ACTO ONLUS
ALLEANZA CONTRO il TUMORE OVARICO

GIORNATA MONDIALE SUL TUMORE **OVARICO**

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

F. Raspagliesi MD

Gynecologic Oncology Unit

FONDAZIONE IRCCS
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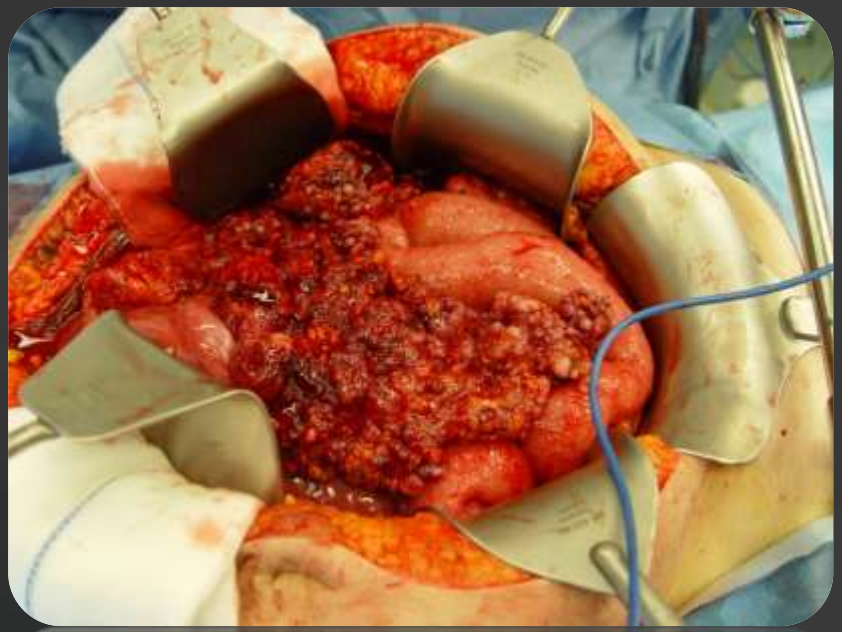
DEI TUMORI

Primary vs Interval Cytoreduction Surgery

Background

- Advanced ovarian cancer is basically an incurable disease.
- An intelligent combination of surgery and chemotherapy may prolong significantly the overall survival in these patients.



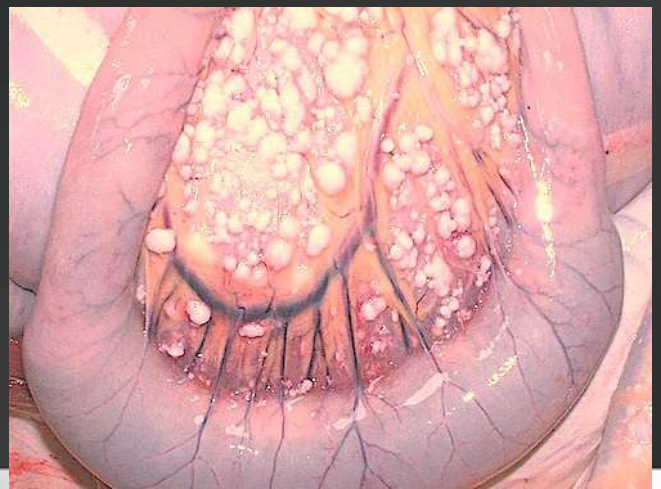
- Surgery is an essential in treating ovarian cancer.
- Diagnosis, staging, and therapy are performed at the time of laparotomy
- Debulking (cytoreduction) is the surgical approach for ovarian carcinoma

Biological Characteristics of Tumour vs. Aggressiveness of Surgery

chemosensitivity

successful debulking surgery

survival



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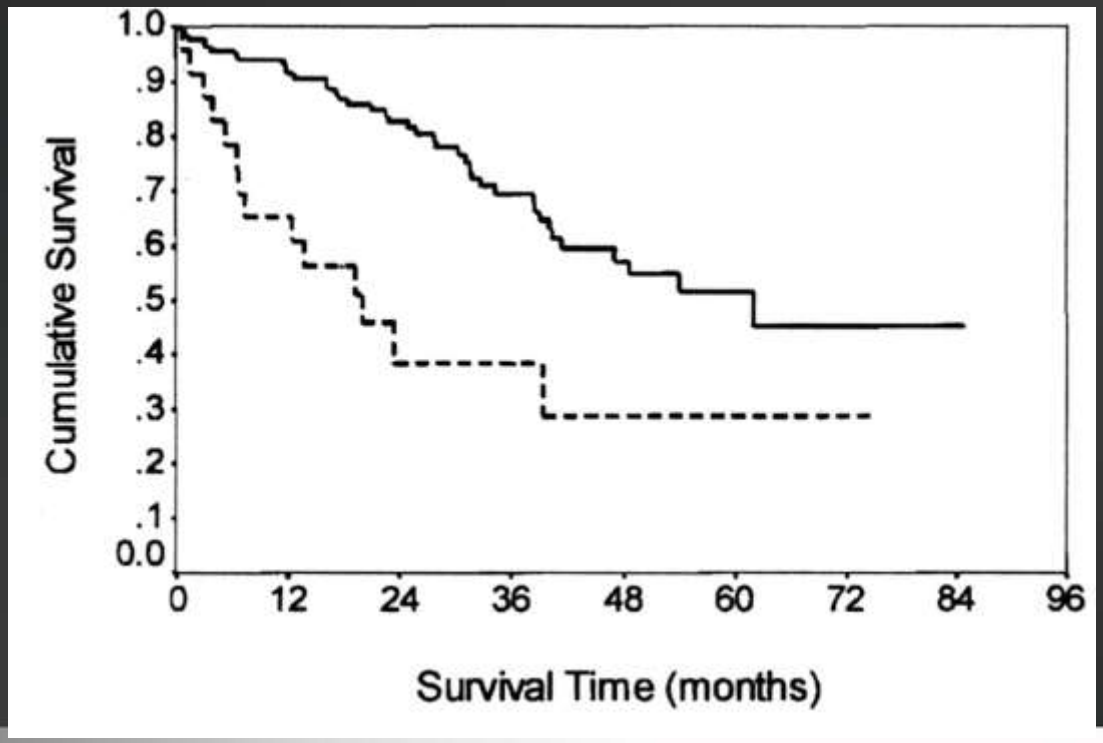
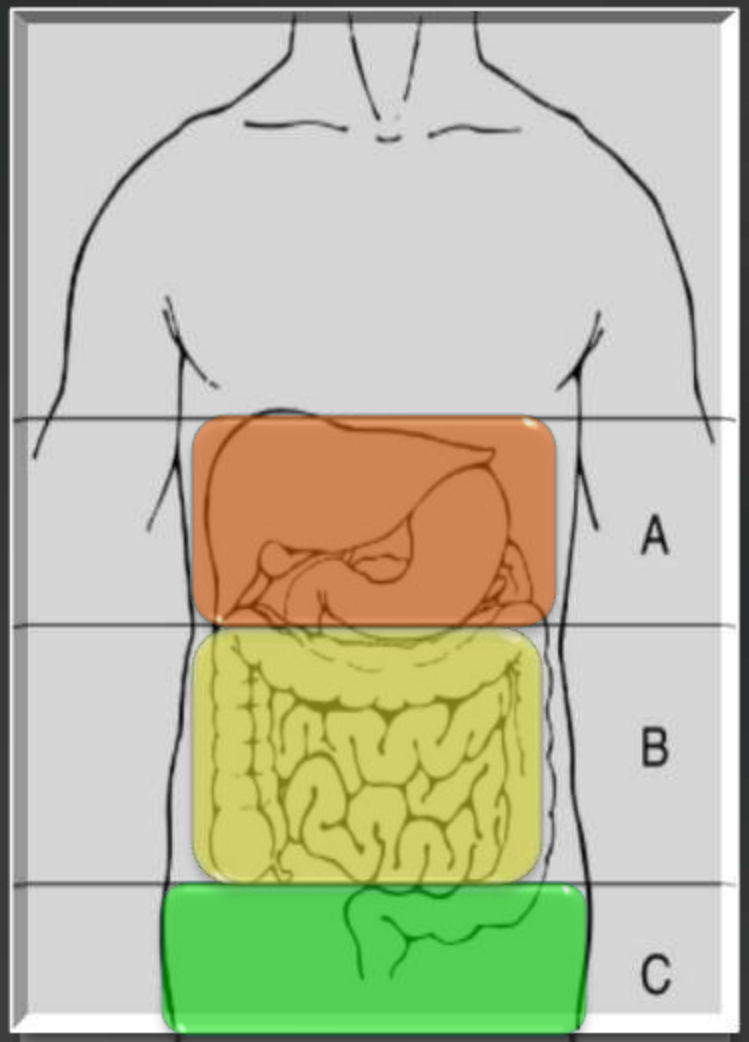
"Complete cytoreduction is feasible and improve survival"

