

Surgery for recurrent ovarian cancer and palliative surgery

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Surgery for
cytoreduction

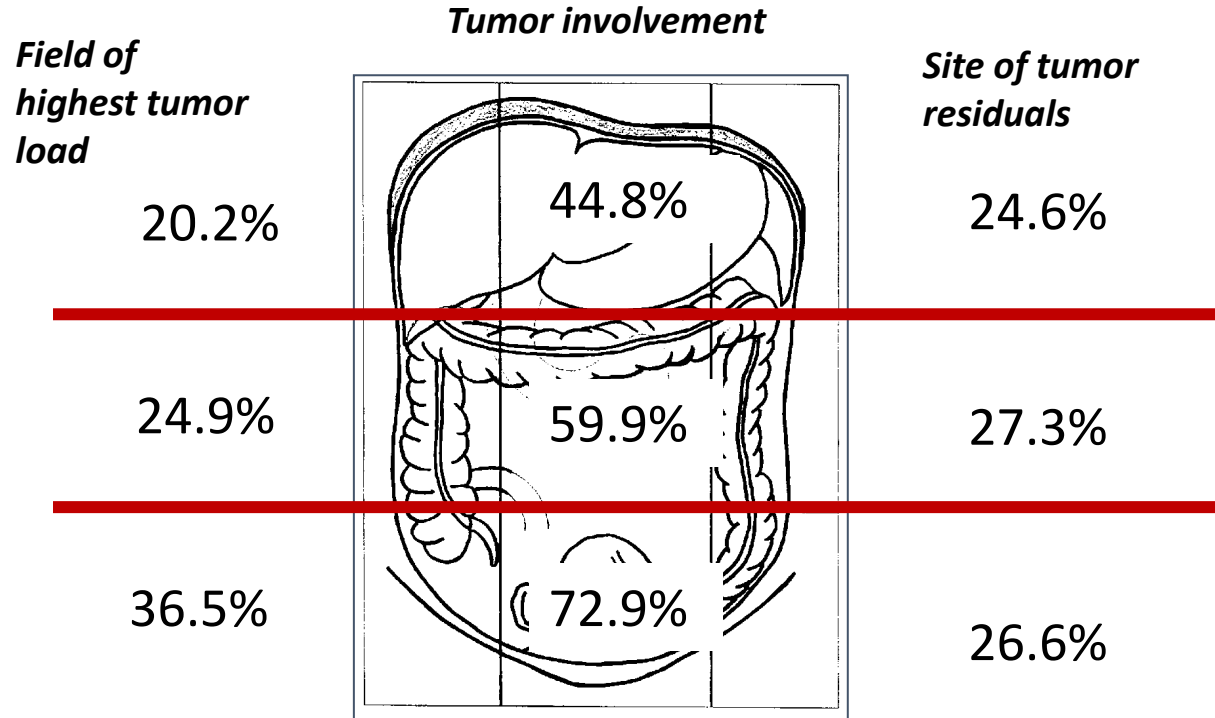
V.S.

Palliative
surgery

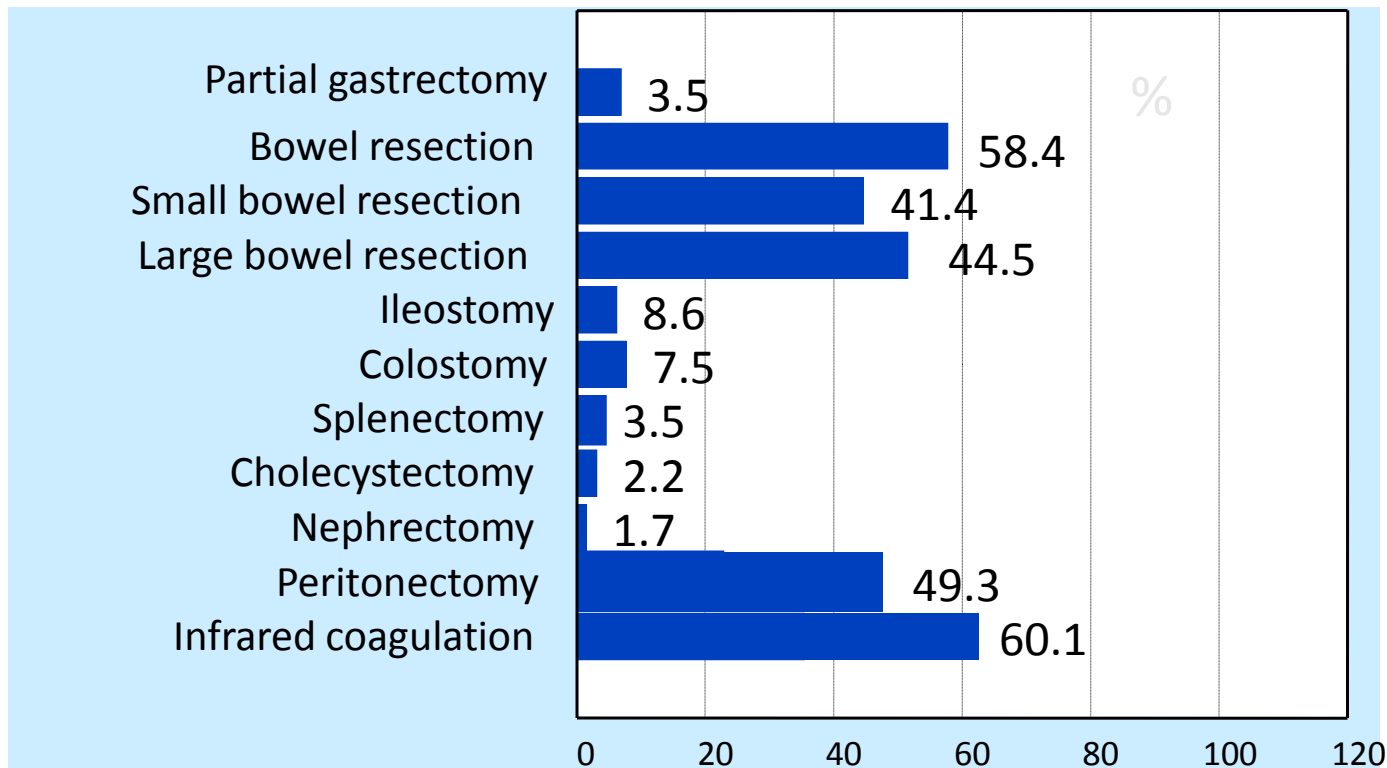
- Surgery in platinum sensitive relapse
- *Objective:* complete tumor resection

- After failure of all conservative treatments
- *Objective:* Improving of QoL

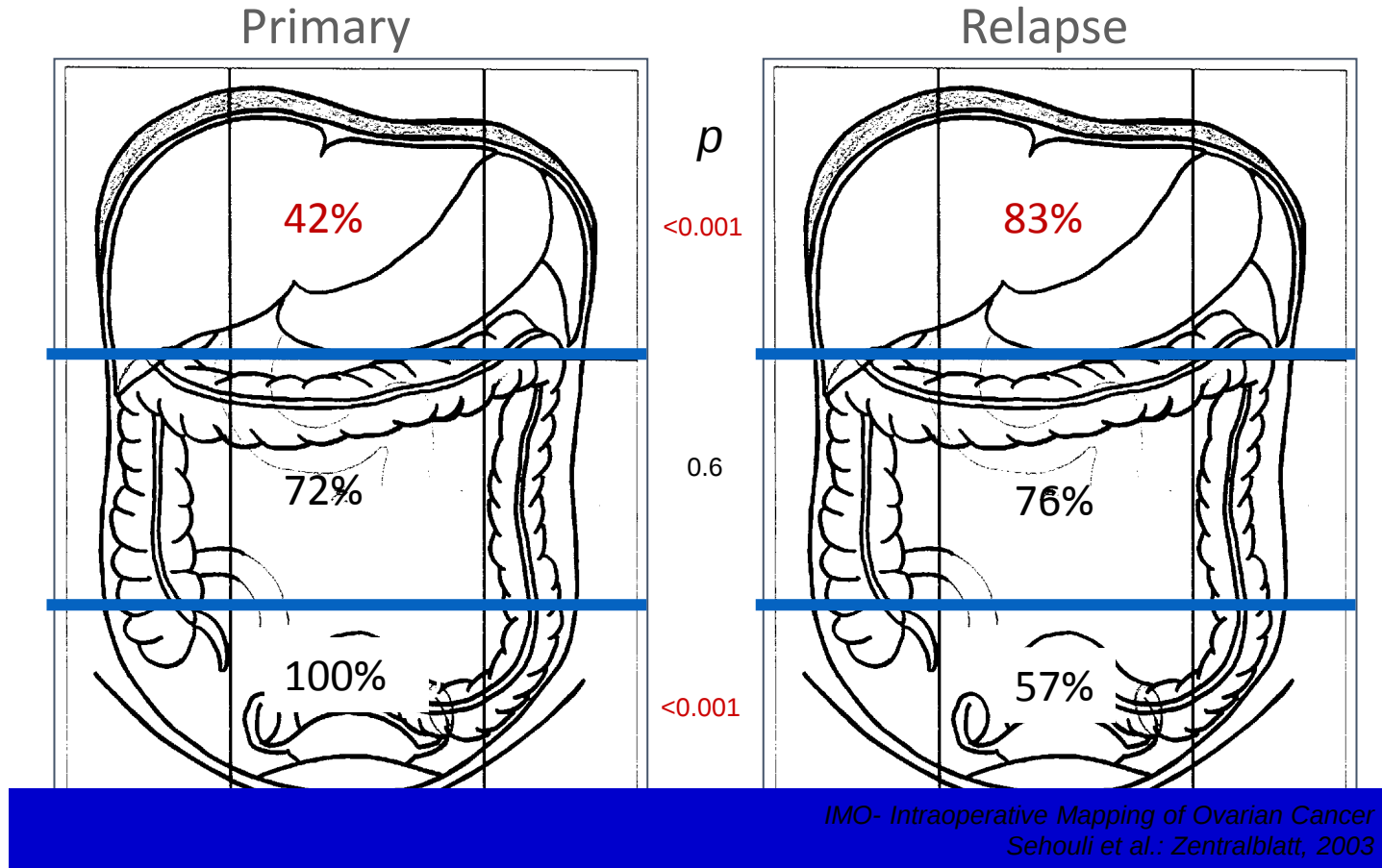
Tumor dissemination patterns at relapse



Multivisceral surgical techniques at relapse operation



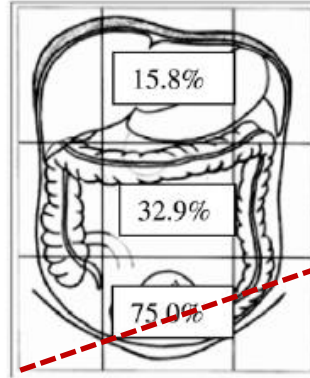
Shifting of tumor burden primary to relapsed disease



