgery
- reduce blood loss
- less morbidity
- shortened hospital stay
- improved quality of life
- selection platinum resistant disease
- no worse prognosis for patients

# Ovarian cancer neoadjuvant chemotherapy

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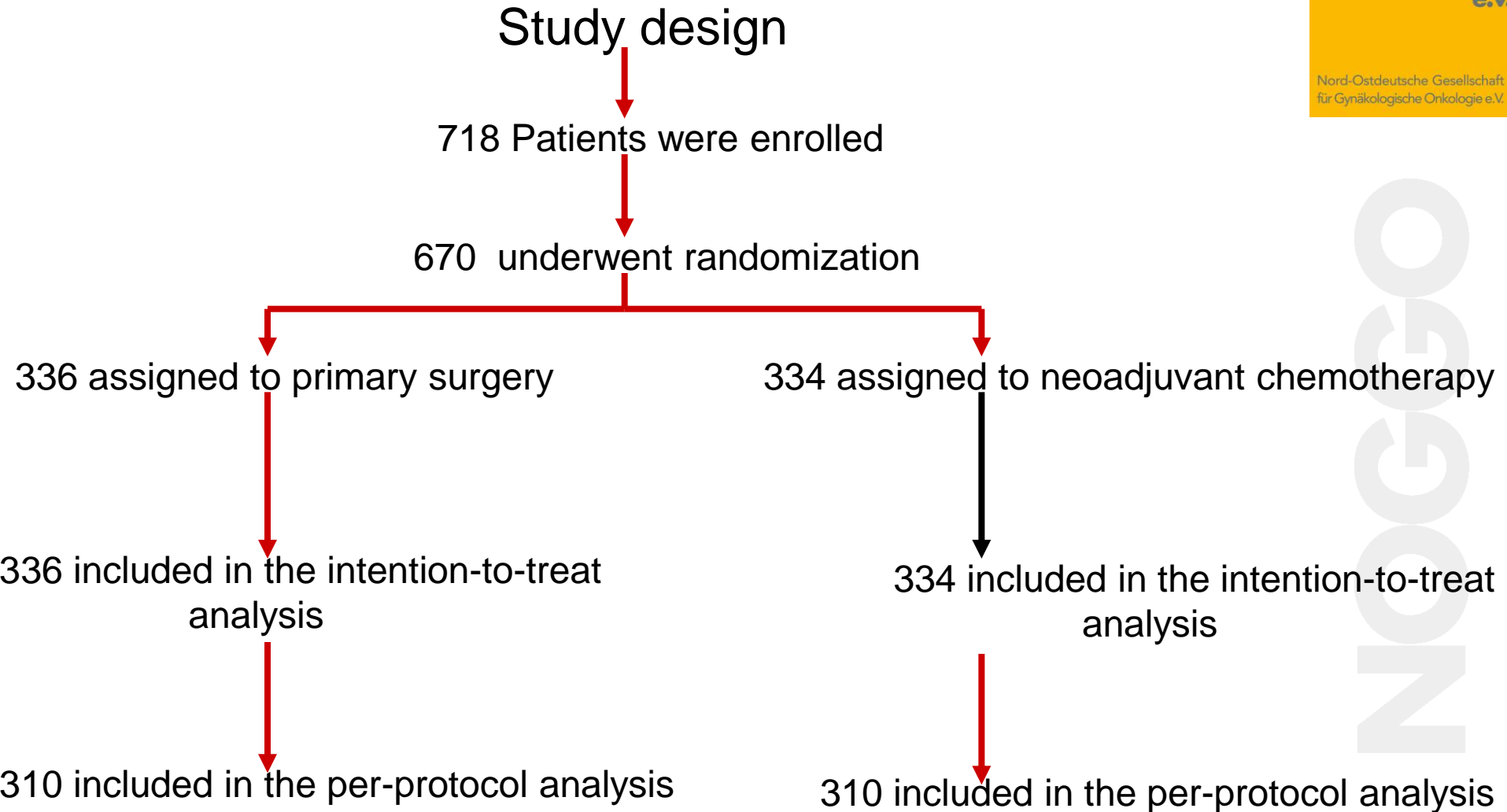


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# Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer

Ignace Vergote, M.D., Ph.D., Claes G. Tropé, M.D., Ph.D.,  
Frédéric Amant, M.D., Ph.D., Gunnar B. Kristensen, M.D., Ph.D.,  
Tom Ehlen, M.D., Nick Johnson, M.D., René H.M. Verheijen, M.D., Ph.D.,  
Maria E.L. van der Burg, M.D., Ph.D., Angel J. Lacave, M.D.,  
Pierluigi Benedetti Panici, M.D., Ph.D., Gemma G. Kenter, M.D., Ph.D.,  
Antonio Casado, M.D., Cesar Mendiola, M.D., Ph.D., Corneel Coens, M.Sc.,  
Leen Verleye, M.D., Gavin C.E. Stuart, M.D., Sergio Pecorelli, M.D., Ph.D.,  
and Nick S. Reed, M.D., for the European Organization for Research and  
Treatment of Cancer–Gynaecological Cancer Group and the NCIC Clinical Trials  
Group\* — a Gynecologic Cancer Intergroup Collaboration

# EORTC 55971

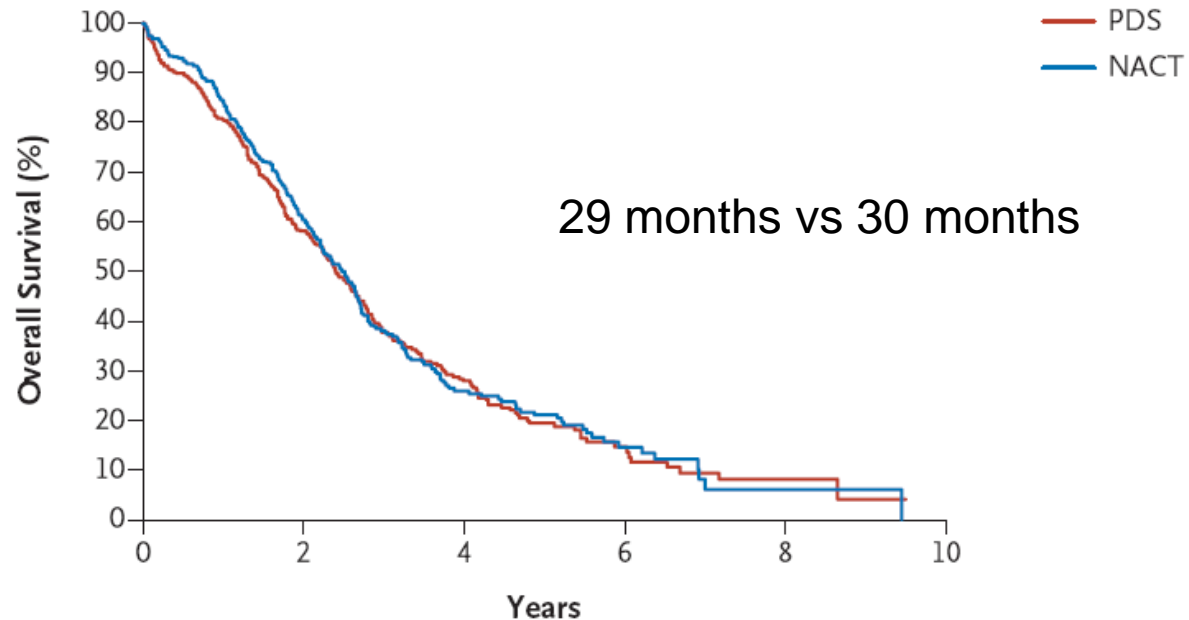




# EORTC 55971

## Survival

### A Intention-to-Treat Analysis

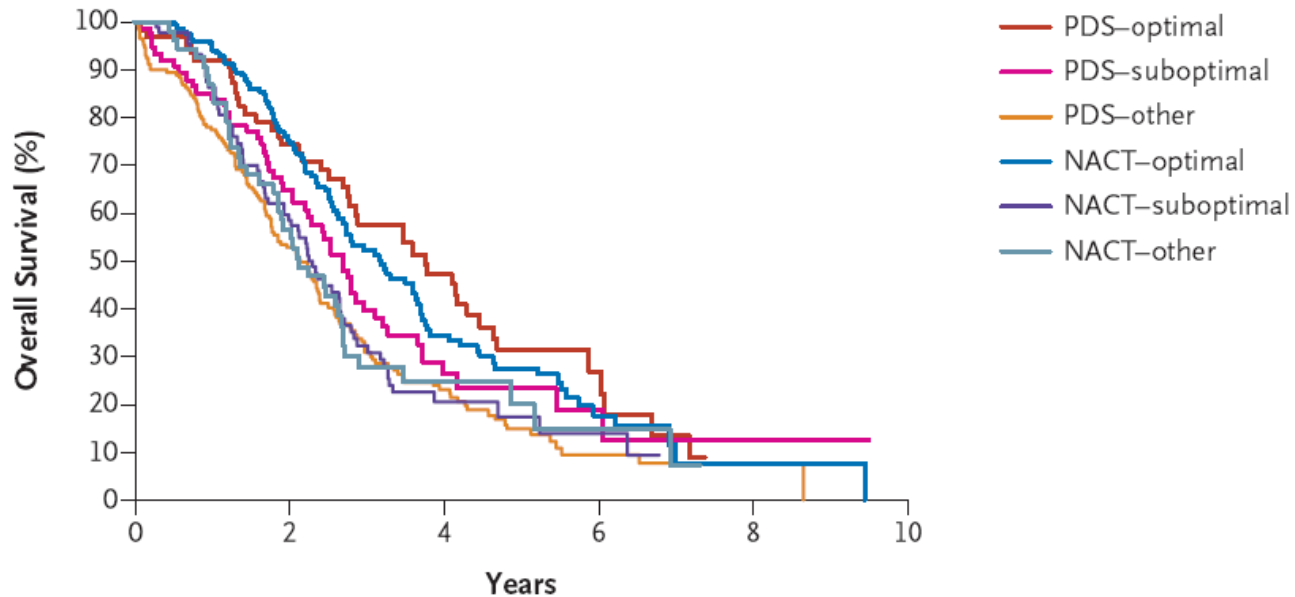


	No. of Events		No. of Patients at Risk			
Primary Debulking Surgery (PDS)	253	336	189	62	14	2
Neoadjuvant Chemotherapy (NACT)	245	334	195	46	13	2

# EORTC 55971

## Survival according to treatment an residual tumor

### B Per-Protocol Analysis



	No. of Events		No. of Patients at Risk			
	0-2	2-4	4-6	6-8	8-10	10+
PDS-Optimal	42	62	46	22	6	0
PDS-Suboptimal	52	74	46	11	3	1
PDS-Other	136	169	86	29	5	1
NACT-Optimal	100	152	110	30	8	2
NACT-Suboptimal	67	87	49	9	3	0
NACT-Other	41	53	29	6	2	0

