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Review Article

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Biological and Molecular Aspects of Endometrial Cancer

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Introduction

The importance of the topic is conditioned by the high level of morbidity due to Endometrial Cancer (EC), constituting a major problem with global impact in public health. Endometrial cancer represents 4.8% of the cases of malignant tumors and ranks, worldwide, on the 6th place in the structure of the incidence of malignant tumors in women [1,2].

In terms of increasing morbidity rate, EC consistently ranks 7th among malignant neoplasms in women [2]. The constant increase in the incidence of CE is explained by the increase in the average life expectancy ("aging") among the population and the level of obesity [3-8].

The incidence of this pathology is constantly increasing not only among elderly patients, but also among young women. Data on EC within the European Union or, in general, for the states of the European continent are presented in (Table 1).

Table 1: CE incidence, prevalence and mortality per 100,000 population (GLOBOCAN, 2025).

Population	Incidence		Prevalence			Mortality	
	Abs.	Rate	1 year	3 year	5 year	Abs.	Rate
Europe	130051	16,6	113 930	312 639	482 952	29963	7,7
Austria	952	9,9	879	2412	3736	250	1,8
France	10982	14,9	9880	27304	42581	2698	2,3
Germany	12356	12,7	11697	32205	50030	2444	1,7
Romania	2355	12,1	1953	5360	8248	516	2,2

The high rate of cure in initial stages with an OS at 5 years around 80-85% have created the false belief that EC is a low-risk disease. Yet, advanced stages and some histologies are associated with poor prognosis. The 5-year survival rate of patients with endometrial cancer in stage I after treatment, according to the data of different authors, decreases depending on the depth of invasion in the myometrium from 97.5 (with invasion less than 5 mm) to 61.5% (with invasion greater than 10 mm), depending on the degree of differentiation - from 81% in patients with highly differentiated tumors to 42% in patients with poorly differentiated tumors [9]. The high variability of the survival rate of patients with endometrial cancer, even in stage I, has contributed to the implementation of aggressive treatment tactics, namely extended surgical interventions. However, in the world literature there is no information about a unified tactic for the treatment of endometrial cancer. There are no generally accepted approaches for choosing the volume of surgical intervention in patients who, in a large percentage of cases, have an aggravated concomitant

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pathology, as well as for the choice of adjuvant treatment. According to the risk of relapse, EC can be subdivided into five risk categories integrating molecular markers [10].

Modern concepts of endometrial cancer pathogenesis

Dualistic model

Endometrial cancer is traditionally classified into two pathogenic types [11]. Type I endometrial cancer is most often associated with good prognosis, while type II is associated with poor prognosis. This dualistic model does not fully capture the wide range of clinical, genetic, and molecular characteristics found in endometrial cancers (Table 2).

Table 2: Pathogenic types – dualistic model.

Type I (80%)	Type II (20%)
Estrogen dependent	Nonestrogen dependent
Arises in hyperplastic endometrium	Arises in atrophic endometrium
Usually local disease	Usually advanced disease
High survival rate	Low survival rate
Grade 1/2 endometrioid	Grade 3 endometrioid high-grade serous clear cell

The pathogenetic value remains indisputable in the face of various risk factors such as metabolic syndrome, hyperglycemia and obesity. However, according to some researchers, at present, this classification is not sufficient to determine the management tactics for patients, as well as to estimate the risk of recurrence. Modern methods of studying the structure of DNA, including cluster analysis, make it possible to determine the genetic profile of tumors, which often does not coincide with the morphological picture. Thus, we can assume that the introduction of a classification based on the molecular characteristics of tumors will give doctors the opportunity to develop individual schemes and increase the effectiveness of cancer treatment. In various studies, N. Bansal et al. carried out a thorough description of the specific genetic changes for each of the two pathogenetic types of EC [12] (Table 3).

Table 3: Frequency of most common targeted alterations in endometrial cancer according to pathogenic type.

Alterations in endometrial cancer	Type I (%)	Type II (%)
Mutation PIK3CA Exon 9 Exon 20	~ 30 7.0-15.5 10-34	~ 20 0 21
Amplification PIK3CA	2-14	46
KRAS	11-26	2
AKT	3	0
Mutation PTEN	83	5
Microsatellite instability	20-45	0-5
Acumularea nucleară de β-catenină	18-47	0
E-cadherin	5-50	62-87
Mutation TP53	~ 20	~ 90
Loss of function p16	8	45
Supraexpression HER2	3-10	32
Amplification HER2	1	17
Mutation FGFR2	12-16	1

