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MOLECULAR-GENETIC PROGNOSTIC FACTORS ENDOMETRIAL CANCER IN STAGES I-II

321.20 – ONCOLOGY AND RADIOTHERAPY

Summary of the thesis of doctor habilitate in medical sciences

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The PhD thesis and the abstract can be consulted at the IP library of the Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova and on the ANACEC website (https://www.anacec.md/).

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RESEARCH CONCEPTUAL HIGHLIGHTS

The topicality of the topic and the importance of the problem addressed.

The topicality of the topic is conditioned by the high level of morbidity through endometrial cancer (CE), constituting a major problem with global impact on public health. Endometrial cancer represents 4.8% of malignant tumor cases and ranks 6th worldwide in the structure of the incidence of malignant tumors in women [16,17,19].

In terms of increasing morbidity rate, EC consistently ranks 7th among malignant neoplasms in women [20]. The steady increase in the incidence of EC is explained by the increase in average life expectancy ("ageing") among the population and the level of obesity [2,3,4,18]. The incidence of this pathology is constantly increasing not only among elderly patients, but also among young women. Over 77.0% of cases are diagnosed in the early stages (stages I and II), with a high survival rate at 5 years [12]. As a result of a detailed analysis, we can see that the results of survival at 5 years vary within the limits of stage I and constitute in stage IA - 91-95%, and in stage IB - 80-65% [12]. Stage II 5-year survival was 50.6% [16]. The incidence of endometrial cancer between 40 and 54 years increases sharply, with a peak at the age of 60-64 years. In the age groups of 40-49 and 50-56 years, there is a significant increase in incidence.

According to the data of the National Cancer Registry of the Republic of Moldova, in the last five years there has been an increase in cancer morbidity of the organs of the female reproductive system. According to statistical data, provided by the National Cancer Registry in the Republic of Moldova, in 2020 the incidence of endometrial cancer was 515 cases, the mortality being 92 cases. The five-year survival rate of patients with stage I endometrial cancer after treatment, according to different authors, varies depending on the depth of myometrial invasion 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 [17].

A recent study, representing an integrative genome analysis of 373 endometrial tumors, conducted by a team of researchers from Washington University (St. Louis, 2013) as part of the *Cancer Genome Atlas (TCGA)* project, revealed that approximately 1/4 of tumors are classified as endometrioid, low-differentiating, with molecular phenotype, similar to serous carcinomas of the uterine body, including TP53 mutations and child count abnormalities of somatic genes [11]. For this reason, 4 new subgroups of endometrial neoplasia were highlighted, depending on the spectrum of genetic and molecular changes. In a multicenter study, Y. Hussein et al. [12] analyzed the morphological and clinical-pathological parameters of 17 tumors from the TCGA "ultramutant" subgroup, as well as a cohort of 8 such tumors, which were studied at the University of Calgary (Canada) [13].

Despite a large amount of research conducted by both domestic and foreign authors focused on the study of molecular biological aspects of endometrial cancer, at present, none of the tumor markers is recommended for widespread clinical use in cancer of the uterine body, as there is not enough information to introduce them into clinical practice.

According to ESMO's current recommendations, for the management of patients with endometrial tumors, treatment tactics are determined by the results of risk stratification [24]. With regard to EC cancer, a large number of prognostic factors are described, which creates certain difficulties in their application in clinical practice. Most factors are morphological, and information about them is obtained on the basis of a standard histological examination. These data are used to assess the risk of lymphoganglionic metastases, to make predictions about the course of the disease and the life of patients with EC and to plan postoperative treatment. The study of clinical and morphological prognostic factors at certain stages, especially early ones, has already been carried out by other authors [6, 9].

However, according to a study conducted by TCGA (2013), 1/4 of the tumors classified as G3 endometrial carcinomas correspond, according to molecular profile, to a subgroup of tumors of serous type [11]. At the same time, another group of researchers [18] analysed 3 cases of tumours, histologically defined as serous, which mutated *PTEN* and *ARID1A* in the absence of *TP53* mutations.

On histopathological reevaluation, all 3 tumours were identified as mixed. In addition, an immunohistochemical analysis was performed, which disputed the existence of a serous tumor profile in relation to normal p53 expression and in the absence of p16 expression. Also, estrogen and progesterone receptor expression was identified in one of the tumors [25]. According to the researchers, this suggests that the classification of endometrial cancer can no longer emerge from a dualistic model. In particular, low-differentiating tumors have pronounced heterogeneity, which is not reflected in the accepted classification, while the mutation profile of highly differentiating and serous tumors varies significantly. Most serous tumours have mutations in the *TP53* gene; 1/3 of 'ultramutant' tumours may also have them, however the clinical prognosis is different. Therefore, when using immunohistochemical analysis to confirm the diagnosis of serous carcinoma, p53 determination and auxiliary panel of immunohistochemical parameters such as *PTEN* and *ARID1A* can be used to differentiate serous carcinoma from endometrioid tumor with *POLE gene mutation* [1].

Despite the large amount of research conducted by both domestic and foreign authors, which focused on the study of biological and molecular aspects of endometrial cancer, at present none of the tumor markers are recommended for widespread clinical use in cancer of the uterine body, because there is not enough information for their introduction into clinical practice. Therefore, the question of prognostic criteria for endometrial cancer remains unaddressed [8]. As a result of analyzing risk groups, it is necessary to establish its own prognostic pattern, expanded due to the integration of additional clinical and morphological features of the tumor.

The purpose of the study: determination of clinical-morphological and molecular-genetic prognostic factors of endometrial cancer (CE) in stages I-II for the elaboration of the mathematical model for prediction of relapses and survival of patients over a period of up to 3 years.

Objectives of the work:

1. Establishing clinical, morphological, immunohistochemical criteria as EC prognostic factors;
2. Estimation of the correlation of molecular-genetic data according to the clinical and morphological characteristics of endometrial cancer;
3. Study of immunohistochemical peculiarities and estimation of the molecular profile of the tumor in the patients of the study group;
4. Multifactorial analysis of the complex of prognostic criteria established with determination of the prognostic value for each particular factor in patients with EC in stages I-II;
5. Creation of the mathematical model of the complex prognostic assessment of EC in stages I-II depending on risk groups and prognostic factors.

Scientific novelty and originality

For the first time, the interface of biomarkers of major pathophysiological events referring to the onset and evolution of stage I and II endometrial cancer was investigated. The role of equilibrium between imminent extreme CE processes such as cell apoptosis and cell proliferation in contiguity with tumor angiogenesis was estimated to strengthen markers with predictive value on pathology prognosis.

Scientific problem solved in the thesis

The scientific problem solved in the thesis consists in that research based on clinical-morphological and molecular-genetic studies has detected novel pathogenetic mechanisms and predictors of EC exacerbation, such as the presence of c.389G>A mutation (p.R130Q) *of the PTEN* gene, methylation of the MLH1 *gene promoter*, Ki-67 proliferation marker, neutrophil/lymphocyte index increase, which allowed the elaboration of a mathematical model for predicting evolution disease in EC patients from different risk groups.