„ In conclusion, among patients with advanced (stage IIIc or IV) ovarian, fallopian-tube, or peritoneal ovarian carcinoma, survival after neoadjuvant chemotherapy followed by intervall debulking surgery is similar to survival after primary debulking surgery followed by chemotherapy“

# EORTC 55971 Disparities in Surgery

	PS	NACT
Residual disease ( $\leq$ 10 millimeter) per country – no. (%) <sup>&amp;</sup>		
Belgium	44 (71.0)	73 (92.4)
The Netherlands	19 (37.3)	49 (75.4)
Norway	12 (32.4)	35 (79.5)
Italy	6 (37.5)	12 (66.7)
Spain	13 (43.3)	17 (70.8)
United Kingdom	15 (30.6)	33 (78.6)
Canada	11 (30.6)	30 (71.4)
No residual disease per country – no. (%) <sup>&amp;</sup>		
Belgium	39 (62.9)	69 (87.3)
The Netherlands	2 ( 3.9)	18 (27.7)
Norway	3 ( 8.1)	22 (50.0)
Italy	1 ( 6.3)	7 (38.9)
Spain	3 (10.0)	10 (41.7)
United Kingdom	5 (10.2)	18 (42.9)
Canada	4 (11.1)	17 (40.5)
Type of Surgery – no. (%) <sup>&amp;</sup>		
Hysterectomy	180 (58.1)	225 (69.9)
Prior hysterectomy	30 (9.7)	33 (10.2)
BSO	223 (71.9)	253 (78.6)
Prior BSO	7 (2.3)	12 (3.7)
USO	27 (8.7)	12 (3.7)
Infracolic omentectomy	231 (74.5)	238 (73.9)
Pelvic lymphadenectomy	58 (18.7)	77 (23.9)
Para-aortic lymphadenectomy	26 (8.4)	49 (15.2)
Bowel resection	48 (15.5)	28 (8.7)
Splenectomy	18 (5.8)	13 (4.0)

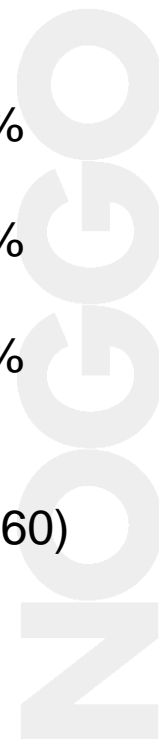
## Conclusions

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- NACT not inferior to PS from this study: HR 0.87 (0.71, 1.05)
- NACT significantly improved optimal debulking rates
- Less post-operative morbidity & mortality with NACT
- Median survival is low in this patient cohort
- Results are consistent with EORTC 55971
- There are now 2 RCTs indicating that neoadjuvant chemotherapy is an alternative to primary surgery in patients with advanced ovarian carcinoma

# EORTC-CHORUS characteristics of treatment

		CHORUS		EORTC	
		PS	NACT	PS	NACT
Any grade 3+ toxicity		48%	40%		
Optimal debulking	0 cm	16%	40%	19.4%	51.2%
	≤1 cm	25%	35%	22.2%	29.5%
	>1 cm	61%	25%	53.0%	17.7%
Length of operation (minutes)	median (Range)	120 (30-450)	120 (30-330)	165 (10-720)	180 (30-560)
Any grade $\frac{3}{4}$ complication		24%	14%	17.1	5.8
Discharge within 14 days		74%	92%		
Deaths within 28 days		5.6%	0.5%	2.5%	0.7%



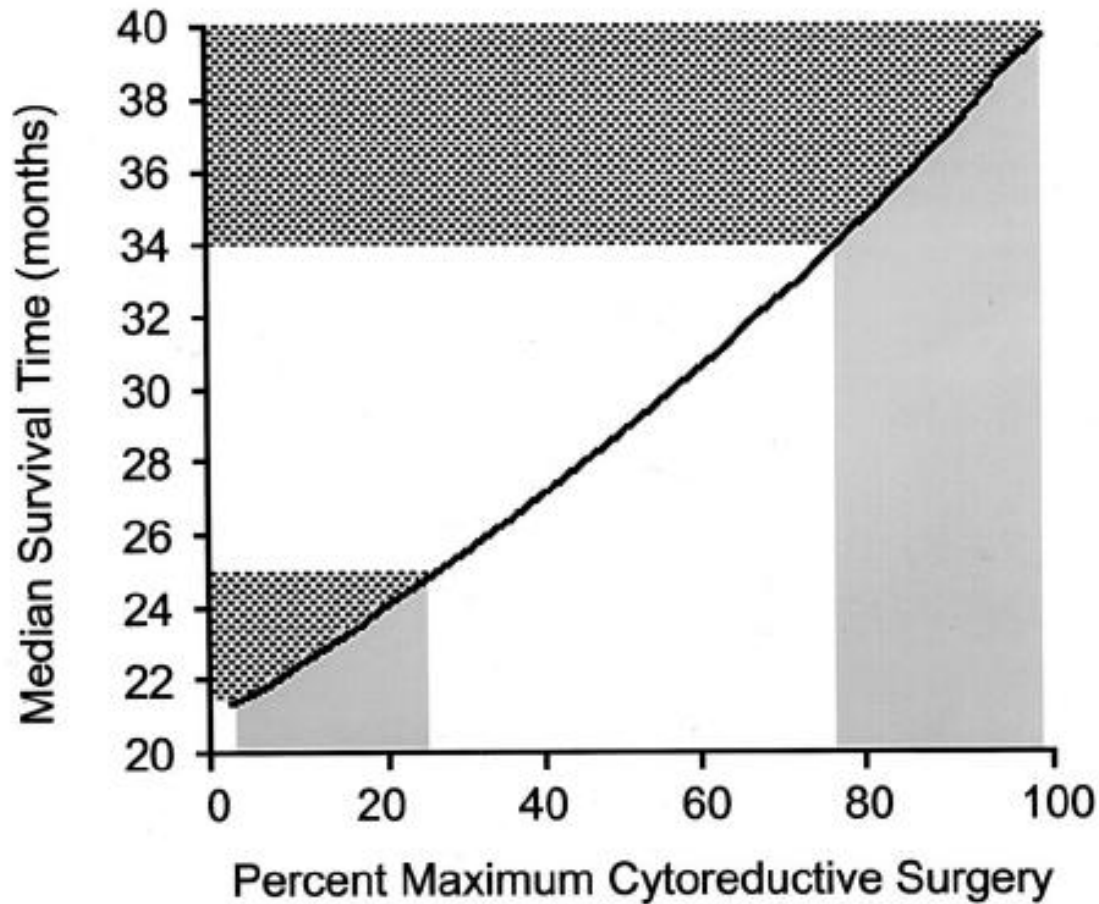
# Median Overall Survival in Ovarian Cancer

Authors	Study	Patients	Survival
Aletti GD et al 2011	retrospective	576	40.2 months
Sehouli J et al 2009	retrospective	214	85 months
Chi D et al 2012	retrospective	316	50 months
du Bois A et al 2003	rct	798	44.1 months
Du Bois A et al 2006	rct	1282	41.0 months
Du Bois A et al 2010	rct	1742	51.5 months



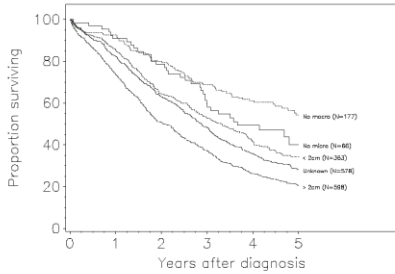
# Cytoreduction and Survival

6885 patients, Stage III or IV



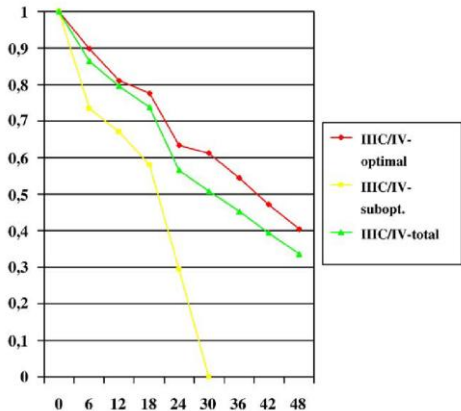


# Residual tumor and Survival



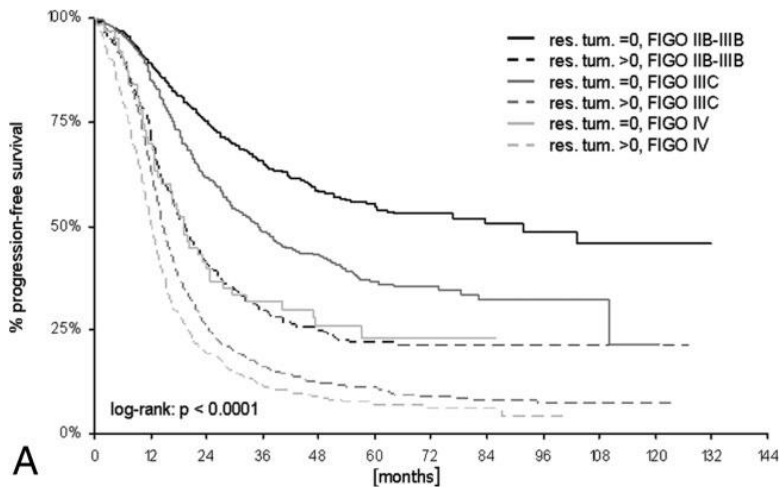
Residual disease	Patients (n)	Mean age (yr)	Overall survival (%) at					Hazard ratio* (95% CI)
			1 year	2 years	3 years	4 years	5 years	
No micro residual	66	57.5	90.8	78.5	59.7	49.0	41.3	Reference
No macro residual	177	58.2	92.6	80.0	68.7	41.0	55.1	0.6 (0.4-0.9)
<2cm	363	57.8	85.3	64.7	53.0	41.4	34.0	1.1 (0.8-1.7)
>2cm	598	61.2	73.9	50.7	36.9	26.2	20.7	1.8 (1.2-2.5)
Unknown	578	60.3	82.4	63.1	48.4	35.6	28.1	1.2 (0.9-1.7)

\*Hazard ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, stage and country.  
Fig. 12. Carcinoma of the ovary: patients treated in 1996-98. Survival in Stage I/II patients by completeness of surgery, n = 1792.

