The Role of CA 125 in the management of ovarian cancer

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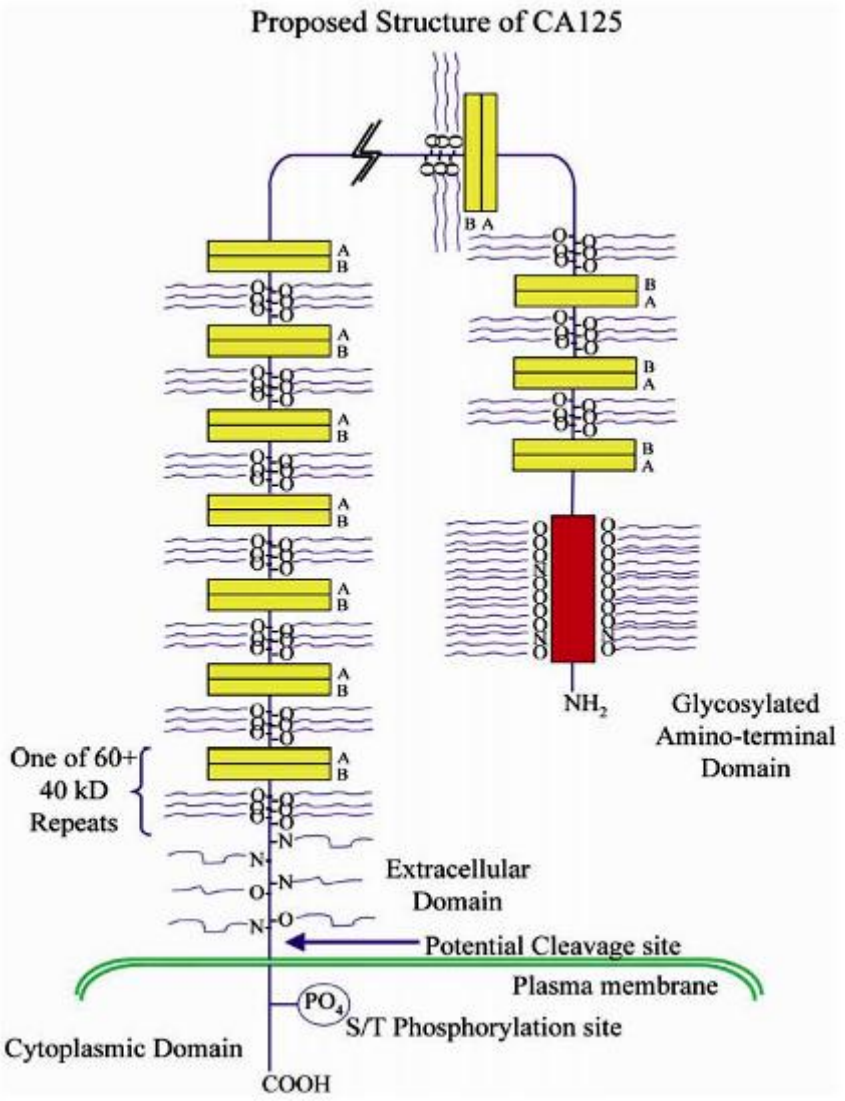
CA 125

- Founded in 1981 by Bast
- High molecular weight glycoprotein
- In 80% of OvCa patients and 1% of healthy people overexpressed
- Elevated in 50% only of stage I and 80% of advanced stage disease



Role of CA 125

- **Screening**
- **Risk assessment and early diagnosis**
- **Monitoring of the disease**
- **Follow up**

Ovarian Cancer

- Despite the effectiveness of surgery and first-line chemotherapy, 50–75% of patients with advanced disease will relapse, underlining the need for effective second-line strategies

- In clinical practice CA-125 monitoring is frequently used as a part of follow-up care for patients with ovarian cancer

- The role of CA 125 in follow-up care remains controversial in regards to the optimal frequency of CA-125 measurements and the impact of an elevated CA-125 level in the absence of symptoms

Recommendation Follow up Ovarian cancer

	1-3 Year	4+5 Year	>5 Year
Anamnesis/ Gynecologic examination	every 3 months	every 6 months	once per year
Vaginal Ultrasound / abd. Ultrasound	every 3 months	every 6 months	once per year
Mammography	once per year	once per year	once per year
Bloodtest (Ca125)/ additional radiological examinations	**Only if**	**symptoms**	**occur!!!**

CA 15-3

CA 125

HCG

CEA

Defining the problem…*?*

- Can CA 125 monitoring detect recurrence earlier?
- Can an earlier treatment of relapse **may**
  delay symptomatic disease
  (ascites, intestinal obstruction, pain etc.)
- Can a earlier treatment of relapse **may** increase:
  - the effect of therapy?
  - *prolong survival (?)*

SCC

AFP

CA 72-4

CA 19-9

Basis of GCIG CA-125 relapse criteria

Analysis after 81 relapses from 255 patients in North Thames Ovary Trial “5 versus 8”

If CA125 rise confirmed

Sensitivity (of eligible patients)	84%
False positive rate	1.4%

Median lead time to clinical progression: 63 days

Conclusion: A confirmed rise of serum CA 125 level to more than twice the upper limit of normal during follow up after first line chemotherapy accurately predicts tumour relapse!!!!