Theoretical significance of the work

Through the conclusive evidence obtained, the concept and theoretical support of endometrial cancer is completed. It is important to decant the contribution of the c.389G>A mutation of the *PTEN gene, the increase in the* proliferative activity of the mitotic cycle evaluated by the increase of the Ki-67 antigen, the mutation of the TP53 gene resulting in the impairment of the Bax/Bcl2 ratio. At the same time, the role of inflammation in promoting EC is highlighted, and the increase of the

neutrophil/lymphocyte index is not only a pathogenetic mechanism, but also a feasible predictor of tumor prognosis. The notable link of EC with the increase in body mass is conceptually important, as well as the absence of a link between EC regarding the risk of recurrence on the one hand and the characteristics of menstruation, number of births and spontaneous abortions on the other. The rate of serous papillary adenocarcinoma in the group of patients with EC with stage II is on average 44-48% higher compared to the index of stage IA and IB. The degree of tumor differentiation has a conclusive impact on the risk of recurrence, so that the low degree of differentiation is estimated in 95% in high-risk patients, and the high degree of differentiation is characteristic of the low risk (80%). Remarkably, the depth of tumor invasion does not authentically correlate with increased risk. The presence of necrotic foci is a true predictor of increased risk. The impact of inflammation is imposed by maximum values of the neutroph/lymphocyte and platelet/lymphocyte ratio in patients with high-risk EC. The marker of Ki-67 proliferation is directly related to the degree of risk, as well as to the stage of the disease (the level of Ki-67>49% expression is detected only in the high-risk group). The presence of the c.389G>A mutation (p.R130Q) of the *PTEN* gene is in the increased risk group 4-8 times higher compared to intermediate and intermediate-high risk. MLH1 epimutation does not demonstrate such a conclusive link with EC evolution compared to c.389G>A mutation (p.R130Q) of the *PTEN gene*.

Applicative value of the work

An own prognostic model has been developed, which includes clinical, morphological, immunohistochemical and genetic features of endometrial cancer. The survival of patients with EC over a 3-year surveillance period is minimal (72.2%) among those older than 60 years who are in the high-risk group of recurrence. The relapse-free survival rate is also minimal in these patients (44%). At the same time, the metastasis rate in patients with CE does not correlate intelligibly with the stage of the disease. The mean time to EC progression is indirectly related to the neutrophil/lymphocyte ratio, which is minimal (6 months: 5 to 9 months) in patients at high risk of recurrence with an INL> 5.0. The marker Ki-67 has a definite predictive value on survival and relapse rates in patients with CE, thus, that increased proliferative activity (>49%) has a negative impact at a distance of 3 years. The presence of *MLH1* epimutation also influences disease relapse in patients with EC 3 years apart, given the minimum mean time to progression value of 10.5 years attested in carriers of this mutation in the high-risk group.

The scientific results obtained during the study were presented, discussed and published in national and international scientific forums:

XXIV edition of the International Specialized Exhibition "MoldMEDIZIN & MoldDENT" Integrated activities within the National Cancer Control Program in Moldova and the role of immunogenetics in the diagnosis and treatment of oncological diseases (Chisinau, 2018); XIII Congress of oncologists and radiologists of CIS countries and Eurasia (Kazani, Russia, 2020); XXI European Congress of Oncogynecologists (Athens, Greece 2020); Congress of Oncologists of the Republic of Moldova with international participation, fifth edition, Cancer Prevention and Control – a continuous challenge (Chisinau 2020); XIV Congress of Oncologists and Radiologists of CIS countries and Eurasia (Moscow, Russia, 2021); Congress dedicated to the 75th anniversary of the foundation of Nicolae Testemitanu State University of Medicine and Pharmacy with international participation (Chisinau, 2021); Training School: Gynocare Conference (Valletta, Malta 2022); XXIII European Congress of Oncogynecologists (Berlin, Germany 2022). Training School in Rare Gynaecological Tumors (Skopje, Macedonia 2022); Training School in Rare Gynaecological Cancers "Bringing the gap between research and cure in gynaecological cancers" (Naples, Italy, 2023).

Publications on the topic of the thesis: 55 scientific papers were published.

Summary of thesis compartments

The thesis is written in Romanian language and includes: annotations in Romanian, Russian and English, list of abbreviations, declaration of assumption of responsibility, introduction, 6 chapters, general conclusions and practical recommendations, bibliography, annexes, mathematical model for predicting the evolution of the disease in patients with EC from different risk groups, author's CV.

CONTENT OF THE THESIS

1. MOLECULAR-GENETIC ASPECTS OF ENDOMETRIAL CANCER. A MODERN APPROACH TO THE PROBLEM

The main landmarks characterizing the epidemiology of endometrial cancer in Moldova and various European countries are exposed. The pathogenetic value vis-à-vis CE of various risk factors, such as metabolic syndrome, lipid profile disorder, hyperglycemia, inflammation, obesity, etc. is detected. Modern pathophysiological prerogative aimed at the onset and evolution of CE is exposed, including the connotation of genetic changes with power to activate the proliferation process against the background of depreciation of apoptosis mechanisms, such as mutations of the *PTEN gene* to the detriment of cell cycle blocking exercise and control of the ratio of proteins with pro-/anti-apoptotic effect, Bax/Bcl2, mutations of tumor suppressor TP53, as well as reducing the expression of E-caaderin, which facilitates tumor growth and dissemination. The multi-marker panel useful in histological differentiation of CE and in estimating tumor aggressiveness is brought to the call, cataloged in 4 patterns of endometrial neoplasia depending on the spectrum of genetic and molecular changes: ultramutant, hypermutant tumors with a large number of copies and tumors with a low number of copies. The role of PD/L ligand on tumor cell surface is analyzed in context with the reporting of cell proliferation markers, Ki-67 antigen and proliferating cell nuclear antigen (PCNA). TP53 gene mutations are highlighted as a condition of inhibition of apoptosis by increasing the expression of antiapoptotic factor Bcl2, and mutation of the PTEN suppressor gene *is* predominantly targeted as the c.389G>A pattern in which guanine at position 389 is substituted with adenine. The pathogenetic, diagnostic and prognostic contribution of angiogenesis markers is also emphasized, and the increase in COX2 expression in association with elevation of proinflammatory markers is imposed as a pathogenetic factor and true predictor of endometrial cancer.

2. RESEARCH MATERIALS AND METHODS

The design of the study contains the main milestones and staging of the prospective study conducted on 269 patients with EC in stages I and II assessed in the histological examination.

