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REVIEW PAPER

The significance of markers in the diagnosis of endometrial cancer

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Abstract

Endometrial cancer is one of the most common cancers experienced by women throughout the world. It is also the most common malignancy within the female reproductive system, representing 37.7% of all disorders. The incidence increases with age, and is diagnosed most frequently in women between 45 and 65 years old. In the last few years, numerous studies have been performed to identify tumour biomarkers. Biomarkers include not only protein routinely used as tumour markers but also genes and chromosomes. The limiting factor in the use of markers in the diagnosis of endometrial cancer is their lack of specificity. However, specific markers for endometrial cancer are the subject of much research attention. Although moderately elevated levels of markers are present in a number of inflammatory or non-malignant diseases, significantly increased levels of markers indicate the development of cancer. Recently, research has been focused on the identification of molecular changes leading to different histological subtypes of endometrial cancer. In this paper the authors reviewed several currently investigated markers. Progress in these investigations is very important in the diagnostics and treatment of endometrial cancer. In particular, the identification of novel mutations and molecular profiles should enhance our ability to personalise adjuvant treatment with genome-guided targeted therapy.

Key words: endometrial cancer, diagnostics, markers.

Introduction

Endometrial cancer is one of the most common cancers experienced by women throughout the world. It is also the most common malignancy within the female reproductive system, representing 37.7% of all disorders [1]. The incidence increases with age and is diagnosed most frequently in women between 45 and 65 years old [2, 3].

The factors that increase the risk of developing endometrial cancer include age, obesity, diabetes, early menarche, late menopause, anovulatory cycles, menstrual disorders, polycystic ovary syndrome, hormone replacement therapy (HRT), childlessness, and oestrogen-secreting tumours [4].

Around 80% of endometrial cancers are adenocarcinomas, 60-65% of which are endometrioidal cancers [5, 6]. Other rare kinds of endometrial cancer include serous and clear cell adenocarcinoma, mixed type endometrial cancer, mucinous adenocarcinoma, squamous cell carcinoma, endometrioidal cancer with squamous metaplasia, small cell neuroendocrine carcinoma, and transitional cell carcinoma [5]. The most important clinico-pathological prognostic variables are FIGO stage, tumour grade, lymph node, and lymph-vascular space status, as well as depth of myometrial invasion.

Endometrial cancers are divided into two types. The characteristics of both types are given in Table I.

In the last few years, numerous studies have been performed to identify tumour biomarkers. As defined by the Biomarkers Definitions Working Group, "a biomarker is a biological molecule present in the blood or any other body fluids or in the tissue. This molecule is a sign of normal or abnormal process, good condition or a disease" [7]. Biomarkers include not only proteins routinely used as tumour markers but also genes and chromosomes. The limiting factor in the use of markers in the diagnosis of endometrial cancer is their lack of specificity. However, specific markers for endometrial cancer are the subject of much research attention. Although moderately elevated levels of markers are present in a number of inflammatory or non-malignant diseases, significantly increased levels of markers indicate the development of cancer.

Recently, research has been focused on the identification of molecular changes leading to different histological subtypes of endometrial cancer.

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Tab. I. Characteristics of type I and II endometrial cancer

	Type I endometrial cancer	Type II endometrial cancer
Type	Endometrioidal cancer	Non-endometrioidal cancer
Development	Perimenopausal age Chronic oestrogen stimulation Anovulatory cycles Obesity Hypertension Diabetes	Age over 65 years No oestrogen stimulation Atrophic endometrium
Incidence	80% of endometrial cancers	20% of endometrial cancers
The initial change	Endometrial intraepithelial neoplasia (EIN) Atopic hyperplasia	Endometrial intraepithelial carcinoma (EIC)
Method of spreading	Infiltration of the myometrium Spreading through the lymphatic vessels	Deep infiltration of the myometrium Spreading through the lymphatic vessels
Course of the disease	Slow and stable High five-year survival rate (80-85%)	Aggressive Peritoneal and lymph nodes metastases Five-year survival rate is low (30-70%)
Grade	Low grade and good prognosis	High grade and poor prognosis
Receptors	ER+ PR+	ER– PR–
Molecular disorders	DNA repair genes PTEN (40-80%) K-ras (20-35%) microsatellite instability (20-40%) PIK3CA β-catenin (30-40%) TP53 (5-10%) E-catherin (10-15%) p16 (10%)	Microsatellite instability (up to 5%) PTEN (10%) K-ras (up to 5%) TP53 (90%) β-catenin (up to 5%) E-catherin (80-90%) p16 (40%)

