11th International Symposium
Advanced Ovarian Cancer
Optimal Therapy. Update

Surgery: The American perspective

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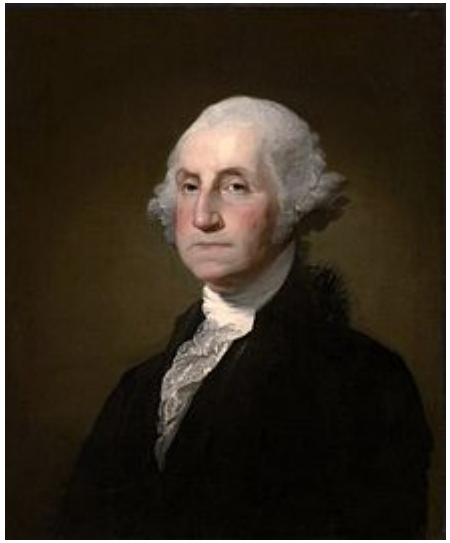
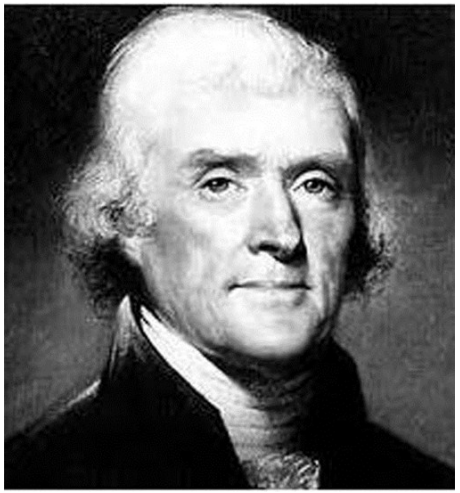
Disclosures

1. I have no disclosures relevant to the content of this discussion





“We hold these truths to be self evident”

“Surgery provides optimum benefit when all gross tumor can be removed safely”

The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma

William J. Hoskins, MD,[a] William P. McGuire, MD,[b] Mark F. Brady, BS,[c]
Howard D. Homesley, MD,[d] William T. Creasman, MD,[e] Michael Berman, MD,[f]
Harrison Ball, MD,[g] and Jonathan S. Berek, MD[h]

Confirmed the prognostic significance of residual disease in patients with advanced ovarian cancer from GOG protocols 52 and 97

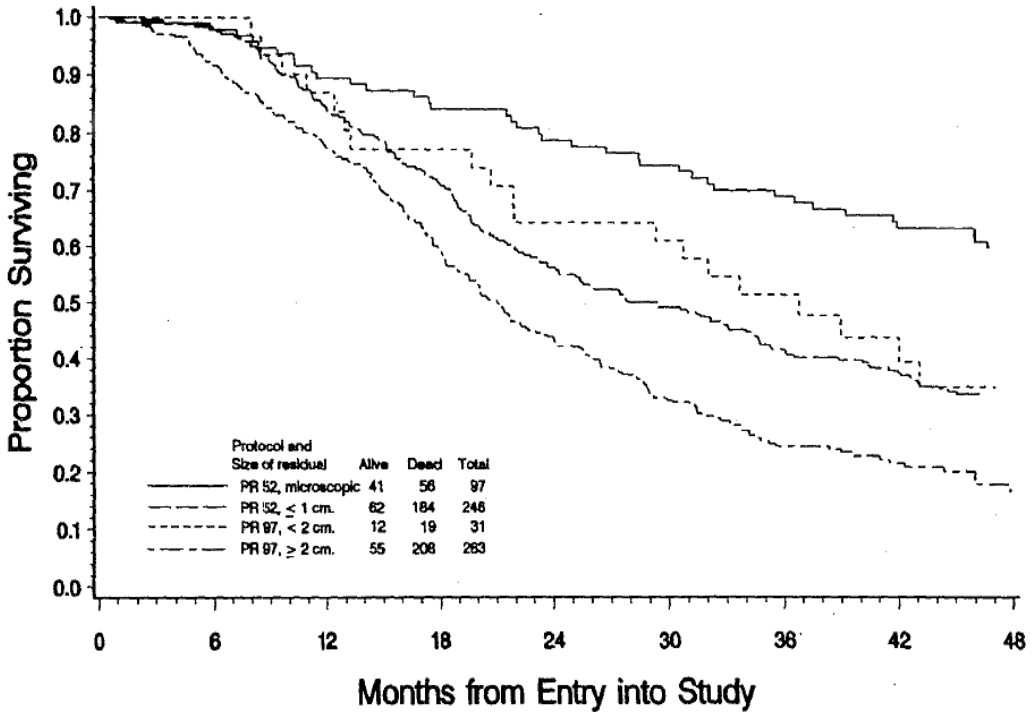
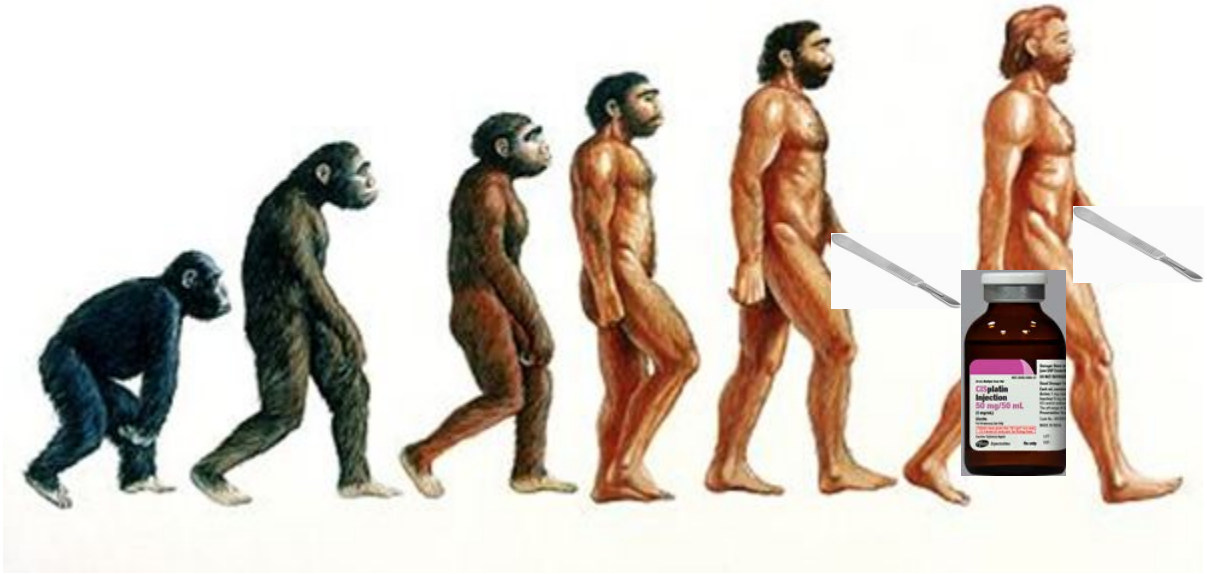
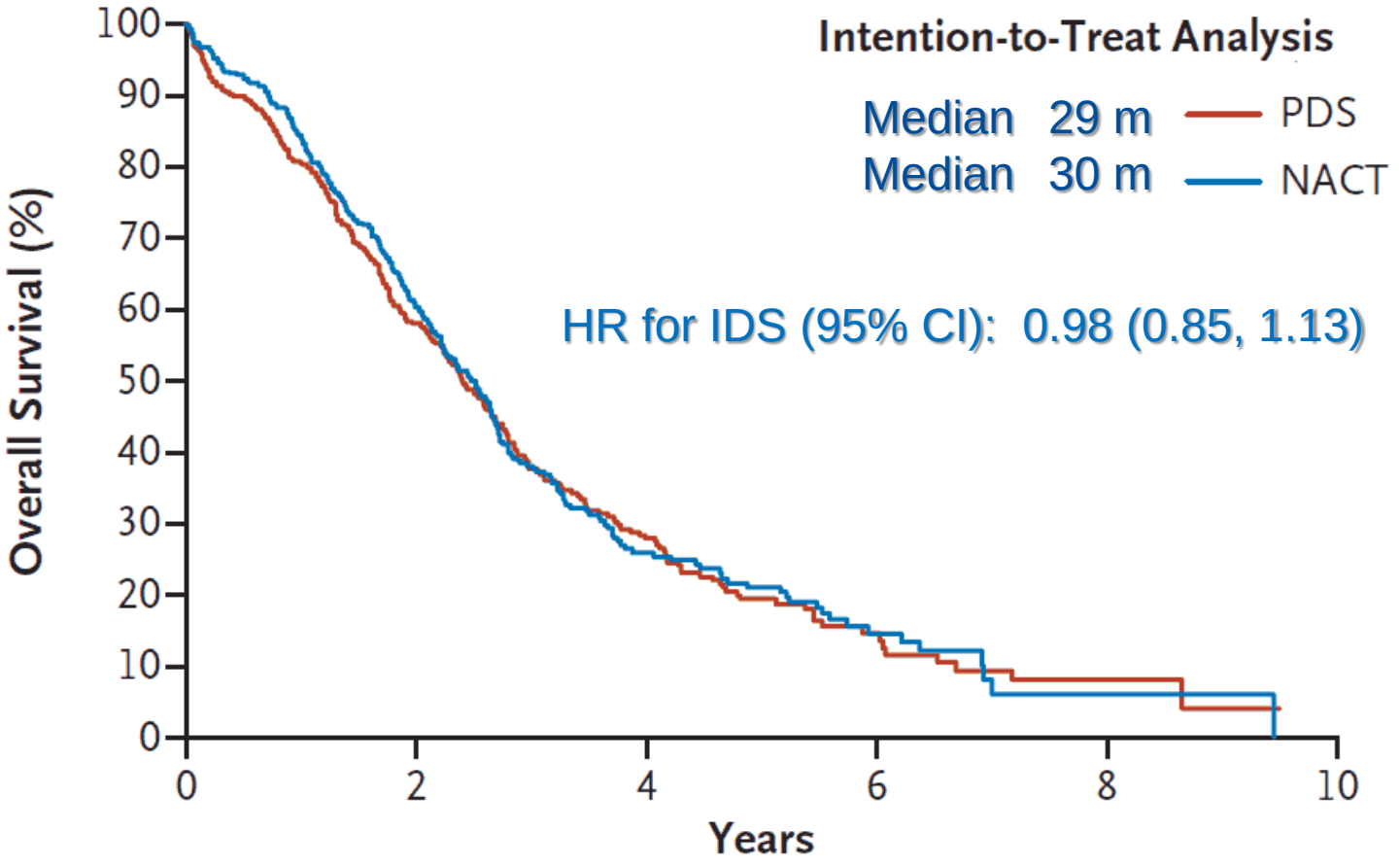


