

The 4th MEMAGO Annual Congress
in Association with the 1st Emirates
Gynecological Oncology Conference

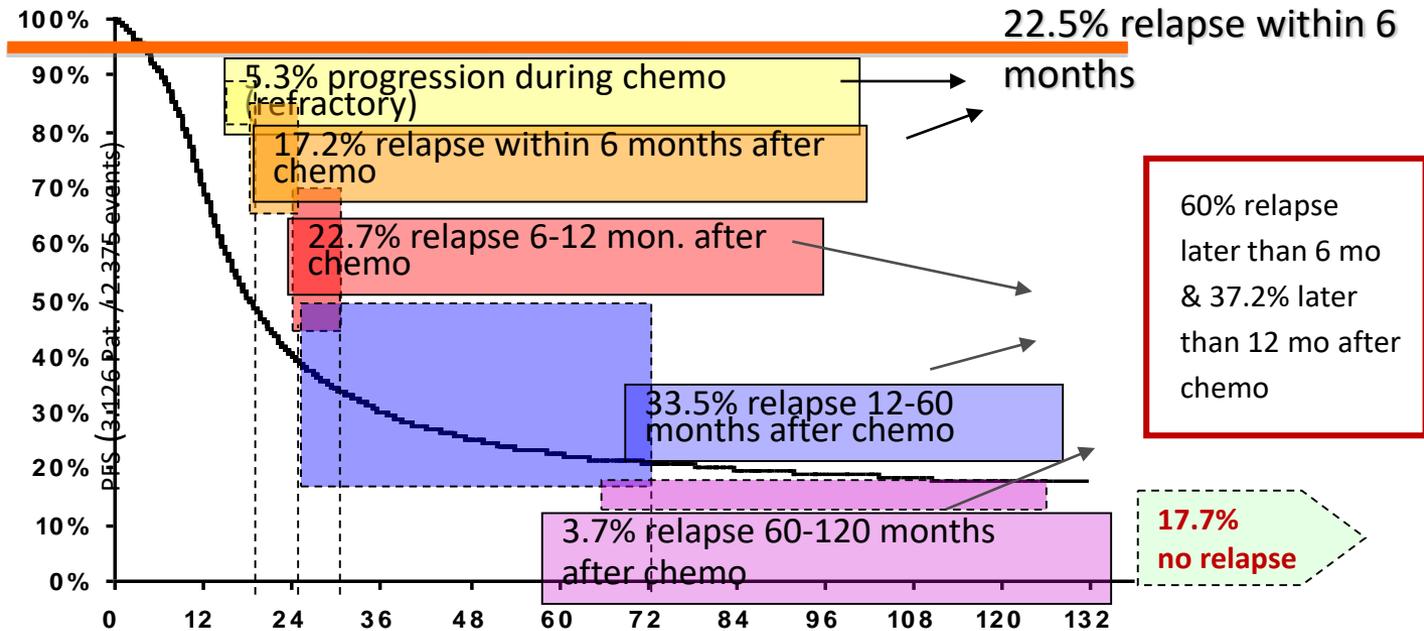
Advanced-stage epithelial ovarian cancer: Role of secondary & tertiary cytoreduction



Professor Christina Fotopoulou
Imperial College, London, UK
Charite' University of Berlin, Germany



The journey of an advanced ovarian cancer patient



Long term follow up of ovarian cancer patients FIGO IIB-IV; a metaanalysis of the first line studies AGO-OVAR 3, AGO-OVAR 5 and AGO-OVAR 7: **3126 patients**

Timing of diagnosis of relapse: what has changed?

- CA125 driven follow up?
- Asymptomatic vs symptomatic relapse?
- When to define relapse in the context of novel maintenance treatments?

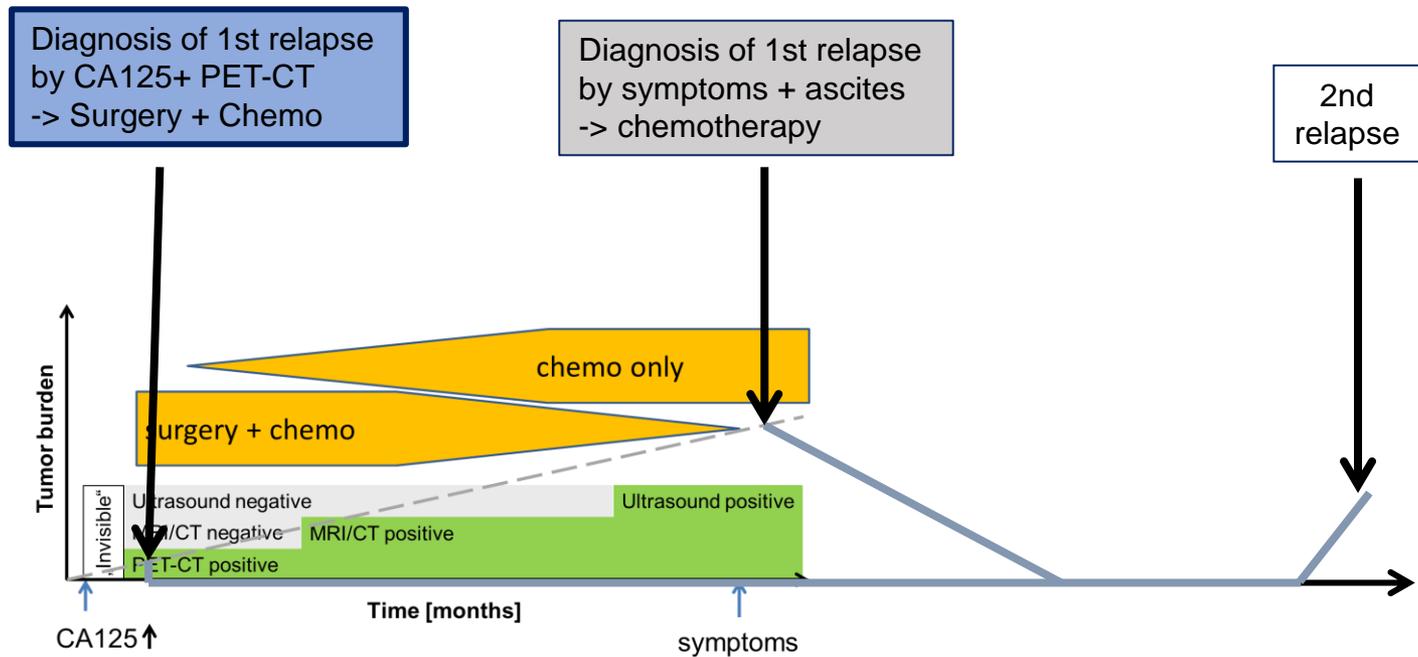


A matter of calendar??

A matter of how advanced the imaging is?

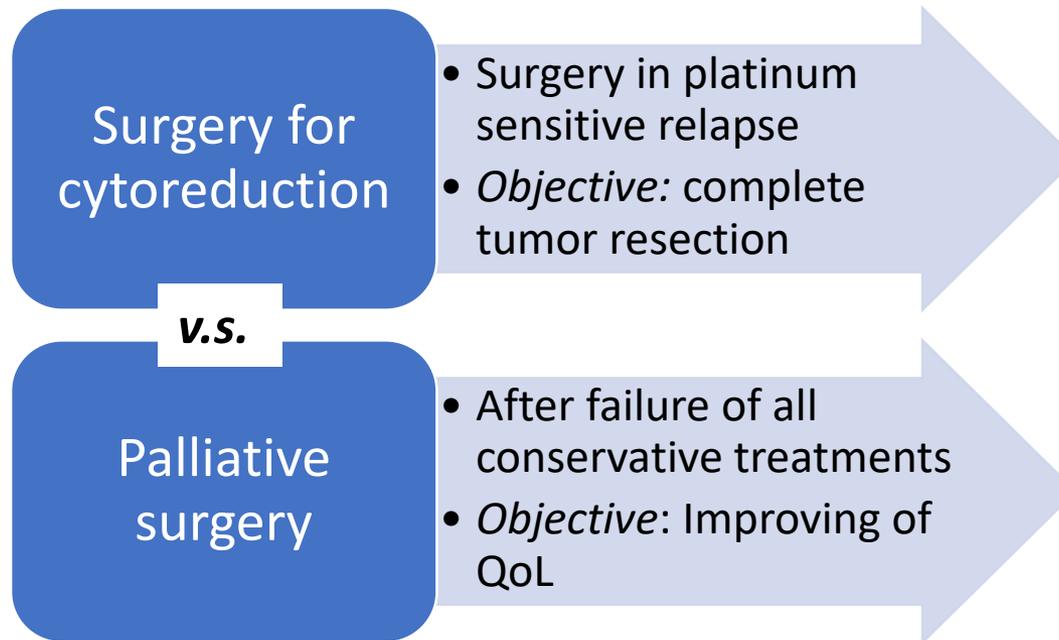
A matter of the sensibilisation of the treating physician?

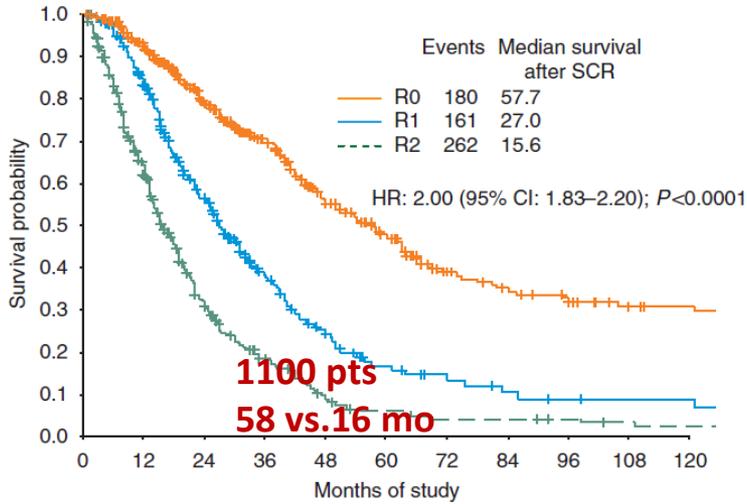
Critical keypoints of the diagnostic pathways of relapse