Thus, endometrioid neoplasias are characterized by multiple changes, the most frequent being mutations of the PTEN gene [13]. Another genetic mutation of this type of tumor is microsatellite instability. Additional microsatellite alleles appear in tumor cells, which develop as a result of deregulated DNA replication. As a rule, it happens due to the inactivation of MLH1, responsible for DNA repair, associated with hypermethylation of the promoter CpG island. The following changes are represented by KRAS (adaptor protein, which transmits the signal from growth factors or protein kinase C on the MAPK cascades) and β-catenin mutations. In the study by Živa Ledinek et al. the authors indicated that while PTEN, KRAS mutations and microsatellite instability often coexist, β-catenin (CTNNB1) gene, a frequently mutated gene in endometrial cancer. This shows mutations mostly at phosphorylation sites of the β-catenin and almost exclusively in the endometrial subgroup of no specific molecular profile [14]. Another frequent change is inactivation of the p16 gene and increased expression of the HER-2/neu gene; p16 is a tumor suppressor whose inactivation causes uncontrolled cell growth. HER-2/neu is an oncogene encoding the transmembrane Epidermal Growth Factor Receptor (EGFR), involved in the transmission of cell signals [15]. Amplification or increased expression of the HER-2/neu gene has an important role in the pathogenesis and evolution of aggressive types of cancer. The next mutation is represented by the decrease in the expression of E-cadherin (cell adhesion transmembrane protein), characterized by a decrease in the strength of adhesion between cells, which causes the separation and spread of tumor cells, that is, the development of metastases [16]. Modern methods of studying the structure of DNA make it possible to determine the genetic profile of tumors, which often does not coincide with the morphological picture. According to the researchers, this fact suggests that the classification of endometrial cancer can no longer emerge from a dualistic model. Thus, the correct determination of the molecular subtype of the tumor represents a fudamental aspect in estimating the prognosis of the disease.

Molecular classification of endometrial carcinomas

In 2013, The Cancer Genome Atlas (TCGA) Research Network published an integrated genomic analysis of 373 EC. For this reason, 4 new patterns of endometrial neoplasia were highlighted, depending on the spectrum of molecular-genetic changes [17].

Ultramutated tumors: These tumors are characterized by a high frequency of somatic mutations, microsatellite stability, low level of gene copy number changes, frequent mutations in the PTEN, PIK3CA, ARID1A, KRAS genes and an expression level of CCNB1 (*β-catenin) increased [18]. “Hotspot mutations” (Pro-286Arg, Val411Leu) have been identified in the structure of the exonuclear domain of the POLE gene [11]. Not all endometrial tumors, which show POLE mutations, can be considered “ultramutant”, also because such mutations occur outside the exonuclear domain [18]. The POLE gene encodes the catalytic subunit of DNA polymerase epsilon and is responsible for main strand synthesis during the DNA replication process. It also has an important role in the recognition and removal of nucleotides [17,18]. Y. Hussein et al. who also studied the morphological structure of the tumors, demonstrated that virtually all endometrial tumors containing a POLE gene mutation had at least a component of endometrioid differentiation, but intratumoral heterogeneity was also identified significant [19]. It is noteworthy that the TP53 mutation, charac-

teristic of serous endometrial tumors, was detected in 6(35%) of 17 tumors of the POLE cluster. Considering the clinical prognosis, "ultramutant" tumors have the best prognosis compared to other molecular subtypes [18].

Hypermutant tumors: TCGA has also described a molecular subgroup characterized by Microsatellite Instability (MSI). MSI results from defects in the post-replicative DNA repair system. In TCGA, MSI was determined by a panel represented by 4 mononucleotide repeat sites (polyadenic sequences BAT25, BAT26, BAT40 and transforming growth factor receptor type II) and three dinucleotide repeat sites (CA repeats in D2S123 , D5S346 and D17S250), tumor DNA was classified as Microsatellite-Stable (MSS) if zero markers were altered, as MSI-low (MSI-L) if 1-2 markers (below 40%) were changed and as MSI-high (MSI-H), if three or more markers (more than 40%) were changed [20]. Tumors of this subgroup are characterized by microsatellite instability caused by MLH1 promoter methylation [11,12]. Also, there is an overall high level of mutations and a small number of gene copy number changes [12]. Tumors with microsatellite instability have a high level of PIK3CA expression, but also a low level of PTEN expression [11]. According to TCGA (2013), none of the tumors with high microsatellite instability had mutations in the POLE gene "hotspot" [12]. Also, Živa Ledinek et al. [13] determined that KRAS and FGFR2 mutations were much more common among tumors with microsatellite instability, in contrast to CTNNB1 mutations, which are specific to tumors with microsatellite stability. It should be noted that, in addition to gene mutations, a significant number of cellular pathway defects have been identified, including the breakdown of threonine II, glycine, and anandamide. According to the histological examination, no tumor with a mixed or serous morphological structure was included in this group [11]. Microsatellite instability was also detected with a higher frequency in poorly differentiated tumors (G3) compared to highly differentiated tumors (G1) [21]. The study of endometrioid tumors by I. Zighelboim et al. demonstrated the absence of a correlation between microsatellite instability and disease outcome [22], which was also confirmed by I. Diaz-Padilla et al. in a meta-analysis that included 23 investigations [23].