Fig. 2. Survival by residual disease, Gynecologic Oncology Group protocols *(PR)* 52 and 97.

Evolution of an Ovarian Cancer Surgeon



EORTC-NCIC: OS (ITT)



Events	No. of Patients at Risk					
253	336	189	62	14	2	PDS
245	334	195	46	13	2	NACT

Vergote I, et al. *N Engl J Med* 363:943-53, 2010

CHORUS SURVIVAL CURVES

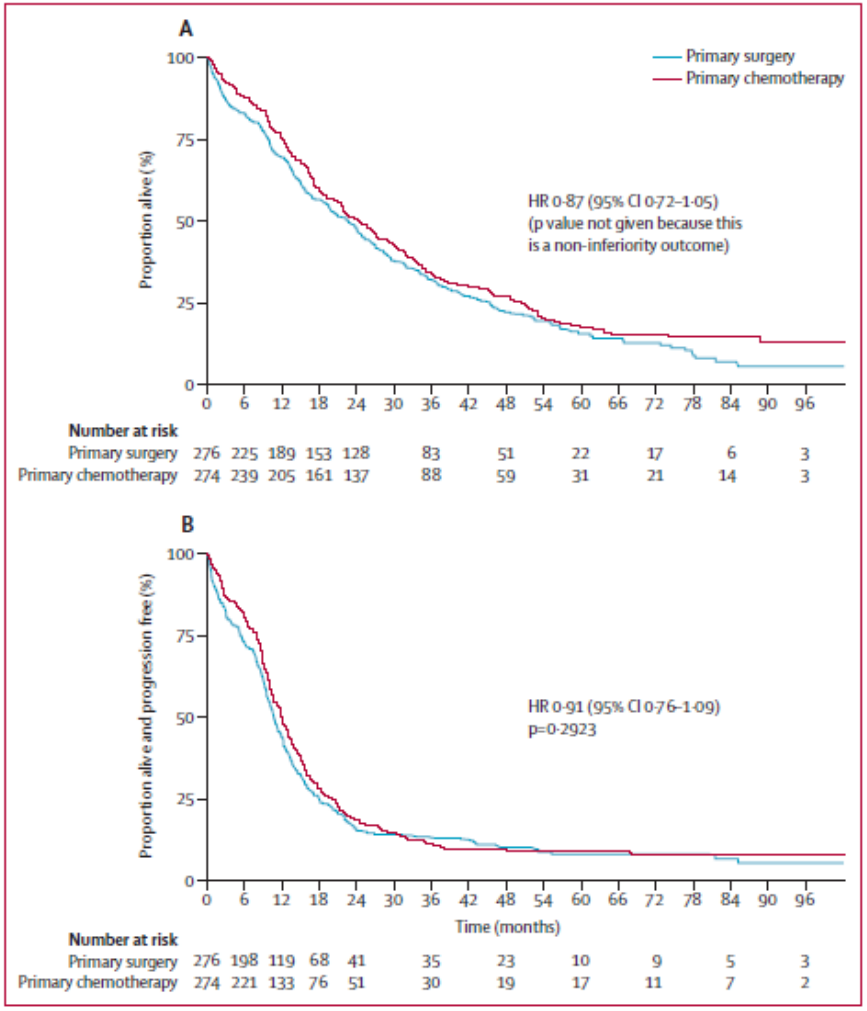
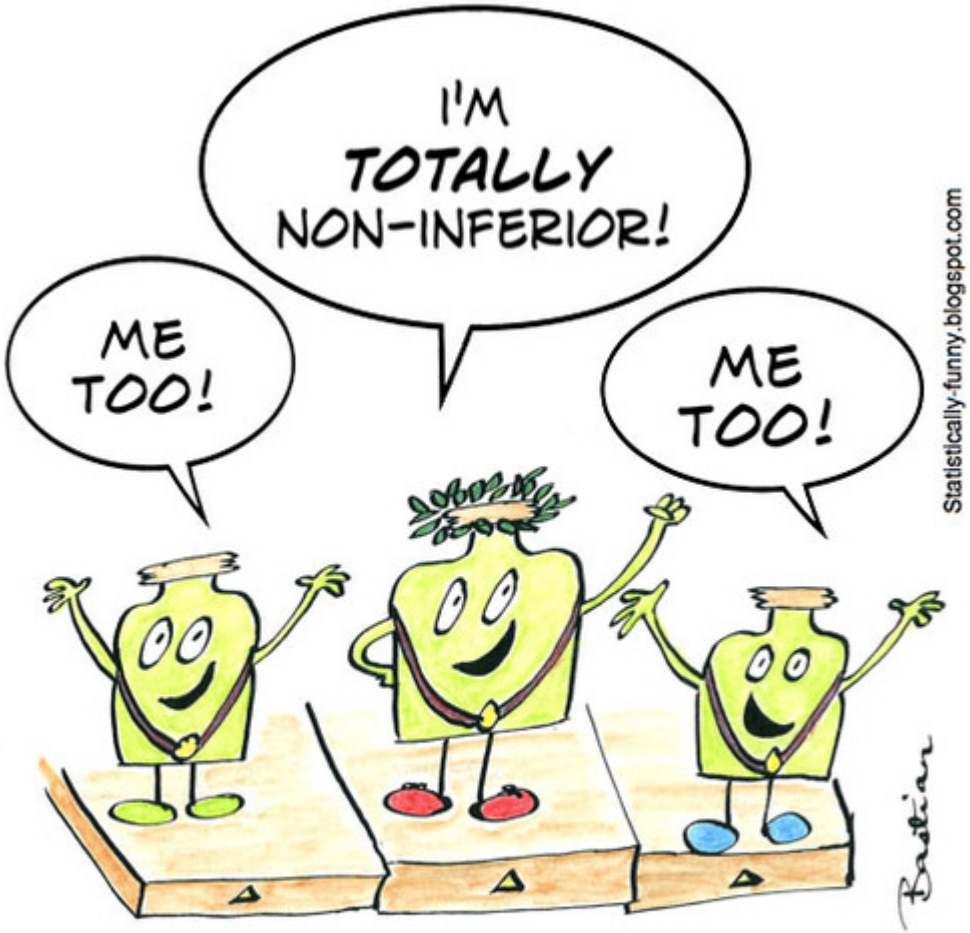


