Surgical intervention for recurrent ovarian cancer after an asymptomatic rise in CA125: the sooner the better?

Ate GJ van der Zee
University Medical Center Groningen
The Netherlands
ESMO Vienna 2012.

Case

A 56 yr old woman, otherwise healthy, has undergone complete debulking of a stage IIIc (one large omental tumor deposit) high grade serous ovarian cancer. Afterwards she received 6 cycles of carboplatin / paclitaxel. Two weeks after her last cycle of chemo she feels well and her CA125 is 6 kU/l.

Questions

What follow-up would you recommend ?

- Office visits (including physical and pelvic exams) every three to six months up to five years posttreatment, then annually.
- CA-125 or other tumor markers (eg, HE4) every visit if initially elevated.
- Other testing (CT scan and / or transvaginal ultrasound)

Todays' presentation

- A few clinical characteristics
- Aims of follow-up in ovarian cancer.
- Pros and cons of CA-125 in follow-up
- Case to be continued…
- Which patients will benefit from surgical intervention ?
- Summary

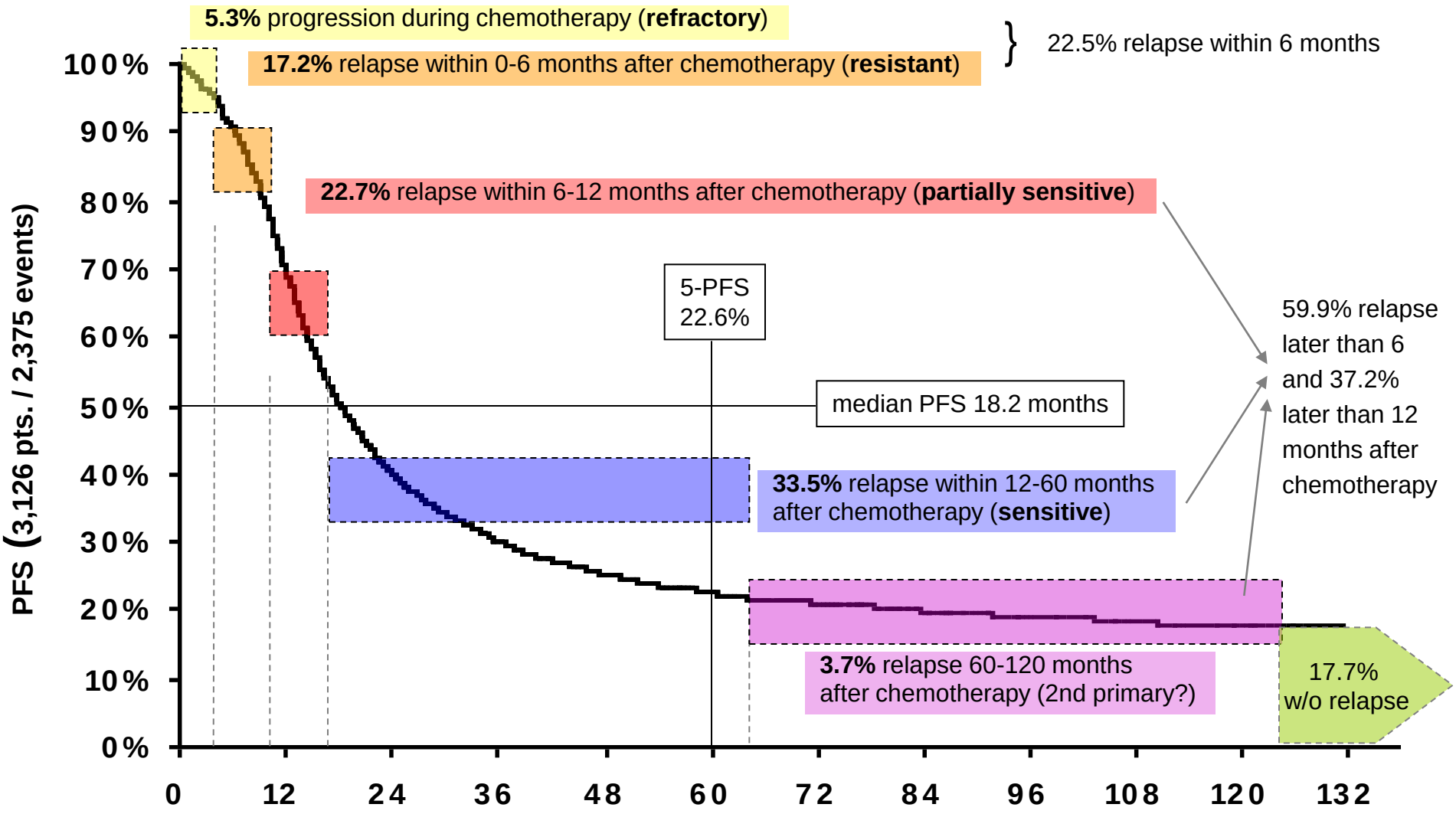
A few clinical characteristics of ovarian cancer.

