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Clinic, pathologicand biologic prognostic factors in endometrial cancer. A literature review

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Abstract

Endometrial cancer (EC) is the most common gynecological malignancy in western countries which primarily affects postmenopausal women. The aim of this review is to outline the most important clinic, pathologic and biologic prognostic parameters in order to obtain the treatment outcomes in EC. Medline and Pubmed were searched for English language articles using keywords (i.e. "endometrial cancer", "prognostic factors"). systematic reviews, retro-prospective studies, controlled and randomized clinical trials focused on prognostic information were selected. Bibliographies of articles found were searched for further relevant titles. The most significant reported prognostic factors are age, International Federation of Obstetrics and Gynecology stage, the histological subtype and grade of the tumor, peritoneal cytology, lymphovascular space involvement, invasion of the myometrum, tumors that extend to the cervical stroma,extra-uterine disease,tumor size,as well as the presence and extent of lymph node metastasis. Molecular biomarkers such as mutations in tumor suppressor genes, deoxyribonucleic acid mismatch repair, and the presence of a triple negative phenotype are considered worse prognostic factors, and may lead to a poor survival.
Keywords: *endometrial cancer, prognostic factors, lymph nodes, survival*

Introduction

Cancer of the uterus is the fourth and seventh among the most common female cancers in developed and developing countries, respectively[1]. Annual incidence rates in European countries range between 15 and 20 per 100,000 women; incidence in the United States is 23 per 105 women per year[2]. Endometrial cancer (EC) constitutes the majority of cases of the corpus uteri with approximately 75% of cases being diagnosed at an early stage with the tumor confined to the uterine corpus[3,4]. Due to the possibility of an early detection, the prognosis of patients with EC is generally good, the 5-year survival rate being higher than 80%[5]. Surgery followed by adjuvant treatment based on the clinical and pathological characteristics of the patient is the standard initial treatment for EC patients[6]. Although surgery is potentially curative in most patients, about 15-20% of women with no signs of locally advanced or metastatic disease at primary treatment still develop recurrent disease with a limited responsiveness to systemic therapy[7]. The risk of recurrence is 10-20% in FIGO stages I-II and 50-70% in stages III-IV[8].

Numerous studies have attempted to identify the prognostic factors (PF) of EC. At present, age, International Federation of Gynecology and Obstetrics stage, the histological subtype and grade of the tumor, lymphovascular space involvement (LVSI), invasion of the myometrum, tumors that extend to the cervical stroma, the presence and extent of lymph node (LN) metastasis, extra-uterine disease, and the completeness of surgical resection are the reported most significant PF[9,10]. However, the ability of these conventional risk factors to accurately predict survival in individual patients in pre-treatment stage is insufficient, as most of them are to be taken into consideration after surgery[11]. Based on multivariate analysis, only a small number of the parameters have independent prognostic value. Other PF such as weight, ethnicity, obstetric history, duration of clinical symptoms, and size of the primary tumor have also been cited in the literature[12].

In recent years, the progress in molecular biology has determined the introduction of a new concept - molecular biomarkers - which have been studied using immunohistochemical, cytofluorometric and molecular biology techniques. These include deoxyribonucleic acid ploidy, proliferation index, S-phase fraction, MIB-1 (Ki-67), expression of p53 and HER 2/neu genes, and angiogenesis[13]. This review will primarily focus on the clinico-pathologic and biologic prognostic parameters in EC.

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Clinical and pathologic prognostic factors

1.Age

EC primarily affects postmenopausal women between 60 and 85 years of age. Many patients have concurrent comorbidities, such as obesity, diabetes, and cardio-

vascular diseases[14]. Based on the PORTEC trial, age is proved to be a risk factor for relapse of disease in the Netherlands[15], and according to the Gynaecologic Oncology Group (GOG), older patients have a worsen prognosis than the younger ones due to a higher incidence of histological grade III tumors or other unfavourable histologic subtypes[16]. In the study of Aalder and contributors[17], the reported mortality and recurrence rate in patients under 60 years was 6.1% in contrast to a rate of 12.3% in patients older than 60 years. Older age predicts a 10-fold higher risk of developing loco-regional recurrences, a 3-fold higher risk in disease-free survival (DFS) events, and a 5-fold higher mortality rate. The adverse effects of increasing age may be related to differences between younger and older patients with regard to tumor biology, neovascularization, immunologic response, and the patient's capability to produce and stimulate proteolytic enzymes[18].

