



FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI



Francesco Raspagliesi

Gynecologic
Oncology
Unit

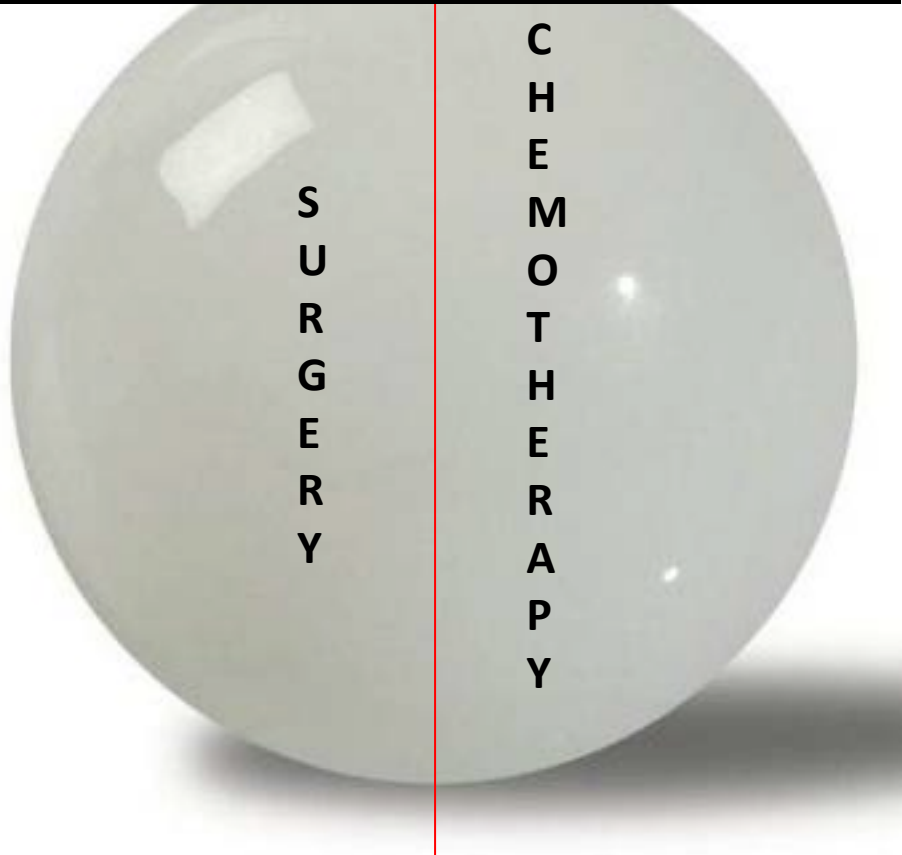


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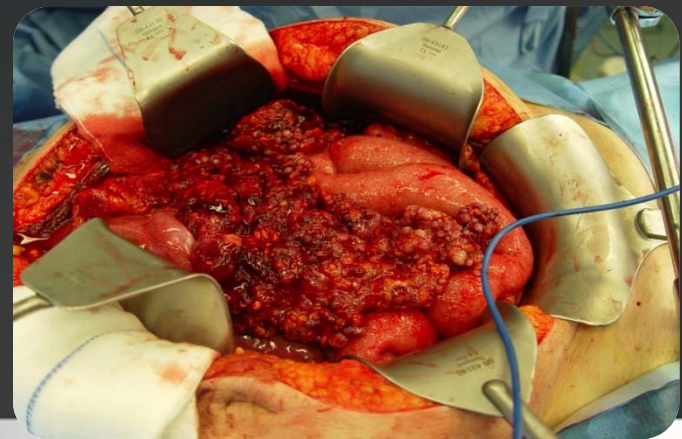
Perché la Chirurgia ha un Ruolo Fondamentale
nel Trattamento del Carcinoma Ovarico

- SURGERY IS ESSENTIAL IN OVARIAN CANCER TREATMENT
- An **intelligent combination** of surgery and chemotherapy may prolong significantly the overall survival in these patients.

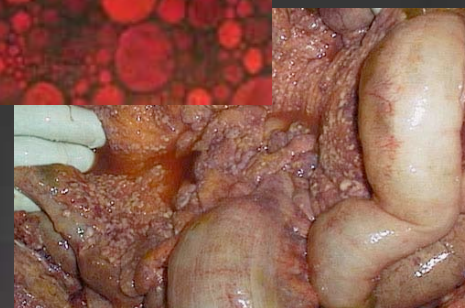
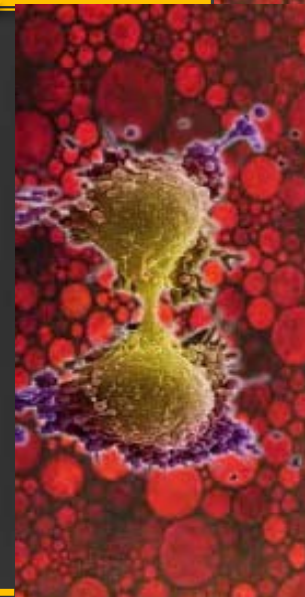
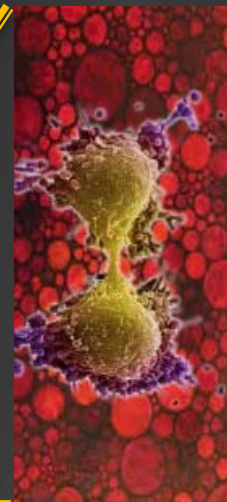
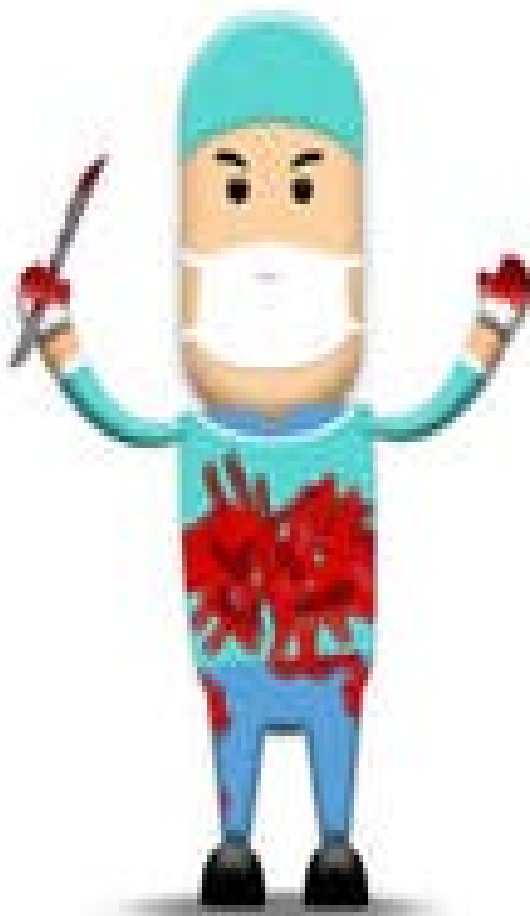
OPTIMAL 1ST LINE TREATMENT



- Histologic diagnosis
- Staging
- Cytoreduction
- Relief of symptoms



Tumor
Biolog



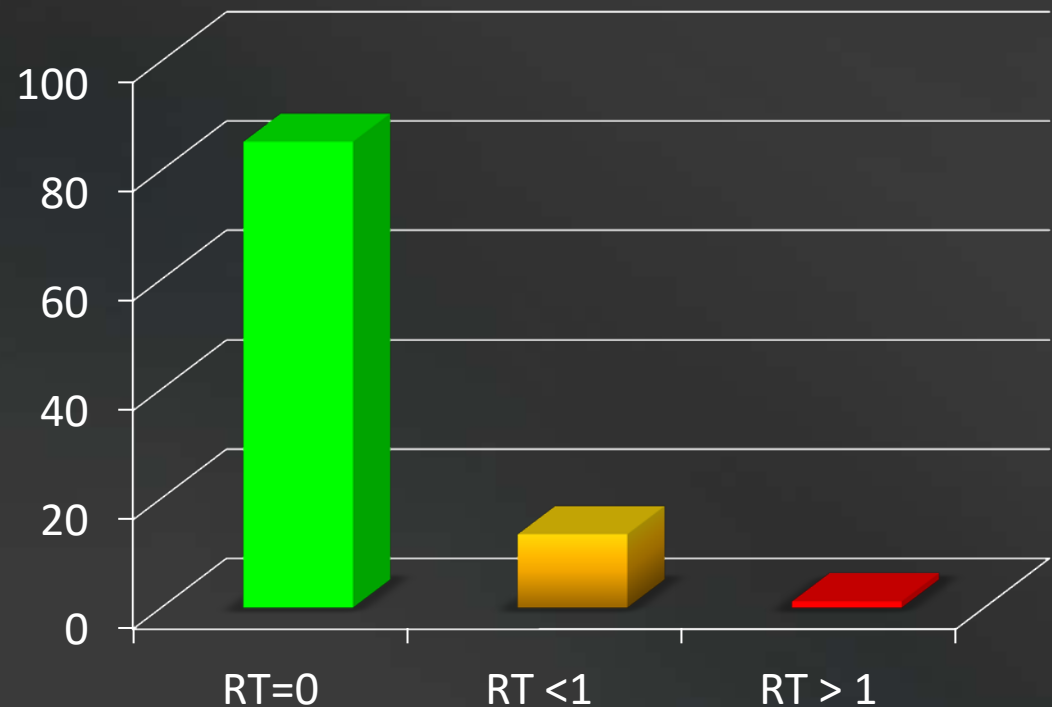
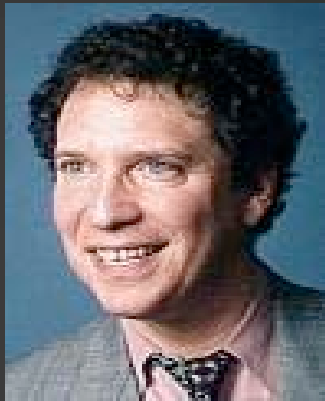
optimal

