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Ovarian cancer

What kind of follow-up?

Anne-Claire Hardy Bessard (St Brieuc),
Patricia Pautier (Villejuif),
Dominique Berton-Rigaud (Nantes),
Nadine Dohollou (Bordeaux)

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Mass Screening

Screening for the general population: recommendations

- **There is no indication for mass screening programs for ovarian cancer via the annual assay of CA125 and/or transvaginal ultrasound in the general population**

Level 1
Grade A

Screening for the at-risk population:

- **Definition of the at-risk population** = women with the BRCA1-2 and HNPCC mutations + women without mutation but with a relevant family history

- **Methods:** CA125-Transvaginal ultrasound

- **See Reco INCa (French national cancer institute) 2009** + other learned societies
  (INCa web site: http://www.e-cancer.fr/, and NEJM 2009; screening for ovarian cancer)

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Follow-up Methods

Clinical examinations and laboratory tests during monitoring

- **Markers**
  - Increase in CA 125 precedes clinical recurrence in 56 to 94% of cases, by approximately 3 – 5 months. A second confirmatory assay reduces the incidence of false positives
  - CA19-9 and ACE are of no use in patients with elevated CA125 at the time of diagnosis, except in specific forms

- **Clinical examination and ultrasound**
  - The clinical examination appears to be more sensitive than ultrasound for the detection of pelvic recurrence
  - However, transvaginal ultrasound is useful for the follow-up of young patients treated with conservative surgery

Imaging examinations performed during follow-up: performance

Imaging indications are presented in the section: “recommendations for indications”

- **CT scan**
  - Sensitivity varies from 40-63%, specificity from 50-94%
  - PPV varies from 67 to 83% and NPV from 25 to 83%

➔ May be useful when discussing possible debulking surgery

- **MRI**
  - Not done routinely. May confirm the results of a doubtful CT scan as increase in specificity

- **PET-scan**
  - Pooled analysis of 6 studies found that sensitivity and specificity were 90% and 86%, respectively. Doubts about mucinous tumours

➔ Value for lymph node and extra-abdominal recurrences

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Follow-up indications

During treatment

- **CA125 should be monitored during treatment**

- **A response is defined as a decrease ≥ 50% in CA125**
  - **if it was ≥ 2N before the start of treatment**
  - **if the decrease is confirmed at 28 days**
    - the CA125 level is not reliable after surgery on the pleura or peritoneum. Therefore, caution should be exercised when interpreting the CA125 level after surgery

- **Imaging during chemotherapy**
  - R0 surgery: no initial imaging before commencing chemotherapy
  - Incomplete surgery
    - Initial CT scan before chemotherapy
    - CT scan at the end of chemotherapy if initial scan abnormal

Early chemotherapy after isolated increase in CA125

- **Compared to chemotherapy started after onset of symptoms, early chemotherapy:**
  - Starts 4.8 months earlier when second line and 4.6 months earlier if subsequent line
  - Does not increase global survival (HR=0.98; 95%CI=0.80, 1.20; p=0.85 and absolute difference at two years 0.7% (95%CI -7.6, 4.5%)
  - Does not improve quality of life

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Rustin G et al. Lancet. 2011

Utility of CA125 for surgery to treat recurrence

- **Retrospective study by Fleming 2011**
  - 74 patients who underwent cytoreduction for recurrence
  - Optimal surgery: better overall survival (47 vs. 23 months, p<0.0001
  - Each week of delay after elevation of CA125 is correlated with a 3% risk of not achieving optimal surgery
- **Retrospective study by Tanner 2010**
  - 121 patients with disease recurrence (RC after 1st treatment)
  - 22 symptomatic, 99 asymptomatic detected from CA125,
    - same PFS at time of recurrence (22.6 vs 24.8 months)
    - same surgery rates at recurrence (32% vs 41%,NS)
    - but more cases of optimal surgery when recurrence is asymptomatic (57% vs 90%, p = 0.053) and
  - Better survival after recurrence in the asymptomatic patients (45 vs 29,4 months, p= 0.006) and better overall survival (71.9 vs 50.7 months, p = 0.004).