CN-high tumors ("High number of copies"): TCGA revealed a molecular subgroup represented by copy number analysis. Copy number was determined using the Affymetrix SNP 6.0 microarray technique with DNA from frozen tissue. Hierarchical clustering revealed significant recurrences of amplifications or deletion areas and a CN-high ("high copy number") subgroup. The "CN-high" subgroup is characterized by pronounced deviations in the number of copies of somatic genes, a general low level of mutations, changes in the genes TP53, PIK3CA, CTNNB1, a decrease in the level of the phospho-AKT protein, which caused the deactivation of the phospho-AKT signaling [11,12]. Focal amplification of ERBB2 (HER-2), often in combination with PIK3CA mutations, was identified in 1/4 of cases [11]. According to K. Berns et al. and P. Eichhorn et al. such a combination of deviations in breast cancer causes resistance to certain types of targeted therapy [33,34]. Overall, this cluster revealed the highest transcriptional activity based on obvious cell cycle dysregulation (CCNE1, PIK3CA, MYC, CDKN2A) and TP53 mutation [11]. Particular attention is paid to the mutation of the CHD4 gene (encodes the catalytic subunit of the chromatin remodeling complex), the presence of mutations in the "hotspots" of which, as mentioned by E. Kuhn et al.; S. Zhao et al. as well as TCGA (2013), allows us to assume that it would have a key role in the carcinogenesis of serous and serous-type tumors [24,25]. The "CN-high" cluster includes the majority of serous adenocarcinomas and 1/4 of serous endometrioid adenocarcinomas of the G3 class, a fact that may cause an underestimation of the prognosis of the disease, which is based only on the results of a morphological study of neoplasms [11,12]. Among all subgroups, these tumors stand out with the least favorable prognosis [12]. It is also relevant that somatic gene copy number abnormalities in endometrioid tumors are rare, but serous and serous-type tumors demonstrate their high frequency, which correlates negatively with survival in the absence of disease progression [11].

CN-low tumors ("Low number of copies"): All remaining samples that were not part of the POLE ultramutant group, the MSI group, or the "CN-high" group were included in "CN-low." The "CN-low" group consists of G1-2 microsatellite stable tumors, with a general low level of mutations, but with changes in the PTEN gene [11,12]. In the process of analyzing the signaling pathway disorders, the most significant changes were identified in the case of this group. These include CTNNB1, KRAS, SOX17 gene mutations (regulates β-catenin activity). In the literature review by M. Le Gallo et al. SOX17 gene mutations are described only in this subgroup [15]. Also, approximately all CN-low tumors (92%) show alterations in the PI3K signaling pathway [11]. According to the morphological structure, endometrioid tumors with different degrees of differentiation predominate (most frequently, G1). The subgroup is also characterized by an increase in the expression of progesterone receptors, which may indicate a sensitivity of these tumors to hormone therapy [11].

Markers of tumor growth aggressiveness

The Microsatellite Instability (MSI) described above as a diagnostic sign of a post-replicative repair defect also has prognostic significance. The cause of MSI is the inactivation of the genes responsible for DNA repair: MLH1, MSH2, MSH6, PMS2. It was found that with the mutation of at least one of the genes of the repair system (MSH2, MLH1, MSH3, PMS2), the risk of developing EC is about 30% [5]. MSI has been found to be more characteristic of CE type 1 [4,6]. Through the fluorescence analysis method, it was shown that there are 2 types of microsatellite changes in EC patients: type A and type B, associated with the molecular, clinical and pathological characteristics of the tumors. At the same time, type B MSI correlates with hereditary nonpolyposis colorectal cancer [7]. The high rate of raw data accumulation with reference to cancer genomics as well as the development of bioinformatics algorithms necessary for the analysis, re-analysis and comparison of cohorts are key elements for obtaining new fundamental knowledge (transforming raw data into smart data). In the present study we aimed to re-analyze a set of genomic data obtained by sequencing 197 endometrial cancer samples and downloaded from the public database cBioPortal for Cancer Genomics - Endometrial Cancer (MSK, 2018) [3-5]. The aim of the research was to separate the genomic data into two cohorts based on the presence or absence of microsatellite instability and analyze the molecular profile of these cohorts. Samples with No Value (NA) were excluded from the study. As a result, two sets of data were obtained: SM (Microsatellite Stability) – 153 samples, IM (Microsatellite Instability) – 25 samples. The comparative analysis of the molecular data in the two subtypes of CE highlights

major differences in the mutational profile (Figure 1).

