Role of Surgery in Ovarian Cancer Treatment

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Disclosures

- Funds: EU, FWF
- Speaker Honoraria: Roche, Novartis, Amgen, MSD
- Advisory boards: Roche, Novartis, Amgen, MSD, Celgene, Astra Zeneca

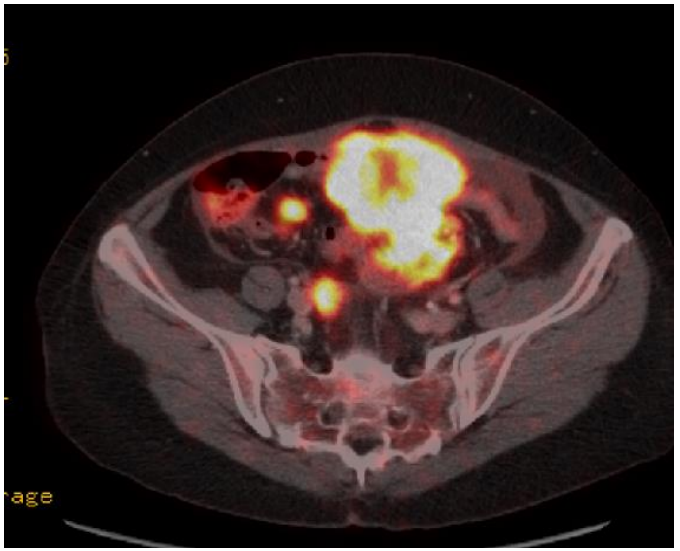
Case presentation

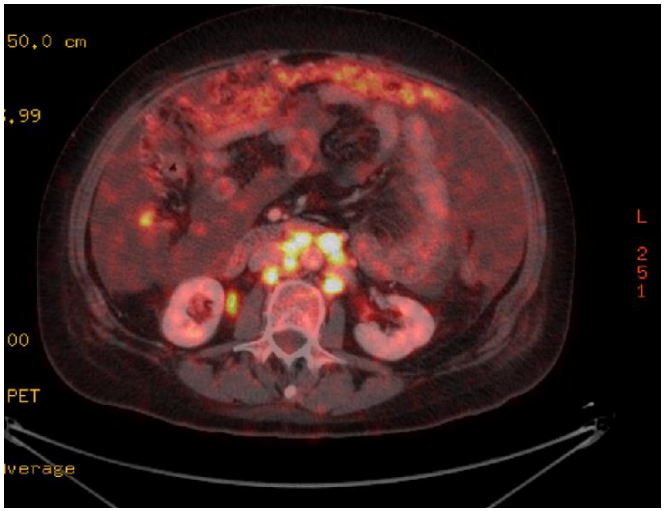
- 48 years old, abdominal pain for 3 months
- Increased abdominal size
- Urinary urgency
- Irregular menstrual bleeding
- Good performance status no comorbidities

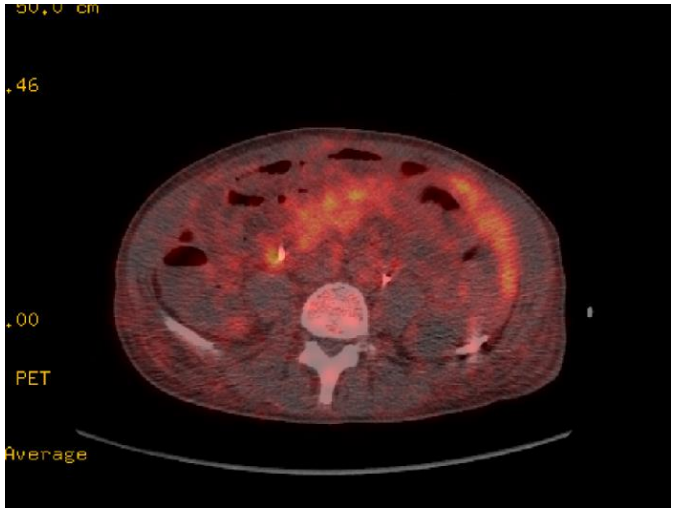
Case history

- Pelvic examination showed a pelvic mass
- CA-125: 1,650 U/mL, CEA: 2.2 ng/mL
- Pelvic ultrasound demonstrated 14cm complex solid and cystic areas with ascites
- CT scan confirmed ultrasound and in addition suspicious lesions in upper abdomen. Possibly peritoneal carcinomatosis and ascites

Ovarian cancer with positive lymph nodes and peritoneal carcinomatosis







How would you treat the patient?

1. Neo-adjuvant Chemotherapy
2. Perform a laparoscopy to assess diagnosis and to predict resectability of disease
3. Upfront debulking surgery

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

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

Randomisation

Primary Debulking Surgery

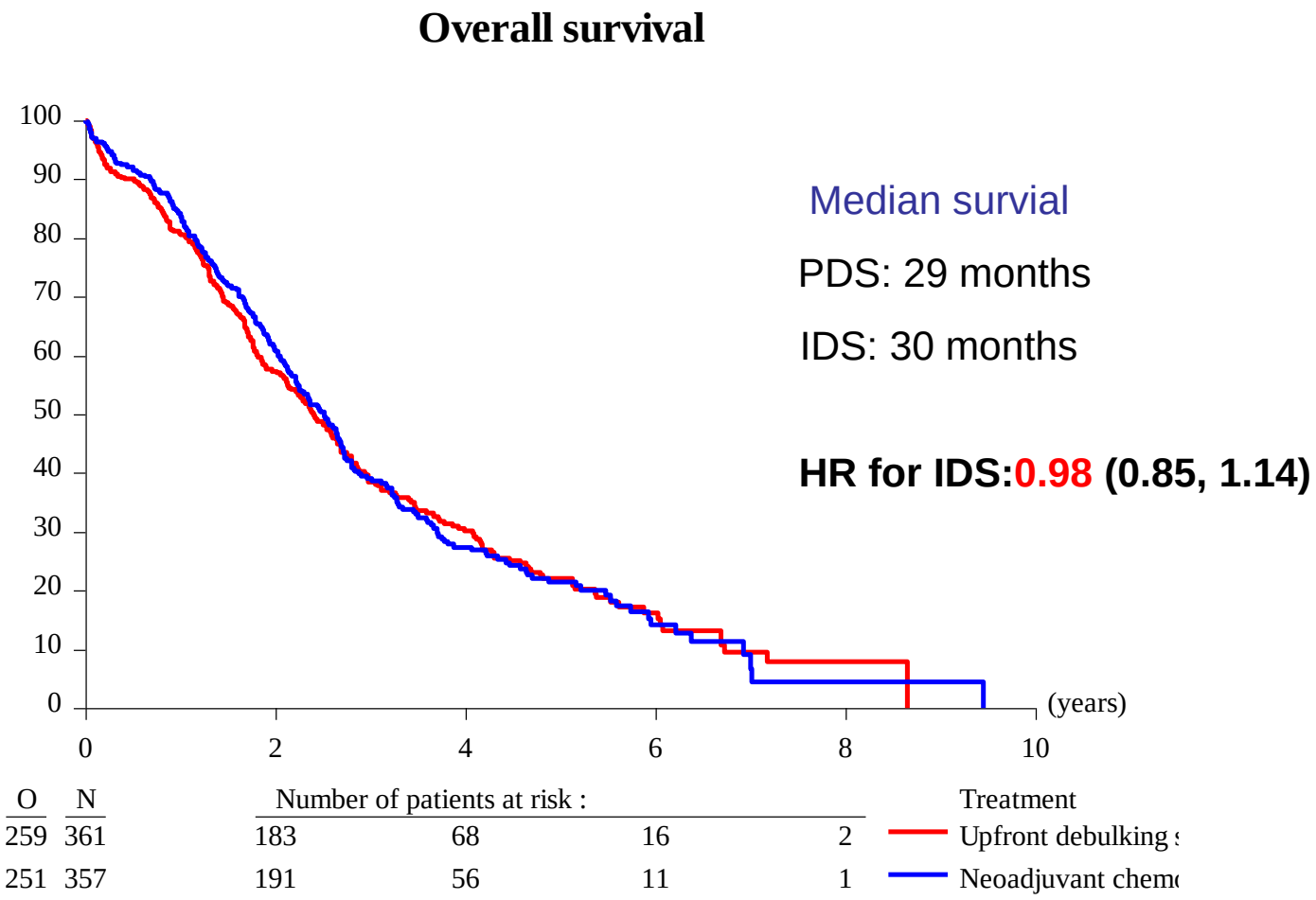
- Surgery
- 6 x Platinum based CT
  - (Interval debulking possible
  - But not obligatory
  - ≥ 6 x Platinum based CT possible)