Debulking
or not

“Complete cytoreduction is feasible and improve survival”

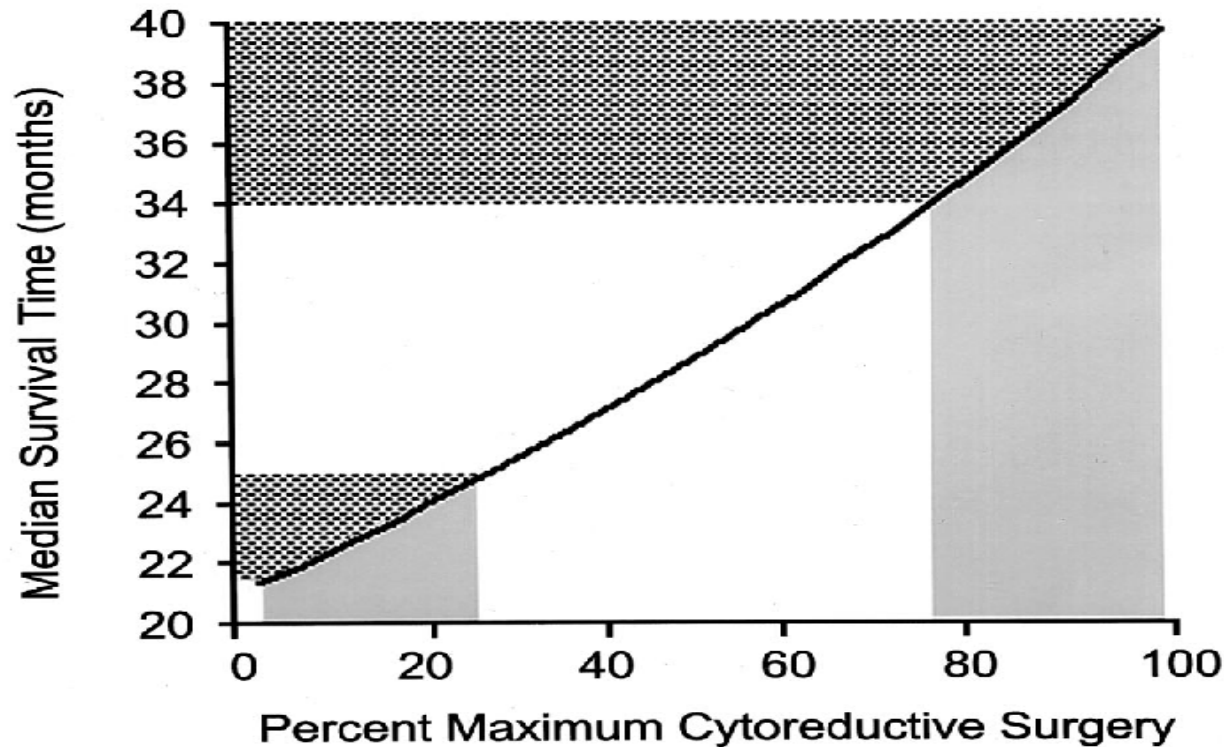
Eisenkop SM, Gynecol Oncol, 1998

- 163 consecutive patients with stage IIIc and IV
 - All patients underwent a combination of pelvic and abdominal procedures with multiple organ resection
 - 85.3 % of patients had complete cytoreduction
 - 13.5 % had optimal reduction with residual disease less than 1 cm
 - 1.2 % had unresected disease
- 98%



Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era: A Meta-Analysis

By Robert E. Bristow, Rafael S. Tomacruz, Deborah K. Armstrong, Edward L. Trimble, and F.J. Montz

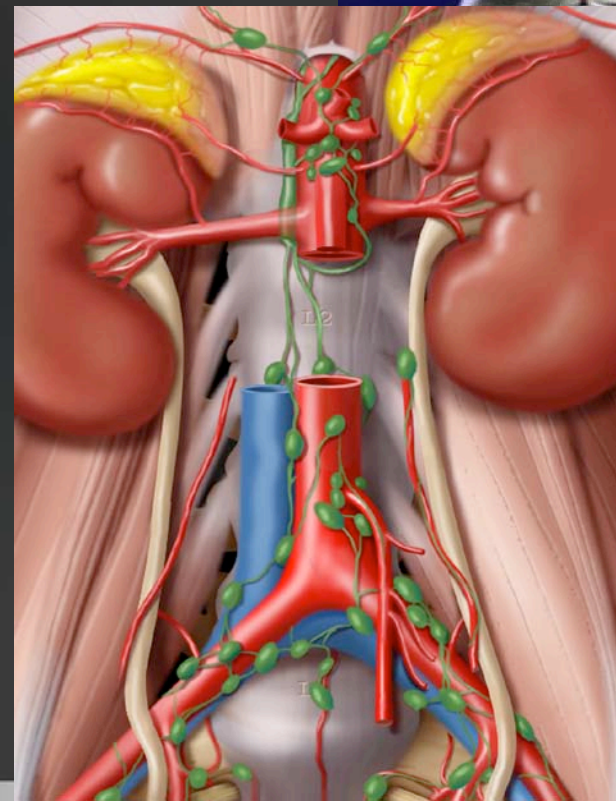
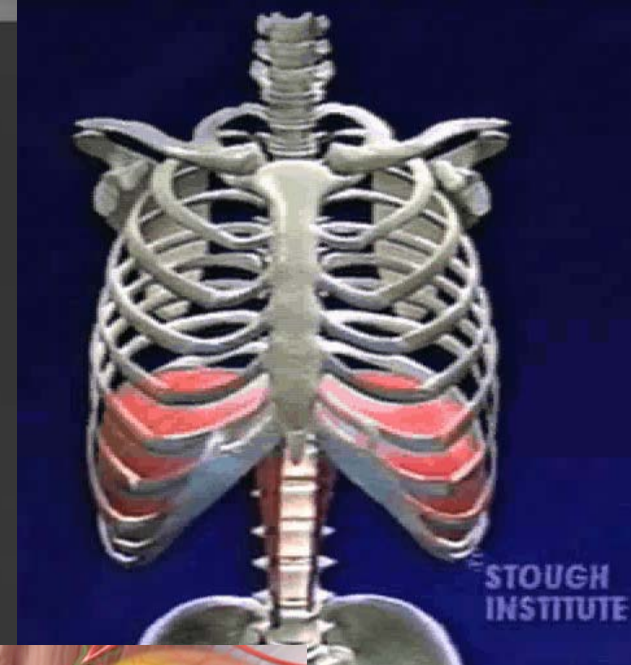
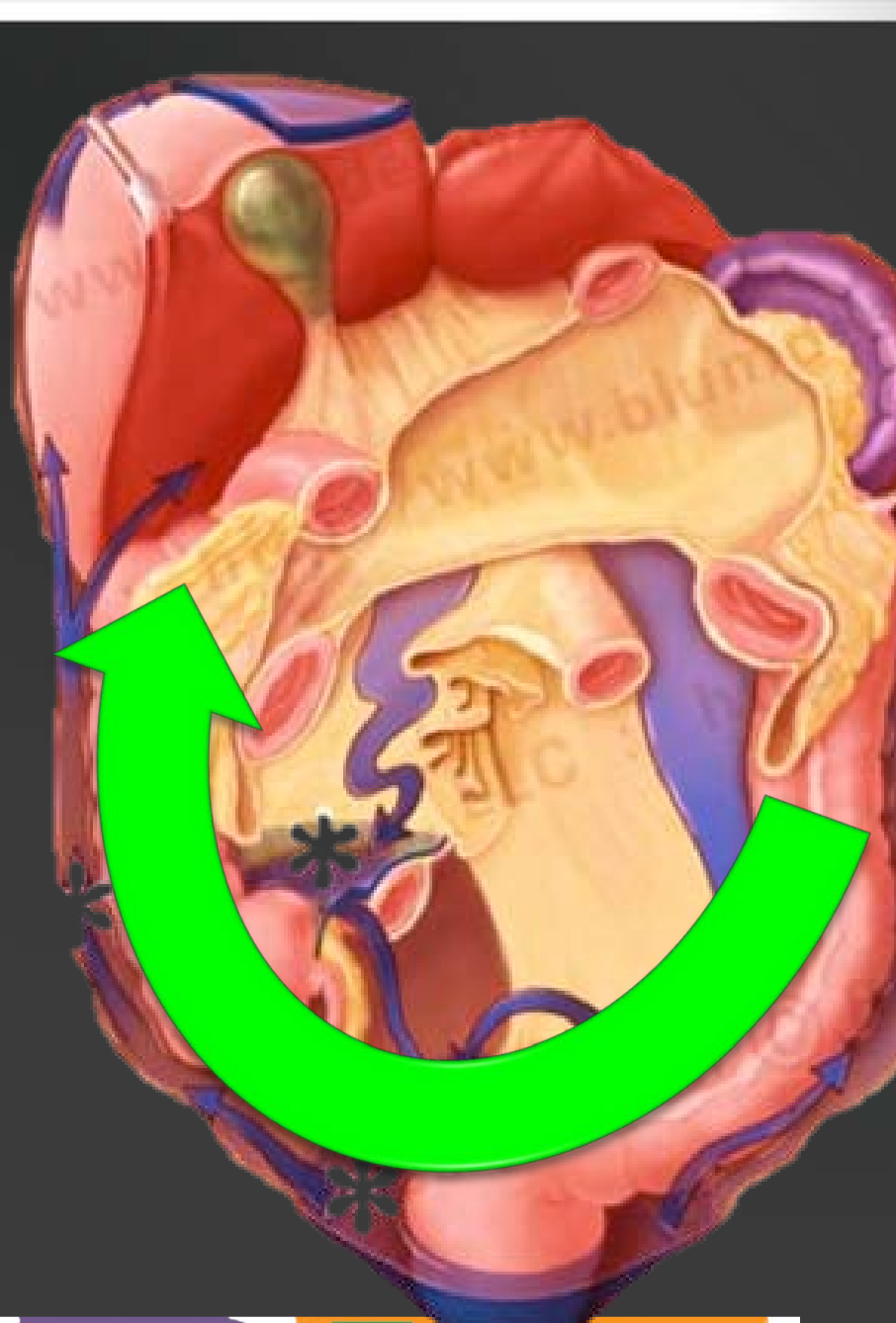


