

“I MARKERS OVARICI: SE, QUANDO E COME?”

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DEFINITION

The term of tumor marker is applied to all substances produced and released either by tumor cells or by host cells and whose presence may be detected in the serum or other biological fluids, behaving as an indicator of the presence of the tumor.

(Ballesta 1993)



Even if very few currently used tumor markers can be considered ideal, some tumor-associated antigens (mainly identified with the monoclonal antibody technology) may represent useful biochemical tools for the management of patients with gynecological malignancies, and particularly of those with ovarian carcinoma

(Gadducci 2004)



Evidence for the clinical use of tumour markers

Michael J Duffy^{1,2}

Abstract

Testing for tumour markers should only be performed if it results in a better patient outcome, increased quality of life or reduced overall cost of care. Ideally, the clinical value of a tumour marker should be validated in a large prospective study or a meta-analysis of small-scale retrospective/prospective studies (i.e. a level 1 evidence study) prior to routine use. Markers that have been validated in such a level 1 evidence study include carcinoembryonic antigen in the surveillance of patients with diagnosed colorectal cancer, alphafetoprotein, human chorionic gonadotrophin and lactate dehydrogenase for evaluating prognosis in patients non-seminomatous germ cell tumours, CA 125 for monitoring therapy in patients with ovarian cancer, oestrogen receptors for predicting response to hormone therapy in breast cancer, HER-2 for predicting response to trastuzumab in patients with advanced breast cancer and urokinase plasminogen activator/plasminogen activator inhibitor type 1 for determining prognosis in breast cancer. Although currently in widespread use, the value of prostate-specific antigen in screening for prostate cancer has yet to be validated in a large prospective randomized trial.

Ann Clin Biochem 2004; **41**: 370–377

FEATURES

The ideal tumor markers should have a high sensitivity (SE) and a high specificity (SP), in order to discriminate cancer patients from healthy subjects or patients with benign conditions, and should be secreted into the circulation in concentrations proportional to tumor burden and activity

(Gadducci 2004)