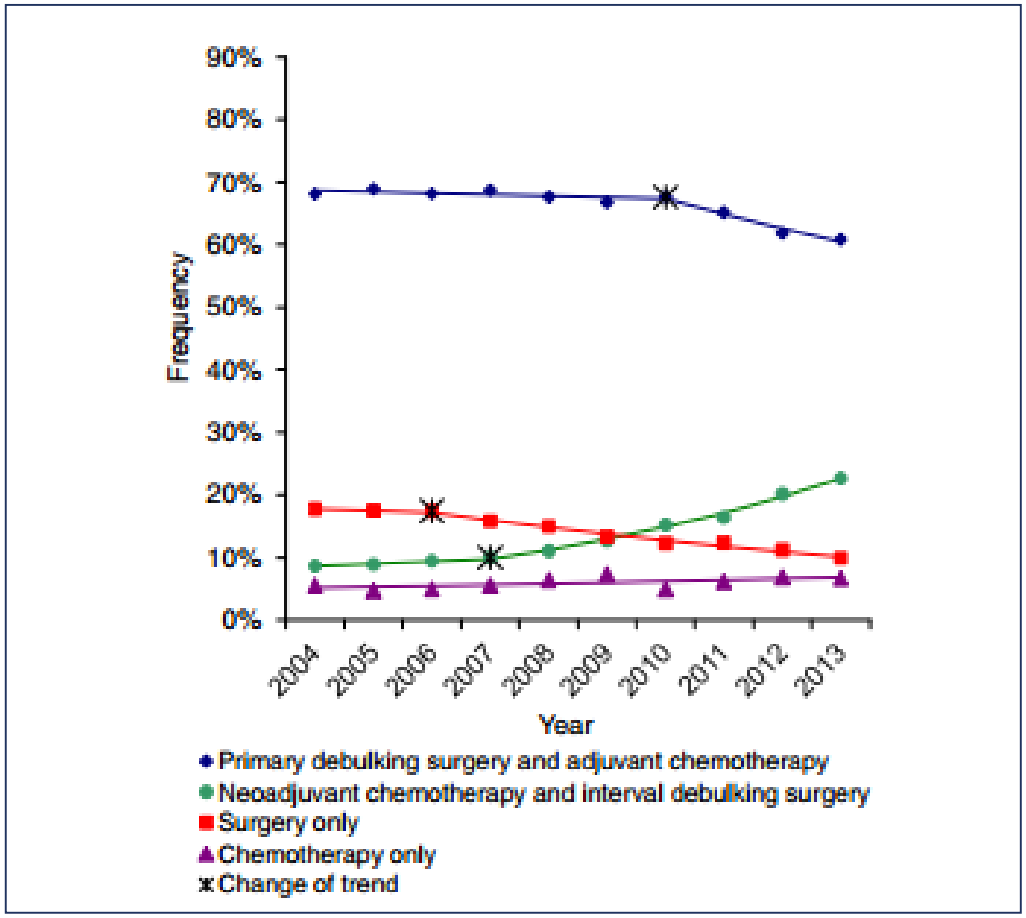
Figure 2: **Kaplan-Meier curves for overall survival (A) and progression-free survival (B)**
Data are unadjusted survival curves in the intention-to-treat population. HR=hazard ratio.

Kehoe, et al, Lancet 2015



HARRY SCORES RECORD-BREAKING
8TH PERSONAL 'NO WORSE'
AT THE PHARMA OLYMPICS!

Trends in the use of Neoadjuvant Chemotherapy for Advanced Ovarian Cancer in the United States



Melamed, et al, Gynecol Oncol 2016

Combined Analysis of GOG 114 and 172

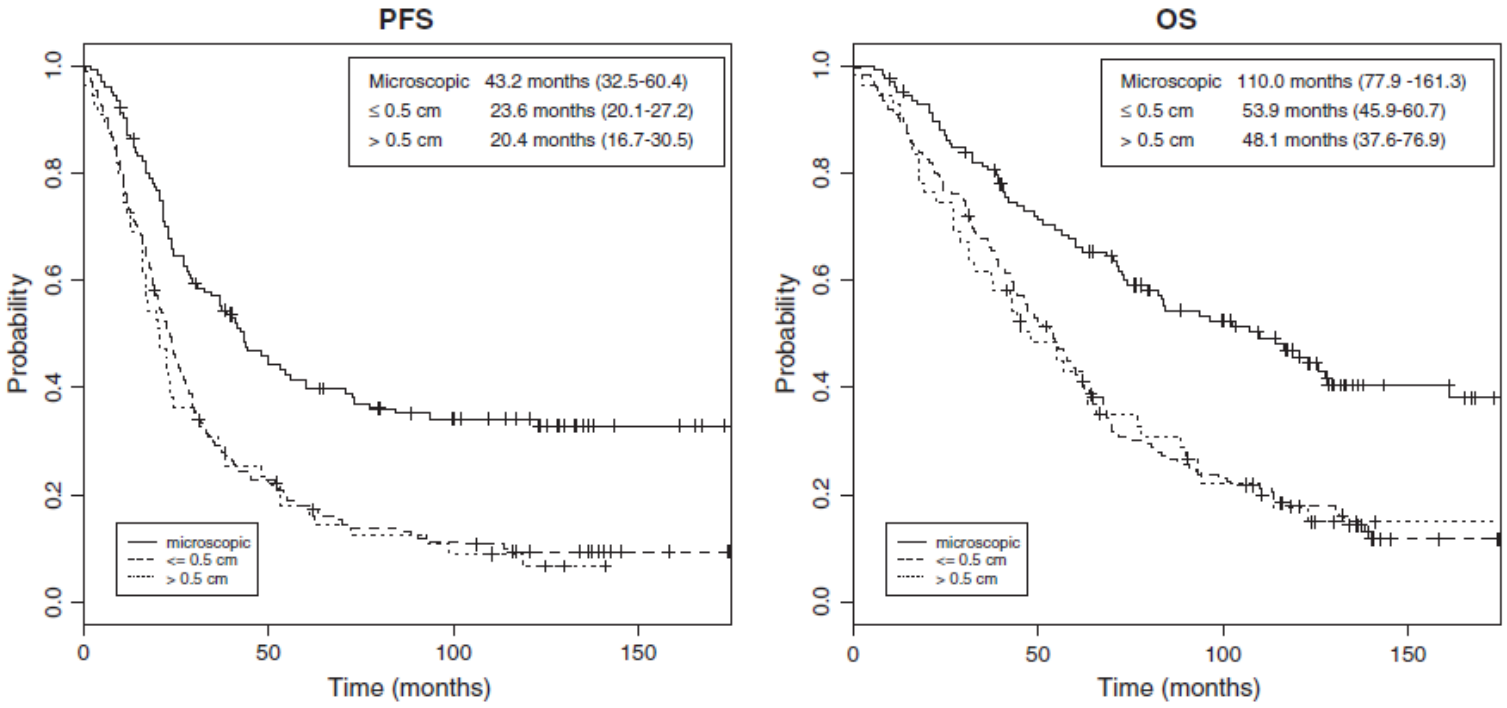


Fig. 2. Progression free (PFS) and overall survival (OS) curves for patients randomized to intraperitoneal chemotherapy stratified by residual disease following primary cytoreductive surgery. Median PFS and OS for patients with microscopic residual disease were 43 months and 110 months, respectively.

JAMA Oncology | Original Investigation

Overall Survival Following Neoadjuvant Chemotherapy vs Primary Cytoreductive Surgery in Women With Epithelial Ovarian Cancer

Analysis of the National Cancer Database

J. Alejandro Rauh-Hain, MD; Alexander Melamed, MD, MPH; Alexi Wright, MD, MPH; Allison Gockley, MD; Joel T. Clemmer, MA; John O. Schorge, MD; Marcela G. del Carmen, MD, MPH; Nancy L. Keating, MD, MPH

2935 per group, matched cohort

Table 2. Median Overall Survival of Patients Receiving Neoadjuvant Chemotherapy (NACT) vs Primary Cytoreductive Surgery (PCS) in the Propensity-Matched Groups, Overall and Stratified by Period of Diagnosis and Stage

Characteristic	Median Overall Survival (95% CI), mo		
	PCS	NACT	HR (95% CI)
All patients	37.3 (35.2-38.7)	32.1 (30.8-34.1)	1.18 (1.11-1.26)
Period of diagnosis			
2003-2005	34.2 (31.5-37.1)	28.7 (25.7-30.9)	1.19 (1.07-1.33)
2006-2009	37.3 (34.9-39.3)	34.1 (31.2-36.7)	1.15 (1.05-1.27)
2010-2011	42.1 (41.1-44.3)	33.1 (31.3-35.3)	1.24 (1.06-1.46)
Stage			
IIIC	46.5 (41.9-51.0)	37.8 (35.9-40.8)	1.24 (1.11-1.37)
IV	31.4 (29.7-33.3)	28.1 (26.3-30.3)	1.13 (1.04-1.23)

Gynecologic Oncology 135 (2014) 595–605

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Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Primary debulking surgery for advanced ovarian cancer: Are you a believer or a dissenter?