Neoadjuvant chemotherapy

- 3 x Platinum based CT
- Surgery if no PD
- ≥ 3 x Platinum based CT

Primary Endpoint: OS Secondary endpoints: PFS, Quality of Life, Complications

NACT + IDS versus PDS: ITT



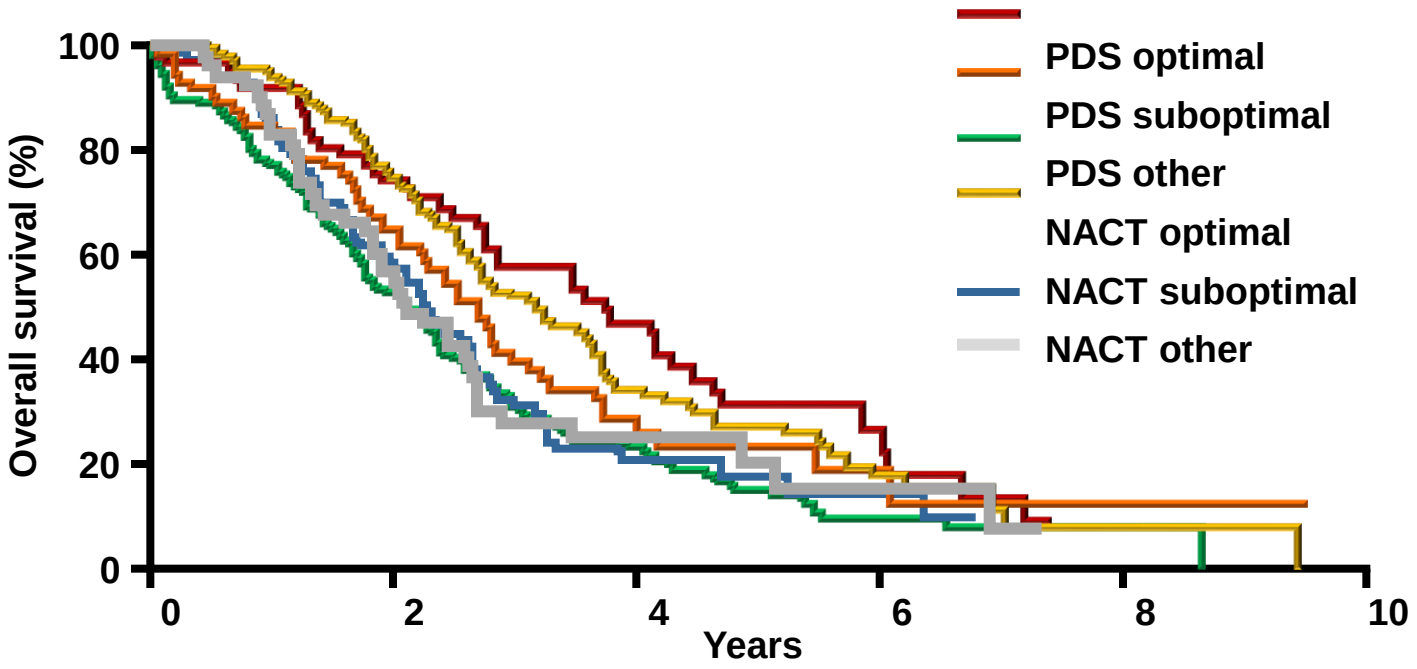
Median survial

PDS: 29 months

IDS: 30 months

HR for IDS:0.98 (0.85, 1.14)

EORTC study: what makes a difference ... and what does not?



Surgical outcome	Median OS (months)		Advantage for upfront surgery vs NACT → surgery	
	Upfront surgery	NACT → surgery	Median OS (months)	5-year survival (%)
Complete resection (no macro residuals)	45.0	*38.2*	+6.8	+3.3
Debulking to residuals 1–10mm	32.3	27.0	+5.3	+5.0
Residual tumour >1cm (no OP benefit at all)	25.7	25.5	+0.2	–1.1

EORTC study: what makes a difference ... and what does not?

Neoadjuvant Chemotherapy Cannot Be Regarded as Adequate Routine Therapy Strategy of Advanced Ovarian Cancer

Andreas du Bois, PhD, MD, Christian Marth, MD, PhD,† Jacobus Pfisterer, MD, PhD,* Philipp Harter, MD,* Felix Hilpert, MD, PhD,* Alain G. Zeimet, MD, PhD,† and Jalid Sehouli, MD, PhD**

Abstract: Minority vote to statement A5 of the Fourth Ovarian Cancer Consensus Conference, Vancouver 2010, on behalf of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Study Group Germany plus North-Eastern Society of Gyneco-Oncology and the AGO Austria.

(*Int J Gynecol Cancer* 2011;21: 1165–1168)