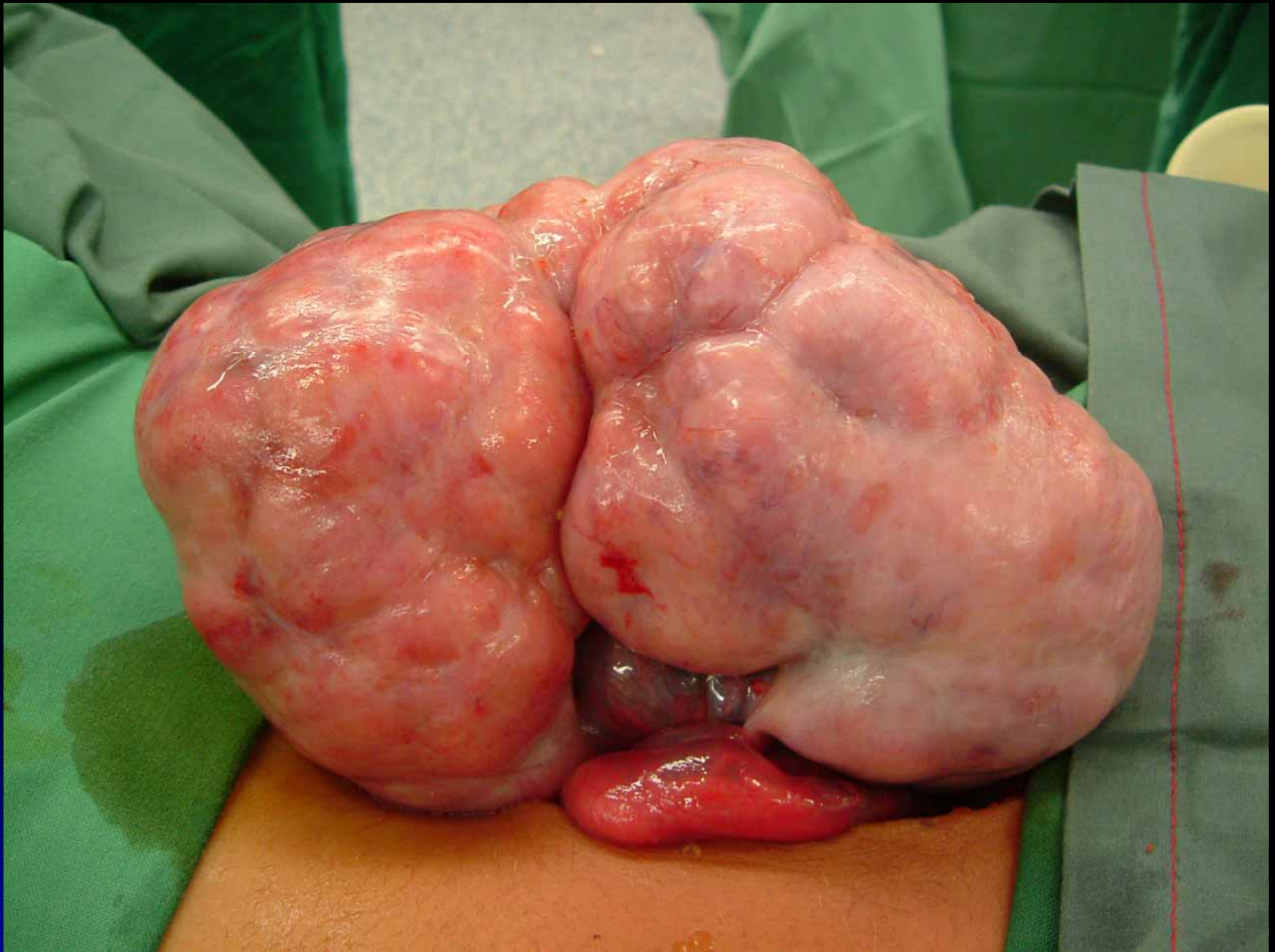
OVARIAN GERM CELL TUMOR

Alpha-fetoprotein (α FP) is produced always by yolk sac tumor, often by embryonal carcinoma and polyembryoma, and sometimes by immature teratoma

(David 2002, Huang 2002)

Beta subunit of the human chorionic gonadotropin (β HCG) is elevated in patients with choriocarcinoma, embryonal carcinoma, polyembryoma and mixed germ cell tumors containing choriocarcinomatous elements

(Talerman 1994- Takemori 1998)





Review

Human chorionic gonadotropin in cancer

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Abstract

Human chorionic gonadotropin (hCG) is mainly used for detection and monitoring of pregnancy and pregnancy-related disorders but it is also an extremely sensitive and specific marker for trophoblastic tumors of placental and germ cell origin. Thus treatment of relapsing choriocarcinomas and testicular germ cell tumors is often initiated on the basis of rising hCG levels even in the absence of clinical or histological evidence of a relapse. While these tumors mostly produce the intact heterodimeric hormone consisting of an α (hCG α), and a β subunit (hCG β), many nontrophoblastic tumors produce only hCG β . This is usually a sign of aggressive disease and elevated serum levels of hCG β are strongly associated with poor prognosis. Elevated serum levels are observed in 45–60% of patients with biliary and pancreatic cancer and in 10–30% of most other cancers. Methods that detect hCG and hCG β together are mainly used for measurement of hCG-like immunoreactivity in serum. However, the reference range for hCG is 5–8 fold higher than that for hCG β and thus moderately elevated levels can be identified only with a specific and sensitive hCG β assay.

CA 125 IN OVARIAN CANCER: EUROPEAN GROUP ON TUMOR MARKERS GUIDELINES FOR CLINICAL USE

M.J. DUFFY, J.M. BONFRER, J. KULPAS, G.J.S. RUSTIN, G. SOLETORMOS, G.C. TORRE, M.K. TUXEN, M. ZWIRNER
Int J Gynecol Cancer 2005; 15:679-691.

Abstract

CA125 is currently the most widely used tumor marker for ovarian epithelial cancer. The aim of this article is to provide guidelines for the routine clinical use of CA125 in patients with ovarian cancer. Due to lack of sensitivity for stage I disease and lack of specificity, CA125 is of little value in the detection of early ovarian cancer. At present, therefore, CA125, either alone or in combination with other modalities, cannot be recommended for screening for ovarian cancer in asymptomatic women outside the context of a randomized controlled trial. Preoperative levels in postmenopausal women, however, may aid the differentiation of benign and malignant pelvic masses. Serial levels during chemotherapy for ovarian cancer are useful for assessing response to treatment. Although serial monitoring following initial chemotherapy can lead to the early detection of recurrent disease, the clinical value of this leadtime is unclear. CA125 is the ovarian cancer marker against which new markers for this malignancy should be judged.