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



Critical steps for a complete cytoreduction

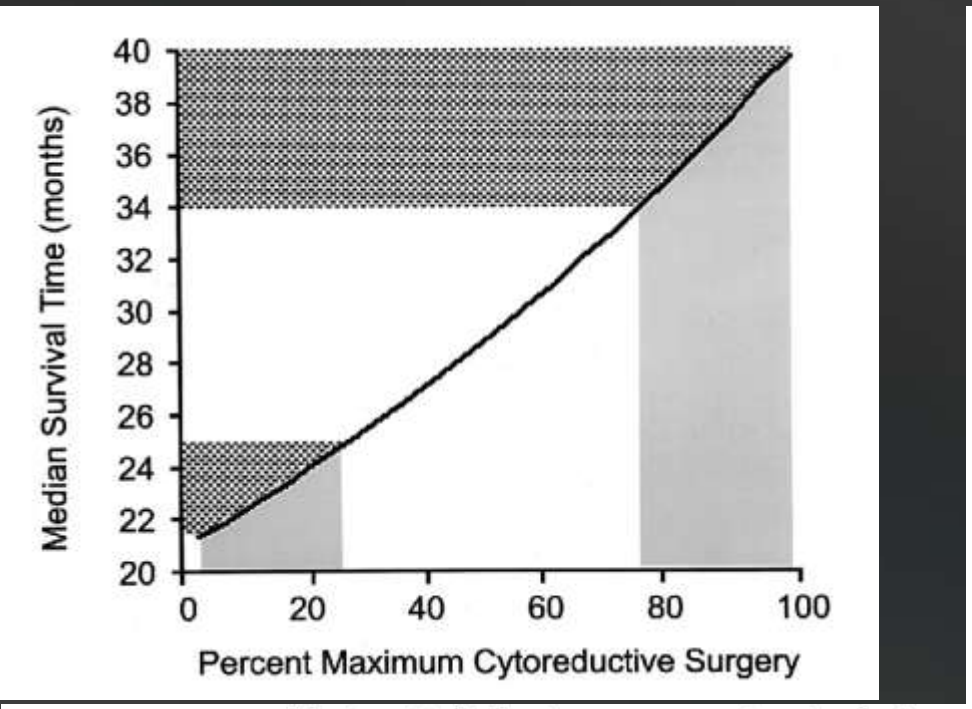


- UPPER ABDOMEN
- MID-ABDOMEN
- RETROPERITONEUM
- PELVIC TUMOR

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

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



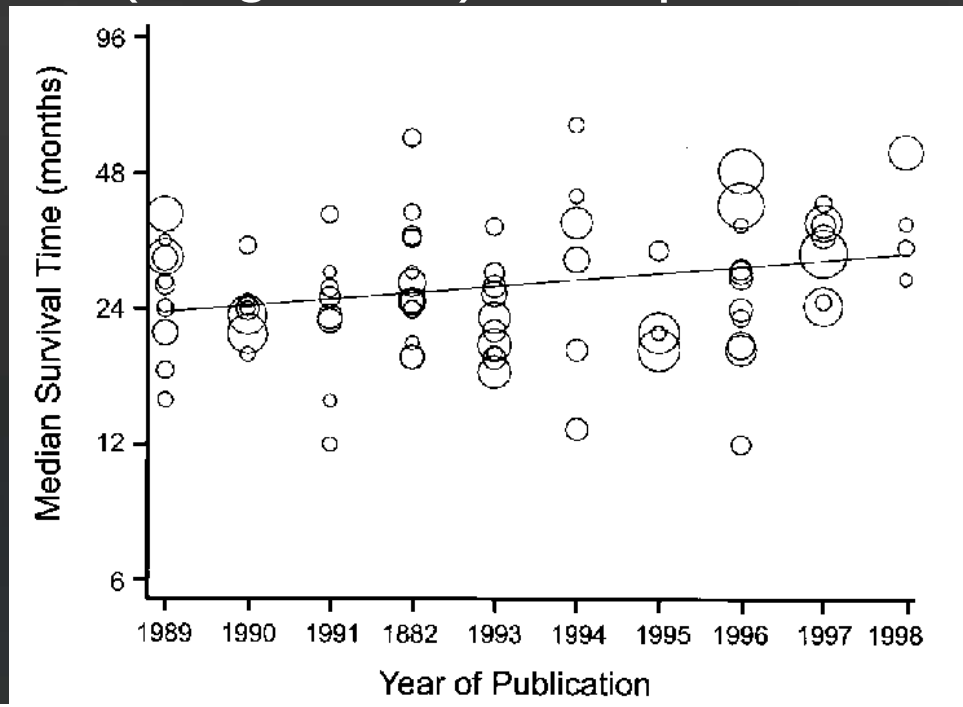


Table 2. Multiple Linear Regression Analysis

Variable	Change in Median Survival Time %	Increase	95% CI or CL	P
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