- Advanced stage: 60-70%
- Clinical complete remission (CCR) after surgery and chemotherapy: majority of patients.

- Frequent (75%) relapse after CCR:
  - Median time: 18-24 mo
  - Prognostic factors for relapse:
    - Extend of residual disease after primary surgery

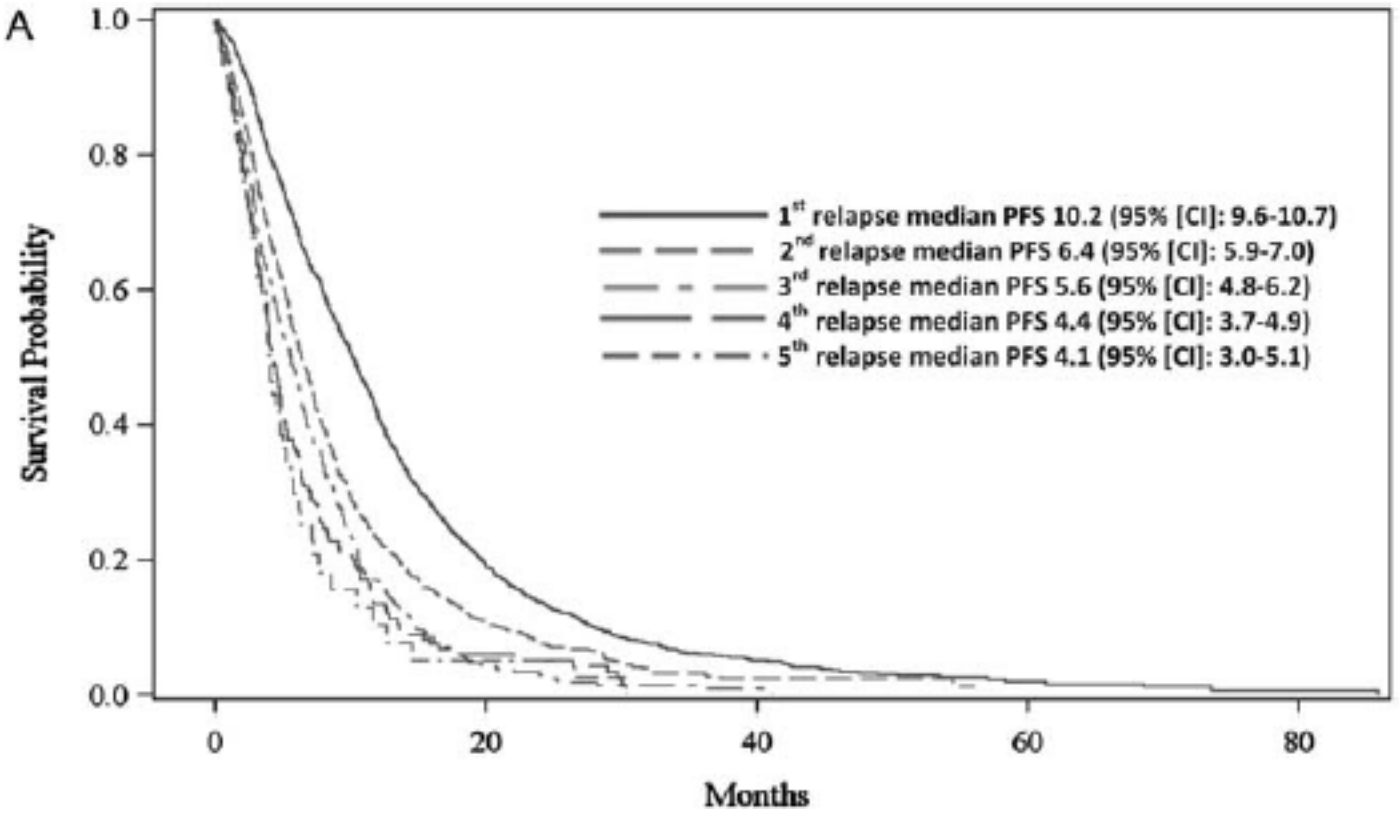
Giaducci & Cosio, 2009
Du Bois et al, 2009

Progression-free survival in ovarian cancer FIGO IIB-IV. An individual pts. metaanalysis of AGO-OVAR 3, AGO-OVAR 5, and AGO-OVAR 7 (calculated with chemotherapy duration 6x21 days)**.**



du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J: Cancer 2009; 15: 1234-1244

The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/ platinum-based therapy



Hanker et al Ann Oncol 2012

Impact of second to sixth line of therapy in recurrent ovarian cancer

Relapse	PFS (mo) (95%CI)	OS (mo)(95% CI)
First	10.2 (9.6-10.7)	17.6 (16.4-18.6)
Second	6.4 (5.9-7.0)	11.3 (10.4-12.9)
Third	5.6 (4.8-6.2)	8.9 (7.8-9.9)
Fourth	4.4 (3.7-4.9)	6.2 (5.1-7.7)
Fifth	4.1 (3.0-5.1)	5.0 (3.8-10.4)

Hanker et al, Ann Oncol 2012

Impact of second to sixth line of therapy in recurrent ovarian cancer

Relapse treatment improved PFS and OS at the second to fourth recurrence.