JCO 20:1248-59, 2002

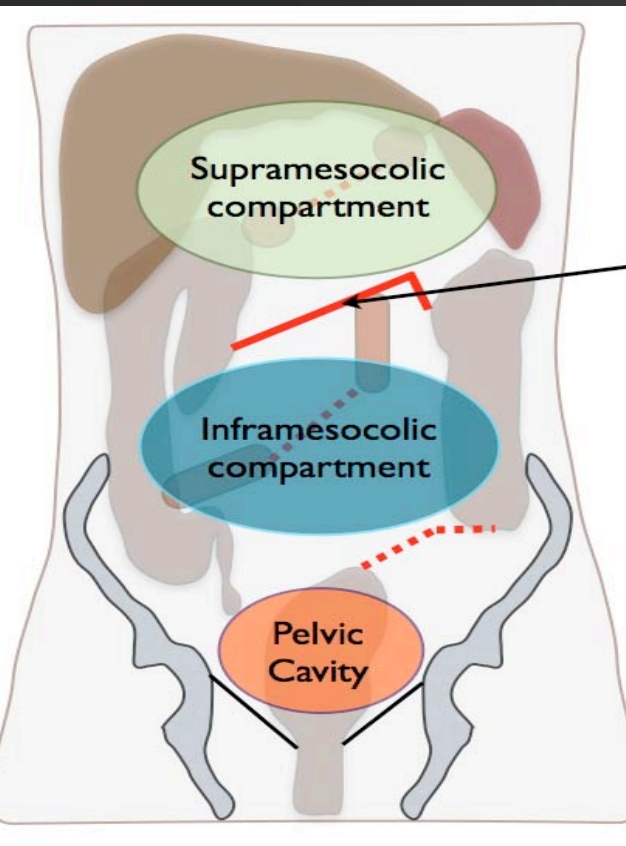
Table 2. Multiple Linear Regression Analysis

Variable	Change in Median Survival Time		95% CI or CL	P
	%	Increase		
Percent maximal cytoreduction	5.5	10%	3.3-7.8	< .001
Year of publication	2.8	1 year	0.9-4.6	.004
Platinum dose-intensity	0.8	10%	-0.7, 2.3	.911
Cumulative platinum dose	1.4	1 U	-1.9, 4.7	.377

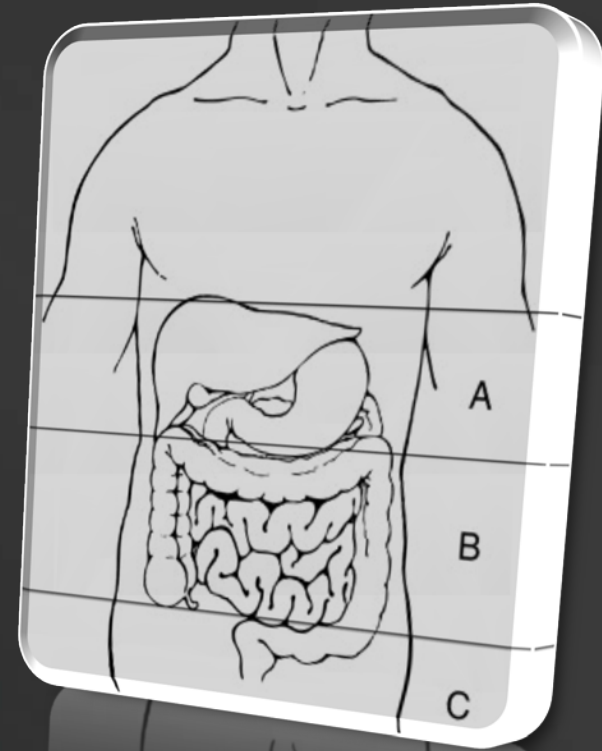
- 1989-1998
- 81 cohorts (Stage III-IV)
- 6885 pts



Critical steps for a complete cytoreduction

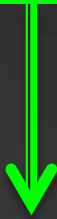


- SUPRAMESOCOLIC
- INFRAMESOCOLIC
- PELVIC CAVITY



Strategie Terapeutiche – Terapia di Prima Linea

Chirurgia
Citoriduttiva
Primaria



Chemioterapia di 1a Linea



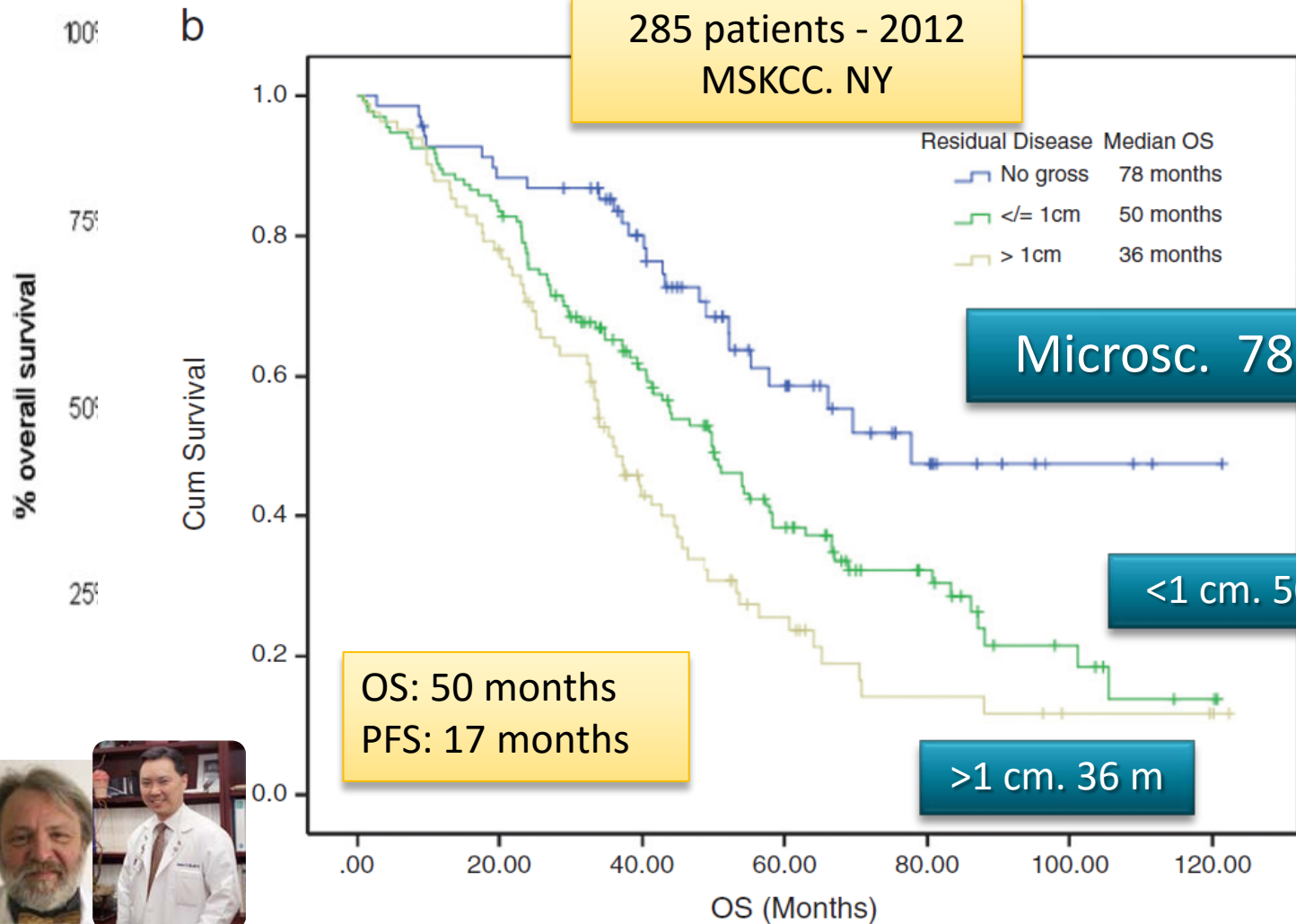
Terapia di
Mantenimento

RT = 0

72 Months and..... beyond

**30 MONTHS
OF ADVANTAGE**

**285 patients - 2012
MSKCC. NY**



The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy

L. C. Hanker^{1*,†}, S. Loibl^{2,†}, N. Burchardi³, J. Pfisterer⁴, W. Meier⁵, E. Pujade-Lauraine⁶, I. Ray-Coquard⁷, J. Sehouli⁸, P. Harter⁹ & A. du Bois⁹ on behalf of the AGO and GINECO study group

