Napovedna in prognostična vrednost CA 125 pri raku endometrija

The predictive and prognostic value of CA 125 in endometrial cancer

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Izvleček

Rak endometrija je najpogostejši maligni tumor ženskega genitalnega trakta. Prizadene predvsem starejše ženske, glavni simptom predstavlja krvavitev po menopavzi. Rak endometrija lahko razdelimo v dve histološki skupini – tip I in tip II. Diagnozo potrdimo s histološkim pregledom vzorca endometrija. Zdravljenje raka endometrija zajema kirurško zdravljenje (histerektomijo z adneksektomijo in odstranitvijo pelvičnih in para–aortnih bezgavk) v kombinaciji z obsevanjem, kemoterapijo in hormonsko terapijo.

Predoperativne serumske koncentracije tumorskega označevalca CA 125 pri bolnicah z rakom endometrija so povezane z globino invazije v miometrij, zasevki v bezgavkah, pozitivno citologijo peritonealnega izpirka ter limfovaskularno invazijo in lahko pomagajo pri odločitvi o obsežnosti operativnega posega. Hkrati predope-

Abstract

Endometrial cancer is the most common malignant tumour of the female genital tract. It affects mainly older women, with postmenopausal bleeding as the primary symptom. The diagnosis of endometrial cancer is confirmed by histological evaluation of tissue specimens and described as either type I or type II. Treatment includes surgery (hysterectomy, adnexectomy and dissection of pelvic and para–aortic lymph nodes), radiotherapy, chemotherapy and hormonal therapy. Preoperative serum CA 125 (Cancer Antigen 125 or Carbohydrate Antigen 125) concentrations are correlated with depth of myometrial invasion, lymph node metastases, positive peritoneal cytology and invasion of the lymphovascular space, and can assist in making decisions about the extent of surgery. Preoperative CA 125 levels have prognostic value; postoperative levels serve as a predictor of early recurrence. El-

rativne vrednosti CA 125 predstavljajo dober prognostični kazalnik, med tem ko imajo pooperativne vrednosti vlogo pri odkrivanju zgodnjih ponovitev bolezni. Vendar povišani nivoji serumskega CA 125 niso povezani le z rakom endometrija, pač pa tudi s številnimi benignimi in malignimi stanji (rak jajčnika). Pri obravnavi bolnic z rakom endometrija lahko uporabimo tudi druge tumorske označevalce – CA 15–3, CA 19–9 in novi obetajoč tumorski označevalec HE4.

evated serum CA 125 is linked not only with endometrial cancer, but also with several benign and malignant conditions, including ovarian cancer. Other tumour markers (e.g., CA 15–3, CA 19–9) and a promising new marker human epididymis protein 4 (HE4) can also be used for managing patients with endometrial cancer.

INTRODUCTION—ENDOMETRIAL CANCER

Endometrial cancer arises from the lining of the uterus and is the most common malignant disease of the uterus (1).

Epidemiology and aetiology

Uterine cancer is, after breast cancer, the most common gynaecologic malignancy in Slovenia, and according to the national cancer registry, there were 336 new cases in 2012, which corresponds to an annual incidence of 32.4 per 100,000 women. The incidence of uterine cancer has been increasing, and includes not only endometrial cancer, but also uterine sarcomas, which represent 4%–9% of cases (2, 3). Endometrial cancer is a disease of older women. The vast majority of cases occur in postmenopausal women between 50 and 65 years of age, with only about 5% of patients younger than 40 (4).

Prolonged elevation of oestrogen levels is known to increase the risk of this type of cancer by stimulating cell division that results in endometrial hyperplasia. Gestagens, which inhibit DNA synthesis and cell division, have the opposite effect (4). Obesity, impaired carbohydrate tolerance and diabetes mellitus, hypertension, late menopause, nulliparity, functional ovarian tumours (which produce oestrogen), excess exogenous oestrogen (e.g., postmenopausal oestrogen therapy without adequate provision of progestin) and tamoxifen therapy all increase the risk of endometrial cancer (4, 5, 6). Endometrial cancer is also more frequent in patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer) (4). Use of combination oral contraception or progestin decreases the risk of endometrial cancer with up to a 50% reduction in incidence (4, 5, 7).

