

**CA 125 in Ovarian Cancer: EGTM
Guidelines for Clinical Use**

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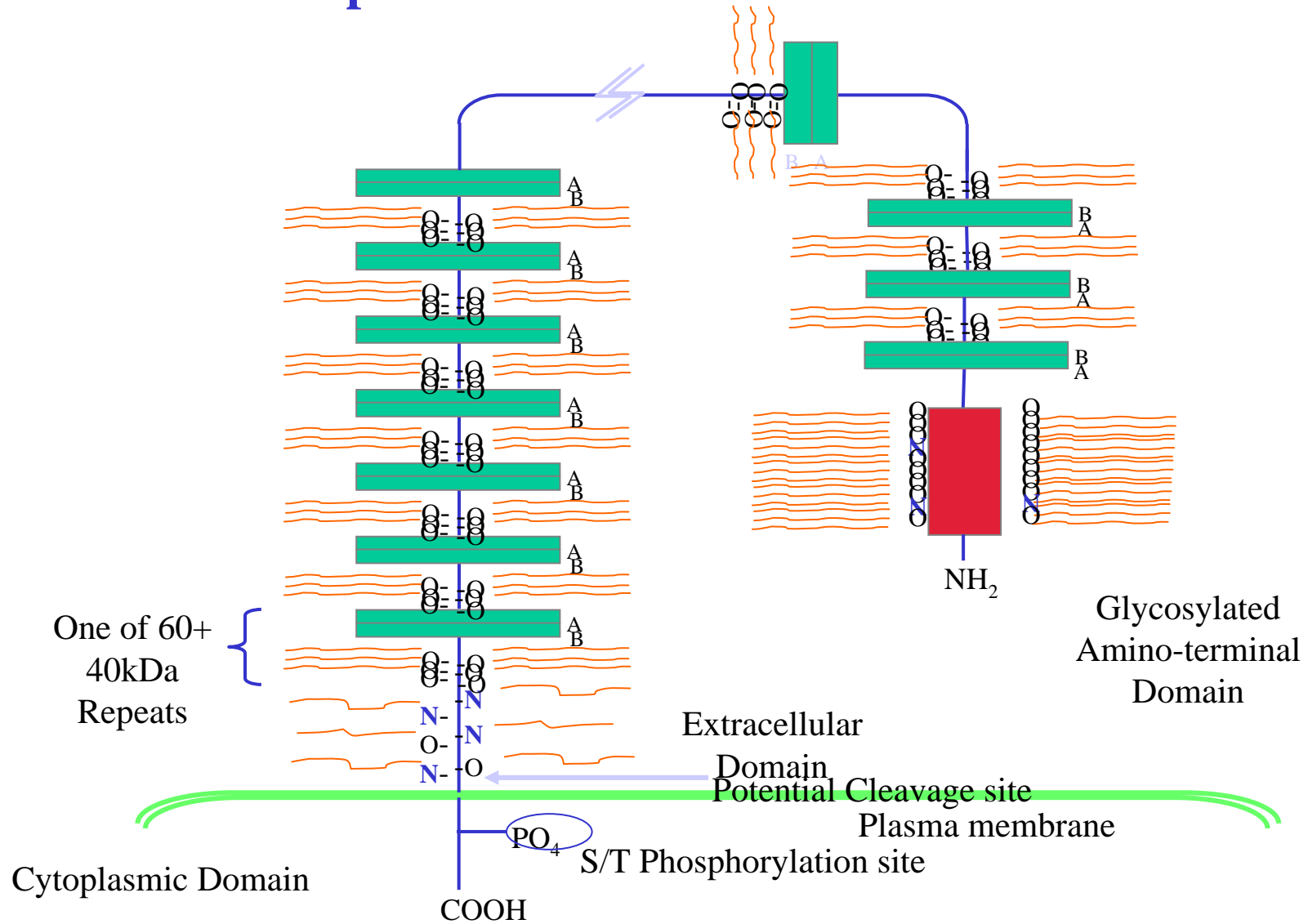
Ovarian Cancer: Introduction

- 4th most common cause of cancer related death in women
- Most lethal gynecological malignancy
- Multiple types of ovarian cancer including epithelial, germ cell, sex-cord and metastatic
- Epithelial type comprise 90% of all ovarian cancers

CA 125: Introduction

- **The gold standard marker for ovarian cancer**
- **High molecular weight glycosylated protein, MUC16**
- **Physiological function is unknown**

Proposed Structure of CA125



Aims

To present the EGTM (2005) guidelines for the use of CA 125 in:

- Screening for ovarian cancer
- Diagnosis of pelvic masses
 - Determining prognosis
 - Monitoring therapy
- Surveillance following therapy

Factors Affecting CA 125 Levels in Healthy Subjects, I

- **Age:** Levels higher in pre than post menopausal women
- **Race:** Levels higher in Caucasian than Asian or African women
- **Menstrual cycle:** Some women have higher levels at time of menstruation
- **Pregnancy:** Levels increase during pregnancy, especially in the first trimester