Serum biomarkers

CA125

CA125 is routinely tested as part of the diagnosis and treatment of endometrial cancer, and its determination before treatment can be valuable in the staging of endometrial cancer. Increased concentrations of CA125 (> 35 U/ml) correlate with clinical stage, depth of tumour invasion, tumour grade, lymph node status, cervical invasion, and peritoneal cytology [8-10].

However, the diagnostic sensitivity of CA125 in endometrial cancer is unsatisfactory, especially in early tumour stages. Also CA125 specificity in endometrial cancer is low: elevated CA125 is commonly known to occur in many non-malignant diseases such as inflammation or endometriosis. Serum concentrations of CA125 are elevated in only 10-20% of women with early stage of endometrial cancer, and 25% of asymptomatic patients with recurrences will present with elevated CA125 levels. The use of CA125 for endometrial cancer detection is restricted to advanced-stage diagnosis [11, 12]. However, an elevated preoperative CA125 level is an independent predictor for poor diagnosis [13, 14]. Saarelainen *et al*. report that the presence of both HE4 and CA125 together has a higher predictive value than when each is tested individually [15].

CA15.3

The clinical utility of other known tumour markers such as CA15.3 have proven to be unsatisfactory in patients with endometrial cancer. Serum CA15.3 levels are increased in 24-32% of patients with endometrial cancer. Scambia *et al*. found a significant relationship between serum CA15.3 levels (> 30 U/ml and > 50 U/ml) and shorter survival (p = 0.0004 and p = 0.00025), respectively [16].

HE4

The human epididymis protein (HE4) is a potential biomarker useful in the diagnosis of ovarian cancer. Elevated levels of HE4 are also observed in patients with endometrial cancer. Moore *et al*. report that serum HE4 was elevated in all stages of disease, and that serum HE4 levels were more sensitive than serum CA125 in early stage disease [17]. The serum concentration of HE4 has been shown to correlate with the depth of myometrial invasion and the stage of endometrial carcinoma (see Table II and III) [18-20].

Mutz-Dehbalaie *et al*. found HE4 to be a prognostic value for overall survival, based on univariate (p = 0.001) and multivariate (p = 0.023) analysis of a group

Tab. II. Relationship between serum HE4 concentration and depth of myometrial invasion

Author [ref.]	Cases (*N*)	EEC (*N*)	Depth of myometrial invasion	Mean HE4 (pmol/l)	*p*
Bignotti *et al*. [18]	153	138	< 50%	66.0	< 0.01
			> 50%	98.0	
Antonsen *et al*. [19]	352	335	< 50%	53.7	< 0.0001
			> 50%	88.5	
Angioli *et al*. [20]	204	101	< 50%	63.4	0.012
			> 50%	108.7	

HE4 – human epididymis protein 4, EEC – endometrioid endometrial carcinoma

Tab. III. Relationship between serum HE4 concentration and FIGO stage

Author [ref.]	Cases (*N*)	EEC (*N*)	FIGO	Mean HE4 (pmol/l)	*p*
Angioli *et al*. [20]	204	101	I	85.8	< 0.05
			II	147.8	
			III	140.3	
			IV	588.3	
Antonsen *et al*. [19]	352	335	AEH	40.1	< 0.0001
			IA	54.4	
			IB	78.4	
			II	74.0	
			IIIA	105.5	
			IIIB	211.2	
			IIIC	111.8	
			IVA	702.4	
			IVB	430.1	
Bignotti *et al*. [18]	153	138	I + II	74	< 0.01
			III + IV	112	

HE4 – human epididymis protein 4, EEC – endometrioid endometrial carcinoma

of patients with endometrial cancer. They suggested that preoperative HE4 serum levels are independent prognostic marker in patients with endometrial carcinoma [21]. Saarelainen *et al*. noted a statistically significant relationship between median concentrations of HE4 and metastases ($p = 0.001$), deep myometrial invasion ($p < 0.001$), patient age ($p < 0.01$), body mass index ($p < 0.01$), and histologic grade ($p = 0.012$) [15].