STRUCTURE DISTRIBUTION OF CA 125 IN NORMAL TISSUES

Antigenic determinant on glycoprotein with molecular weight ranging from 200 to 2000 kd, present in:

- Normal adult tissues derived from coelomic epithelium (endometrium, endocervix, fallopian tube)
- Cells of mesothelial origin (pleural, pericardial, peritoneal cells)
- Epithelia of kidney, lung, stomach, gallbladder, pancreas and colon

CA 125 HAS A WIDESPREAD DISTRIBUTION AND
LACKS ORGAN SPECIFICITY

(Duffy 2005)

SERUM CA 125 LEVELS IN HEALTHY SUBJECTS

- Premenopausal women > postmenopausal women
- Time of menstruation ↑
- Pregnancy ↑
- Smoking ↓
- Caffeine consumption ↓

(Duffy 2005)

INCREASED CA 125 IN GYNECOLOGICAL BENIGN DISEASES

- Endometriosis
- Uterine myomas
- Acute and chronic salpingitis
- PID
- Meigs syndrome

(Jacobs and Bast 1989, Tuxen 2001)

INCREASED CA 125 IN NONGYNECOLOGICAL BENIGN DISEASES

- Liver cirrhosis
- Chronic active hepatitis
- Acute and chronic pancreatitis
- Lung and pleural diseases
- Any disorder that inflames the peritoneum, pericardium or pleura

(Jacobs and Bast 1989, Tuxen 2001)

INCREASED CA 125 IN NONOVARIAN CANCERS

Elevated levels of CA 125 can occur in most types of adenocarcinoma (breast, colorectum, pancreas, lung, endometrium, cervix, fallopian tube), especially if distant metastases are present

(Jacobs and Bast 1989, Tuxen 2001)



SERUM CA 125 LEVELS AND DISEASE STAGE IN OVARIAN CANCERS

STAGE FIGO

● I

● II

● III

● IV

CA 125 INCREASED

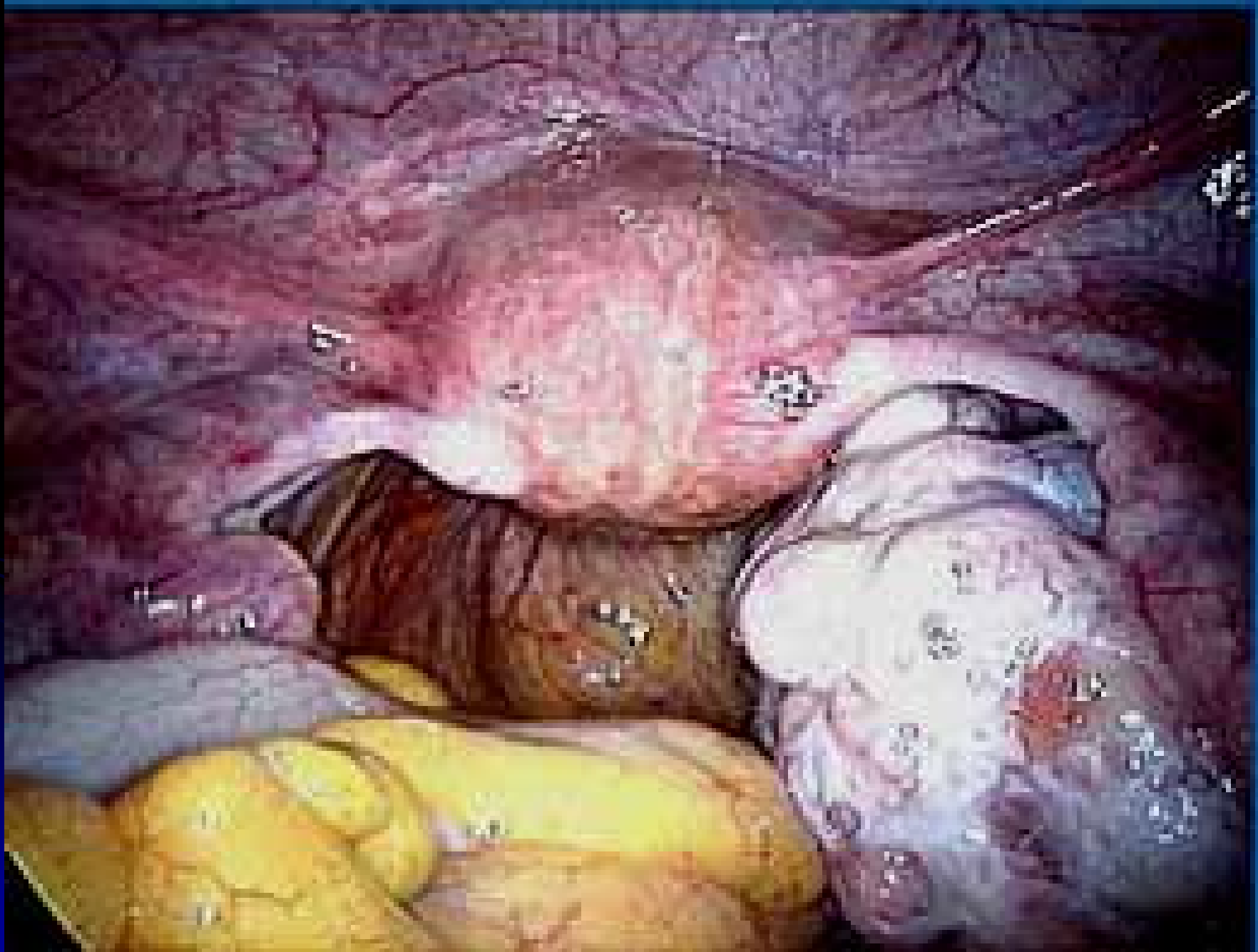
● 49/96 (50%)