Pauler et al, Cancer Epid Biomarkers Prev 2001:10:4 89

Factors Affecting CA 125 Levels in Healthy Subjects, II

- **Smoking: decreases levels,**
- **Caffeine: decreases levels**
- **HRT and OC: no affect**
- **Hysterectomy: decreases levels**

**Pauler et al, Cancer Epid Biomarkers Prev
2001:10:489**

Rationale for Screening for Ovarian Cancer

- 5-yr survival for advanced disease: 10%
- 5-yr survival for early disease: 90%
- Currently 65-75% of ovarian cancers diagnosed at advanced stage but only 25-35% diagnosed with disease confined to the ovary

Kristensen & Trope, Lancet 1997;349:113-117

Challenges of Ovarian Cancer Screening

- A premalignant precursor lesion for ovarian cancer has not been identified
- Ovarian cancer is rare, approx 40 per 100,000 postmenopausal women
- Consequence of a positive screening test is surgery
- Possibility that the complications of surgery for false positive results will outweigh benefits of early detection in women with true positive results

Requirement of an Ovarian Cancer Screening Strategy

- Must have a minimum PPV of 10% (ie, no more than 9 false positives for each true positive).
- In order to achieve this in the general population of postmenopausal women, screening test(s) must have a specificity of >99.6% and a sensitivity of >75%

Jacobs and Bast, 1989, Human Reprod 1989;4:1

Bast et al. J Clin Oncol 2003;21:200s-205S

CA 125: As a Screening Test for Ovarian Cancer

- Lack of sensitivity for early disease
- Lack of specificity, especially in premenopausal women

Lack of sensitivity and specificity when combined with the low prevalence of ovarian cancer in the general population means that use of CA 125 alone has a low positive PPV in asymptomatic women

CA 125: As a Screening Test for Ovarian Cancer

- **Assume CA 125 has a sensitivity of 80% and a specificity of 99% and prevalence of ovarian cancer in the general population of 0.0003,**
- **CA 125 would have a PPV of 2.3%**

Hensley et al. Oncology 2000;14:1601

Strategies to Enhance CA 125 as a Screening Test for Ovarian Cancer

- **Use multimodal screening: CA 125 + US**
- **Monitor sequential changes in serial levels of CA 125**
- **Combine assay of CA 125 with complimentary markers**

CA 125 + US: Pilot Screening for Ovarian Cancer

- **Postmenopausal women >45 yr (n=22,000)**
- **Initial test, CA 125**
- **If CA 125 > 30 kU/L, then US**
- **If ovarian volume > 8.8 ml, refer for gynecological investigation**

Jacobs et al, Lancet 1999;353:1207

CA 125 + US: Pilot Screening for Ovarian Cancer

- **In women screened, 29 had surgery and 6 cancers detected (ie, PPV, 20.7)**
- **In women who developed cancer, survival was longer in the screened than in the control group ($p = 0.01$)**
- **9 deaths in screened vs 18 in control group ($p = ns$)**

Jacobs et al, Lancet 1999;353:1207

Ovarian Cancer Screening Trials in Progress

UKCTOCS

- **200,000 women will be randomized to either a control arm, screening with US or combined US + CA 125**
- **Results expected approx 2015**

PLCO

- **CA 125 + US vs control groups**

CA 125 as a Screening Test for Ovarian Cancer: EGTM Guidelines

- **Although screening with CA 125 can detect ovarian cancer in some women, there is no evidence that screening reduces mortality.**
- **The EGTM therefore recommends that outside of a clinical trial, that screening for ovarian cancer in asymptomatic women without a family history of the disease using either CA 125 alone or in combination with other modalities should not be carried out**

CA 125 in the Differential Diagnosis of Benign and Malignant Pelvic Masses: EGTM Guidelines

Since a knowledge of preoperative levels of CA 125 may help differentiate between benign and malignant pelvic masses, the EGTM Panel recommends its measurement in postmenopausal women presenting with such masses. Patients with elevated levels (eg > 35 U/L) should be considered for referral to a surgeon who routinely performs thorough abdominal exploration, node sampling, omentectomy and cytoreductive operations

CA 125: as a Prognostic Factor in Ovarian Cancer

Several, small-scale retrospective studies have shown that either the rate of fall of CA 125 following initial chemotherapy or the absolute levels after 1, 2 or 3 courses of chemotherapy can be used to predict short-term outcome.