In multivariate analysis, platinum sensitivity (disease free interval) and optimal **primary** tumor debulking were revealed as independent prognostic factors for PFS up to third relapse.

Hanker et al, Ann Oncol 2012

Treatment goals after recurrence

DFI < 6 mo:

- Symptoms relief
- Maintain stable disease
- Response ?
- Cure: no

DFI > 12 mo:

- Symptoms relief
- Response !
- To prolong overall survival
- Cure:
  - Highly unlikely

Treatment goals after recurrence

Prolonging survival is an important objective of treatment but, in the context of advanced disease and the debilitating side effects of ongoing treatment, maximizing quality of life is a priority issue.

Beesley et al, Psycho-Oncology 2012

How do current follow-up protocols fit these treatment goals ?

Post-treatment Surveillance and Diagnosis of Recurrence in Women with Gynecologic Malignancies:

Ovarian cancer surveillance recommendations

	Months			Years	
Variable	**0-12**	**12-24**	**24-36**	**3-5**	**>5**
Review of symptoms and physical examination	Every 3 mo	Every 3 mo	Every 4-6 mo	Every 6 mo	Yearly[a]
Papanicolaou test/ cytologic evidence	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Cancer antigen 125	Optional	Optional	Optional	Optional	Optional
Radiographic imaging (chest x-ray, positron emission tomography/ computed tomography, magnetic resonance imaging)	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use
Recurrence suspected	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan	Computed tomography and/or positron emission tomography scan
	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125

[a] May be followed by a generalist or gynecologic oncologist.

Salani. Surveillance for gynecologic cancers. Am J Obstet Gynecol 2011.

American Journal of Obstetrics & Gynecology JUNE 2011

Aims of follow-up in ovarian cancer

- To detect disease that if treated early might improve overall survival
- To identify relapse without recourse to further endoscopic and imaging investigations
- To deal with ongoing toxicity related to previous therapy
- To collect data for research as part of clinical trials
- (To educate and help patients plan their lives, outlining different treatment and timing options).

Hall & Rustin, 2011

No evidence for efficacy of routine follow-up in ovarian cancer

Observational studies

- Asymptomatic vs. symptomatic recurrences
  - Results: conflicting

Gadducci et al 2009, Tanner et al 2010, Geurts et al 2011

Impact of Routine Follow-Up Examinations on Life Expectancy in Ovarian Cancer Patients

A Simulation Study

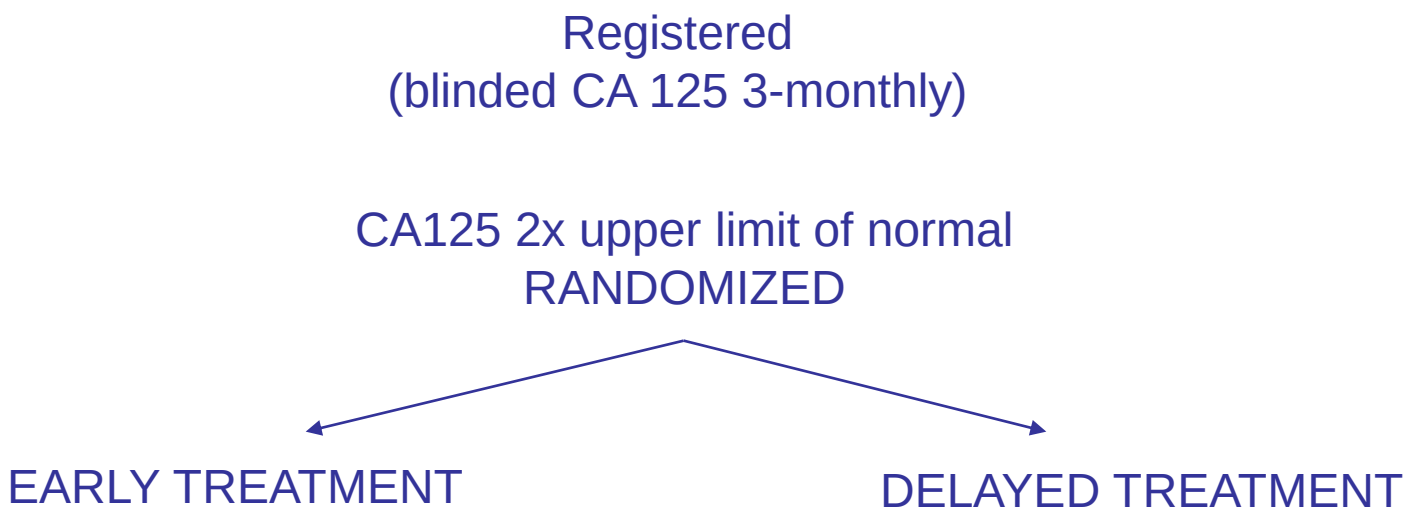
Sandra M. E. Geurts, MSc, Femmie de Vegt, PhD,* Anne M. van Altena, MD,†*
*Vivianne C. G. Tjan-Heijnen, MD, PhD,‡ Leon F. A. G. Massuger, MD, PhD,† Eddy M. Adang, PhD,**
Jos A. A. M. van Dijck, PhD, and André L. M. Verbeek, MD, PhD**