Follow-up after chemotherapy Recommendations (1)

- CA125 levels rise before clinical recurrence (Rustin)
- Standard follow-up includes a clinical examination and possibly a marker assay every three months, without imaging – **Expert opinion**
- Value of monitoring using CA125 for the diagnosis of early recurrence for surgical treatment of recurrence (N Fleming 2011) **Level 2 Grade B**

Follow-up after chemotherapy. Recommendations (2)

- Radiological examination if increase in markers or symptoms – **Expert opinion**
- Value of PET scan if surgery potentially indicated – **Expert opinion**
- No chemotherapy recommended on basis of increase in markers only – **Level 1 Grade** A

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Follow-up for special cases

Follow-up: special cases

Level 2
Grade B

- **Treatment with mouse antibodies**
  - May interfere with CA125 levels (human anti-mouse antibodies).
    No modification of treatment on basis of CA125 alone
  - No recommendations for other targeted therapies
- **CA125 normal at diagnosis**
  - Rare at diagnosis (98% of stage III-IV have high pre-operative CA125 and 67% of stages I-II)
  - Recommendation: clinical monitoring, imaging if symptoms emerge
- **Mucinous forms**
  - Recommendations: approach similar to serous forms Assay of CA 125. If CA125 initially normal, ACE and CA 19-9 assays

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Additional slides

Screening methods

CA125 alone (low Se and Sp)

CA125 with Skates algorithm (Se=80% Sp=98%**)**

Ultrasound (TVUS)= **many scoring index false positives** (Se=89%,Sp=70%), **Colour Doppler** (?**)**

Multimodality = CA125+ TVUS: improvement in specificity (99.9%) **and PPV** (26.8%**)**

New markers (HE4/ROMA) **and proteonomic study: currently being evaluated**

3 randomised mass screening studies

Shizuoka study (Int J Gynecol Cancer 2008) **=**

- **Control group vs annual TVUS + Ca 125**;
- FU 9.2 years. Objective: detection of early stage disease;
- 27 detected, 8K interval vs 32K (control group);
- St I 63% vs 38% NS; **33 surgery/**1K

UKCTOCS study (Lancet 2009) **=**

- **Control group** vs annual **TVUS** vs **MMS** (CA125 algorithm then US)
- Preliminary results after 4 years. Objective: survival
- Se,Sp,PPV =**89.4 / 99.8 / 43.3** (MMS) vs **84.9 / 98.2 / 5.5** (TVUS)
- **8 surgery / 1K (MMS) 20 surgery / 1K (TVUS)**

PLCO (JAMA 2011) **=**

- **Control group** vs annual **CA125+TVUS**
- Objective = survival; NB = few early stage cases;
- 19 surgery/1K;
- 212k/118 DC vs 176K/100 DC RR=1.18

Post-treatment follow-up

MRC OV05 randomised study and EORTC 55955 trials

Gordon Rustin and &

- To investigate the **benefit of early chemotherapy** for relapsed ovarian cancer, based on a raised CA125 level alone, versus delayed chemotherapy based on conventional clinical indicators

Study design

Ovarian cancer in complete remission
After a first-line of platinum-based chemotherapy
and normal CA125

Recruitment between 1997-2008

CA125 LEVELS RECORDED EVERY 3 MONTHS BLIND CONDITIONS

N = 1442

If CA125 ≥ 2N RANDOMISATION

N = 529

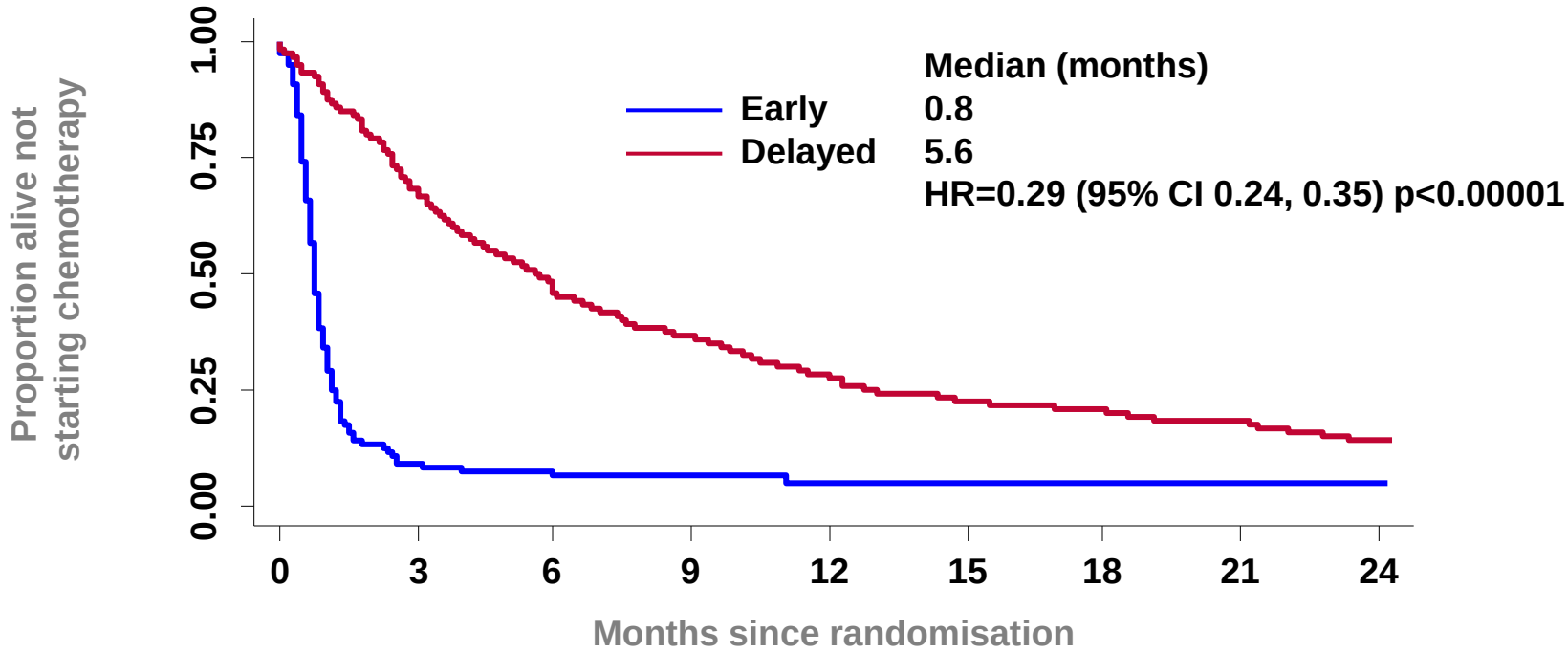
Healthcare professional and patient informed
Early treatment