VEGF

Angiogenesis is an essential process in the development of tumours. The role of angiogenic factors in the development of endometrial cancer has been a persistent subject of study. The most powerful angiogenic factor is known to be vascular endothelial growth factor (VEGF). VEGF plays a crucial role in the initiation of physiological and pathological angiogenesis. Elevated levels of VEGF have been shown in patients with endometrial cancer [22]. Studies have shown a relationship between the blood level of VEGF and the clinical stage of cancer [23].

Overexpression of VEGF and its receptors are related to poor prognosis in patients with endometrial carcinomas [23]. Several anticancer treatments are being studied as possible means of targeting VEGF and its receptors, but the success with these agents has been limited. VEGF and VEGFR1 overexpression was associated with poor prognosis compared to patients with negative tumours ($p < 0.001$). VEGF and VEGFR-1 overexpression may be a useful marker for predicting five-year DFS in patients with endometrioid endometrial cancer [24].

Kamat *et al*. reported that patients with high VEGF expression had a 19-fold higher risk of death compared to patients with low VEGF expression ($p = 0.002$). They also found a statistically significant relationship between the high risk of death due to disease and the presence of a grade 3 ($p < 0.001$) or high stage ($p < 0.001$) tumour [25]. These studies confirm the results of other researchers [26, 27]. Conversely, Fine *et al*. did not report any significant relationship between the expression of VEGF, flt-1, or KDR/flk-1 receptors and the presence of metastases, rates of recurrence, or patient survival [28].

Another factor belonging to the VEGF family is placental growth factor (PLGF), which is a positive regulator of angiogenesis. The role of PLGF has been investigated in several cancer types, including breast or colorectal cancer [29, 30]. Coenegrachts *et al*. found that PLGF serum levels were increased only in stage 4 endometrial cancer. In addition, local PLGF protein levels had no effect on disease-free survival or overall survival [31]. Despite this, the role of PLGF in the development of endometrial cancer has not been thoroughly investigated.

Genetic biomarkers

Different molecular profiles are known to be involved in endometrial carcinogenesis (see Tables I and IV).

DNA ploidy

Aneuploidy is an abnormal number of chromosomes. It is the most common genetic abnormality observed in cancer cells. Aneuploidy is associated with mutations in tumour suppressor genes and loss of mismatch repair genes. Many investigators report that DNA ploidy is an important prognostic factor in patients with endometrial carcinoma. Aneuploid tumours account for approximately 16-28% of endometrial cancers. Aneuploidy is correlated with such clinico-pathological variables as histological type of cancer, especially non-endometrioid cancers, old age at diagnosis, lymph node involvement, high tumour grade, and increased risk of disease recurrence [32]. Generally, aneuploid endometrioid endometrial carcinomas have a DNA index (DI) below 1.20, whereas aneuploidy serous adenocarcinomas have a DI greater than 1.60. Pradhan *et al*. reported that patients with aneuploid endometrial carcinomas with a DI above 1.20 demonstrate a poorer progression-free survival rate and overall survival rate compared to patients with diploid cancers [33].

Similarly, Susini *et al*. demonstrated that patients with aneuploidy tumours demonstrate higher recurrence rates of the disease (44.9%) than patients with diploid tumours (11.2%) ($p < 0.0001$). The disease-free interval was also shorter in patients with aneuploid tumours, compared with diploid tumours, the durations being 16 and 37 months, respectively. They also demonstrated a statically significant relationship between DNA ploidy and mortality ($p < 0.0001$). The authors suggest that DNA ploidy and disease stage should be taken into account when planning treatment [34].