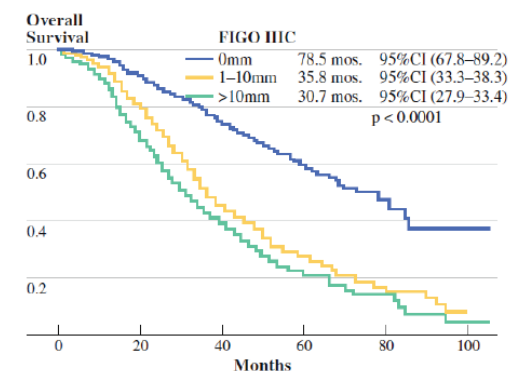
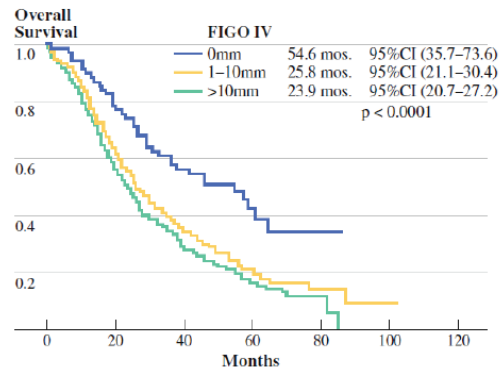


Annual report 2003

E.S. Andersen et al. Gynecologic Oncol 99(2005) 552-556



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Wimberger P. et al. Ann Surg Oncol. 2010; 17(6)1642-1648

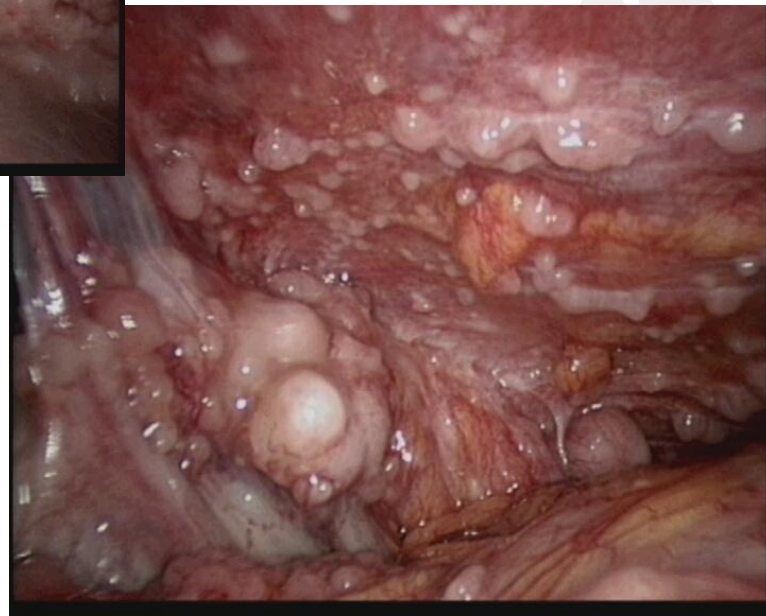
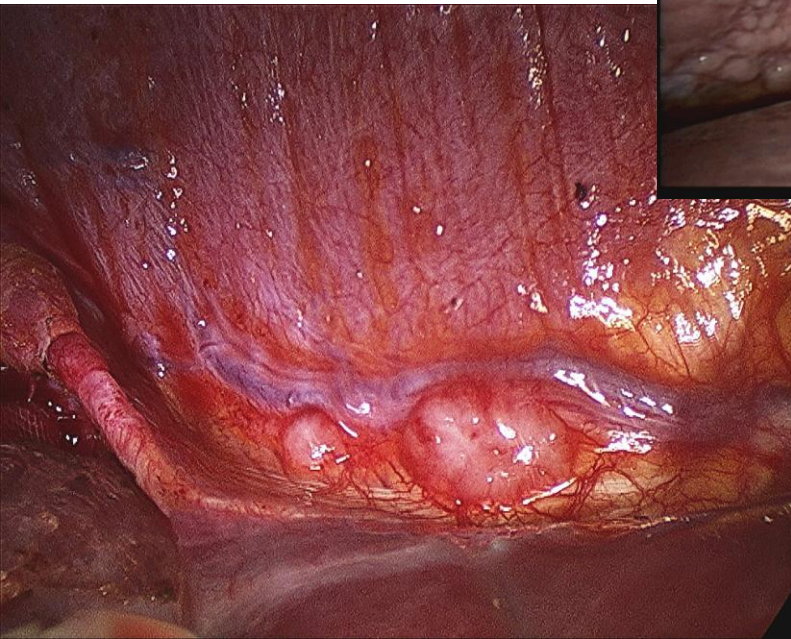
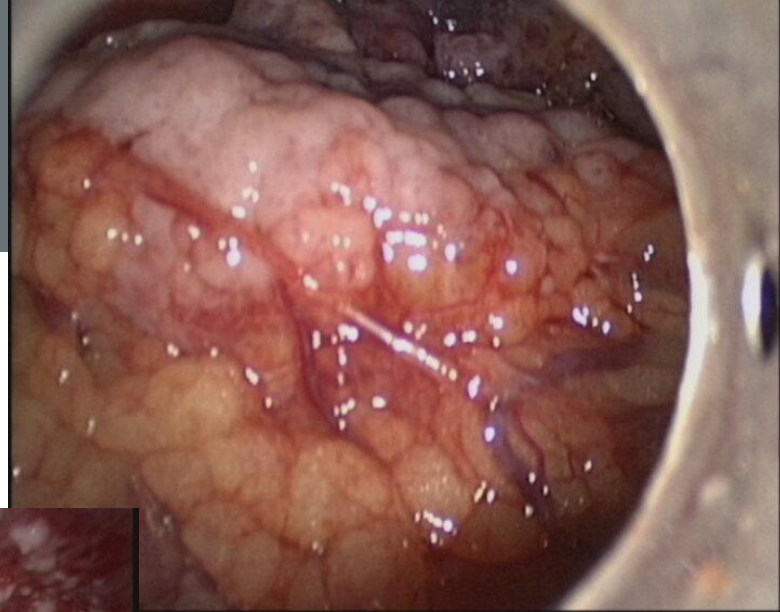
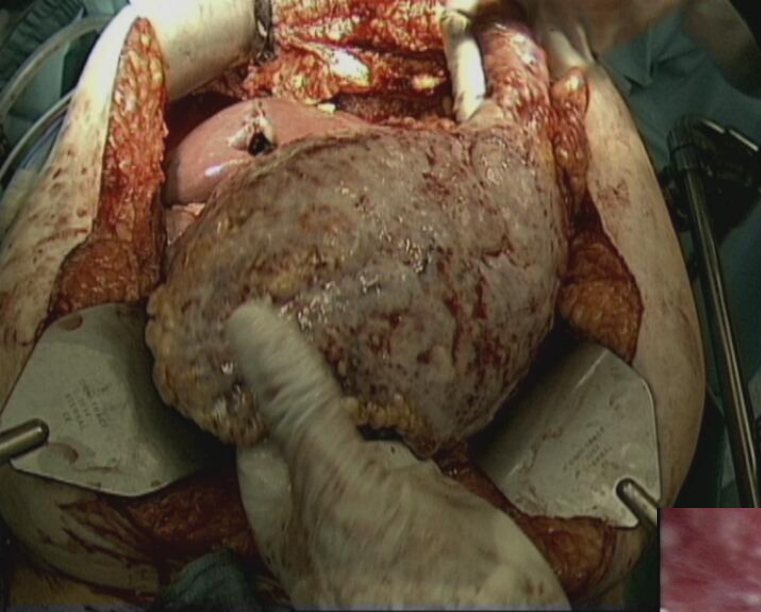
# Optimal Cytoreduction

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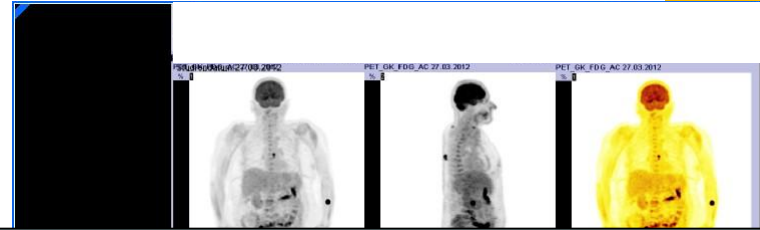
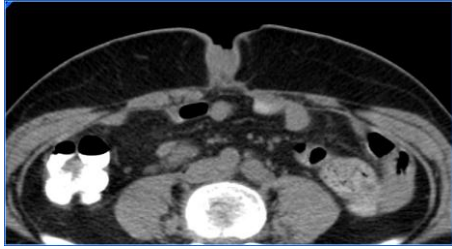
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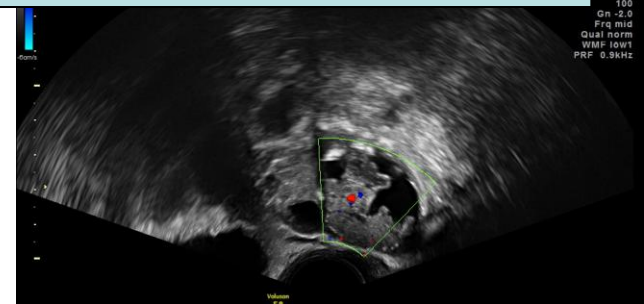
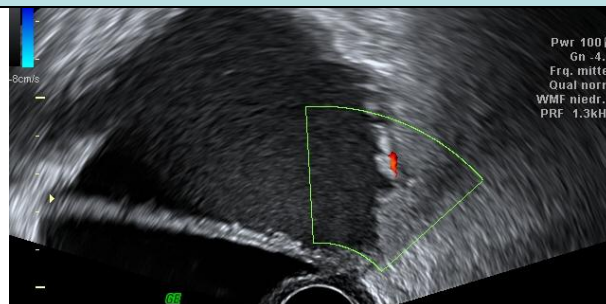
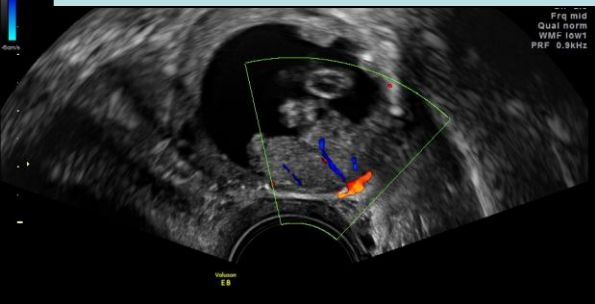
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# Accuracy of Imaging predicting Resectability



To date, no single preoperative predictor has demonstrated sufficient accuracy to predict surgical outcome