No correlation of tumour dissemination patterns in paired primary & relapsed cases

Maximal tumor load

Primary

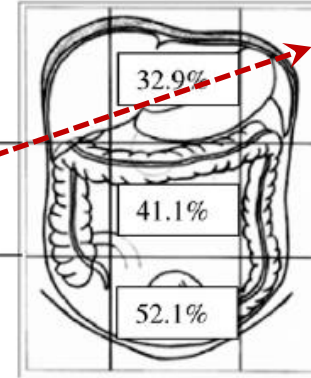


$p=0.045$

$p=0.34$

$p=0.002$

Relapse



peritoneal carcinosis
(RR 1.53;
95%CI: 0.89–2.63)



bowel involvement
(RR 0.92;
95% CI: 0.65–1.31)

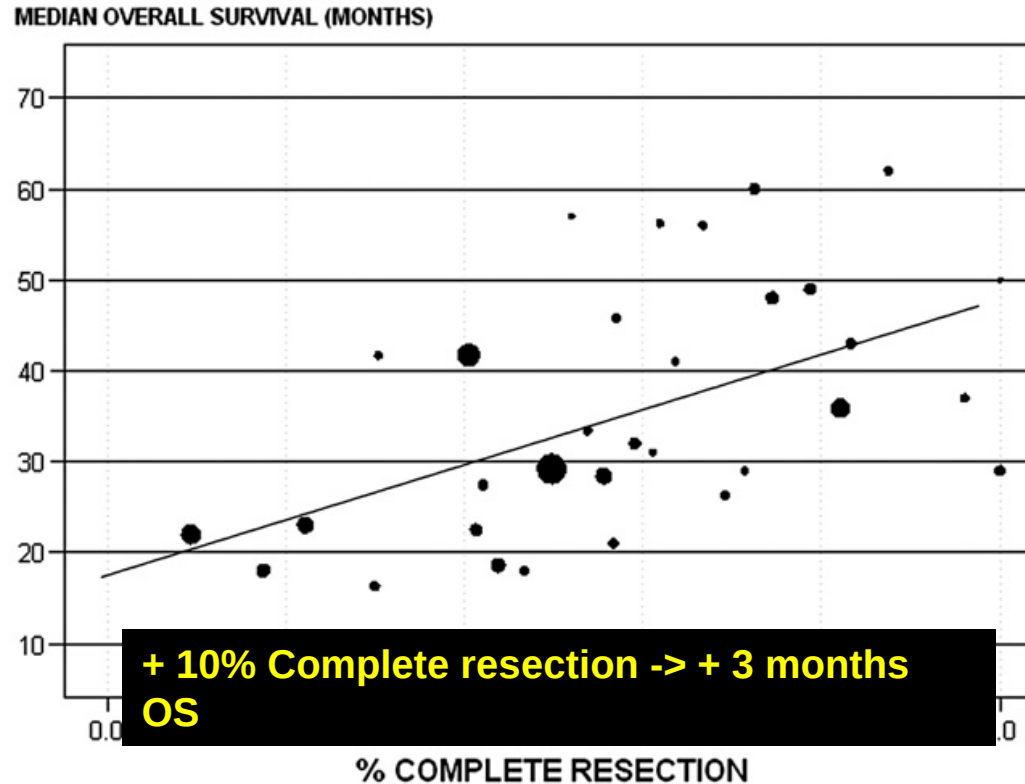


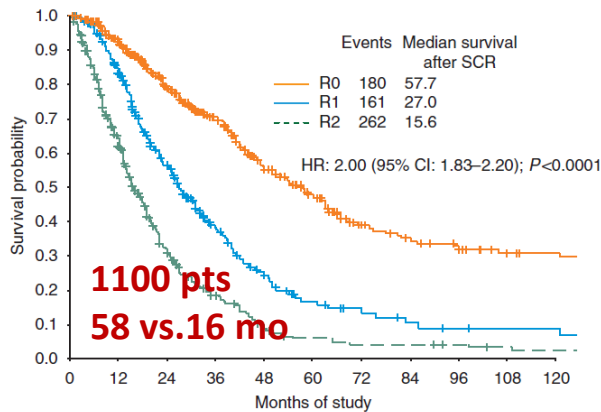
lymph node involvement (RR
1.49; 95% CI: 0.83–
2.68)

Indications for surgical cytoreduction at relapse

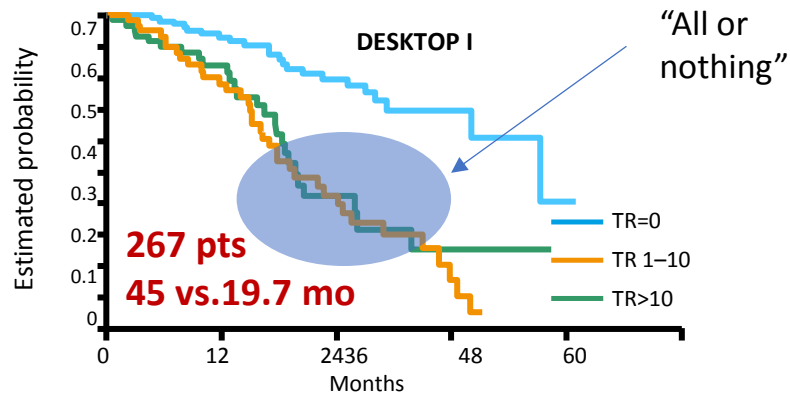
- Early – platinum resistant/refractory- relapse
 - → **NO evidence for survival benefit in cytoreduction (except in very rare cases)**
 - → median OS $\simeq$ 8-9 months
 - → low complete resection rates $\simeq$ 30%
 - → high surgical morbidity
- Late – platinum sensitive-relapse
 - Significant prolongation of OS and PFS in retrospective trials *in tumofree pts*
 - High complete tumor resection rates in selected patient population
 - Low/ acceptable surgical morbidity and mortality

Cytoreductive surgery for recurrent OC: a meta-analysis



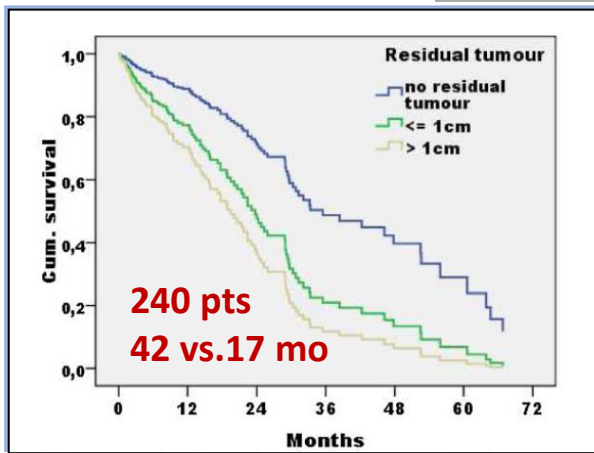


Zang R, et al. Br J Cancer 2011

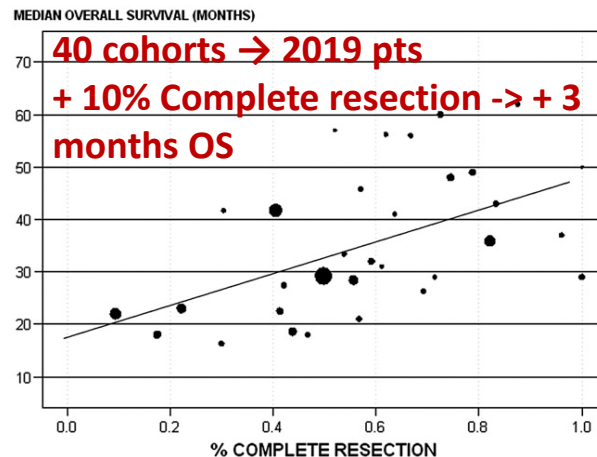


Harter P, et al. Ann Surg Oncol 2006;13:1702–10.