N = 265 256 CT (96%)

Healthcare professional and patient not informed
Treatment delayed until clinically indicated

N = 264 233 CT (88%)

Time from randomisation up to 2nd line chemo

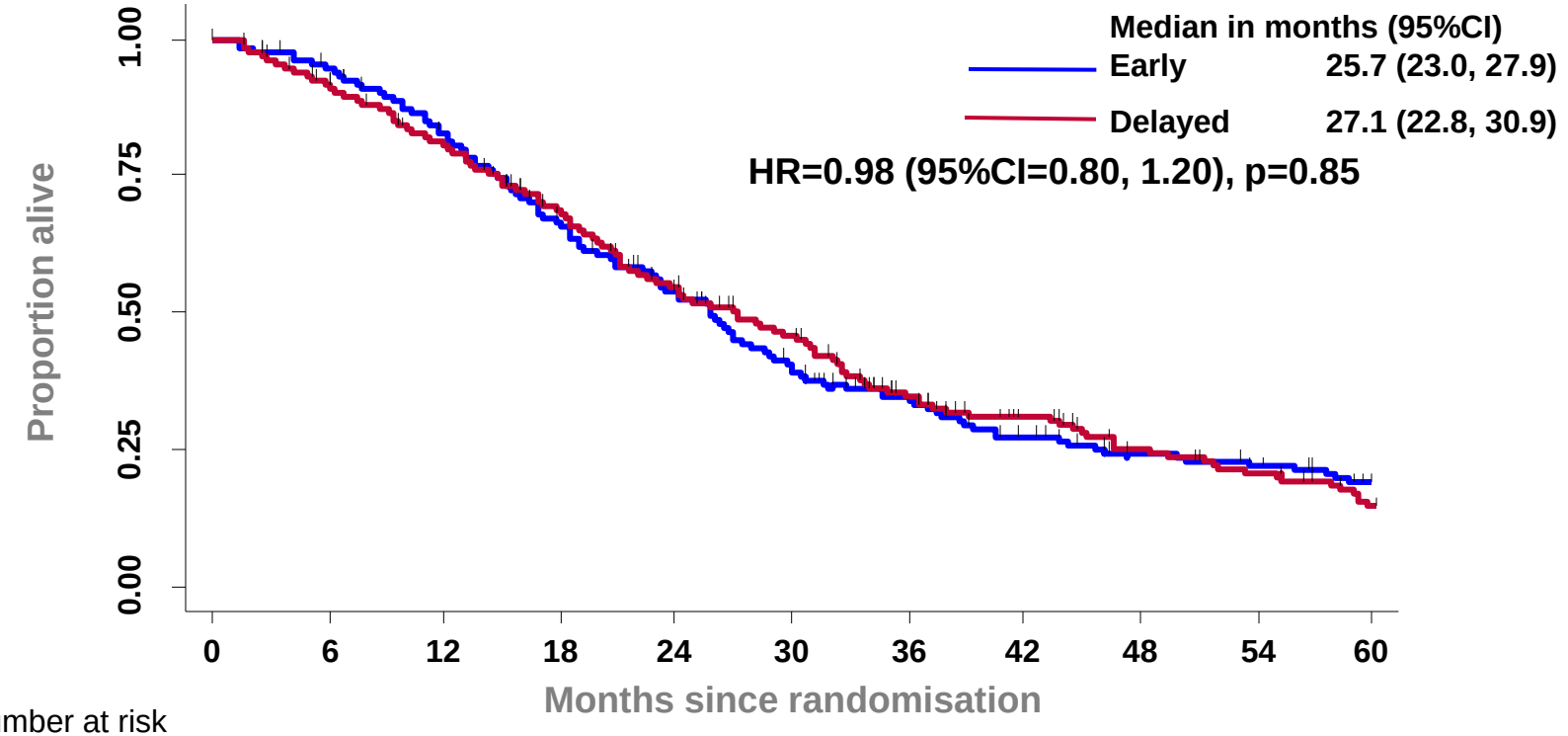


Number at risk

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

Median follow-up 56.9 months

Overall survival