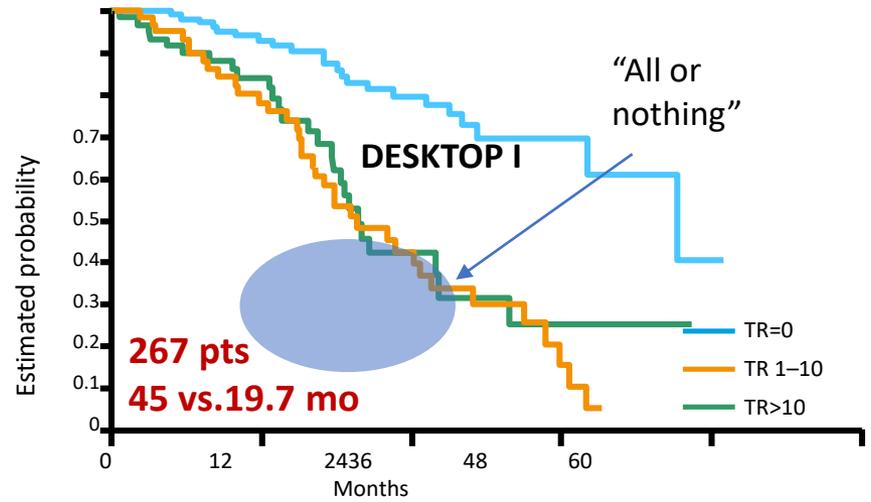
**Role of CTCs?
Tumor DNA
etc etc**

Surgery at relapse



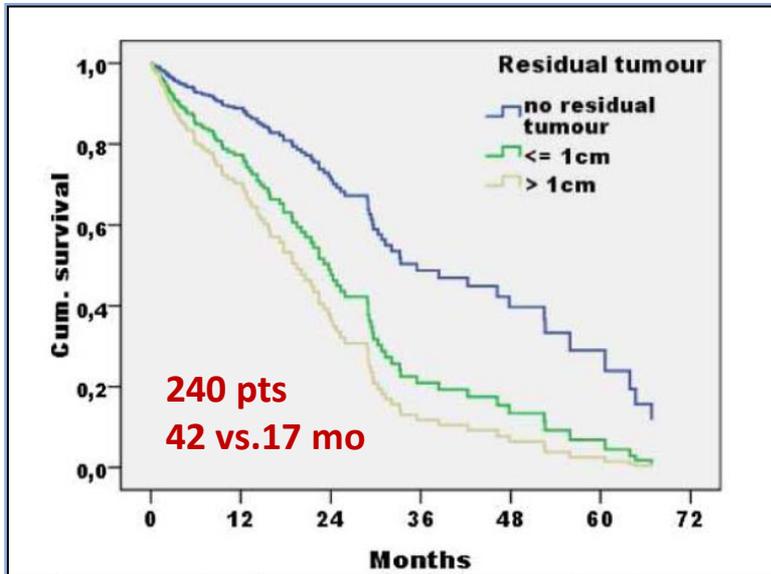


Zang R, et al. Br J Cancer 2011

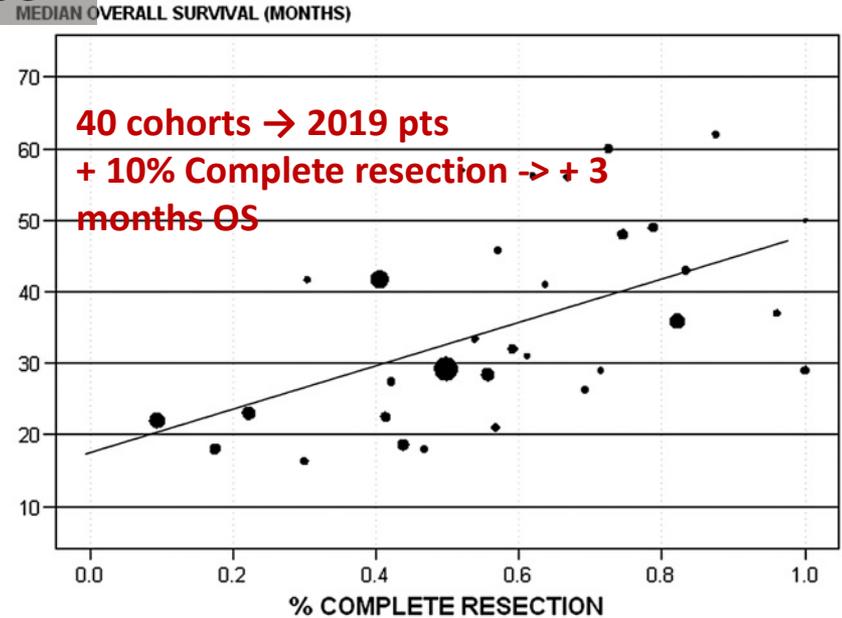


Harter P, et al. Ann Surg Oncol 2006;13:1702–10.

First relapse

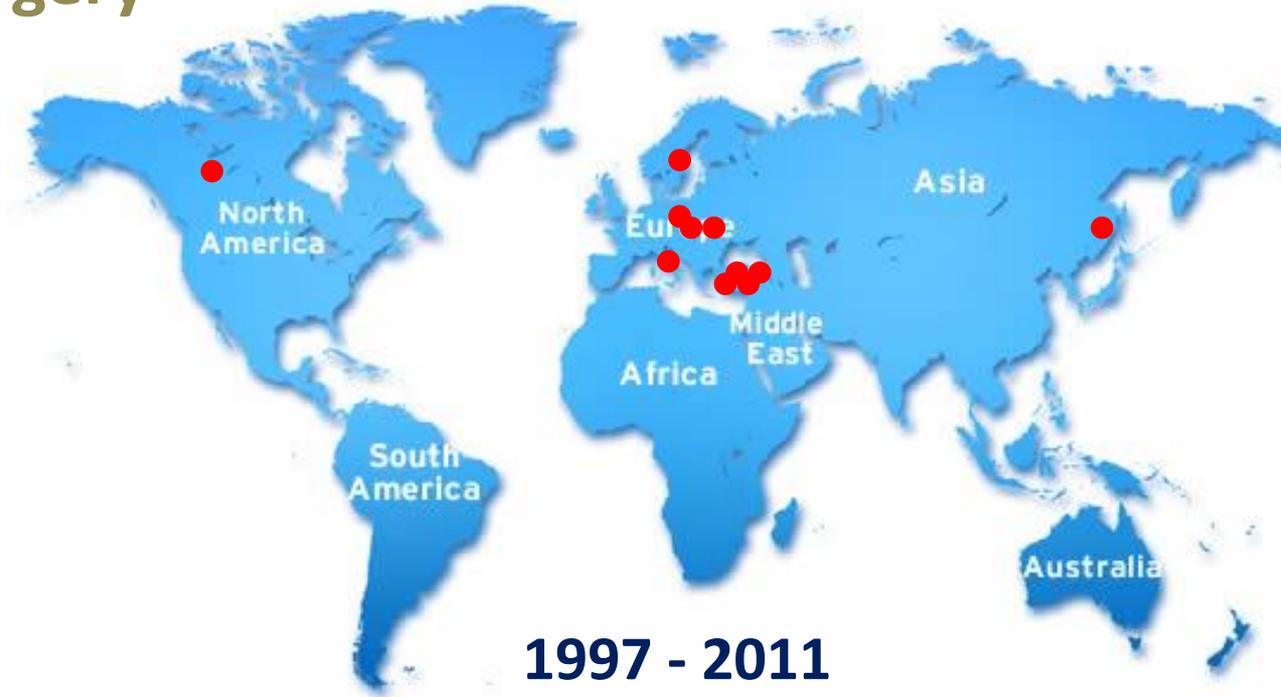


Sehoul, Fotopoulou, et al. J Surg Oncol 2010



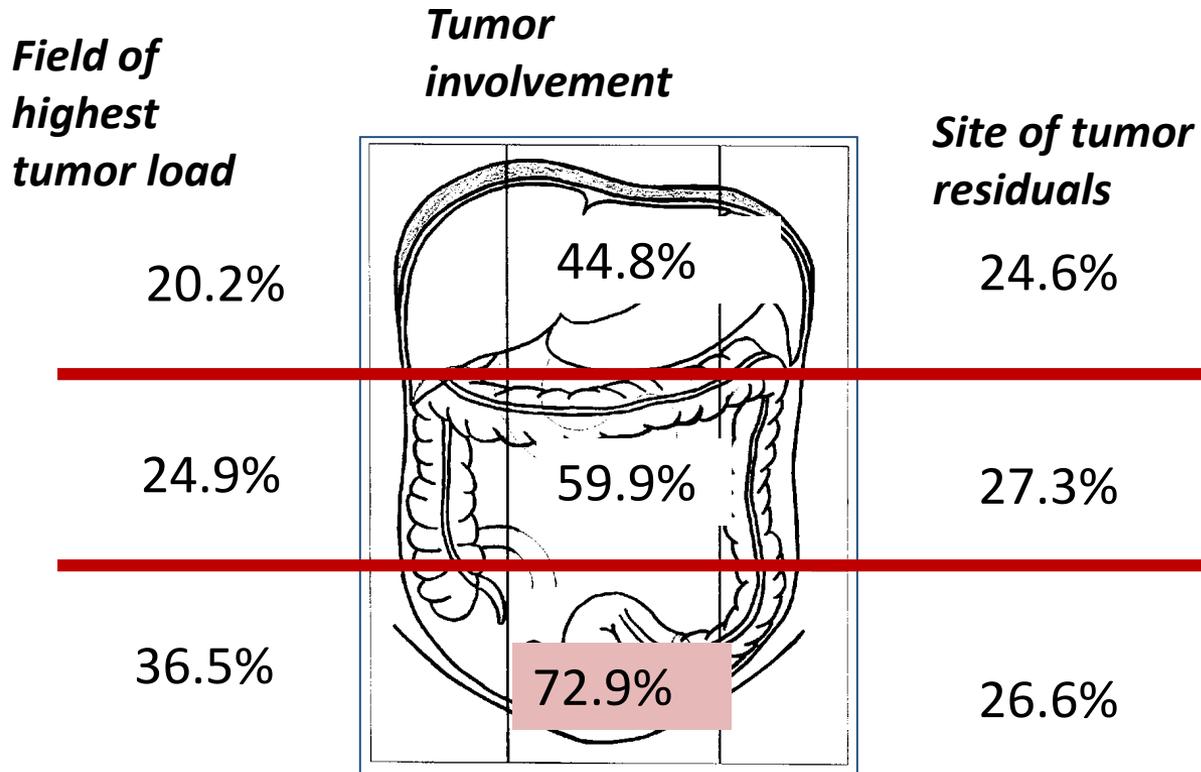
Bristow RE, Puri I, Chi DS. Gynecol Oncol 2009

The first multicenter analysis in tertiary debulking surgery

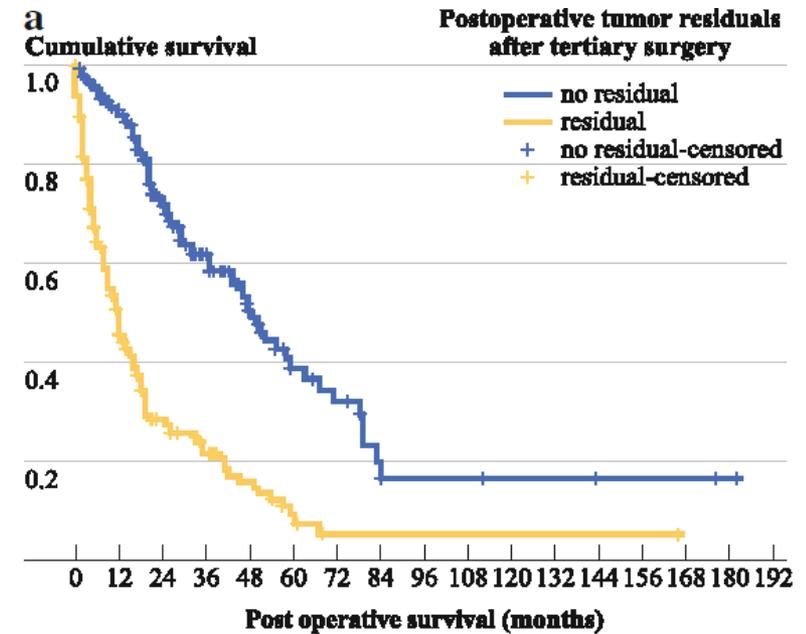
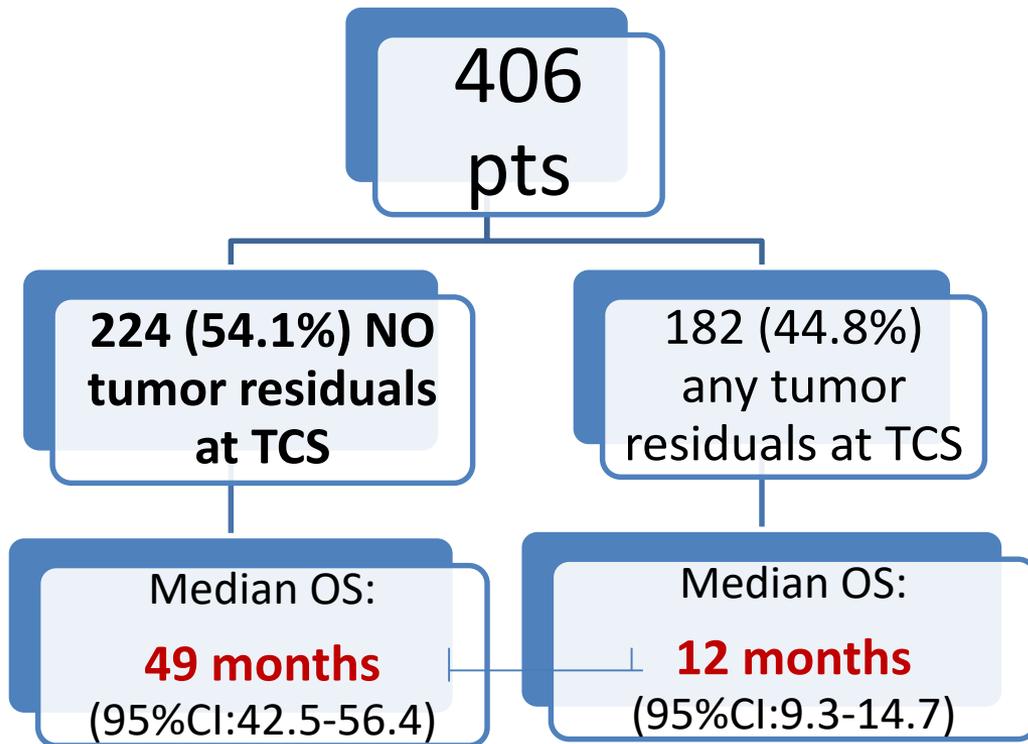