	First (HR) n = 1552	95% CI		Second (HR) n = 829	95% CI		Third (HR) n = 414	95% CI		Fourth (HR) n = 178	CI 95%	
PFS												
Age	1.01*	1.00	1.01	1.01	0.99	1.01	1.00	0.99	1.01	1.00	0.99	1.02
ECOG 2 versus 0/1	1.08	0.92	1.28	1.43*	1.13	1.81	0.74	0.50	1.09	1.12	0.60	2.08
FIGO IIIc-IV versus Ib-IIIb	1.12	0.98	1.29	1.26*	1.03	1.54	1.28	0.97	1.71	1.10	0.70	1.74
Grading 2,3 versus 1	1.16	0.86	1.56	1.71*	1.12	2.62	1.74	0.82	3.71	0.17*	0.07	0.40
Endometrioid versus serous	1.07	0.79	1.44	1.19	0.72	1.97	1.37	0.55	3.38	2.61	0.77	8.82
Mucinous versus serous	1.00	0.82	1.21	0.80	0.60	1.07	1.11	0.73	1.68	0.71	0.39	1.28
Tumorrest >0 mm versus 0 mm	1.19*	1.04	1.36	1.27*	1.05	1.54	1.08	0.82	1.41	0.72	0.48	1.09
Platinum sensitive versus resistant	0.67*	0.59	0.75	0.64*	0.54	0.76	0.88	0.69	1.11	0.99	0.68	1.42
Treatment versus no treatment	-	-	-	0.59*	0.49	0.71	0.49*	0.39	0.63	0.88	0.60	1.29
OS												
Age	1.01*	1.01	1.02	1.00	0.99	1.01	1.00	0.99	1.01	1.00	0.98	1.02
ECOG 2 versus 0/1	1.28*	1.07	1.52	1.43*	1.11	1.83	0.77	0.50	1.17	0.85	0.44	1.67
FIGO IIIc-IV versus Ib-IIIb	1.20*	1.03	1.39	1.29*	1.04	1.59	1.37*	1.01	1.87	1.42	0.85	2.36
Grading 2,3 versus 1	1.68*	1.18	2.38	1.26	0.82	1.95	1.48	0.70	3.15	0.44	0.18	1.11
Endometrioid versus serous	0.90	0.73	1.12	0.77	0.56	1.06	0.81	0.52	1.25	0.72	0.39	1.36
Mucinous versus serous	1.63*	1.20	2.21	1.59	0.96	2.63	2.12	0.86	5.24	4.65*	1.40	15.42
Tumorrest >0 mm versus 0 mm	1.27*	1.10	1.47	1.22	0.99	1.50	1.00	0.75	1.33	0.68	0.44	1.05
Platinum sensitive versus resistant	0.59*	0.52	0.66	0.70*	0.59	0.84	1.09	0.85	1.40	1.18	0.80	1.74
Treatment versus no treatment	-	-	-	0.36*	0.30	0.44	0.35*	0.27	0.45	0.55*	0.37	0.81

*P < 0.05.

Annals of Oncology 23: 2605-2612, 2012

doi:10.1093/annonc/mds203

Published online 21 August 2012

1,334 Surgeries for Ovarian Cancer

INT –
2000 - 2014



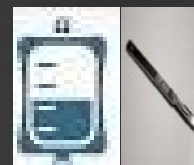
194 Interval Debulking Surgery (IDS)

IDS

14%

**PRIMARY
SURGERY
N=116**

**NACT +
SURGERY
N=40**



INT - 2014

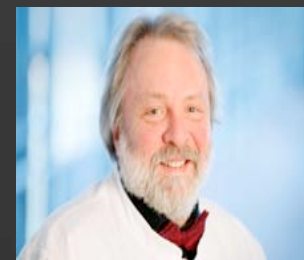
	PRIMARY SURGERY N=116	NACT + SURGERY N=40	
TR 0	86 (74%)	31 (78%)	P = 0.53
TR <1 cm	12 (10%)	5 (12%)	P = 1.00
TR > 1 cm	18 (15%)	4 (10%)	P = 0.44

Role of Surgical Outcome as Prognostic Factor in Advanced Epithelial Ovarian Cancer: A Combined Exploratory Analysis of 3 Prospectively Randomized Phase 3 Multicenter Trials

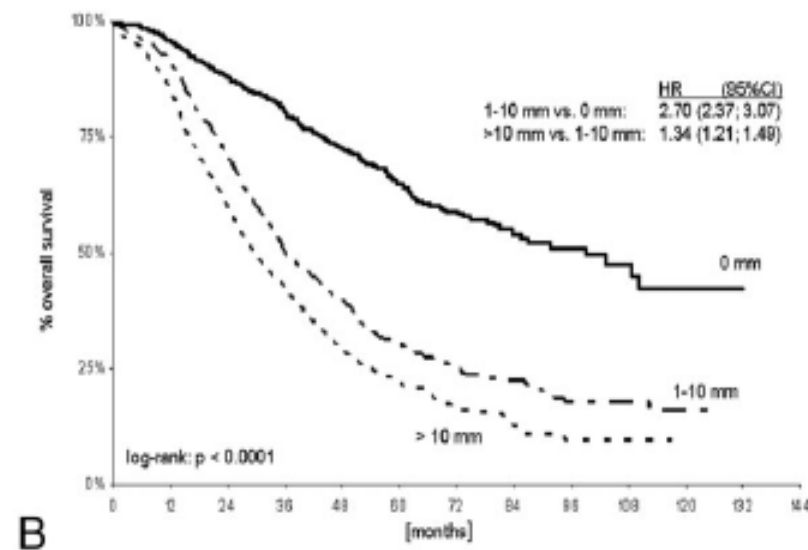
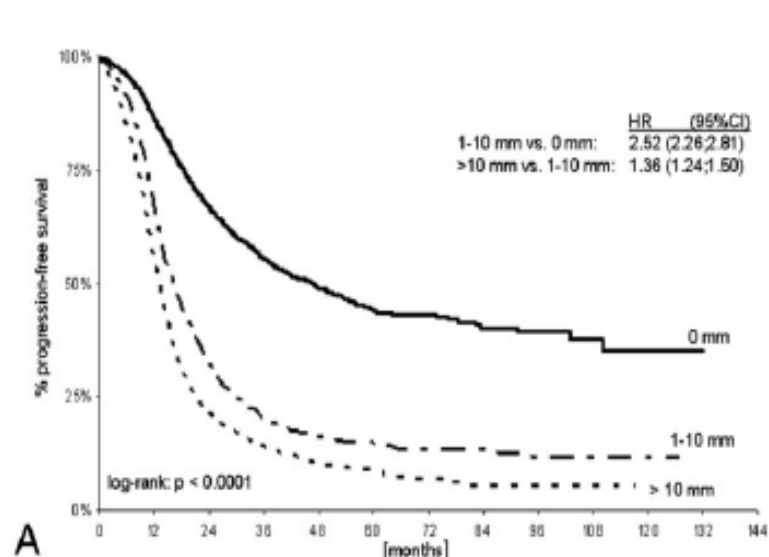
By the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO)

Andreas du Bois, MD¹, Alexander Reuss, MD², Eric Pujade-Lauraine, MD³, Philipp Harter, MD¹, Isabelle Ray-Coquard, MD⁴, and Jacobus Pfisterer, MD⁵

3126
pts



CANCER, 2009



Time to Recurrence in Patients With Recurrence or Death

Outcome 1 st OP	Alive Without Recurrence		0-6 Months		6-12 Months		≥12 Months	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No residuals	483	46.2	93	8.9	120	11.5	350	33.5
Residuals 1-10 mm	158	16.2	213	21.8	263	27.0	341	35.0
Residuals >10 mm	110	10.0	376	34.0	321	29.0	298	27.0
All	751	24.0	682	21.8	704	22.5	989	31.6

The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy

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Mucinous versus serous	1.63*	1.20	2.21	1.59	0.96	2.63	2.12	0.86	5.24	4.65*	1.40	15.42
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Treatment versus no treatment	-	-	-	0.36*	0.30	0.44	0.35*	0.27	0.45	0.55*	0.37	0.81