● 55/61 (90%)

● 199/216 (92%)

● 77/82 (94%)

(Jacobs and Bast 1989)





SERUM CA 125 LEVELS AND HISTOLOGY TYPE IN OVARIAN CANCERS

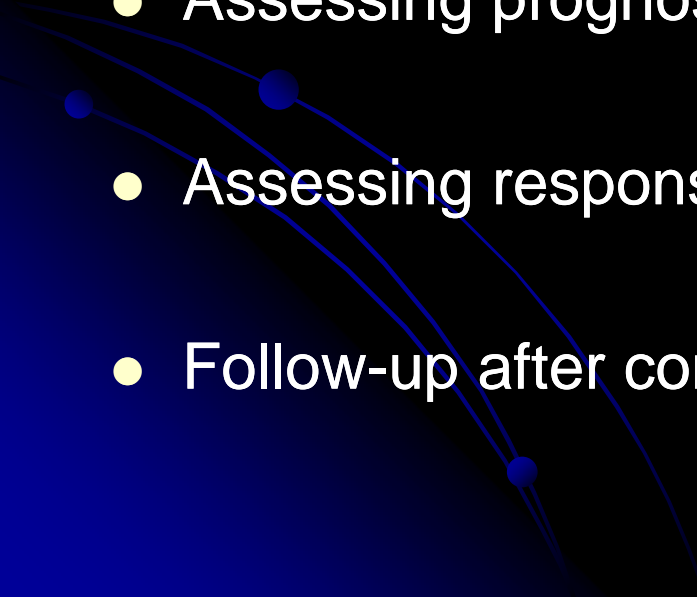
HISTOLOGY TYPE

CA 125 INCREASED

- | | | |
|--------------------|-----------|-------|
| ● Serous | ● 254/317 | (80%) |
| ● Mucinous | ● 35/51 | (69%) |
| ● Endometrioid | ● 39/52 | (75%) |
| ● Clear cells | ● 28/36 | (78%) |
| ● Undifferentiated | ● 56/64 | (88%) |

(Jacobs and Bast 1989)

CA 125 AS A MARKER FOR OVARIAN CANCER

- Screening
 - Differential diagnosis of pelvic masses
 - Assessing prognosis
 - Assessing response to therapy
 - Follow-up after completion of initial therapy
- 

SCREENING I

CA 125 alone has a low positive predictive value (PPV=2.3%).

This would mean that 50 women would need undergo laparoscopy or laparotomy in order to detect one ovarian cancer

(Hensley 2000)

SCREENING II

In multimodal screening, CA 125 is assayed first and ultrasound only carried out if elevated marker levels are found.