Pathway Enrichment Analysis (PEA) and Tumor Mutational Burden (TMB) analysis results are shown in (Figures 3 and 4).

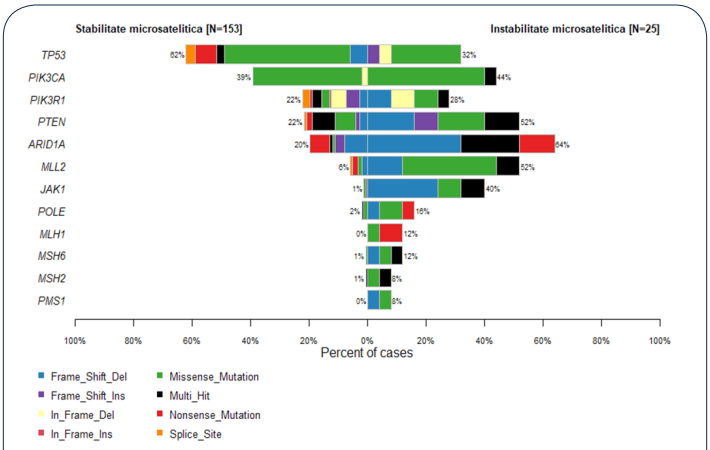

Figure 1: Mutational profiling of endometrioid tumors with microsatellite stability and microsatellite instability.
In the MS cohort, an almost 2-fold higher frequency of changes in the tumor suppressor TP53 is observed, while in IM – a considerably increased rate of PTEN, ARID1A, MLL2, JAK1, POLE, MLH1, MSH6, MSH2 and PMS1 mutations. SNV (Single Nucleotide Variation) classes in the IM group compared to SM have higher rates of T>C transitions that associate with mutational signature no. 5 and lower C>G transversions - markers of signature 13 (Figure 2). A higher frequency of deletions with the displacement of the reading frame (Frame Shift Deletions) is also observed in the IM cohort.

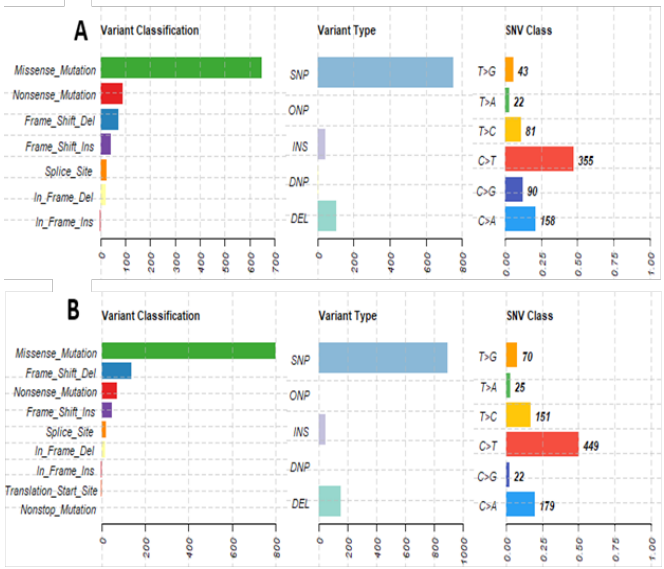

Figure 2: Type of genetic variants and classes of SNVs **(A)** Microsatellite stability; **(B)** Microsatellite instability).

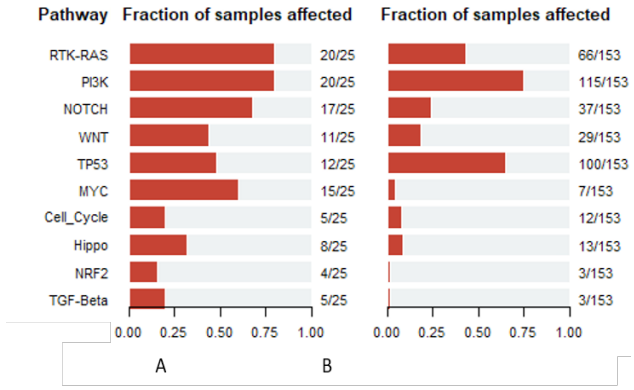

Figure 3: Pathway Enrichment Analysis (PEA) **(A)** Microsatellite stability; **(B)** Microsatellite instability).