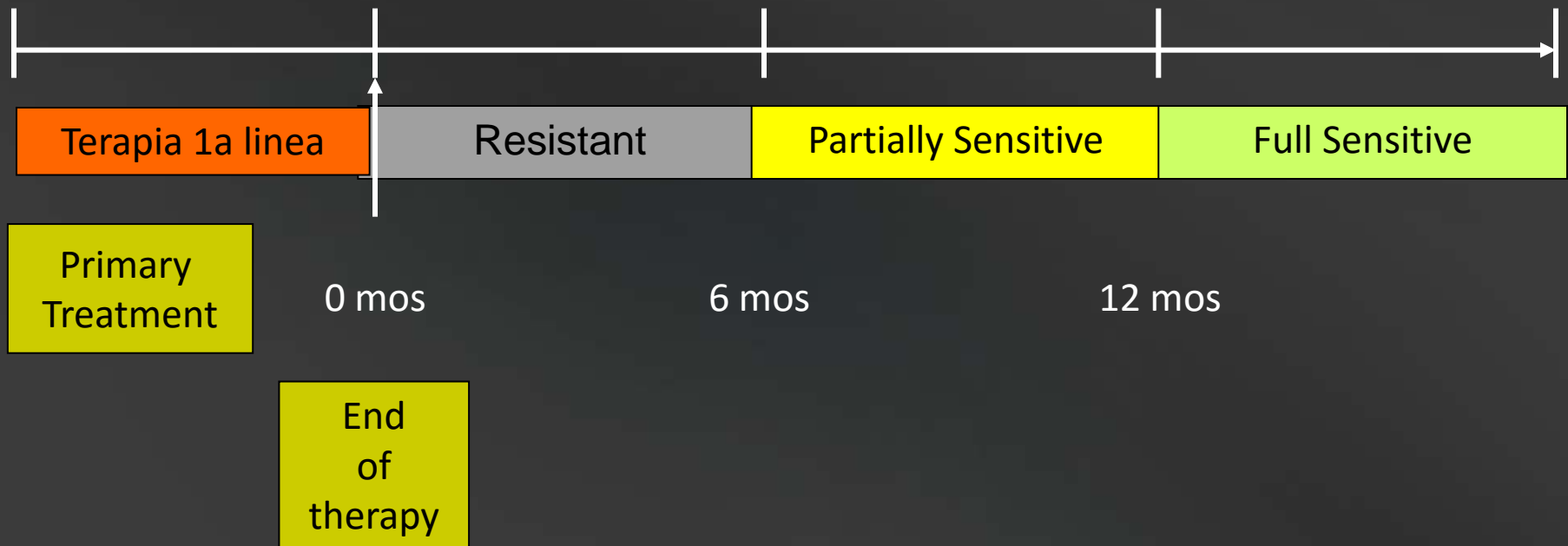
*P < 0.05.

Annals of Oncology 23: 2605-2612, 2012

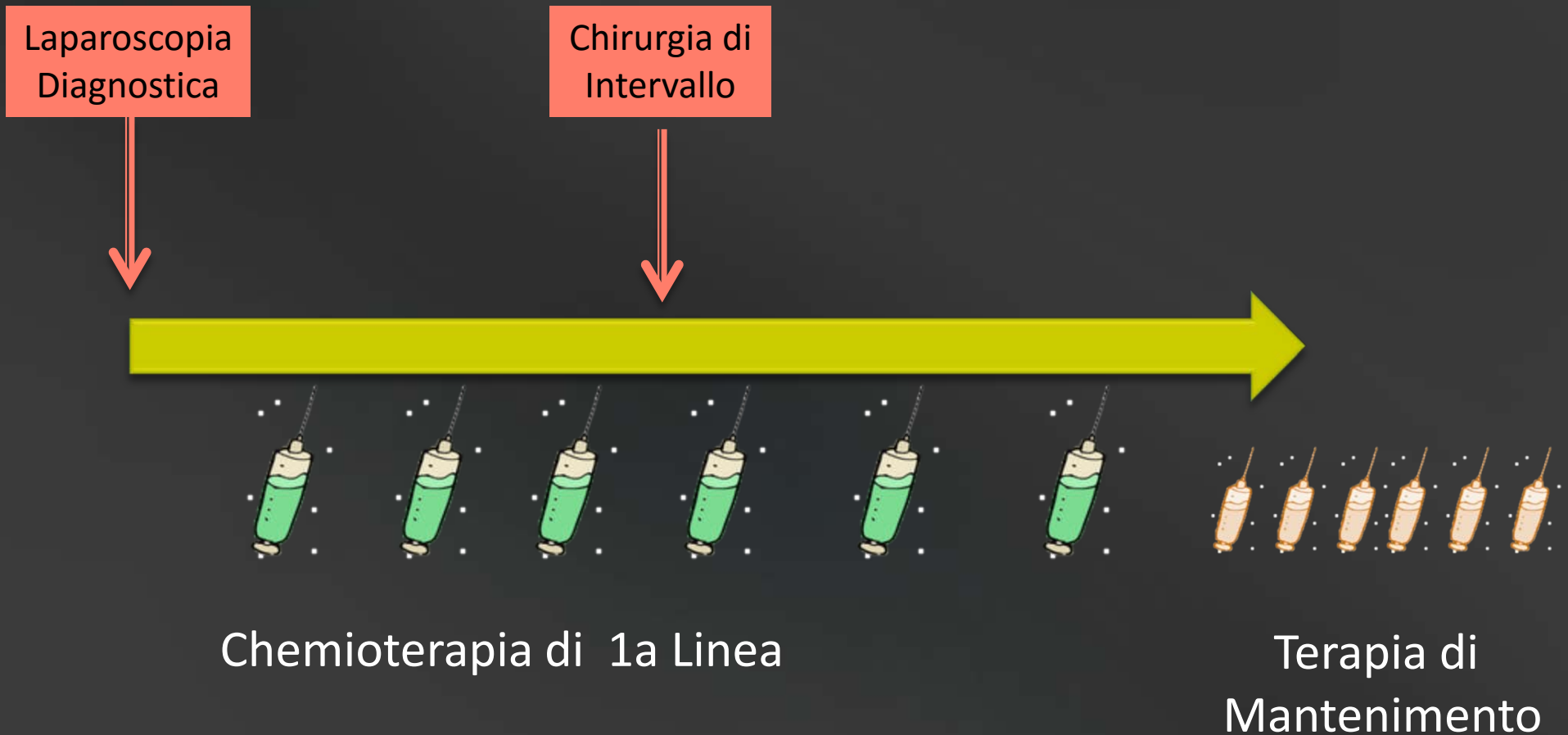
doi:10.1093/annonc/mds203

Published online 21 August 2012

Primary Cytoresduction



Strategie Terapeutiche – Terapia di Prima Linea



NEOADJUVANT-INTERVAL DEBULKING

Author	N	SURVIVAL (MONTHS)
VAN DER BURG (EORTC)	140	21
ROSE (GOG)	216	33
BRISTOW, CHI (META-ANALYSIS)	835	23
VERGOTE (EORTC)	320	29
	1511	27

HISTORICAL SERIES OF SUBOPTIMAL DEBULKING

TRIAL-STUDY	N	SURVIVAL (MONTHS)
GOG 97	65	21
GOG 111	680	38
GOG 114	845	26
GOG 152	216	33
ICON-5	459	33
AGO-OVAR	1046	29

Patients' survival seems to be limited by
Neoadjuvant approach ?

30 months



Our current goal.....



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.,

Ignace Vergote, M.D., Ph.D., Claes G. Tropé, M.D., Ph.D.,

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

Randomisation

Primary Debulking Surgery

3 x Platinum based CT

**Interval debulking
(not obligatory)**

≥ 3 x Platinum based CT

Neoadjuvant chemotherapy

3 x Platinum based CT

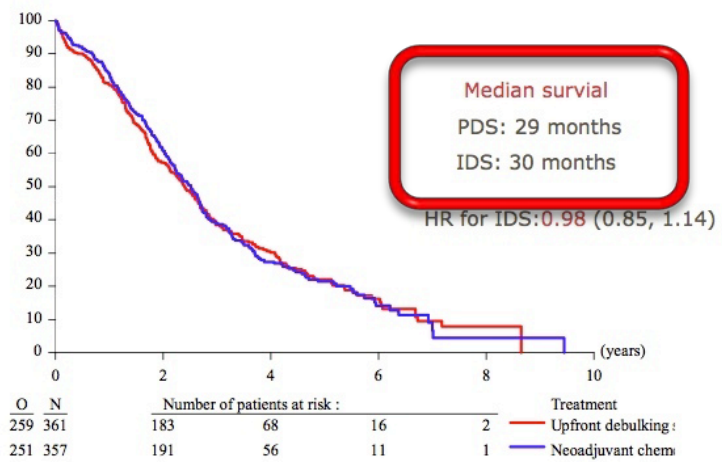
Interval debulking if no PD

≥ 3 x Platinum based CT



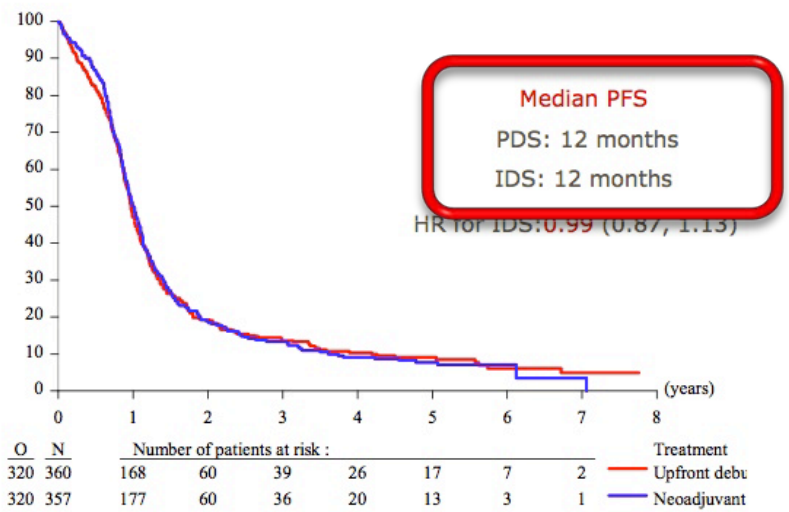
NACT + IDS versus PDS: ITT

Overall survival



NACT + IDS versus PDS: ITT

Progression-free survival



Should Neoadjuvant Chemotherapy
be considered the new standard of
care for advanced ovarian
carcinoma?