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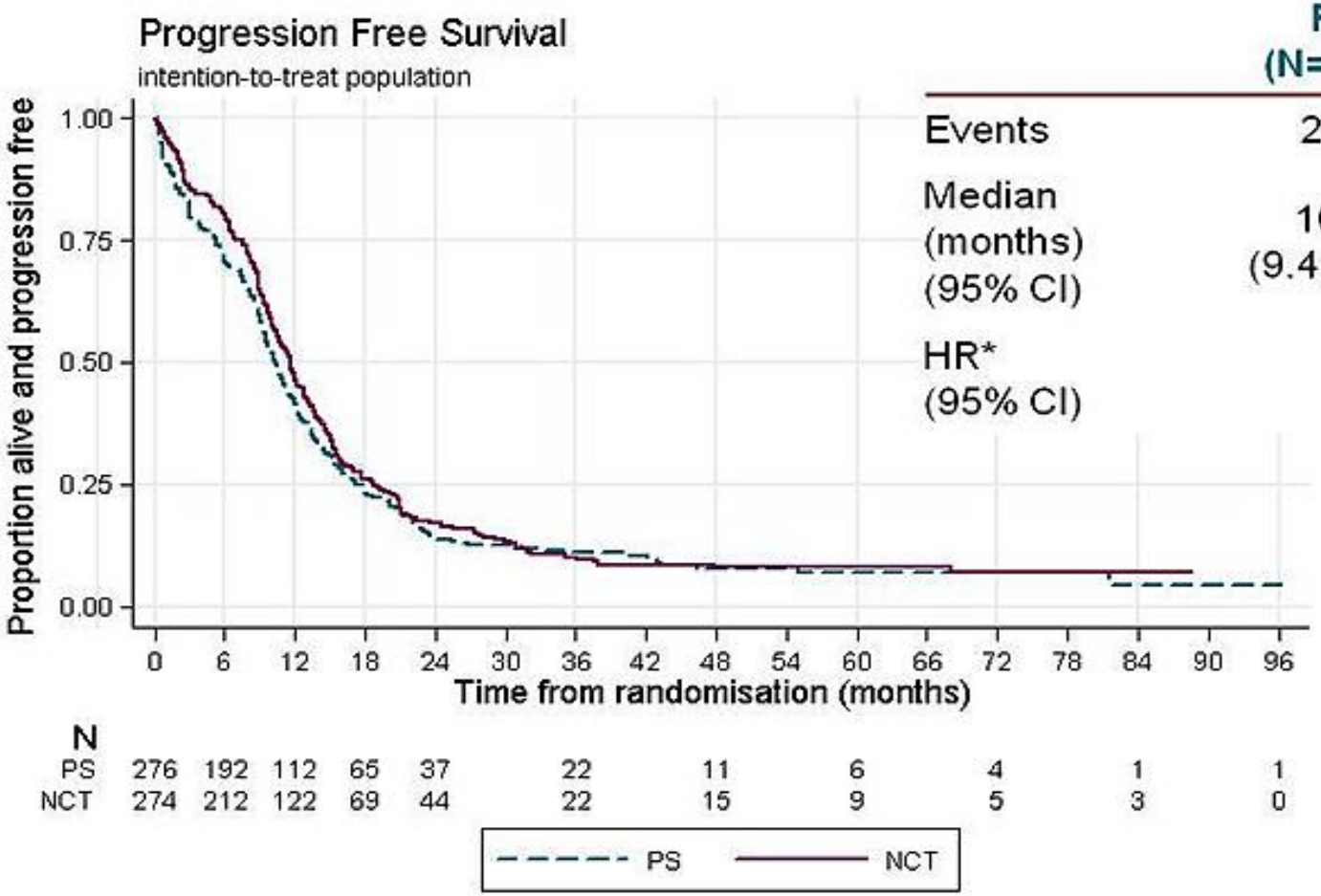
Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer

Results from the MRC CHORUS trial

S Kehoe, JM Hook, M Nankivell, GC Jayson, HC Kitchener, T Lopes, D Luesley, TJ Perren, S Bannoo, M Mascarenhas, S Dobbs, S Essapen, J Twigg, J Herod, WG McCluggage, M Parmar, AM Swart on behalf of the CHORUS trial collaborators and NCRI Gynaecological Cancer Studies Group

ASCO Annual '13 Meeting

Progression-Free Survival



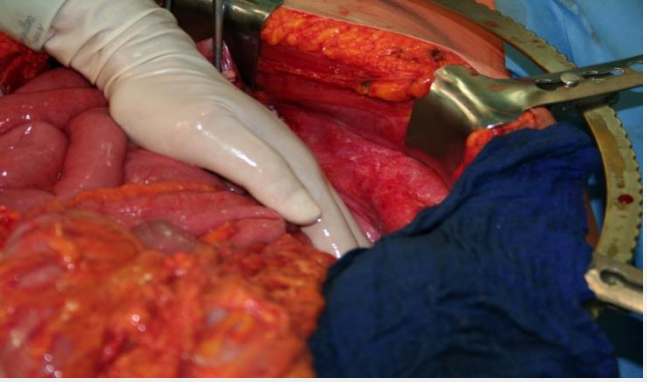
	PS (N=276)	NACT (N=274)
Events	246	241
Median (months) (95% CI)	10.3 (9.4, 11.3)	11.7 (10.4, 12.7)
HR* (95% CI)	0.90 (0.75, 1.07)	

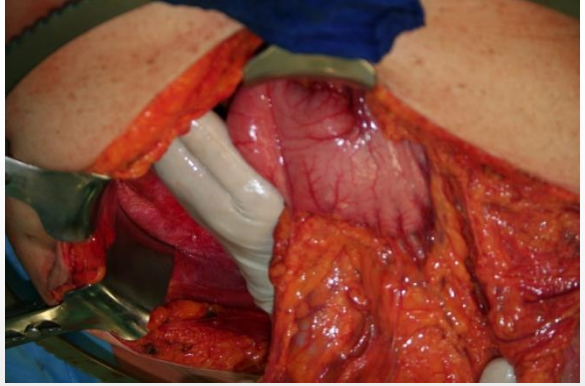
*HR adjusted for baseline stratification factors.

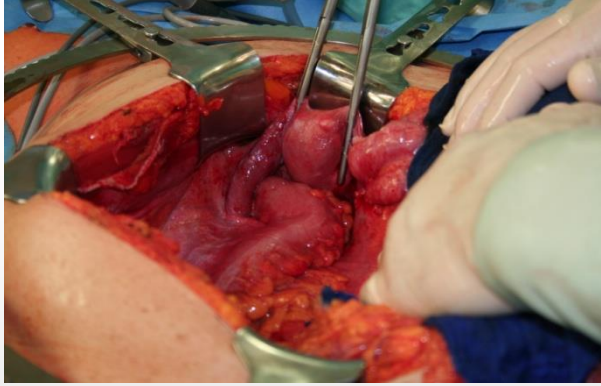
Surgery details

		PS (N=250)*	NACT (N=216)*
Optimal debulking	**0cm**	**37 (16%)**	**77 (40%)**
	≤1cm	57 (25%)	67 (35%)
	>1cm	135 (61%)	49 (25%)
	Missing	*21*	*23*
Length of operation (minutes)	Median (Range)	120 (30 – 450)	120 (30 – 330)