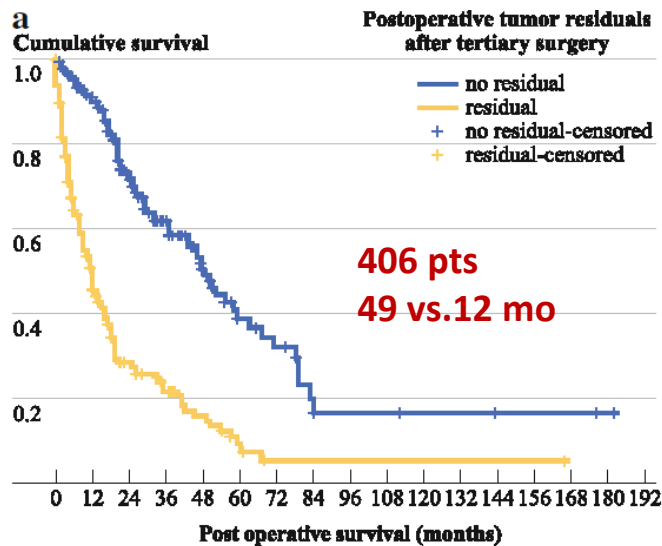
First relapse



Sehoul, Fotopoulou, et al. J Surg Oncol 2010

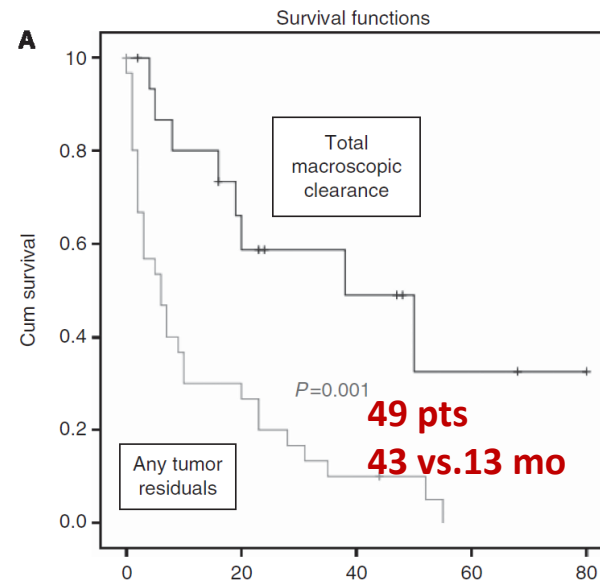


Bristow RE, Puri I, Chi DS. Gynecol Oncol 2009



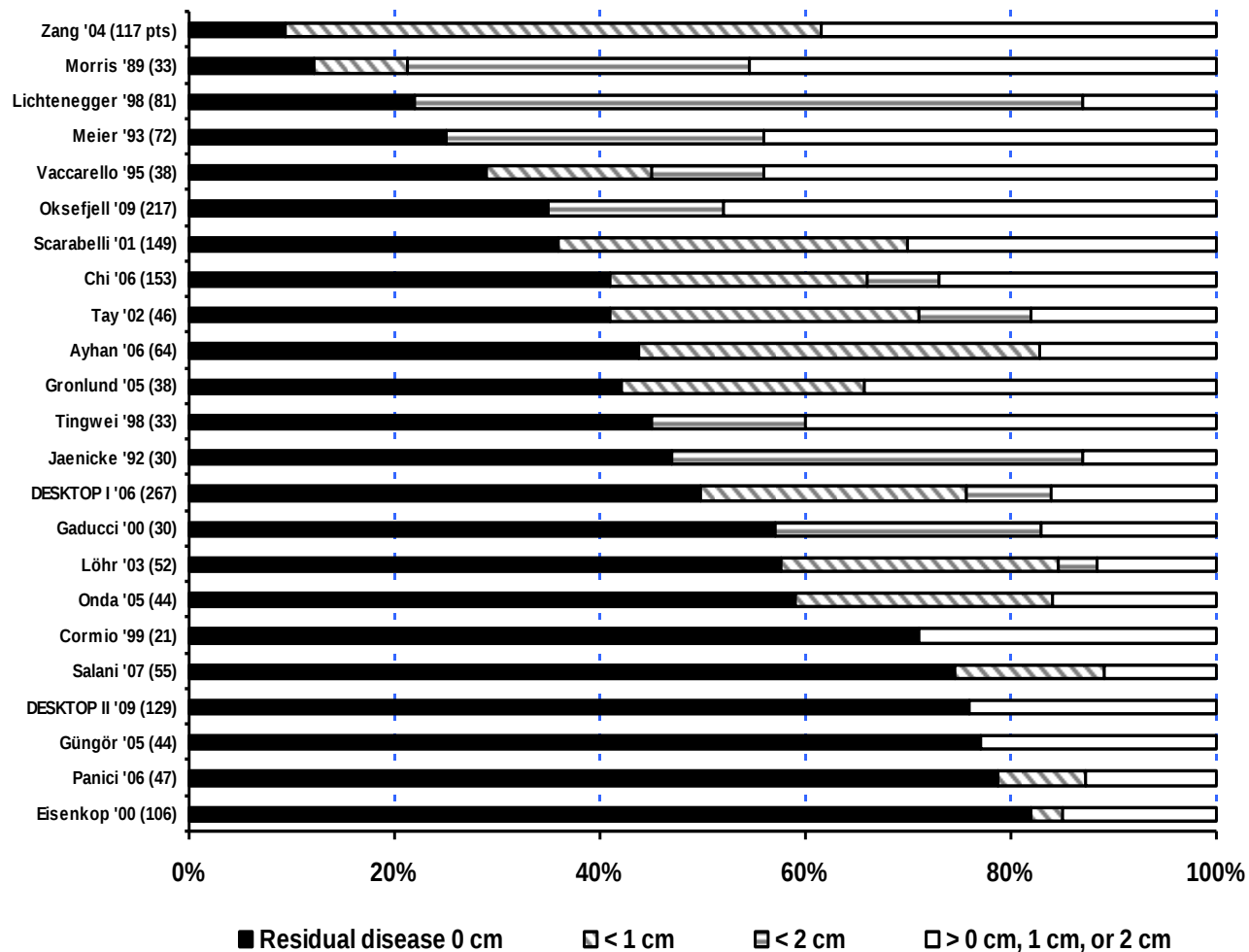
Fotopoulou et.al. Ann Surg Oncol 2012

Second relapse



Fotopoulou et.al. Br J Cancer 2012

Third relapse



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)

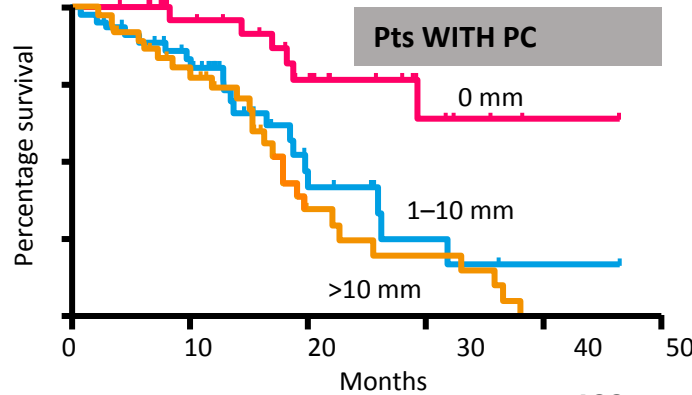
Multivariate analysis

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.

Is peritoneal carcinosis/ multifocal relapse a contraindication for secondary cytoreductive surgery? DESKTOP DATA

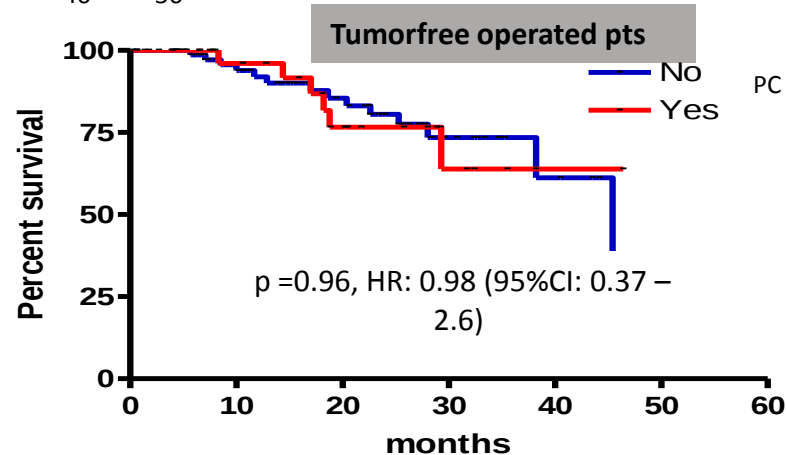


Median OS (months):