The general scheme of the research project includes the description of the first stage of the study, marked by the assessment of clinical-morphological peculiarities (localization, tumor size, growth form, invasion, peculiarities of immune status) and stage 2 marked by the research of immunohistochemical and molecular-genetic peculiarities: determination of the Ki-67 marker, c.389G>A mutation of the *PTEN gene*, hypermethylation of the promoter of the *MLH1* gene with the determination of the molecular profile and subtype of the tumor.

According to the modified recommendations of ESGO, the general group of patients with EC was divided into 4 groups regarding the risk of recurrence: low, intermediate, intermediate-high and high. The criteria for stratifying patients into groups at risk of recurrence were: stage of disease, degree of tumor differentiation, depth of tumor invasion, presence of perilymphovascular and perineural invasion.

Thus, the patients in the total group of the study were divided into 4 risk groups:

1. group 1 includes 75 patients with low-risk EC,
2. group 2, which consisted of 84 patients with intermediate-risk EC
3. group 3, which consisted of 50 patients with intermediate-high risk EC
4. 60 patients with high-risk EC, forming group 4.

These 4 groups are also mapped out according to age and reproductive activity, stage of disease, histopathological subtype and degree of tumor differentiation. At the same time, each group is analyzed in detail in terms of age, length of menstrual cycle and postmenopause, number of pregnancies and abortions, age of disease. On the other hand, the groups underwent exegesis according to diseases of the organs of the reproductive system: pelvic inflammatory disease, endometriosis, endometrial hyperplasia, ovarian cyst, myoma of the uterus body, polyp of the uterine body, etc.

The diagnosis and treatment of patients with EC corresponded to the algorithms recommended

for the field of diagnosis and treatment of malignant neoplasms in the National EC Protocol approved by the Ministry of Health.

All immunohistochemical, histopathological, molecular-genetic research methods are described in association with the exposure of the technical equipment used. The maneuvers of statistical processing of cipherical material are reported in detail.

When distributing patients by age, the highest percentage is recorded in the age categories 60-69 years in 116 (48.3%) cases. The age groups least affected by endometrial cancer are 30-39 years (0.7%), 40-49 years (8.9%), 70+ years (10.4%). The age group 30-39 years was recorded in patients in the high and intermediate-high risk groups more often, compared to patients with CE in the intermediate and low risk group, in which no case of CE was reported.

The overall study group included 269 patients with EC in stages I-II, mean age 59.9±0.64 years (Figure 2.1).

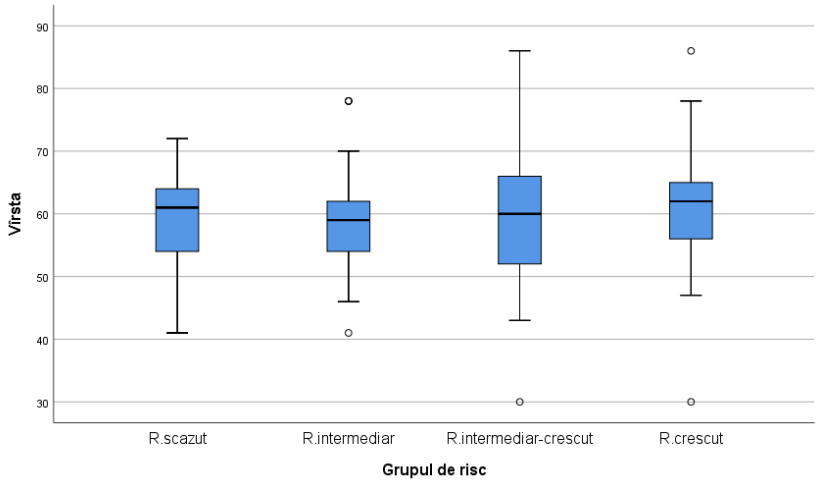

Figure 2.1. Age of study patients by risk group, years

At disease onset, the mean age of EC patients in the high-risk reproductive age was 41.7±5.84 years, compared to data from the intermediate and increased risk group, respectively 45.5±0.96 years and 45.9±1.08 years. Thus, the mean age of EC patients in the perimenopausal high-risk group was 50.0±0.58 years, compared to data from the intermediate and increased risk group, respectively 50.0±0.0 years and 51.3±0.67 years. The mean age of EC patients in the postmenopausal high-risk group was 62.9±0.95 years, compared to data from the intermediate and elevated risk group, respectively 60.8±1.0 years and 61.2±0.65 years.

Table 2.1. Mean age of onset of EC in patients according to risk group

Age period	Risk group				P
	Low	Intermediate	Intermediate-high	High	
Reproductive period	41.7±5.84	45.5±0.96	43.3±2.85	45.9±1.08	F=0.624; p=0.608
Perimenopausal period	51.3±0.67	50.0±0.0	50.8±0.25	50.0±0.58	F=1.684; p=0.219
Postmenopausal period	61.2±0.65	60.8±1.0	63.2±1.01	62.9±0.95	F=1.699; p=0.168

The age differences, at which the disease occurs, are probably conditioned by genetic factors. Thus, molecular-genetic research in patients with endometrial cancer gives the opportunity to determine the molecular subtype of the tumor. This fact must be taken into account in assessing the evolution of endometrial cancer and the degree of aggressiveness of the tumor.

Clinical examination

In order to verify the validity of the hypotheses and achieve the objectives, we applied the

following methods and tools: general investigation methods (anamnestic questioning and research of medical documentation), special (gynecological clinical examination, examination by instrumental and imaging method), histopathological examination and laboratory methods (blood count, urogram, biochemical blood analysis).

The ultrasound examination of the internal genital organs was performed in real time with the ultrasonograph type SAL-77A, produced by the company "Toshiba" (Japan), equipped with a set of sectoral and linear transducers with frequency from 3.5 to 7.5 MHz. The investigations were carried out in the USG Department of Internal Organs of IMSP IO. In the present study, transvaginal and transabdominal ultrasonography of the internal pelvic organs was performed. During the study, the location of the uterus and ovaries and their sizes were determined. Particular attention was paid to the state of the endometrium (M-Echo). The thickness of the endometrium, according to M-Echo in menopause, is normally 4-5 mm.

Diagnostic curettage of the uterine cavity *was* performed according to the results of ultrasound examination (thickness M-Echo) in patients who had complaints of metrorrhagia during menopause.

For ***cytological investigation,*** smears were taken from the cervix, cervical canal, uterine cavity. Cytological investigations to confirm the diagnosis were performed in the cytological laboratory of IMSP IO. The fixation of the preparations was carried out by the Leishman method, and the coloring – according to Romanowski.

Morphological and immunohistochemical studies

In the morphological study of malignant endometrial tumors, the histological type and degree of tumor differentiation were assessed, the depth of tumor invasion in the myometrium, the spread of the process in the cervical canal, the stage of the disease and the condition of the fallopian tubes and ovaries were evaluated. Fixation of preparations by the standard method and their staining was carried out in most cases with hematoxiphylline – eosin, and in some cases – in additionally highly differentiated mucinous adenocarcinoma – with muciracmin and alkali blue after Stidmen, Carmine Best.