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







Peritonectomy

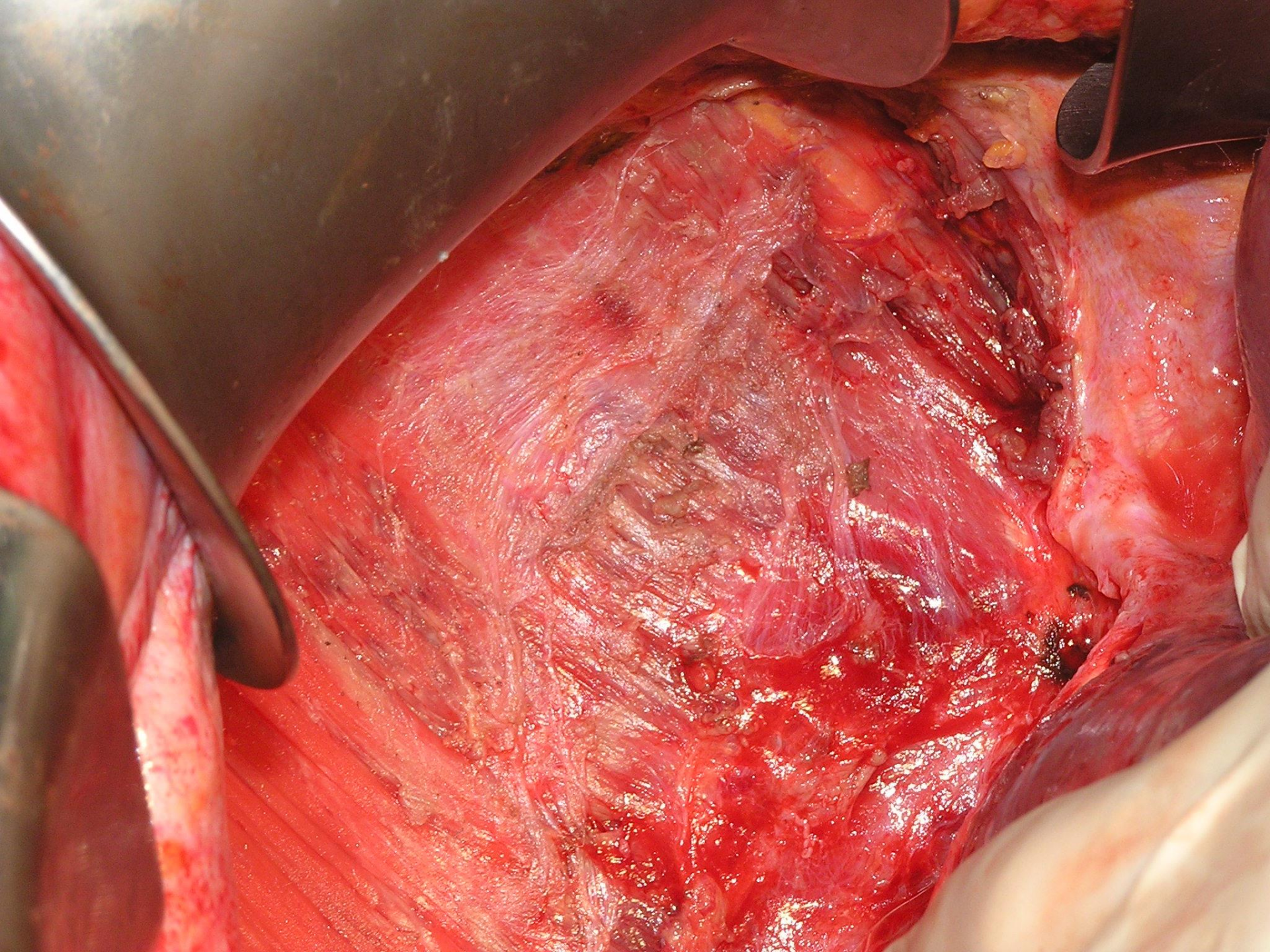
Infragastric Omentectomy

Bowel resection

Pelvic / paraaortic Lymphadenectomy

Total Hysterectomy bilateral salpingo-oophorectomy

Debulking of all peritoneal or abdominal lesions



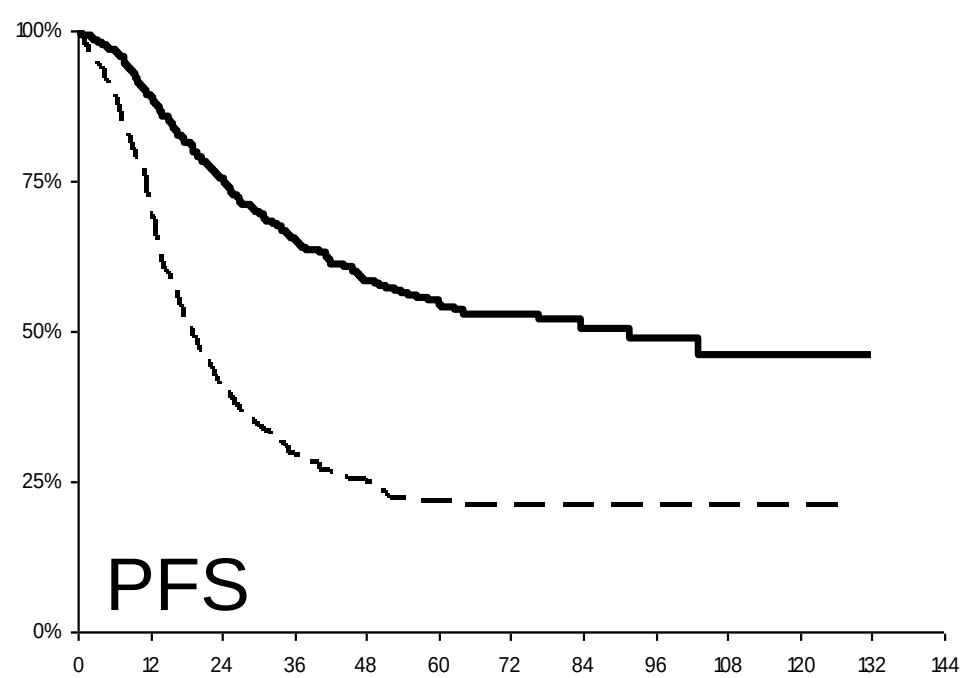
Advanced Ovarian Cancer
Residual Disease: Survival Analysis

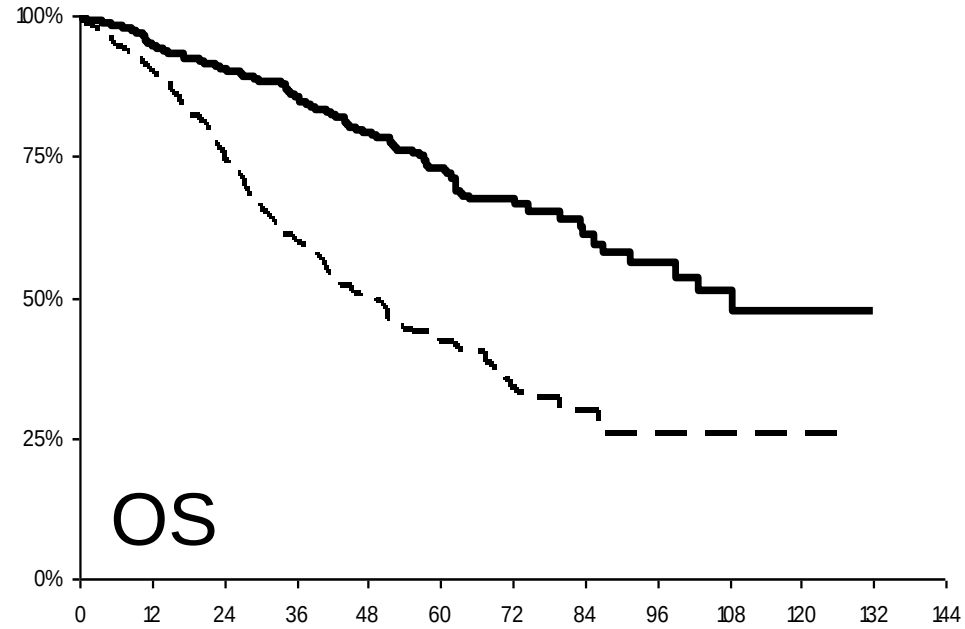
Stage IIIC Ovarian Cancer

Residual Disease	% 5-Year Survival
None	76
<1 cm	31
1-2 cm	13
>2 cm	5

Aletti et al., Obstet Gynecol 2006

Does tumor resection improve prognosis in every stage ?