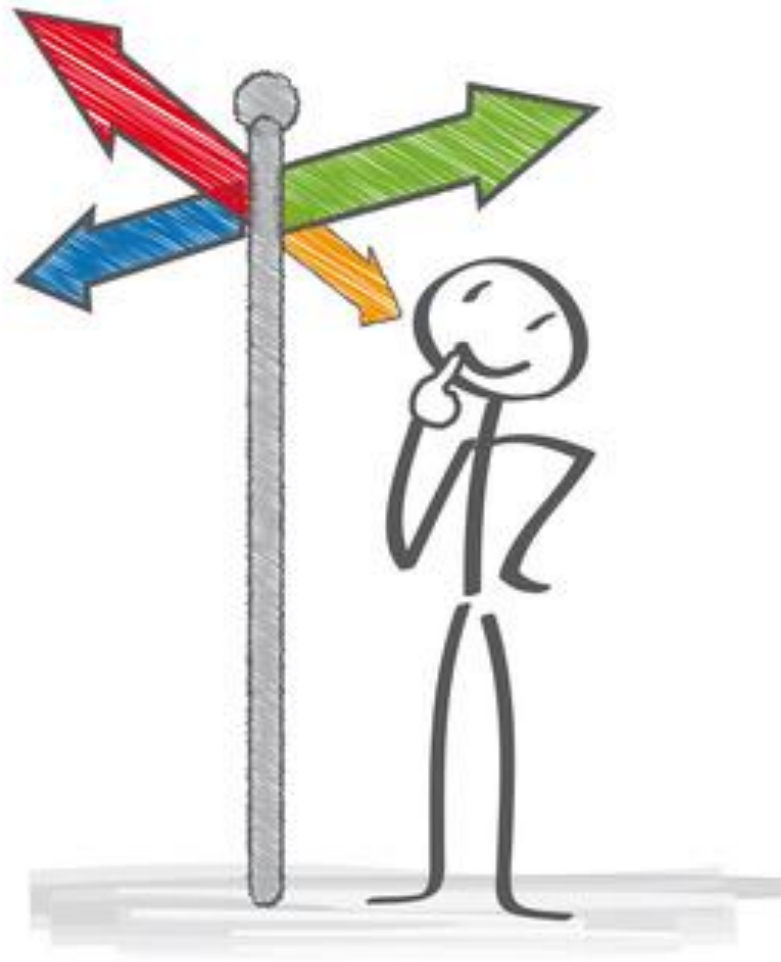
46:09  
Routine  
Harlow  
ST  
Gn -1  
CS / Ma  
P4 / E3  
SRI II 3

100  
Gn -2.0  
Frq. mid  
Qual norm  
WMF low  
PRF 0.9kHz

# Ovarian Cancer Treatment

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Gynecologic Oncology 120 (2011) 23–28



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## Gynecologic Oncology

journal homepage: [www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)

## Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment

Giovanni D. Aletti<sup>a</sup>, Eric L. Eisenhauer<sup>c</sup>, Antonio Santillan<sup>d</sup>, Allison Axtell<sup>b</sup>, Giacomo Aletti<sup>e</sup>,  
Christine Holschneider<sup>b</sup>, Dennis S. Chi<sup>c</sup>, Robert E. Bristow<sup>d</sup>, William A. Cliby<sup>a,\*</sup><sup>a</sup> Department of Gynecologic Surgery, Mayo Clinic, Rochester, MN, USA<sup>b</sup> Department of Obstetrics and Gynecology, Olive View-UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA<sup>c</sup> Department of Surgery, Gynecology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA<sup>d</sup> The Kelly Gynecologic Oncology Service, Department of Gynecology and Obstetrics, The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins Medical Institutions, Baltimore, MD, USA<sup>e</sup> Department of Mathematics and Statistics, University of Milan, Milan, Italy

# Surgical Complexity Score

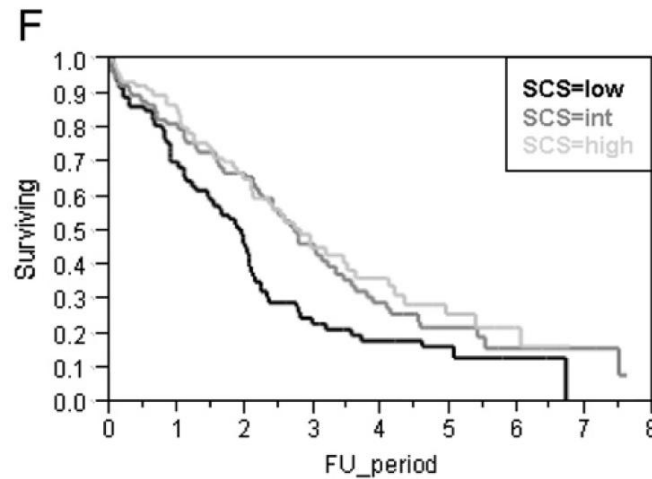
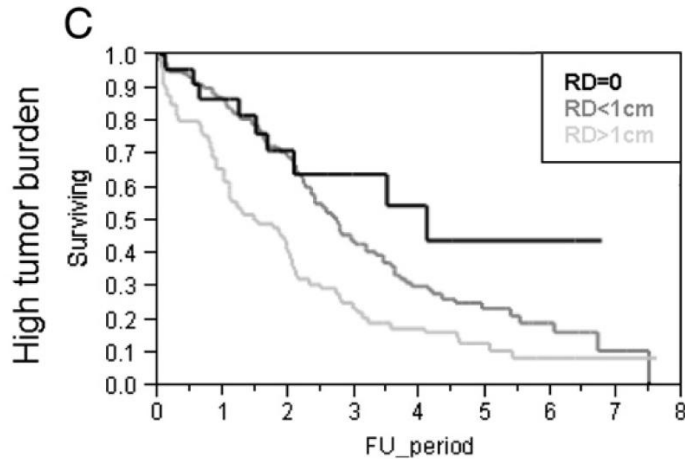
**Table 1**

Surgical complexity scoring system based upon complexity and number of surgical procedures performed (online only).

Procedure	Points
TH-BSO	1
Omentectomy	1
Pelvic lymphadenectomy	1
Para-aortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping	1
Recto-sigmoidectomy_termino-terminal anastomosis	3
Large bowel resection	2
Diaphragm stripping/resection	2
Splenectomy	2
Liver resection/s	2
Small bowel resection/s	1
Complexity score groups	Points
1 (low)	≤3
2 (intermediate)	4-7
3 (high)	≥8

TH-BSO, total hysterectomy, bilateral salpingo-oophorectomy.

# Surgical Complexity Score

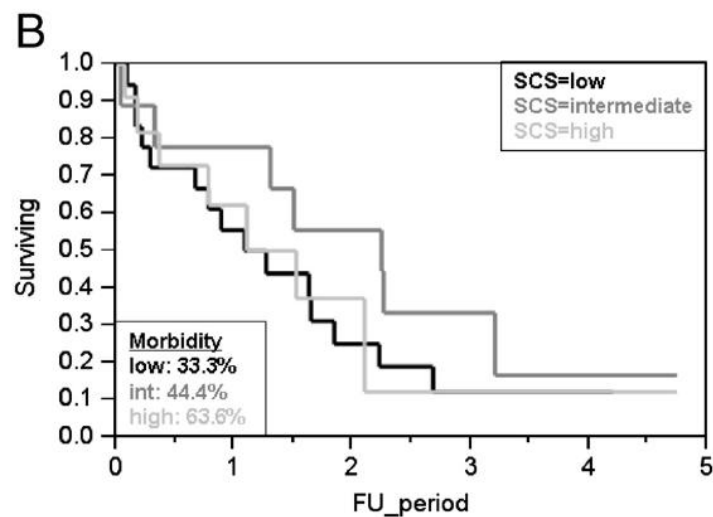
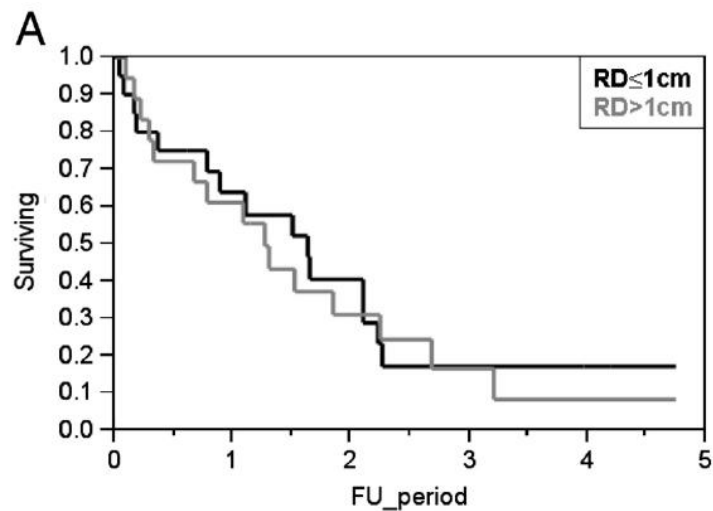


High tumor dissemination or stage IV  
Poor performance status (ASA $\geq$ 3) or nutritional status  
(preoperative albumin levels<3.0 g/dl)  
Age $\geq$  75 years

38 patients (6.6%) at very high risk  
major morbidity 63.6% for high SCS and 33.3% for low SCS  
7 patients died within 3 months from surgery-Mortality rate 18.4%



# Surgical Complexity Score very high risk group



# Surgical Outcome in Ovarian Cancer

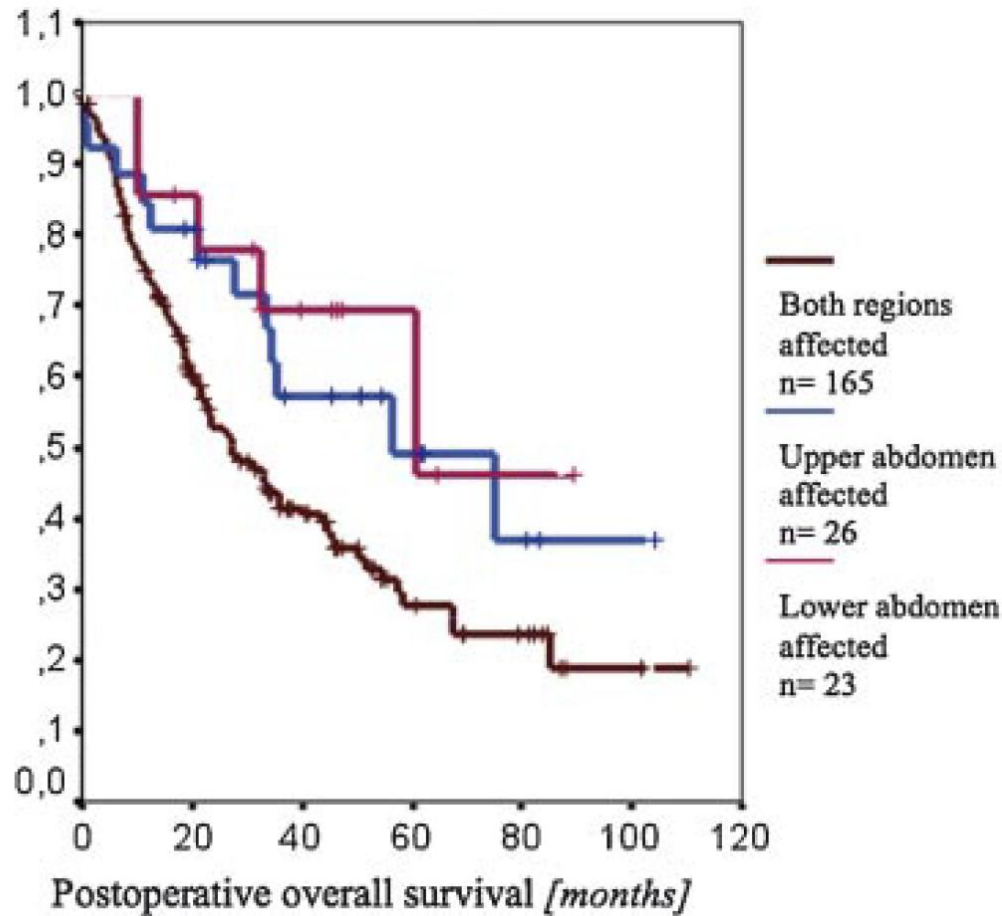
**TABLE I. Intraoperative Tumor Localization in 214 Patients With Primary Ovarian Cancer**