Exclusion of non-epithelial histologies, insufficient data, <30days intervall between secondary and tertiary debulking

Tumor dissemination patterns



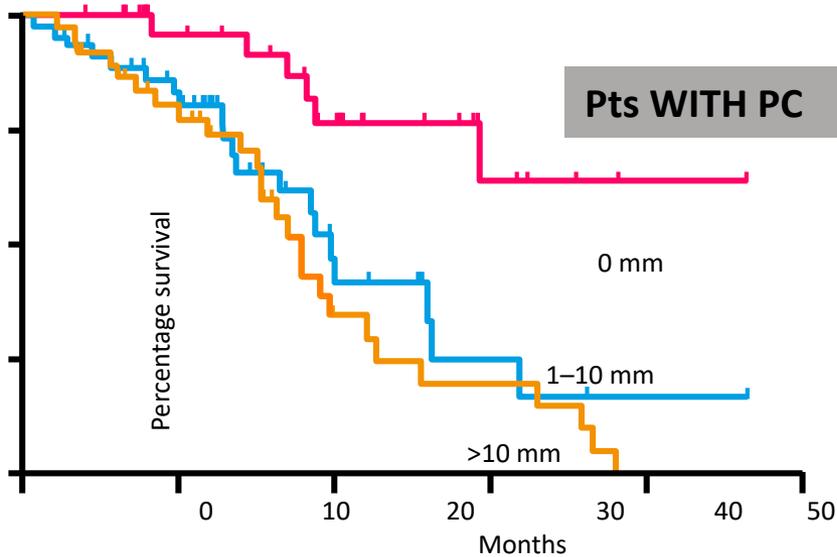
Survival impact of TCS



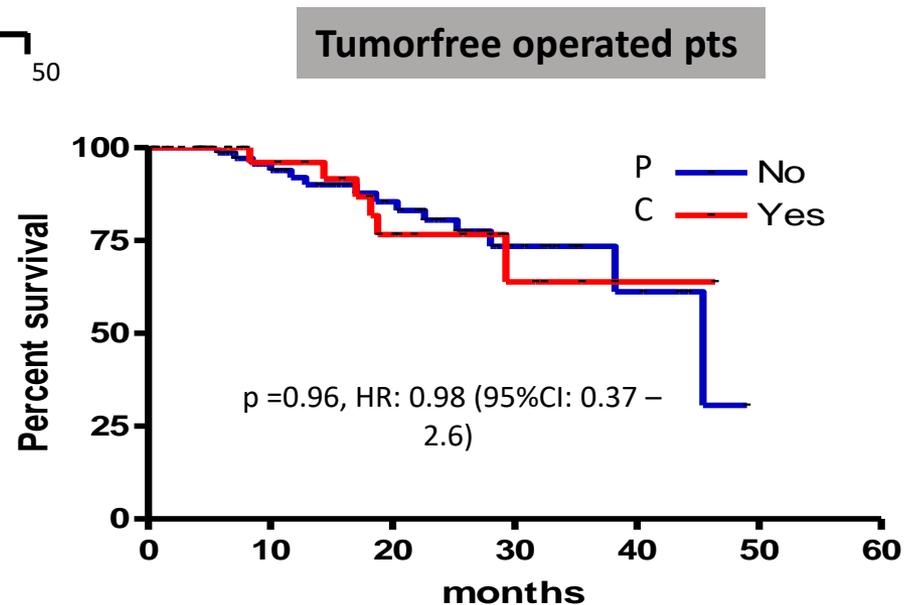
p=<0.001

.... what about tumorbiology?

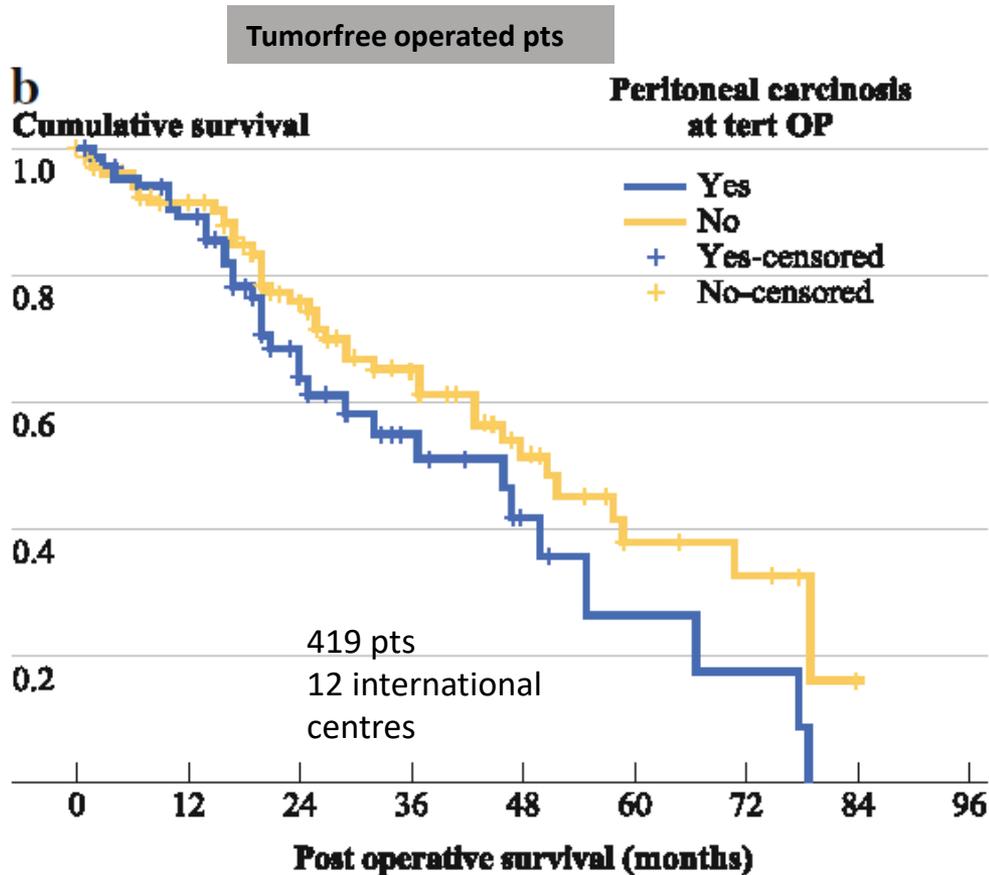
Is peritoneal carcinosis a sign of “worse” tumor biology? DESKTOP DATA



Median OS (months):
 0 mm: nyr
 1-10 mm: 17.9
 >10 mm: 19.8

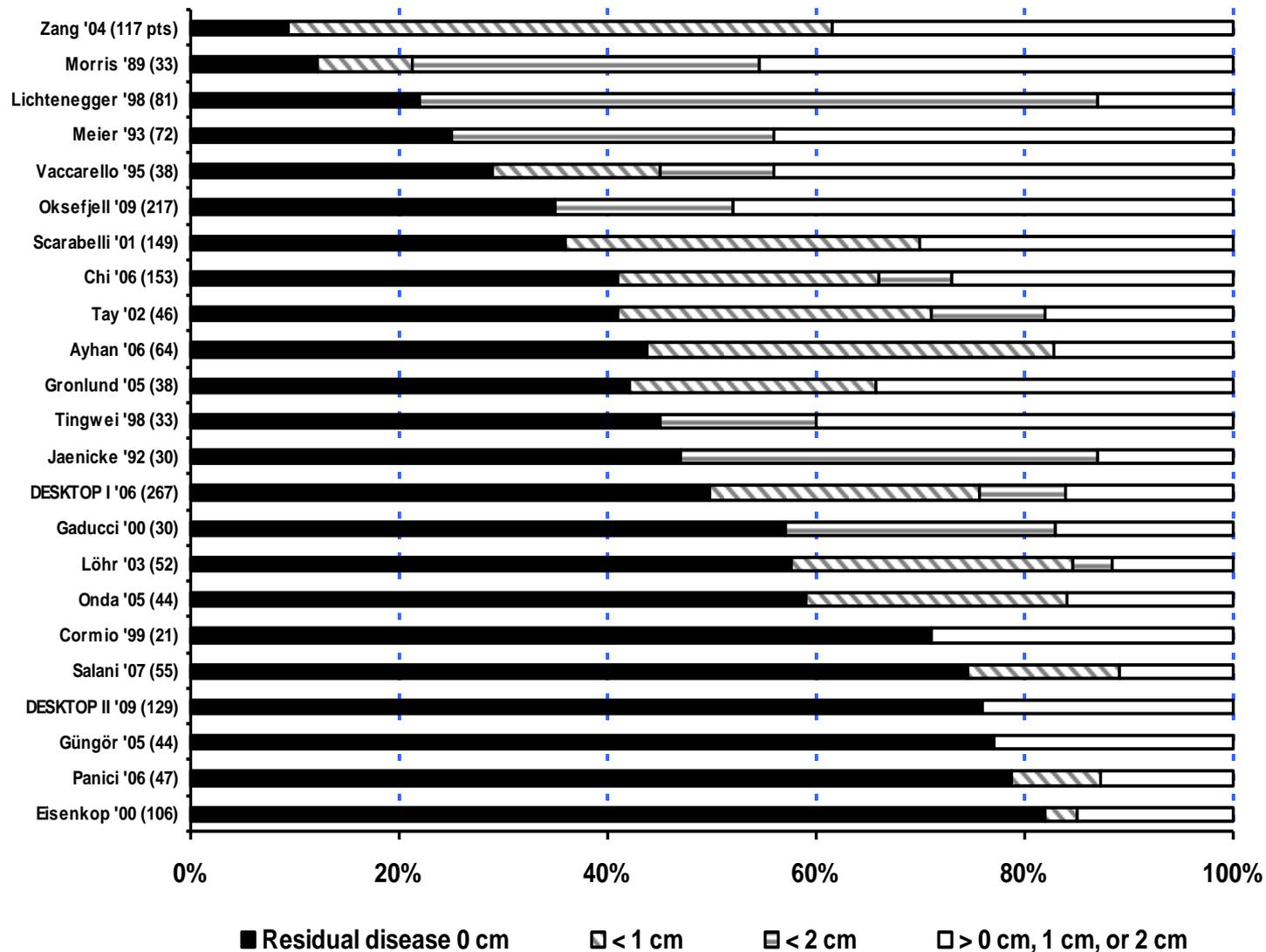


Is peritoneal carcinosis a sign of “worse” tumor biology? Tertiary debulking data



Interaction of surgical effort and tumorbiology

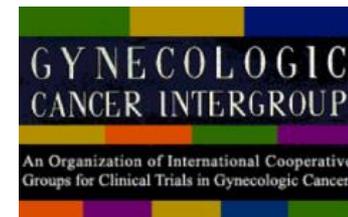
peritoneal carcinomatosis at TCS in tumorfree operated patients	p=0.099	
	median OS	95%-CI
yes	46.0	27.94 - 64.5
no	51.0	37.8 - 64.5
Total	47.0	36.4 - 57.6



Harter P, Hilpert F, Mahner S, Kommos S, Heitz F, du Bois A: Role of cytoreductive surgery in recurrent ovarian cancer
Expert Rev Anticancer Ther 2009 917-922

DESKTOP-OVAR I

Predictive factors for complete tumour resection



Pre-op factor	OR	(95% CI)	p-Value
Performance status (ECOG 0 vs. >0)	2.65	(1.56–4.52)	<0.001
Tumour residuals at primary surgery (0 vs. >0)	2.46	(1.45–4.20)	<0.001
or: initial FIGO (I/II vs. III/IV)	1.87	(1.04–3.37)	0.036
Ascites (cut-off 500 ml)*	5.08	(1.97–13.16)	<0.001

*exclusively CA125 (correlation with ascites)

