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Review

Endometrial cancer: molecular and therapeutic aspects

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ABSTRACT

Endometrial cancer (EC) is the most commonly diagnosed gynecologic malignancy. Although early-stage EC is effectively treated surgically, commonly without adjuvant therapy, the treatment of high-risk and advanced disease is more complex. Chemotherapy has evolved into an important modality in high-risk early-stage and advanced-stage disease, and in recurrent EC. Multi-institutional trials are in progress to better define optimal adjuvant treatment for subsets of patients, as well as the role of surgical staging in reducing both overuse and underuse of radiation therapy.

Understanding and identifying the molecular biology and genetics of EC are central to the development of novel therapies. A number of molecular and genetic events have been observed in ECs, which have enabled us to have a better understanding of the biology and development of the disease. For example, the PTEN/AKT pathway and its downstream targets and the mTOR pathway have been shown to play an important role in EC pathogenesis. This review summarizes the background of the known molecular alterations, and the management of patients with EC.

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Contents

1. Introduction

Endometrial cancer (EC) is the seventh most commonly diagnosed cancer among women, with 189,000 new cases and 45,000 deaths occurring worldwide each year [1]. Approximately 90% of cases of EC are sporadic, whereas the remaining 10% of cases are hereditary [2]. A dualistic model of endometrial tumorigenesis is currently recognized, broadly termed type 1 and type 2, based on a classification system hypothesized by Bokhman in 1983 [3]. This model serves as a useful way to categorize these cancers in terms of both etiology and clinical behavior. Type 1 EC represents the majority of sporadic cases of EC, accounting for 70–80% of new cases [3]. These cancers are typically of endometrioid type and therefore are primarily associated with unopposed estrogen

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exposure [3]. Clinically, type 1 cancers are more often low-grade tumors with a favorable prognosis [3]. In contrast, type 2 ECs are less common, accounting for 10–20% of ECs [4]. They are often of non-endometrioid, high-grade histology, usually serous or clear cell. Type 2 ECs are unrelated to estrogen exposure [4]. Patients with type 2 EC are generally older, and they have a propensity for early spread and poor prognosis [3].

Although a serious public health problem, EC has long been a neglected disease, receiving less attention from researchers than cancers of other organ systems. In this review, we examine the major risk factors for the development of EC, describe the background of the known molecular alterations, outline diagnostic approaches and provide an overview of the treatment algorithm currently in use at our institution for patients with EC. We also discuss the treatment of young patients with EC. We focus on carcinomas arising from the endometrial glands, which account for more than 80% of ECs.

2. Molecular biology of endometrial cancer

The endometrium undergoes structural modification and changes in specialized cells in response to fluctuations of estrogen and progesterone during the menstrual cycle. Long-lasting unopposed estrogen exposure leads to endometrial hyperplasia, which increases the chance of development of type I EC. The molecular basis of this process is still not known, since the involvement of only a minority of factors is reproducible [5]. Aside from their morphologic and clinical features, type 1 and type 2 ECs are further distinguished by genetic alterations. Endometrioid and nonendometrioid cancers are associated with mutations from independent sets of genes [6].

ECs are characterized by a variety of genetic alterations, the most frequent of which is to the *PTEN* gene. A number of tumor suppressor genes have been shown to contribute to the genesis of endometrial cancers. The genes code for proteins inhibiting tumor growth [7]. *PTEN*, located at chromosome10q23, encodes a protein (phosphatase and tensin homolog, PTEN) with tyrosine kinase function and behaves as a tumor suppressor gene. PTEN has been reported to be altered in up to 83% of endometrioid carcinomas and 55% of precancerous lesions [7]. PTEN inactivation is caused by mutations that lead to a loss of expression and, to a lesser extent, by a loss of heterozygosity. Thus, loss or altered PTEN expression results in aberrant cell growth and apoptotic escape. Loss of PTEN is furthermore probably an early event in endometrial tumorigenesis, as evidenced by its presence in precancerous lesions, and is likely initiated in response to known hormonal risk factors. Its expression is highest in an estrogen-rich environment; in contrast, progesterone promotes involution of PTEN-mutated endometrial cells. These observations are consistent with the well-documented clinical effects of progesterone-mediated suppression and resolution of invasive EC and its precursors [8]. PTEN mutation is well documented in endometrial hyperplasia with and without atypia [9].