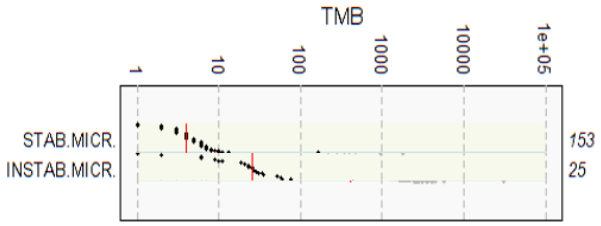

Figure 4: The value of the TMB index (tumor mutational load) in the studied cohorts.

According to the FDA (Food and Drug Administration) decision of June 16, 2020, unresectable metastatic tumors with a TMB index greater than or equal to 10 mut/Mb (mutations per megabase of coding regions of the tumor genome) are approved to be treated with the drug pembrolizumab (Keytruda, Merck & Co., Inc.), thus tumor mutational load is emerging as an important biomarker for immunotherapy. TMB in the two study groups revealed an index of less than 10 mut/Mb in MS and more than 10 mut/Mb in IM. This is confirmation that tumors with microsatellite instability have a better response to treatment with immune checkpoint inhibitors. In the MSI study of 342 patients with stage I - IV EC aged 30-80 years, it was found that in stage I EC, the MSI detection rate was 30.8%, depending on tumor invasion [8]. In the group of patients with tumor localization in the uterine fundus, the incidence of MSI was higher than in the groups with other tumor localization - 89.8%. The frequency of MSI detection in patients with endometrioid forms of cancer was 40.4% of cases, and in the group of patients with non-endometrioid forms - 6.0% [8]. It has been shown that MSI is detected in 19.0% of cases in tumors with a high degree of differentiation, with a moderate degree of differentiation - 41.5% and with a low degree of differentiation - 59.2% [8]. Thus, the MSI index can be used to determine the aggressiveness of malignant tumor growth as an additional criterion for predicting the prognosis of the evolution of endometrial cancer.

The trans-membrane protein PD as a receptor for programmed cell death

The trans-membrane protein, PD, has an important role in the differentiation and proliferation of immune cells, and for the elucidation of different aspects of this protein in the immune control

of the tissue and the possibility of reactivating cytotoxic lymphocytes by annihilating the inhibitory properties of PD regarding the anticancer exercise James P. Allison and Tasuku Honjo were awarded the 2018 Nobel Prize in Medicine.

Sustained antigenic stimulation in cancer leads to sustained expression of the PD-1 receptor on T lymphocytes (CD8) and, respectively, to an increase in the expression of PD-L1 ligands on tumor cells [9,62]. Thus, the tumor can escape the immune response by expressing the PD-L1 ligand, which, by binding to the PD-1 receptor on T lymphocytes, disrupts their cytotoxic activity by reducing the release of cytokines. Moreover, PD-L1 is not only an inhibitor of the immune response, but also an inducer of T-lymphocyte apoptosis. When assessing the expression of PD-L1, PDL2 (programmed cell death ligands 1 and 2) an increase in PD expression was found -L1 in 92% of CE patients, while PDL2 expression remains diminished [9].

Study of the expression levels of IDO (indolamine 2,3 - dioxygenase), PD-L1, PD-L2, B7-H4, galectins 1 and 3 in tissue samples from EC patients (72 patients aged between 39 and 74 years) showed increased IDO expression in 38%, 63%, and 43% of primary tumors, recurrent carcinomas, and metastatic carcinomas, respectively.PD-L1 expression was positive in 83% of primary tumors, 68% of recurrent carcinomas, and 100% of metastatic carcinomas, while B7-H4 expression was found in 100% of primary and recurrent carcinomas and 96% of metastatic carcinomas. At the same time, the expression levels of galectin 1 and 3 did not differ significantly in normal and tumor samples [10]. PD-L1 / PD-1 inhibition is a promising path in CE therapy, as it will lead to the activation of immune system cells, especially T lymphocytes, which have a cytotoxic effect on cancer cells. The clinical efficacy and low toxicity of antiPD-L1/antiPD antibodies (BMS936559, MPDL3280A and MEDI-4736) have been proven in the treatment of CE [11]. It has been established that in the case of CE chemotherapy (paclitaxel, doxorubicin and carbopalatin) in combination with anti-PD-L1 / PD-1 can reduce the dose of chemotherapy drugs and therefore reduce their side effects [12].

Markers of proliferative activity in endometrial cancer

Proliferative activity is a major factor in the mechanism of malignant transformation of cells and in the biological behavior of an already formed tumor [26]. To date, tumor cell proliferation has been examined by counting mitoses, determining the mitotic regime, and cytometry [27].

However, currently, new more informative methods have been developed to determine the characteristics of the proliferation of malignant tumor cells [28].