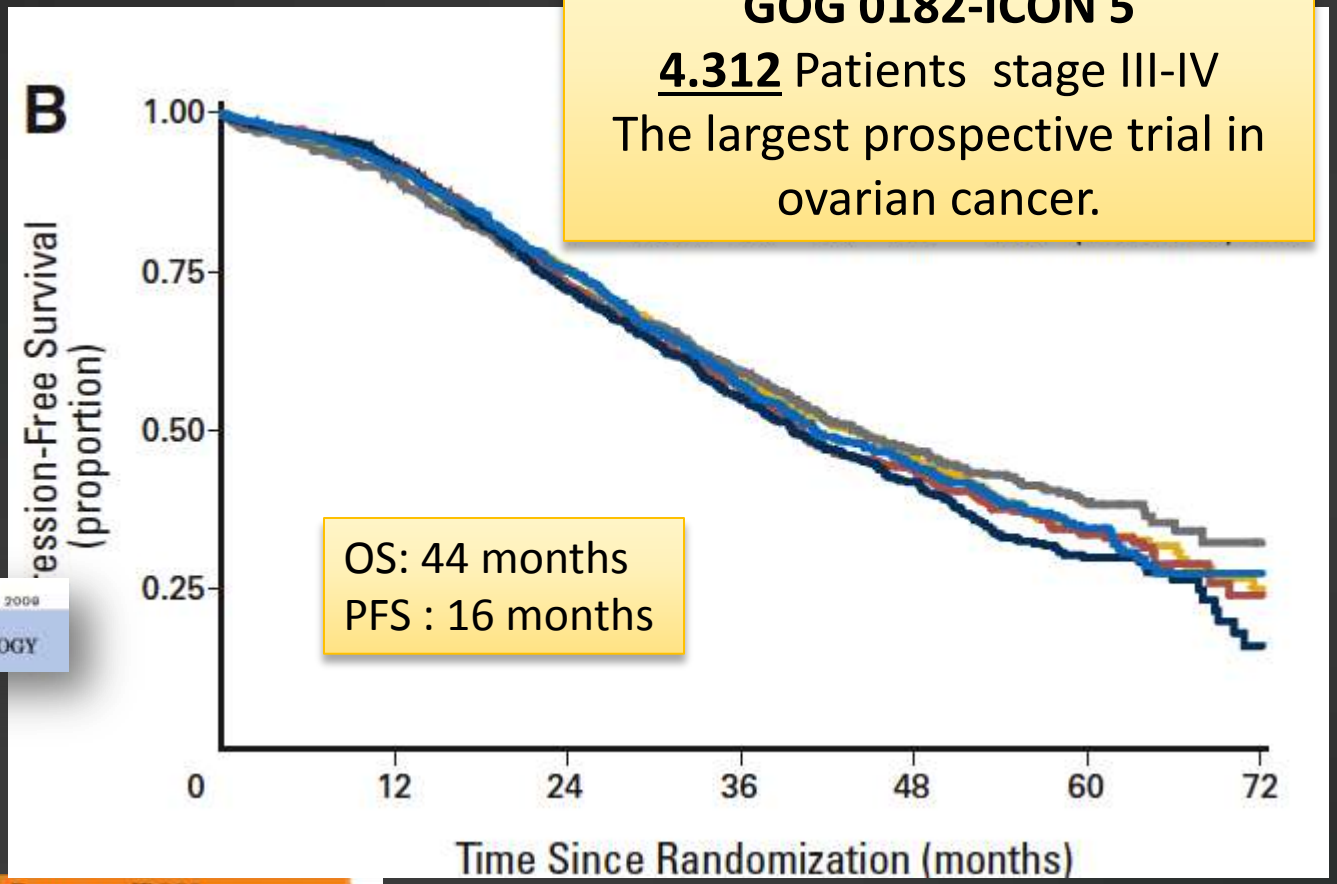
Bristow E et al, JCO 20:1248-59, 2002

Our current goal……

Background

- A large fraction of patients with ADVANCED ovarian cancer may expect today an average survival of more than 40 months.

GOG 0182-ICON 5
4.312 Patients stage III-IV
The largest prospective trial in ovarian cancer.



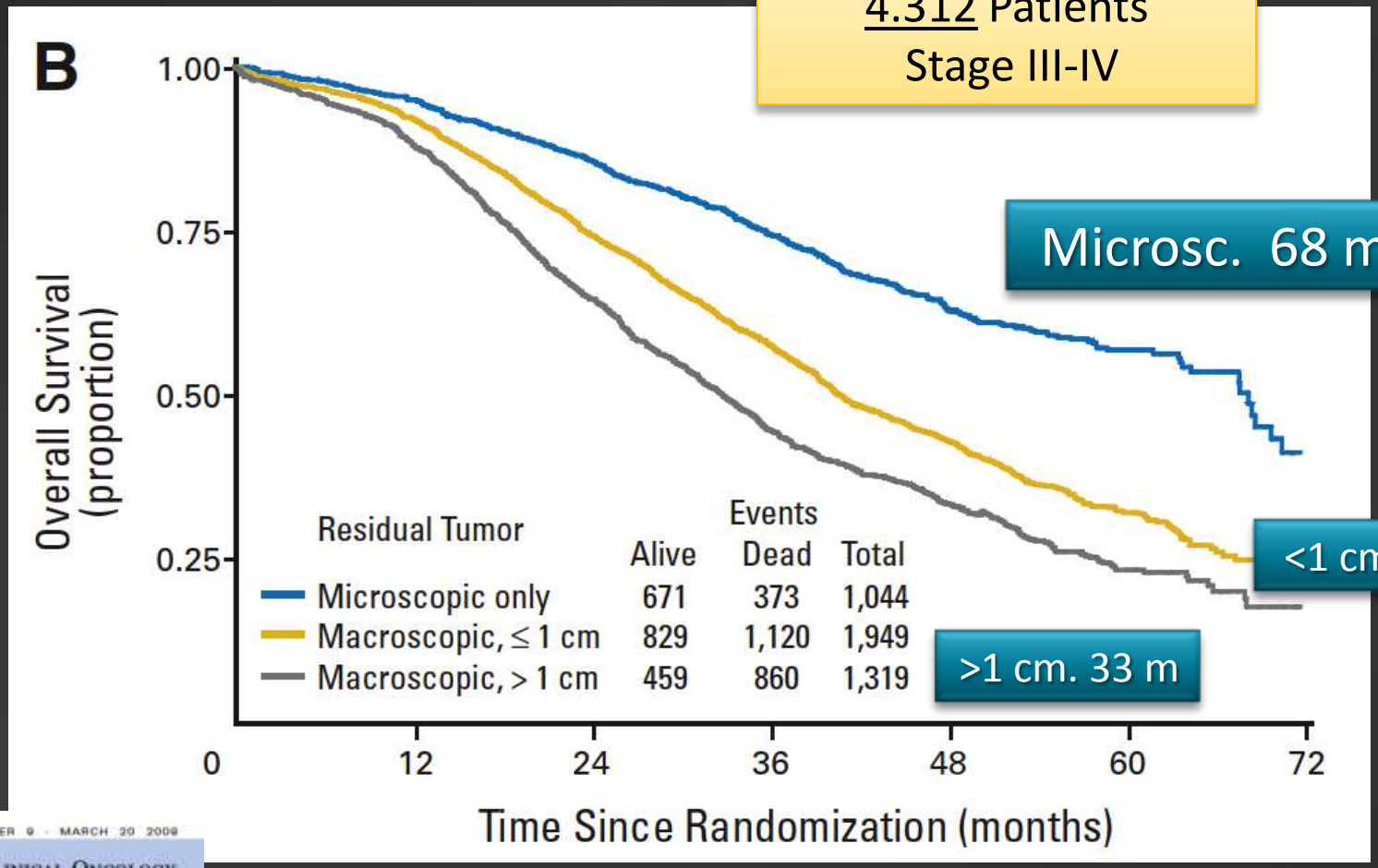
OS: 44 months
PFS : 16 months

VOLUME 27 · NUMBER 9 · MARCH 20 2009
JOURNAL OF CLINICAL ONCOLOGY

(2009)

- Selected patients can reached average survival rates up to 70 months depending on the grade of residual disease after surgery