The immunohistochemical study was conducted by peroxidase-antiperoxidase method according to the traditional method. We used Ki-67 antibodies (Dako, MIB clone, ready dilution, citrate buffer unmasking (pH=6.0).

Molecular-genetic investigations of the c.389G>A mutation (p.R130Q) of the PTEN gene

To identify the c.389G>A (p.R130Q) mutation in the *PTEN* gene, DNA was isolated from 50 paraffin tissue samples from patients with endometrial cancer. The histopathology of each FFPE tumor specimen was reviewed by histopathologists to confirm the diagnosis and determine the percentage of tumor cells.

Tissue and DNA samples. Genomic DNA was isolated from 50 paraffin tumor tissue (FFPE) samples using the GeneJET FFPE DNA Purification Kit (ThermoFisher) according to protocol from the manufacturer. From each paraffin block, 4 sections of 10 um were sectioned with the microtome. The next steps are carried out in accordance with the protocol related to the kit from the manufacturer.

castPCR (Competitive Allele-Specific TaqMan PCR). Genomic DNA samples were analyzed for *PTEN*:c.389G>A mutation (p.R130Q) by castPCR method using specific primers and samples (Fig. 2.2.)

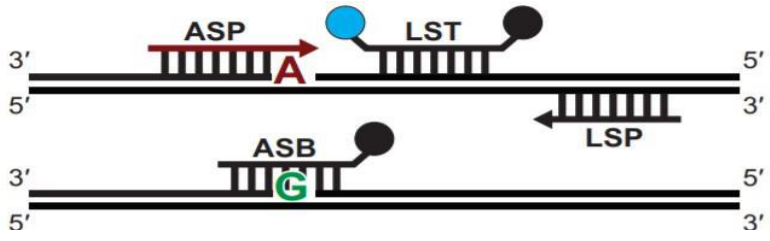

Figure 2.2. Primers and samples used for specific identification of *PTEN*:c.389G>A mutation by castPCR method. ASP – allele-specific primer, ASB – allele-specific blocker, LST – locus-specific TaqMan sample, LSP – locus-specific primer

The sample flow for castPCR is shown in Figure 2.3.

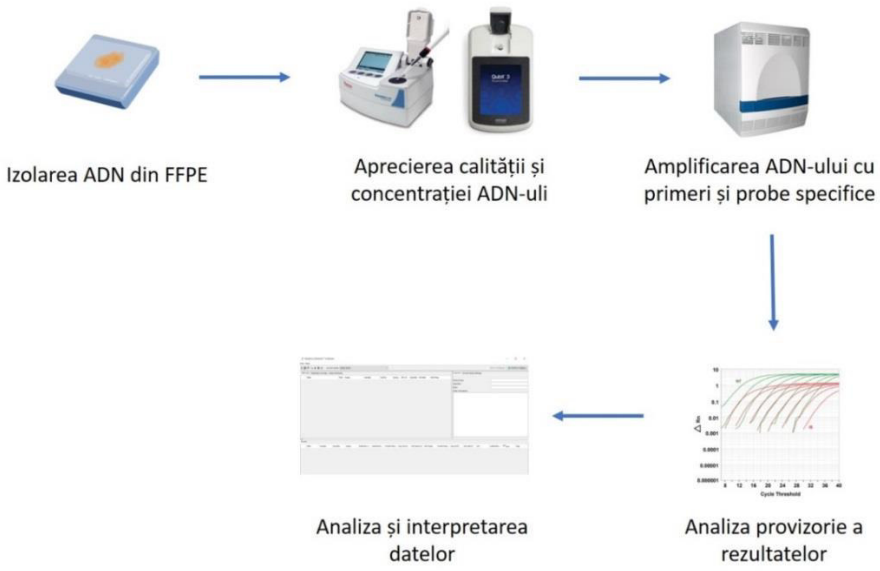

Figure 2.3. Workflow for castPCR.

Molecular-genetic investigations of methylation of the promoter of the MLH1 gene

To generate MLH1 gene methylation data, DNA was isolated from 50 paraffin tissue samples from endometrial cancer patients. The histopathology of each FFPE tumor specimen was reviewed by expert histopathologists to confirm the diagnosis and determine the content of tumor cells. Case selection was based on clinically confirmed diagnosis of endometrial cancer.

Tissue and DNA samples. The quality, integrity, quantity and concentration of DNA meet the criteria described in subchapter 2.2.5., as the same paraffin tissue samples and isolated DNA samples were used.

MS-PCR (Methylation specific Polymerase Chain Reaction). To identify methylation of the promoter of the *MLH1* gene, 120 ng/isolated DNA sample was modified by treatment with sodium bisulphite using the EpiJET Bisulfite Conversion Kit (ThermoFisher) according to protocol. The methylation status of the *MLH1* gene was determined using the methylation specific Polymerase Chain Reaction (MS-PCR) method and specific primers for both non-methylated and methylated fragments.

The PCR reaction was performed using the Platinum PCR SuperMix kit (ThermoFisher) and the protocol related to the kit with the modification of the primer alignment temperature based on the size and sequence of nucleotides.

Evaluation of neutrophil/lymphocyte and platelet/lymphocyte index parameters

To identify the prognostic value of clinical markers of inflammation, we calculated the following ratios:

The neutrophil/lymphocyte index (INL) was calculated as the ratio of absolute neutrophil counts to absolute peripheral blood lymphocyte counts.

Platelet/lymphocyte index (TLTI), which has been calculated as the ratio of absolute platelet count to absolute peripheral blood lymphocyte count.

Methodology for statistical processing of research results

All results are presented in tables like M±m, where M is the sample mean, m is the error of the mean.

When statistical processing of the obtained results, the following methods were used:

- Fisher test for independent variables - to assess the significance of differences between groups with a normal trait distribution. The differences were considered significant at $p < 0.05$;

- Pearson test $\chi 2$ - to assess the significance of differences between groups in terms of qualitative characteristics. The differences were considered significant at $p < 0.05$; - single variance analysis (ANOVA, IBM STATISTICS 26.0) was used to assess the significance of differences between groups under the influence of individual factors;
- logistic linear regression was used

3. ANALYSIS OF CLINICAL AND MORPHOLOGICAL CHARACTERISTICS IN PATIENTS WITH ENDOMETRIAL CANCER IN STAGES I-II

Clinical and anamnestic parameters were studied in 269 patients with EC in stages I - II. The age of patients in all CE groups did not differ significantly and ranged from 30 to 86 years, with no statistically significant difference between risk groups ($\chi 2=11.681$; gl=15, $p>0.05$). The age of 30-39 years met at 2 (0.7%; CI 95% [0.0-1.9]) patients, and the age of 60-69 years was most commonly observed and was recorded in 116 (43.1%; I 95% [37.5-49.1]) patients.