res. tum. =0, FIGO IIB-IIIB

res. tum. >0, FIGO IIB-IIIB

log-rank: p < 0.0001

YES

Du Bois A.: Cancer 2009; 15: 1234-44

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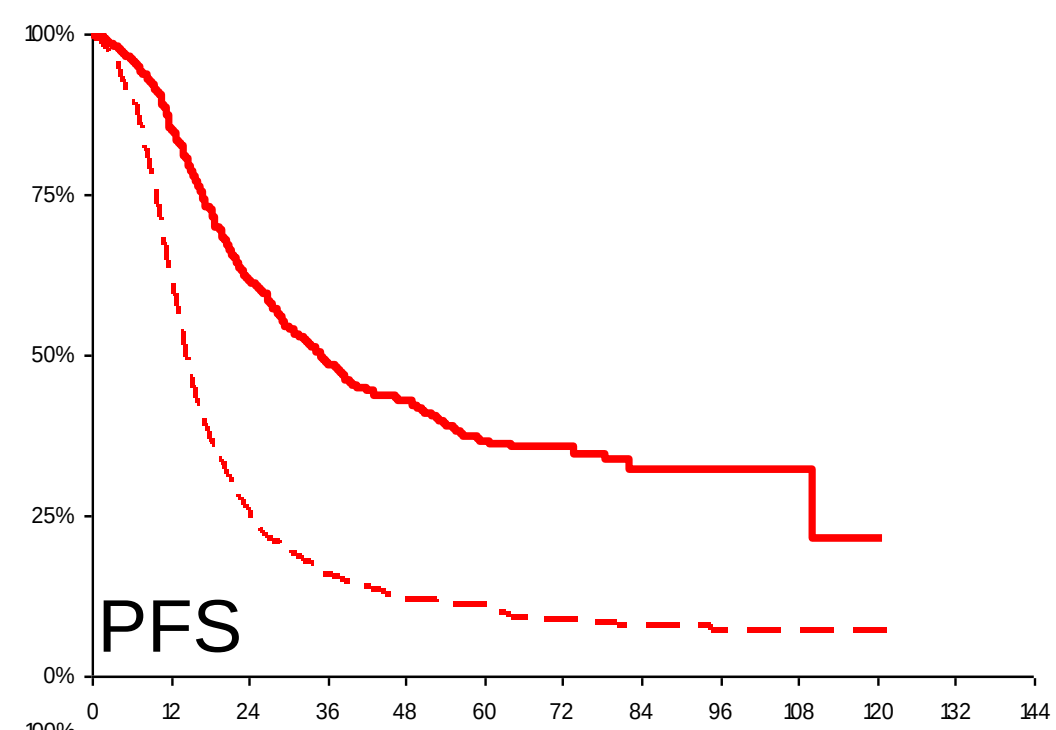

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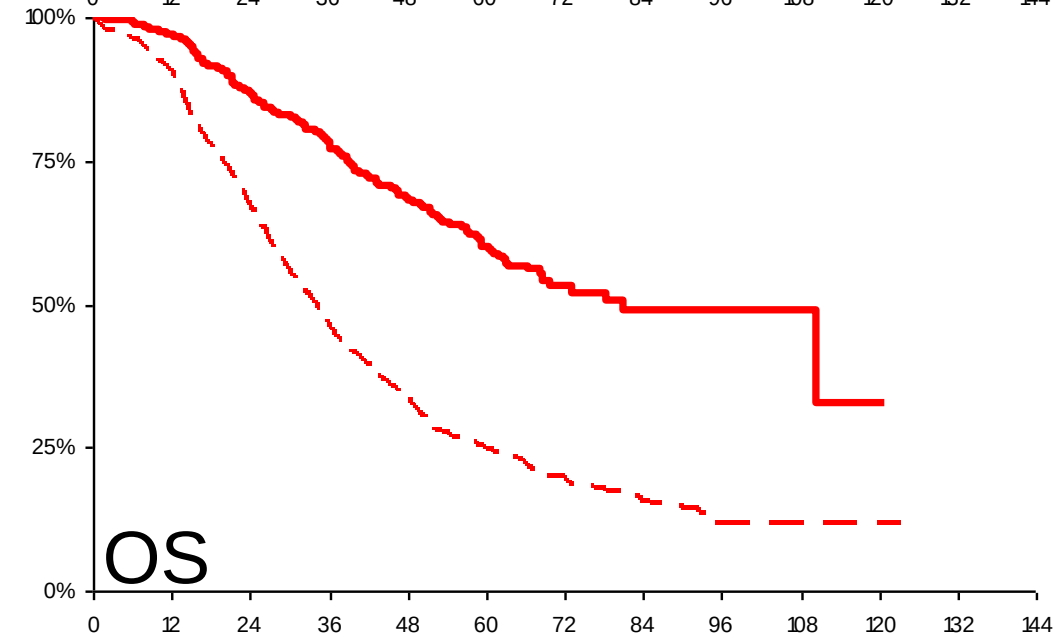

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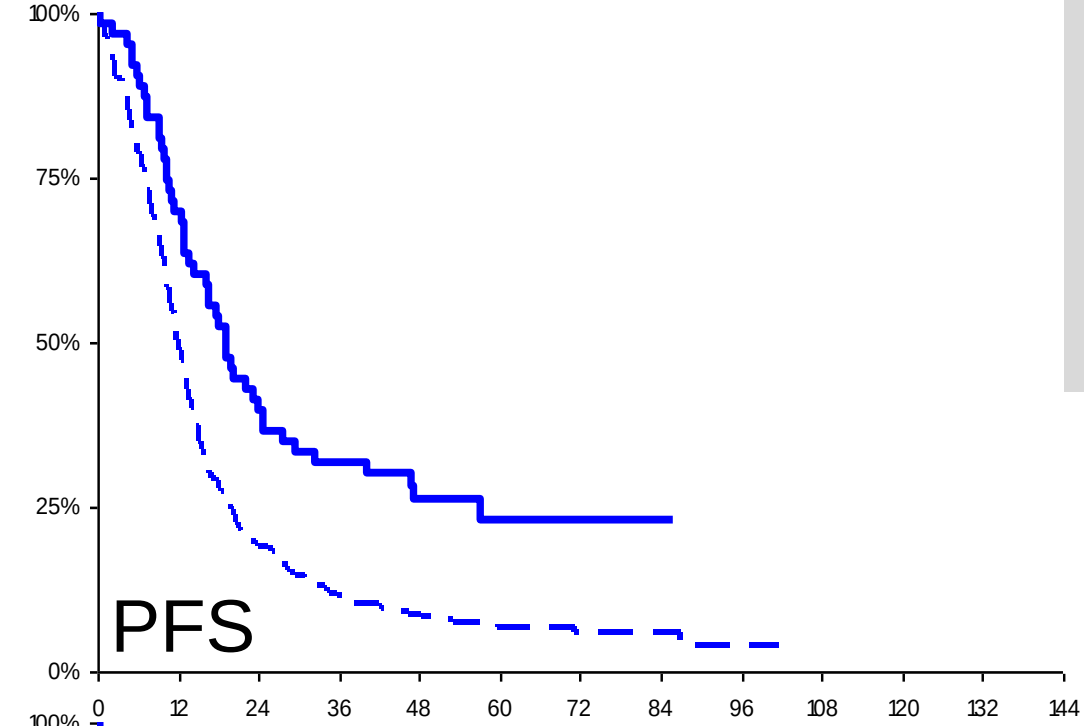