ICON 5
4.312 Patients
Stage III-IV

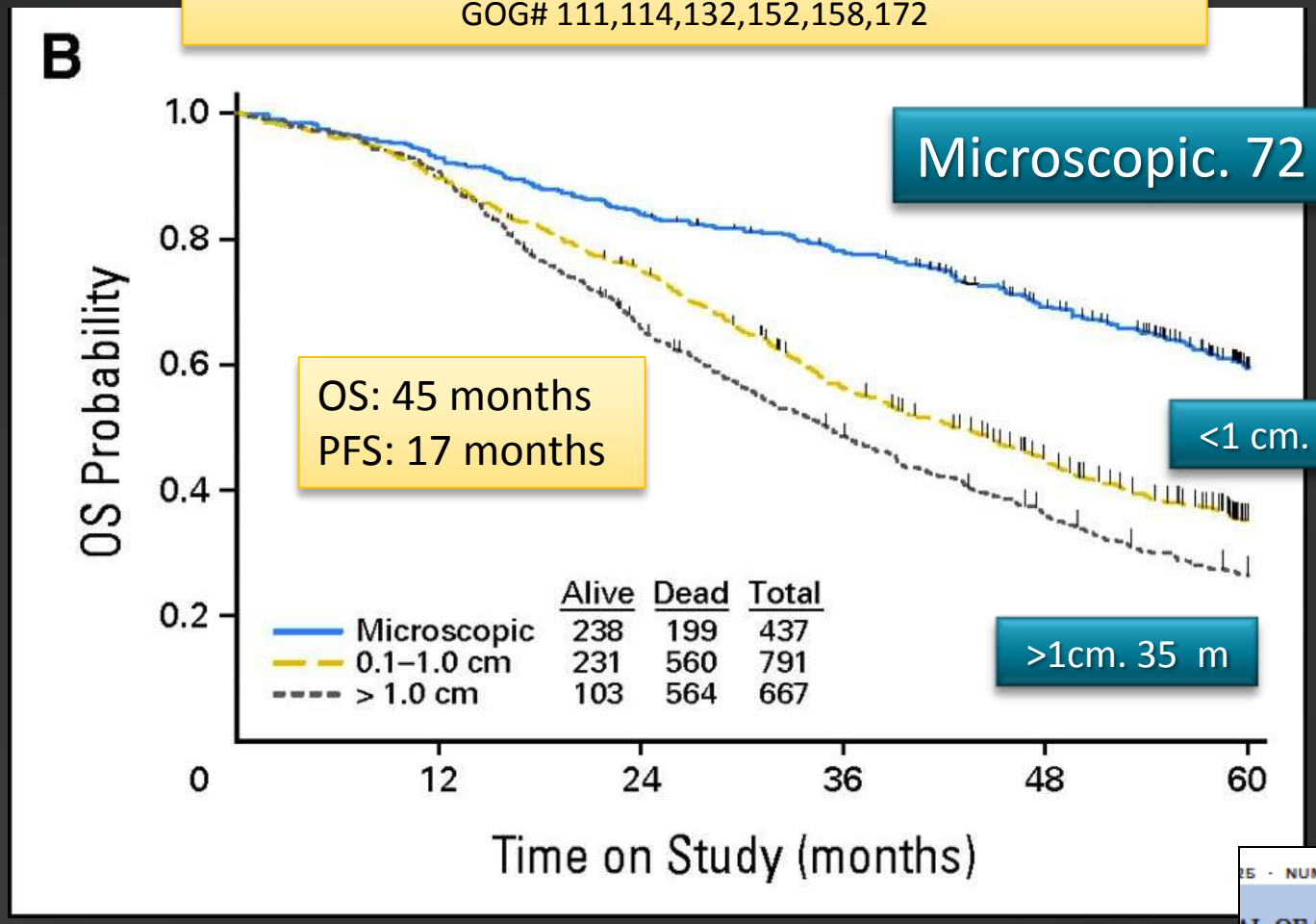


VOLUME 27 · NUMBER 9 · MARCH 20 2009
JOURNAL OF CLINICAL ONCOLOGY

The GOG experience.....

Winter, 2008: 1895 pt . Stage III

GOG# 111,114,132,152,158,172



Microscopic. 72 m

OS: 45 months
PFS: 17 months

<1 cm. 42 m

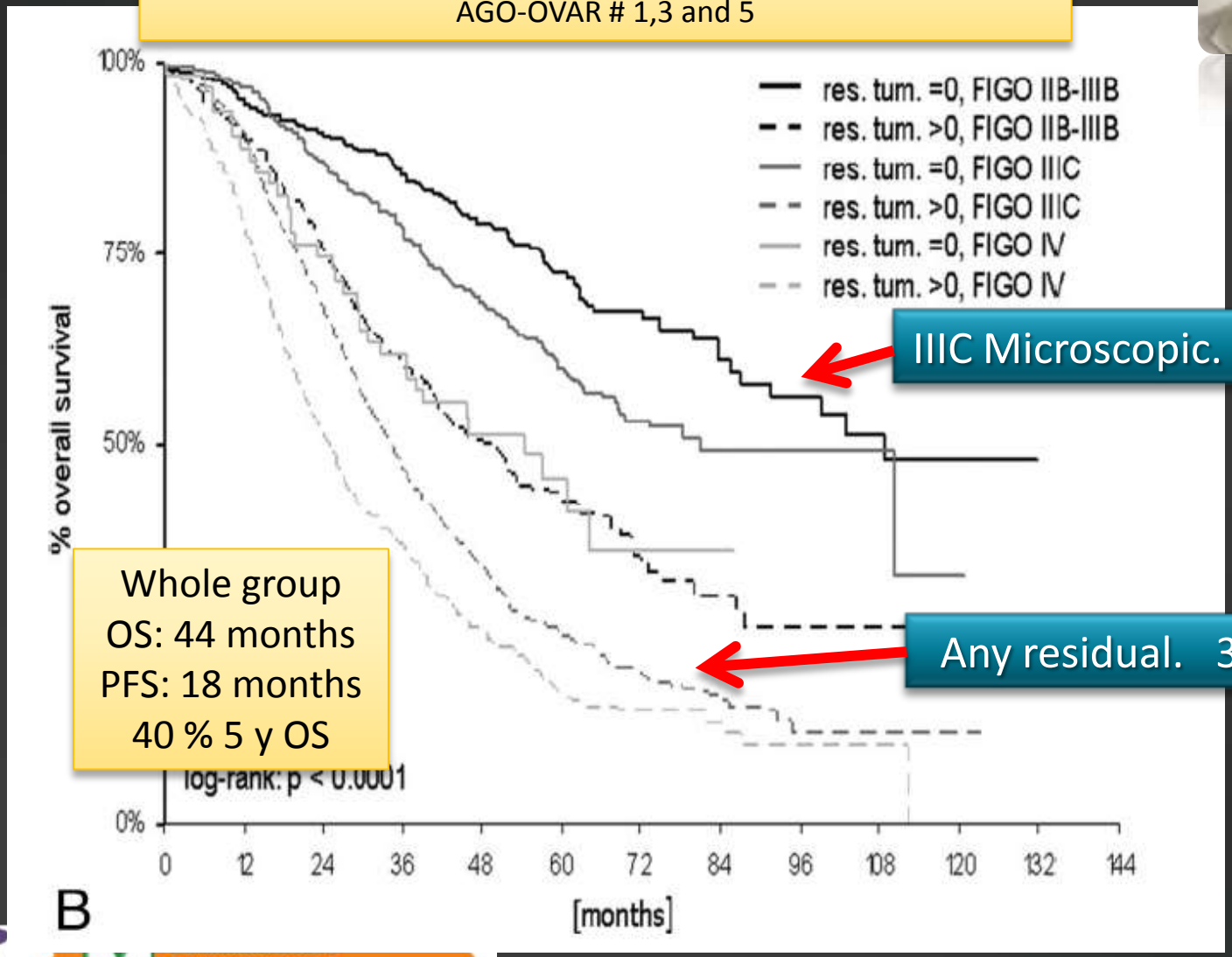
>1cm. 35 m

25 · NUMBER 24 · AUGUST 20 2007
AL OF CLINICAL ONCOLOGY

The AGO-OVAR experience.....