Routine follow-up in ovarian cancer patients is not expected to improve the life expectancy. The timing of detection of recurrent ovarian cancer is immaterial until markedly improved treatment options become available.

Geurts et al, Int J Gyn Cancer 2012

Early treatment based on CA125 alone vs. Delayed treatment.

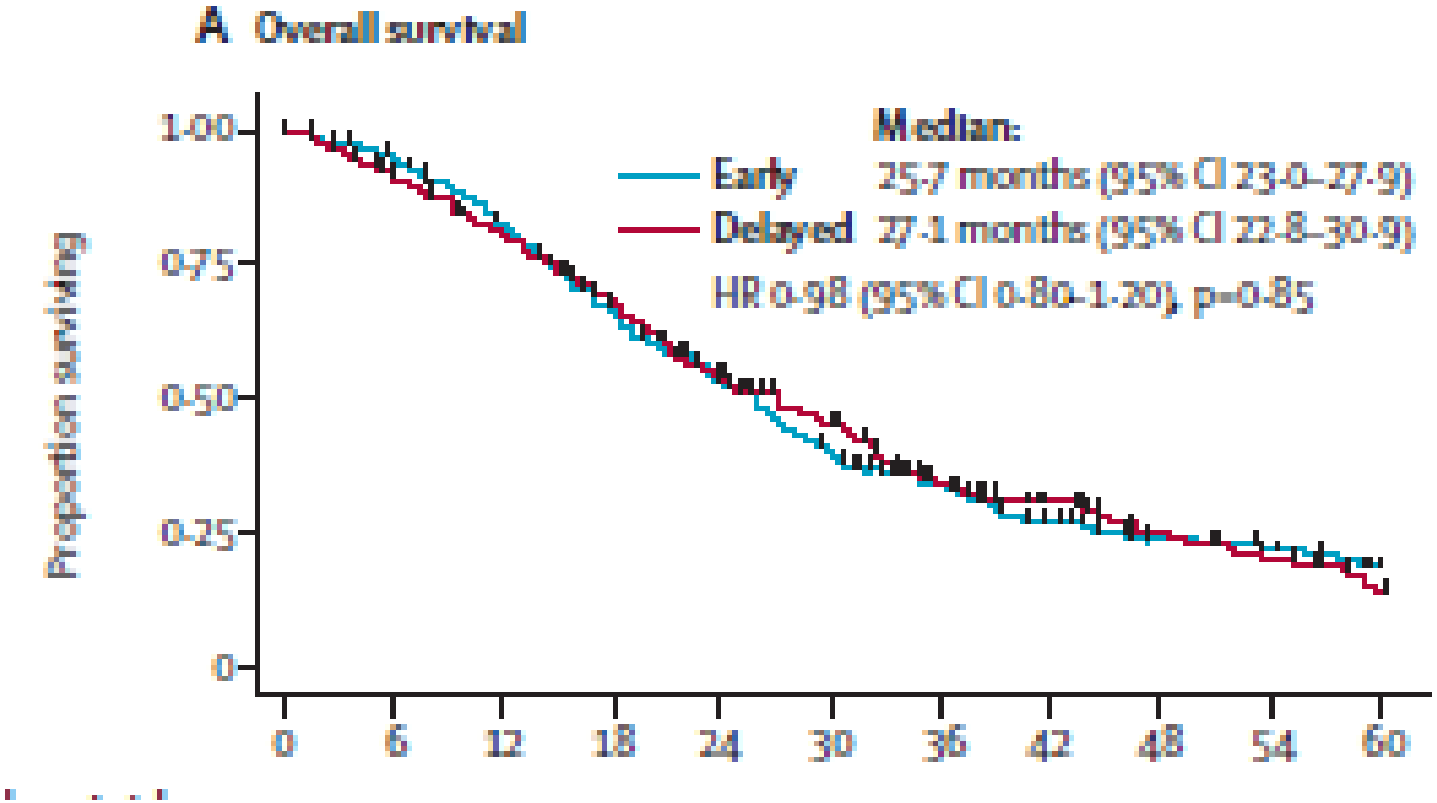
Patients with ovarian cancer in complete remission
After first pt-based chemo and normal CA125



MRC OV05/EORTC 55955

Rustin et al, Lancet 2010

Early treatment based on CA125 alone vs. Delayed treatment.