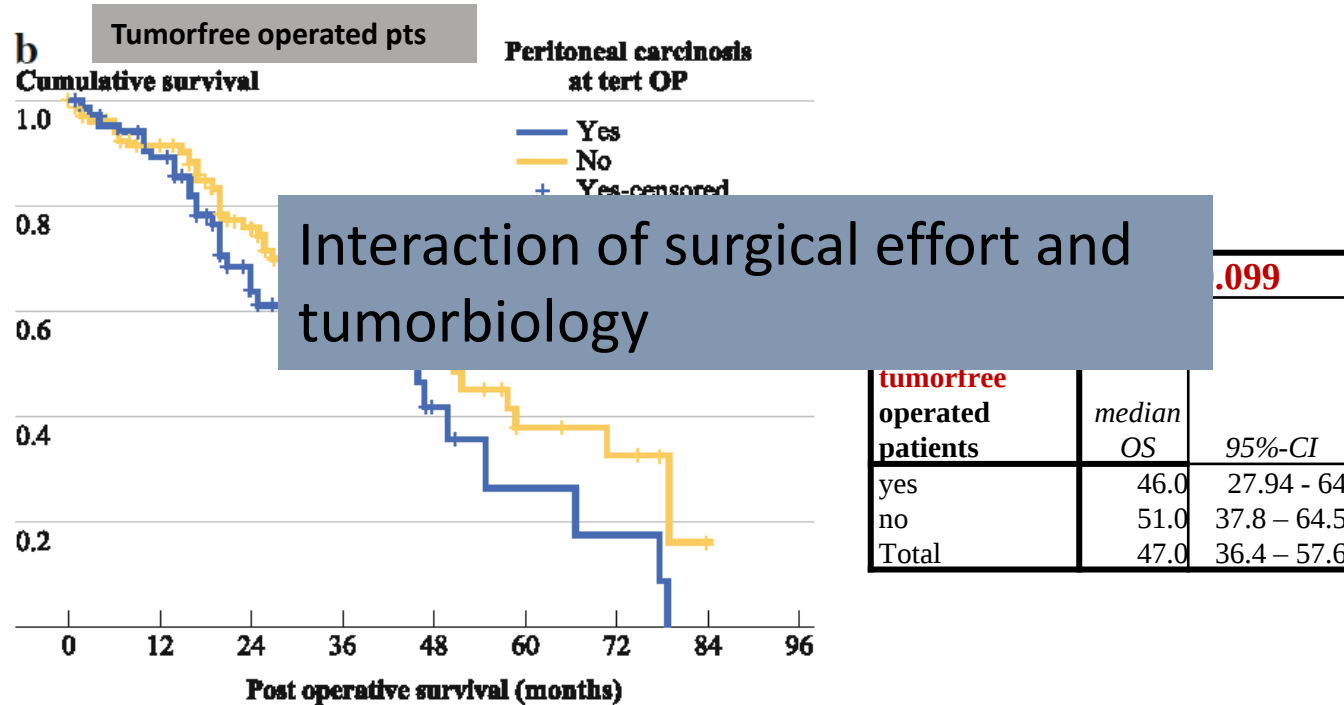
0 mm: nyr

1-10 mm: 17.9

>10 mm: 19.8

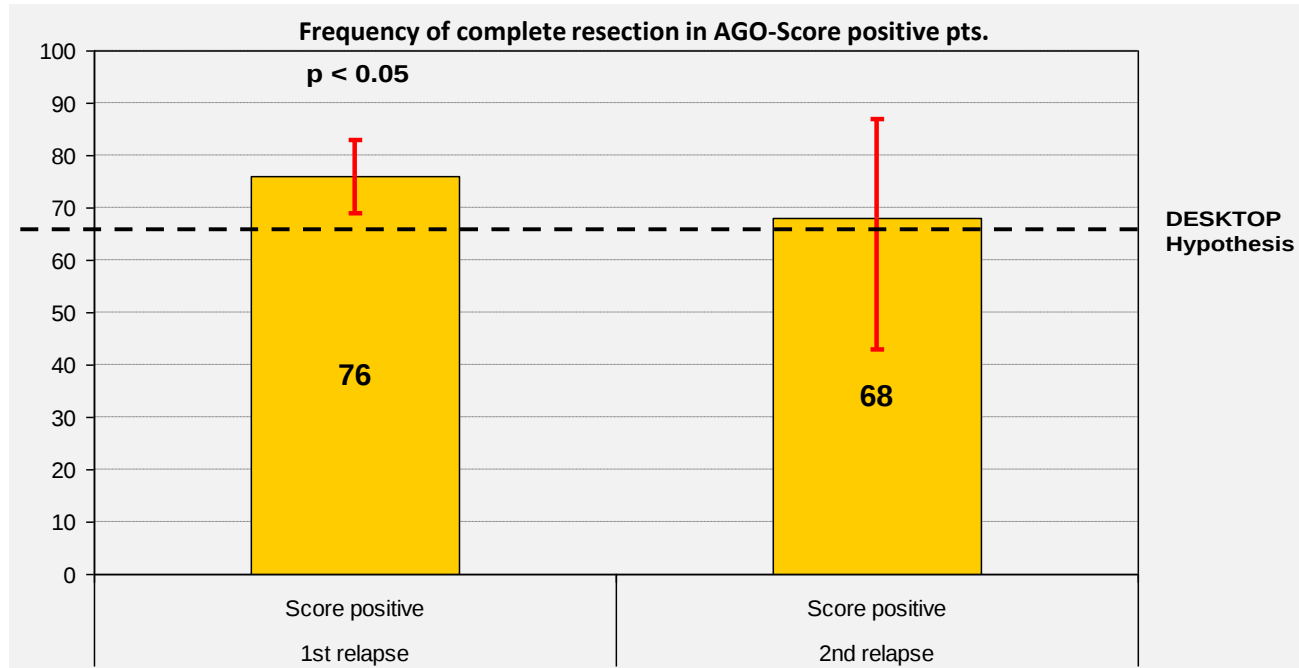


Is peritoneal carcinosis/ multifocal relapse a contraindication for secondary cytoreductive surgery? TCS DATA



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

Timing of Surgery: when to operate?

- CA125 driven follow up?
- Asymptomatic vs symptomatic relapse?
- Operate too early (reduction of QoL) vs too late (low PS)
- Is the retrospective evidence a result of tumorbiology or of surgical effort?

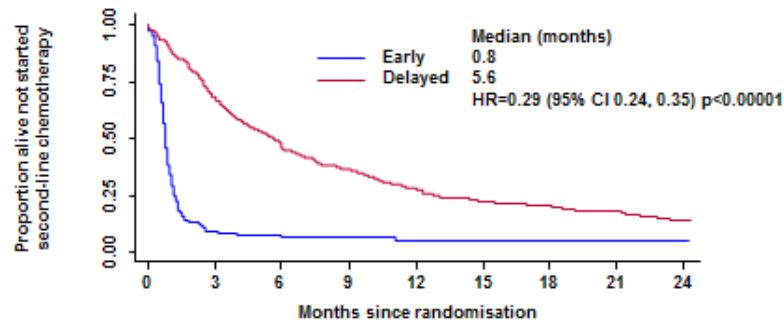


A matter of calender??
Taking into consideration all
parameters: radicality and
quality of previous surgery,
residual length of bowel, etc

Candidates for surgery

- Rarely relapse diagnosed by symptoms

Time from randomisation to second-line chemotherapy



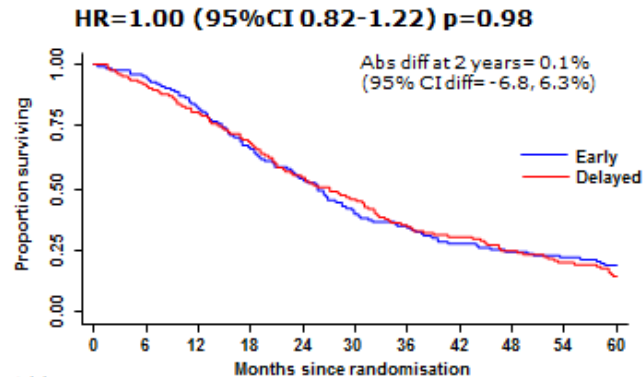
Number at risk

Early	265	23	16	14	11	11	10	10	9
Delayed	264	177	116	91	69	56	49	42	33

MRC | Medical Research Council Rustin G, et al. Lancet 2010



Overall Survival



Number at risk

Early	265	247	211	165	131	94	72	51	38	31	22
Delayed	264	236	203	167	129	103	69	53	38	31	19

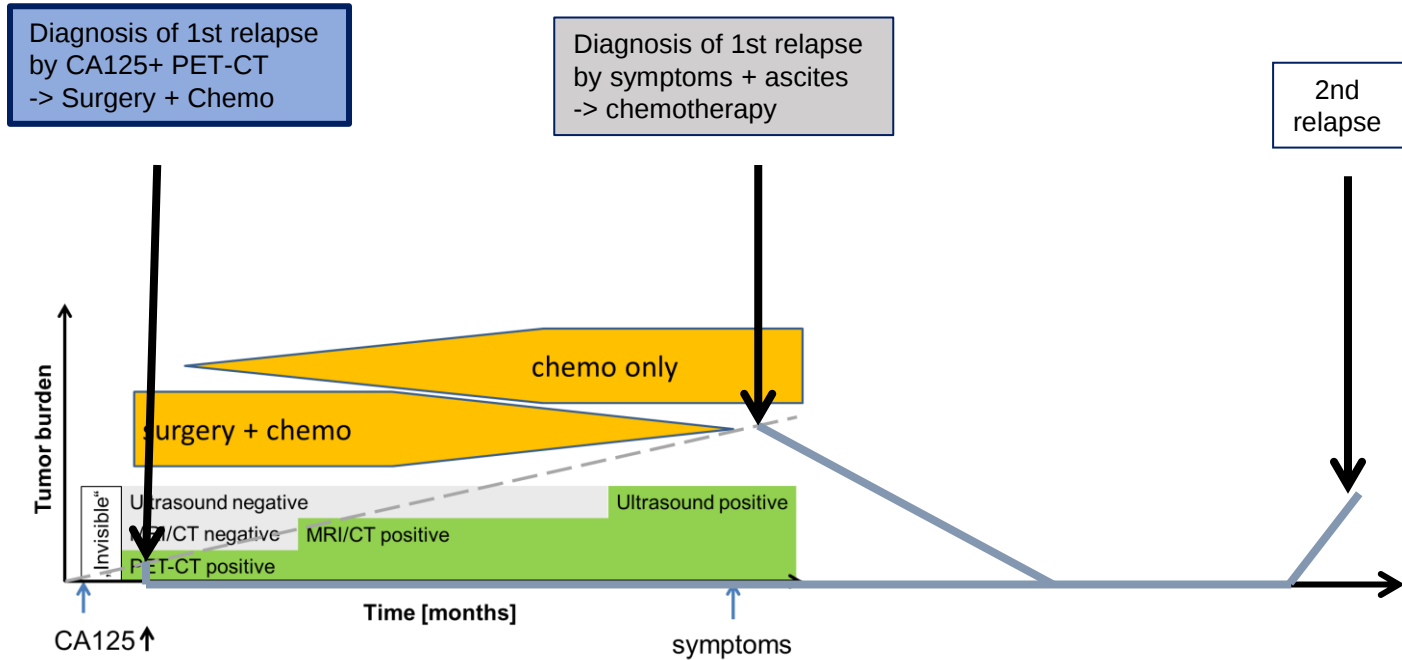
MRC | Medical Research Council



CA-125 elevation 5 months before clinical relapse!