Du Bois, 2010: 1779 pt . Stage IIIC

AGO-OVAR # 1,3 and 5



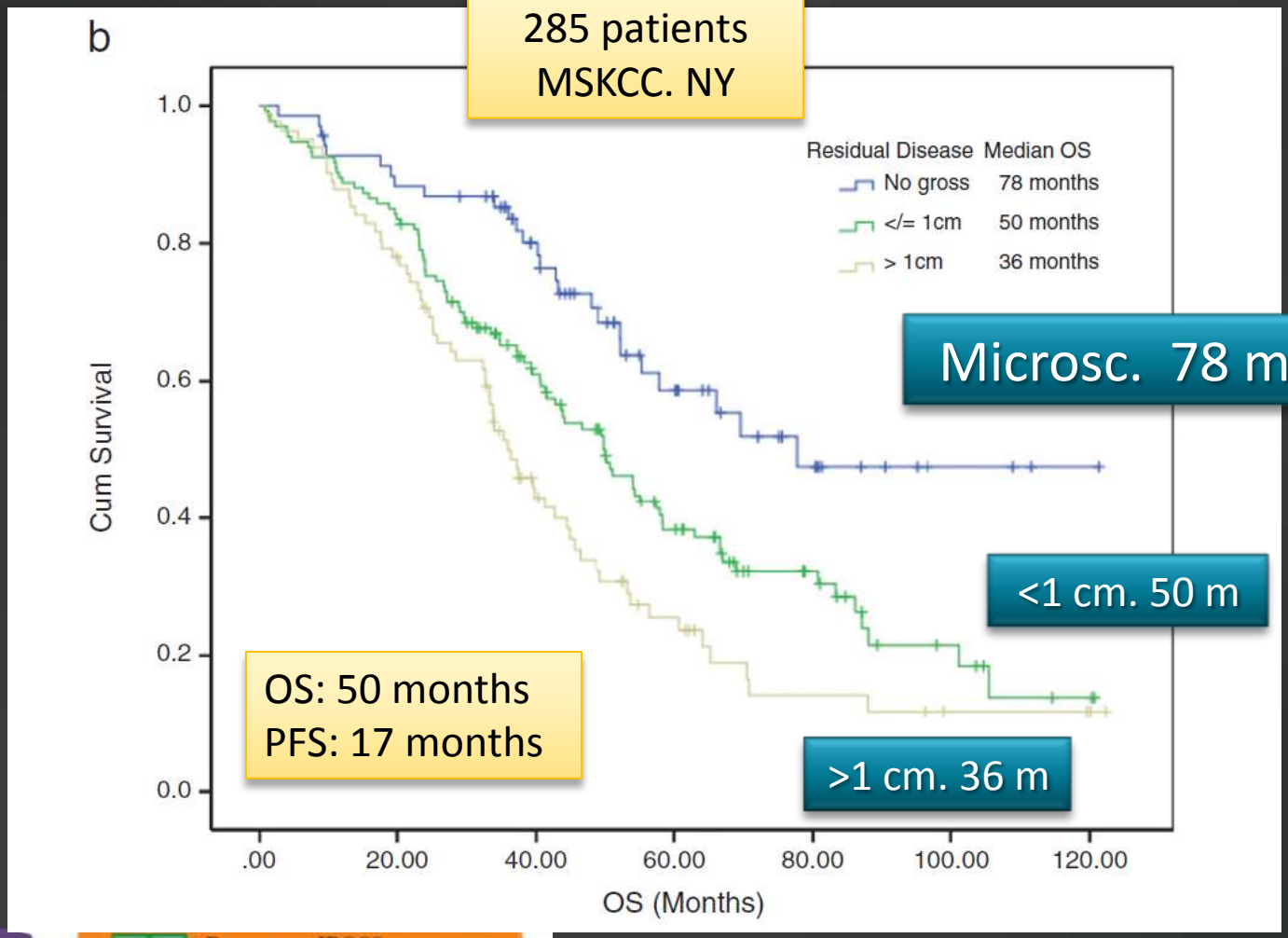
IIIC Microscopic. 81 m

Any residual. 34 m

Whole group
OS: 44 months
PFS: 18 months
40 % 5 y OS

An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT) ☆

285 patients
MSKCC. NY



Microsc. 78 m

<1 cm. 50 m

>1 cm. 36 m

OS: 50 months
PFS: 17 months

UPFRONT SURGERY

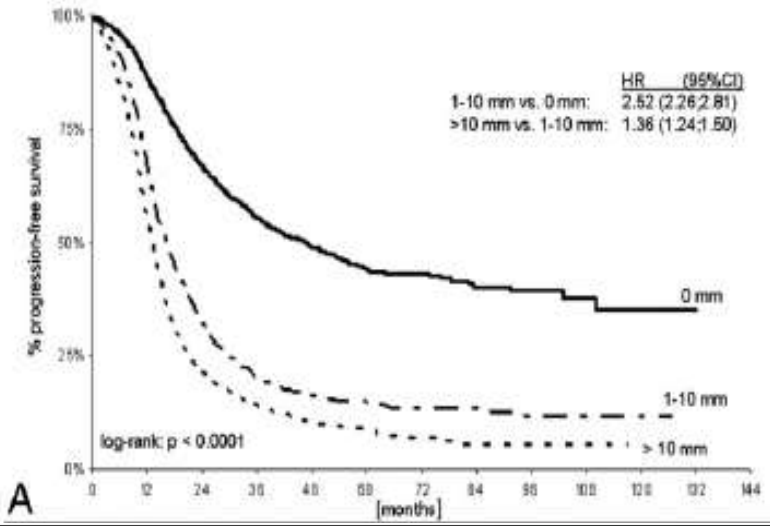
Role of Surgical Outcome as Prognostic Factor in Advanced Epithelial Ovarian Cancer: A Combined Exploratory Analysis of 3 Prospectively Randomized Phase 3 Multicenter Trials

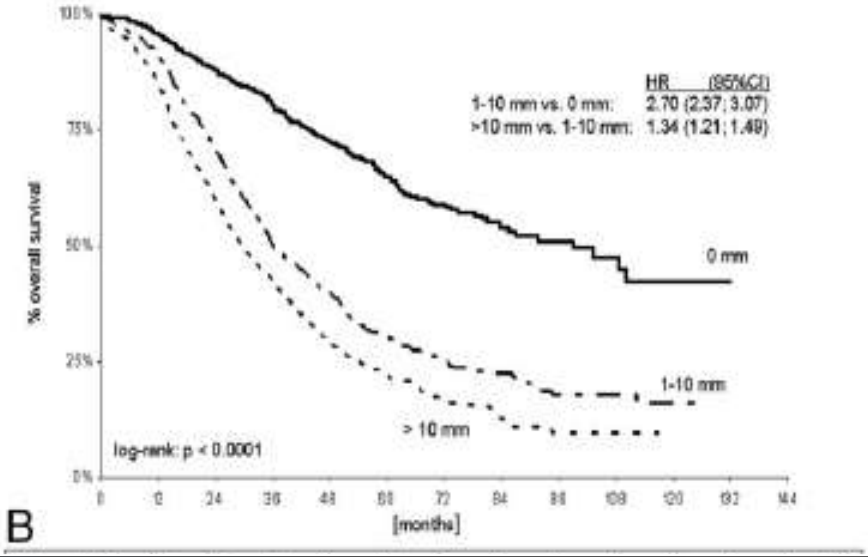
By the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO)

Andreas du Bois, MD[1], Alexander Reuss, MD[2], Eric Pujade-Lauraine, MD[3], Philipp Harter, MD[1], Isabelle Ray-Coquard, MD[4], and Jacobus Pfisterer, MD[5]

3126 pts

CANCER, 2009





			Time to Recurrence in Patients With Recurrence or Death					
	Alive Without Recurrence		0-6 Months		6-12 Months		≥12 Months	
Outcome 1st OP	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

L. C. Hanker[1*,†], S. Loibl[2,†], N. Burchardi[3], J. Pfisterer[4], W. Meier[5], E. Pujade-Lauraine[6], I. Ray-Coquard[7], J. Sehouli[8], P. Harter[9] & A. du Bois[9] 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

1620 patients

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Interval Cytoreduction Surgery

THE EFFECT OF DEBULKING SURGERY AFTER INDUCTION CHEMOTHERAPY ON THE PROGNOSIS IN ADVANCED EPITHELIAL OVARIAN CANCER

Maria E.L. van der Burg, M.D., Ph.D., Mat van Lent, M.D., Ph.D., Marc Buyse, M.B.A., Sc.D., Anna Kobierska, M.D., Nicoletta Colombo, M.D., Giuseppe Favalli, M.D., Angel J. Lacave, M.D., Mario Nardi, M.D., Josette Renard, M.Sc., and Sergio Pecorelli, M.D., Ph.D.,