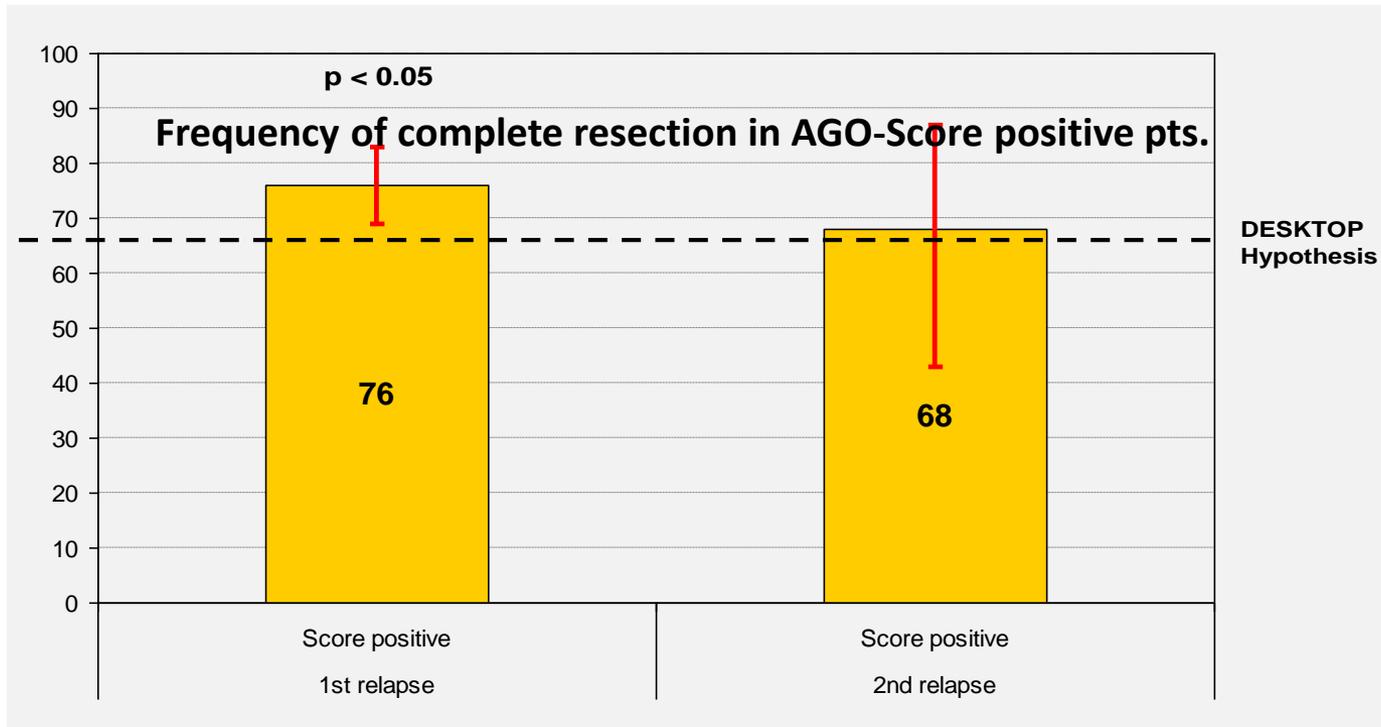
Multivariate analysis

Non-significant for a complete resection:

- Site of relapse (pelvis vs. extra-pelvis)
- Therapy-free interval

OR = objective response; ECOG = Eastern Cooperative Oncology Group;
 FIGO = International Federation of Gynecology and Obstetrics.
 Harter P, et al. Ann Surg Oncol 2006;13:1702–10.

AGO-DESKTOP II: An International Multicentre GCIG Trial Prospective Validation of a Predictive Score for Resectability in Platinum-Sensitive ROC

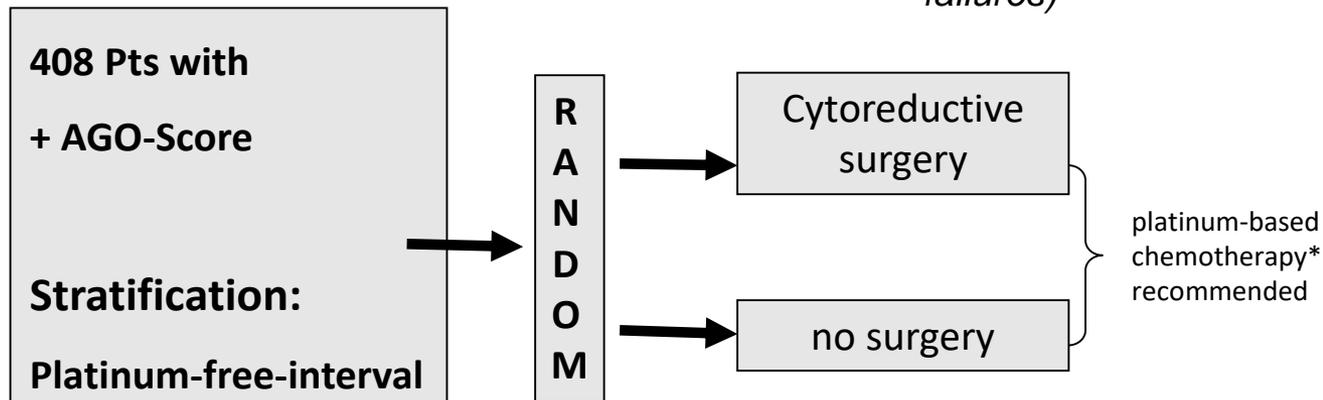


DESKTOP II = positive
Positive AGO score predicts complete resection in more than 2 out of 3 pts

AGO-OVAR DESKTOP III (Protocol AGO - OVAR OP.4)

A randomized trial evaluating cytoreductive surgery
in patients with platinum-sensitive recurrent ovarian cancer

- *80 centres in 12 countries*
- *Recruitment 9/2010 - 3/2015*
- *407 of 409 pts evaluated (2 screening failures)*

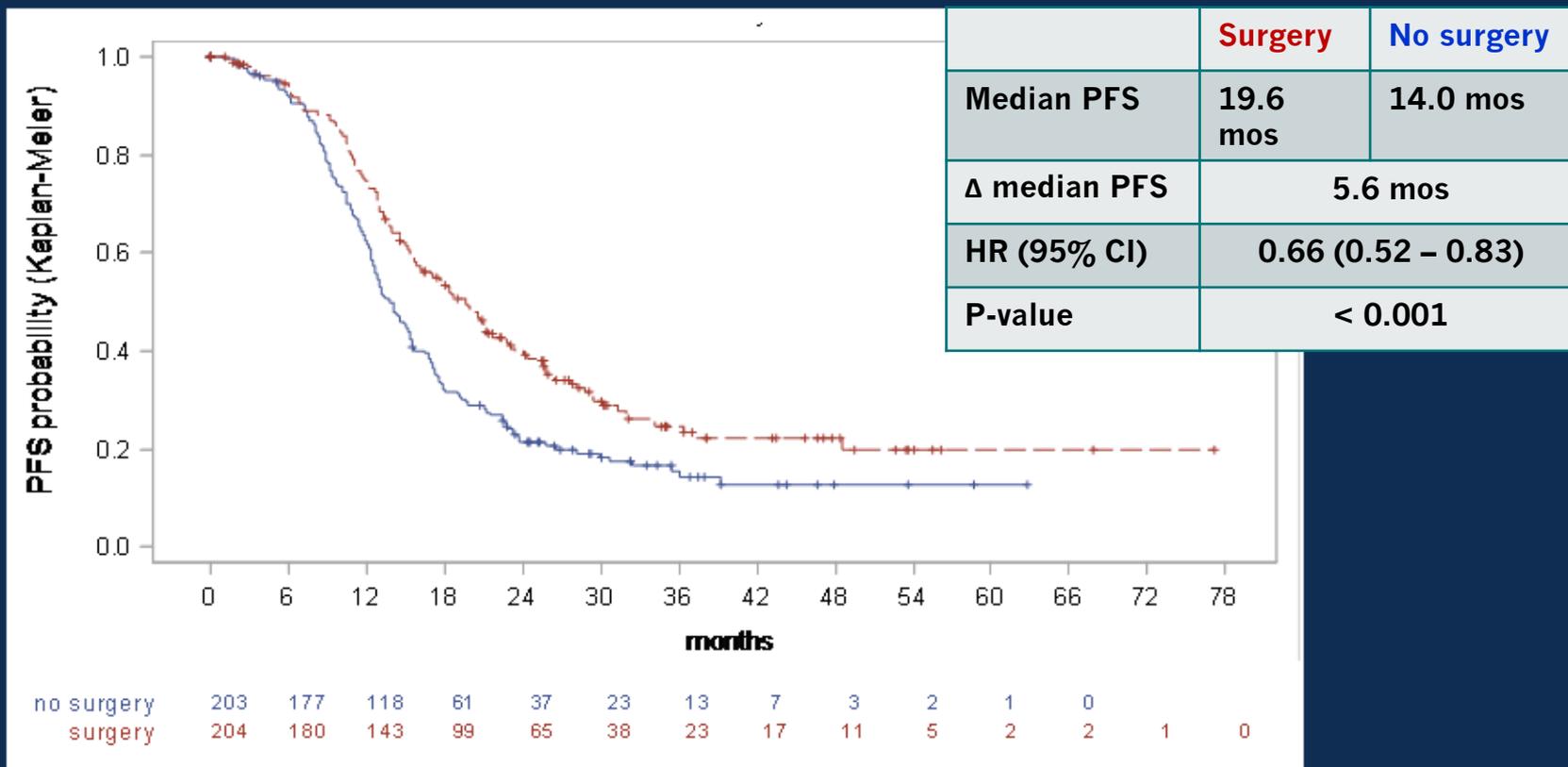


* Recommended platinum-based chemotherapy regimens:

- carboplatin/paclitaxel
- carboplatin/gemcitabine
- carboplatin/pegliposomal doxorubicin
- *or other platinum combinations in prospective trials*

AGO DESKTOP III: PFS, ITT population

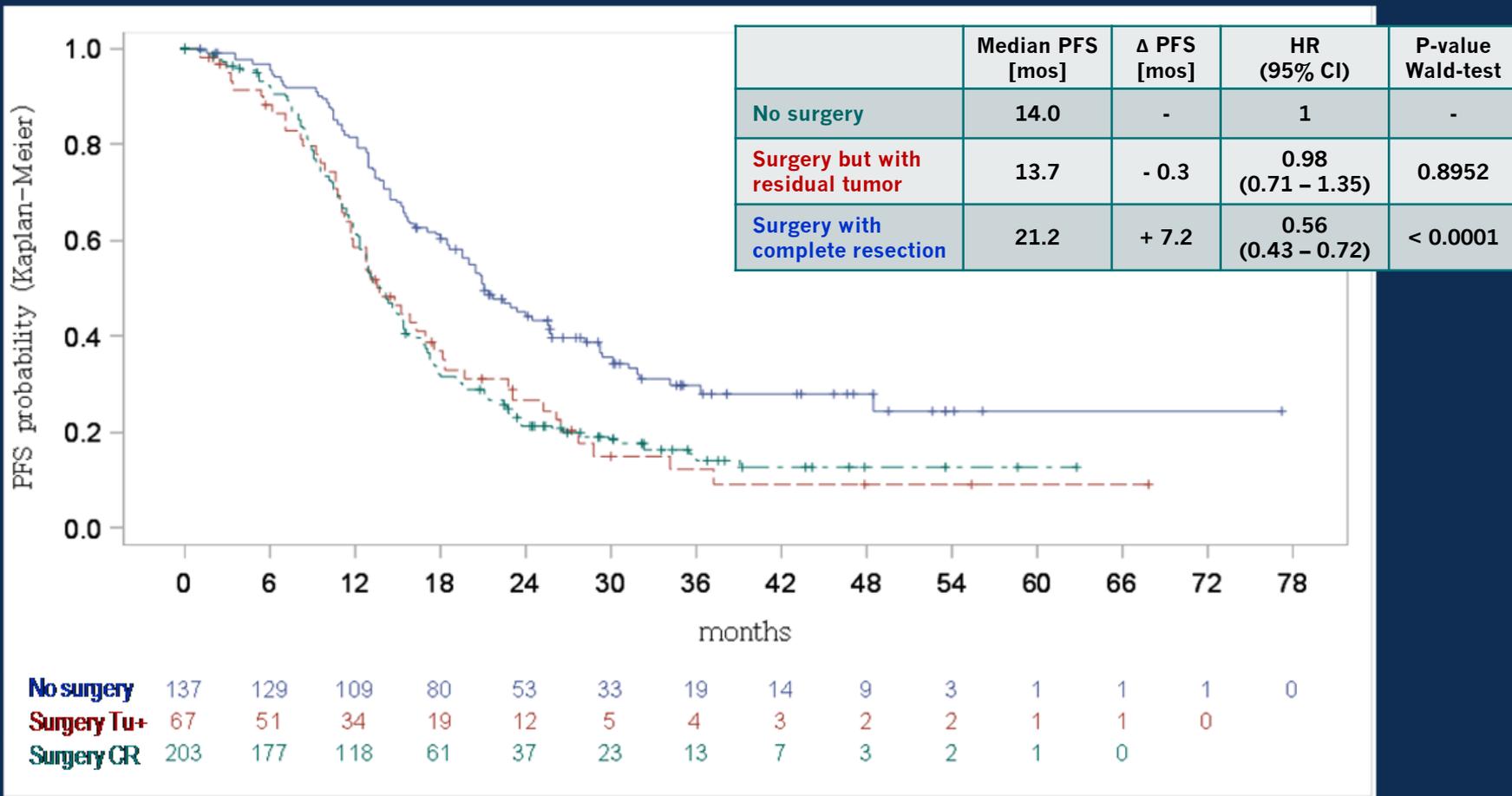
(AGO-OVAR OP.4; ENGOT-ov20; NCT01166737)