ASCO Annual '09 Meeting

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

EORTC European Organisation for Research and Treatment of Cancer

Early treatment of relapsed ovarian cancer based on CA125 level alone versus delayed treatment based on conventional clinical indicators

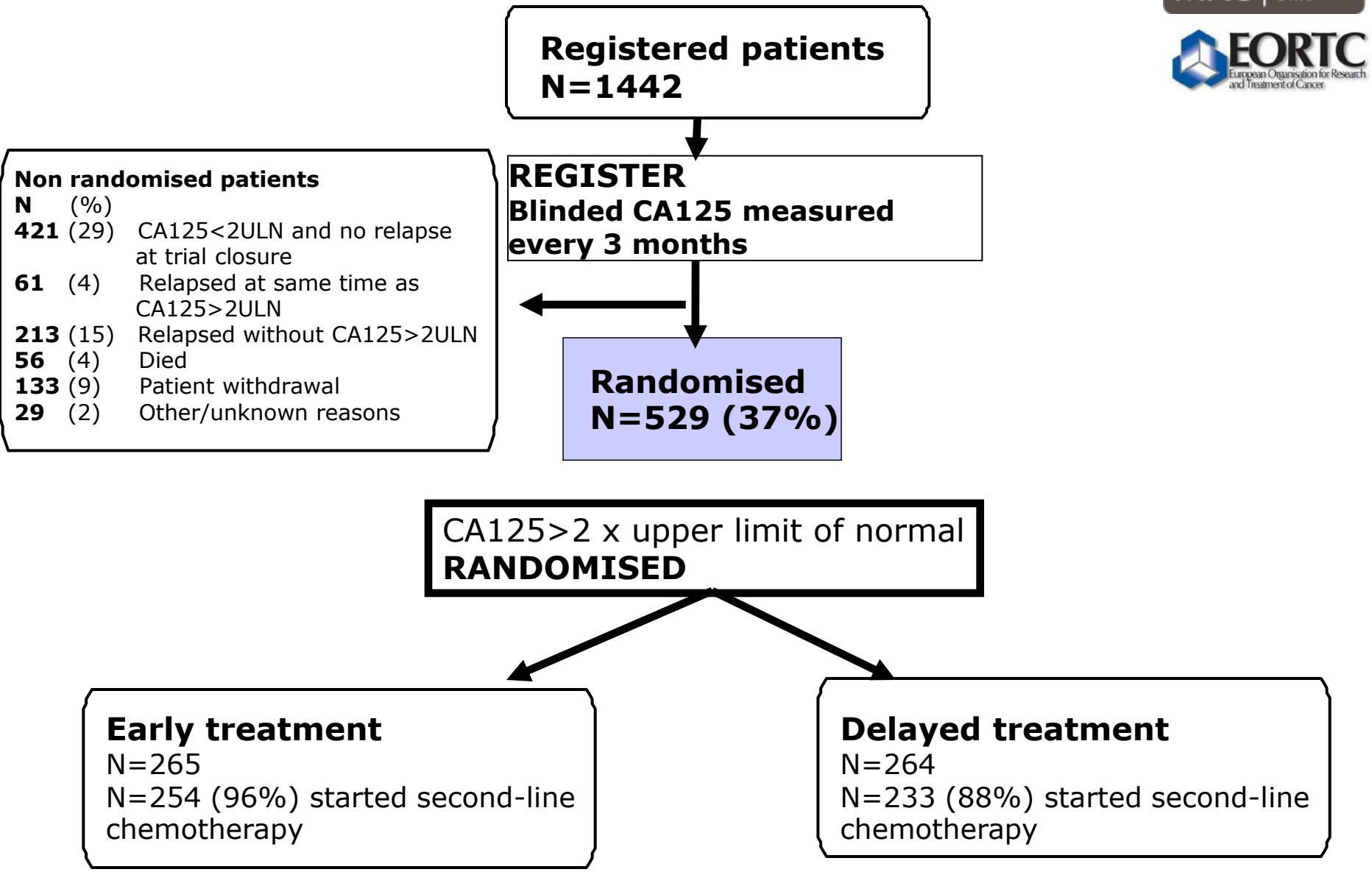
Results of the randomized MRC OV05 and EORTC 55955 trials