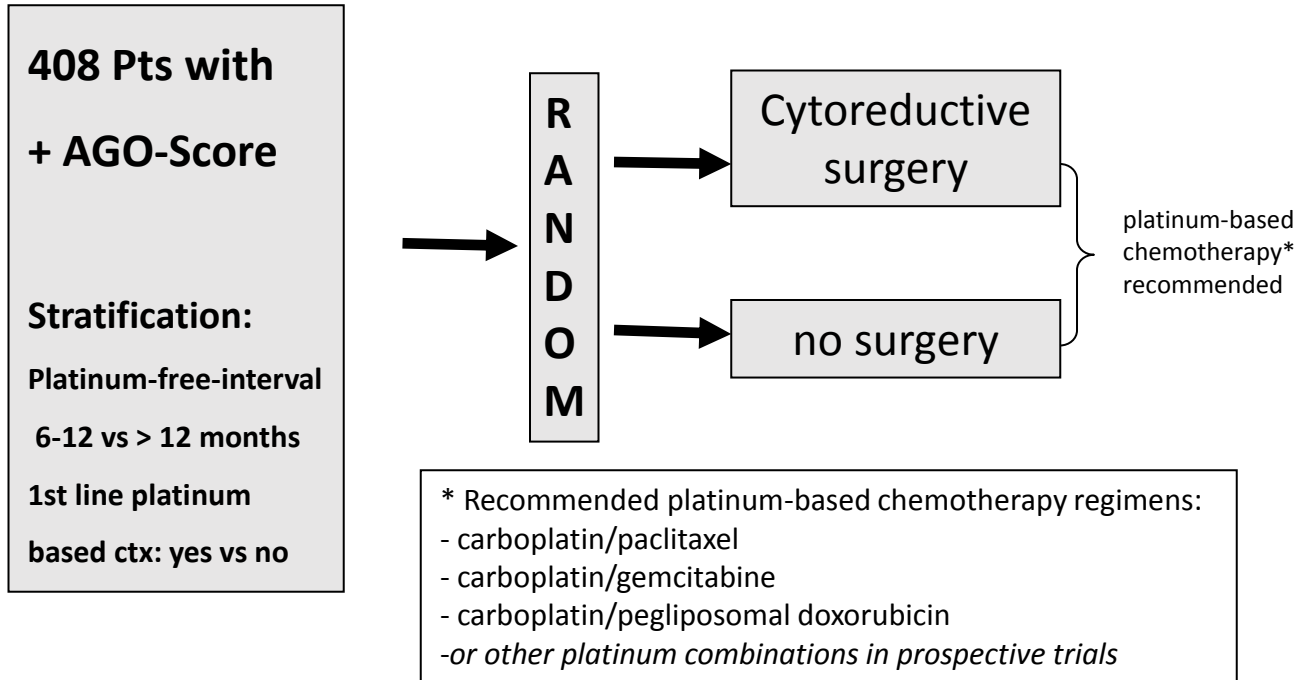
* only ~ 6% with surgery for recurrent disease

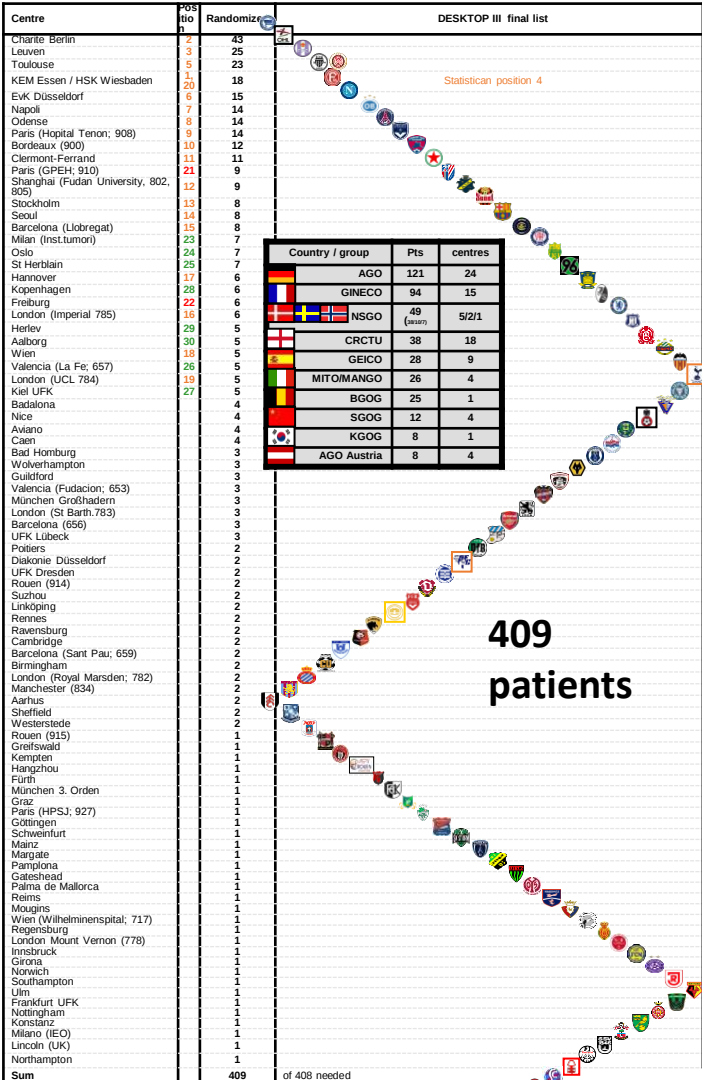
Real benefit by earlier diagnosis and surgery?



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

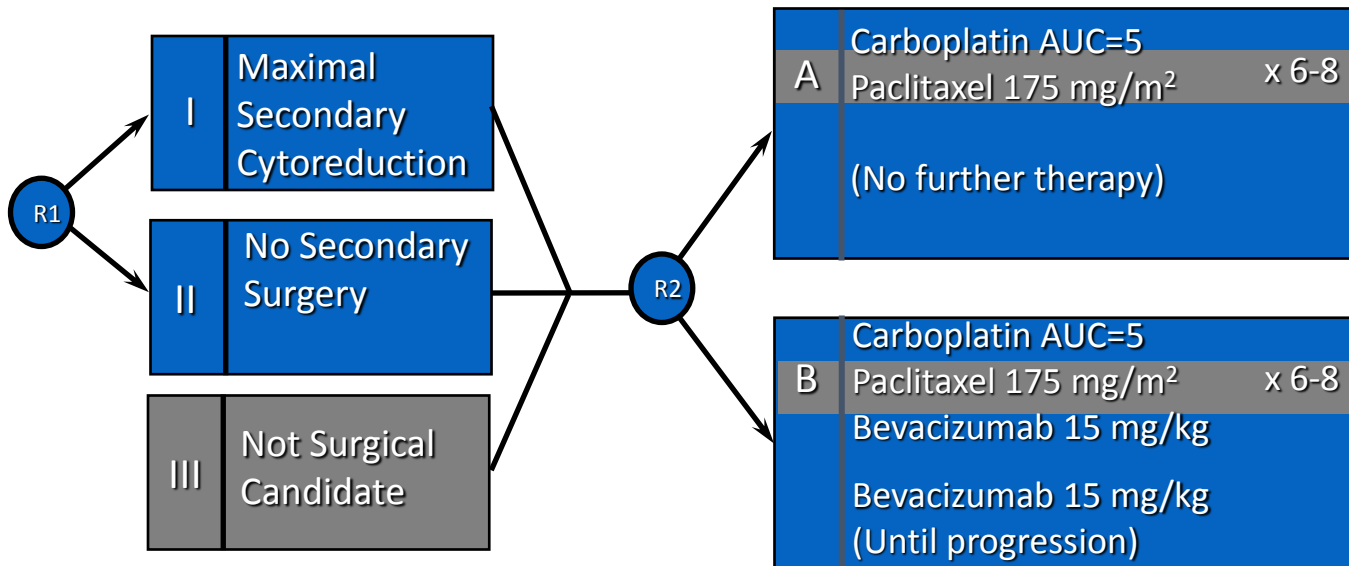
A randomized trial evaluating cytoreductive surgery
in patients with platinum-sensitive recurrent ovarian cancer





GOG 0213: Secondary Cytoreduction

- Epithelial Ovarian, Fallopian, or Peritoneal Cancer
- One prior therapy, Platinum-free interval > 6 months
- Primary Endpoint: OS



•AGO-DESKTOP II – PERIOPERATIVE MORBIDITY

Patients in intensive care unit	67 (52%)
Days intensive care unit [median]	2 (range: 1-20)
No of pts adm. packed blood cells	55 (44%)
No of pts with at least one complication	42 (33%)
Infections requiring antibiotic treatment	31 (24%)
urinary tract	14 (11%)
peritonitis	10 (8%)
pneumonia	4 (3%)
others	7 (5%)
Re-laparotomy	14 (11%)
bowel leakage/perforation	6 (5%)
abscess/infection	3 (2%)
bleeding	3 (2%)
fistula	2 (2%)
Thrombosis / Embolism	3 (2%) / 4 (3%)
Other severe complications	12 (9%)
Mortality within 60 days	1 (0.8%)

Surgical morbidity

Primary Surgery	Year	Patients [n]	Mortality [%]
Aletti	2006	194	1.5
Chi	2010	141	1.4
Harter	2011	187	2.3
Sehouli	2011	332	3.1
Gerestein	2009	pop. based	3.7
Surgery for relapse			
DESKTOP II	2011	129	0.8
Chi	2006	153	0
Tian	2010	123	0
Sehouli	2010	240	3.8
Oksefjell	2010	217	Not reported