In this regard, the most promising marker of proliferation is the Ki-67 antigen, which is expressed in almost all phases of the mitotic cycle and, consequently, reflects the size of the proliferative phase [28,29].

According to some studies, the proliferative activity is directly correlated with the degree of histological malignancy, the degree of invasion, the presence of metastases [30], while there is an inverse relationship between the Ki-67 level and the presence of steroid hormone receptors [31].

Currently, quite a large number of studies have been conducted to study proliferation markers in various tumors [32]. The proliferation index has been found to be an independent prognostic marker that determines the probability of recurrence, overall and recurrence-free survival [33].

The pathophysiological role of Ki-67 antigen in cellular life is not yet clear. However, its presence in all active phases of the mitotic cycle allows this protein to be used as a universal marker of proliferation in the assessment of the growth activity of malignant neoplasms. The tumor growth rate contains very important information for determining the oncological nature of the tumor and its aggressiveness [34]. In such cases, the indicator of its proliferative activity is one of the decisive factors taken into account when choosing a treatment strategy. In addition, currently, along with the assessment of quantitative parameters of proliferation, an active study of substances that regulate the passage of cells through the mitotic cycle has begun [34]. These substances include cyclins and inhibitors of cyclin-dependent kinases, which regulate the transition of cells from the presynthetic G1 phase to the S phase (DNA synthesis). The activity of cyclin-dependent kinase depends on the corresponding inhibitor in such a way that, with its intense operation, a block occurs in the G1 phase and apoptosis is induced, and, on the contrary, when its activity is suppressed, the cells move freely through the mitotic cycle [34]. The following cyclin-dependent kinase inhibitors have been the most studied: p15, p16, p18, p19, p21, p27, p57. According to the literature, a decrease in the expression of cyclin-dependent kinases is due to ubiquitin-proteasome-dependent degradation, which is accompanied by tumor progression and poor prognosis [34].

Molecular markers of apoptosis as a prognostic factor for endometrial cancer

The analysis of data from the specialized literature showed that, in hyperplastic and CE processes, only the individual links of mitochondrial apoptosis mechanisms mediated by tumor necrosis factor and mitochondria have been studied [29,36]. In CE, the prognostic value of oncogenes bcl-2, bax, c-erb B-2\HER-2 \ neu, c-myc and anti-oncogene p53 has been best studied. Bcl-2 is the main gene that determines the mechanism of cell death, suppressing apoptosis. This gene encodes the formation of a protein that accumulates in mitochondria [36-38]. Bcl-2 expression is associated with factors that indicate a favorable prognosis, as it correlates with the presence of receptors for steroid hormones and a low degree of malignancy [38]. According to the literature, high expression of Bcl-2 is detected in normal proliferative and hyperplastic endometrium without atypia, while in atypical hyperplasia and adenocarcinoma, its expression significantly decreases [37]. This confirms that this proto-oncogene is not involved in the processes of carcinogenesis, but the significant differences revealed in the expression of the proto-oncogene in simple and atypical hyperplasias suggest the possibility of using Bcl-2 in the differential diagnosis of these forms of hyperplasia [39]. Recently, there is evidence that Bcl-2 expression, Bcl-2/Bax index can be independent indicators of overall and relapse-free survival. In addition, in endometrial tumors, in contrast to normal, atrophic or hyperplastic endometrium, Bax expression is usually quite high (85–89%). A functional antagonist of the Bcl-2 protein is p53. The p-53 gene mutation plays a key role in carcinogenesis. P-53 is a product of a suppressor gene that regulates the passage of cells through the cell cycle; if DNA repair is required, it inhibits cell prolifera-

tion. The suppressor gene p53 encodes a nuclear protein that modulates the expression of genes responsible for DNA repair, cell division and apoptosis [40,41]. In at least half of all malignant tumor cases, mutations are found in chromosome 17 in the location of the p53 suppressor gene [42]. The AF-2 domain and the C-terminal regulatory domain of the tumor suppressor gene p53 have been found to be capable of interaction [1,9]. Formation of this complex leads to the loss of transcription of p53-dependent genes, which include: genes whose activation contributes to cell cycle suppression; genes involved in p53-dependent apoptosis (Bax, Fas receptor gene, IGFBPs gene); genes encoding inhibitors of angiogenesis (thrombospodin I) [43]. Thus, p53 mutations play an important role in the pathogenesis of tumor growth and are associated with the aggressiveness of the clinical course of the disease and tumor resistance to chemotherapy and radiotherapy [44].