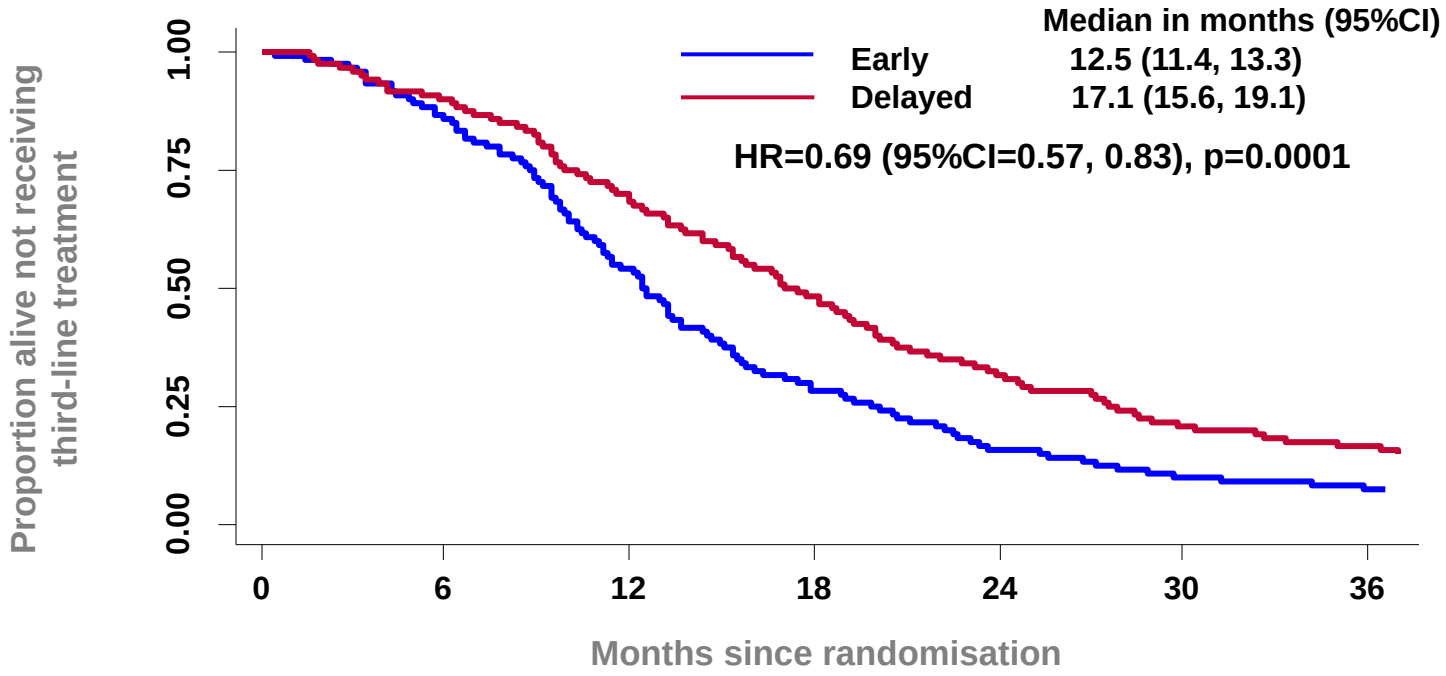


Number at risk

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

Median follow-up 56.9 months 370 deaths (70%)

Time from randomisation up to 3rd line or death



Number at risk

Early	265	224	138	70	38	22	17
Delayed	264	232	173	117	76	48	35

67% in early arm and 54% in the delayed arm received a third line p = 0.0021