Palliative surgery



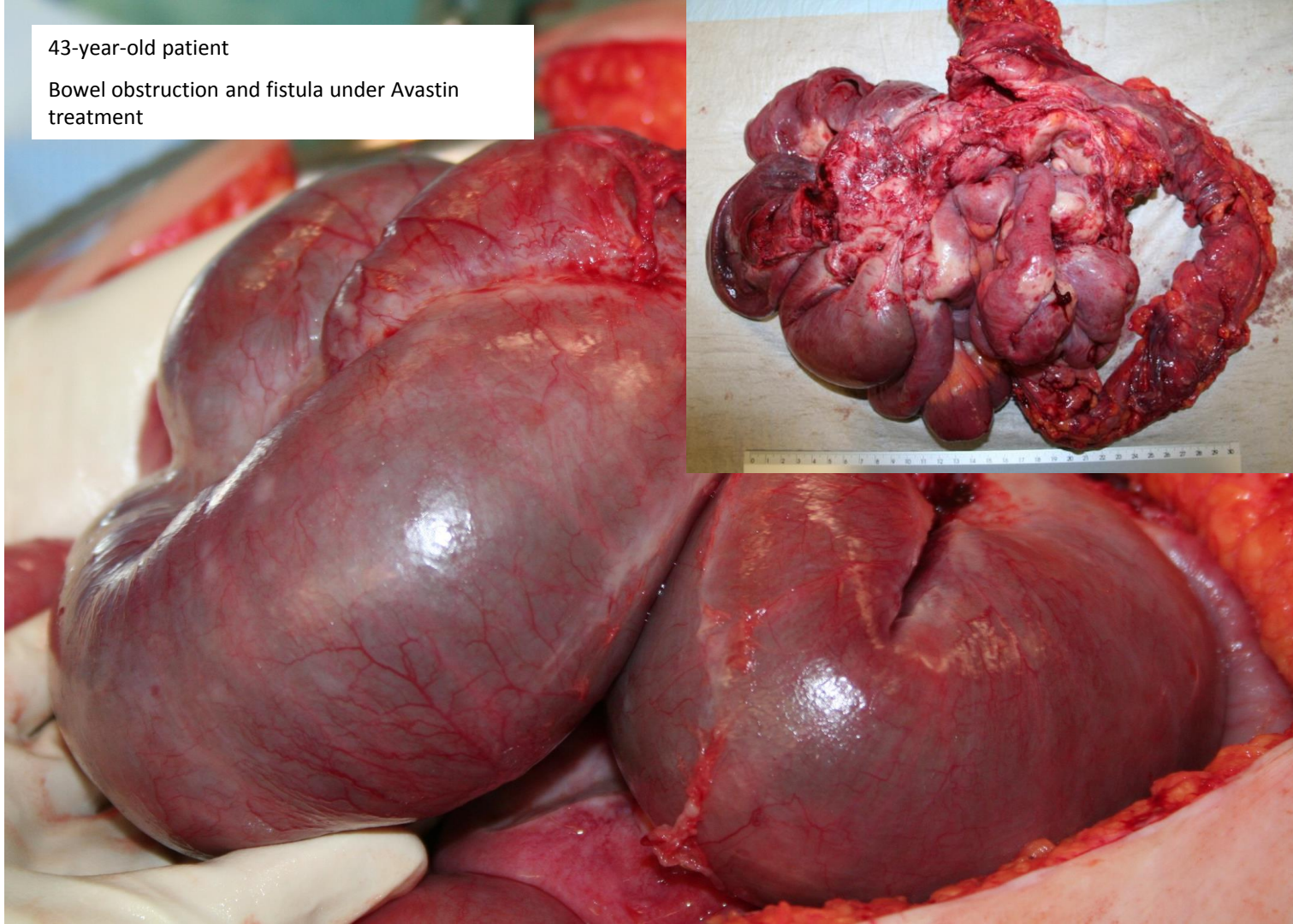
...New Agents On The Horizon

- Chemotherapy: Epothilone, Pemetrexed (Alimta), TLK 286, ...
- Antibodies: Anti-Epcam, ACA125, ...
- EGFR: Gefitinib, Erlotinib, Cetuximab,..
- Antiangiogenesis and VEGF: Bevacizumab, DXMAA, VEGF trap, PlGFab, ..
- c-erb-family (Trastuzumab, pertuzumab, TAK-165, CP724,714, 2C4, IMC-225, EMD72000), Lapatinib (GW572016),
- FTI (Lonafarnib, SCH6636, R115777, BMS214662),
- Raf-1 (Bay 43-90006), MEK (CI-1040), Erbitux, ...
- M-tor inhibitors
- Multiple targets: Enzastaurin, ...