Table 3.1. Distribution of EC patients in stages I to II in different risk groups by age

Age groups	Risk group								TOTAL	
	Low		Intermediate		Intermediate -high		High			
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
30-39 years	0	0,0	0	0,0	1	1,2	1	1,7	2	0,7
40-49 years	8	10,7	6	12,0	6	7,1	4	6,7	24	8,9
50-59 years	24	32,0	22	44,0	33	39,3	20	33,3	99	36,8
60-69 years	37	49,3	18	36,0	32	38,1	29	48,3	116	43,1
>70 years	6	8,0	4	8,0	12	14,3	6	10,0	28	10,4

Aggravated heredity for endometrial cancer was observed in patients of all risk groups. When studying aggravated heredity in EC, the following data were obtained, presented in Table 3.2.

Table 3.2. EC dependence on the presence of malignant tumors in relatives of patients with EC in stages I - II of different risk groups

Relatives of EC patients	Risk group								P GL=3
	Low		Intermediate		Intermediate-high		High		
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
First-degree relatives (parents, brothers and sisters) 3 and more	13	17,3	9	18,0	16	19,0	10	16,7	$\chi 2=0,154$; $p>0.05$
First degree relatives (parents, brothers and sisters) 2 relatives	8	10,7	10	20,0	10	11,9	11	18,3	$\chi 2=3,277$; $p>0.05$
First-degree relatives (parents, brothers and sisters) a relative	13	17,3	9	18,0	22	26,2	8	13.3	$\chi 2=4,167$; $p>0.05$

Malignant tumors in first-degree relatives were registered in 64 (85.3%; 95% CI [77.3-93.3]) patients in the low risk group, 44 (88.0%; 95% CI [79.0-97.0]) of intermediate risk group, 80 (95.2%; 95% CI [90.7-99.8]) in the intermediate-high risk group and 59 (98.3%; 95% CI [95.1-101.6]) of the high-risk group. We can find a more aggravated heredity in the statistically true high risk group ($\chi 2=9.870$; gl=3, $p<0.05$).

It was observed that hormone-dependent tumours (gastrointestinal tract, genitals) were found in a higher percentage of cases in relatives of EC patients in the high risk group (48.6%) than in patients in the low risk group (40.8%) (Table 3.3).

Table 3.3. Localization of malignant tumors in relatives of patients with EC stage I - II.

Localization of malignant tumors	Risk group								P GL=3
	Low		Intermediate		Intermediate-high		High		
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
Lungs	8	10,7	9	18,0	15	17,9	11	18,3	$\chi2$=2,196; p>0.05
Gastrointestinal tract	9	12,0	9	18,0	17	20,2	15	25,0	$\chi2$=3,944; p>0.05
Mammary gland	17	22,7	17	34,0	23	27,4	15	25,0	$\chi2$=2,089; p>0.05
Genitals	10	13,3	4	8,0	6	7,1	4	6,7	$\chi2$=2,551; p>0.05
Kidneys, bladder	1	1,3	1	2,0	3	3,6	1	1,7	$\chi2$=1,069; p>0.05
Larynx	-	-	-	-	1	1,2	-	-	$\chi2$=2,211; p>0.05
Brain	4	5,3	7	14,0	8	9,5	5	8,3	$\chi2$=2,838; p>0.05
Leukemias	2	2,7	1	2,0	1	1,2	1	1,7	$\chi2$=0,492; p>0.05
Malignant melanoma and skin tumors	-	-	-	-	1	1,2	-	-	$\chi2$=2,211; p>0.05

The regular menstrual cycle with hypermenorrhea was recorded in patients in the intermediate-high risk group and in the high-risk group, 16.7% and 35.0%, respectively; while in the low risk group and intermediate risk group was registered only 13.3% and 6.0%, respectively. There is a statistically significant difference between groups ($\chi2$=17.951; gl=3, p<0.001). The duration of the menstrual cycle up to 26 days was observed in half of the patients - 131 (48.7%; 95% CI [42.4-55.0]). The menstrual cycle lasting 27-30 days was recorded at 58 (21.6%; I 95% [16,4-26,4]) patients. Menstrual cycle length did not differ significantly between study groups (F=0.439; p>0.05).

Table 3.4. Menstrual cycle character according to risk group in patients with EC stages I-II

Features of the menstrual cycle	Risk group								P
	Low		Intermediate		Intermediate -high		High		
	Abs.	%	Abs	%	Abs	%	Abs	%	
Age of onset of menarche									
Up to 12 years	6	8,0	11	22,0	10	11,9	9	15,0	$\chi2$=6,979; GL=6; p>0.05
12- 14 years	49	65,3	25	50,0	56	66,7	36	60,0	
15- 16 years	20	26,7	14	28,0	18	21,4	15	25,0	
Type of menstrual cycle									
Regular cycle	10	13,3	3	6,0	14	16,7	21	35,0	$\chi2$=17,951; gl=3; p<0.001
Polymenorrhea	17	22,7	14	28,0	30	35,7	24	40,0	$\chi2$=5,686; gl=3; p>0.05
Hypermenorrhea	24	32,0	18	36,0	36	42,9	19	31,7	$\chi2$=2,722; gl=3; p>0.05
Proiomenorea	6	8,0	1	2,0	6	7,1	6	10,0	$\chi2$=2,842; gl=3; p>0.05
The length of the menstrual cycle									
Up to 26 days	37	49,3	28	56,0	37	44,0	29	48,3	$\chi2$=2,896; GL=6; p>0.05
27- 30 days	14	18,7	11	22,0	19	22,6	14	23,3	
31 days and more	24	32,0	11	22,0	28	33,3	17	28,3	
Age of onset of menopause									
Up to 40 years	-	-	-	-	4	4,8	2	3,3	$\chi2$=14,194; GL=9; p>0.05
40- 44 years	6	8,0	1	2,0	2	2,4	-	-	
45- 49 years	13	17,3	8	16,0	16	19,0	14	23,3	
50 years and older	56	74,7	41	82,0	62	73,8	44	73,3	
Uterine bleeding (HU)									
Present	48	73,8	24	55,8	58	75,3	43	82,7	$\chi2$=9,156; gl=3; p<0.05
Climacteric syndrome									
Present	63	84,0	40	80,0	72	85,7	41	68,3	$\chi2$=2,896; GL=6; p>0.05

The age of menopause in the general group is 50.2±0.22 without statistically significant

difference between groups (F=1.52; p>0.05). Postmenopausal metrorrhagia were observed in patients from all risk groups, but the highest frequency was recorded in the high-risk group – 43 (82.7%; 95% CI [72.0-92.3]) and intermediate-high risk - 58 (75.3%; 95% CI [65.8-84.2]), being attested statistically significant difference ($\chi2$=9.156; gl=3, p<0.05). Climacteric syndrome was present in 53 (19.7%; 95% CI [15.2-24.9]) patients in the overall group, without statistically significant difference between groups ($\chi2$=7.639; gl=3, p>0.05).