● Let's see

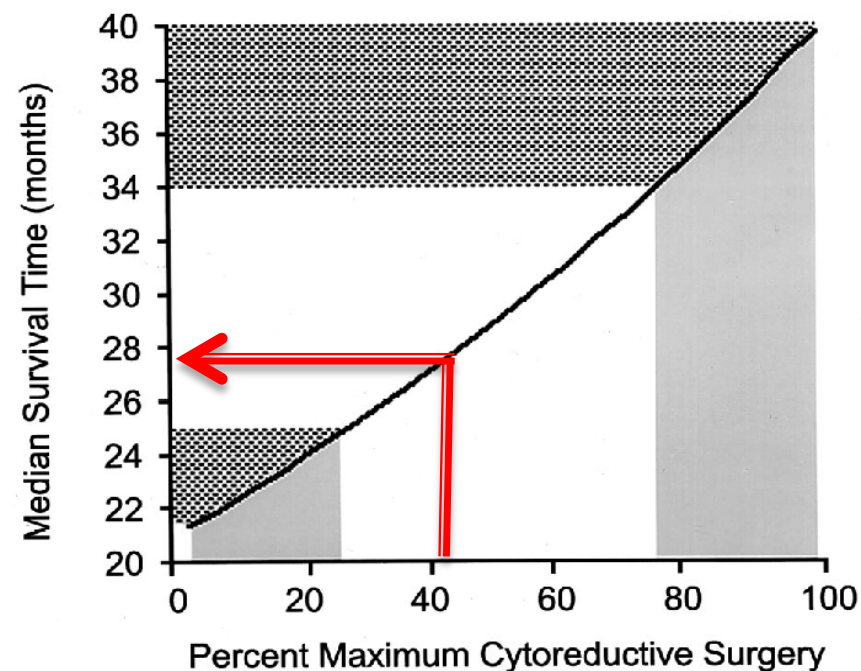
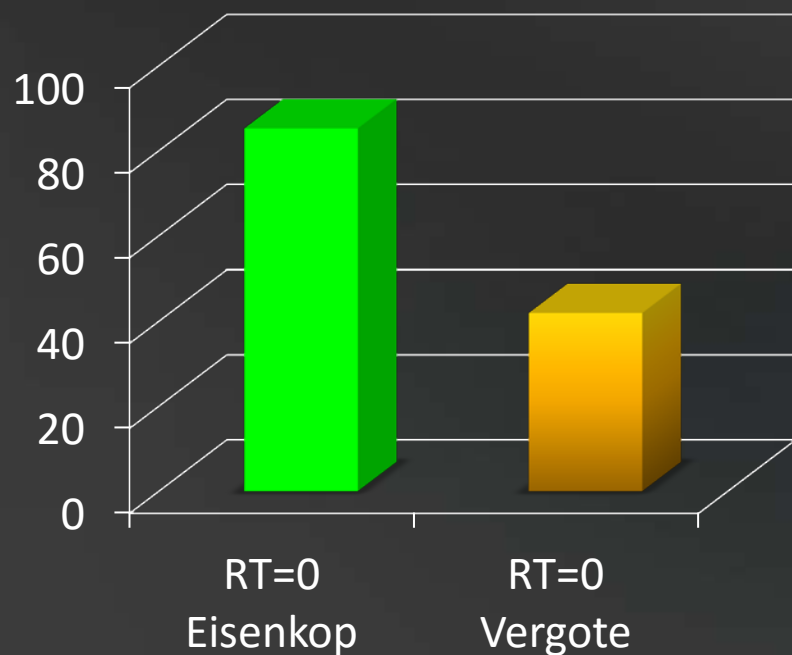


Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer



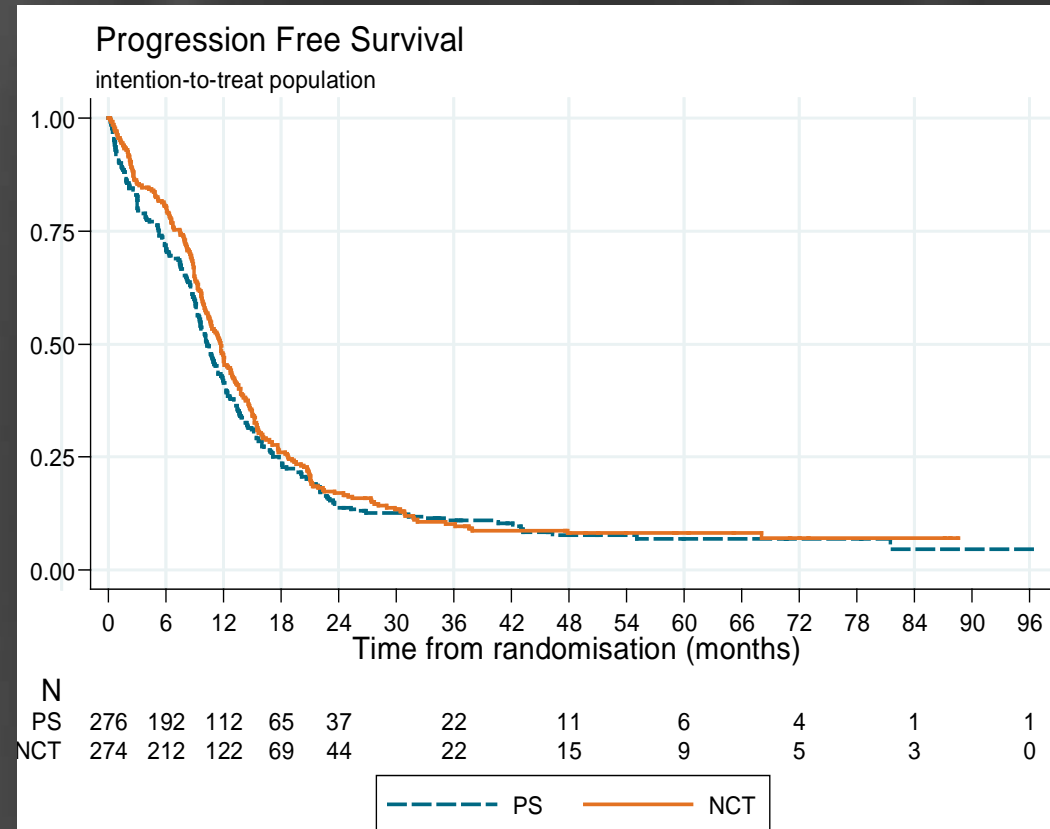
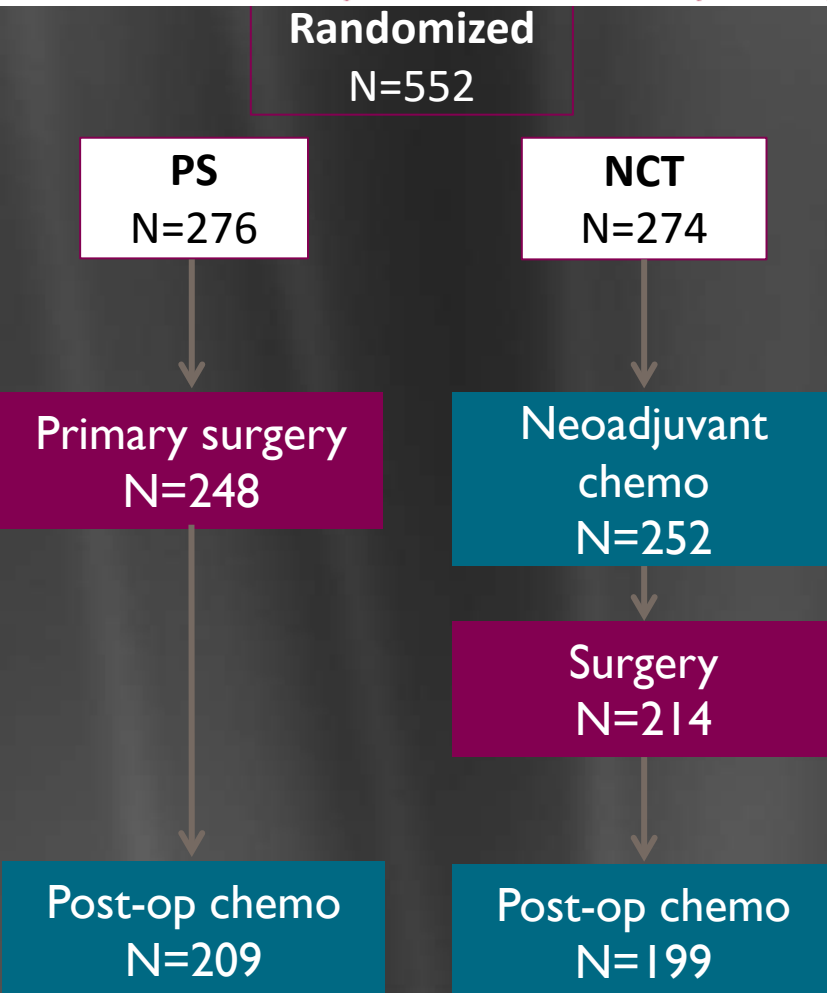
Ignace Vergote, M.D., Ph.D., Claes G. Tropé, M.D., Ph.D.,