Suppressor genes

PTEN

PTEN mutations are the most frequent genetic alterations seen in endometrial cancer. The *PTEN* gene is a tumour suppressor gene located on chromosome 10q23. PTEN inactivation is caused by mutations and leads to loss of expression [35]. PTEN mutations occur in about 55% of endometrial cancers, particularly in endometrioid endometrial carcinomas and tumours with microsatellite instability (MSI) [36, 37].

PTEN mutations occur in endometrial hyperplasia and in the early stages of endometrial cancer, suggesting that PTEN mutations may be an early diagnostic factor. PTEN is an important regulator of the PI3K–AKT pathway, and it plays a significant role in the maintenance of genomic integrity [38, 39]. McConechy *et al*. studied the differences in the expression of PTEN in ovarian endometrioid carcinomas and endometrial endometrioid carcinomas. They found that PTEN mutations are more frequent in endometrial endometrioid carcinomas compared to ovarian endometrioid carcinomas ($p < 0.0001$) [40]. Loss of PTEN function is associated with better clinical outcome in patients with advanced or recurrent disease. In patients with early stage of disease, this did not appear to impact on survival [41].

TP53 gene and p53 protein

The *TP53* tumour suppressor gene, located on chromosome 17, is the most commonly mutated gene in human cancers, and it plays an important role in the biology of gynaecological carcinomas. Its role is to prevent the proliferation of cells with damaged DNA. TP53 arrests the cell cycle by increasing the expression of p21. TP53 mutations are twice as common in serous carcinomas than in endometrioid endometrial carcinomas and occur at an early stage of disease [36, 42]. p53 protein overexpression is correlated with advanced state of the disease, poor differentiation, deep myometrial invasion, lymph node metastases, and lower survival rates [43-45]. Lia *et al*. examined the expression of TP53 in normal endometrium (0%), endometrial hyperplasia (43%), endometrial intraepithelial carcinoma (72%), and serous endometrial carcinoma (96%) and found the incidence of TP53 gene mutations to be highest in poorly differentiated tumours (43% in G3, 8% in G2, and 0% in G1) [46-48].

Patients with p53 gene mutations and p53 protein overexpression demonstrate a higher mortality rate than patients without p53 alterations [49, 50]. Saffari *et al*. found that patients with p53 gene mutations had

Tab. IV. The most common gene mutations present in endometrial cancers

	Suppressor genes	Oncogenes
Endometrioid endometrial carcinoma	PTEN	K-ras PI3K
Serous endometrial carcinoma	p53 p21 p16	HER2/neu

the same survival rates as untreated patients without p53 mutations [51].

p21 and p16

TP53 increases the expression of the *p21/WAF1* gene, whose protein product is an inhibitor of cyclin-dependent kinases. p16 is a cell cycle regulator. Loss of p15/CDKN2A protein expression occurs in approximately 67% of endometrial cancers [52]. Researchers have demonstrated high p16 expression in serous endometrial carcinoma. Overexpression of p16 was found in 36% of endometrioid patients compared to 78% of serous papillary patients.

However, this high expression has not been shown to have any significance in the context of endometrial cancer. Further studies must be performed [53, 54]. Abu Backer *et al*. reported p21/WAF1 expression to be significantly associated with infiltration of the corpus and lymph node metastasis for adenocarcinoma of the cervix. P16/INK4a expression is associated with histological grade but not histological type of endometrioid endometrial carcinoma [55].

Oncogenes

Her2/neu

HER2/neu (ErbB2) is a member of the human epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinases consisting of EGFR (HER1, ErbB1), HER2/neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) [56]. It is normally inactivated, but its activation causes uncontrolled cell division. HER2/neu overexpression was found in about 10-20% of endometrioid carcinomas and is a potential factor indicating late progression, differentiation events, and poor survival [57, 58]. Patients with HER2-amplified uterine endometrial carcinoma had shorter overall survival rates than those without. In addition, patients with high HER2 copy numbers had poorer prognoses than patients with low HER2 amplification ratios [59]. Some researchers have reported a correlation between HER2 overexpression/amplification and tumour grade [58, 60].