Presented by: Andreas du Bois
AGO & KEM Essen, Germany

AGO DESKTOP III: PFS by surgical outcome

(AGO-OVAR OP.4; ENGOT-ov20; NCT01166737)



AGO DESKTOP III: Morbidity of the surgical arm

(AGO-OVAR OP.4; ENGOT-ov20; NCT01166737)

Duration of surgery (minutes; median / quartiles)	220 (150 – 300)
Bowel resection	33.2%
Stoma diversion temporary / permanent	3.5% / 3.5%
Blood loss (ml; median / quartiles)	250 (50 – 500)
RBC transfusion	20.3%
Fever > 38°C	4.8%
Antibiotic treatment (mainly for urinary tract infections)	19.0%
Peri-OP thrombosis	1.1%
Re-laparotomy rate	3.2%
Macroscopic complete resection rate	72.5%

AGO DESKTOP III: Outcome 2 (Mortality / Morbidity)

(AGO-OVAR OP.4; ENGOT-ov20; NCT01166737)

	No surgery	Surgery	
30-days mortality (%)	-	-	Peri-OP 1
60-days mortality (%)	1 pt (0.49%)	-	Peri-OP 2
90-days mortality (%)	1 pt (0.49%)	1 pt (0.49%)	Peri-OP _{MAYO}
6 months mortality (%)	5 pts (2.46%)	1 pt (0.49%)	End of 2 nd line thx
G 3/4 adverse events occurring within 60 days with a frequency of at least 1% (2 pts) in one arm:			
Fatigue	2 (1%)	1(0.5%)	0.56
GI-Fistula	2 (1%)	2 (1%)	0.99
Ileus	2 (1%)	1(0.5%)	0.56
Leucopenia / Neutropenia	10 (5%)	2 (1%)	p= 0.02
Neuropathy	2 (1%)	0 (0%)	0.16
Thrombosis / Embolism	2 (1%)	1(0.5%)	0.56

.... *not so fast*

A Phase III Randomized Controlled Trial of Secondary Surgical Cytoreduction followed by Platinum-Based Combination Chemotherapy, With or Without Bevacizumab in Platinum-Sensitive, Recurrent Ovarian Cancer: A NRG Oncology/Gynecologic Oncology Group Study

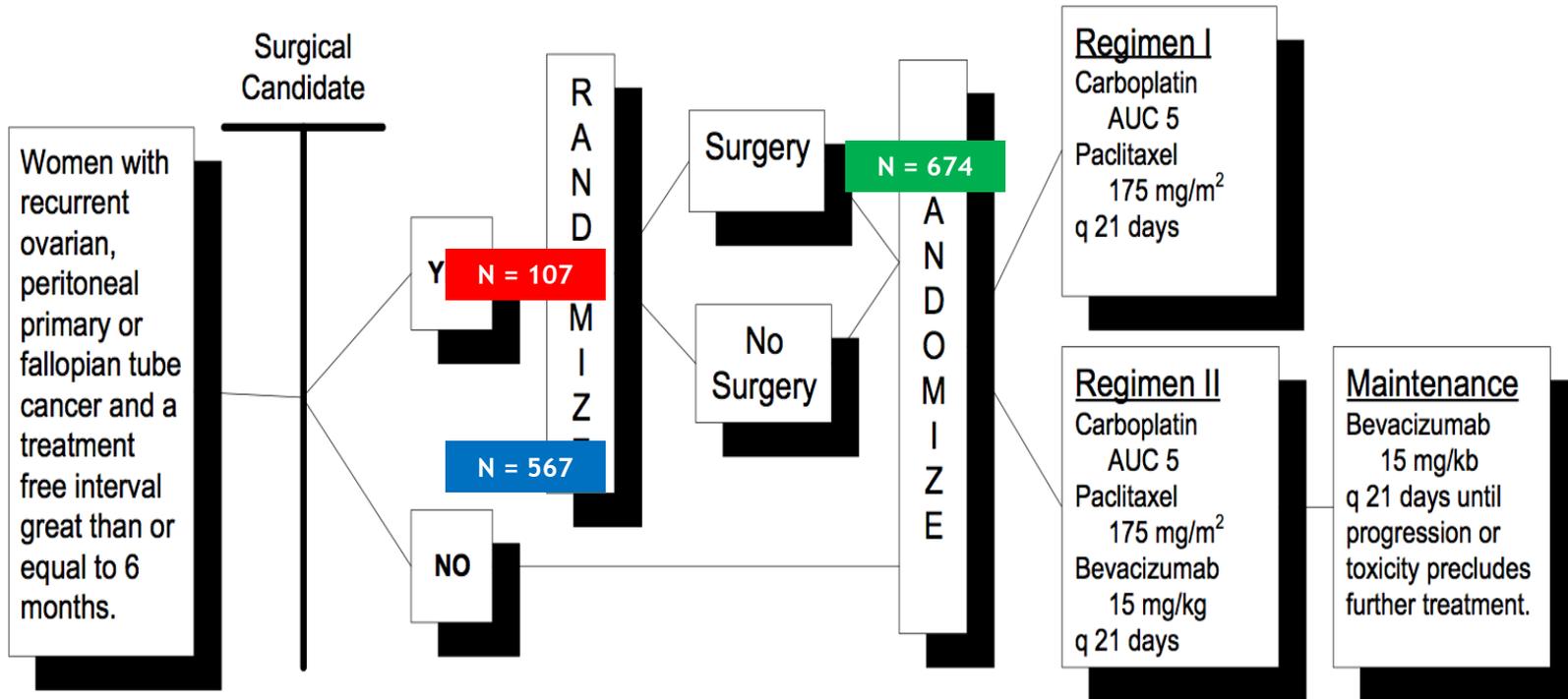
Robert L. Coleman, Nick Spirtos, Danielle Enserro,
Thomas J. Herzog, Paul Sabbatini, Deborah Kay
Armstrong, Byoung Kim, Keiichi Fujiwara, Joan L.
Walker, Patrick J. Flynn, Angeles Alvarez Secord,
David E. Cohn, Mark F. Brady, Robert S. Mannel



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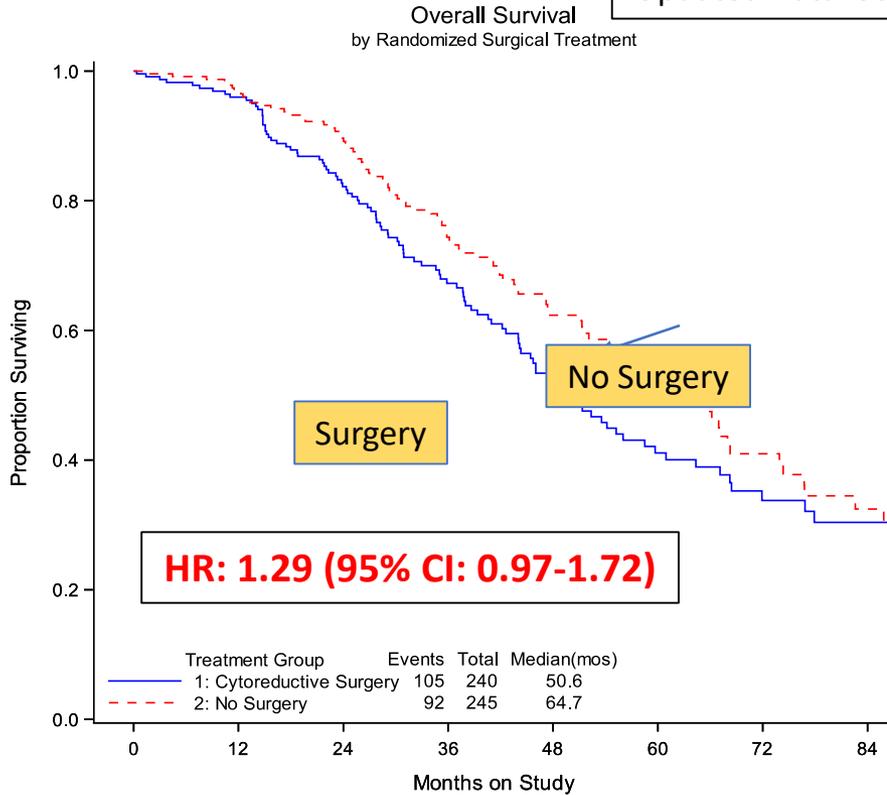
ROBERT L. COLEMAN,
MD