John O. Schorge [a,*], Rachel M. Clark [a], Susanna I. Lee [b], Richard T. Penson [c]

[a] Vincent Gynecologic Oncology Service, Massachusetts General Hospital, USA
[b] Division of Abdominal Imaging, Massachusetts General Hospital, USA
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Gynecologic Oncology 119 (2010) 1–2

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Editorial

Neoadjuvant chemotherapy in advanced ovarian cancer: What kind of evidence is needed to convince US gynaecological oncologists?

Vergote, et al, 2010

Much like targeted therapeutic strategies, there are predictive and prognostic biomarkers for the role of surgery….and we should use them”

Surgical Biomarkers

(here come the “alternative facts”)

1. A good night’s sleep

2. First case of the day

Surgical Biomarkers

1. Good night’s sleep
2. First case of the day
3. Get a CT scan

Imaging Predictors

Table 1
Criteria for inoperable disease in newly diagnosed primary epithelial ovarian cancer

Peritoneal sites	Nodal sites	Other
Porta hepatis	Retroperitoneal (above the renal hila)	Hepatic metastases
Intersegmental fissure	Celiac axis	Abdominal wall invasion
Gallbladder fossa	Supradiaphragmatic	
Subphrenic space		
Gastrohepatic ligament		
Gastrosplenic ligament		
Lesser sac		
Small bowel mesentery		
Dome of the liver surface		

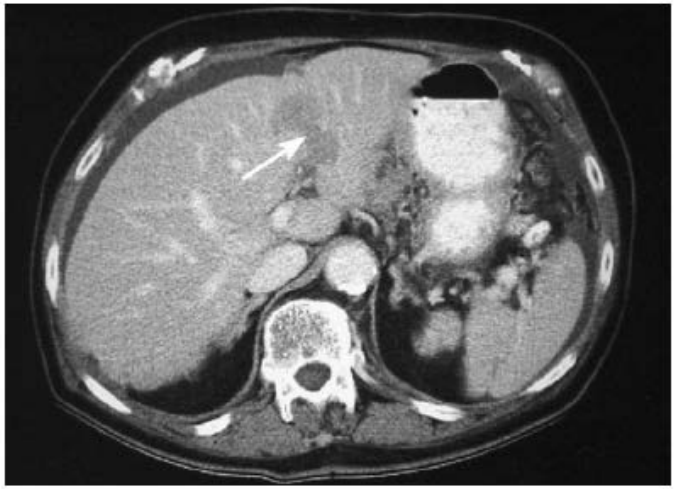


Fig. 1. Contrast-enhanced CT demonstrating a metastatic surface implant in the intersegmental fissure of the liver (arrow).

In 137 patients, “preoperative imaging predicted suboptimal cytoreduction with a sensitivity of 76%, specificity of 99%, a positive predictive value of 94%, and a negative predictive value of 96%.”

Qayyum, et al, Gyn Onc, 2005

Surgical Biomarkers

1. Good night's sleep
2. First case of the day
3. Get a CT scan
4. Assess laparoscopically

Olympia MITO-13

TABLE 2
Accuracy of laparoscopic assessment for each parameter (per-protocol analysis)

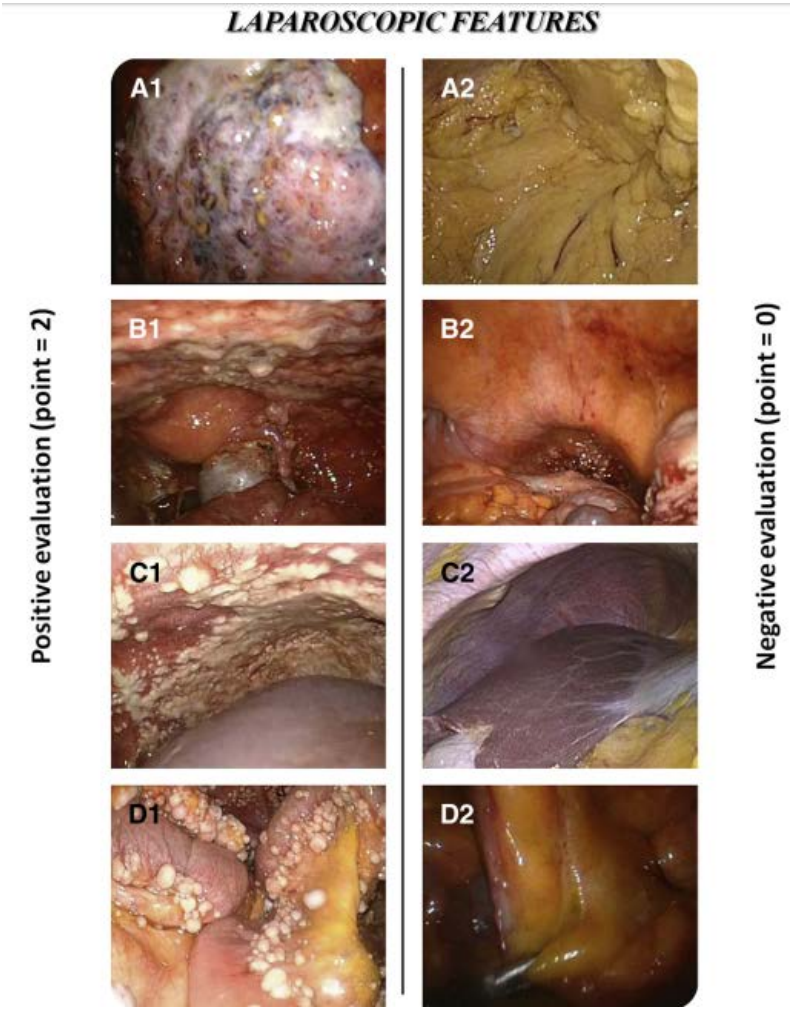
Parameter	Not evaluable, n (%)	False positive, n (%)	False negative, n (%)	NPV, %	PPV, %	Specificity, %	Accuracy, n (%)	Cohen's kappa
Omental cake	3 (2.5)	5 (4.2)	2 (1.7)	95.8	92.8	90.2	110 (94.0)	0.878
Peritoneal carcinomatosis	1 (0.8)	15 (12.6)	1(0.8)	97.9	78.9	75.8	103 (86.5)	0.733
Diaphragmatic carcinomatosis	2 (1.6)	8 (6.7)	3 (2.5)	92.9	89.6	83.0	107 (90.7)	0.802
Mesenteral retraction	31 (25.8)	4 (4.4)	4 (4.4)	94.0	82.6	94.0	81 (91.0)	0.766
Bowel infiltration	12 (10.0)	8 (7.4)	11(10.1)	81.7	83.3	86.0	89 (82.4)	0.646
Stomach infiltration	8 (6.6)	4 (3.5)	3 (2.6)	97.0	63.6	96.1	105 (93.7)	0.632
Superficial liver metastasis	4 (3.3)	5 (4.3)	4 (3.4)	95.7	78.3	94.7	107 (92.2)	0.752

NPV, negative predictive value; *PPV*, positive predictive value.

Fagotti. Diagnostic accuracy of laparoscopy in advanced ovarian cancer. Am J Obstet Gynecol 2013.

Fagotti, et al, AJOG 2013

Olympia MITO-13



Fagotti, et al, AJOG 2013

PCS vs Laparoscopic Triage

"Current, noninvasive diagnostic methods such as physical examination, ultrasonography, abdominal computed tomography (CT), and serum tumor markers like CA125 and carcinoembryonic antigen fail to predict completeness of surgery accurately."