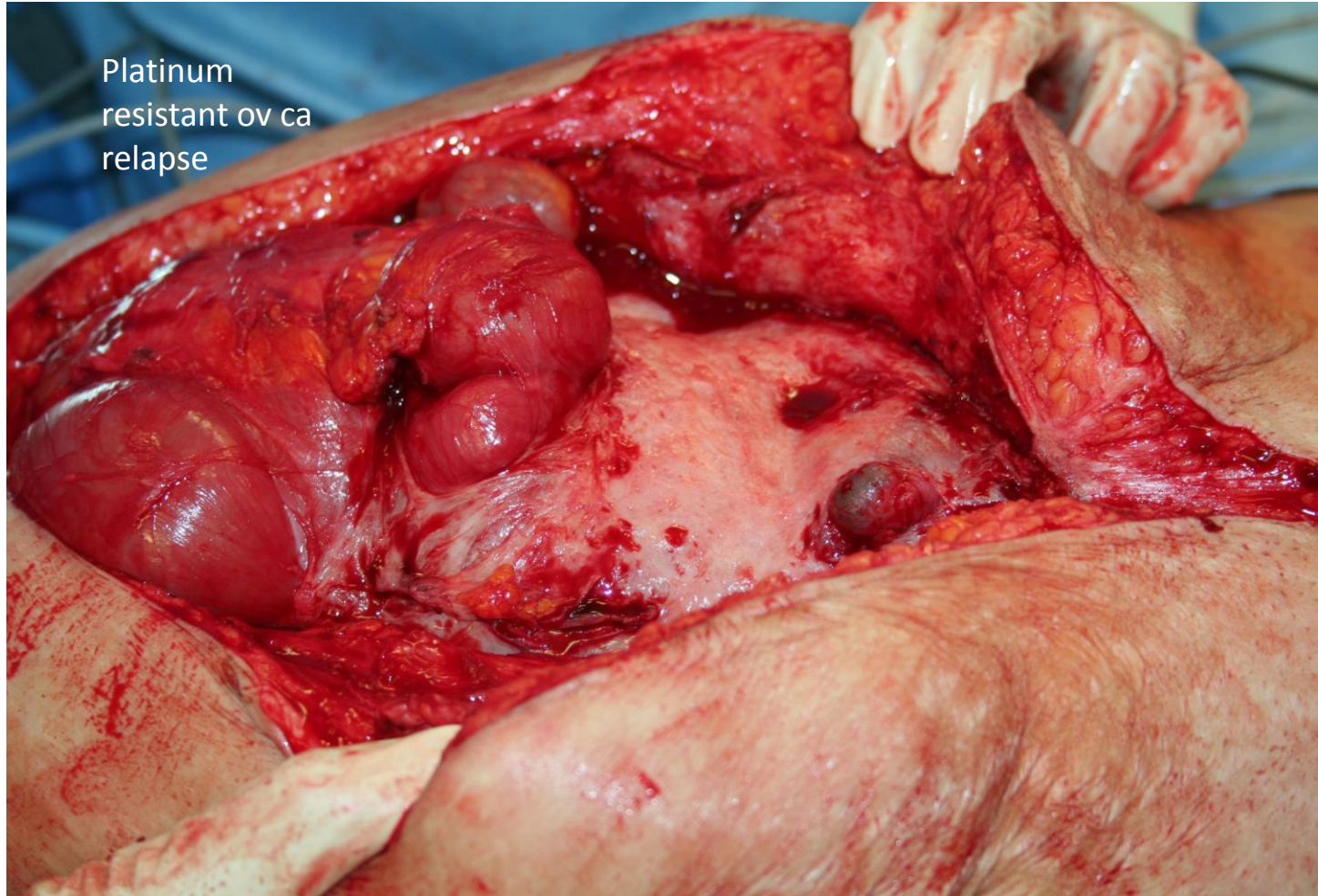
AND MANY MANY OTHERS

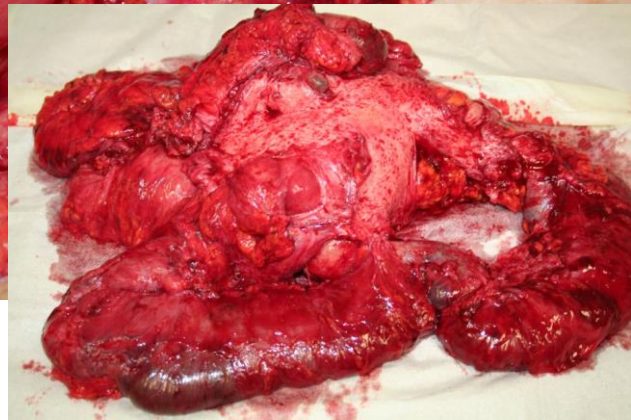
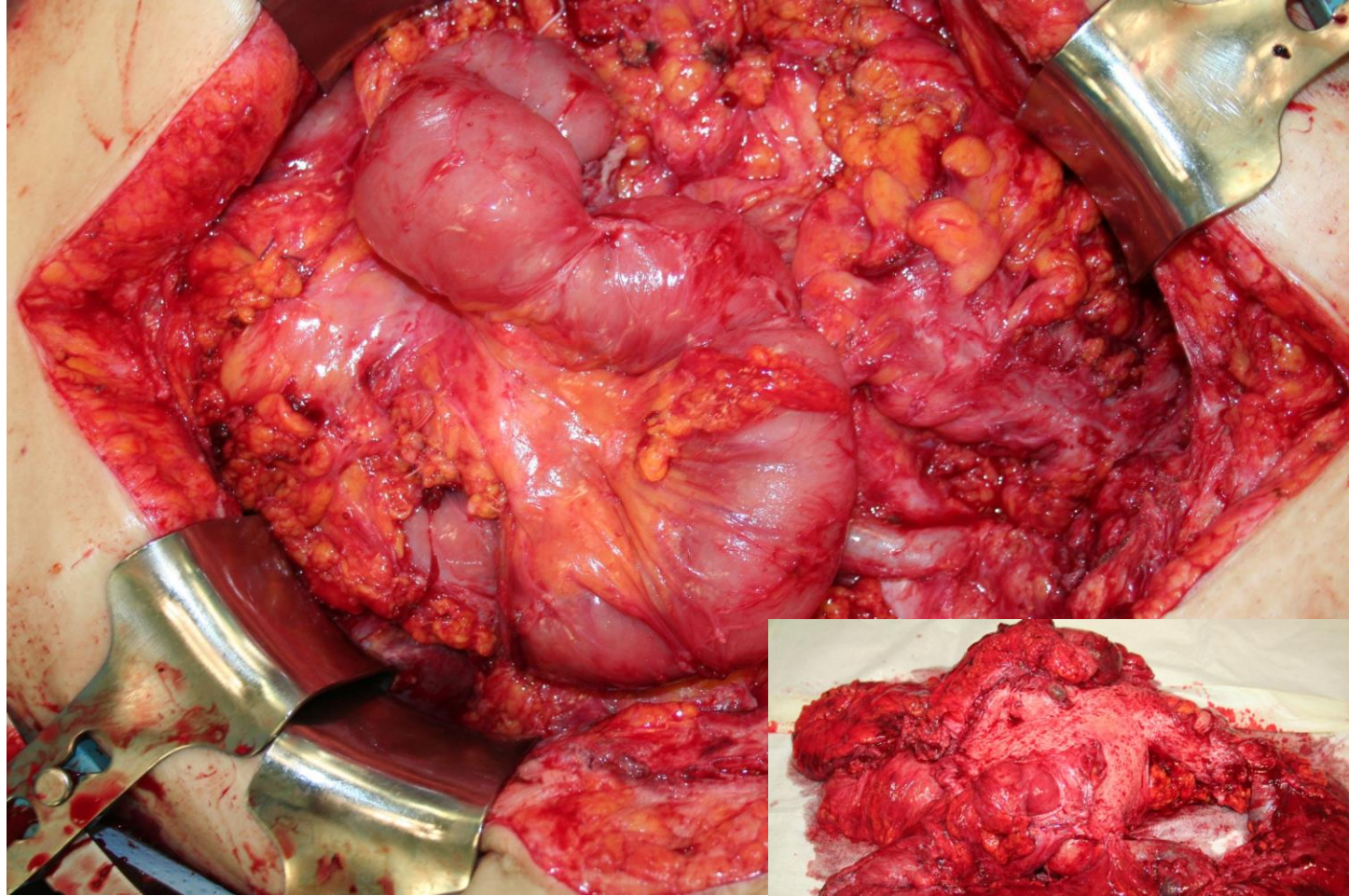
43-year-old patient

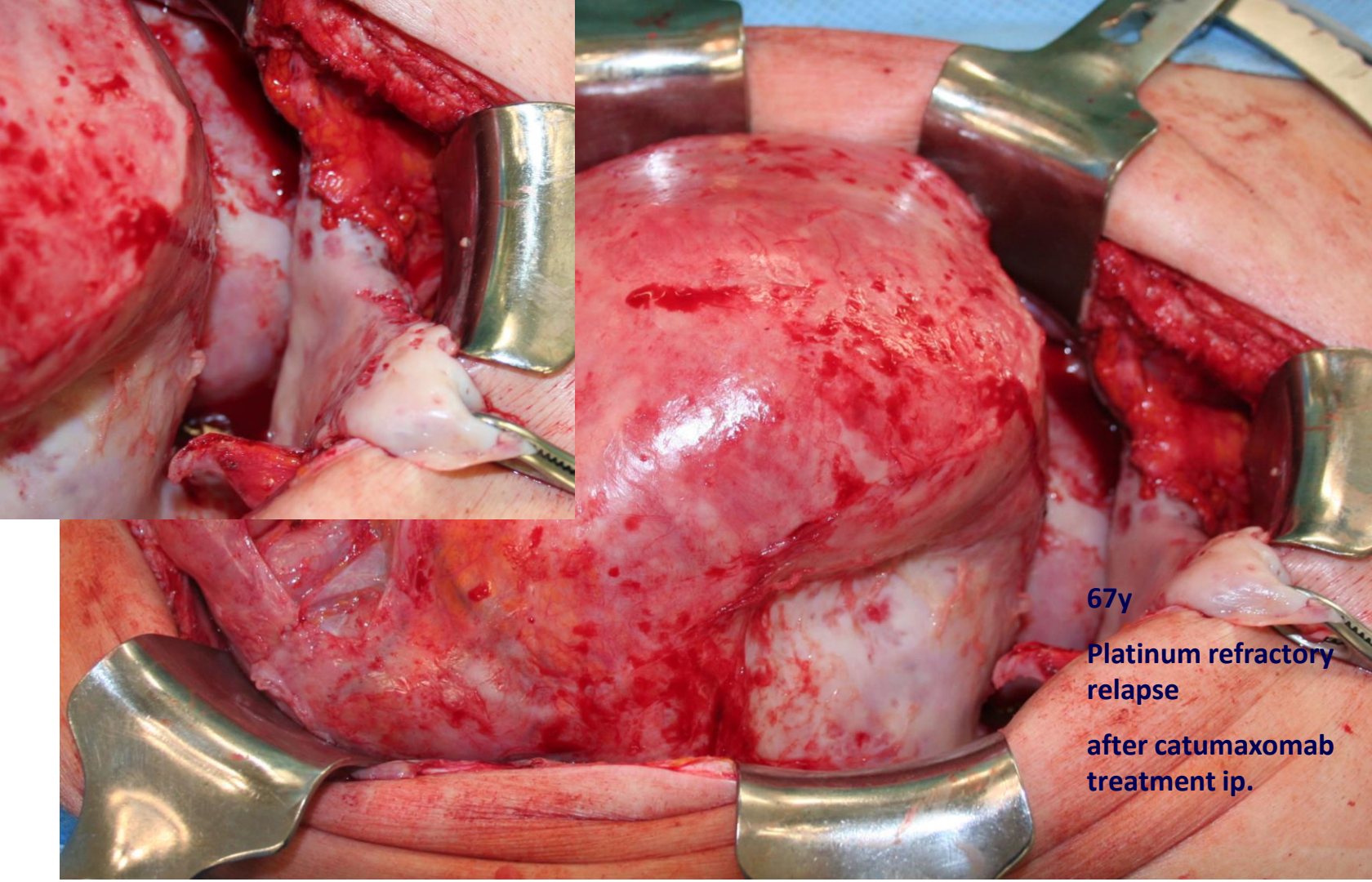
Bowel obstruction and fistula under Avastin
treatment