Statistically significant differences were obtained between study groups in relation to pathologies of the reproductive organs in women. Polyps of the cervical canal and uterine cavity were detected more often in the group of patients of low and intermediate risk, with statistically significant difference between groups ($\chi2$=10.722; gl=3; p<0.05) and ($\chi2$=24.408; gl=3; p<0.001), respectively, statistically significant difference was observed ($\chi2$=1.868; gl=3; p>0.05). The incidence of uterine myoma was higher in the intermediate-high and high risk groups, 33.3% and 30.0%, respectively, with a statistically significant difference ($\chi2$=8.011; gl=3; p<0.05). When analyzing the incidence of ovarian cysts, statistically significant difference is not attested ($\chi2$=6,370; gl=3; p>0,05). Endometriosis was recorded more frequently in patients in intermediate-high and high risk groups, 28.6% and 25.0%, respectively, with statistically significant difference between groups ($\chi2$=14.419; gl=3; p<0.01).

Table 3.5. Distribution of patients with EC in stages I-II according to risk group and presence of pathologies of the organs of the reproductive system

Pathologies of the organs of the reproductive system	**Risk group**								**P GL=3**
	Low		**Intermediate**		**Intermediate-high**		**High**		
	Abs	%	Abs	%	Abs	%	Abs	%	
Fibrocystic mastopathy	23	30,7	23	46,0	33	39,3	30	50,0	$\chi2$=10,533; p>0.05
Cervical ectropion	7	9,3	10	20,0	10	11,9	21	35,0	$\chi2$=17,932; p<0.001
Pelvic inflammatory disease	9	12,0	3	6,0	6	7,1	2	3,3	$\chi2$=3,898; p>0.05
Cervical canal polyp	4	5,3	7	14,0	2	2,4	1	1,7	$\chi2$=10,722; p<0.05
Polyp of the uterine cavity	28	37,3	22	44,0	12	14,3	8	13,3	$\chi2$=24,408; p<0.001
Hyperplasia of the endometrium	39	52,0	23	46,0	36	42,9	25	41,7	$\chi2$=1,868; p>0.05
Endometriosis	11	14,7	2	4,0	24	28,6	15	25,0	$\chi2$=14,419; p<0.01
Uterine myoma	11	14,7	12	24,0	28	33,3	18	30,0	$\chi2$=8,011; p<0.05
Ovarian cysts	20	26,7	7	14,0	13	15,5	17	28,3	$\chi2$=6,370; p>0.05
Leukoplakia and kraurosis of the vulva	4	5,3	1	2,0	4	4,8	2	3,3	$\chi2$=1,037; p>0.05

As a result of the data obtained, we can conclude the following: most gynecological morphologists and oncologists consider the problems of pathogenesis of endometrial cancer in close connection with hyperplastic processes of the endometrium.

It is known that endometrial hyperplastic processes in most cases are associated with hormonal disorders [4]. Numerous studies have proven, that hyperplastic processes of the endometrium carry an increased risk of malignant transformation [11,18]. Atypical hyperplasia, in particular, turns into endometrioid cancer in almost 52% of cases [11]. Our data coincide with the data of the literature and show, that typical endometrial hyperplasia against the background of uterine fibroids usually develops in the reproductive period, and atypical - in perimenopause and postmenopause. To

determine the risk group for CE according to ESGO criteria, the following criteria were used: the degree of differentiation of the tumor, the depth of tumor invasion, the presence of perilymphovascular invasion.

If we focus only on these criteria, it is noted that in the low-risk group, the frequency of metastases increases, as well as the risk of progression of the process after treatment. This may have the following explanation: insufficient accuracy of morphological prognostic factors.

Attention is drawn to the predominance of hormone-dependent pathogenetic variant in EC patients in the low (85.0%) risk group compared to intermediate (74.7%) and high (57.3%) risk groups (Table 3.6).

Table 3.6. Comparison of EC prevalence in patients in different risk groups by pathogenetic variant

Risk group	Pathogenetic variant		P
	I (hormonally-dependent), %	II (autonomous), %	
Low	85,0	15,0	$\chi 2=4,955$; gl=3; p>0.05
Intermediate	74,7	25,3	
Intermediate-high	84,0	16,0	
High	57,3	42,7	

As a result of the histopathological examination it was found that in most patients with EC in stages I-II (55%) the primary tumor occupied the entire uterine cavity without or with passage into the cervical canal. In 31 (28.5%) patients, the tumor was located in the lower third of the uterine body without or with passage into the cervical canal. In 18 (16.5%) patients, the tumor was located at the bottom of the uterus and/or tubal corners and/or walls of the uterus.

Endometrial cancer with tumor spread to the myometrium up to 50% (stage IA) was observed in 77 (28.6%; CI 95% [23.0-34.2]) patients, with myometrial invasion more than 50% (stage IB) in 128 (47.6%; 95% CI [41.3-53.5]) patients with spread to the cervix (stage II) to 64 (23.8%; 95% [18.7-28.9]) sick.

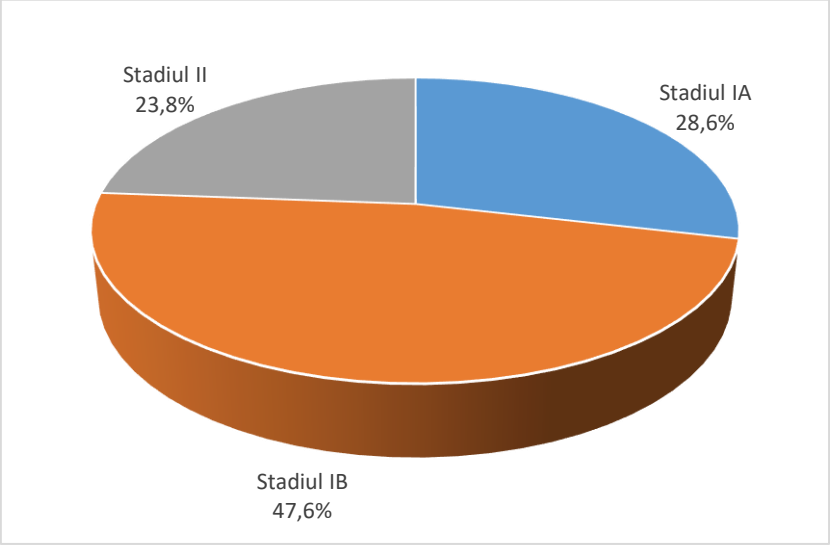

Fig. 3.1. Structure of patients with EC in the study group according to disease stage

A number of morphological features characteristic of EC in stages I-II were revealed. When analyzing data on the distribution of patients with stage I CE, taking into account the morphological structure, it should be noted the relatively rare occurrence of rare histological forms (clear cell adenocarcinoma, glandular squamous cell carcinoma, serous papillary adenocarcinoma and mucinous adenocarcinoma) , while in patients with stage II EC we observed a fairly frequent occurrence of rare histological forms 9 (3.3%; 95% CI [1.2-5.5]).