GOG 213: Schema Objective #1

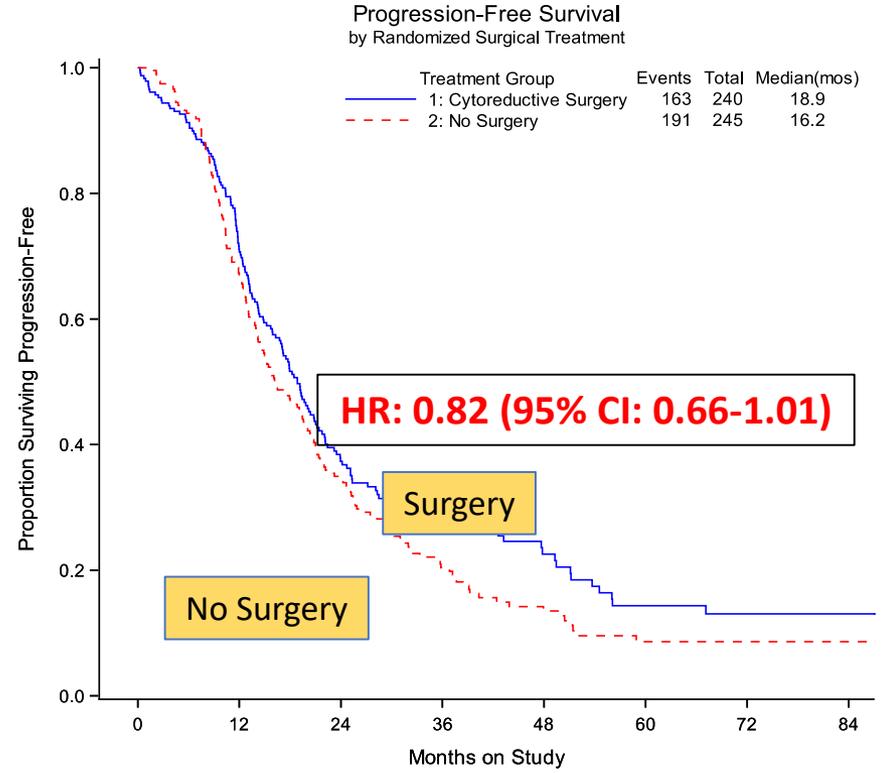


Primary/Secondary Endpoints: Surgery vs. No Surgery

Updated Data lock: April 26, 2019



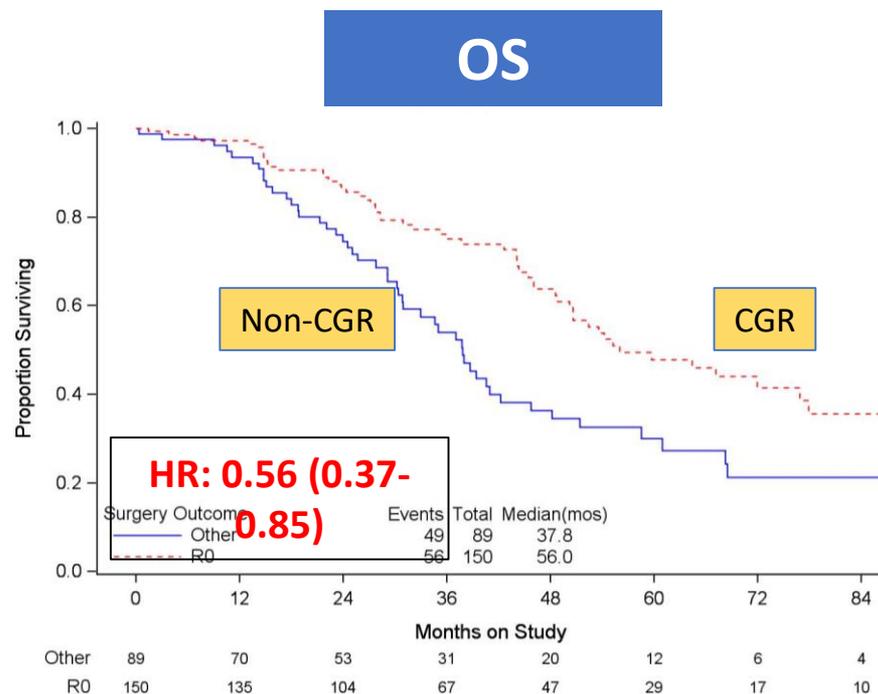
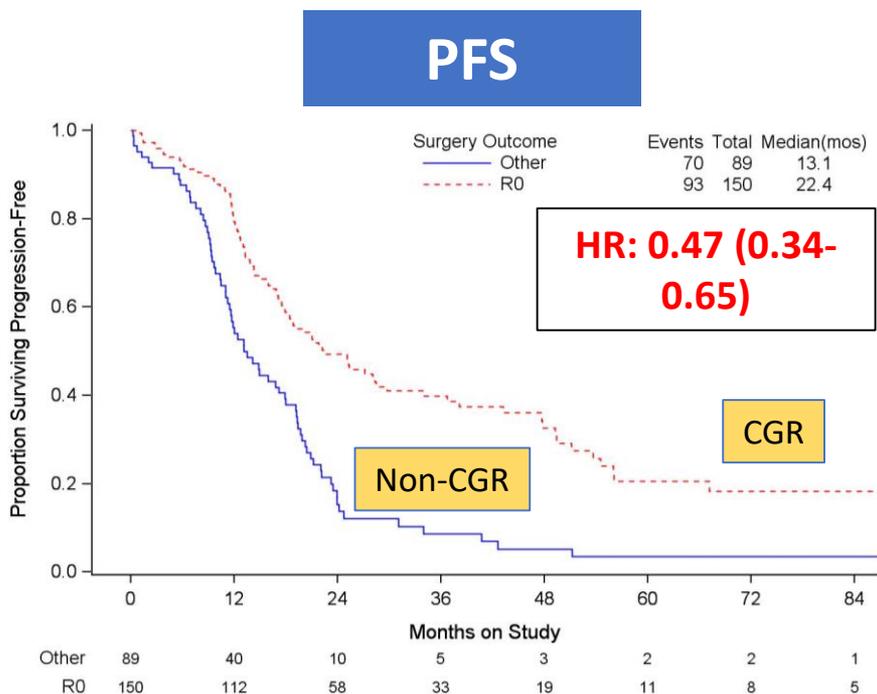
	0	12	24	36	48	60	72	84
1	240	205	157	98	67	41	23	14
2	245	217	172	124	75	50	28	16



	0	12	24	36	48	60	72	84
1	240	152	68	38	22	13	10	6
2	245	153	68	36	19	8	6	5

Exploratory Endpoint: Prognostic Impact of CGR

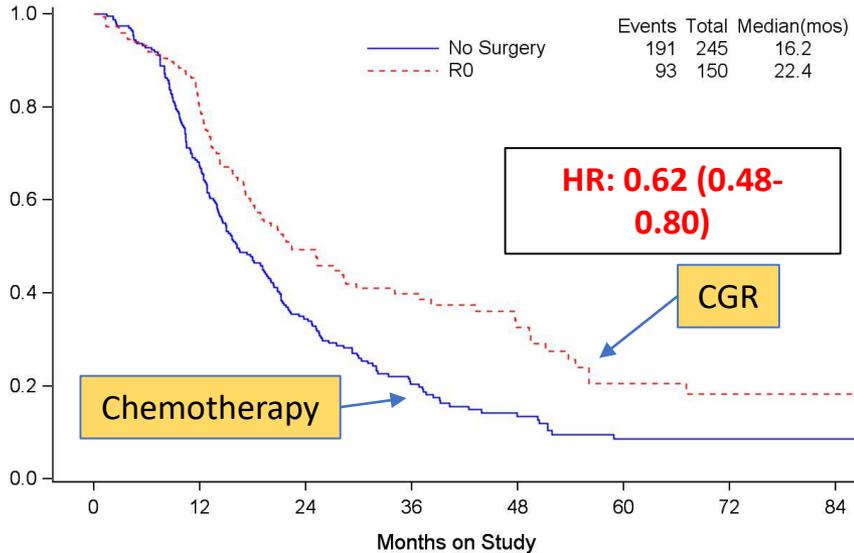
Updated Data lock: April 26, 2019



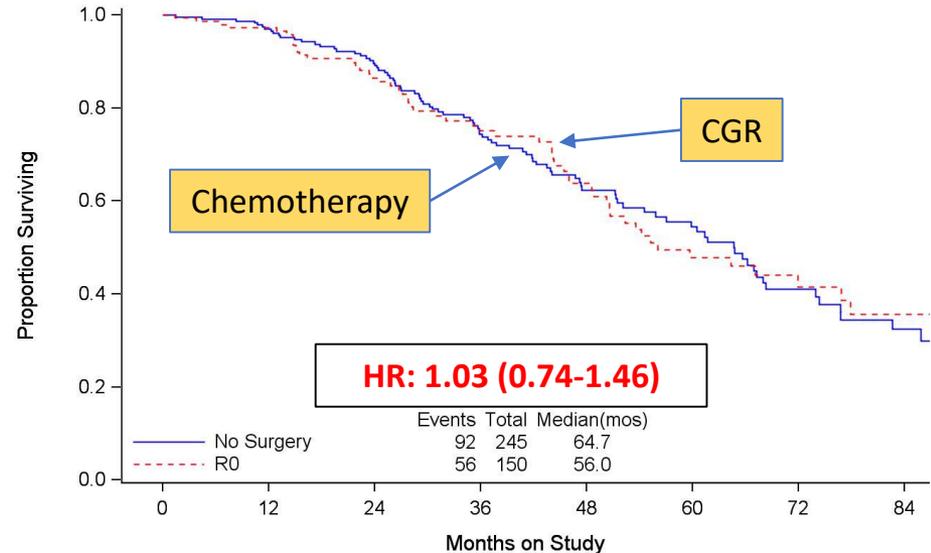
Exploratory Endpoint: CGR (68% of Surgical Patients) vs. Chemotherapy (All)

Updated Data lock: April 26, 2019

Progression-Free Survival
R0 vs No Surgery



Overall Survival
R0 vs No Surgery



	0	12	24	36	48	60	72	84
No Surgery	245	153	68	36	19	8	6	5
R0	150	110	50	30	16	11	8	7

	0	12	24	36	48	60	72	84
No Surgery	245	217	172	124	75	50	28	16
R0	150	125	101	77	57	33	17	10

Conclusions GOG 213

- Secondary cytoreduction was **NOT** associated with an improvement in either OS or PFS compared to no surgery in this population
- Complete gross resection (CGR) was 67% in the per protocol population
 - R0 resection statistically improved PFS and OS relative to those with post-operative residual disease
 - However, relative to chemotherapy alone, CGR was not associated with better OS despite extending PFS

Positive Phase III 2nd Line Therapy Trials in Platinum sensitive ovarian cancer relapse

Trials	Treatment	Med PFS (months)	PFS gain (months)	HR / p-value	OS (months)	HR / p-value
ICON 4 (n=802) Lancet 2003	Platinum	9	3	0.76 /	24	0.82 / 0.02
	Platinum+Taxol	12		<0.001	29	
AGO Ovar 2.5 (n=366), JCO 2006	Carboplatin	5.8	2.8	0.72 /	17.3	0.96 / 0.73
	Gem+Carbo	8.6		0.003	18	
CALYPSO (n=976) JCO 2010	Carbo+Taxol	9.4	1.9	0.82 /	33.0	0.99 / 0.94
	Carbo+PLD	11.3		0.005	30.7	
OCEANS (n=484) JCO 2012, Gyn Onc 2015	Gem+Carbo	8.4	4.0	0.48 /	33.6	0.96 / 0.65
	Gem+Carbo+Bev	12.4		<0.0001	32.9	
ICON 6 (n=456) Lancet 2016	Carbo+Taxol	8.7	2.4	0.56 /	21	0.77 / 0.11
	Chemo+cediranib	11.1		<0.0001	26.3	
GOG 213 (n=674) Lancet Oncol 2017	Carbo+Taxol	10.4	3.4	0.63 /	37.3	0.829 (0.823)* / 0.056 (0.044)*
	Carbo/Taxol+Bev	13.8		<0.0001	42.2	
DESKTOP III ASCO 2017	Platin based	14.0	5.6	0.66 /	n.a.	n.a.
	chemo +/- OP	19.6		<0.001	n.a.	

* Sensitivity analysis with corrected PFI data

by du Bois A

....so?



- Role of antiangiogenetic agents?
- Different populations: quality of treatment overall, insurance/ funding, quality of primary treatment
- Quality of surgery?
- Eligibility criteria? (AGO score yes vs no)
- Tradition and philosophy of surgery at relapse?