Histopathology and histopathologic subtypes

Endometrial cancers can be divided into two histologic types that differ in incidence, responsiveness to oestrogens, clinical behaviour, and prognosis (6, 8) as shown in Table 1 (8).

Type I tumours are endometrioid with lower–grade (G1 or G2) histology, and type II tumours include those with high–grade (G3) endometrioid histology

Table 1: *Characteristics of type I and type II endometrial cancer (6, 8, 9)*

Characteristic/Group	Type I	Type II
Incidence	80% of endometrial cancers	20% of endometrial cancers
Responsiveness to oestrogens	Yes	No
Precursor lesion	May be preceded by intra-epithelial neoplasm	Rarely identified
Prognosis	Favourable	Poor

and tumours with non–endometrioid histology (6). The most common non–endometrioid tumours are serous, clear cell, mucinous, squamous, transitional cell, mesonephric and undifferentiated (8). Tumours can also be divided into three additional categories depending on the extent of cell differentiation. Grade 1 (G1) tumours are well differentiated, grade 2 (G2) are moderately differentiated, and grade 3 (G3) are poorly differentiated (4).

Clinical presentation

The primary symptom in patients with endometrial cancer is irregular bleeding. Postmenopausal women present with bleeding or bloody postmenopausal discharge; premenopausal women present with intermenstrual bleeding, bloody vaginal discharge, or just heavy periods. Endometrial cancer can also present with dyspareunia or lower abdominal pain (7).

Diagnosis

The first steps in patient management are a physical examination and obtaining a history that focuses on the risk factors mentioned previously (7). The initial diagnostic procedure is usually a transvaginal ultrasound to determine endometrial thickness, and if endometrial pathology is suspected, a histologic evaluation should be performed. Tissue specimens can be obtained by endometrial biopsy, dilation and curettage, or hysteroscopy (9). The preoperative evaluation should include laboratory assay of serum tumour markers (described below) (5, 9). If more extensive disease is suspected, imaging studies are recommended (9). Contrast–enhanced magnetic resonance imaging is the most appropriate for determining myometrial or cervical invasion and detecting lymph node metastases (10). Endometrial cancer is surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO) criteria (Table 2) (1). Spreading of the disease can be exfoliative, in which malignant cells pass through fallopian tubes, lymphogenus, haematogenous, or most often by tumour growth into the surrounding tissue (1, 7).

Treatment

The primary treatment of endometrial cancer is surgical and includes hysterectomy with bilateral adnexectomy (10). Removal of the uterus and adnexa can be performed either by laparotomy or laparoscopy (1). Further evaluation of pelvic and para–aortic lymph nodes is necessary in patients with high risk of nodal metastasis (i.e., tumours with serous, clear cell, or high–grade histology, invasion of more than half the myometrium thickness, or a large tumour) (10). In women with serous or clear cell cancer, omentectomy is also performed (1).

Table 2: *Surgical staging of endometrial cancer by 2009 FIGO criteria (1)*

FIGO stage	Description
I	Tumour confined to the uterine body
IA	< ½ myometrial invasion
IB	> ½ myometrial invasion
II	Cervical stromal invasion, but no spread beyond uterus
III	Local and/or regional spread of tumour
IIIA	Tumour invades serosa of uterus and/or adnexa
IIIB	Tumour invades vagina and/or parametrium
IIIC	Locoregional lymph node involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic node involvement
IV	Tumour invades bladder or bowel mucosa or distant metastases
IVA	Tumour invades bladder and/or bowel mucosa
IVB	Distant metastases (including abdominal metastases and/or inguinal lymph nodes)

In patients with higher stages of endometrial cancer, the surgical procedure is followed by radiotherapy, chemotherapy, or both. Radiotherapy can be either percutaneous (teleradiotherapy) or intracavitary (brachyradiotherapy) (1). In low risk tumours (stage I disease or grade 1), hormonal progestin therapy is appropriate for patients who want to preserve fertility (1, 6). Radiotherapy, chemotherapy and hormonal therapy can be used in patients without previous surgery, inoperable patients, patients who are not indicated for surgery and patients with recurrent or metastatic disease (1, 6, 10).

