What kind of follow-up?

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Ovarian cancer

Mass Screening
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

Ovarian cancer

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
Follow-up indications

Ovarian cancer
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

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 1\(^{st}\) 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**
Follow-up for special cases

Ovarian cancer
Follow-up: special cases

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
Ovarian cancer

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 proteonomics 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

If CA125 ≥ 2N RANDOMISATION

Healthcare professional and patient informed Early treatment

Healthcare professional and patient not informed Treatment delayed until clinically indicated

N = 1442
N = 529
N = 265 256 CT (96%)
N = 264 233 CT (88%)
Proportion alive not starting chemotherapy

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Number at risk

Median follow-up 56.9 months

Median (months)
- Early: 0.8
- Delayed: 5.6

HR=0.29 (95% CI 0.24, 0.35) p<0.00001
Overall survival

Median in months (95%CI)
- Early: 25.7 (23.0, 27.9)
- Delayed: 27.1 (22.8, 30.9)

HR = 0.98 (95%CI = 0.80, 1.20), p = 0.85

Median follow-up 56.9 months  370 deaths (70%)
Time from randomisation up to 3rd line or death

HR=0.69 (95%CI=0.57, 0.83), p=0.0001

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