Structure affected	Patients (%)
Peritoneum	162 (76%)
Lymph nodes	145 (68%)
Colon	111 (52%)
Diaphragm	94 (44%)
Pelvic wall	77 (36%)
Mesentery	70 (33%)
Ascites	62 (29%)
Small bowel	58 (27%)
Abdominal wall	38 (18%)
Bursa omentalis	26 (12%)
Spleen	15 (7%)
Stomach	15 (7%)

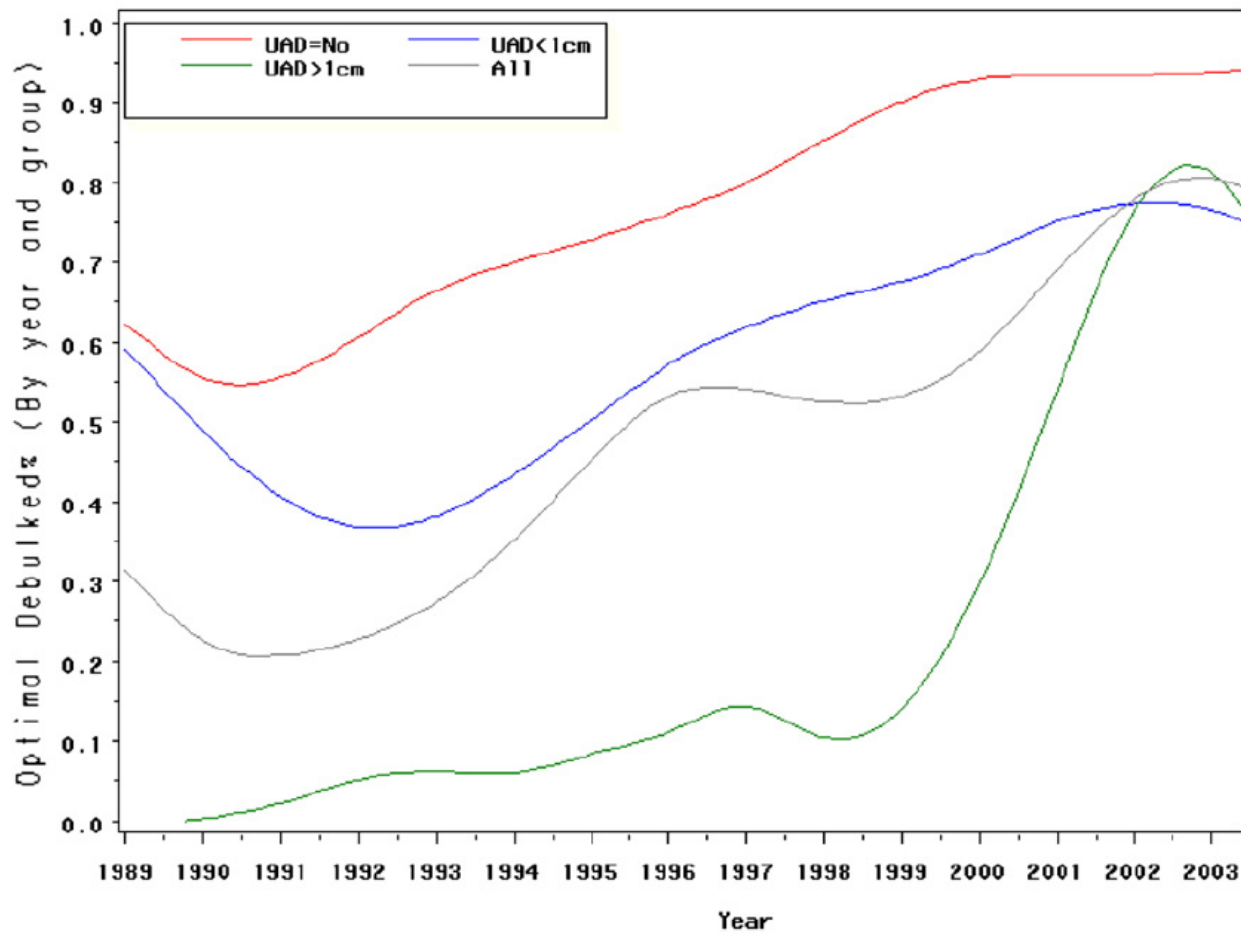


# Surgical Outcome in Ovarian Cancer

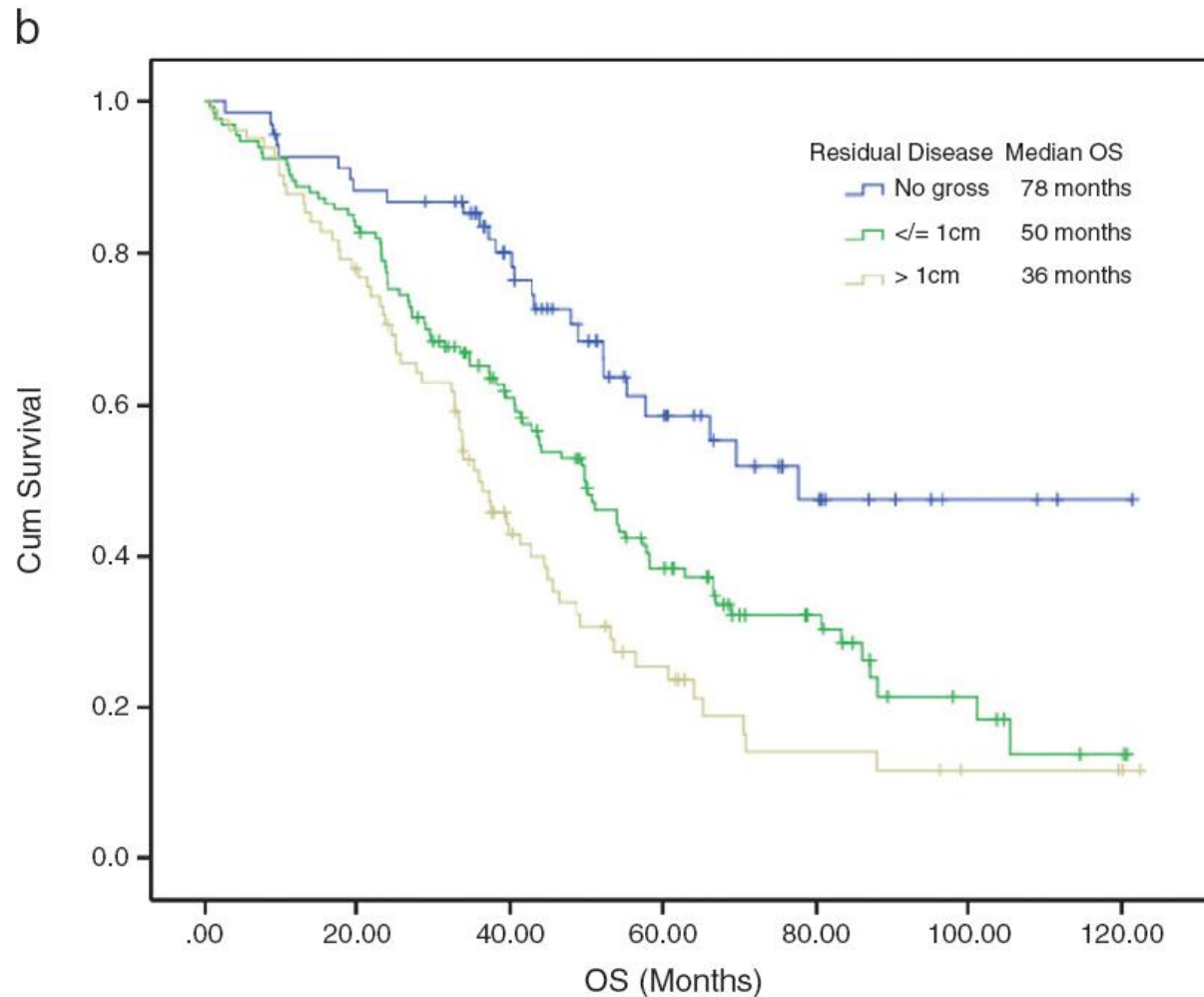
## Impact of tumor localization on overall survival



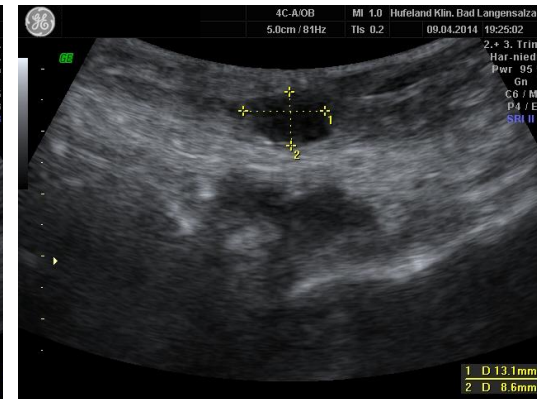
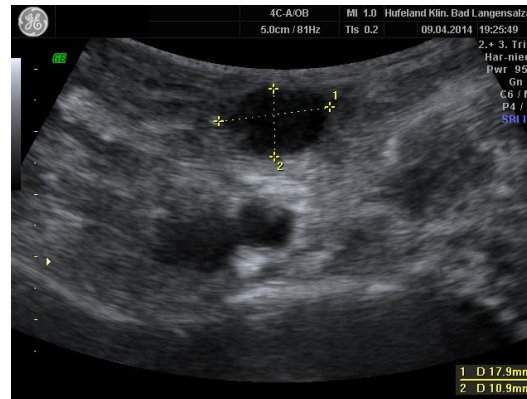
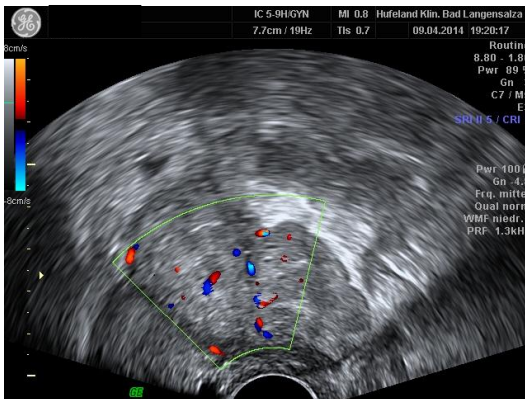
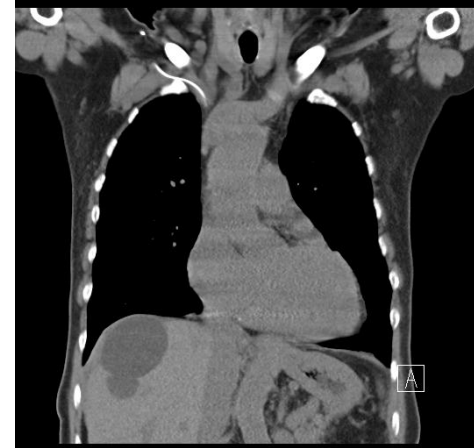
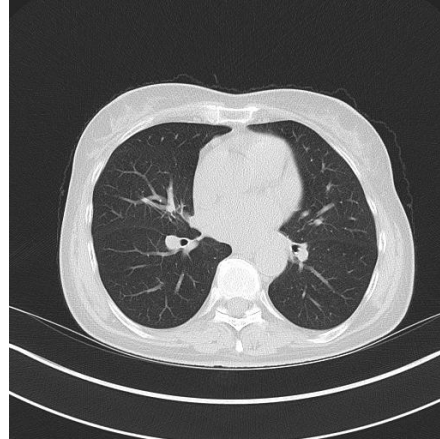
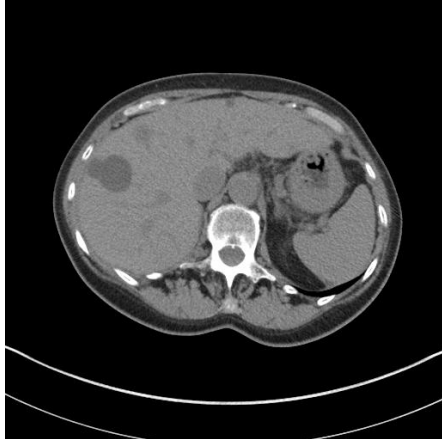
# Tarteging the upper abdomen