Rutten, et al, JCO 2017

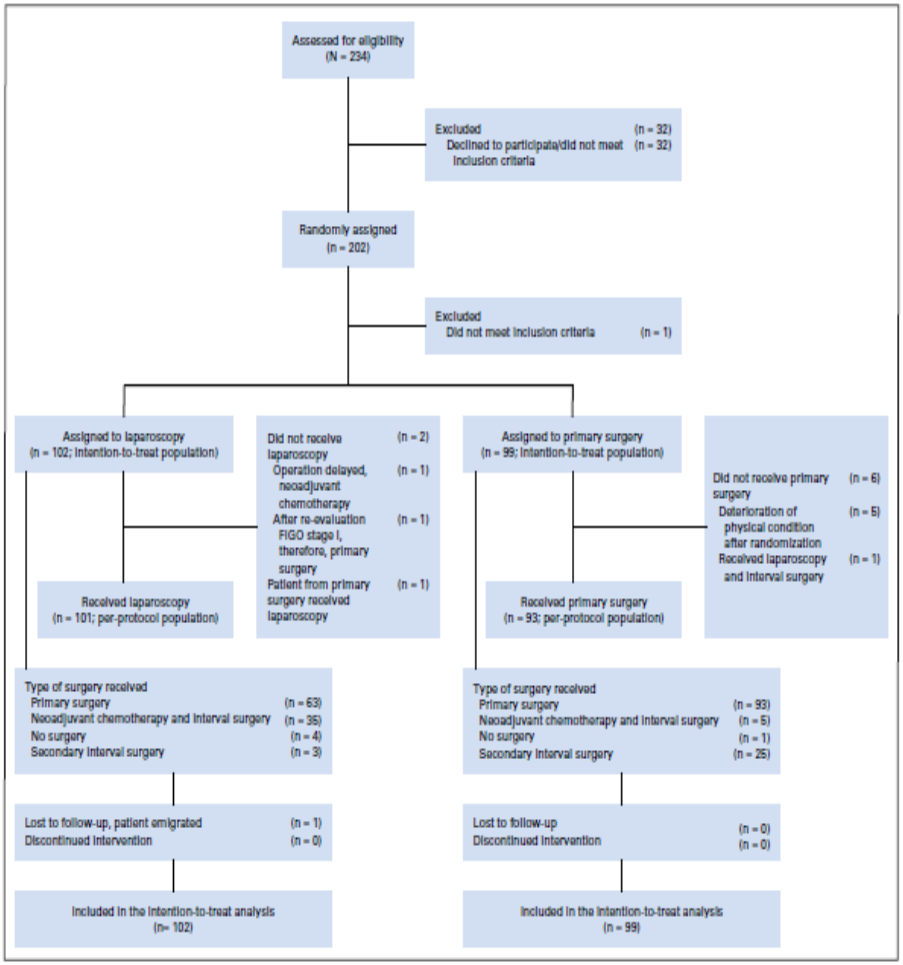


Fig 1. CONSORT diagram. FIGO, International Federation of Gynecology and Obstetrics.

PCS vs Laparoscopic Triage Approach

Table 3. Primary Outcome (futile laparotomies per treatment arm [intention-to-treat analysis]) and Secondary Outcome (patients who underwent zero, one, or two laparotomies per intervention arm) for All Patients and for Patients With Histologically Confirmed Stage IIIC or IV Ovarian Cancer

Outcome	Laparoscopy Before Surgery, No. (%)	Primary Surgery, No. (%)	RR (95% CI)	*P*
All patients	102	99		
Futile laparotomy*	10 (10)	39 (39)	0.25 (0.13 to 0.47)	< .001
Futile laparotomy any residual disease†	27 (27)	56 (57)	0.47 (0.32 to 0.68)	< .001
No. of laparotomies				
0	4 (4)	1 (1)		< .001
1	94 (92)	70 (71)		
2	4 (4)	28 (28)		
No. in FIGO stage IIIC or IV	71	69		
Futile laparotomy*	6 (8)	32 (46)	0.18 (0.08 to 0.41)	< .001
Futile laparotomy any residual disease†	20 (28)	47 (68)	0.41 (0.28 to 0.62)	< .001
No. of laparotomies in FIGO stage IIIC or IV				
0	3 (4)	1 (1)		< .001
1	64 (90)	46 (67)		
2	4 (6)	22 (32)		

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; RR, relative risk.
*> 1 cm of residual disease after primary cytoreductive surgery.
†> 0 cm of residual disease after primary cytoreductive surgery.

Rutten, et al, JCO 2017

Surgical Biomarkers

1. Good night's sleep
2. First case of the day
3. Get a CT scan
4. Assess laparoscopically
5. Make an accurate assessment

Make an Accurate Assessment

Table 2
Residual disease in patients regarded as optimally debulked at surgery.

Patients – R0 resection by surgery	Reader 1		Reader 2	
N = 104	(N)	(%)	(N)	(%)
CT-RD	**32**	(30.7)	**34**	(32.7)
Supradiaphragmatic disease	12	(11.5)	7	(6.7)
Perihepatic	21	(20.2)	13	(12.5)
Perisplenic	6	(5.8)	3	(2.9)
Omental	9	(8.7)	10	(9.6)
Organ metastasis	3	(2.9)	5	(4.8)

HBOC = Hereditary breast/ovarian cancer syndrome; ASA = American Society of Anesthesiologists' score.
N = Number.

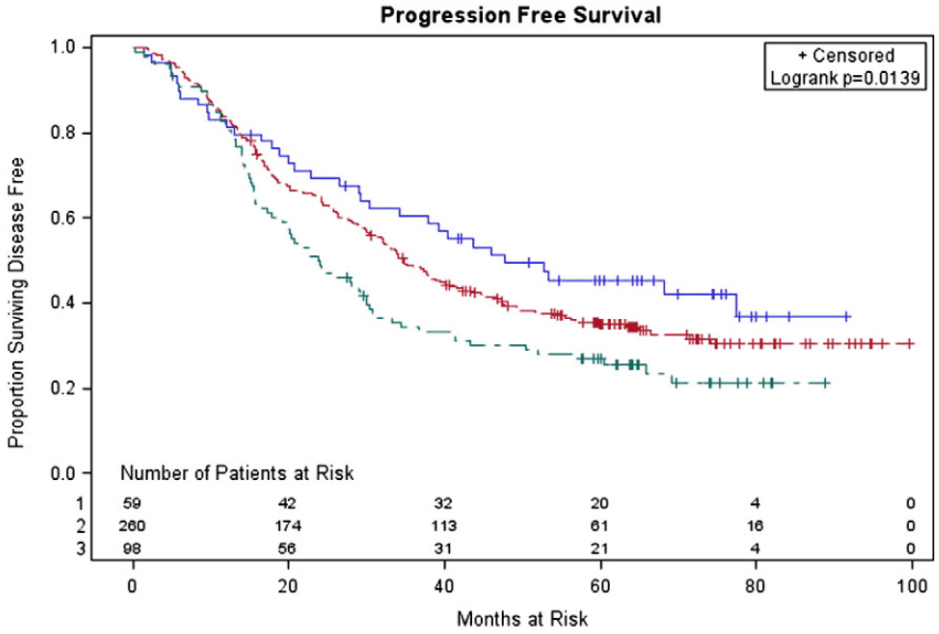
Burger, et al, Gynecol Oncol 2015

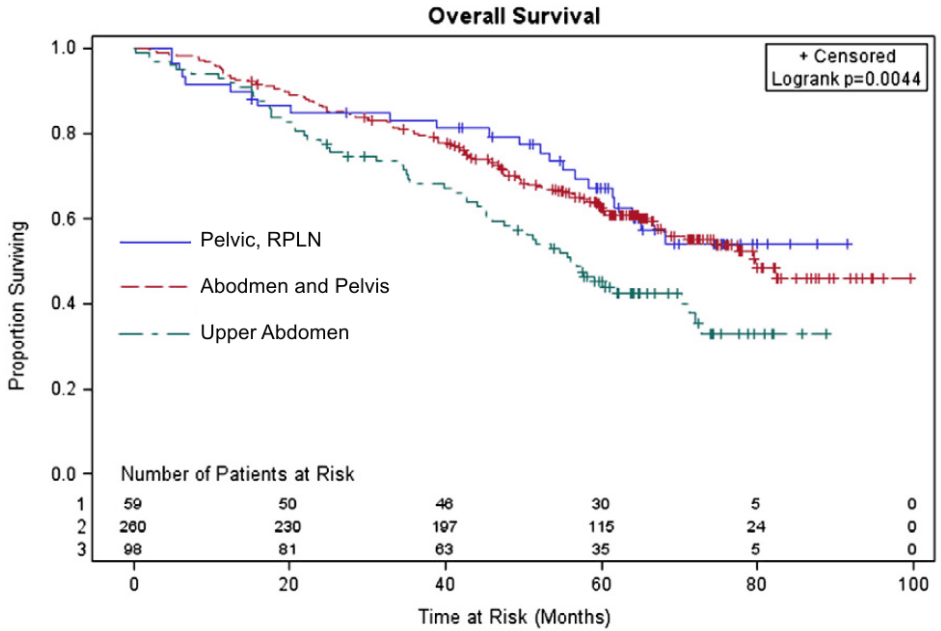
Surgical Biomarkers

1. Good night's sleep
2. First case of the day
3. Get a CT scan
4. Assess laparoscopically
5. Make an accurate assessment
6. Be willing to perform upper abdominal procedures

Cytoreduction: Extent of Initial Disease

- Does pre-surgical tumor distribution predict post-surgical outcomes?