Prognosis

Prognosis depends primarily on tumour stage and histology (type and grade) (6). The overall 5–year survival rate of endometrial cancer patients is 83%, 96% in stage I, but only 17% in stage IV (1).

TUMOUR MARKER CA 125

Structure and function

CA 125 is a glycoprotein with a high molecular mass, a member of the mucin family, and is also known as MUC 16 (11, 12). It was identified in the 1980s in ovarian cancer cells by a monoclonal antibody, OC 125 (12). The CA 125 protein consists of a large extracellular and small transmembrane and intracellular regions (11, 13). The role of protein CA 125 in malignant processes is not fully understood, but it is assumed to promote cancer cell proliferation and to suppress anti–tumour immune responses by inhibiting the cytotoxic activity of natural killer cells (11, 14). CA 125 also binds to mesothelin, which allows cancer cells to adhere to each other and expand the tumour mass and to attach to the mesothelium and facilitate metastasis (14).

Determination of tumour marker levels and normal values

CA 125 levels are determined by enzyme–linked immunosorbent assay (11) using monoclonal antibodies to detect antigenic determinants of the extracellular region of the glycoprotein that are present in the serum or other bodily fluids (7, 11). Normal serum CA 125 concentrations are below 35 U/mL (15, 16), and postmenopausal women have lower concentrations than premenopausal women (12, 15).

Causes of elevated CA 125

CA 125 is present in mesothelial cells of the peritoneum, pericardium, pleura, and in cells derived from embryonal Müllerian ducts (i.e., tubal, endometrial and endocervical cells) (12). CA 125 can be detected not only on the cell surface, but also in bodily fluids including blood, ascites, or pleural effusions if cells are damaged (14). As shown in Table 3, CA 125 can be elevated in numerous conditions in which cells that express it are affected; not only in gynaecological and other malignancies, but also in various benign and physiologic conditions (13).

CA 125 AND ENDOMETRIAL CANCER

Serum CA 125 is correlated with disease stage and is used in preoperative assessment

Assay of CA 125 is easy, repeatable, cheap, and objective (17), and the preoperative concentration provides information correlated with the stage of disease including depth of myometrial invasion, lymph node metastases, positive peritoneal cytology and lymphovascular space invasion (12, 18, 19, 20). Preoperative serum CA 125 has prognostic value (20) such that patients with normal serum concentrations have better outcomes and survival rates than those with elevated concentrations (12, 20).

Table 3: *Conditions causing elevation of CA 125 (7, 11, 12, 13, 18, 25)*

Physiologic	Pregnancy, menstrual cycle
Benign	Endometriosis, leiomyoma, pelvic inflammatory disease, ascites, liver disease, pancreatitis, diverticulitis, congestive heart failure, pleural effusion, tuberculosis
Malignant	Ovarian cancer, endometrial cancer, breast cancer, fallopian tube cancer, lung cancer, tumours of gastrointestinal tract (colon, pancreas), non-Hodgkin lymphoma

Serum CA 125 concentration can assist in surgical planning, as it can predict which patients are likely to need lymphadenectomy (15). In early stage of endometrial cancer high serum CA 125 concentrations may indicate microscopic extra–uterine spread of cancer cells and the need for pelvic or para–aortic lymphadenectomy (12, 21). Serum CA 125 is significantly correlated with, and is an independent predictor, of extra–uterine spread. It has better predictive value than tumour grade and depth of myometrial invasion, which are normally used to determine which patients should undergo surgical staging with lymphadenectomy of pelvic or para–aortic lymph nodes (18, 20).

Many investigators have suggested a decrease in cut–off level, with a normal concentration below 20 U/mL, or 15 U/mL in postmenopausal women, for endometrial cancer (15, 18). The lower cut–off improves assay sensitivity, finding more patients with positive lymph nodes who undergo lymphadenectomy, but also results in more patients who undergo unnecessary staging (15).