MRC OV05/EORTC 55955

Rustin et al, Lancet 2010

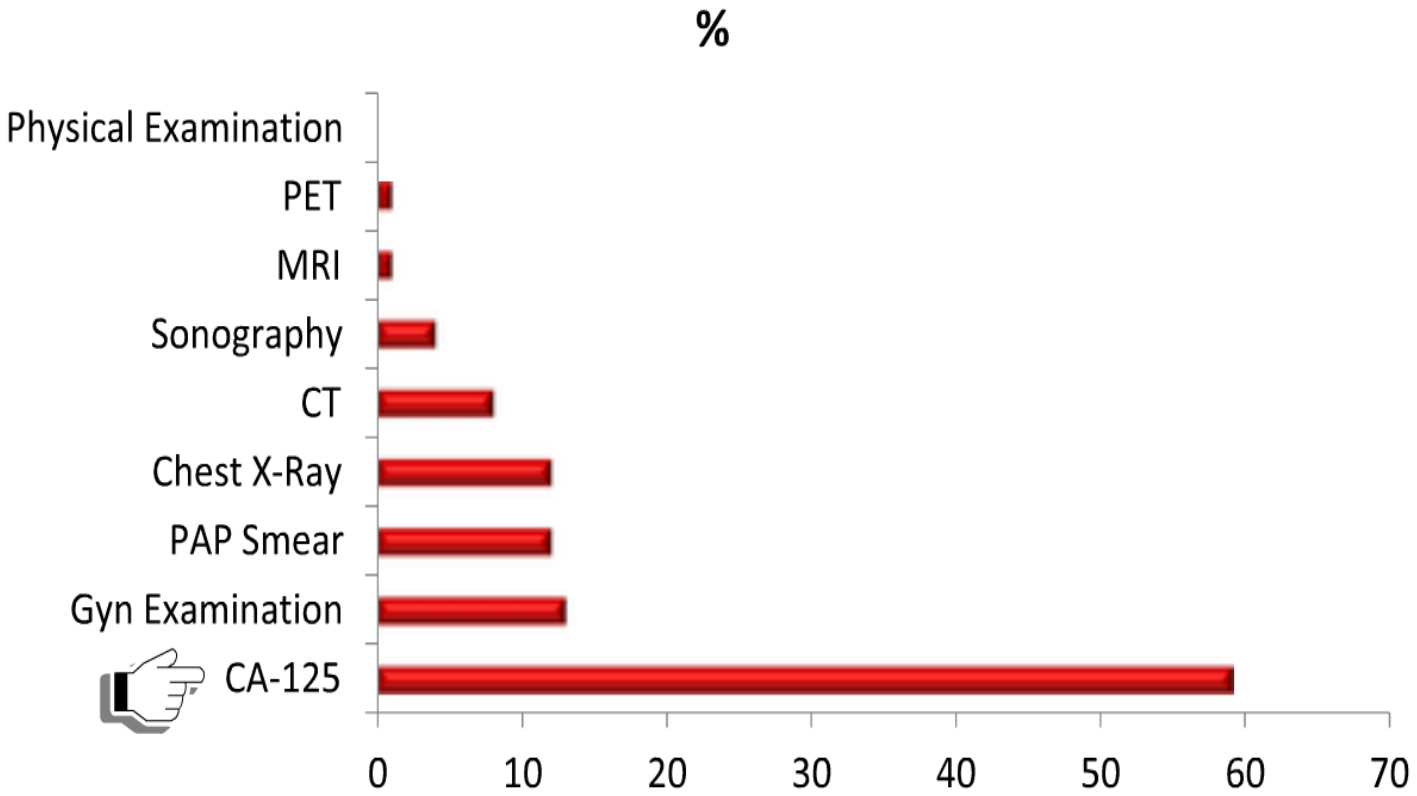
Deficiences OVO5/EORTC 55855

- Long accrual period
- Heterogeneous ovarian cancer patient population
- No control of initial treatment regimens
- No control of subsequent surgery or chemotherapeutic management for recurrence.
- Treatment type, number of cycles, number of treatments, and other important factors varied between the early and delayed groups
- Etc….

Morris and Monk 2010, Schwarz IJGC 2010

What do patients think about CA-125 monitoring in the follow-up?
Multicenter trial in 1060 ovarian cancer patients

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



Guelten Oskay-Oezcelik et al., ASCO 2009

Unmet needs during routine follow-up in ovarian cancer (patients' perspective)

- Help with fear about cancer spreading (25%)
- Concerns about worries of those close (20%)
- To be informed about things to help get well (20%)
- Uncertainty about future (19%)
- Lack of energy (18%).