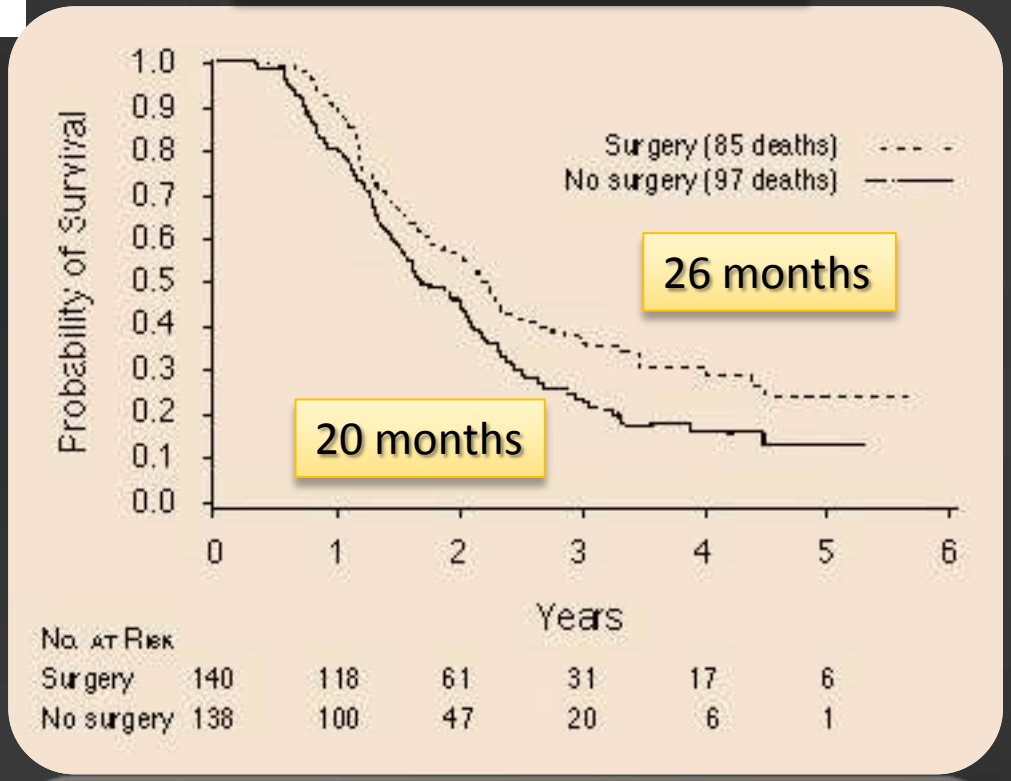
EORTC **1995**

The NEW ENGLAND JOURNAL of MEDICINE

All suboptimal>1 cm

- **INTERVAL DEBULKING**
  140 PT
  26 months of survival

- **JUST CHEMOTHERAPY**
  138 PT
  20 months of survival



The NEW ENGLAND JOURNAL of MEDICINE

GOG-152
2004

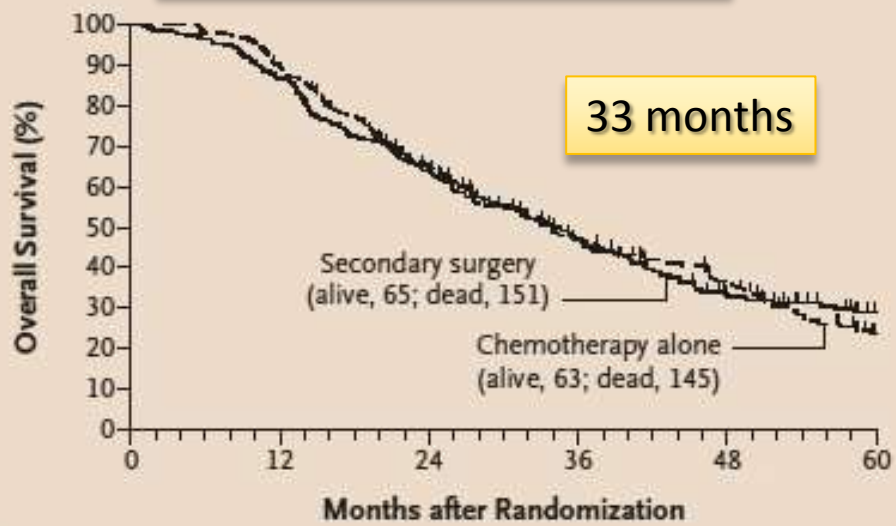
ORIGINAL ARTICLE

Secondary Surgical Cytoreduction for Advanced Ovarian Carcinoma

Peter G. Rose, M.D., Stacy Nerenstone, M.D., Mark F. Brady, Ph.D., Daniel Clarke-Pearson, M.D., George Olt, M.D., Stephen C. Rubin, M.D., David H. Moore, M.D., and James M. Small, M.D., Ph.D., for the Gynecologic Oncology Group

All suboptimal>1 cm

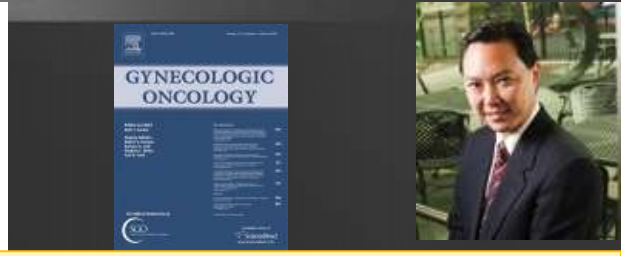
- **INTERVAL DEBULKING**
  216 PT
  33 months of survival
- **JUST CHEMOTHERAPY**
  208 PT
  33 months of survival



No. at Risk						
Secondary surgery	216	187	129	83	49	31
Chemotherapy alone	208	185	124	81	56	22

Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: A meta-analysis☆

Robert E. Bristow [a,*], Dennis S. Chi [b]