Postoperative levels of serum CA 125 and follow–up

CA 125 concentration usually parallels the clinical course of disease (22). After initial treatment, determination of serum CA 125 concentration is used during follow–up as a marker of cancer recurrence, if it was elevated preoperatively (10, 21). Postoperative increase in serum CA 125 has an 84%–94% sensitivity for detecting cancer relapse (23). Also for follow–up of patients with endometrial cancer, some investigators recommend a threshold of 20 U/mL to detect early relapses (20). However, it should not be forgotten that patients who have been given radiotherapy of the abdominal region may have elevated levels of CA 125 even though they are disease free. Thus, as previously mentioned, other possible causes of elevated CA 125 have to be considered (12).

CA 125 AND OTHER GYNAECOLOGICAL CANCERS

Ovarian cancer

CA 125 was initially used as a marker in ovarian cancer (11), for which there is a need for screening because the characteristics of the disease often lead to diagnosis at advanced stages and consequent high mortality (24). Elevated tumour marker levels are detected in approximately 50% of ovarian cancers in the early stages and 92% in late stages of disease (25). CA 125 alone cannot be used as a screening modality in the general population because of a high risk of false–positive results associated with the overall low incidence of ovarian cancer (24). The Risk of Ovarian Cancer Algorithm includes screening by serial CA 125 measurements combined with transvaginal ultrasound in high risk patients (26). CA 125 is also used to determine whether adnexal masses are benign or malignant, to monitor response to ovarian cancer treatment and to detect its recurrence (14, 24).

Breast cancer

CA 125 levels are elevated in advanced stages of breast cancer (metastatic disease). Increased values are more closely associated with abdominal and pleural metastasis than with bone metastasis, which is explained by the fact that CA 125 is synthesized by mesothelial cells (27). High levels of CA 125 in breast cancer therefore indicate poor prognosis (28).

OTHER TUMOUR MARKERS USED IN DIAGNOSIS, TREATMENT AND FOLLOW–UP OF PATIENTS WITH ENDOMETRIAL CANCER

CA 125 can be useful tumor marker in endometrial cancer, but its limitations in diagnosis, monitoring treatment and patient follow–up have prompted evaluation of other potential markers. Tumour marker CA 15–3 is used mainly in breast cancer patients (19), but serial measurement of CA 15–3 is correlated with the clinical behaviour of disease in patients with endometrial cancer (12). Serum CA 15–3 concentrations >30 U/mL indicate worse prognosis and decreased survival (12, 19). CA 19–9 is used as a marker of treatment response and of recurrence in several cancer types (19), and similar to CA 15–3, elevated CA 19–9 is associated with worse prognosis and decreased survival in patients with endometrial cancer (19). When combined with CA 125, CA 19–9 increases the sensitivity for detecting recurrence of en-

dometrial cancer compared with CA 125 alone (12). Carcinoembryonic antigen (CEA) and alpha fetoprotein are glycoproteins found in embryonic or fetal tissues, and their expression decreases soon after birth (19). CEA is elevated in many malignancies, with its highest diagnostic value for tumours of colon and rectum, but it is also increased in benign diseases (19, 29). CEA level is increased in only 14%–22% of patients with endometrial cancer, with higher levels in advanced stage disease. CEA was found to be useful to detect recurrence of disease, having a sensitivity of 75.9% (29). Alpha fetoprotein is elevated primarily in hepatocellular cancer and germ cell tumours, but it has no evident correlation with endometrial cancer (19). Human epididymis protein 4 (HE4) is a novel tumour marker with potential for detecting patients with endometrial cancer (23). HE4 is elevated in early stages of endometrial cancer (type I and type II), has higher sensitivity than CA 125 (12, 23) and is less influenced by the menstrual status of the patient (24). Its use in detecting recurrence of the disease and response to therapy requires further study (12).

CONCLUSION

CA 125 is a widely used gynaecologic tumour marker. It was first demonstrated in ovarian cancer cells and used as an ovarian cancer marker. Over the years, CA 125 has also shown its usefulness in endometrial cancer. Its primary roles in managing endometrial cancer are in detecting disease recurrence and in monitoring treatment response. In the early stages of endometrial cancer, CA 125 is predictive of extra–uterine spread and has a role in planning the extent of surgery. To act in the best interests of our patients, we must also consider its limitations: other reasons for elevated serum CA 125 and the dependence on menstrual status.

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