Gordon Rustin (Mount Vernon Cancer Centre)
and Maria van der Burg

On behalf of all OV05 and 55955 Collaborators

31st May 2009

Trial Profile

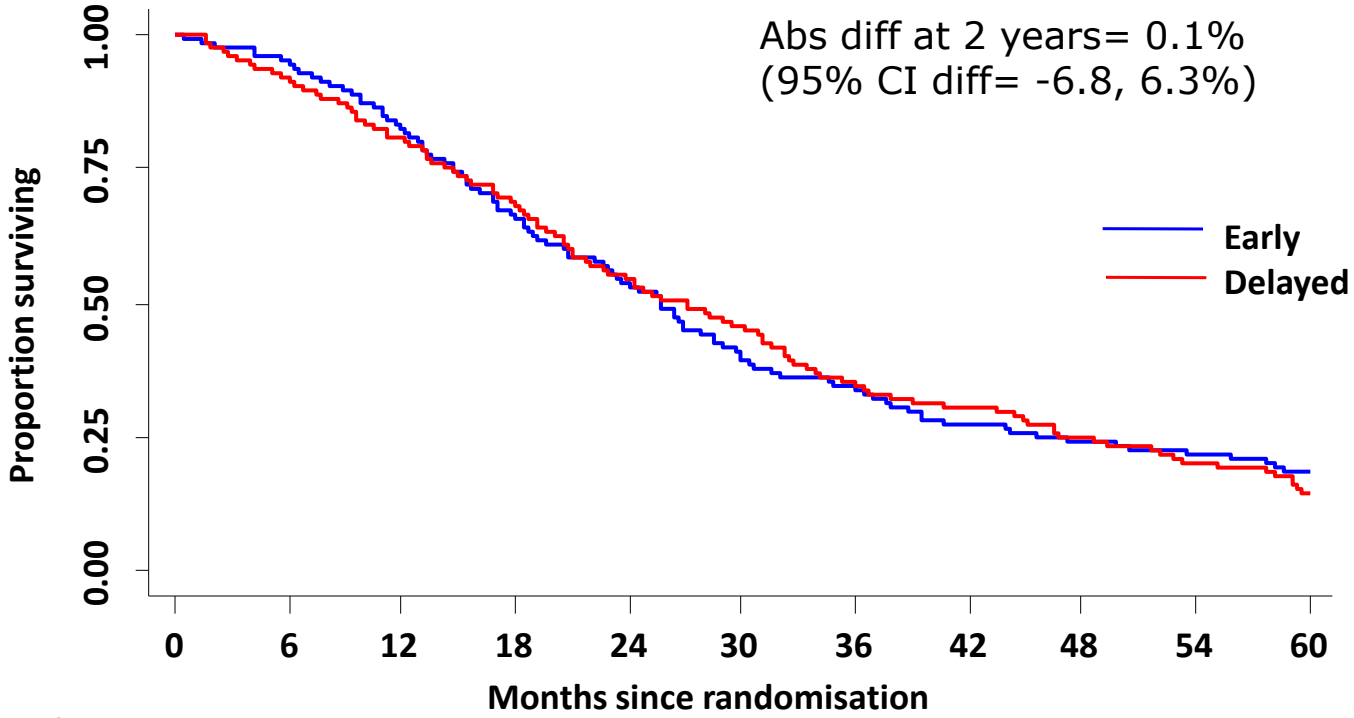


Baseline characteristics: All randomised patients (N=529)

		Early	Delayed
Age	**Median (range)**	60 (35-86)	61 (37-93)
FIGO stage	**I**	9%	8%
	II	11%	10%
	III	68%	69%
	IV	12%	13%
WHO PS	**0**	69%	75%
	1	29%	25%
	2 & 3	2%	<1%
Histology	**Serous**	66%	59%
	Endometroid	12%	12%
	Mucinous	3%	3%
	Clear cell	4%	4%
	Undifferentiated	8%	6%
	Adenocarcinoma not otherwise specified	6%	15%
	Other	1%	1%

Overall Survival

HR=1.00 (95%CI 0.82-1.22) p=0.98



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

Conclusions

- This early treatment did not improve overall survival
  - HR=1.00, 95% CI 0.82 – 1.22, p=0.98
  - Absolute difference at 2 years 0.1% (95%CI – 6.8, 6.3%)
- Early chemotherapy does not improve Qol

MRC OV05 and EORTC 55955 trials

Points to discuss!!!