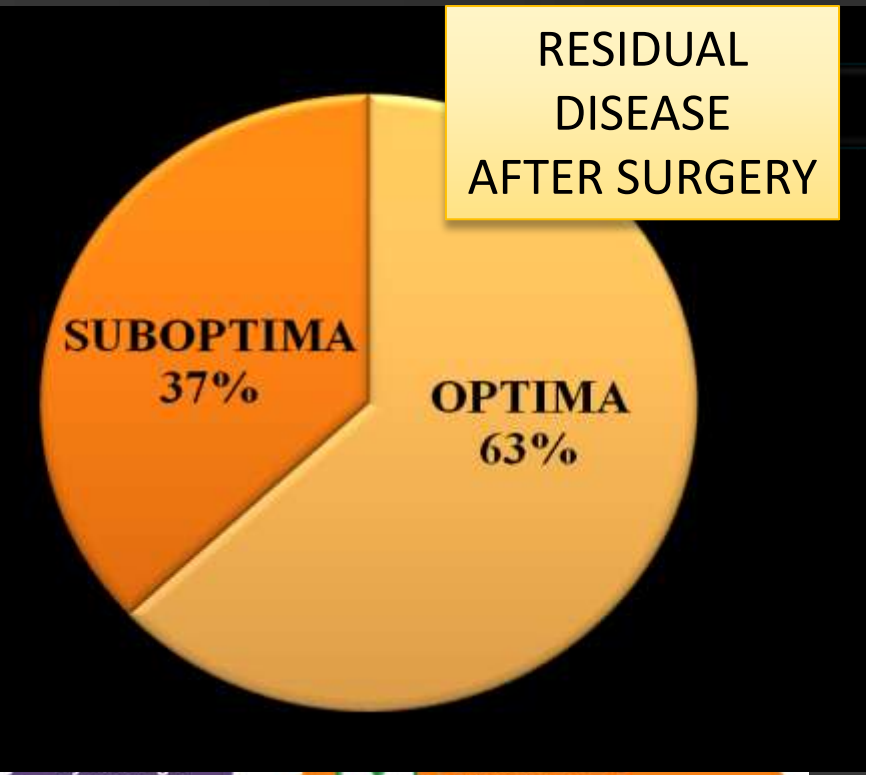
Gynecologic Oncology 2006

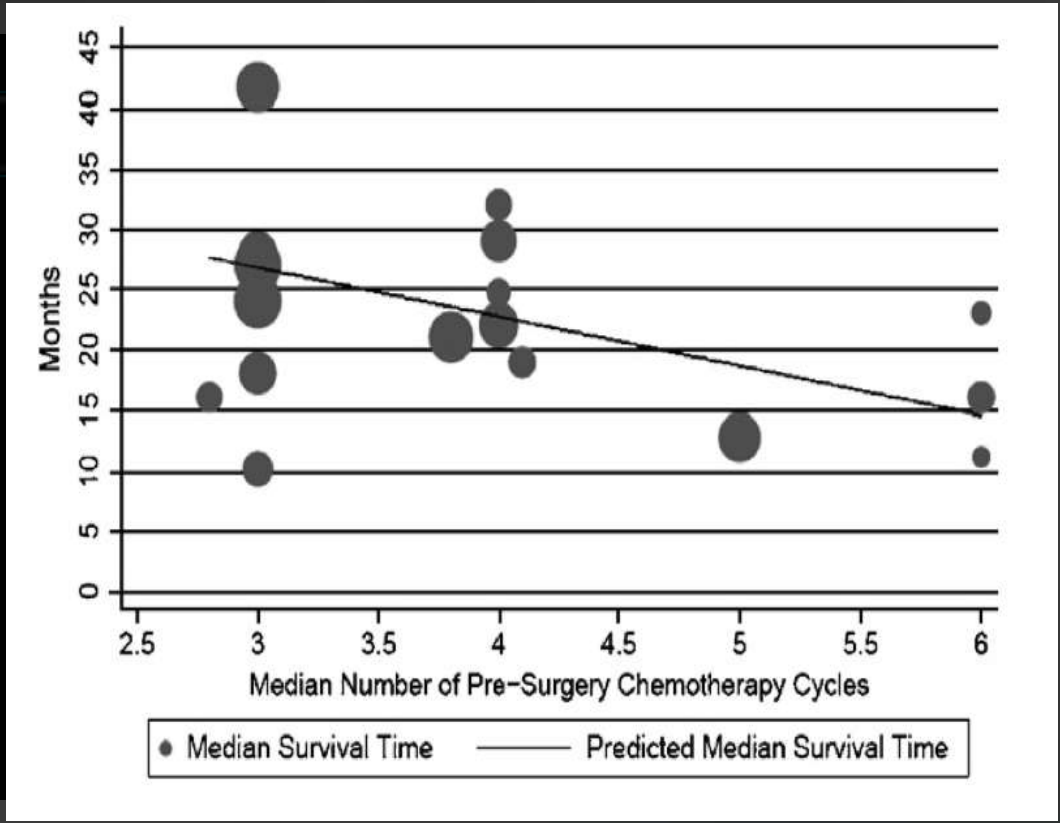
Meta analysis 1989-2005.

22 PUBLICATIONS

N= 835 PATIENTS

RESIDUAL DISEASE AFTER SURGERY





Oncology Unit

Istituto Nazionale dei Tumori

ORIGINAL ARTICLE

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.,

N Engl J Med 2010

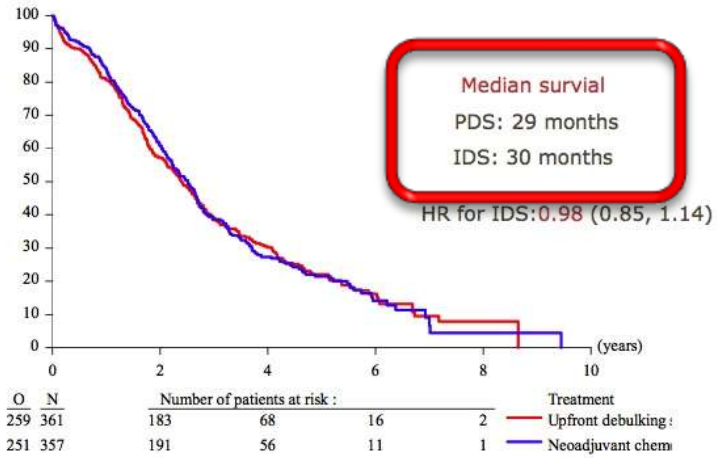
Ovarian, tuba or peritonal cancer
FIGO stage IIIc-IV (n = 718)

Randomisation

Primary Debulking Surgery	Neoadjuvant chemotherapy
3 x Platinum based CT	3 x Platinum based CT
↓	↓
Interval debulking (not obligatory)	Interval debulking if no PD
↓	↓
≥ 3 x Platinum based CT	≥ 3 x Platinum based CT

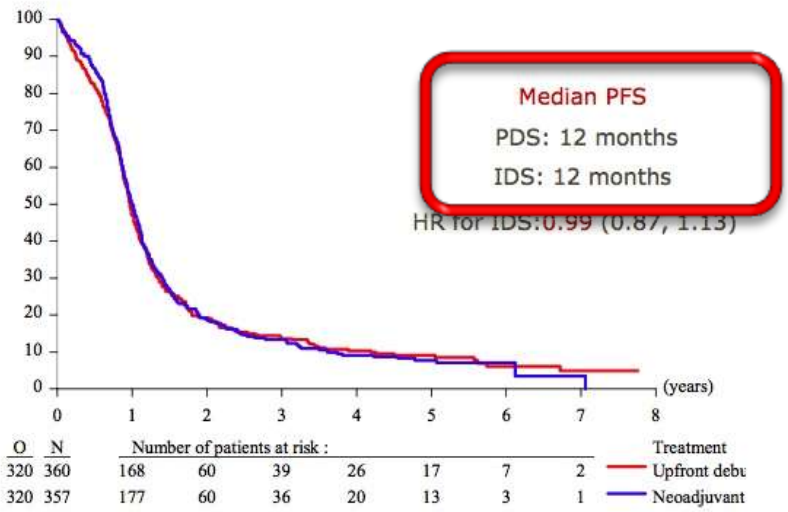
NACT + IDS versus PDS: ITT

Overall survival



NACT + IDS versus PDS: ITT

Progression-free survival



Conclusions (2)

3. Optimal debulking surgery is the strongest independent prognostic factor for overall survival. Hence, optimal debulking (to no residual tumor) should remain the goal of every surgical effort. The timing of this procedure (PDS or IDS) does not seem to play a role.
4. Due to the lower morbidity of IDS compared with PDS and the similar survival, NACT can be considered as the preferred treatment in patients, as included in this study, with Stage IIIc-IV ovarian, peritoneal and fallopian tube carcinoma.

Should Neoadjuvant Chemo y
be considered the new stand t
care for advanced ovarian
carcinoma?