Beesley et al, Psycho-Oncology 2012

Evaluation of follow-up strategies for patients with epithelial ovarian cancer following completion of primary treatment (Review)

Kew F, Galaal K, Bryant A, Naik R

- Lack of RCTs on most aspects of follow-up
- CA125: no survival benefit
- RCT needed to compare different types of follow-up on outcomes of
  - Survival
  - QoL
  - Psychological effects

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ESGO Statement on the Role of CA-125 Measurement in Follow-Up of Epithelial Ovarian Cancer

Consider CA-125 follow-up:

Patients after complete response on primary treatment for epithelial ovarian cancer, who

- have been or are being treated as part of a clinical trial
- are considered for (future) studies on second-line treatment;
- will not have routine (3 monthly) follow-up including regular imaging;
- may be eligible for secondary surgery at recurrence.

Van der Zee et al, IJGC 2012.

ESGO Statement on the Role of CA-125 Measurement in Follow-Up of Epithelial Ovarian Cancer

Individual discussions between patients and physicians should take place either at the time of diagnosis or at completion of chemotherapy, with the physicians explaining the rationale of follow-up procedures and why CA-125 may be measured but not necessarily lead to intervention.

Local teams are encouraged to give patients written information about this process.

Van der Zee et al, IJGC 2012.

Personal interpretation

- Rethink our follow-up protocols
- More emphasis on patients' needs
- A personalized follow-up plan needs to be discussed with every patients after completion of first line treatment.
- What, when and by whom ?

Conditions:

  - Education of patient and doctor

Case continued

A 56 yr old woman, otherwise healthy, has undergone complete debulking of a stage IIIc (one large omental tumor deposit) high grade serous ovarian cancer. Afterwards she received 6 cycles of carboplatin / paclitaxel. Two weeks after her last cycle of chemo she feels well and her CA125 is 6 kU/l.

After 16 months the patient feels well, at examination no signs of disease. However, her CA125 has gradually increased from 24 to 267 to 420 (4 wk interval). CT shows some ascites and 3-4 intraabdominal tumor deposits (3-4 cm).

Case continued

What would be your policy ?

- Wait and see until symptoms ?
- Start chemo ?
- Surgery ?

Surgery for recurrent ovarian cancer

Controversial role

- Missing data from prospective randomized trials
- Different studies with different groups of patients
  - Platinum refractory to platinum sensitive
  - Retrospective (LOROCSON / EORTC stopped prematurely)
  - Significant selection bias

