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MINIREVIEW

TUMOR MARKERS IN ENDOMETRIAL CANCER

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Summary

Endometrial cancer is the most common gynecological cancer worldwide which is usually treated by surgery. Although most cases are diagnosed in early stages when complete surgical removal of the tumor is possible, a high percentage of the patients will develop recurrences. An important test during the follow-up period of these patients remains tumor markers' serial determinations. This is a literature review of the most useful endometrial cancer tumor markers including CA 125, CA 15-3 and CA 72-4.
Key words: endometrial cancer; follow-up; CA 125; CA 15-3

Résumé

Les marqueurs tumoraux dans le cancer de l'endomètre

Le cancer de l'endomètre est le cancer gynécologique le plus fréquent dans le monde, qui est habituellement traité par chirurgie. Bien que la plupart des cas soient diagnostiqués à un stade précoce lorsque l'élimination chirurgicale complète de la tumeur est possible, un pourcentage élevé des patients développera des récidives. Un test important pendant la période de suivi de ces patients reste les déterminations en série des marqueurs tumoraux. Il s'agit d'une revue de la littérature des marqueurs tumoraux du cancer de l'endomètre les plus utiles, y compris CA 125, CA 15-3 et CA 72-4.
Mots-clés: cancer de l'endomètre, suivi, CA 125, CA 15-3

Introduction

Endometrial cancer is known as the most common gynecological cancer worldwide. Histopathologically and molecularly, there are two types of endometrial cancer. 80% of the new cases are oestrogen-dependent and are well or moderately differentiated, having an endometrioid morphology. The other 20% of the cases are non-oestrogen-dependent, low differentiated, having a clear cell or serous papillary morphology. The latest category is characterized by a worse prognosis, about half of the patients having recurrences. In terms of histopathology, there are several intermediate stages from normal epithelium to carcinoma (1,2).

The treatment of this disease is mainly based on surgery. Although the diagnosis is usually made in the early stages, there is still a recurrence rate of 15-20%, patients presenting with high risk of relapse being treated by radiotherapy. Chemotherapy is also used in patients with advanced disease. However, an individualized treatment will be possible after discovering new biomarkers. A possible known tumor suppressor is progesterone, which inhibits the growth of the endometrium and promotes its differentiation (3,4).

Literature data show that the most useful tumor markers for the management of the endometrial and cervical cancer are: CA 125, SCC-Ag (squamous cell carcinoma antigen), TPA (tissue polypeptide antigen), TPS (tissue polypeptide specific antigen) and CYFRA 21-1, VEGF (vascular growth factor), G-SCF (granulocyte colony stimulating factor) and M-SCF (macrophage colony stimulating factor) (5).

M. Kanat-Pektas realized a study on 135 endometrial

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cancer women and healthy controls. The serum concentrations of some tumor markers were measured and compared. The patients with endometrial cancer had significantly higher concentrations of CA 125, CA 19-9, prolactin and thyroid-stimulating hormone than the group of healthy patients and significantly lower concentrations of α-fetoprotein, CA15-3, FSH and LH. The authors found a statistically significant correlation between the levels of CA 125, CA 19-9, prolactin and tumor stage and between the levels of LH, estradiol, prolactin, CA 125 and the tumor grade. Using a cut-off CA 125 concentration of 35 U/ml, the sensitivity and specificity of this marker were of 42.2% and 87.4%. Using a cut-off prolactin concentration of 30 ng/ml, the sensitivity and specificity of this marker was 16.3% and 100% respectively. This study couldn't identify an appropriate single tumor marker which can be used for the endometrial cancer screening (6).

CA 125

CA 125 is one of the most useful tumor markers for the management of endometrial cancer. This antigen is found in the mesothelial cells and in the tissues derived from the Mullerian epithelium. In healthy individuals, the CA 125 concentrations vary with age (postmenopausal women have lower values than premenopausal women) and the menstrual cycle. They are elevated in pregnant women and in those who have endometriosis. So, the CA 125 specificity is quite low and so it is the sensitivity, the marker being elevated in only 11-33.9% of patients (cut-off value is considered 35 U/ml). The reduced entry of CA 125 in the circulation is suggested by the fact that 89.3% of the patients have tissue immunostainings that are positive for CA 125 (7).

The CA 125 concentrations measured in serum, in urine or in the body tissues can be used for determining prognosis. Other prognostic factors in endometrial cancer are: histological type, histological grade, surgical-pathological stage, depth of myometrial invasion, vascular invasion and cervical involvement (5,8).

A study realized by I. Mutz-Dehbalaie found that pre-treatment values of HE4 and CA 125 can be used for the assessment of the overall survival and of the disease-free survival, HE4 having an independent prognostic value and the association of the two markers being a good overall survival predictor (9).