- **Long time period of study recruitation**

- **High drop out rate** (1442 patients registered> 529 only randomised (37%))

- **Different treatments after recurrence**
(only one-third received a combination of carboplatin and paclitaxel)

- **Which examination tool** (gynec. exa.,new imaging technology) were used to reduce the proportion of patients with Ca 125 increase alone

- **Not homogenous population** (platinum sensitive and resistant patients)

- **No data regarding secondary cytoreduction**

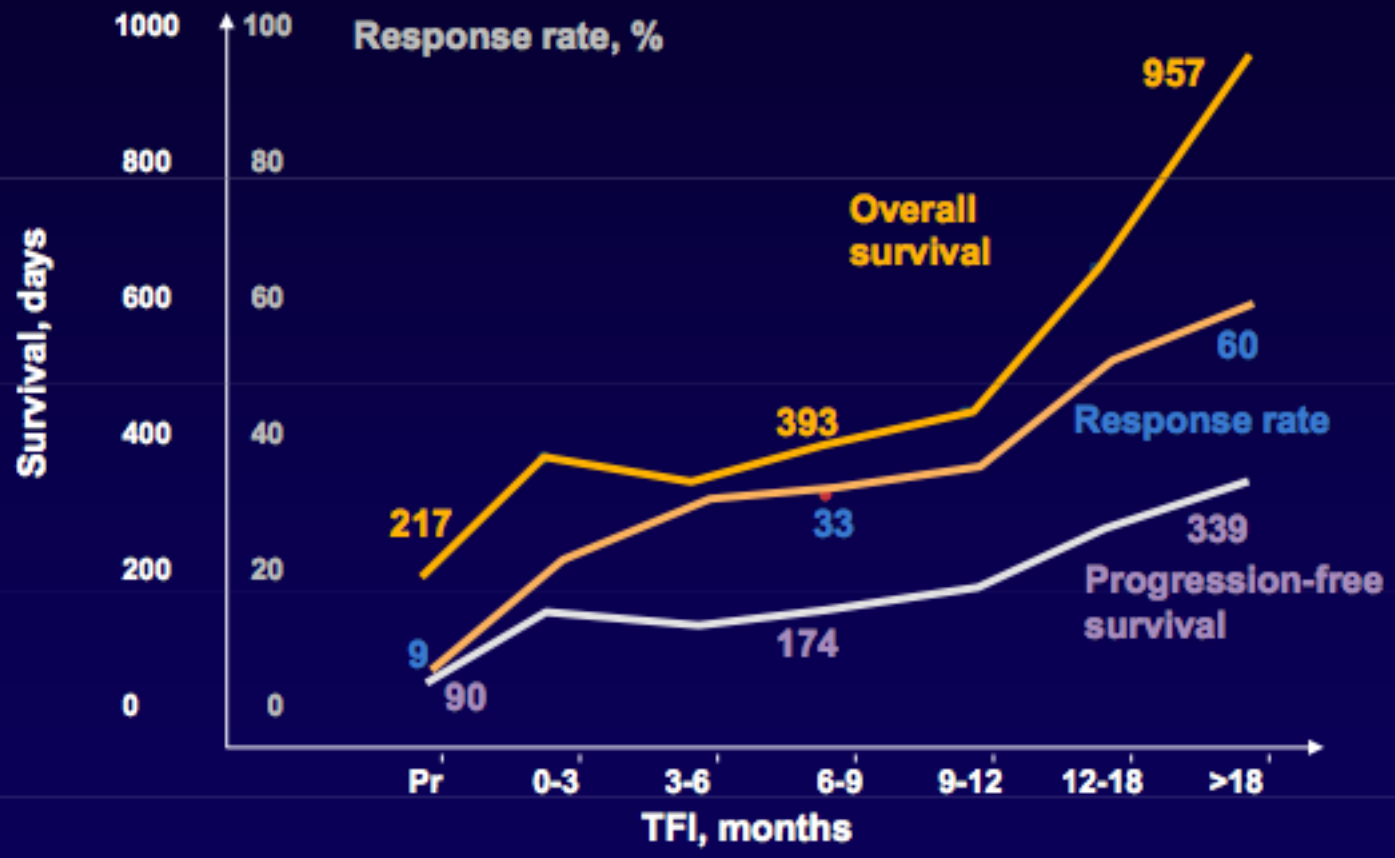
Patients outcome in relapse depends on:

Treatment free intervall

Treatment at Recurrence:

- Chemotherapy
- Surgery

Outcome by Treatment-Free Interval (TFI)