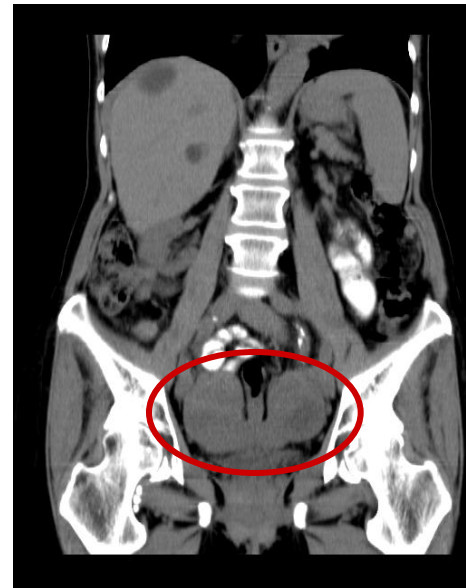
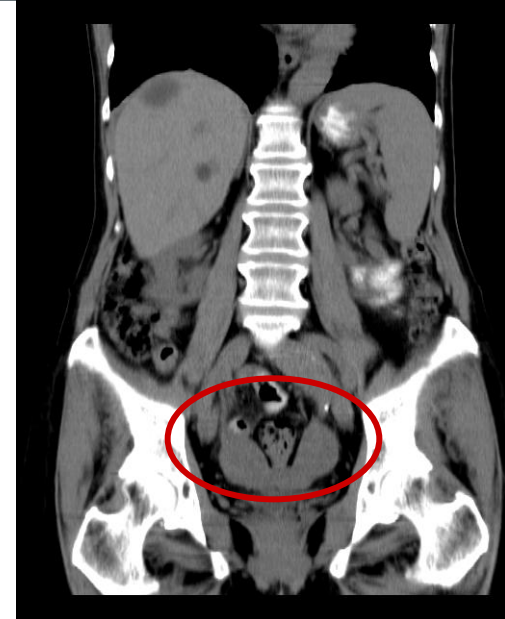
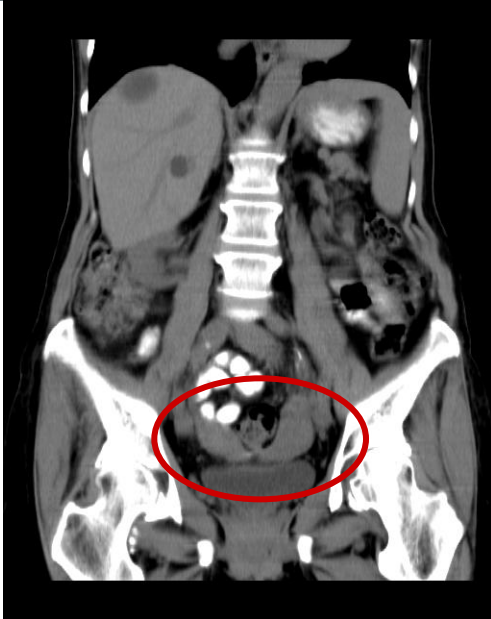
# Cohort with primary debulking surgery during an identical time period as the EORTC-NCIC trial



# Clinical case 66y

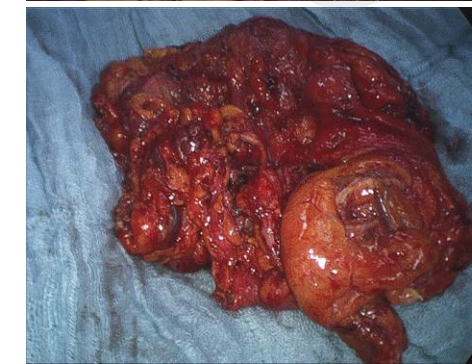
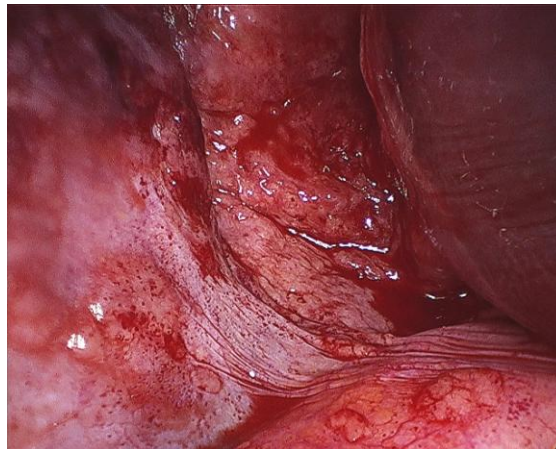
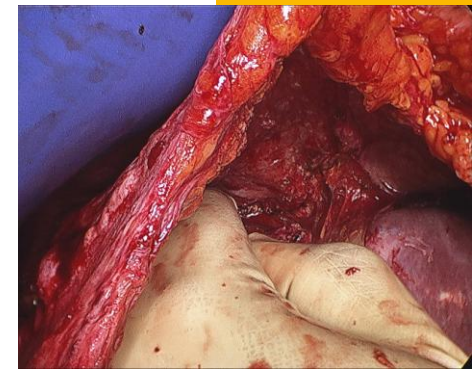
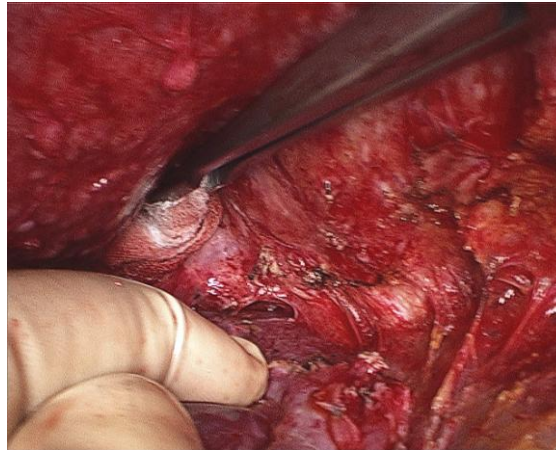
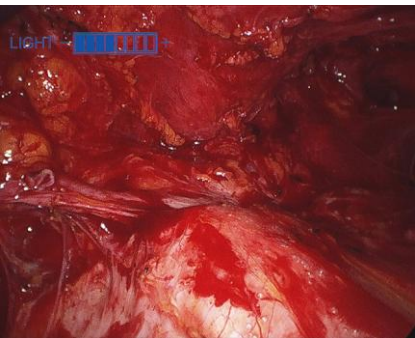
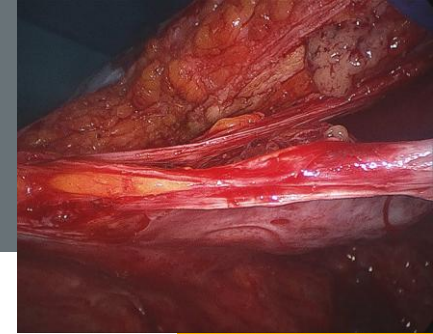
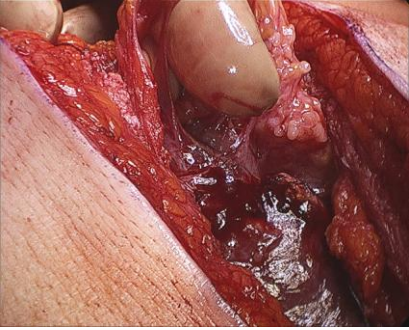