2. Stage

The clinical stage is the most important PF of EC. In 2009, the revised FIGO staging system replaced the 1988 FIGO's classification. When evaluating literature data, there are changes in stage IA, IB, FIGO 1988 stage IA and IB being grouped together in FIGO 2009 as stage IA, and FIGO 1988 stage IC is now IB in FIGO 2009[19]. The surgical staging is based on multiple factors such as histologic grade, myometrial invasion (MI), peritoneal cytology (PC), adnexal involvement, isthmus-cervix extension, and LN metastasis.

Histologic grade

A statistically significant association between histologic grade and MI has been reported in the study of Boronow and co-workers(20), in which 4.3% of patients with stage I grade I EC and 39% patients with stage I grade III presented with deep MI. The 5-year survival rate was 81% in stage I grade I patients, and 50% in stage III grade I patients, while the recurrence was 4% in grade I and 42% in grade 3 patients. The study of Kim and contributors[21] demonstrates an association between the high histologic grade and LN metastasis, as, of the 64 patients with defined histologic grade, 10% of grade 1, 19% of grade 2 and 30% of grade 3 patients had metastases in the pelvic LNs.

Myometrial invasion

Based on staging studies, prospective and retrospective data, patients with EC can present with low-risk, intermediate-risk, or high-risk for LN metastases and/or early disease spread to the abdominal cavity and to distant sites. About 55% of patients have low to intermediate risk, and 30% have high-intermediate risk features[22]. Based on FIGO 2009 classification, low-risk patients are stage IA (with no or superficial [<50%] MI) EC, grade 1 or 2, of endometrioid type histology. High-risk patients are stage IB (i.e. outer [>50%] MI) of grade 3 or of non-endometrioid histology, stage II or III EC(23). Deep MI is as an independent PF for a low 5-year overall survival (OS) and DFS in intermediate risk patients, and the adverse effects are mainly due to distant failure[24], which is concordant with the study of Gadducci and colleagues[25] who indicated that deep MI was a strong predictor for distant haematogenous metastasis in patients with stage I-II endometrioid-type EC. Graesslin et al.[26] revealed that the aggressive behavior of cancer with deep MI is related to a lower expression of tissue inhibitors of metalloproteinase-2, a member of zinc dependent endopeptidases.

Peritoneal cytology

Whether PC serves as a PF for EC is controversial, some reports being positive, others negative. The causes of these differences of opinion were outlined in the study of Kasamatsu et al.[27] and they refer to: a) insufficient number of investigated cases (i.e. less than 300), PC positivity rate being about 10% in EC; b) some stages were postoperatively other were clinically classified; c) there were various types of intra- and post-operative adjuvant therapies; and d) there are no prospective studies, and multivariate analysis was not performed. Moreover, in the same study on 280 patients, the 5-year survival rate was 91% in PC-positive patients, lower than in PC-negative patients (95%)[28,29].

Two other previous studies showed that PC is an independent PF for EC on multivariate analysis, and, more recently, Saga and contributors[30] showed that PC may be an important PF when disease is confined to the uterus and accurate staging including retroperitoneal LN dissection is performed.

Adnexal involvement, istmus-cervix extension and LN metastasis

When the myometrium or isthmus cervix is invaded, there is a high probability of adnexal involvement, a higher rate of LN metastasis (23-35%), and a poor prognosis[21]. EC only with endocervical glandular involvement has a higher survival rate than cases of EC with cervical stromal invasion[31].

The rate of LN metastasis is higher in patients with advanced clinical stage, poor histologyc grade, long uterine cavity length, and deep MI. The proportion of N1-EC patients with positive para-aortic LN is 76%, and more than half of them have affected LN above the inferior mesenteric artery-level, therefore being necessary an extended lymphadenectomy up to the renal veins, equivalent to the dissection performed for epithelial ovarian cancer[21].

3. Histology type

The most common basis for determining the risk of recurrent disease has been classified into two subtypes: type I, associated with a hyperestrogenic state, which occur in obese women, tend to be well-differentiated and early stage, and type II not associated with hyperestrogenism, occur in thin women, are often high grade and more likely to be into advanced stage[32]. Type II EC accounts for less than 15% of all EC, includes serous and clear cell carcinomas, and is biologically much more aggressive than the endometrioid type I[33]. The majority of EC is low grade, early stage, and carries an excellent prognosis. However, the 5-year survival of advanced stage (stages III and IV) EC ranges between

23 and 67%[34]. Type II EC is responsible for over 45% of the total uterine cancer deaths[35].