The role of PTEN in endometrial cancer

Currently, great importance in the processes of carcinogenesis is given to tumor suppressors, including the PTEN protein, which has tyrosine-phosphatase activity. PTEN is a tumor suppressor gene and encodes the synthesis of a protein with a role in cell cycle regulation. It participates in the PI3K-AKT signaling pathway which in turn is involved in the pathogenesis of cancer. The substitution c.389G>A is one of the most frequent mutations of the PTEN gene, it is a pathogenic alteration (FATHMM pathogenicity score 0.99) and involves the replacement of guanine at position 389 with adenine. It usually occurs sporadically as a somatic mutation, but sometimes it can also be transmitted through the germ line (Cowden syndrome) (Figure 5).

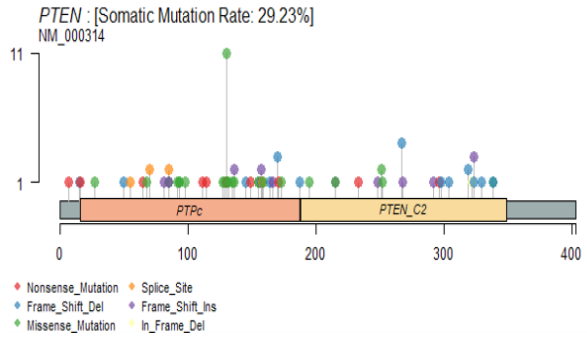

Figure 5: Frequency of PTEN mutations in the Endometrial Cancer genomic dataset Reprinted/adapted with permission from reference [1]. Copyright year: 2018, copyright name: Memorial Sloan-Kettering Cancer Center.

Thus, PTEN suppresses the antiapoptotic effects of the P3K-PKB/AKT signaling pathway (phosphoinositol-3 kinase/serine-threonine protein kinase/AKT signaling pathway). The activated form of PKB/AKT is able to block apoptosis in several ways without involving Bcl-2 [45]. Thus, the important antitumor role of PTEN becomes clear. The biological effect of IGF has been shown to be partially mediated by activation of the phosphoinositol-3 kinase/serine-threonine protein kinase/AKT signaling pathway. Meanwhile, new data have emerged showing that PTEN is also involved in cell adhesion and migration, suggesting an important role of PTEN in tumor invasion and metastasis [46,47] (Figure 6).

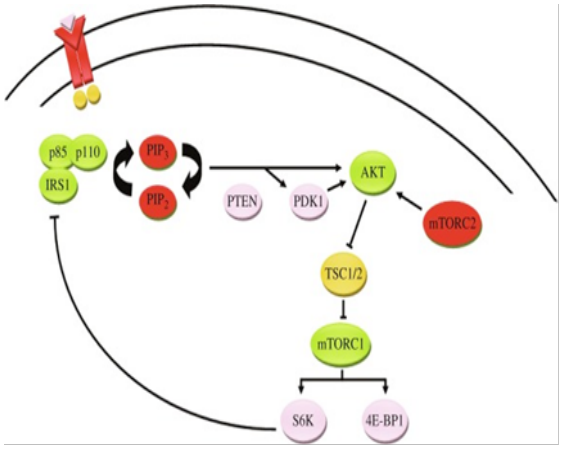

Figure 6: The role of PTEN mutations in the P3K-PKB / AKT signaling pathway (phosphoinositol 3 kinase / serine-threonine protein kinase / AKT signaling pathway). Reprinted/adapted with permission from reference [48]. Copyright year: 2014, copyright name: Scientific World Journal.

In general, PTEN mutations are found in approximately 35-40% of endometrial tumors [48,49]. In a small percentage of cases, PTEN mutations are detected in the hyperplastic endometrium, which reflects the early stages of carcinogenesis in the endometrium, because the function of basis of the PTEN gene is to temper uncontrolled cell growth and division [50]. However, morphological and epidemiological studies of atypical endometrial hyperplasia have shown that loss of endometrial PTEN expression is not the specific marker that detects the transformation of atypical glandular hyperplasia into adenocarcinoma [51]. The relationship between microsatellite instability and PTEN mutations in endometrial tumors has been studied in several studies. Microsatellite Instability (MSI) is a reflection of the dysfunction of DNA repair system genes in cells and, moreover, is an important prognostic sign of CE.