# Clinical case 66y





# Clinical case 66y



**CA-125**

**161.9 - U/ml <35**

**CA-125**

**102.4 - U/ml <35**

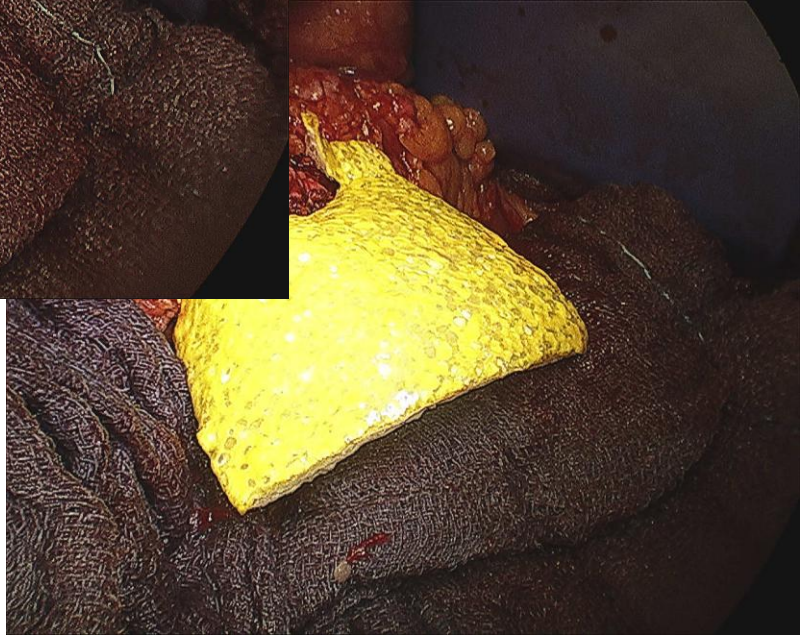
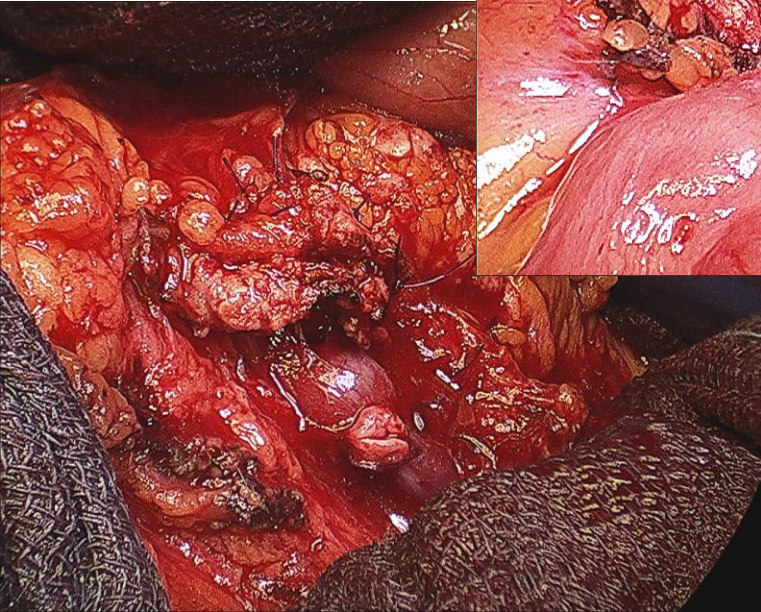
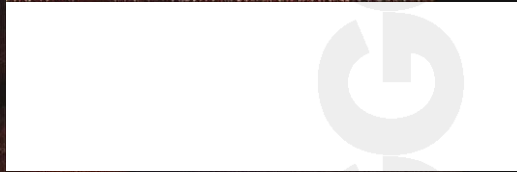
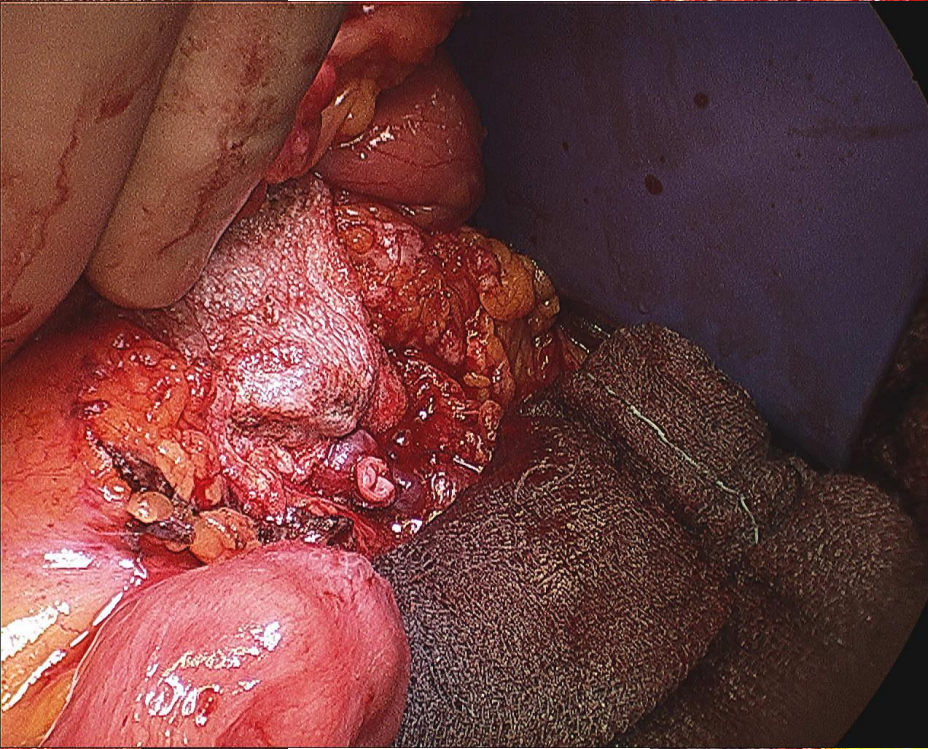
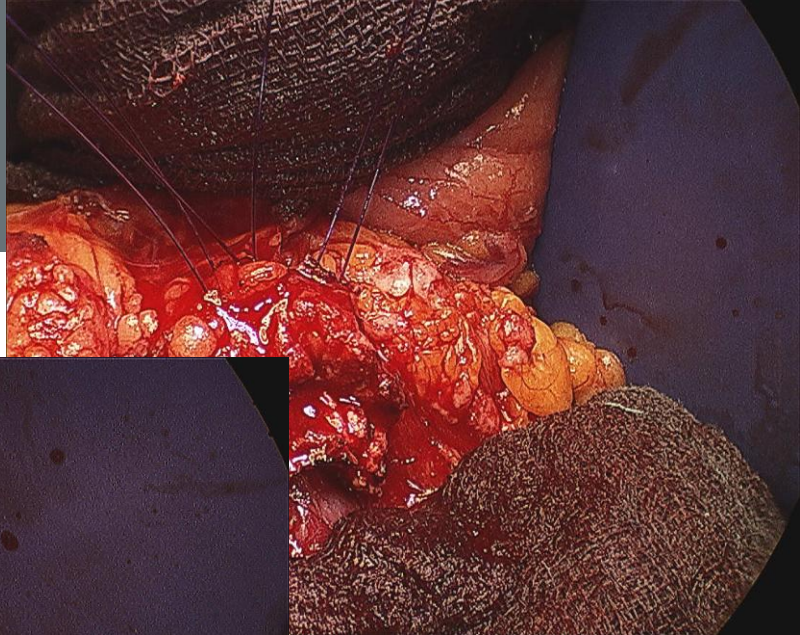
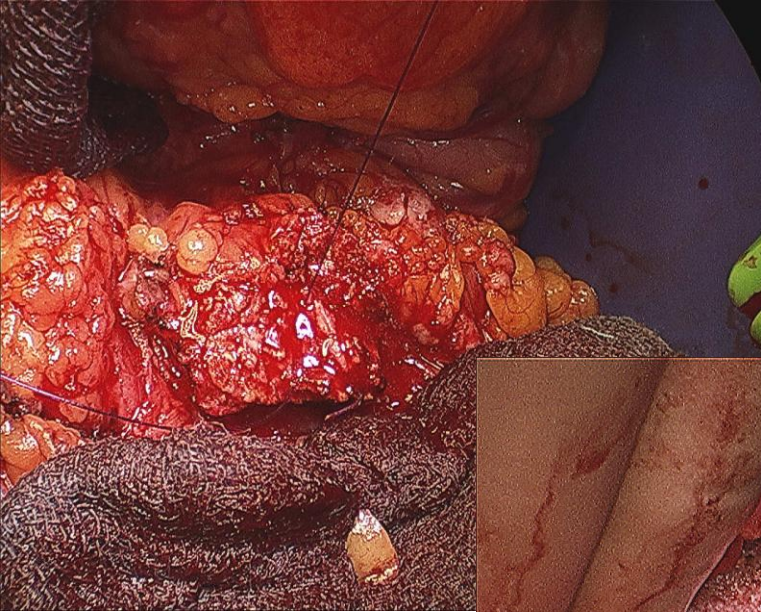


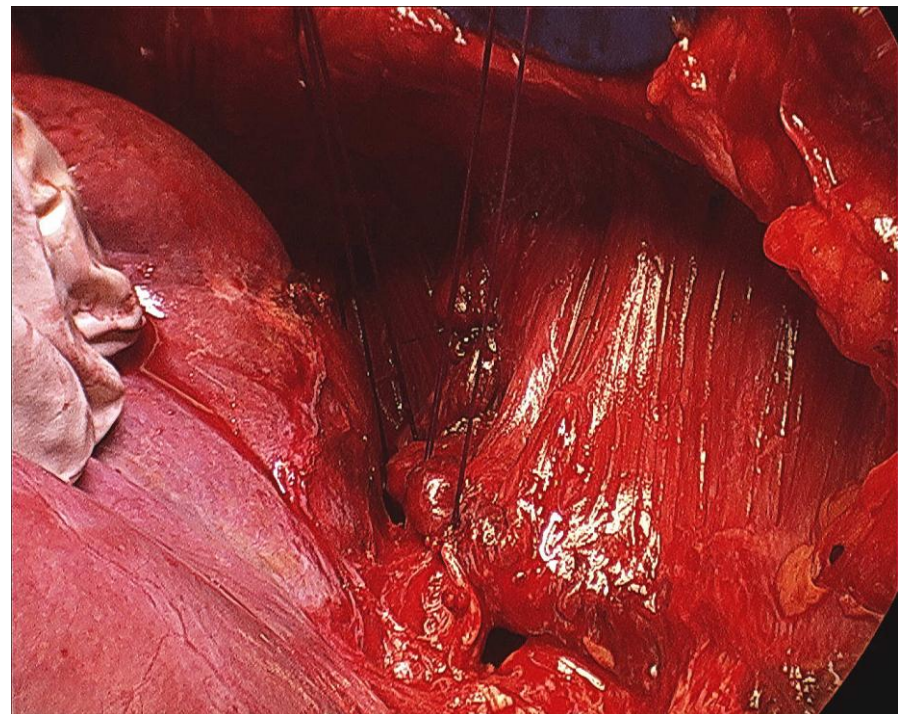
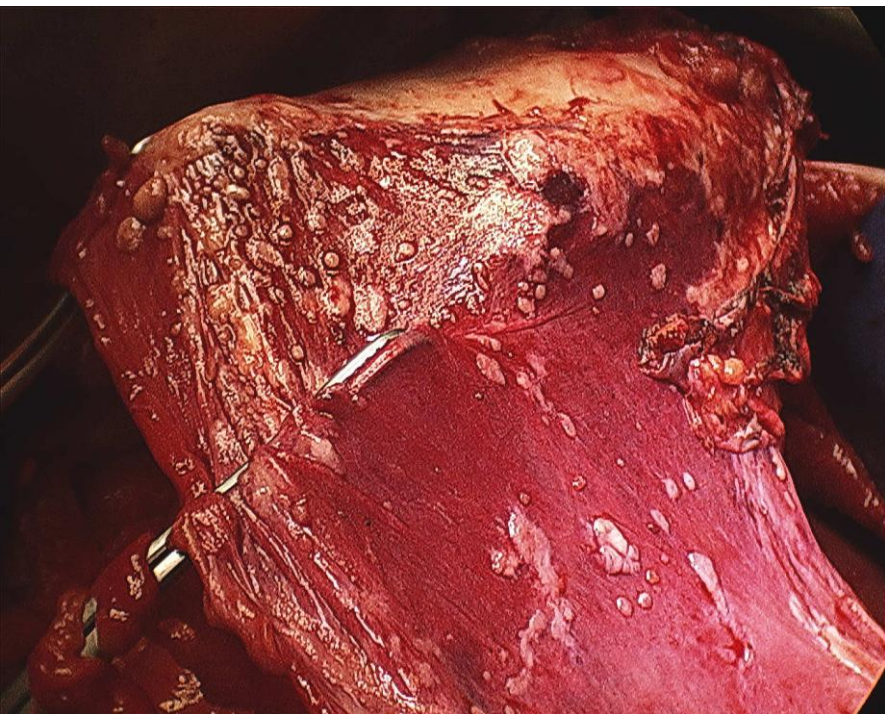
# Who should be treated with neoadjuvant chemotherapy?