The prognostic role of CA 125 in endometrial cancer patients was studied by M.S. Lundstrom et al. They found a significant correlation between the preoperative levels of CA 125 and tumor stage. The CA 125 concentrations higher than 35 U/ml proved to be poor prognosis indicators (10).

A study effectuated by Scambia - et al. (11) found a correlation between short survival and CA 125 concentrations of > 65 U/ml. Another study, effectuated by Sood et al. (12), proved that the CA 125 concentrations of > 35 U/ml are an independent predictor factor for poor survival.

A study realized on 112 patients found that between tumor stage and CA 125 levels (cut-off 35 U/ml) there is a good correlation. Increased CA 125 concentrations were found in 15.2% of patients with stage I, 33.3% of patients with stage II, 61.5% of patients with stage III and 100% of patients with stage IV (1).

In a study realized by A. Sebastianelli, which included 254 patients, increased concentrations of CA 125 (>35 kU/l) were found in 16% of the patients with I and II stages of endometrial cancer (in these patients deep myometrial invasion was present) and in 58% of the patients with stages III or IV. The authors didn't find a correlation between the histologycal type and the serum CA 125 levels. Their conclusion was that the serum CA 125 concentrations can help identify the high-risk patients (13).

Another clinical utility of this tumor marker resides in the assessment of the disease activity and in the treatment monitoring (14).

Several studies tried to find the utility of CA 125 with a cut-off value of 20 U/ml. The marker detected myometrial infiltration with a sensitivity, specificity, positive predictive value and negative predictive value of 69.0%, 74.1%, 58.8% and 81.6% (15). It detected extrauterine disease with a probability of 3% (12). The marker had a sensitivity of 75% and a specificity of 69.51% for the detection of the lymph node metastases and advanced stages of endometrial carcinoma. (Yildiz et al.) (16).

Although some studies indicated a correlation between the CA 125 concentrations and the activity of the disease in patients receiving chemotherapeutic treatment, the CA 125 utility in the therapy monitoring is still controversial. There are studies that demonstrate the utility of CA 125 for the detection of recurrences, with a sensitivity of 50%. In the case of radiotherapeutic treatment, the serum CA 125 levels can be influenced by the irradiation of the mesothelial cells. A sensitivity of 83.3% was found by Cherchi et al. for the association of CA 125 and CA 19-9 (17).

CA 15-3

Literature data sustain that CA 15-3 concentrations are increased in 24%-32% of the patients with endometrial cancer and that using a cut-off of 30 U/ml, CA 15-3 is increased in 18% of the patients with stages I and II and in 47 % of the patients with stage III (11). The marker can also be used for assessing prognosis and for differentiating between intrauterine and extrauterine disease (17).

CA 72-4

According to literature data, 22%-32% of the endometrial cancer patients have elevated levels of CA 72.4 and, in some cases, these levels correlate with adnexal metastases (1).

Other tumor markers

Over 22%-24% of the patients with endometrial cancer have increased levels of CA 19-9 and 14%-22% of the patients have increased levels of CEA. YKL-40, another tumor marker, is elevated in 76% of the cases and

its preoperative concentrations can be used to estimate prognosis (1).

HE4 is a tumor marker that has been proposed for monitoring of the high-risk patients, such as those with severe obesity, diabetes, hereditary non-polyposis colorectal cancer syndrome (Lynch), PTEN gene defects or those who have breast cancer and receive tamoxifen treatment. This is because it can detect the early endometrial cancer stages with a sensitivity that is higher than that of CA 125 (RG Moore et al.) (18). Some studies proved the high diagnostic specificity of HE4 (Y.Bie, Z. Zhang et al. in 2014) (19). The role of HE4 in monitoring treatment and in the detection of recurrences has not been yet confirmed (1,19)

Other tumor markers are M-CSF (which is increased in 75% of cases and can be used for the early diagnosis), OVX1, sFas (which has much higher levels in patients with carcinoma than in healthy individuals) and STN (which has a role of determining prognosis, being correlated with the stage, the tumor histology, the presence of metastasis, the age, the menopause status, the body mass index and the presence of recurrence) (1,20,21).

In a study effectuated in 1992, R. Matorras et al. determined the concentrations of several markers in endometrial cancer patients. The sensitivities of CA 125, SCC, CA 19-9 and CA 15-3 in the detection of recurrence or disease progression were 45%, 9%, 51% and 21%, respectively. The specificities in the detection of "no evidence of disease" varied between 95% and 99%. The sensitivity of the association between CA 125 and CA 19-9 was 77% and the sensitivity of the association between CA 125, CA 19-9 and CA 15-3 was 85%. All the four markers didn't have a higher sensitivity. The conclusion of the study was that these tumor markers have a relatively low accuracy in the diagnostic of recurrences and that more research is still necessary (22).

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