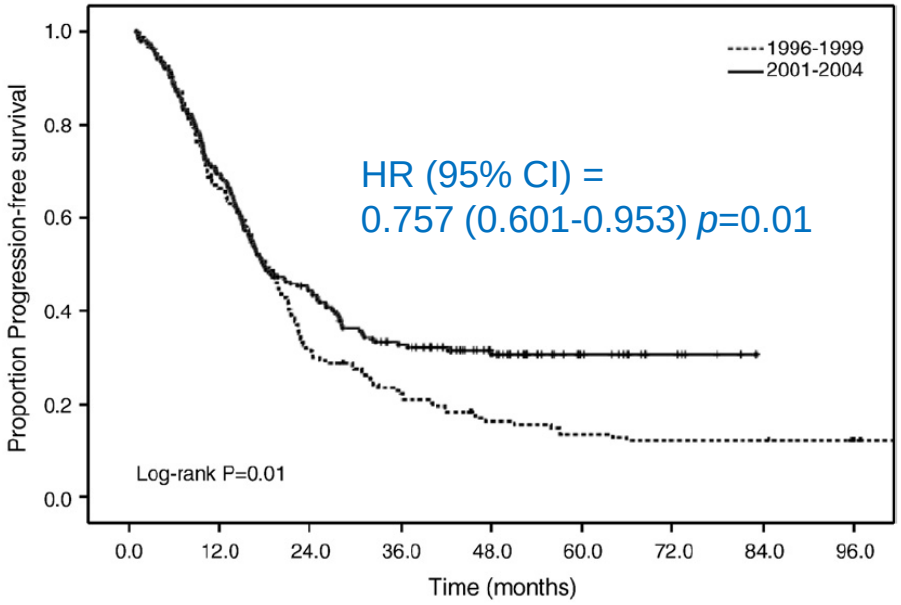


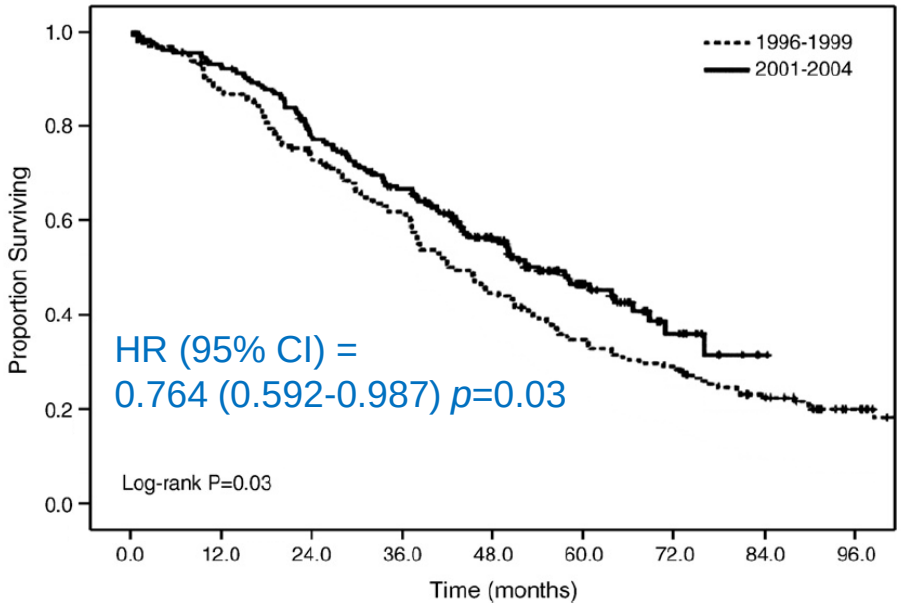
"These findings support that other factors and perhaps tumor biology are important in predicting survival, but the importance of these factors do not preclude benefit from aggressive cytoreductive surgery."

Hamilton CA, et al. *Gynecol Oncol* 122:521-6, 2011

Cytoreduction: Beyond the Pelvis

- Stg IIIC-IV Ovarian, Fallopian, and Peritoneal
  - Cohort 1: Jan-96 through Dec-99
  - Cohort 2: Jan-01 through Dec-04





"This study demonstrates that the incorporation of extensive upper abdominal surgery into the operative strategy can lead to a significant increase in optimal cytoreduction rates and consequent improved PFS and OS"

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

Surgical Biomarkers

1. Good night's sleep
2. First case of the day
3. Get a CT scan
4. Assess laparoscopically
5. Make an accurate assessment
6. Be willing to perform upper abdominal procedures
7. If unwilling to do #6, send to someone else

High vs Low Volume Centers

Table 4
Predictors of overall survival for EOC within NCDB cohort (1998–2002).

Risk factor	N	%	Unadjusted HR	95% CI		Adjusted HR	95% CI	
				Lower	Upper		Lower	Upper
Patient characteristics								
Age (years)								
<60	21,087	42.89	Referent			Referent		
60–75	18,610	37.86	1.750	**1.704**	**1.796**	1.282	**1.240**	**1.325**
>75	9463	19.25	3.267	**3.155**	**3.383**	2.095	**1.999**	**2.195**
Race								
Whites	43,995	89.49	Referent			Referent		
Non-Whites	4568	9.29	1.232	**1.167**	**1.301**	1.204	**1.149**	**1.261**
Unknown	597	1.21	1.012	0.908	1.127	1.108	**1.001**	**1.227**
Payer information								
Private insurance	9680	19.69	Referent			Referent		
Medicare/medicare supplements	19,371	39.40	2.155	**2.082**	**2.230**	1.236	**1.186**	**1.289**
Managed care/TRICARE/military	14,221	28.93	1.026	0.988	1.065	1.019	0.982	1.058
Medicaid/federal insurance programs/public health service	1949	3.96	1.481	**1.385**	**1.584**	1.263	**1.177**	**1.355**
Not insured—self pay	1744	3.55	1.385	**1.281**	**1.498**	1.276	**1.171**	**1.391**
Insurance status unknown	2195	4.47	1.438	**1.323**	**1.562**	1.119	**1.001**	**1.252**
Adherence to NCCN guidelines for Rx								
Yes	21,286	43.30	Referent			Referent		
No	27,874	56.70	1.322	**1.284**	**1.361**	1.403	**1.362**	**1.446**
Tumor characteristics								
Tumor stage								
Stage I	8625	17.54	Referent			Referent		
Stage II	4042	8.22	2.402	**2.208**	**2.613**	2.131	**1.963**	**2.313**
Stage III	21,888	44.52	6.399	**6.010**	**6.812**	5.881	**5.516**	**6.270**
Stage IV	14,605	29.71	11.785	**11.074**	**12.542**	9.476	**8.893**	**10.098**
Tumor grade								
Well/moderately differentiated	13,244	26.94	Referent			Referent		
Poorly/undifferentiated/anaplastic	25,538	51.95	1.786	**1.724**	**1.850**	1.200	**1.159**	**1.242**
Missing	10,378	21.11	3.114	**2.987**	**3.246**	1.472	**1.416**	**1.531**
Facility characteristics								
Facility type								
Academic/research cancer program	20,987	42.69	Referent			Referent		
Comprehensive community cancer program	22,087	44.93	1.124	**1.080**	**1.169**	1.020	0.980	1.061
Community cancer program	6086	12.38	1.256	**1.190**	**1.325**	1.054	0.996	1.114
Average hospital ovarian cancer case volume/year (1998–2002)								
1–6 cases/year	12,398	25.22	Referent			Referent		
7–14 cases/year	12,200	24.82	0.848	**0.813**	**0.885**	0.955	0.912	1.000
15–25 cases/year	12,146	24.71	0.785	**0.751**	**0.821**	0.920	**0.876**	**0.966**
≥26 cases/year	12,416	25.26	0.738	**0.702**	**0.775**	0.910	**0.858**	**0.964**
Total	49,160	100.00						

Hazard Ratios Bolded for $p < 0.05$.