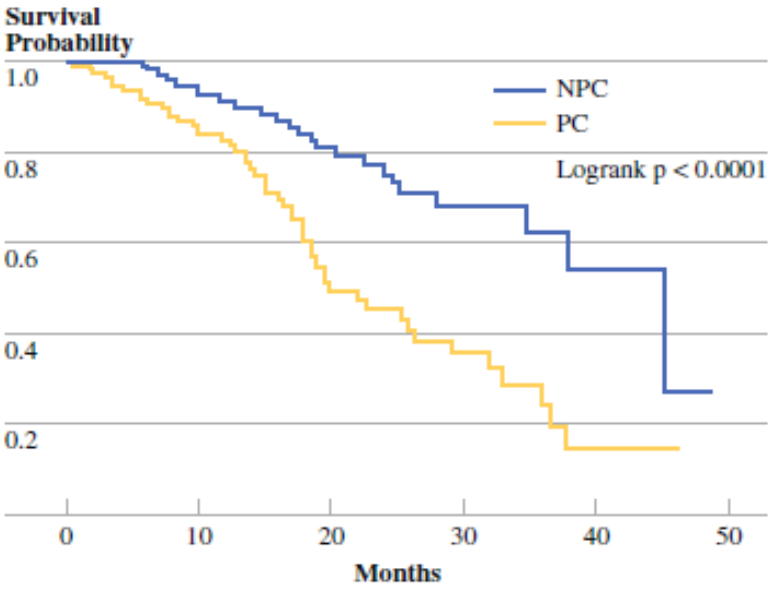
Lorusso et al Int J Surg Oncol 2012

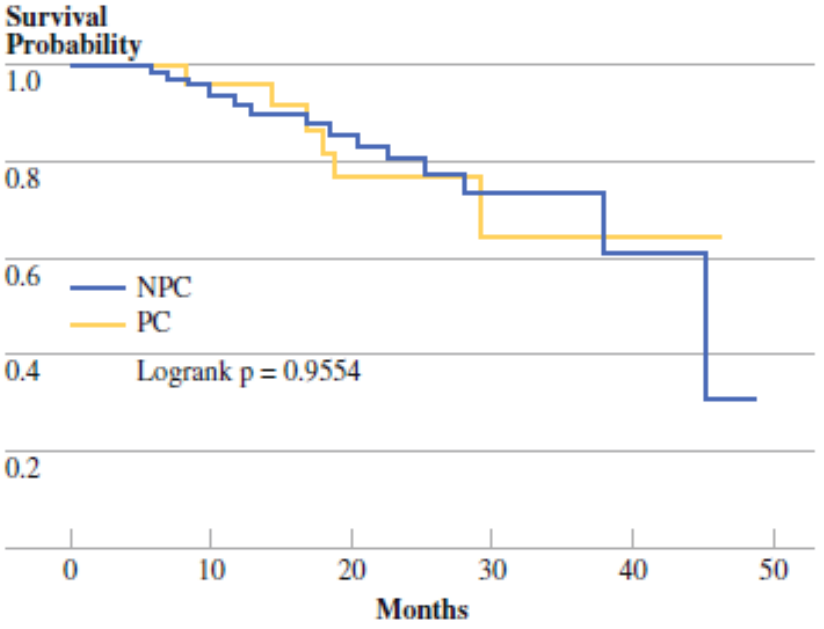
Ann Surg Oncol (2009) 16:1324–1330
DOI 10.1245/s10434-009-0357-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Surgery for Recurrent Ovarian Cancer: Role of Peritoneal Carcinomatosis: Exploratory Analysis of the DESKTOP I Trial About Risk Factors, Surgical Implications, and Prognostic Value of Peritoneal Carcinomatosis





Harter et al, Ann Surg Oncol 2009

Surgery for recurrent ovarian cancer DESKTOP 1.

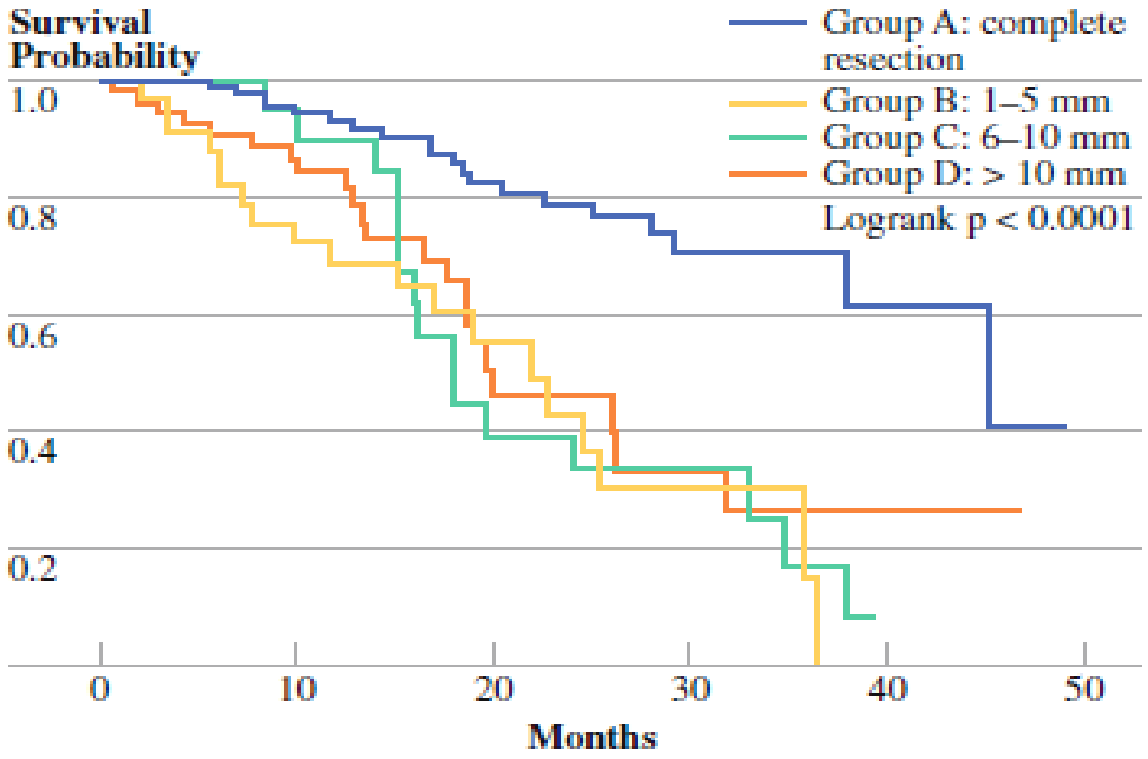


FIG. 2 Survival of patients with peritoneal carcinomatosis (PC) after cytoreductive surgery and residual disease

Harter et al, Ann Surg Oncol 2009

Surgery for recurrent ovarian cancer DESKTOP 1.

Aim of surgery (in pts with dfi > 6 mo)

No macroscopic disease

Predictive factors (AGO score):

- Good performance status
- Macroscopically complete resection at first surgery
- Absence of ascites > 500 ML at recurrence.