Mutations in PIK3CA may contribute to the alteration of the phosphatidylinositol 3 kinase (PI3K)/AKT signaling pathway in EC [10]. A high frequency of mutations in the PIK3CA gene has been reported recently in EC. PIK3CA mutations occur in 24–39% of the cases, and frequently coexist with PTEN mutations [11]. PIK3CA mutations have been associated with adverse prognostic factors such as high-grade and myometrial invasion.

Other genetic alterations in endometrioid EC include microsatellite instability (MSI) and specific mutations of K-ras and β-catenin genes [10]. MSI has been demonstrated in 20% of sporadic endometrioid EC [10]. Microsatellites are short segments of repetitive DNA bases that are scattered throughout the genome. The accumulation of sequence changes in these DNA segments, which occurs because of inactivation of intranuclear proteins constituting the mismatch repair system, is known as MSI [11]. Inactivation of MutL protein homolog 1 (MLH1), a component of the mismatch repair system, is a common event in type I EC. This alteration occurs through hypermethylation of CpG islands in the gene promoter, a process known as epigenetic silencing [11]. MSI and abnormal methylation of MLH1 are early events in endometrial carcinogenesis and have also been described in precancerous lesions [12].

The most common genetic alteration in type 2 serous carcinomas is in p53, the tumor suppressor gene [13]. The p53 gene is located on chromosome 17 and is important in preventing the propagation of cells with damaged DNA. Mutations in p53 are present in about 90% of serous carcinomas [13]. The exact mechanism behind the cause of this mutation is still unclear. It is postulated that mutation in one allele occurs early during the development of serous carcinoma, and loss of the second normal allele occurs late in the progression to carcinoma. Other frequent genetic alterations in type 2 ECs are inactivation of p16 and overexpression of HER-2/neu [14]. P16 inactivation was found in 45% of serous carcinomas and some clear cell cancers. The p16 tumor suppressor gene is located on chromosome 9p21 and encodes for a cell cycle regulatory protein. Thus, inactivation of p16 leads to uncontrolled cell growth.

The distinct molecular alterations also underscore prognostic differences. HER-2/neu overexpression has been associated with a metastatic phenotype and poor survival in type 2 EC [14]. In addition, approximately 67% of type I endometrial carcinomas are diploid, as evaluated by flow cytometry [15]. In contrast, 55% of the type 2 carcinomas exhibit aneuploid DNA patterns. Diploid tumors are usually low-grade type I carcinomas with only superficial invasion and are associated with longer survival than aneuploid carcinomas. Differences in disease-free survival for stage I tumors have been as significant as 94% for diploid carcinomas versus 64% for aneuploid carcinomas [15]. Finally, the presence of the classic steroid receptors ERα and PR-A have correlated with stage, grade and survival in several studies [16]. Additionally, it is thought that the ER and PR status constitute independent prognostic factors [16].

3. Treatment of endometrial cancer

The cornerstone of curative therapy for patients with EC is surgical treatment, including complete hysterectomy, removal of remaining adnexal structures and appropriate surgical staging in patients considered at risk for extrauterine disease [17]. Survival is heavily dependent on surgical stage: this is determined by using the classification system adopted by the International Federation of Gynecology and Obstetrics in 2009 (Table 1), which is the form that superseded the older 1988 version (Table 2).

The FIGO system is most commonly used for staging. The original 1970 criteria for staging endometrial cancer incorporated only information gained from presurgical evaluation (including physical examination, diagnostic fractional dilation, and curettage). Several studies have shown that clinical staging was inaccurate and did not reflect actual disease extent in 15–20% of patients [18]. Therefore, in 1988 the Cancer Committee of FIGO modified its staging system to emphasize complete surgicopathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases).

Most patients (90%) with endometrial carcinoma have abnormal vaginal bleeding, usually during the postmenopausal period [18]. Diagnosis can usually be made through office endometrial biopsy. The histologic information from the endometrial biopsy should be sufficient for planning definitive treatment. Office

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