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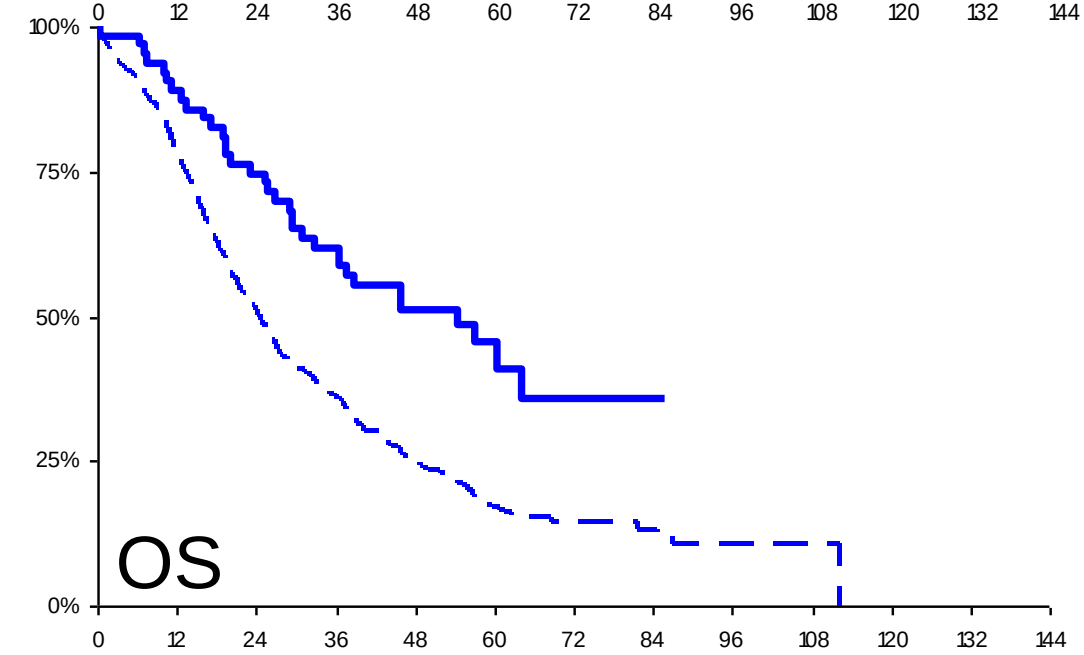


res. tum. =0, FIGO IIIC
res. tum. >0, FIGO IIIC

log-rank: p < 0.0001

YES

res. tum. =0, FIGO IV
res. tum. >0, FIGO IV

log-rank: p < 0.0001

YES

Du Bois A.: Cancer 2009; 15: 1234-44

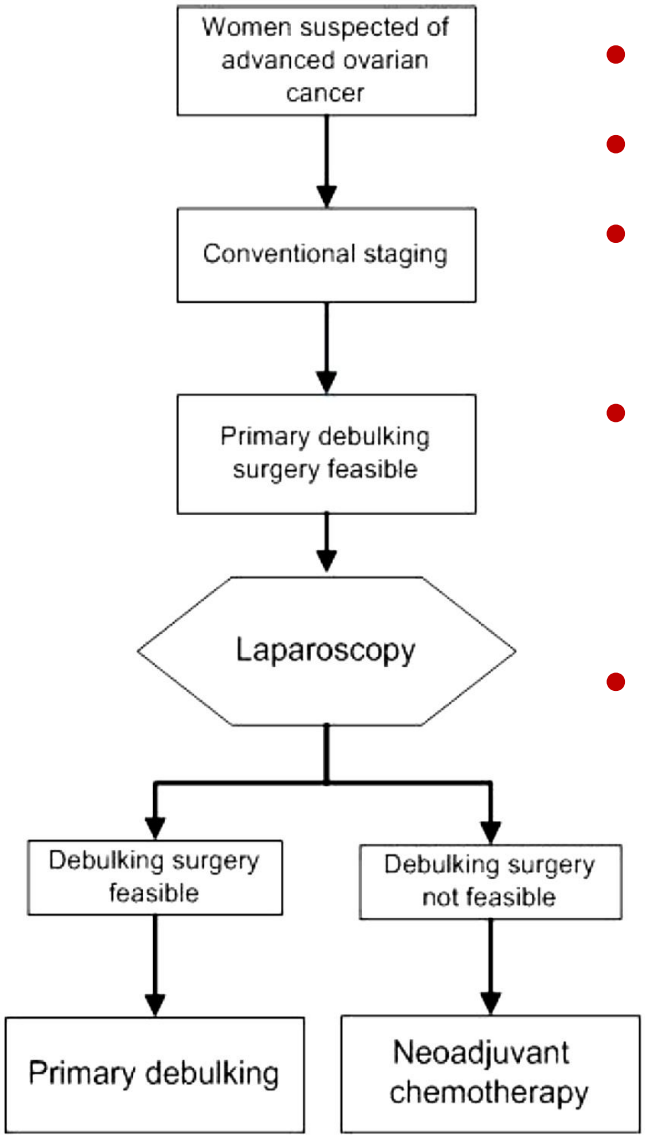
Which residual tumor must be acchieved in every stage to improve prognosis ?

Initial FIGO stage	No residual tumor	Any residual tumor	HR (95% CI)	
	Median Survival (Months)			
FIGO IIB-IIIB	108.6	48.3	**0.37** (0.30; 0.47)	+ 60.3 Mos.
FIGO IIIC	81.1	34.2	**0.36** (0.31; 0.42)	+ 46.9 Mos.
FIGO IV	54.6	24.6	**0.49** (0.34; 0.70)	+ 30.0 Mos.

HR = Hazard Ratio, reference class for HR is “Any residual tumor”

Du Bois A: Cancer 2009; 15: 1234-44

Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer



- Laparoscopy is a promising test
- Heterogeneous and small studies
- Wide range in negative predictive values
- Despite laparoscopy, there will still be patients undergoing unsuccessful primary laparotomy.
- Using a prediction model does not increase the sensitivity and will result in more unnecessarily explored patients, due to a lower specificity.