Harter et al, Ann Surg Oncol 2009

Prospective validation of AGO score and estimation of perioperative morbidity and mortality in patients with recurrent ovarian cancer and DFI > 6 mo.

DESKTOP 2.

Patients (operable and AGO score positive):

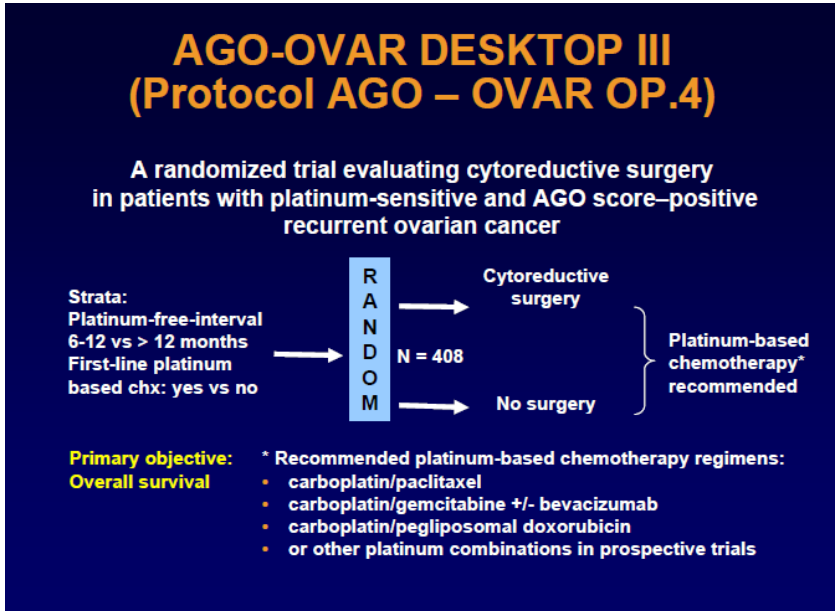
- Complete debulking in 76%
- Perioperative morbidity: 11%
- Perioperative mortality: 0.8 %

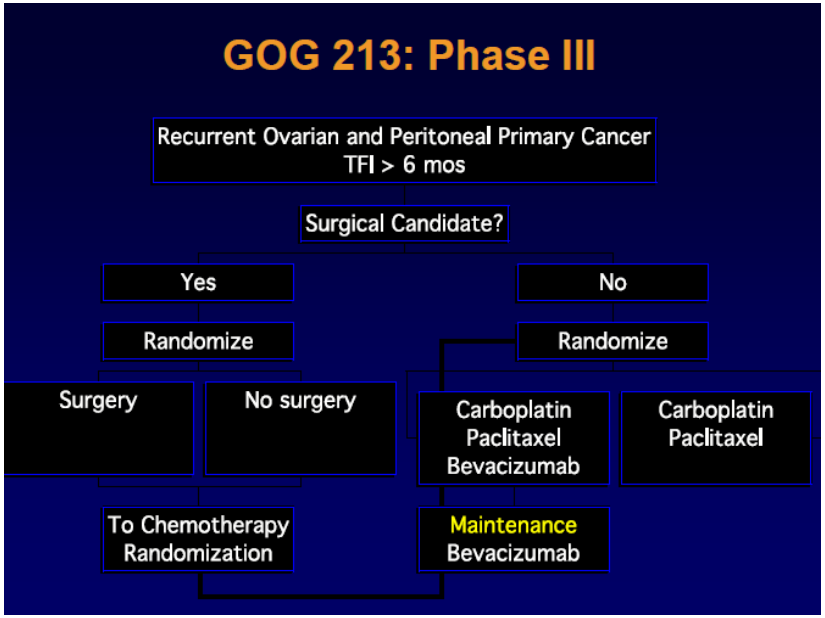
Very limited value of preoperative imaging.

Harter et al, Ann Surg Oncol 2009

No level I evidence to support surgery for recurrent ovarian cancer

Two ongoing RCTs





ClinicalTrials.gov Identifier:
NCT01166737

ClinicalTrials.gov Identifier:
NCT00565851

In the mean time…

- Current studies suggest that secondary cytoreductive surgery may have survival benefits in selected patients (eg AGO score positive).
- Complete cytoreduction is associated with increased overall post-recurrence survival time.

Bristow et al, Gyn Onc 2009

Summary

- In ovarian cancer efficacy of any follow-up modality with respect to survival is unproven.
- Role of surgery in recurrent ovarian cancer remains to be established.
- Every patient after completion of first line therapy deserves an individualised follow-up plan, taking into account patients' needs and wishes.

Back to our case

A 56 yr old woman, otherwise healthy, has undergone complete debulking of a stage IIIc (one large omental tumor deposit) high grade serous ovarian cancer. Afterwards she received 6 cycles of carboplatin / paclitaxel. Two weeks after her last cycle of chemo she feels well and her CA125 is 6 kU/l.

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