Markers of angiogenesis in the prognosis of endometrial cancer metastasis and recurrence

The main manifestations of malignant dissemination are invasive growth and metastasis. Neoangiogenesis - the process of formation of new blood vessels - is the most important pathogenetic factor against the spread of the tumor process [52]. Conclusive clinical and experimental evidence has now been obtained confirming the dependence of metastasis on neoangiogenesis [53]. Determining the risk of recurrence, the development of metastases is possible by assessing the degree of development of blood vessels in the tumor. EGFR (epidermal growth factor receptor gene) and RAS-RAFMAP (mitogen-activated protein kinase) are considered genes with increased responsiveness to tyrosine kinase inhibitor therapy. Three genes of this class have been identified: PIK3R1, PIK3R2 and PIK3R3, which are activated in human tumor cells under the influence of somatic mutations. The IA PI3K-mTOR kinase cascade is triggered by receptor tyrosine kinases. PI3K kinase can also be activated by RAS protein or G protein receptors. The resulting reaction product PIP3 is hydroxylated at the 3-position of PIP2.The main function of EGFR is phosphatidylinositol metabolism and participation in the RAS gene system. EGFR overexpression was detected in 50-80% of patients with CE type 2 [15]. It has been shown that the frequency of EGFR detection

in patients with EC decreases significantly at the age of over 65 years and is most often detected in patients under the age of 55 years, while no correlation was found between the age of the patients and the presence of EGFR in tumor tissue [16]. An increase in Bcl-2 gene expression in endometrial carcinomas compared to normal tissues, as well as an increase in gene expression for Interleukin 8 (IL-8) and matrix metalloproteinases – MMP-3, MMP-8 [54], which are involved in angiogenesis, cell proliferation, migration and differentiation, apoptosis, inhibition of tumor growth, can be considered as indisputable markers of EC oncogenesis. When studying the role of Adrenomedullin (AM) and Bcl-2 expression in carcinogenesis, an increase in AM expression in patients and a decrease in Bcl-2 expression was determined [55,56]. AM expression has been found to increase in the transformation from benign endometrial pathologies to endometrial intraepithelial neoplasias and adenocarcinomas, while Bcl-2 expression decreases during the transformation from intraepithelial neoplasias to carcinoma [57-59]. It has been established that FGF (fibroblast growth factor), together with the tyrosine kinase pathway, is involved in the regulation of cellular activity [60-63]. Therefore, the possibility of using FGF Receptor (FGFR) inhibitors is currently being studied. However, currently anti-FGFR therapy is at the initial stage of study, because it is very difficult to implement this approach due to the increased toxicity of the drugs [64-66]. A significant increase in the expression of c-erbB-2, which encodes the protein p185 (transmembrane receptor of the epidermal growth factor receptor family) and MIF (macrophage migration inhibitory factor) was detected in patients with endometrial carcinoma, but the correlation was not determined in contiguity with age, tumor stage, degree of tumor differentiation, myometrial invasion and tumor metastasis [67-75].

COX-2 molecular marker as a prognostic factor for endometrial cancer recurrence

It should be noted that a promising direction in antitumor therapy in EC is the use of COX-2 inhibitors. Nimesulide has been shown to significantly inhibit angiogenesis in endometrioid adenocarcinoma cells [76], and acetylsalicylic acid and rofecoxib accelerate apoptosis [77]. It is known that Cyclooxygenase-2 (COX-2) is expressed in cancer cells, leading to the inhibition of apoptosis, the activation of neoangiogenesis and the increase of cell adhesion to the extracellular matrix, which leads to an increase in the metastatic potential of the tumor and an unfavorable prognosis of cancer. Cyclooxygenases, mainly COX-2, have been found to be overexpressed in CE, which is accompanied by a deterioration in overall survival in patients with CE after surgical treatment. Endometrial cancer had an extremely poor prognosis with increased expression of COX-2 and COX-1 [78]. Overall survival at 5 years in EC patients with an elevated COX-2 level decreases significantly, Independent of stage (I-II), age, degree of tumor differentiation, depth of myometrial invasion [78].

When studying the role of COX-2 and COX-1, mucins (MUC-1, MUC-2), estrogen and progesterone receptors, Ki-67 antigen, HER2 / neu oncoprotein, it was found that the only factor that significantly reduces survival at 5 years (p=0.04) and without relapses (p=0.05) of CE patients is a high expression of COX-2 in tumor cells [79,80].

Conclusions

As a result of analyzing the risk groups, it is necessary to establish an own prognostic model, extended due to the integration of additional clinical and morphological characteristics of the tumor. It is necessary to develop a unique approach to the assessment of disease evolution in patients with endometrial cancer in stages I-II by taking into account prognostic factors, ensuring satisfactory results and a high quality of life. The results of the introduction of such a multimodal approach in the treatment of endometrial cancer will allow recommending it as a model for the creation of a new direction – the personalized treatment of EC.

Declarations

Author contributions: T.I., C.V., P. A.C., V.S. designed the project and wrote the manuscript; T.I., K.H. designed the figures and tables, and wrote the manuscript; T.I., J.C.A. wrote and checked the manuscript; P.K., M.V.S, N.C, P.V. collected and reviewed articles.

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