E. Pujade-Lauraine et al.

The Treatment Paradigm
Second Line

Platinum Refractory/Resistant

↓

<6 months

↓

Non-Platinum Montherapy

Platinum sensitive

↓

>6 months

↓

Discuss surgery

↓

Platinum-Based Combination

Trials of Combination vs Monotherapy in Platinum-Sensitive AOC

Author/ Group	Year	No. Pts	Regimens Evaluated	PFS	OS
Bolis[1]	2001	190	Carboplatin + Epirubicin vs Carboplatin	NS	NS
Cantù[2]	2002	97	Cyclophosphamide + Doxorubicin + Cisplatin vs Paclitaxel	S	S
ICON IV[3]	2003	802	Paclitaxel + Platinum vs Platinum	S	S
González-Martín GEICO[4]	2005	81	Paclitaxel + Carboplatin vs Carboplatin	S	S
Pfisterer	2006	356	Carboplatin + Gemcitabine vs Carboplatin	S	NS
Pujade-Lauraine	2009	976	Carboplatin+Caelyx vs Carboplatin	S	NS

Second-Line Chemotherapy

Regimen Administered	Early N (%)	Delayed N (%)
Combination platinum	**131 (49)**	**134 (51)**
Combination platinum (no taxane)	40 (15)	33 (13)
Platinum + taxane based	91 (34)	101 (38)
Carboplatin alone	**78 (29)**	**67 (25)**
Nonplatinum regimens	**43 (17)**	**24 (9)**
Taxane without platinum	15 (6)	9 (3)
Other	28 (11)	15 (6)
Absence of defined treatment	**13 (5)**	**39 (15)**
Unknown treatment	2 (1)	8 (3)
No treatment given	11 (4)	24 (9)
Not yet given (no clinical relapse)	0	7 (3)
Total	265	264

Rustin G, et al. *J Clin Oncol.* 2009;27(18S): Abstract 1.

Role of Surgery
Recurrent ovarian cancer

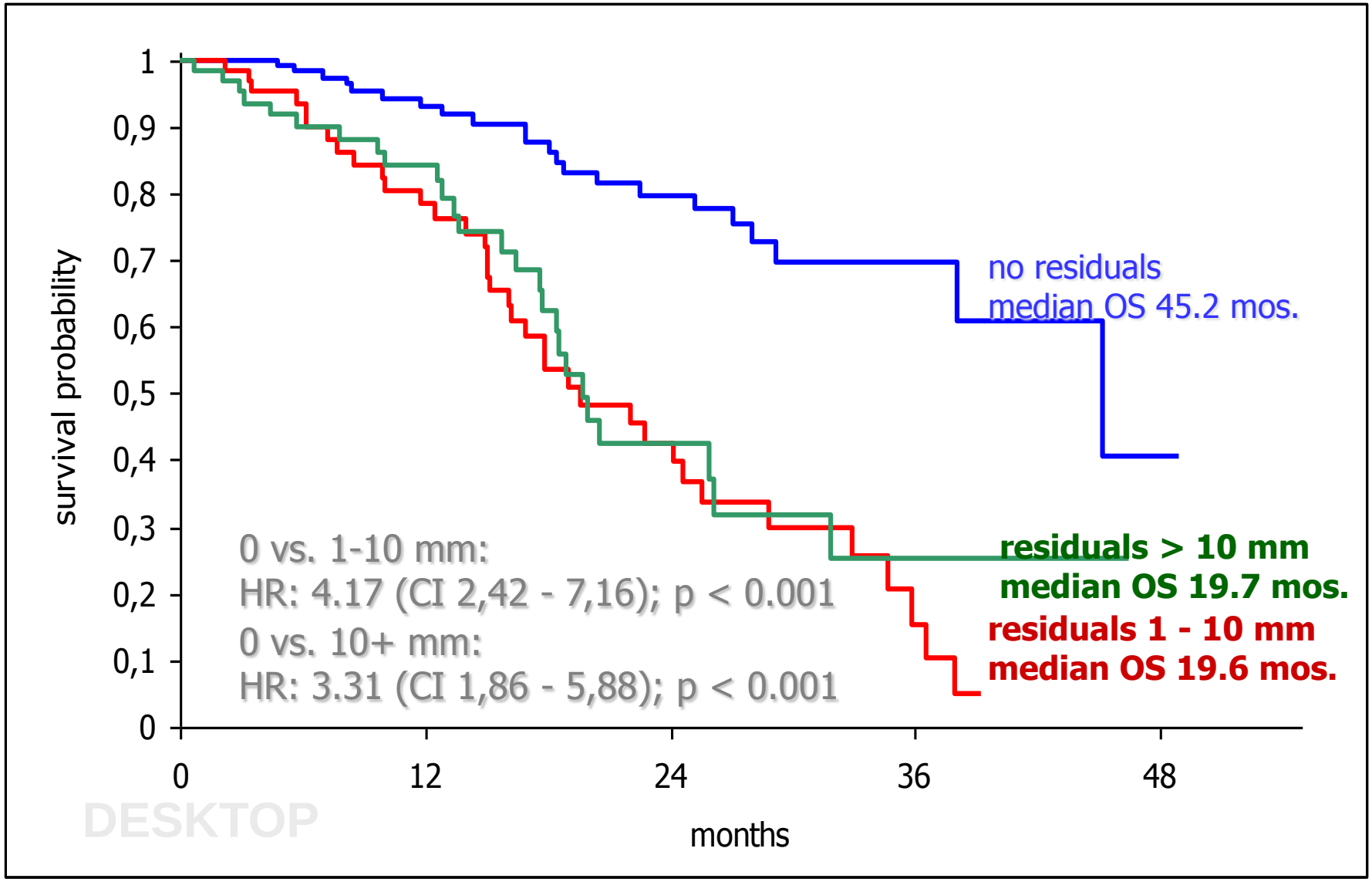
Due early detection….