In a study on 22000 women, the PPV of CA 125 followed by ultrasound for the detection of ovarian cancer was 26%

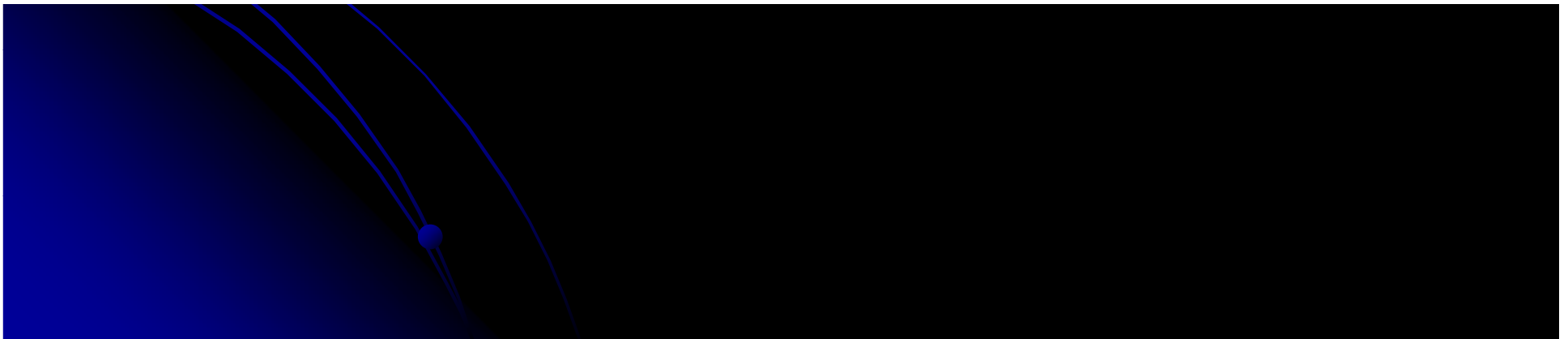
(Jacobs 1993)

[Lancet Oncol.](#) 2009 Mar 10.

Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).

[Menon U](#), [Gentry-Maharaj A](#), [Hallett R](#), [Ryan A](#), [Burnell M](#), [Sharma A](#), [Lewis S](#), [Davies S](#), [Philpott S](#), [Lopes A](#), [Godfrey K](#), [Oram D](#), [Herod J](#), [Williamson K](#), [Seif MW](#), [Scott I](#), [Mould T](#), [Woolas R](#), [Murdoch J](#), [Dobbs S](#), [Amso NN](#), [Leeso S](#), [Cruickshank D](#), [McGuire A](#), [Campbell S](#), [Fallowfield L](#), [Singh N](#), [Dawnay A](#), [Skates SJ](#), [Parmar M](#), [Jacobs I](#).

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SCREENING III

Another approach involves the additional assay of complementary markers:

- OVX1 and macrophage colony stimulating factor (M-CSF)
(Woolas 1993)

- Tumor-associated trypsin inhibitor, CA 19-9, CA 72.4 and inhibin

(Stenman 1995, Robertson 1999)

DIFFERENTIAL DIAGNOSIS OF PELVIC MASSES

For women presenting with a pelvic mass, CA 125 can aid to know preoperatively whether the mass is likely to be benign or malignant, especially in postmenopausal subjects.

(Schutter 1994)



ASSESSING PROGNOSIS

Several small-scale retrospective studies have shown that either the rate of fall of CA 125 levels after one, two or three courses of chemotherapy correlated with patient survival, but conflicting data also exists.

(Canney 1984, Clark 2001)

Moreover, the prognostic value of CA 125 was found to be time dependent, i.e., was only of value for the first year after surgery

(Peters-Engl 1999)

ASSESSING RESPONSE TO THERAPY

Assay of CA 125 is recommended for monitoring chemotherapy in patients with ovarian cancer.

Levels or trends suggesting treatment failure should result in discontinuation of ineffective therapy, switch to an alternative therapy, or randomization in trials evaluating novel treatments

(Rustin 2003, Duffy 2005)



FOLLOW UP AFTER COMPLETION OF INIZIAL THERAPY

Following primary treatment of ovarian cancer, many patients are regularly monitored with CA 125, in order to preclinically detect recurrent /metastatic disease, the assumption being that early administration of salvage chemotherapy enhances outcome

(Tuxen 2001)

Anyway, the clinical value of this early warning remains unclear, because it is well known that recurrent ovarian cancer is usually incurable with existing treatments.

Prospective randomized trials are in progress.