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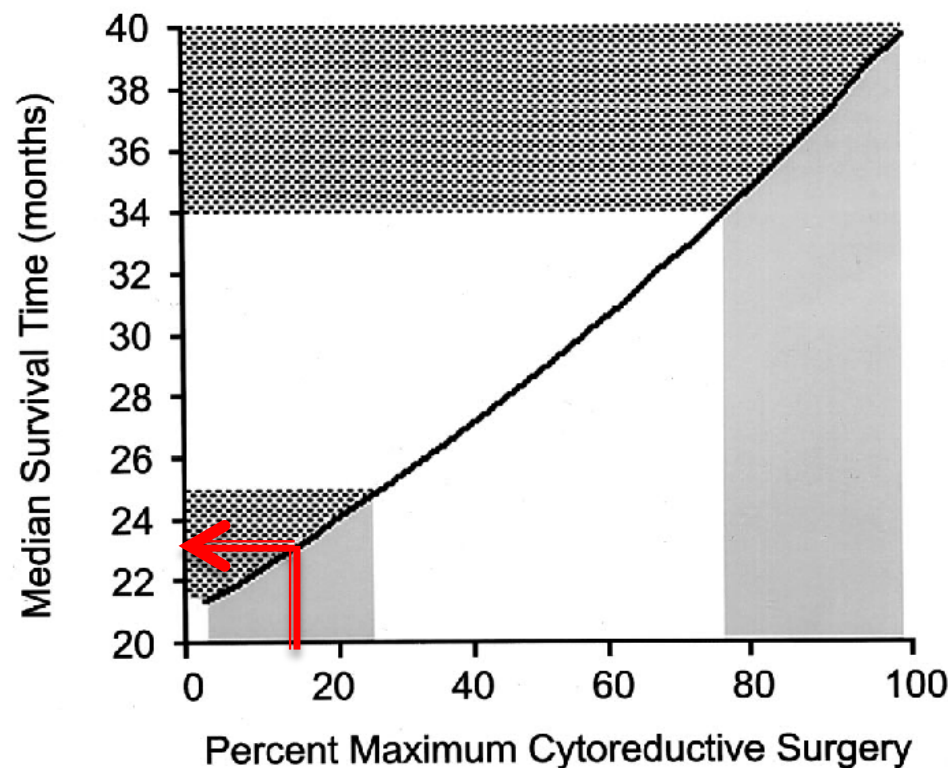
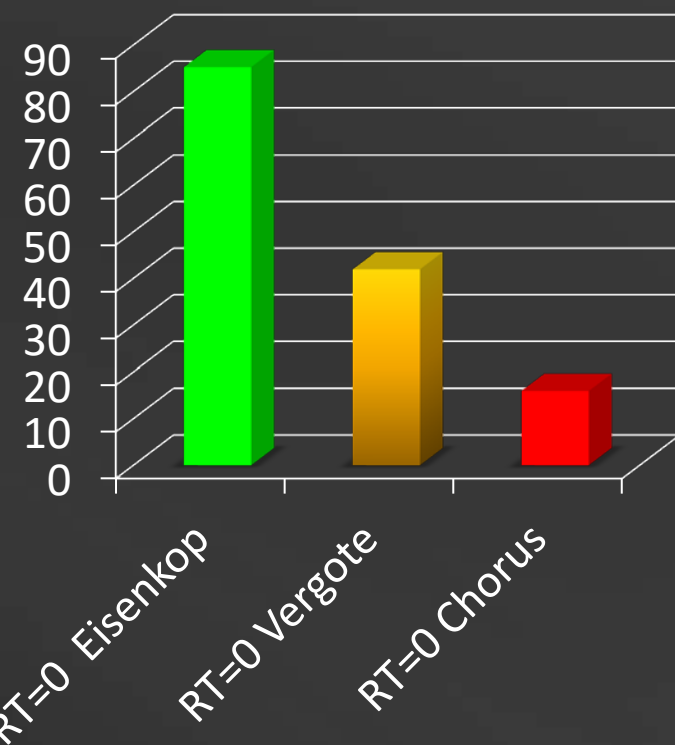


Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial

Sean Kehoe, Jane Hook, Matthew Nankivell, Gordon C Jayson, Henry Kitchener, Tito Lopes, David Luesley, Timothy Perren, Selina Bannoo, Monica Mascarenhas, Stephen Dobbs, Sharadah Essapen, Jeremy Twigg, Jonathan Herod, Glenn McCluggage, Mahesh Parmar, Ann-Marie Swart



		PS (N=250)*		NCT (N=216)*
Optimal debulking	0cm	37 (16%)	41%	77 (40%)
	≤1cm	57 (25%)		67 (35%)



(25%)
20
- 330)

“All surgery was done in 64 centers by specialist gynaecological oncologist who have been accredited by the Royal College of Obstetricians and Gynecologists . Such surgeons operate on at least 15 with ovarian cancer each year patients”

What Should We Expect After a Complete Cyto-reduction at the Time of Interval or Primary Debulking Surgery in Advanced Ovarian Cancer?

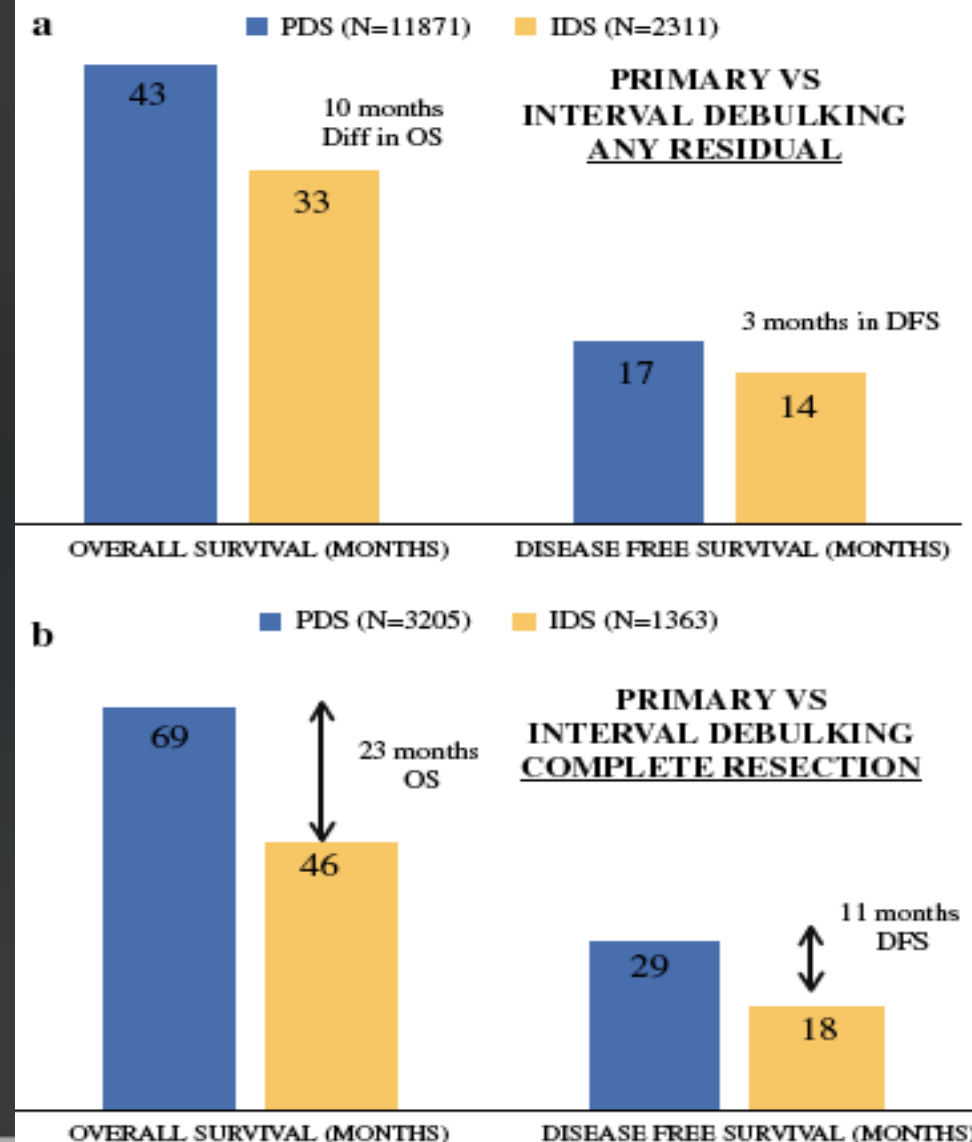
Luis Chiva, MD, PhD¹, Fernando Lapuente, MD¹, Teresa Castellanos, MD¹, Sonsoles Alonso, MD, PhD¹, and Antonio Gonzalez-Martin, MD²

Purpose. To compare the impact, in terms of survival, of complete cyto-reduction after primary debulking surgery (PDS) and interval debulking surgery (IDS) in patients with advanced ovarian cancer (International Federation of Gynecology and Obstetrics stages III–IV) by reviewing the recent literature.

Methods. A search of the PubMed database during the last 7 years (2008–2014) was carried out looking for studies specifically showing data on median survival or disease-free survival after complete cyto-reduction after either PDS or IDS.

Results. We found 24 publications including 14,182 patients with stages III to IV ovarian cancer. A total of 11871 patients (83.7 %) underwent PDS and 2311 (16.3 %) underwent interval debulking after neoadjuvant chemotherapy. A total of 4684 patients (33 %) were considered completely resected with microscopic residual disease. After PDS, the weighted average of median overall and progression-free survival was 43 and 17 months, respectively, for the whole group. After IDS, median and progression-free survival were 33 and 14 months. The rate of complete cyto-reduction after PDS was inferior to the obtained in patients with IDS (27 vs. 59 %). However, the median survival in patients with complete cyto-reduction with primary cyto-reduction was 23 months longer than in the group with interval debulking (69 vs. 45 months).