Cliby, et al, Gynecol Oncol, 2015

Surgical Biomarkers

1. Good night's sleep
2. First case of the day
3. Get a CT scan
4. Assess laparoscopically
5. Make an accurate assessment
6. Be willing to perform upper abdominal procedures
7. If unwilling to do #6, send to someone else
8. Check their identification

Age and Surgical Co-morbidity

Table 2
Outcomes with primary open cytoreduction surgery in older women with ovarian cancer.

Series	*n*	Pt age/characteristics	Surgical morbidity	Surgical mortality
Wright, 2004 [56]	46	≥70 years *n* = 46 Compared to pts younger than 70 years *n* = 129	20% ICU admission for pts ≥70 years No overall morbidity difference between pts over and under age of 70 years	No perioperative mortality (0%)
Moore, 2008 [58]	68	≥80 years	50% discharge to nursing facility	Death prior to discharge 13% 60-day mortality 20%
McLean 2009 [63]	11	≥80 years	–	No postoperative death
Aletti 2010 [62]	38	≥75 years AND extensive disease AND ASA score ≥3 AND albumin <3 g/dL	63.6% major morbidity if high surgical complexity 33.3% if low surgical complexity	3 month mortality 18.4%
Langstraat 2011 [61]	280	Age ≥65 *n* = 280 Age >75 *n* = 115	10% perioperative morbidity for age 65–74 37.5% perioperative morbidity for age >75 Age independent predictor of poor perioperative outcome	30 day mortality for age 65–74 = 1% 3 month mortality for age 65–74 = 4% 30 day mortality for age ≥75 = 7.8% 3 month mortality for age ≥75 = 20.8%
Thrall 2011 [57]	4,475	Age ≥65 *n* = 4,475 Age ≥75 *n* = 2668 SEER Medicare Analysis		8.2% overall 30 day mortality 12.7% 30 day mortality for women ≥75 with stage IV disease or stage III disease and comorbidity score of ≥1

Tew, et al, Gynecol Oncol 2015

“What would you want done for your loved one?”

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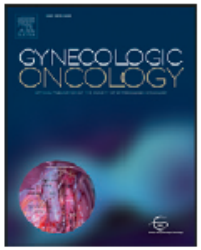


Practice Guidelines

Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline☆

Alexi A. Wright [a,1], Kari Bohlke [b], Deborah K. Armstrong [c], Michael A. Bookman [d], William A. Cliby [e], Robert L. Coleman [f], Don S. Dizon [g], Joseph J. Kash [h], Larissa A. Meyer [i], Kathleen N. Moore [j], Alexander B. Olawaiye [k], Jessica Oldham [l], Ritu Salani [m], Dee Sparacio [n], William P. Tew [o], Ignace Vergote [p], Mitchell I. Edelson [q,*,1]

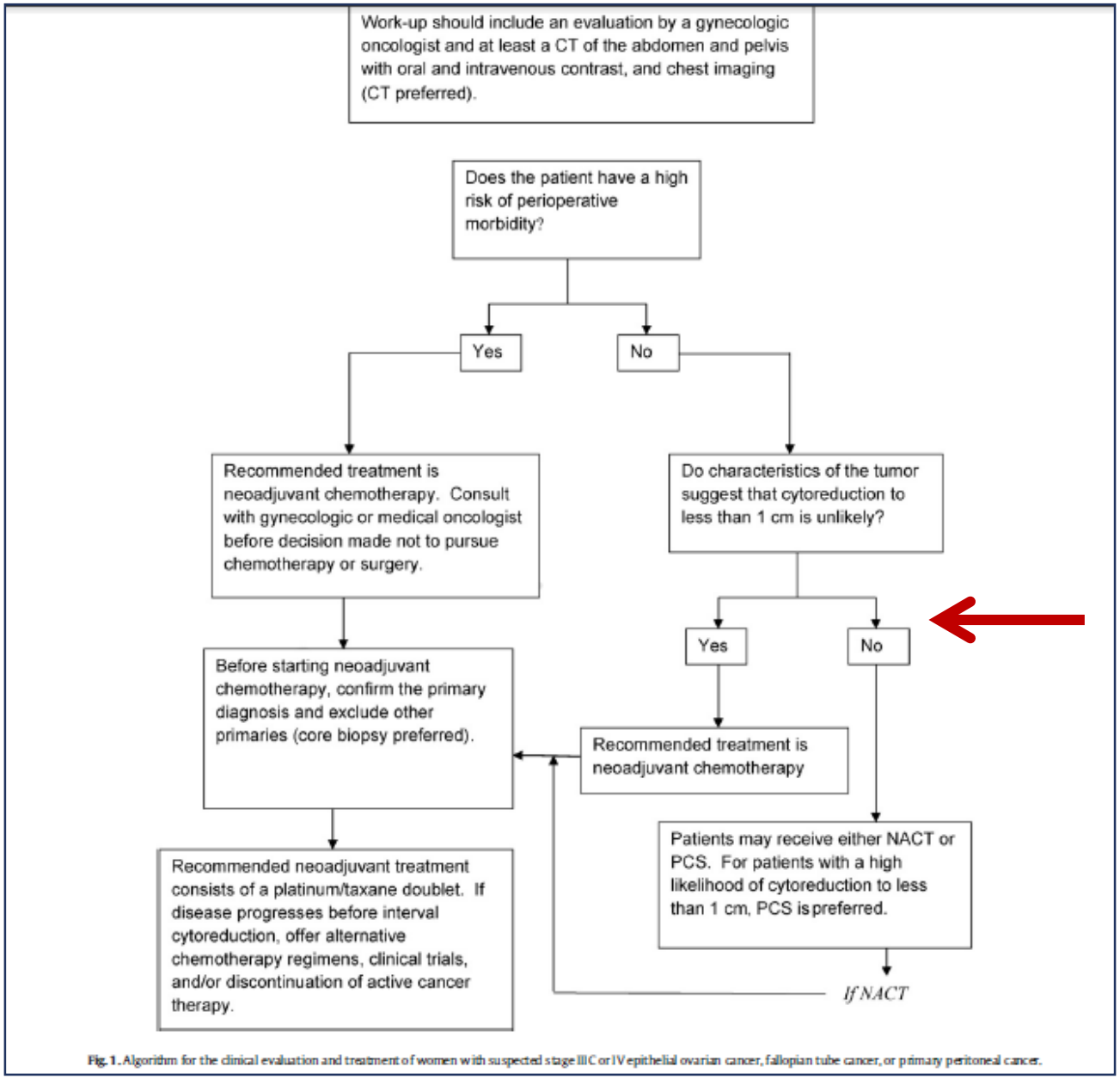


Fig. 1. Algorithm for the clinical evaluation and treatment of women with suspected stage IIIC or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

What are the future questions?

1. Will we drop the IDS in NACT treated patients?
2. What other role could surgery play in advancing the science?
    1. Window of opportunity studies
    2. Image guided resection
    3. Accelerated drug approval

FDA Breast Cancer model 2014

- Rationale to support accelerated approval of new agents in breast cancer therapy
- Define pCR
- Define relationship between pCR and survival
- Lend guidance to trial design to confirm clinical benefit if pCR rates support accelerated approval

Definition of pCR in Breast Cancer Model

- Absence of residual invasive cancer on H & E evaluation of the complete resected breast specimen and all sampled regional lymph nodes (18% rate)

or

- Absence of residual invasive and in situ cancer as described above (13% rate)

Ovarian/FT/PP Model Background

- Rates of pCR ranged from 6 to 23% in prior studies but were hampered by small numbers and variability of pre- and post-surgery chemotherapy
- At least two larger clinical trials have reported on pCR rates, i.e. CHORUS and GOG 152
- Nature of the disease differs greatly from neoadjuvant breast cancer model

GOG 152 Analysis

Disease extent at secondary cytoreductive surgery is predictive of progression-free and overall survival in advanced stage ovarian cancer: An NRG Oncology/Gynecologic Oncology Group study

Peter G. Rose, MD [a,*], James J. Java, PhD [b], Mark A. Morgan, MD [c], Angeles Alvarez-Secord, MD [d], Joshua P. Kesterson, MD [e], Frederick B. Stehman, MD [f], David P. Warshal, MD [g], William T. Creasman, MD [h], Parviz Hanjani, MD [i], Robert T. Morris, MD [j], Larry J. Copeland, MD [k]