Rutten MJ, Leeflang MMG, Kenter GG, Mol BWJ, Buist M. Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer. *Cochrane Database of Systematic Reviews* 2014

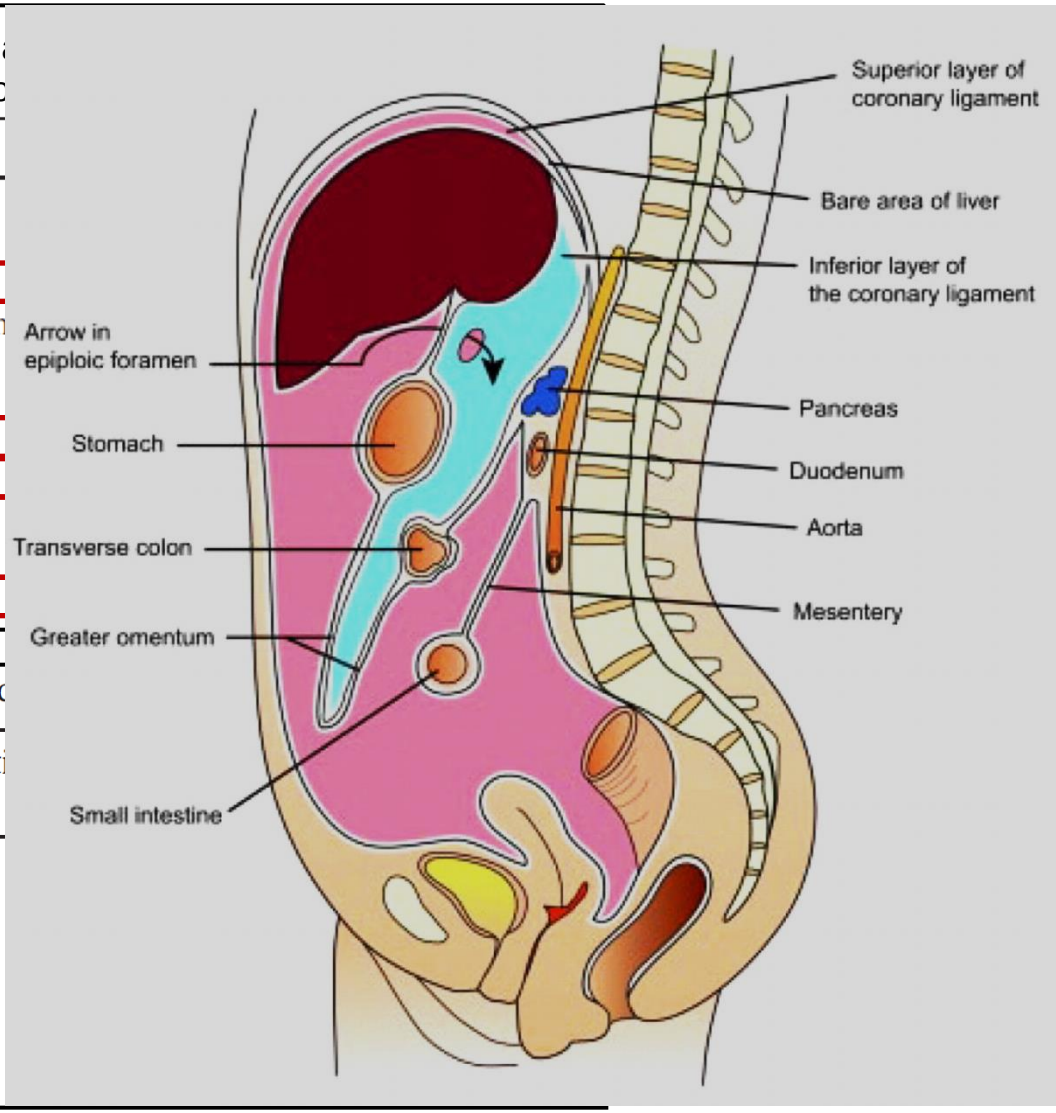
A multicenter prospective trial evaluating the ability of preoperative computed tomography scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer

Multivariate model of significant clinical
suboptimal cyto

Criteria
Age ≥60 years
CA-125 ≥ 500 U/mL
ASA 3–4
Retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) >1 cm
Diffuse small bowel adhesions/thickening
Perisplenic lesion >1 cm
Small bowel mesentery lesion >1 cm
Root of the superior mesenteric artery lesion >1 cm
Lesser sac lesion >1 cm

Predictive value score and suboptimal cytoreduc

Total predictive value score	Total patients *n* (%)	Opti (n)
0	22/349 (6%)	21
1–2	79/349 (23%)	71
3–4	109/349 (31%)	91
5–6	85/349 (24%)	56
7–8	31/349 (9%)	15
≥9	23/349 (7%)	6



Rudy S. Suidan et al; Gynecologic Oncology 2014

Role of Radical Surgery and Neoadjuvant Chemotherapy in Advanced Ovarian Cancer: Report on the Consensus Paper

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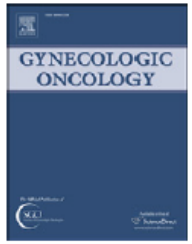
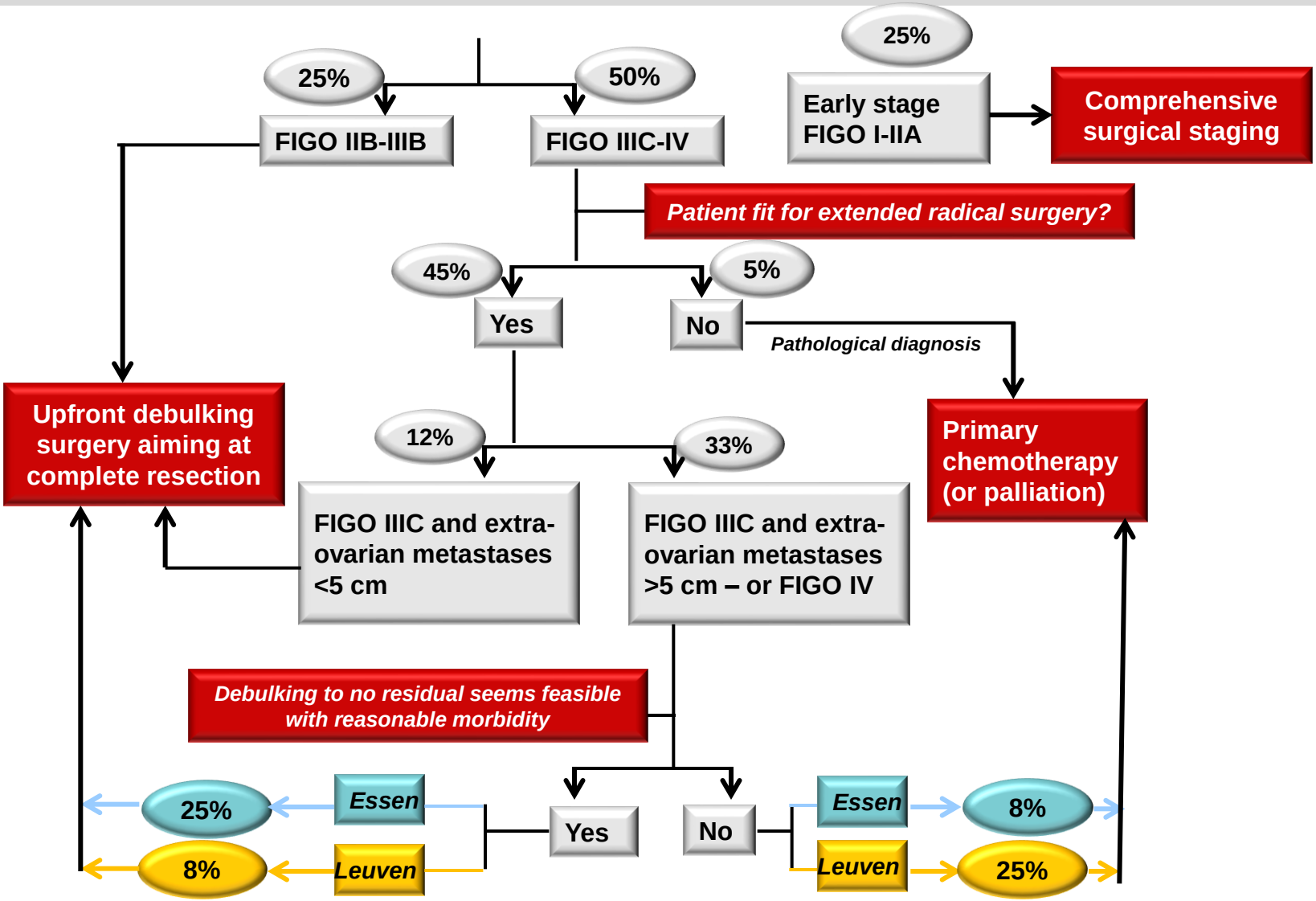