Conclusions. Complete cyto-reduction after IDS yields a inferior outcome in terms of median survival than PDS of



Primary Cytoresduction

**Interval
Surgery**

Refractory

Resistant

Partially Sensitive

Full Sensitive

Primary
Treatment

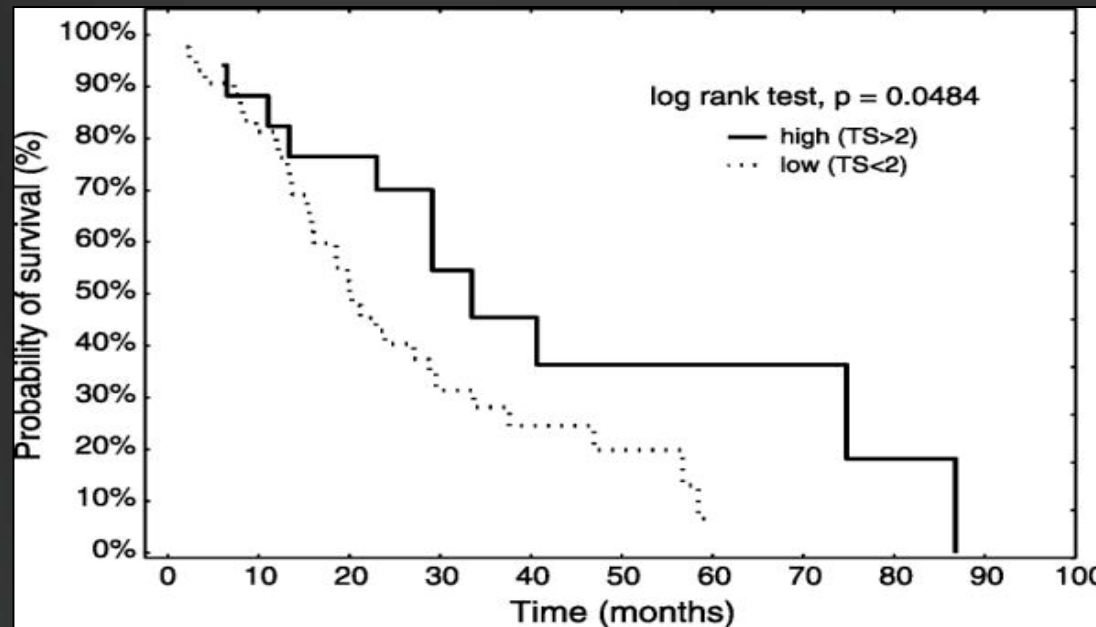
0 mos

6 mos

12 mos

End
of
therapy

Survivin Expression as a Prognostic Factor in Patients With Epithelial Ovarian Cancer or Primary Peritoneal Cancer Treated With Neoadjuvant Chemotherapy



We observed significant decrease in nuclear survivin expression in ovarian cancer cells in the tumor tissues taken after NAC compared with that collected before NAC.

TP53 K351N mutation-associated platinum resistance after neoadjuvant chemotherapy in patients with advanced ovarian cancer

(Zhang Gynecol Oncol 2014)

TP53 K351N mutations were detected in:

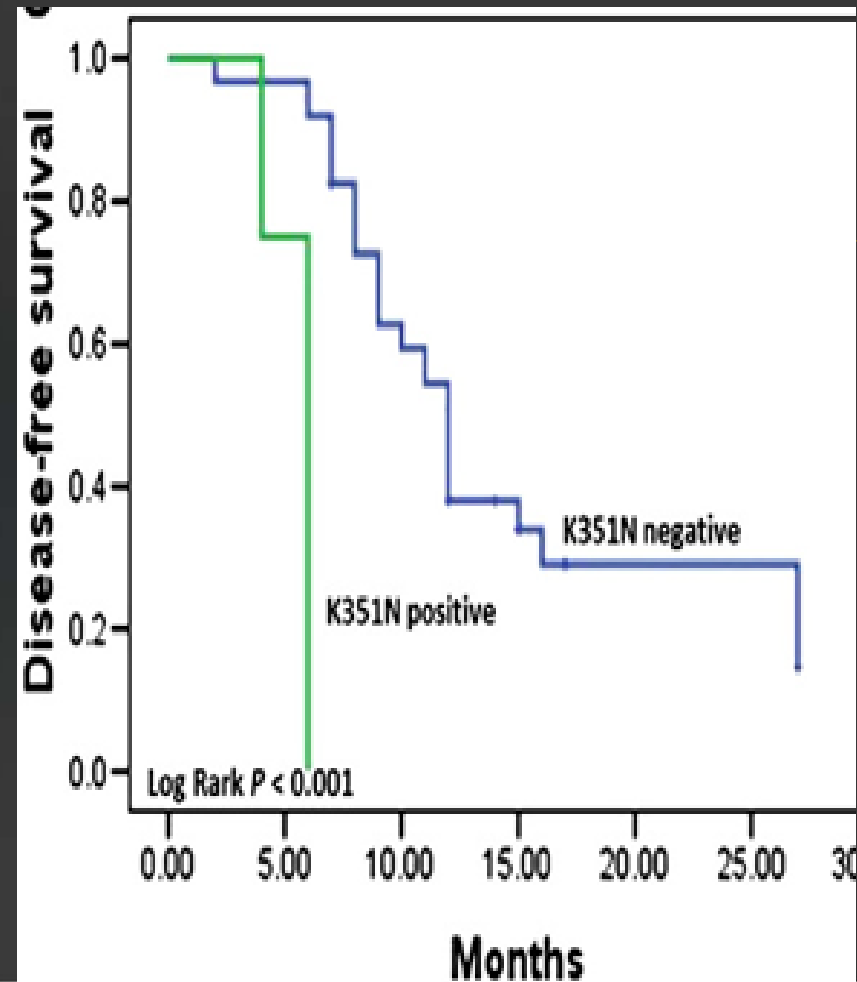
NACT-IDS 8/71 (11.27%)

PDS 0/82 (0%)

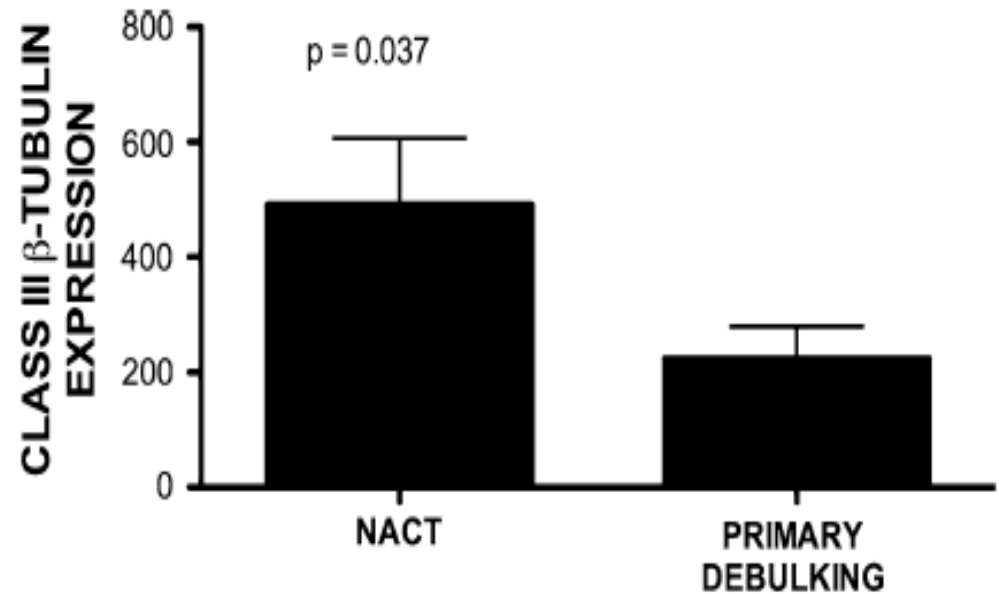
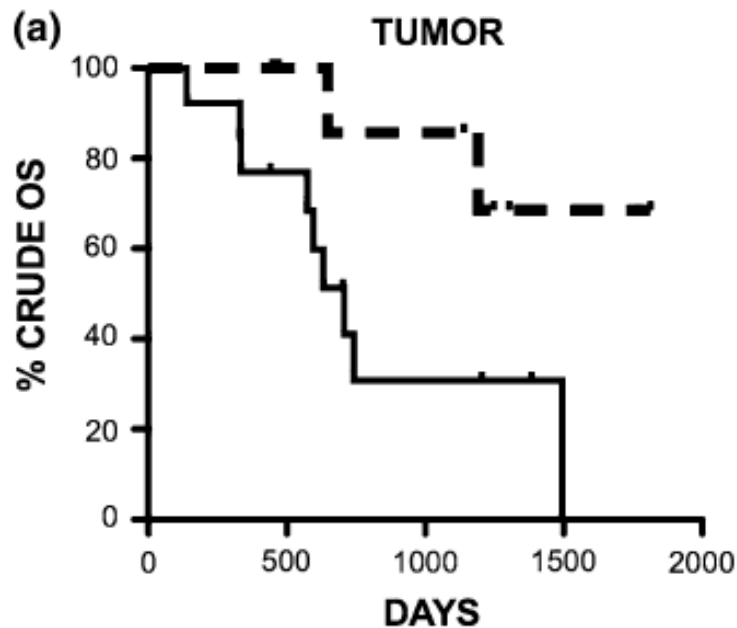
(P 0.01)

Conclusions.

TP53 K351N mutation may be associated with induction of platinum resistance after NACT in advanced EOC



Class III β -tubulin overexpression within the tumor microenvironment is a prognostic biomarker for poor overall survival in ovarian cancer patients treated with neoadjuvant carboplatin/paclitaxel





Gyn Onc Surgeon

- Thorough Knowledge of Anatomy
- Abdominal Surgeon Skills
- Knowledge of the literature
- Motivated Surgeon
- Awareness that the surgical procedure may change the prognosis of the patient



Thanks

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