MARKERS THAT MAY COMPLEMENT CA125 IN OVARIAN CANCER

Marker	Type of molecule	Reference
OVX1	Mucin	Woolas et al.(34) and van Haaften-Day et al.(35)
M-CSF	Growth factor	Woolas et al.(34) and van Haaften-Day et al.(35)
TATI	Protease inhibitor	Stenman et al.(36)
CA19-9	Mucin	Stenman et al.(36)
Inhibin	Glycoprotein	Robertson et al.(37)
HMFG1 and HMFG2	Milk globulin	Dhokia et al.(38)
CASA	Mucin	Devine et al.(39)
TPS	Cytokeratin 18	Devine et al.(39) and van Dalen et al.(40)
Lysophosphatidic acid	Lipid	Xu et al.(41)
Prostasin	Serine protease	Mok et al.(42)
Osteopontin	Glycophosphoprotein	Kim et al.(43)
Kallikrein 6 and 10	Serine protease	Diamandis et al.(44) and Luo et al.(45)

M-CSF, macrophage colony stimulating factor; TATI, tumor-associated trypsin inhibitor; HMFG, human milk fat globulin; CASA, cancer-associated serum antigen; TPS, tissue polypeptide specific antigen.

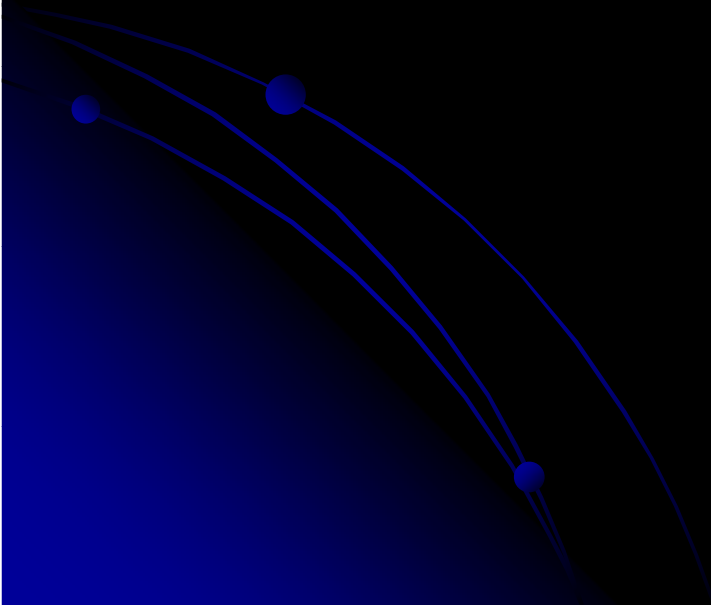
OTHER TUMOR-ASSOCIATED ANTIGENS

- CA 19.9
- CA 15.3
- CA 72.4
- Inhibin
- Interleukin-6 (IL-6)
- Macrophage colony-stimulating (M-CSF)
- Immunosuppressive acidic protein (IAP)
- OVX1
- sFas
- CYFRA 21.1
- Vascular endothelial growth factor (VEGF)

(Gadducci 2004)

A multicentric Italian study showed that the combination of CA 125 and CA 72.4 did not significantly increase the reliability of CA 125 in the preoperative evaluation of adnexal masses in postmenopause

(Maggino 1995)



In patients with positive CA 125 assay at diagnosis, the concomitant evaluation of CA 19.9 or CA 72.4 or CA 15.3 did not offer any additional benefit for monitoring ovarian carcinoma.

Conversely, the serial measurements of these other antigens may represent an interesting biochemical tool for the management of patients with negative CA 125 assay.

(Gadducci 2004)

INHIBIN I

Serum inhibin is an ovarian product with decreases to non-detectable levels after menopause: however some ovarian tumors, such as mucinous carcinomas and granulosa cell tumors, continue to produce inhibin which provides a basis for a serum diagnostic test