CA 125 as a Prognostic Marker for Ovarian Cancer: UK Multicenter Study

Prognostic factors investigated:

- **CA 125 half life**
- **Absolute value of CA 125 after CT X 2**
 - **> or < 7-fold decline in CA 125**
 - **Patient age,**
 - **Tumor stage**
 - **Residual tumor bulk**

Fayers et al. Int J Gynecol Cancer 1993;3:285

CA 125 as a Prognostic Marker for Ovarian Cancer: UK Multicenter Study

- Most important factor in predicting patient outcome was absolute value of CA 125 after 2 courses of chemotherapy.**
- However, the best predictor gave a false positive rate of 20%**

Fayers et al. Int J Gynecol Cancer 1993;3:285

CA 125: as a Prognostic Factor in Ovarian Cancer: EGTM Guidelines

Based on available data, the EGTM Panel conclude that the prognostic information supplied by CA 125 during initial chemotherapy is not accurate enough to manage individual patients. CA 125 levels during the early phases of initial chemotherapy should therefore not be used to predict long-term outcome

Monitoring Response to Chemotherapy in Ovarian Cancer

- Apart for those with localised disease (ie, stages 1a/1b), patients with ovarian cancer receive chemotherapy following surgery**
- Monitoring response is particularly difficult using standard criteria**
- Approx 50% of patients with ovarian cancer have non-evaluable disease by WHO or RECIST criteria**
- Approx 2X as many patients can be monitored using CA 125 compared to standard criteria**

CA 125 Response Criteria

- **50% response definition: If there is a 50% decrease in CA 125 levels from 2 initially elevated samples, the sample showing a 50% decrease must be confirmed**
- **75% response definition: If there has been a decrease in CA 125 levels of more than 75% over 3 samples.**

Rustin, J Clin Oncol 1996;14:1545

CA 125 Response Criteria: Validation

- **Initially based on a pilot study with subsequent testing in 2 further studies**
- **Validated in 19 phase 2 clinical trials investigating 14 different cytotoxic drugs for the treatment of ovarian cancer**

Rustin et al, J Clin Oncol 1996;14:1545

Rustin et al, J Clin Oncol 20018:1733

Response Rate to Paclitaxel: Effect of Different CA 125-Defined Response

CA125 change	Response rate %
• 15% Change	62
• 90% decrease	10
• 50% decrease	42
• Rustin 50/70%	21
• Clinical response	21

Eisenhauer et al. J Clin Oncol 1994;12:2654

CA 125 Response Criteria: GCIG

- **Response has occurred if there is at least a 50% fall in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 20 days.**
- **Patients can be evaluated by CA 125 only if they have a pretreatment value that is 2X upper limit of normal**

Rustin et al. JNCI 2004;96:487

Possible Further Approach for Defining CA 125-Based Response

Based on both:

- **Analytical variation of assay and**
- **Intra-individual biological variation**
- **For a change to be significant, it should exceed random fluctuations due to both analytical and biological variation**

Tuxen et al, Scand J Clin Lab Invest 2000;69:713

Tuxen et al, Br J Cancer 2001;84:1301

CA 125: Use in Monitoring Chemotherapy: EGTM Guidelines

- The EGTM Panel recommends the use of CA 125 for monitoring chemotherapy in patients with ovarian cancer.**
- For evaluating response based on CA 125, either the 50 or 70% response of Rustin or the 2004 GCIG criteria may be used**

CA 125: Use in Follow-up After Initial Chemotherapy

- **Serial CA 125 levels can provide a short lead time (3-4 months) for the detection of relapses**
- **Recurrent ovarian cancer is incurable**
- **If palliative therapy is to have any real value, early administration might be expected to be more effective than late administration**
- **Any potential advantage from palliative therapy must be balanced against the side effects and decreased quality of life**

CA 125: Use in Follow-up After Initial Chemotherapy

**Value of CA 125 during follow-up
after initial chemotherapy in
enhancing outcome or increasing
quality of life is unclear**

Role of CA 125 in Follow-up After Initial Treatment: EGTM Guideline

- There is no evidence at present that initiating treatment in an asymptomatic patient based on rising CA 125 levels improves outcome.**
- The EGTM Panel therefore recommend that serial measurements of CA 125 should not be routinely carried out on patients with a prior diagnosis of ovarian cancer and who are apparently well, unless part of a clinical trial**

Role of CA 125 in Follow-up After Initial Treatment: EGTM Guideline

- **However, should a patient develop symptoms suggestive of relapse, CA 125 levels should be determined both to confirm recurrent disease and establish a base-line value for possible future therapy**
- **Some patients however, may wish to have serial levels of CA 125 determined during follow-up**
- **The ultimate decision to use CA 125 must be taken in the best interest of the patient**

CA 125 Defined Disease

Progression: EGTM Guidelines

- **Progression has occurred if there is a confirmed doubling of CA 125 from the upper limit of normal or a doubling of nadir value (GCIG definition). Rustin, J Clin Oncol 2003;21:187s**
- **For a change to be significant, it should exceed random fluctuations due to both analytical and biological variation**

Tuxen et al, Scand J Clin Lab Invest 2000;69:713

Tuxen et al, Br J Cancer 2001;84:1301

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Int J Gynecol Oncol 2005;15:679-691