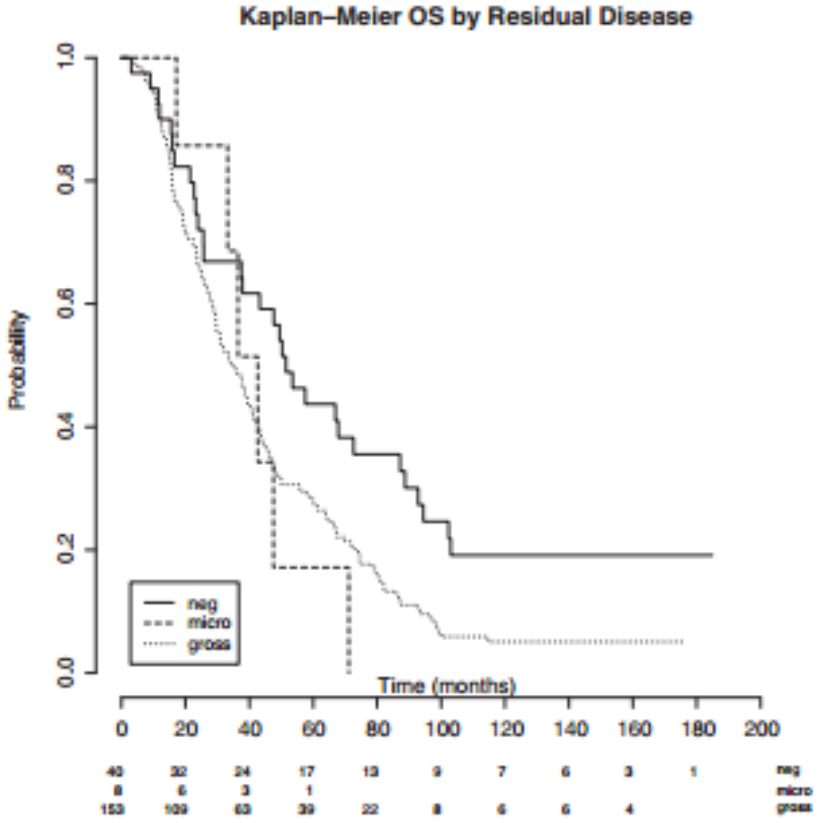


Fig. 2. Kaplan–Meier OS by residual disease.

CHORUS

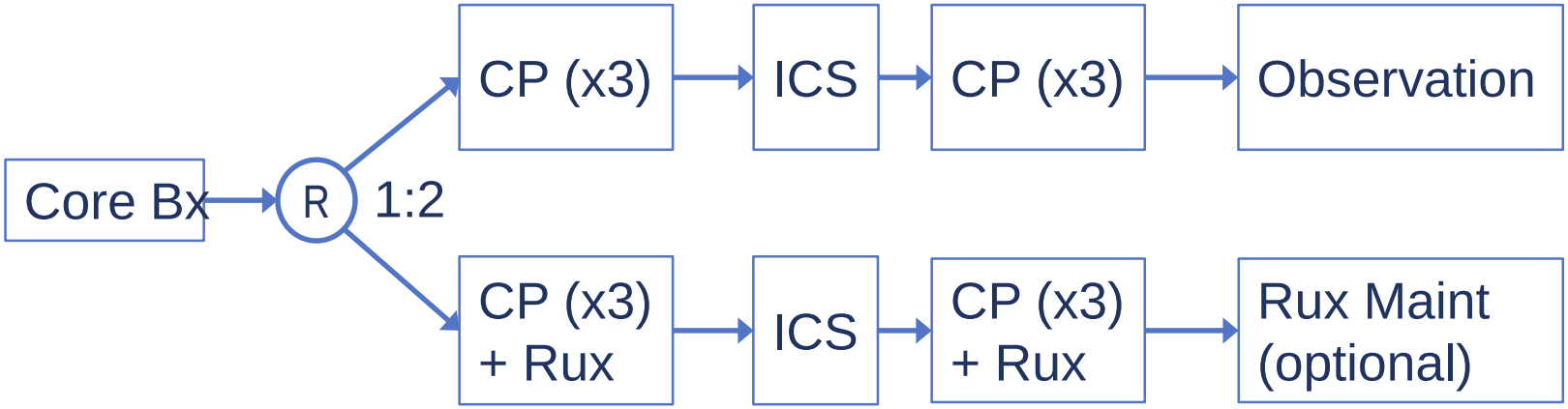
Timepoint of Surgery	No gross residual	Macro ≤ 1cm	Macro > 1m
PCS	2%	6%	92%
Interval	4%	12%	84%

The recommended surgical procedures were: a midline incision; sampling of free fluid or peritoneal washings for cytology; a thorough inspection of the abdomen and pelvis including upper abdominal viscera, diaphragm, and retroperitoneal spaces; and hysterectomy, bilateral oophorectomy, and omentectomy. Pelvic and para-aortic nodes were to be sampled for women who were thought to have FIGO stage IIIB disease or less.

Kehoe, SGO 2016

NRG-GY007: NACT +/- Ruxolitinib

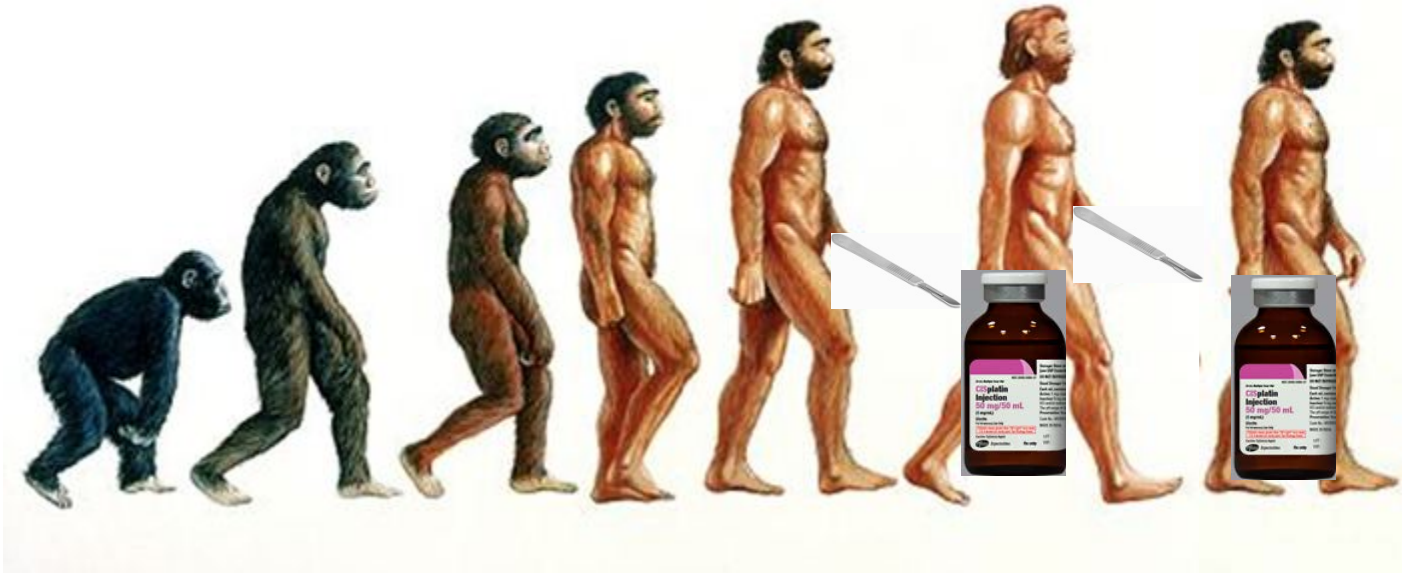
- Epithelial ovarian, peritoneal, or fallopian carcinoma (EOPFC)
- Stage IIIC-IV and suitable for NACT with interval cytoreductive surgery
- Phase I to evaluate acute toxicity (C1) and cumulative tolerability
- Maintenance ruxolitinib permitted in patients tolerating concurrent therapy
- Primary Endpoints: PFS and molecular targeting (stem cells and IL6)



CP = Carboplatin AUC 5 or 6 (D1), Paclitaxel 80 mg/m2 (D1,8,15)
Rux = Ruxolitinib 10-15 mg PO BID (pending Phase 1)
ICS = Interval Cytoreductive Surgery

PI: R Burger

Evolution of an Ovarian Cancer Surgeon



THANK YOU