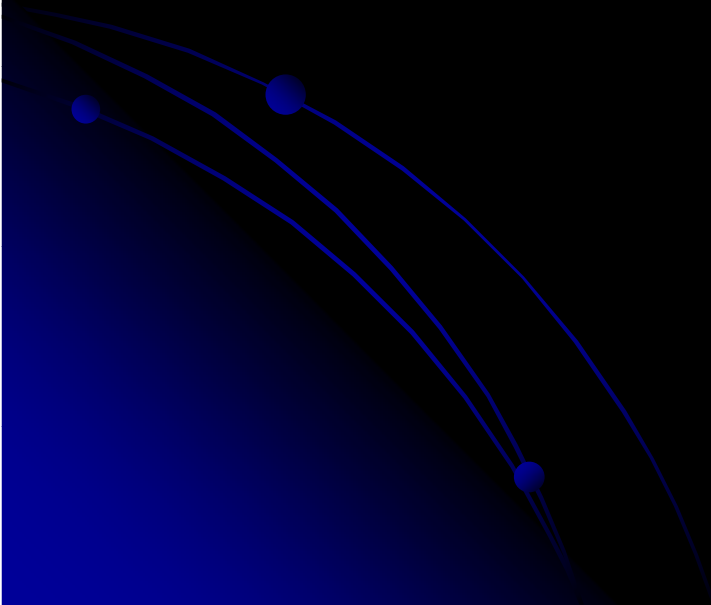
(Robertson 2002)



INHIBIN II

Serum inhibin reflects tumor burden and its measurement may be useful for assessing response to chemotherapy and the follow-up of patients

(Boggess 1997- Stuart 2003)



KEY POINTS RELATING TO THE EGTM GUIDELINES FOR THE USE OF CA125 IN OVARIAN CANCER

- At present, CA125, either alone or in combination with other modalities, should not be used in screening asymptomatic subjects outside the context of a clinical trial.
- Preoperative CA125 levels in postmenopausal women may aid in the differentiating of benign and pelvic masses.
- Alterations in serial levels of CA125 during initial therapy, using defined criteria, can be used to assess disease response or progression.
- Although serial determinations of CA125 following initial chemotherapy can lead to the early detection of recurrent disease, the clinical value of this lead-time remains to be established.
- CA125 is the ovarian cancer marker against which new markers for this disease should be compared.

ENDOMETRIAL CARCINOMA

Raised CA 125 levels (> 35 U / ml) have been reported in 11-33.9% of patients with this malignancy.

Preoperative CA 125 levels correlate with stage, depth of myometrial invasion, histologic grade, cervical invasion, peritoneal cytology and lymph node status

(Scambia 1994- Sood 1997- Hsieh 2002)



CERVICAL CARCINOMA

SCC antigen, a subfraction of the glycoprotein TA-4 isolated from squamous cell cervical cancer tissues, is the most commonly used marker for cervical cancer.

Elevated antigen levels have been found in 27-87.7% of patients with SCC of the cervix.

Pretreatment SCC levels are related to tumor stage, tumor size, depth of cervical invasion, lymph-vascular space involvement and lymph node status.

(Gadducci 1992- Scambia 1996- Takeda 2002)

Table 1

Main serum tumor markers in gynecological cancers

Gynecological cancer	Main marker	Marker reliability			
		Diagnosis	Prognosis	Treatment monitoring	Follow-up
Ovarian carcinoma	CA 125	++	+++	+++	+++
Ovarian yolk sac tumor (pure or mixed)	α FP	++++	++++	++++	++++
Ovarian choriocarcinoma (pure or mixed)	β HCG	++++	++++	++++	++++
Endometrial carcinoma	CA 125	+	++	++	++
Cervical carcinoma	SCC	+	++	++	++

α FP, alpha-fetoprotein; β HCG, beta-subunit of the human chorionic gonadotropin; SCC, squamous cell carcinoma antigen.

New tumor markers: CA125 and beyond

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K.A. BAGGERLY*, E.N. ATKINSON*, S. SKATES†, Z. ZHANG‡, A. LOKSHIN§,
U. MENON||, I. JACOBS|| & K. LU*

“...More than 30 serum markers have been evaluated alone and in combination with CA125 by different investigators. Some of the most promising include: HE4, mesothelin, M-CSF, osteopontin, kallikrein(s), and soluble EGF receptor. Two proteomic approaches have been used: one examines the pattern of peaks on mass spectroscopy and the other uses proteomic analysis to identify a limited number of critical markers that can be assayed by more conventional methods. Both approaches are promising and require further development. Several groups are placing markers on multiplex platforms to permit simultaneous assay of multiple markers with very small volumes of serum. Mathematical techniques are being developed to analyze combinations of marker levels to improve sensitivity and specificity. In the future, serum markers should improve the sensitivity of detecting recurrent disease as well as facilitate earlier detection of ovarian cancer.”

GRAZIE PER L'ATTENZIONE