Overexpression of HER2/neu was detected in approximately 14% and 80% of serous endometrial carcinomas, with HER2 amplification ranging from 21% to 47% [61-65]. Satin *et al*. reported the highest frequency of Her2/neu overexpression in uterine serous papillary cancer to be approximately 80%, whereas Togami *et al*. reported the lowest level of HER2 overexpression: approximately 14% [66, 67].

The wide range of HER2 overexpression can be explained by the small sample size used in individual studies, differences in clinical and histopathological factors, entry mixed histologic tumours, and differences in research methods. Several publications suggest that HER2 may be a promising therapeutic target.

Trastuzumab (Herceptin, Genentech, San Francisco, California) is a human monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of HER2/neu-overexpressing breast cancer and metastatic gastric cancer. Although some studies have reported that trastuzumab shows activity in patients with advanced or recurrent endometrial cancer, the results of study GOG-181B, a Phase II trial of single agent trastuzumab in patients with advanced or recurrent endometrial cancer, reveal no significant clinical activity of the drug [62, 68, 69].

PI3K-AKT-mTOR

The PIK3-PTEN-AKT signalling pathway is the most commonly altered pathway in endometrial carcinoma. It regulates multiple processes such as proliferation, apoptosis, cell growth, or angiogenesis. In normal cells, the *PTEN* gene product, a lipid phosphatase, inhibits the activity of the PI3K-AKT-mTOR pathway. The lack of PTEN function leads to excessive activation of this pathway [70, 71]. Alterations in these pathways are commonly observed in endometrioid endometrial cancer: they have been noted in about 80% of cases [72]. In endometrial cancer, the most common mutations are for the *PIK3CA* gene, which in 24-36% of cases coexist with PTEN mutations and are associated with poor prognosis. Oda *et al*. indicate that PIK3CA mutations are more common in tumours with PTEN mutations, but did not show poorer survival rates compared with patients without PIK3CA mutations. Mutations in the PIK3CA exon 20 are most common in high-grade tumours while mutations in exon 9 occur in low-grade carcinomas. Patients with PIK3CA and p53 alterations had shorter survival compared with patients with only p53 mutations ($p = 0.0001$) [73, 74]. No *et al*. report that overexpression of mTOR occurred in 7.1% of endometrial carcinomas. mTOR overexpression showed a positive correlation with patient age, menopausal status, and COX-2 expression ($p < 0.05$), but it was not associated with depth of myometrial invasion, tumour grade, stage and histological type, lymph node status, and survival [75].

FGFR2

Fibroblast growth factor receptor (FGFR2) is a tyrosine kinase that regulates cell angiogenesis and metastasis. Mutations of FGFR2 have been found in about 12% cases of endometrial cancer [76]. Byron *et al*. report the presence of FGFR2 mutations in 10% of tested primary uterine samples. They note that FGFR2 mutations coexist with PTEN loss of function mutations, but FGFR2 and K-ras mutations were mutually exclusive. Endometrial

cancer cells with FGFR2 mutations are more sensitive to killing by PD173074, a pan-FGFR inhibitor. These findings suggest that mutant FGFR2 is a potential therapeutic target [77, 78].

K-ras

Mutational activation of K-ras oncogene is another genetic change involved in endometrial carcinogenesis. K-ras mutations are present in 10-30% of sporadic endometrial cancers, especially in endometrioid endometrial cancers, as well as in atypical endometrial hyperplasia. K-ras mutations coexist with MSI [79-81]; however, they are very rare in serous and clear cell carcinomas. Although the relationship of Tamoxifen with K-ras mutations in endometrial cancer is inconclusive, some authors have reported a close relationship between them. Hachisuga *et al*. reported a significantly higher frequency of K-ras mutations in endometrial polyps in patients treated with tamoxifen (64%), and Wallen *et al*. reported increased occurrence of K-ras mutations in normal endometrial tissue in patients treated with tamoxifen [82, 83]. K-ras mutations have been associated with patient age, tumour stage, deeper myometrial invasion, lymph node metastases, and poor survival [84, 85].