Let's see

1. Why NEOAD chemotherapy has never crossed the frontier of 30-35 months of survival? ?

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

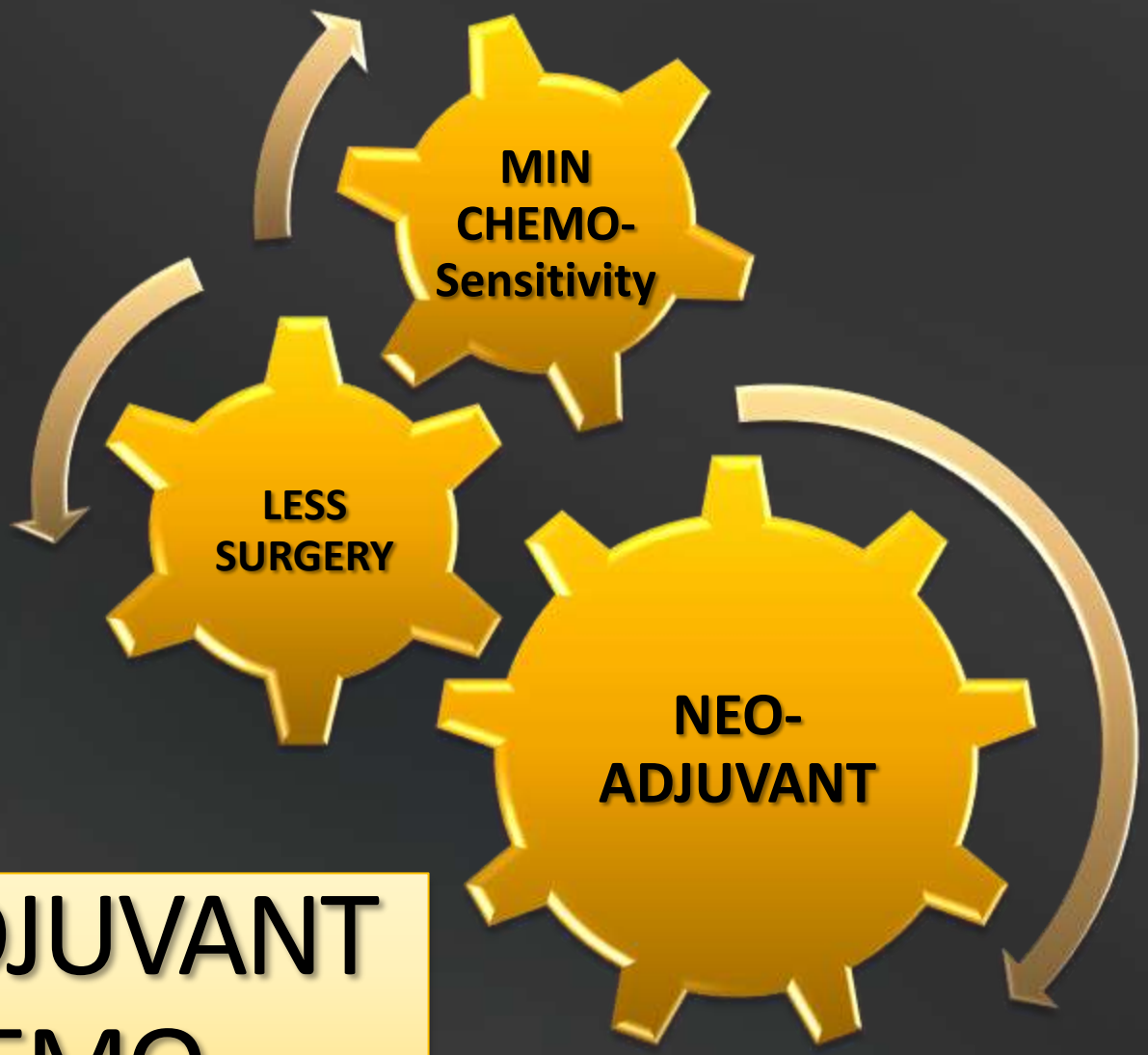
1. Why NEOAD chemotherapy has obtained always same results that suboptimal surgery?

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

Is patients´ survival somehow limited by the Neoadjuvant approach ?

35 months

Gynecologic Oncology Unit



NEOADJUVANT CHEMO

4. Great differences among countries

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

≤ 1cm residual per country (PP1)

	Total	PDS (n = 329)	NACT -> IDS (n = 339)*
Belgium (n=133)	83%	72%	94%
Argentina (n=48)	71%	68%	74%
The Netherlands (n=104)	59%	40%	77%
Sweden (n=23)	59%	40%	75%
Norway (n=82)	55%	35%	73%
Italy (n=38)	52%	40%	64%
Spain (n=62)	49%	44%	58%
UK (n=101)	47%	37%	63%
Canada (n=84)	44%	29%	59%

© Vergote

5. Short operative times in the surgical arm

	PDS (n = 329)	NACT -> IDS (n = 339)*
Postoperative mortality (< 28 days)	2,7%	0,6%
Postoperative sepsis	8%	2%
Fistula (bowel/GU)	1,2% / 0,3%	0,3% / 0,6%
Operative time (minutes)	180	180
Red blood cell transfusion	51%	53%
Hemorhage Grade 3/4	7%	1%
Venous Gr 3/4	2,4%	0,3%

© Vergote

Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer

Results from the MRC CHORUS trial

Randomized
N=552

PS
N=276

NCT
N=274

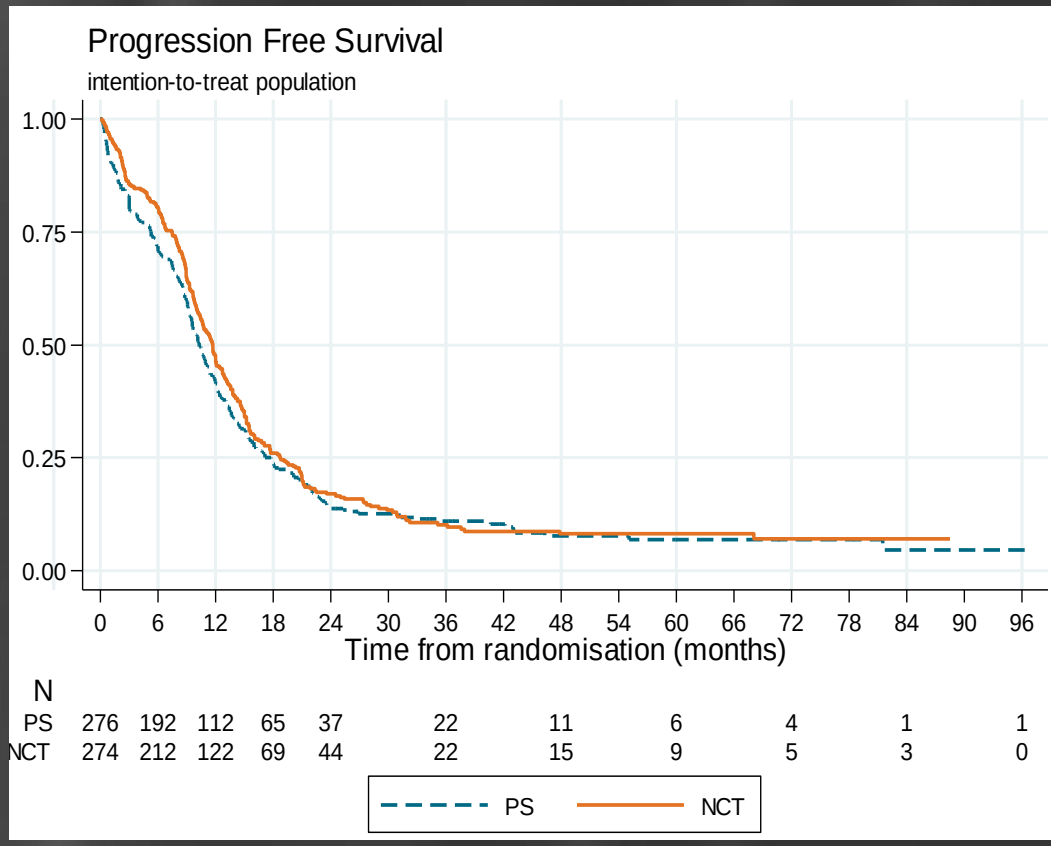
Primary surgery
N=248

Neoadjuvant chemo
N=252

Surgery
N=214

Post-op chemo
N=209

Post-op chemo
N=199



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Surgery details (CHORUS)

		PS (N=250)*		NCT (N=216)*	
Optimal debulking	**0cm**	37 (16%)	41%	77 (40%)	75%
	≤1cm	57 (25%)		67 (35%)	
Length of operation (minutes)	Median (Range)	120 (30 – 450)		120 (30 – 330)	

* **Includes:** PS - 2 pts who had NCT + surgery; NCT – 2 pts who had PS

VOLUME 29 · NUMBER 31 · NOVEMBER 1 2011

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Is the Easier Way Ever the Better Way?

Dennis S. Chi, *Memorial Sloan-Kettering Cancer Center, New York, NY*
Robert E. Bristow, *University of California, Irvine Medical Center, Irvine, CA*
Deborah K. Armstrong, *Johns Hopkins Kimmel Cancer Center, Baltimore, MD*
Beth Y. Karlan, *Cedars-Sinai Medical Center, Los Angeles, CA*

Moreover, 5 to 6 hours in the operating room resulting in an optimal cytoreduction may provide the patient with a median survival of 50 to 100 months (as reported in the literature with successful surgery)

Surgical treatment should be modulated on the basis of the extent of the disease and not on the basis of the technical skills of the surgeon

Our current goal……

Thanks

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Gynecologic Oncology Unit

Fondazione IRCCS Istituto Nazionale dei Tumori

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ALLEANZA CONTRO il TUMORE OVARICO

GIORNATA MONDIALE SUL TUMORE **OVARICO**