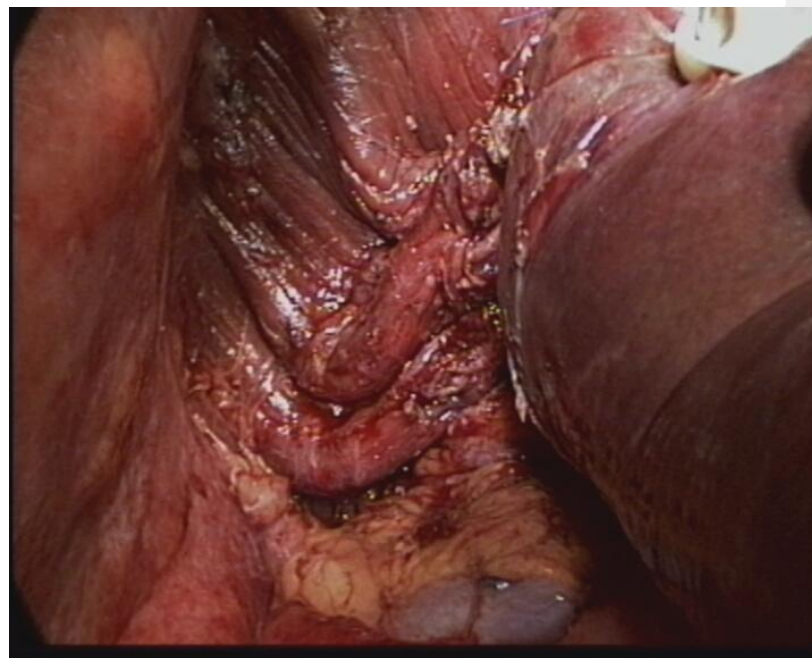
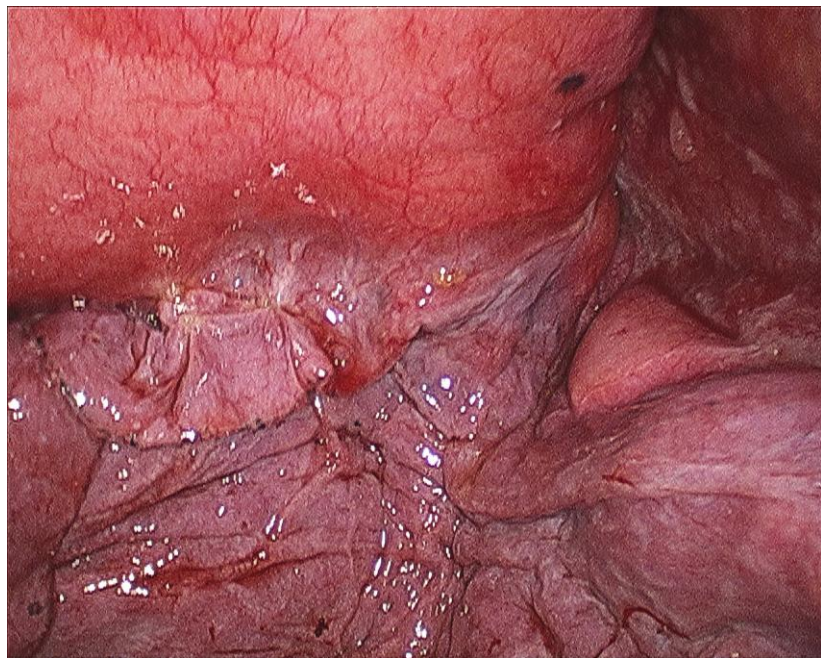
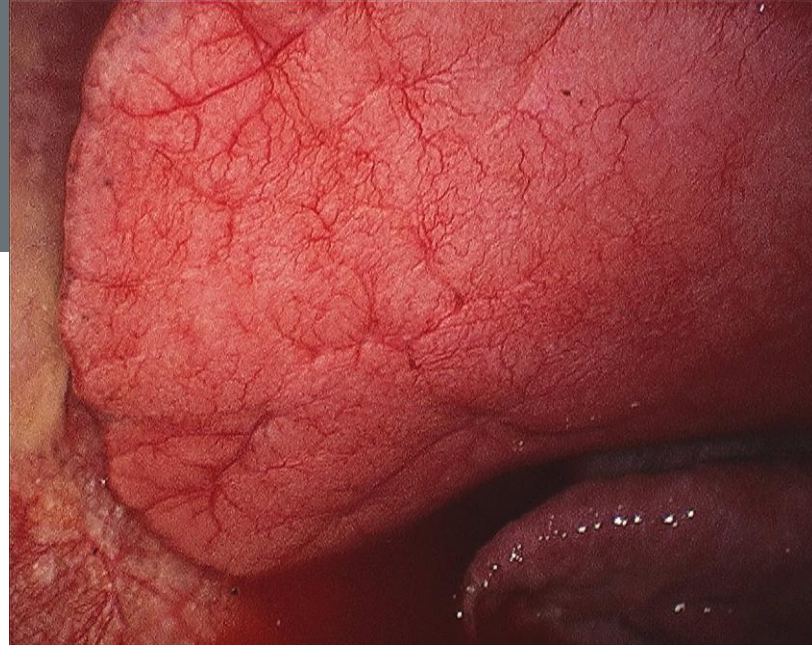
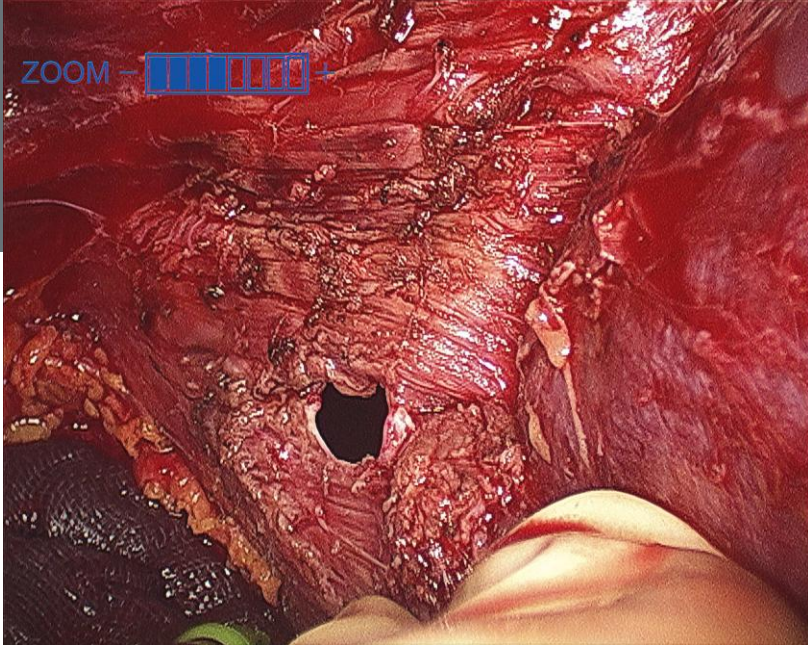
Primary chemotherapy should be restricted to

- FIGO IIIc, IV
- Intraabdominal IIIc
- metastatic tumor > 5 cm

The strategy of neoadjuvant therapy should not be abused for excuses regarding suboptimal surgical care







„optimal“ cytoreduction should no longer be defined  
as residual tumor <1 or <0.5 cm, but as a resection  
without macroscopic residual tumor

# potential pure study design

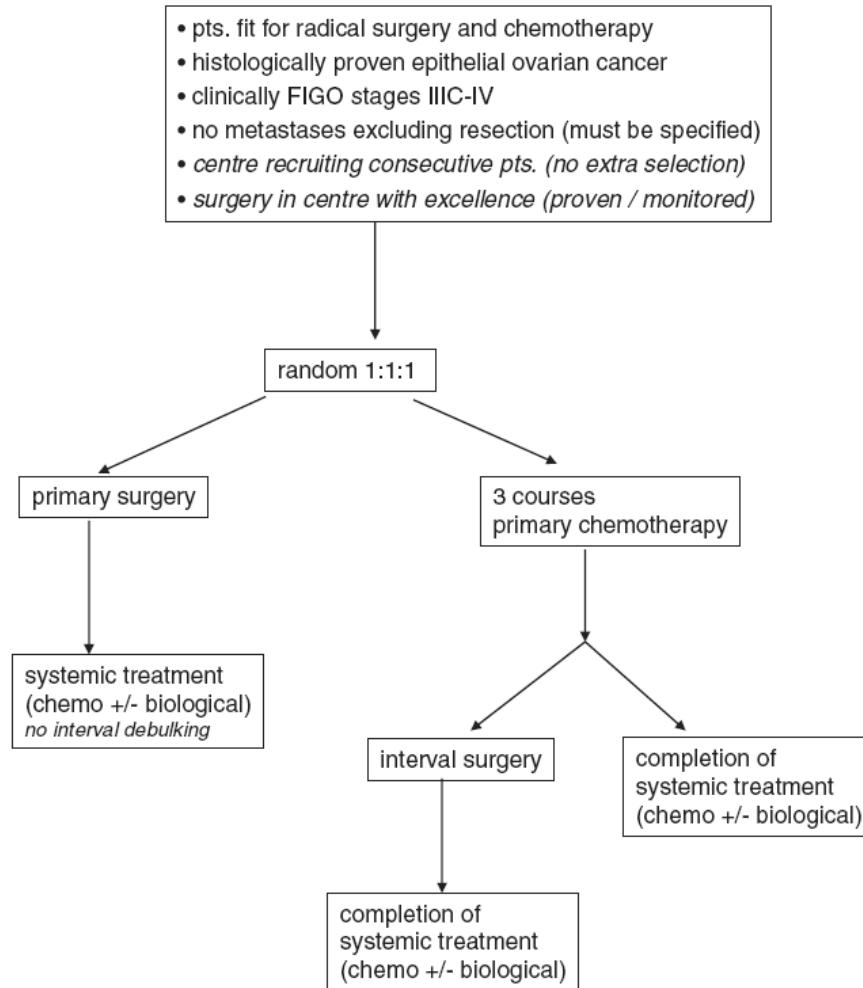


Fig. 2. Design of a theoretical future trial evaluating the role of surgery in advanced ovarian cancer.