MSI

Microsatellite instability (MSI) is the condition of genetic hypermutability that results from impaired DNA Mismatch Repair (MMR). DNA MMR corrects errors that spontaneously occur during DNA replication, like single base mismatches or deletions and short insertions. Cells with an abnormally functioning MMR system, indicated by the presence of MSI, tend to accumulate errors. Microsatellite instability may result in colon cancer, gastric cancer, endometrial cancer, ovarian cancer, hepatobiliary tract cancer, urinary tract cancer, brain cancer, and skin cancers [86]. This association between MSI and malignancy was first recognised in patients with hereditary nonpolyposis colorectal cancer (HNPCC), in which germline mutations occur in the genes of the MMR system.

While MSI in 15% of sporadic colorectal and endometrial cancers result from the hypermethylation of the *MLH1* gene promoter, MSI tumours in Lynch syndrome are caused by germline mutations in MLH1, MSH2, MSH6, and PMS2 [87, 88]. *MLH1* is a mismatch repair gene responsible for preserving genomic stability, and loss of MLH1 function leads to an accumulation of mutations, which leads to carcinogenesis [89]. Colorectal tumours with MSI are associated with poor differentiated tissue, high mucinogen content, as well as the presence of tumour infiltrating lymphocytes and a Crohn's-like host response [87].

Microsatellite instability occurs in 75% of endometrial cancers associated with HNPCC. Women with HNPCC have a 10-fold greater risk of endometrial cancer compared with women from the general population [90]. Microsatellite instability overexpression has been found to be higher in endometrial cancer tissue compared with controls (40% vs. 12%, $p < 0.05$).

However, the role of MSI in predicting the clinical course of endometrial cancer is unclear. Mackay *et al*. report that MSI occurs in the early stages of the disease, and it has been associated with a worse prognosis [41, 91]. An *et al*. note that MSI is much more common in endometrioid endometrial carcinoma than serous endometrial carcinoma (20% vs. 0%, $p < 0.001$). They also demonstrate a statistically significant relationship between the incidence of MSI and histologic grade, lymph vascular metastases, higher clinical stage, deep myometrial invasion, and unfavourable course of disease [92]. Conversely, Black *et al*. and Maxwell *et al*. report that MSI is associated with good prognosis [93, 94]. However, other authors have not shown any significant association between MSI and clinical course [95, 96]. Steinbakk *et al*. report that MSI positivity is an indicator of an unfavourable course of endometrial cancer in FIGO 1, but not in FIGO 2-4 [97].

ER and PR

Oestrogen receptor (ER) and progesterone receptor (PR) expression has been observed in 60-70% of endometrial cancers. The expression of these receptors correlates with tumour stage and survival and is associated with well differentiated tumours [98]. Mingzhu *et al*. found ER- and PR-positive tumours to be associated with better clinical outcome: early age, early stage, endometrioid subtype, high grade, less lymph node involvement, and less recurrence [99]. Ferrandina *et al*. investigated the expression of ER and PR in endometrial cancer and association of ER and PR with clinicopathological parameters. They found that ER and PR positivity was higher in patients with early stage of disease ($p < 0.05$), in cases of endometrioid cancer ($p < 0.05$) and in tumours with better grades of differentiation ($p < 0.05$). Furthermore, they showed a statistically significant relationship between ER positivity and negative lymph node status ($p < 0.05$) [100]. Huvilla *et al*. demonstrated that PR negativity is an independent prognostic factor for relapse in patients with early stage of endometrioid endometrial carcinoma [48].