Table 3.7. Distribution of EC patients in stages I-II by risk group and histological subtype of cancer

Histological type of cancer	Risk group								P GL=3
	Low		Intermediate		Intermediate-high		High		
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
Endometrial adenocarcinoma	70	93,3	46	92,0	69	82,1	46	76,7	(χ2=10.144; p>0.05)
Serous papillary adenocarcinoma	4	5,3	-	-	12	14,3	8	13,3	(χ2=10.498; p<0.05)
Endometrial adenocarcinoma with squamous cell metaplasia	-	-	3	6,0	2	2,4	1	1,7	(χ2=5,.065; p>0.05)
Clarocellular adenocarcinoma	-	-	-	-	1	1,2	2	3,3	(χ2=4.091; p>0.05)
Carcinoma pavimentos	-	-	-	-	-	-	2	3,3	(χ2=7.019; p>0.05)

In 231 (85.9%; take 95% [81.7-90.0]) patients with EC was diagnosed endometrial adenocarcinoma of varying degree of differentiation, 6 (2.2%; 95% CI [0.5-4.0]) patients had endometrial adenocarcinoma with squamous metaplasia. Rare histological forms of cancer of the uterine body were diagnosed in 29 (10.8%; I 95% [7.1-14.5]) patients, of whom 3 (1.1%; 95% CI [0.0-2.4]) patients had clear cell adenocarcinoma in 2 (0.7%; 95% [0.0-1.8]) cases glandular squamous cell carcinoma was detected in 24 (8.9%; I 95% [5.5-12.3]) patients - serous papillary adenocarcinoma. Highly differentiated endometrial adenocarcinoma was recorded in 60 (80.0%; 95% CI [70.9-89.1]) patients with EC in the low-risk group, moderately differentiated adenocarcinoma - to 12 (16.0%; 95% [7.7-24.3]) patients. In the intermediate risk group, highly differentiated endometrial adenocarcinoma predominates in 26 (52.0%; CI 95% [38.2-65.8]) patients, moderate grade adenocarcinoma - to 22 (44.0%; I 95% [30.2-57.8]) patients. In the intermediate-high risk group, highly differentiated endometrial adenocarcinoma was observed in 22 (26.2%; 95% CI [16.8-35.6]), moderate and low-grade adenocarcinoma - to 48 (57.1%; 95% CI [46.6-67.7]) and 12 (14.3%; 95% [6.8-21.8]) patients. In the high-risk group, low-grade endometrioid adenocarcinoma predominates in 57 (95.0%; 95% CI [89.5-100.0]), moderately and highly differentiated adenocarcinoma - to 3 (3.3%; 95% CI [0.0-7.9]) and - 1 (1.7%; 95% CI [0.0-4.9]) patients, respectively (Table 3.8.).

Table 3.8. Distribution of EC patients in stages I-II of different risk groups according to degree of tumor differentiation

Degree of tumor differentiation	Risk group								P, gl=3
	Low		Intermediate		Intermediate-high		High		
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
High	60	80,0	26	52,0	22	26,2	2	3,3	(χ2=92.539; p<0.001)
Moderate	12	16,0	22	44,0	48	57,1	1	1,7	(χ2=62,975; p<0.001)
Low	-	-	-	-	12	14,3	57	95,0	(χ2=200.122; p<0.001)

Analyzing the distribution of patients with EC in stages I-II, taking into account the depth of tumor invasion in the myometrium, it was found that tumor growth in the endometrium occurred in 15 (5.6%; 95% [2.8-8.3]) patients; up to 50% of the myometrium - to 77 (28.6%; 95% [23,2-34,0]) patients; over 50% of the myometrium - to 127 (47.2%; 95% [41,2-53,2]) patients; and spread throughout the thickness of the myometrium - to 17 (6.3%; 95% [3.4-9.2]) patients. As a result, invasion of more than 50% into the myometrium occurred in 53.5% of cases. In patients in the low-

risk group, the depth of invasion up to 50% of the myometrium was observed most often – 49 (65.3%; 95% CI [54.6–76.1], depth of invasion only within the limits of the endometrium to 10 (13.3%; 95% [5.6-21.0] patients. In high-risk patients, invasion of more than 50% was observed in 38 (63.3%; 95% CI [41.4-53.4] patients, and 4 patients (6.7%; 95% CI [0.4–13.0]), the tumor invaded the entire thickness of the uterus (Table 3.9).

Table 3.9. Distribution of EC patients in stages I-II by depth of tumour invasion

Depth of tumor invasion	Risk group								P,gl =3
	Low		Intermediate		Intermediate-high		High		
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
Within the limits of the endometrium	10	13,3	1	2,0	1	1,2	3	5,0	$\chi2$=12,892; p<0.01
Infiltrates <50% into the myometrium	49	65,3	2	4,0	16	19,0	10	16,7	$\chi2$=72,276; p<0.001
Infiltrates >50% into the myometrium	-	-	47	94,0	42	50,0	38	63,3	$\chi2$=200,122; p<0.001
All thickness of the myometrium	-	-	-	-	13	15,5	4	6,7	$\chi2$=200,122; p<0.001

To identify the prognostic value of clinical markers of inflammation, we calculated the following ratios

1) neutrophil/lymphocyte index (INL), which was calculated as the ratio of absolute neutrophil count to absolute peripheral blood lymphocyte count,

2) platelet/lymphocyte index (ITL), which was calculated as the ratio of absolute platelet count to absolute peripheral blood lymphocyte count.

Table 3.10. Clinical markers of inflammation in patients with EC in stages I-II by risk group

Relative blood index	Risk group				P
	Low	Intermediate	Intermediate-high	High	
	Median	Median	Median	Median	
INL	2,29	2,39	2,46	5,34	$\chi2$=12,892; p<0.01
ITL	120,19	124,0	147,1	355,7	$\chi2$=72,276; p<0.001

INL ranged across risk groups from 0.65 to 7.22. In the high risk group, the median neutrophil/lymphocyte index was the highest and was 5.34, which corresponds to literature data on the interdependence between INL and the spread of tumor process and the level of tumor aggressiveness. ITL ranged from 55.03 to 428.10 across all risk groups, but in the high-risk group the average ITL value was 355.70. Data on INL levels in EC patients show statistically significant differentiations between groups (F=0.011; gl=3; p>0.05) as well as ITL ratio (F=1.381; gl=3; p>0.05).