Platinum
resistant ov ca
relapse



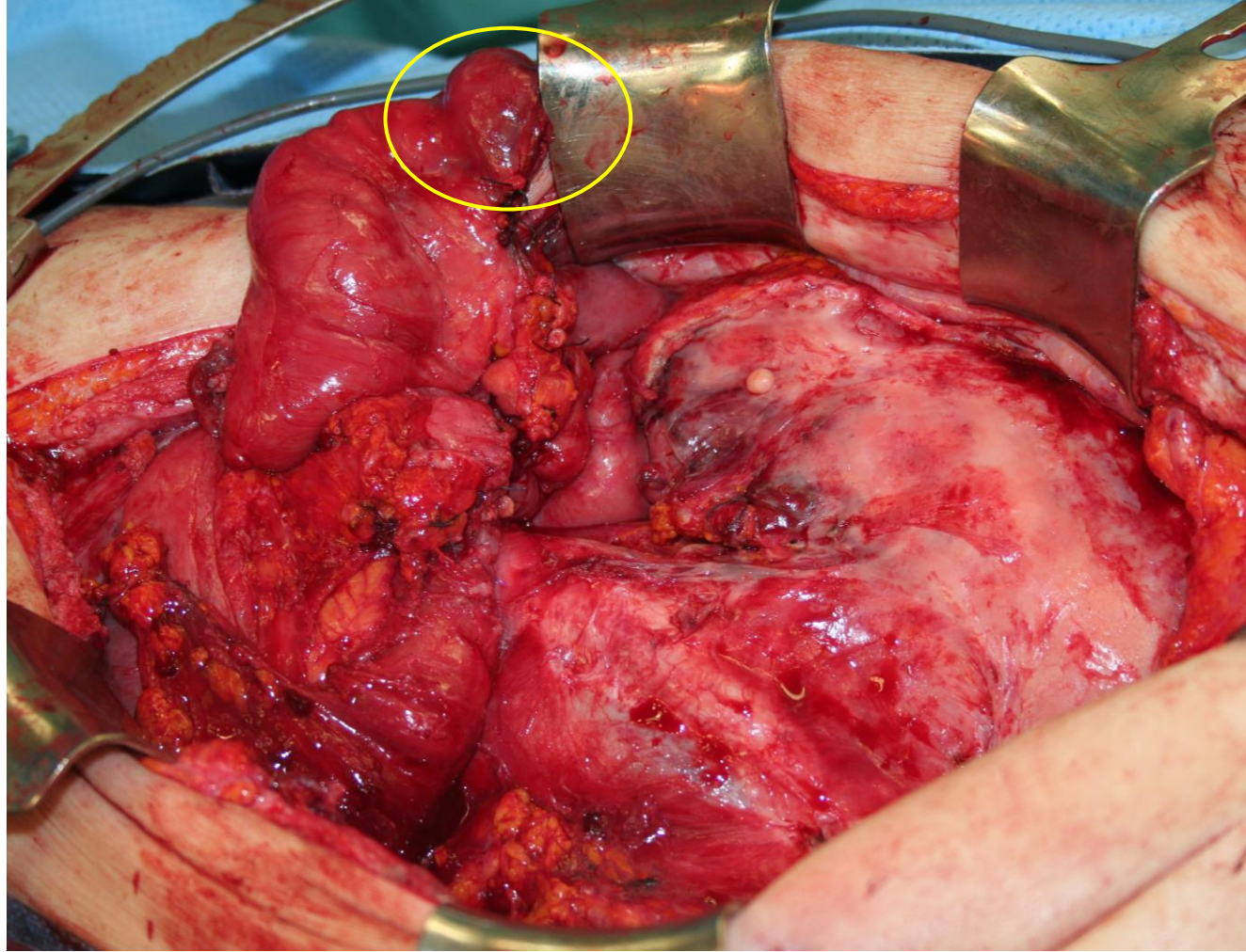




67y

**Platinum refractory
relapse**

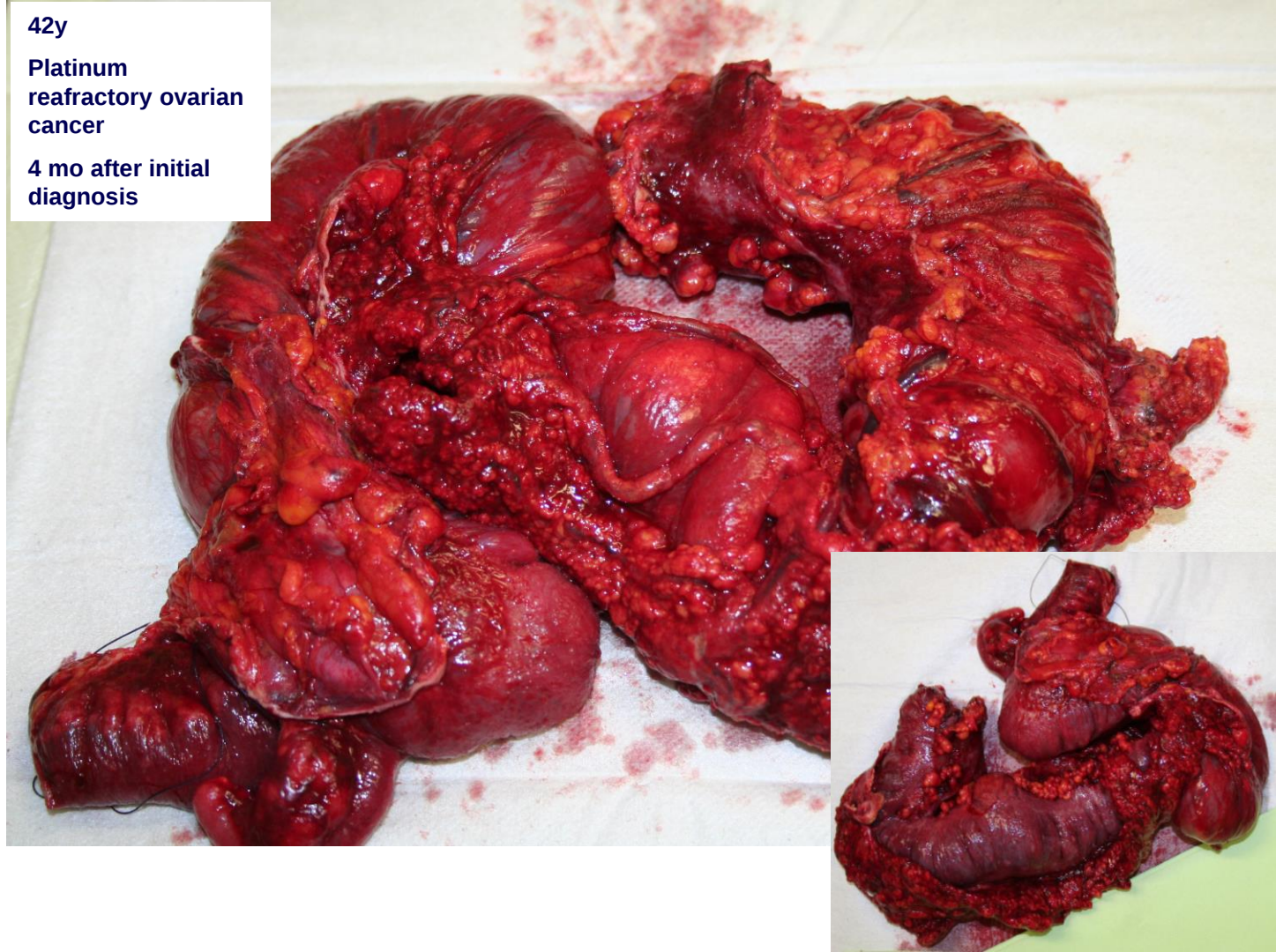
**after catumaxomab
treatment ip.**



42y

Platinum
refractory ovarian
cancer

4 mo after initial
diagnosis





62y

Taxol weekly
induced bowel
perforation with
peritonitis and ileus

Salvage Surgery Due To Bowel Obstruction in Advanced or Relapsed Ovarian Cancer Resulting in Short Bowel Syndrome and Long-Life Total Parenteral Nutrition

Surgical and Clinical Outcome

IJGC, 2013

Christina Fotopoulou, PhD, MD,† Elena Ioana Braicu, MD,* Sara-Lea Kwee,* Marc Kuhberg, MD,* Rolf Richter,* Klaus Pietzner, MD,* Aarne Feldheiser, MD,‡ Marcus Bahra, MD,§ Sven Christian Schmidt,§ and Jalid Sehoul, PhD, MD**

TABLE 2. Data of Perioperative Management, Operative Mortality and Morbidity (n = 44)

	Median (Range)
Operation time, min	270 (148–596)
Transfusion of erythrocyte concentrates, U	2 (0–12)
Length of stay in intensive care unit, d	2.5 (0–31)
Length of hospital stay, d	24 (10–76)
Intestinal length	70 cm (10–180)
<1 m	21 (56.8%)
>1 m	16 (43.2%)

Any mayor complications 19 (51)

Sepsis	1
Pulmonary embolism	2
Peritonitis	4
Pleura effusion	3
Relaparotomy	12
Anastomotic insufficiency	5
Abscess, secondary wound healing	1
Postoperative bleeding	2
Intestinal perforation	1
Rupture of abdominal wall closure	1
Peritonitis	1

30 day operative mortality: 10%

QoL & Survival

TABLE 4. Assessment of the Quality of Life of the 4 Alive Patients With EOC Who Underwent Salvage Surgery Resulting in SBS According to the SF-12 Health Survey Validated Questionnaire

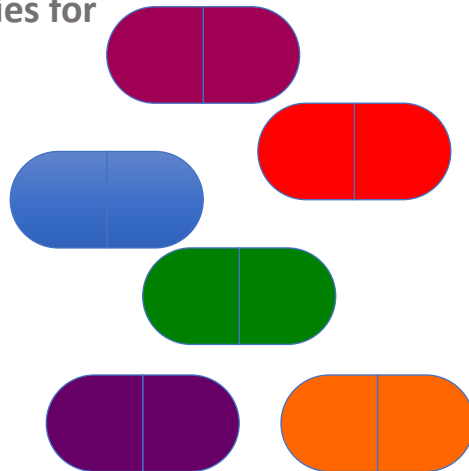
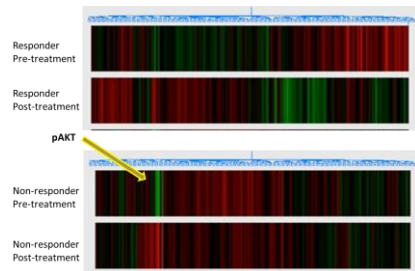
	Patients With EOC	Healthy Population	<i>P</i>
SF-12 physical score, mean (SD)	36.68 (2.2)	50 (10)	0.009
SF-12 psychological score, mean (SD)	21.36 (6.5)	50 (10)	0.017

The physical and mental scores of the patients were significantly lower than the scores of the general healthy population.

- ✓ Median OS: 5.6 months (range, 0.1-49 months)
- ✓ 1-year and 2-year OS: 18.3% and 8.1%
- ✓ Within a median FU- period of 5 mo (range, 0.2-49 months), 4 patients (10.8%) are still alive.
- ✓ No significant differences in survival were seen between patients with or without major complications, tumor residuals, or residual intestinal length of less than 1 m versus greater than 1 m.

Epithelial Ovarian Cancer Surgery in the Era of Personalised Medicine

Novel targeted approaches allowing to extend the window of opportunities for platinum resistance relapse?



Caris Target Now
Sequenom
Exome Seq
Expression Microarray

Surgery at relapse

- No value of cytoreuction in „platinum resistant“ patients apart from palliation
- OS and PFS prolongation in tumorfree operated patients (retrospective), data from prospective trials awaited
- Therapeutic decisions individualized and tailored to patients prior treatments, tumor dissemination pattern and patients overall status
- At emergency situations after failure of conservative measures: en-block resection techniques; avoidance of numerous anastomoses; ileostomy/colostomy preferred.