more patients can may be selected for surgery.

more patients can may be operated macroscopic tumorfree

> may prolong Overall survival!!!!!

DESKTOP- OVAR I



Harter P, du Bois A, Hahnmann M, et al. Ann Surg Oncol 2006

DESKTOP-OVAR I

Prediktiv factors for complete resection

Multivariate analysis

pre-OP variable	OR	(95%CI)	p
General condition (ECOG 0 vs. > 0)	2.65	(1.56-4.52)	< 0.001
Tumor residual at primary-OP (0 vs. > 0)	2.46	(1.45-4.20)	< 0.001
or: initial FIGO-stage (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

* exclusiv CA 125 (Correlation with ascites)

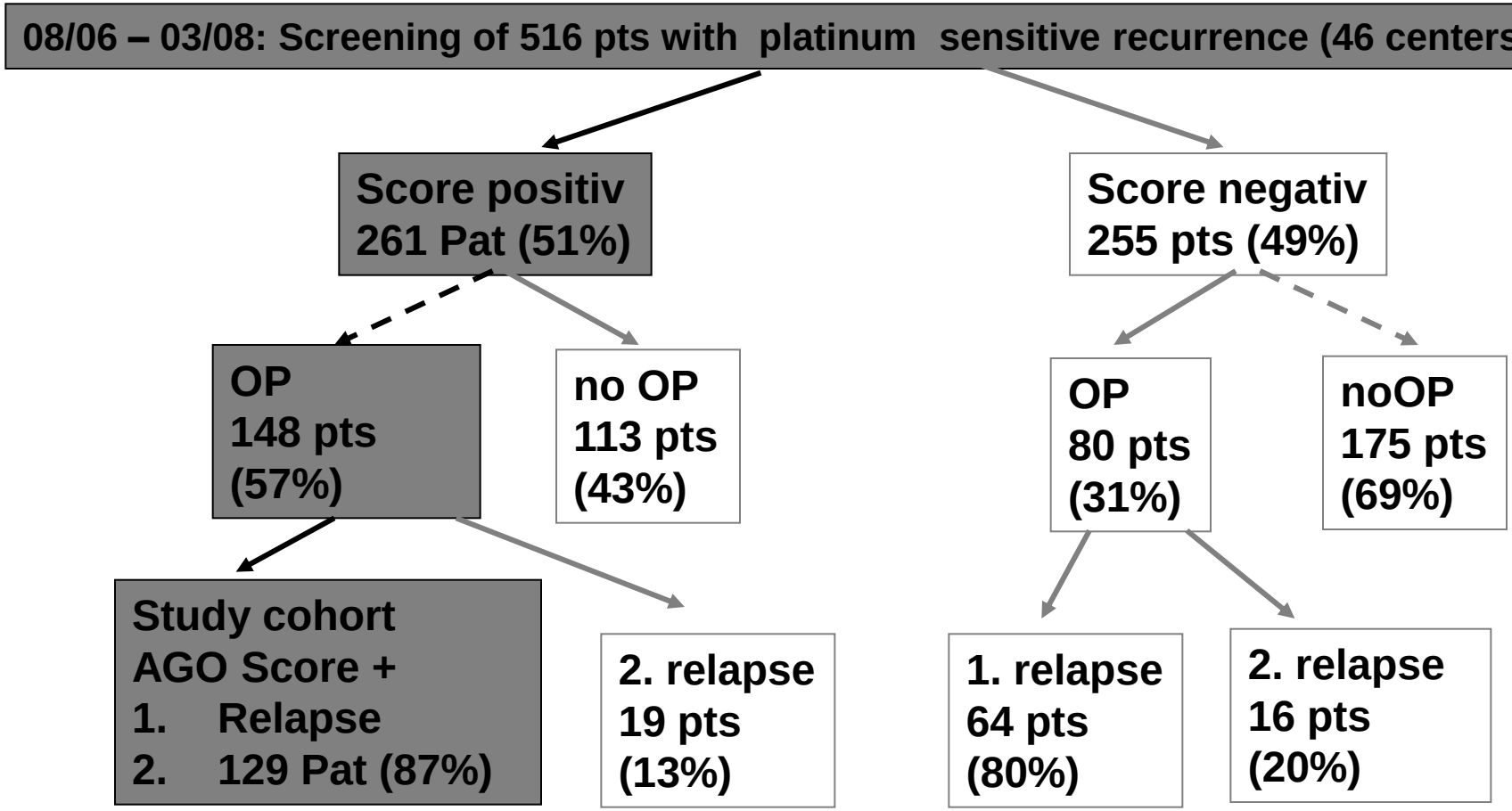
Not significant for complete resection:

- Localisation of relapse (pelvis vs. andere)
- treatment free interval

Harter P, du Bois A, Hahmann M, et al. Ann Surg Oncol 2006;13: 1702-1710

AGO-OVAR OP-2 (DESKTOP II)

Preoperative Selection



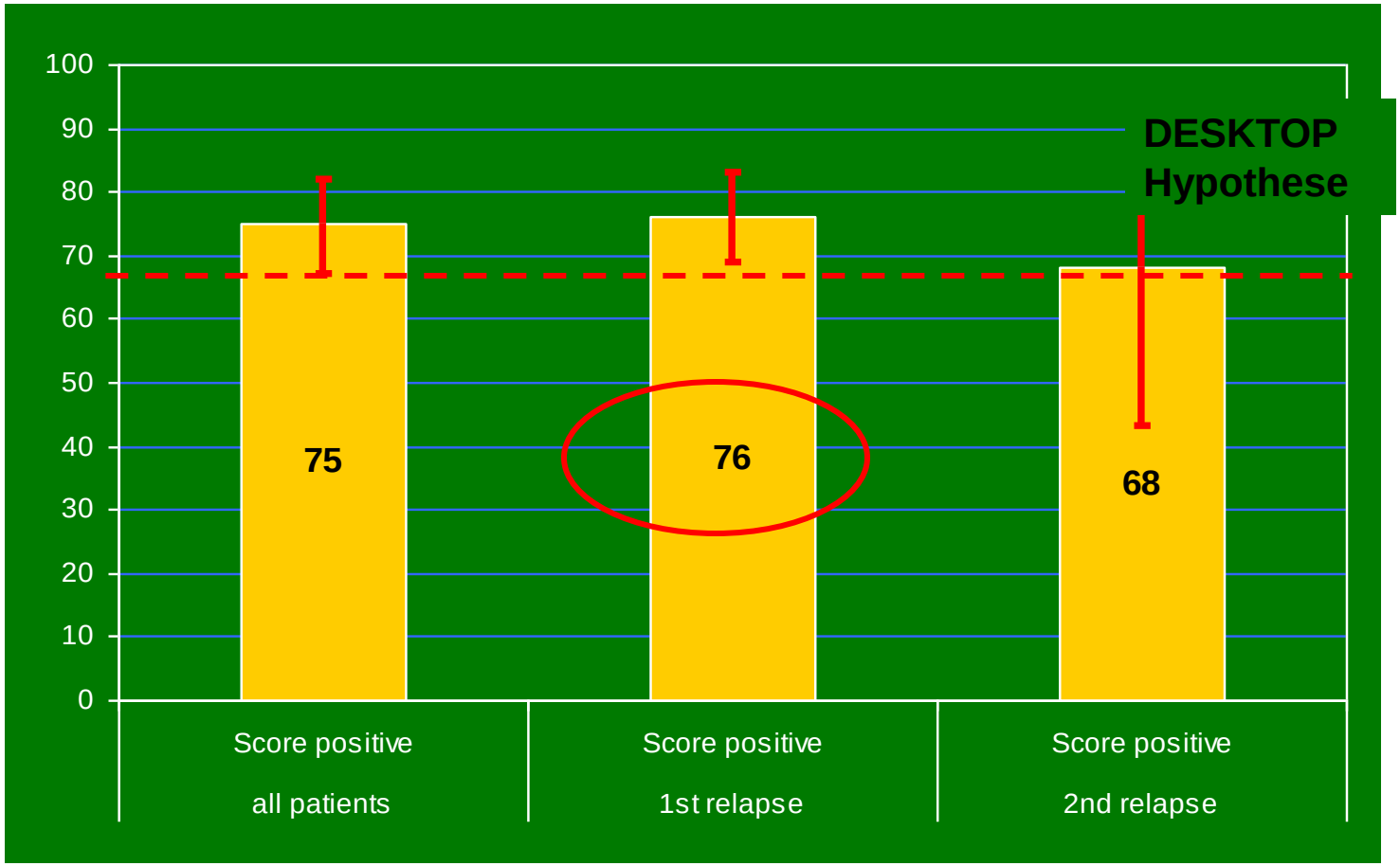
Preoperative Selektion:

228 Pat (44.2%) with relapse-OP

Harter et al 2008, IGCS

AGO-OVAR OP-2 (DESKTOP II)

Rate of complete resection using the the AGO-Score



Complete resection in 76%

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

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

Platinum-sensitive recurrent cancer of the ovaries, fallopian tubes, or peritoneum

PFI > 6 mos since last chemotherapy which was platinum-based

No prior chemotherapy for this 1st relapse

Complete resection seems feasible and positive AGO score:
- **PS ECOG 0**
- **no ascites > 500 ml**
- **prior complete debulking or initial FIGO I/II**

Post-OP Standard chemotherapy planned

RANDOM

Cytoreductive surgery

no surgery

platinum-based chemotherapy* recommended

* Recommended platinum-based chemotherapy regimens:
- carboplatin/paclitaxel
- carboplatin/gemcitabine
- carboplatin/pegliposomal doxorubicin

What do our patients think and expect?

What do patients think about CA-125 monitoring in the follow-up? Results from a multicenter trial in 1060 patients with ovarian cancer.

ASCO 2009, selected Poster
Guelten Oskay-Oezcelik, ‚Jalid Sehouli, Andreas du Bois et al.

Patient Characteristics

No. of pts.	1060
Routine measurements of CA 125 in follow-up	699 (66%)
Analyzed questionnaires (without current treatment)	589 (56%)
Time period of survey	02-12.2007
Median age, years (range)	58 (49-65)
Primary ovarian cancer	437 (74%)
Relapsed ovarian cancer	139 (24%)
Unknown	22 (2%)
Second Malignancy (pts.)	129 (22%)
• Breast cancer	29 (5%)
• Colon cancer	34 (6%)
• Other	66 (11%)
Profession	
• Academics	97 (16%)
• Non academics	228 (39%)
• unknown	264 (45%)

Which of the following methods are the most important for you ? (mark 3 answers maximum)

Primary

1.CA 125	***64%***
2.Vaginal sonography	**49%**
3.PAP	**45%**
4.Gyn. examination	**33%**
5. Physical examination	**29%**
6.Chest x-ray	**26%**
7.CT	**15%**
8. Abdominal Sonography	**9%**
9. MRI	**5%**
10.PET	**1%**

Relapsed

1.CA 125	***59%***
2.PAP	**47%**
3.Vaginal sonography	**43%**
4.Gyn. examination	**40%**
5.Chest x-ray	**32%**
6.Physical examination	**23%**
7.CT	**13%**
8.Abdominal sonography	**10%**
9.MRI	**3%**
10.PET	**1%**

Which of the following methods induce the highest anxiety ? (mark maximum 3 answers)

Primary

1.CA 125	***16%***
2.Gyn. Examination	**14%**
3.PAP	**12%**
4.Vaginal sonography	**11%**
5.Chest x-ray	**6%**
6.CT	**3%**
7. Abdominal Sonography	**2%**
8.MRI	**1%**
9.PET	**1%**
10.Physical Examination	**0%**

Relapsed

1.CA 125	***59%***
2.Gyn. Examination	**13%**
3.PAP	**12%**
4.Chest x-ray	**12%**
5.CT	**8%**
6. Abdominal sonography	**4%**
7.Vaginal sonography	**1%**
8.MRI	**1%**
9.PET	**1%**
10.Physical Examination	**0%**

www.expression3.de

Perceptions and expectations on clinical management of ovarian cancerEuropean survey: Expression III

- Germany
- Belgium
- Austria AGO
- Italy (MITO)
- Poland
- Romania
- Bulgaria
- Denmark
- Spain (Geico)

Oskay, Sehouli et al.: Posterpresentation in ASCO 2014

Should we continuing to use CA 125 during FU ?

YES, because.....

- Reassurance while levels remain normal
- Simple and cost-effective
- CA 125 increase can select the patients that need other 2nd level examinations (PET, CT, …..)
- To start treatment earlier before symptoms occure > treatment will be better tolerated> more effective (🡻 dose reduction,treatment delay)
- To select patients who can benefit from surgery
- To select patients for the right and effective therapy (sensitive; resistant)
- Patients learn during the first line the value of Ca125 (.. and would ask why not during FU)> Respect patients wish and expectations

➔ **effective treatment maybe prolong survival????**