Abeler and contributors[36] reported 5-year survival rate of 42.3% in clear cell carcinoma compared with 27% in papillary serous carcinoma. The study of Vance et al.[37] specifically evaluated the prognostic significance of older age in women diagnosed with early stage type II EC and demonstrated that women older than 65 years had a worse recurrence-free survival when compared to younger patients.

4. Lympho-vascular space invasion and tumor size

LVSI is a standard pathologic parameter which has been defined as follows: morphological vital tumor emboli in endothelial lined lumina containing erythrocytes and/or lymphocytes outside the tumor mass[38]. LVSI has been demonstrated to be a significant and independent PF for relapse of disease, pelvic LN metastasis and poor survival[39]. Furthermore, Keys and contributors[40] in the GOG-99 trial also revealed that LVSI is a factor associated with an increased recurrence rate, and should be added to the group of traditional surgico-pathologic variables used to assign patients with EC to adjuvant therapy. Moreover, women with early stage EC and negative LN have an increased risk for relapse of disease if LVSI is present, even though, generally speaking, these patients are not eligible for adjuvant therapy[40].

Tumor size is an important PF for LN metastasis and survival in EC. In stage I EC, the rate of LN metastasis is 4% when the tumor is less than 2 cm, 15% in women with tumors ≥2 cm, and 35% when the tumor involves the entire uterine cavity. The 5-year survival rates are 98%, 84%, and 64%[41].

5. Biologic prognostic parameters

Long-lasting unopposed estrogen exposure leads to endometrial hyperplasia, which increases the chance of development of type I EC. The development of EC is also characterized by self-sufficiency in growth signals, insensitivity to growth inhibition, apoptosis, angiogenesis, invasion and metastasis[42,43]. Progresses made in molecular biology demonstrated the existence of more than 60 proto-oncogenes, which can be activated by different processes such as translocation, deletion, gene amplification, and sequence alteration. The tumor suppressor genes as well as the association between gene anomalies, poor histologic grade, advanced stage and poor prognosis have been showed to play an important role in the pathogenesis of EC[21].

Biomarkers such as oestrogen (ER) and progesterone (PR) receptor expression lead to a more favorable prognosis while other markers suchas overexpression of p53, HER2, and the expression of epidermal growth factor receptor predict a poor prognosis[42,43]. Overexpression of HER2 occurs in 43% of EC, and overexpression and amplification are associated with high grade and high stage EC[42]. Similarly with breast cancer, overexpression and amplification of HER2 in patients with EC predict a shorter OS[44].

The triple negative phenotype (TNP) is a group of immunohistochemical markers which does not include ER, PR expression and HER2 protein overexpression. The TNP is mainly encountered in hereditary breast cancers due to mutations in the breast cancer susceptibility gene. As in breast cancer, the presence of TNP in EC could help predict which therapies are best suited for patients based on the pattern that their disease markers show[45].

In surgically staged EC, TNP strongly correlates with the traditional poor prognostic surgical and pathologic factors such as advanced stage disease, high grade and deeply invasive tumors, and may be associated with poor prognosis. Independently, both the loss of ER and PR expression and HER2 overexpression has been shown to predict a poor prognosis[46]. Based on the receptor status, adjuvant therapy could be specifically tailored in order to improve outcomes in patients who currently have a poor prognosis[46].

Conclusions

The identification of clinical, pathologic and biologic PF is warranted in patients with EC in order to anticipate prognosis, optimize and individualize treatment, as well as prevent recurrence. Tumor stage, grade, histologic type, and depth of MI are the currently PF implemented in the patient's management. LVSI is a predictor of nodal disease and an independent PF for relapse of disease in all stages of EC.

The above mentioned biologic prognostic indicators could help determine which patients would benefit from either adjuvant treatment or more aggressive primary treatment.

The TNP is associated with advanced stage, high grade, and high risk histology, as well as poor survival. However, the clinical value of these markers for establishing a diagnosis and predicting response to targeted treatment remains to be settled. Further investigation of the molecular model of EC may lead to improved outcomes similar to that seen in the novel recommendationsfor TNP breast cancers. ■

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