Eligibility for Surgery in GOG 0213

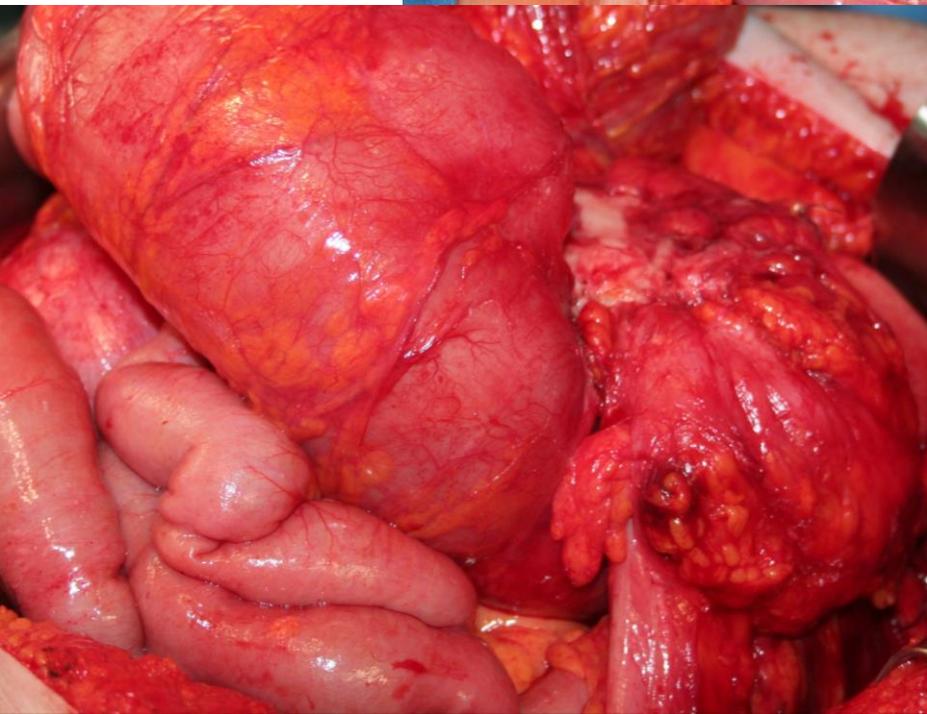
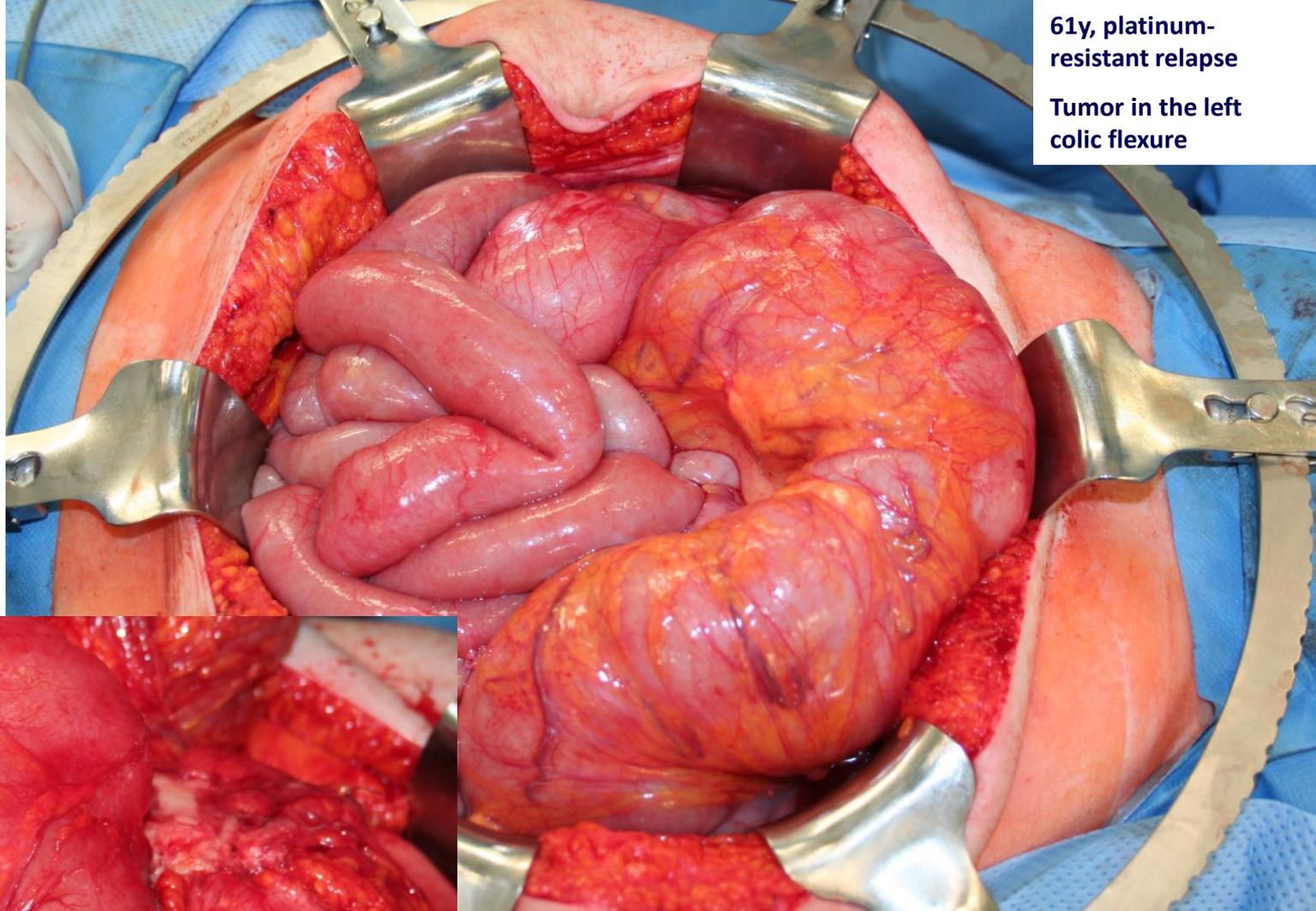
- No specific eligibility criteria provided
- The goal of secondary cytoreduction is:
 - **COMPLETE REMOVAL OF ALL VISIBLE DISEASE.**
- Protocol Guidance:
 - “Women with carcinomatosis and/or ascites make poor surgical candidates as the diffusion of disease usually precludes complete cytoreduction.”
 - Similarly, women with parenchymal organ disease (e.g. lung, liver, pancreas, kidney, bone, etc.) are poor candidates, if the disease is felt unresectable by preoperative evaluation.”
- Assessment of candidacy will be made by physical exam, laboratory and imaging (MRI, PET/CT and/or CT).

*..... waiting for the OS analysis of
DESKTOP III*

...until then

*bowel obstruction and
palliative surgery*

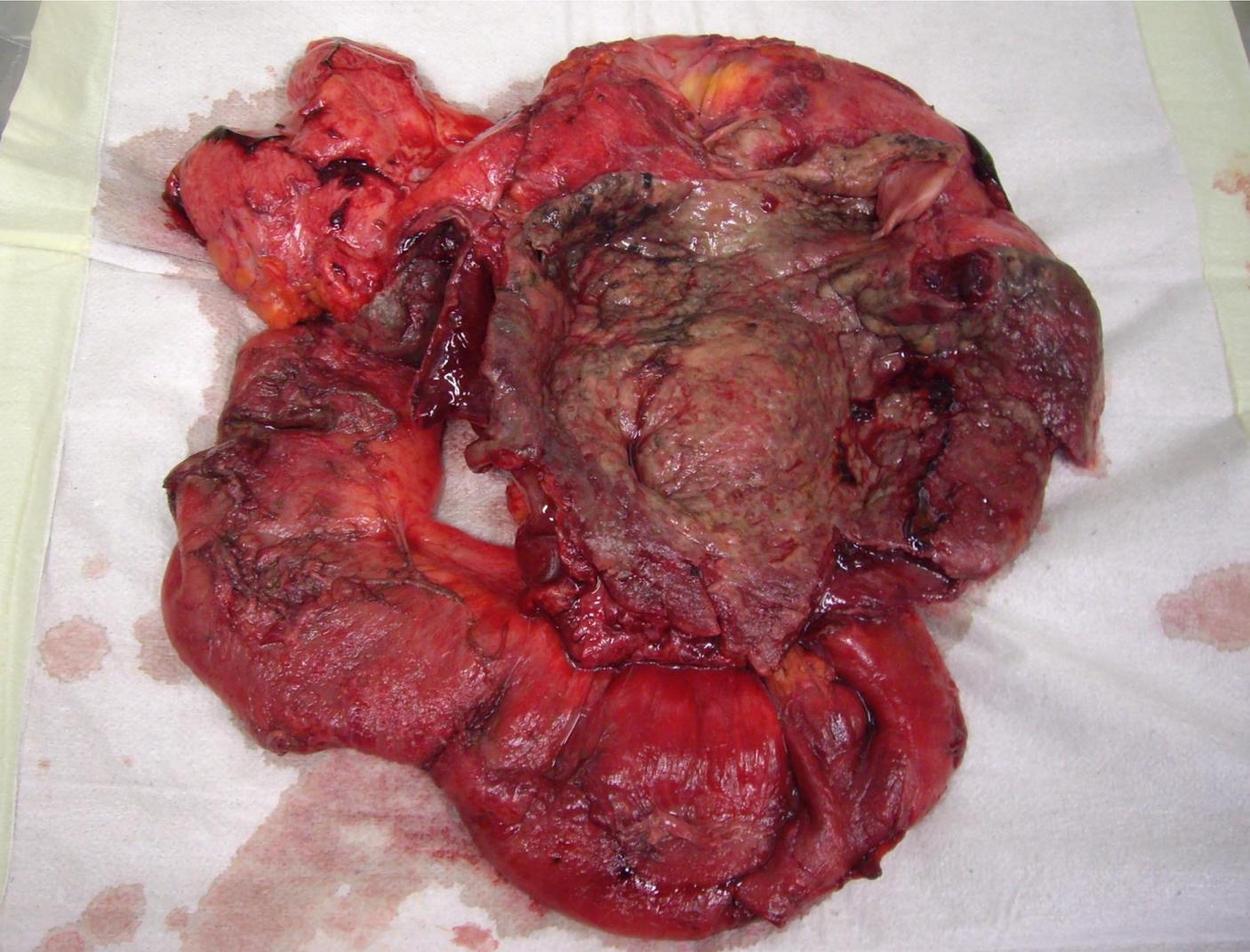
61y, platinum-resistant relapse
Tumor in the left colic flexure



42y

Platinum resistant
ovarian cancer with
multiple perforations





62y

**Taxol induced bowel
perforation with peritonitis
and ileus**

**In the era of novel
targeted therapies....**

Feasibility of Surgery After Systemic Treatment with the Humanized Recombinant Antibody Bevacizumab in Heavily Pretreated Patients with Advanced Epithelial Ovarian Cancer

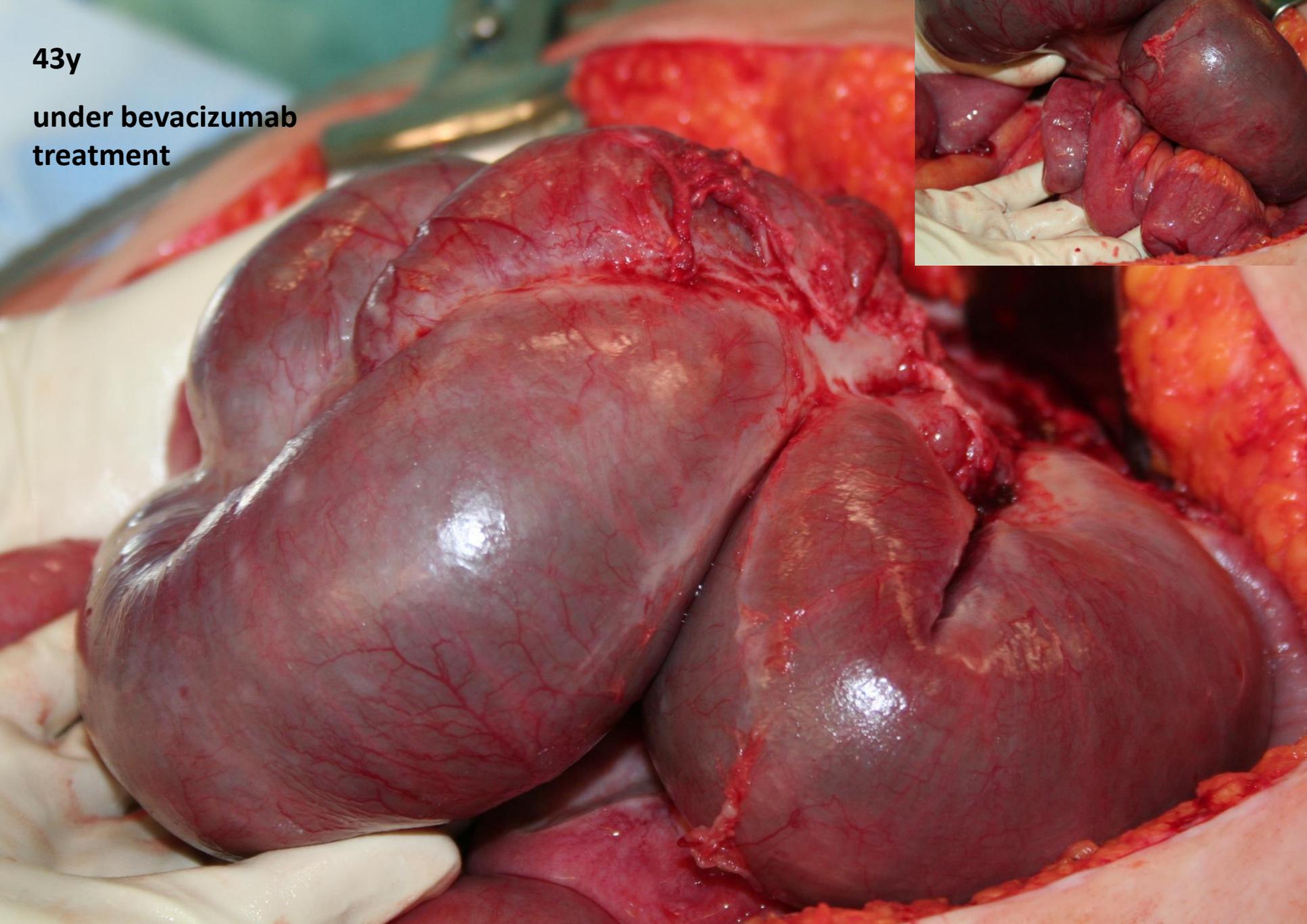
Jalid Sehouli, MD, PhD¹, G. Papanikolaou, MD¹, E.-I. Braicu, MD¹, K. Pietzner, MD¹, P. Neuhaus, MD, PhD², and
C. Fotopoulou, MD, PhD¹