Ki-67

Ki-67 is a marker of cell proliferation. In the majority of endometrioid endometrial cancers, the Ki-67 proliferation index is low and has a good prognosis. In con-

Tab. V. E-cadherin expression in type I and II endometrial carcinoma

Authors [ref.]	Cases		Negative E-cadherin expression, *n* (%)		*p*
	EEC	NEEC	EEC	EEC	
Stefansson *et al*. [114]	255	29	135 (53)	24 (83)	0.002
Moreno-Bueno *et al*. [115]	95	33	41 (50)	27 (87.1)	0.001
Holcomb *et al*. [116]	63	13	3 (5)	8 (62)	< 0.001

EEC – endometrioid endometrial carcinoma, NEEC – non-endometrioid endometrial carcinoma

trast, most serous and clear cell tumours have a high proliferation index, which is associated with increased tumour aggressiveness [101]. Ferrandina *et al*. demonstrate a statistically significant relationship between Ki-67 positivity and tumour type-endometrioid endometrial carcinomas, advanced clinical stage of the disease, poor grade of differentiation, and deeper myometrial invasion ($p < 0.05$). They also report an inverse relationship between ER and Ki-67 ($p < 0.009$) and between PR and Ki-67 ($p < 0.008$) [100]. Tumours with positive expression of Ki-67 and negative expression of ER and PR were associated with higher grade and poorer prognosis [48]. However, there are reports of a statistically significant relationship between increased expression of Ki-67 and advanced tumour stage, as well as relapse of the disease [102, 103].

Cox-2

Cyclooxygenase is an enzyme responsible for prostaglandin synthesis. Cyclooxygenase-2 (Cox-2) overexpression is correlated with neoangiogenesis, metastatic ability and poor prognosis, and the protein may play a critical role in carcinogenesis [104]. Cox-2 overexpression has been found in many tumours, including lung, skin, gastrointestinal tract, ovary, and cervical cancers [105, 106]. Ferrandina *et al*. observed no clear correlation between Cox-2 positivity and any clinicopathological features [100]. However, Knapp *et al*. reported higher Cox-2 expression in endometrial carcinoma compared to samples from a healthy endometrium. They suggest that Cox-2 plays a role in carcinogenesis. Similarly, Keser *et al*. suggest that Cox-2 might be a new therapeutic target, but further studies are needed [107, 108].

Adhesive molecules

E-cadherin and β-catenin are two basic adhesion molecules relevant to endometrial cancer [109]. High expression of β-catenin is characteristic of endometrioid endometrial carcinoma (31-47%) in contrast to non-endometrioid endometrial carcinoma (0-3%) [110].

Mutations in the *CTNNB1* gene, leading to high expression of β-catenin, are associated with low potential for metastasis. Loss of protein is an independent predictor of poor prognosis in patients with endometrial cancer [111, 112]. Low expression of E-cadherin and β-catenin correlates with poor prognosis.

Nei *et al*. reported greater β-catenin nuclear expression in endometrial hyperplasia than in endometrial carcinoma [113], which suggests that β-catenin is involved in the early stages of endometrial carcinogenesis. Saegusa *et al*. noted a significant relationship between β-catenin expression and low histological grade ($p = 0.048$), and that β-catenin expression was stronger in patients without lymph node metastases than in patients with them ($p = 0.027$) [111]. Low E-cadherin expression is characteristic of serous and clear cell endometrial carcinomas (Table V) [114-116].

Stefansson *et al*. reported low E-cadherin expression to be associated with high FIGO grade ($p = 0.04$), deep myometrial invasion ($p = 0.02$), high FIGO stage ($p = 0.01$), and vascular invasion ($p = 0.04$) [114]. E-cadherin overexpression is a positive prognostic factor in the clinical course of endometrioid endometrial cancer [117]. High E-cadherin expression is associated with reduced mortality, disease progression, and rate of disease recurrence [118].

Conclusions

The identification of novel mutations and molecular profiles should enhance our ability to personalise adjuvant treatment with genome-guided targeted therapy. In conclusion, mutations of PTEN and β-catenin are predictive of good prognosis, while DNA aneuploidy, p53 abnormalities, and elevated serum CA125 levels are usually associated with poor prognosis.

Disclosure

Authors report no conflict of interest.

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