Clinical Commentary

Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree?

Algorithm for Ovarian Cancer



Vergote I, du Bois A , et al. *Gynecol Oncol.* 2013;128(1):6-11.

Criteria for Primary Chemotherapy and Interval Debulking Surgery in FIGO Stage IIIc and IV

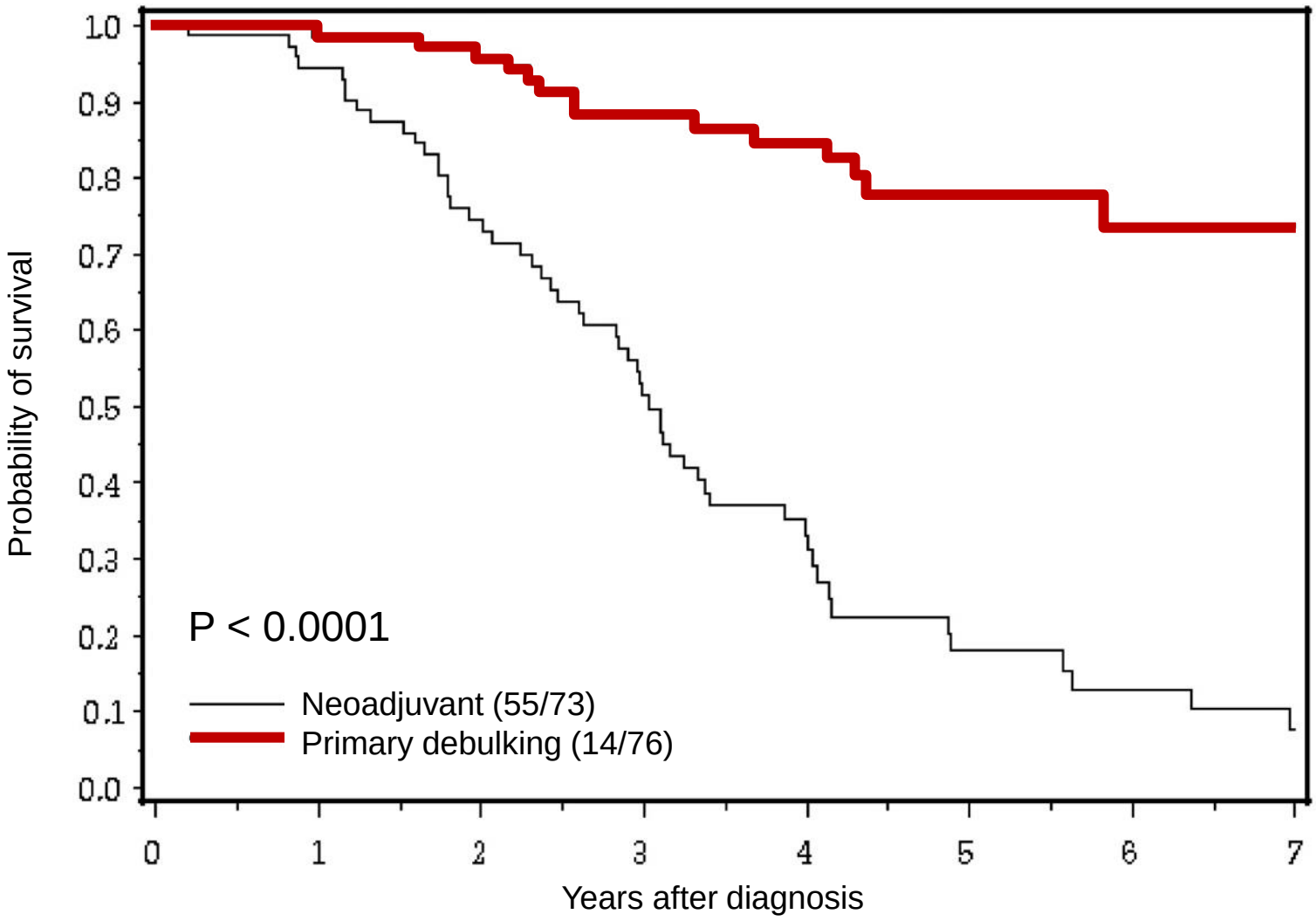
- Involvement of the superior mesenteric artery
- Diffuse deep infiltration of the radix mesenterii of the small bowel
- D
- M
- T
- T
- Brain metastases
- Impaired performance status and comorbidity not allowing a “maximal surgical effort” to achieve a complete resection
- Patients nonacceptance of potential supportive measures as blood transfusions or temporary stoma

Upfront surgery is still state of the art for the majority of ovarian cancer patients

Vergote I, du Bois A, et al. *Gynecol Oncol.* 2013;128(1):6-11.

The impacts of neoadjuvant chemotherapy and of debulking surgery on survival from advanced ovarian cancer

Survival in subjects with no residual disease, by timing of chemotherapy, stage 3c or stage 4 subjects only.



Barry Rosen et al; Gynecologic Oncology 2014

COMMENTARY

Is Neoadjuvant Chemotherapy in Ovarian Cancer an Excuse for Insufficient Surgery?

By Christian Marth, MD, PhD[1], Alain Zeimet, MD, PhD[1], Andreas Du Bois, MD, Phd[2] | 13. September 2011

[1] Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria

[2]Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany

- more than 30% higher optimal resection rate after NACT did not improve prognosis !
- NACT destroys the chance of improving outcome by improving surgery.
- NACT risks development of secondary resistant clones
- The uncritical adaption of NACT even for cohorts not included in the EORTC trial or cohorts in whom the EORTC trial did not show equivalence bears a serious risk of worsening outcome in OC globally.

Results of a Survey conducted in Europe 2013:

How many ovarian cancer patients will undergo neoadjuvant chemotherapy?

		ResponsePercent	ResponseCount
0-20%		**53,3%**	**48**
21-40%		31,1%	28
41-60%		10,0%	9
61-80%		3,3%	3
> 80%		2,2%	2
		AnsweredQuestion	**90**

Case history

- Upfront surgery has been selected
- After 12 hours of surgery including bowel resection, removal of spleen, resection of the diaphragm, extensive nodal dissection
- no residual disease was left
- After 12 months of follow-up the patient is with no evidence of disease