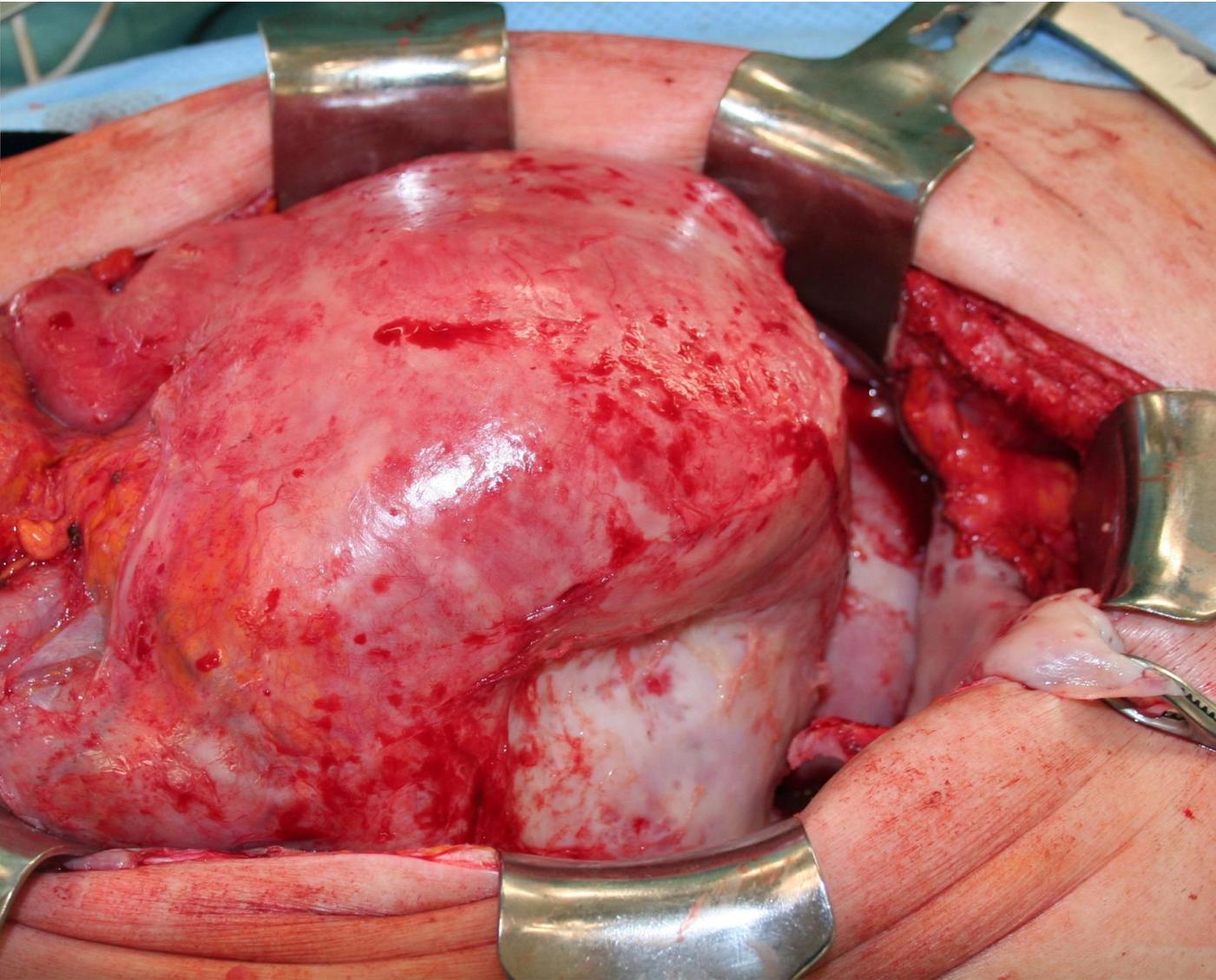
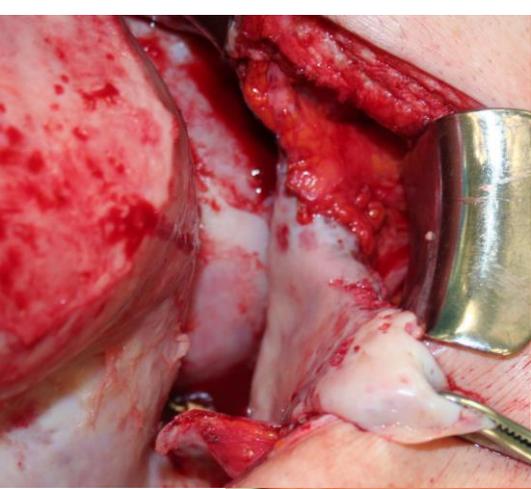
Emergency surgery after bevacizumab due to bowel obstruction and/or fistulas seems to be associated with an impaired wound healing in advanced heavily pretreated platinum-resistant ovarian cancer patients.

*10 patients in a mean time of 134 days
(range: 10–20) after bevacizumab*

43y

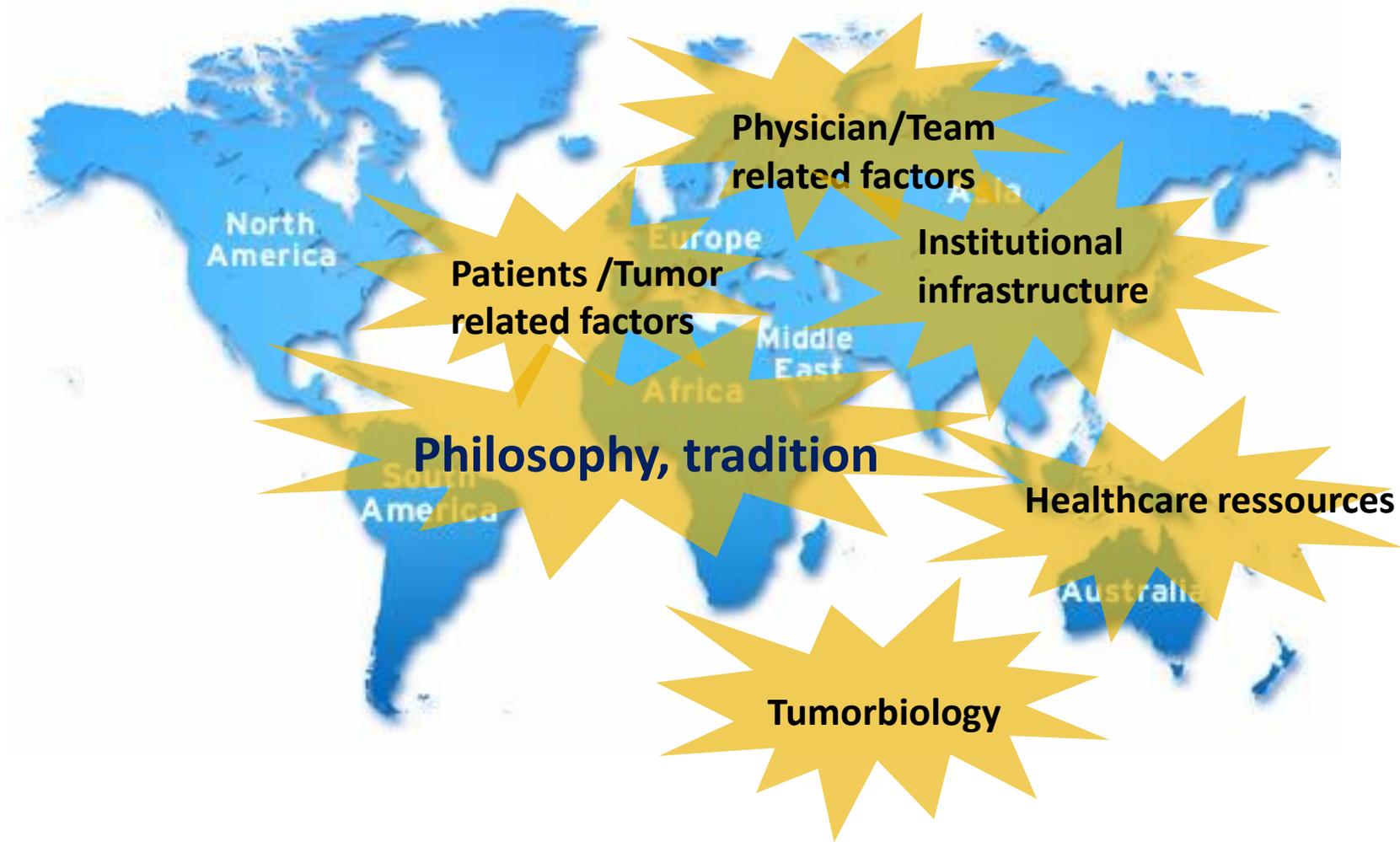
under bevacizumab
treatment





67y Platinum refractory relapse after catumaxomab treatment ip.





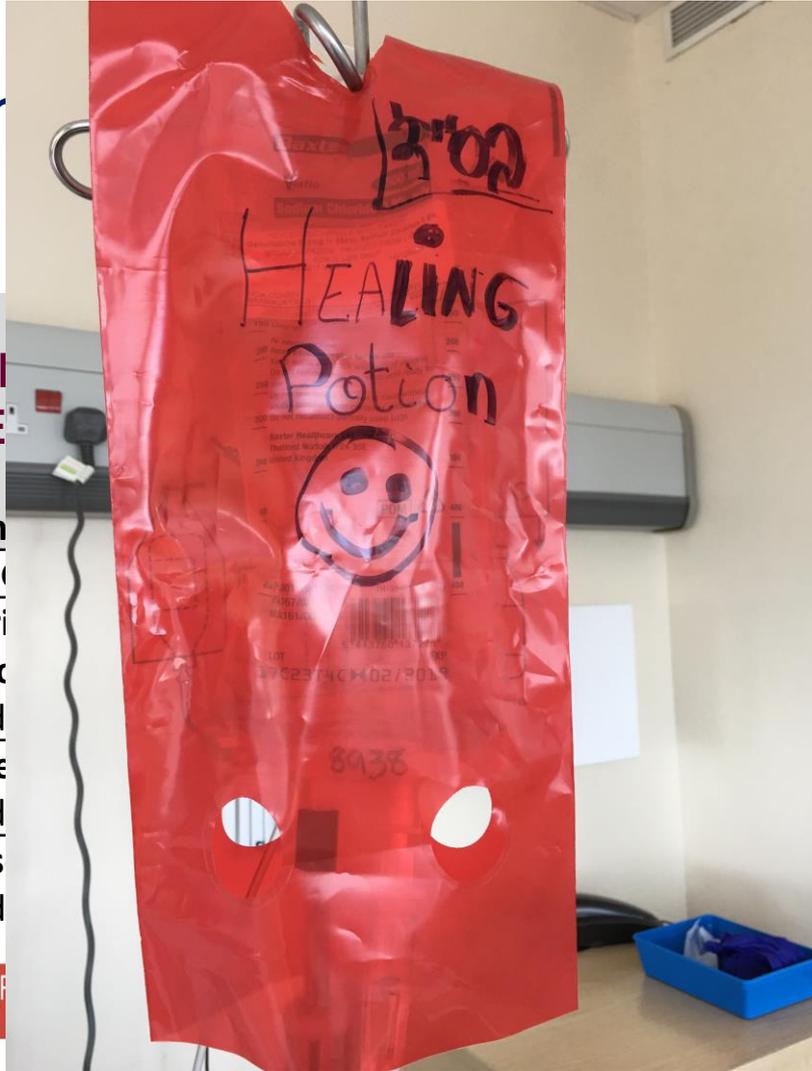
- *...translating surgical effort into survival benefit*

*...while balancing iatrogenic
morbidity*

As a m

**ICOL
EVE**

**Num
Any
Febrile
episo
Grad
Anaes
Grad
Sens
Grad**



**Arm 3
Weekly
carbo-
aclitaxel
N=511**

69 53%

16 3%

25 5%

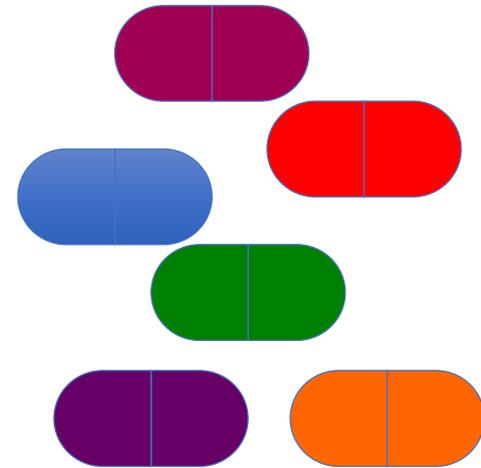
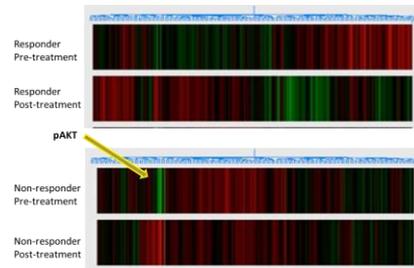
17 23%

o A, et.al. 2017



...and costs

Extending the window of opportunity through novel targeted agents at relapse



Caris Target Now
Sequenom
Exome Seq
Expression Microarray

**Aim: individualization of care with tailoring
of surgical treatments matching the
maximal effort therapeutic approach of
systemic advances**