4. MOLECULAR-GENETIC FACTORS IN ENDOMETRIAL CANCER PROGNOSIS

Ki-67 antigen expression was determined in the endometrium in 50 EC patients by immunohistochemical method. The value of the proliferative activity marker, Ki-67 in patients with endometrial cancer in stages I-II was exposed by the correlation of this marker with age, number of pregnancies, beginning and duration of the menstrual cycle. The dependence of Ki-67 index expression on the degree of tumor differentiation in patients with endometrial cancer according to the risk group is demonstrated, as well as the marker link with the CE stage and the degree of tumor infiltration. When analyzing the data obtained, it was revealed that in patients with CE, the minimum value of the Ki-67 index was 14%, the maximum value was 75%, and the average value was

43.6±12.4%. In patients with non-endometrial EC (n=9), the Ki-67 index ranged from 16 to 77%, the mean index value was 37.9±7.65%. Study results are presented in Table 4.1.

Table 4.1. Correlation relationships and Spearman correlation coefficients between Ki-67 expression and menstrual characteristics, reproductive function in patients with EC in stages I-II by risk group

Risk group	Correlation	Spearman correlation coefficient
Low risk	Ki-67 - age	0,415
	Ki-67 – length of menstrual cycle	-0,212
	Ki-67 — age of menstruation	0,362
	Ki-67 – number of tasks	0,126
Intermediate risk	Ki-67 - age	-0,242
	Ki-67 – length of menstrual cycle	-0,203
	Ki-67 — age of menstruation	-0,242
	Ki-67 – number of tasks	0,069
Intermediate-high risk	Ki-67 - age	0,017
	Ki-67 – length of menstrual cycle	0,293
	Ki-67 — age of menstruation	0,044
	KiÏ-67 – number of tasks	0,451
Increased risk	Ki-67 - age	0,147
	Ki-67 – length of menstrual cycle	-0,047
	Ki-67 — age of menstruation	0,278
	Ki-67 – number of tasks	-0,179

Thus, when analyzing the data obtained in all groups, it was revealed that the Ki-67 expression index does not depend on the patient's age. At the same time, there was no dependence on the length of the menstrual cycle and the age of menopause. Analysis of KI-67 levels in tumors was performed in relation to the degree of tumor differentiation, depth of invasion in the myometrium, prevalence of tumor process and disease stage in patients with CE. It was observed that the degree of tumour differentiation in all groups of patients with endometrial cancer correlated with the level of proliferation index, the results are presented in Table 4.2.

Table 4.2. Dependence of Ki-67 expression on degree of tumor differentiation in endometrial cancer patients by risk group (abs.)

Tumor differentiation	Risk group								P
	Low		Intermediate		Intermediate-high		High		
	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	
High	13	4	1	2	-	3	-	-	$\chi2$=10,6; gl=2; p<0.05
Moderate	1	1	4	2	-	6	-	-	$\chi2$=6,015; gl=2; p<0.05
Low	-	-	-	-	2	1	1	9	$\chi2$=4,174; GL=1; p<0.05

In patients with stage I-II EC with highly differentiating endometrial adenocarcinoma, the Ki-67 index was predominantly below the mean value, while in cases with moderately differentiating adenocarcinoma, approximately the same number of patients (54% and 46%) had a mean Ki-67 index higher and lower than 49%. In 75% of patients with low-grade endometrial adenocarcinoma, the proliferation index was higher than the median.

When the dependence of proliferative activity index expression was studied, it was revealed that in patients with EC the index value increases with the spread of the tumor process in the myometrium. Thus, in patients with EC with depth of invasion in the myometrium up to 50%, the

Ki-67 index below the mean value was in 9 cases and higher in 6 cases. And, in tumors with myometrial invasion more than 50%, the Ki-67 index below the average value was registered in 6 cases and higher in 16 cases.

Table 4.3. Dependence of Ki-67 index expression on depth of myometrial invasion in patients with stage I-II endometrial cancer by risk group (abs.)

Depth of invasion in myometrium	Risk group								P, GL=2
	Low		Intermediate		Intermediate-high		High		
	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	
Infiltrate < 50%	14	5	-	-	-	3	-	-	$\chi2$=3,556; p>0.05
Infiltrate > 50%	-	-	5	4	2	7	1	9	$\chi2$=6,385; p<0.05

The determination of the dependence of the Ki-67 expression index on the stage of the disease was carried out, the results are presented in Table 4.4. It was observed that in the group of patients with EC stage I disease, in 12 of the patients the proliferation index was below the mean value. In EC stage II, the proliferation index was predominantly higher than 49% - in 15 patients.

Table 4.4. Dependence of Ki-67 index expression on disease stage in patients with stage I-II endometrial cancer by risk group (abs.)

Stage of the disease	Risk group								P
	Low		Intermediate		Intermediate-high		High		
	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	Ki-67<49%	Ki-67>49%	
I	12	6	5	3	2	11	1	1	$\chi2$=13,440; gl=3; p<0.01
II	-	-	-	-	-	-	-	9	$\chi2$=4,000; GL=2 p>0.05

Thus, the analysis of the obtained results showed that in patients with EC the proliferation index value was significantly lower in stage I of the disease compared to stage II and in 50.0% of patients with stage I, the index was below average (p=0.037). No significant differences were obtained in EC patients in the low-risk group.

The value of the proliferation marker Ki-67 in EC patients had a general trend: in all groups there was significant dependence on patient age, menstrual cycle length and menopausal age. In addition, it was found that the value of Ki-67 expression changes depending on tumor differentiation, degree of invasion in the myometrium and stage of disease. The associations of Ki-67 expression with tumor differentiation, myometrial invasion, spread to the cervical canal, and disease stage were similar in all groups, but significance in the high-risk group apparently indicates greater proliferation index informativeness for this particular group, which requires further research.

In endometrial cancer, in more than 50% of cases, the *PTEN* suppressor gene is inactive, which, according to many authors, is a key stage in the malignant transformation of the endometrium. According to studies, mutational damage in promoter regions (regulatory regions) of genes can lead to their complete inactivation, thereby stimulating carcinogenesis [18]. However, in Moldova, such studies have not been conducted on the *PTEN gene*. The results of molecular genetic testing to determine the c.389G>A mutation (p.R130Q) of the *PTEN gene* in 50 women with CE are exposed by the rate of presence and absence of mutation relative to the risk group (Table 4.5).

Table 4.5. Proportion of *PTEN-positive* tumours among patients with EC stages I-II by risk group

Presence of c.389G>A (p.R130Q) mutation of PTEN gene	Risk group								P
	Low		Intermediate		Intermediate-high		High		
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
Absent	17	34,0	8	16,0	5	10,0	2	4,0	$\chi2$=17,459; gl=3; p<0.01
Present	2	4,0	1	2,0	7	14,0	8	16,0	

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. Of particular interest is the study *of PTEN* mutations in various pathogenetic variants of CE. Analysis of the data obtained revealed that the c.389G>A mutation (p.R130Q) *of the PTEN* gene was determined in 18% of patients with CE in the first pathogenetic variant.

Table 4.6. Proportion of *PTEN-positive* tumours in patients with stage I-II endometrial cancer depending on pathogenic variant

Pathogenetic variant	C.389G>A (p.R130Q) mutation of PTEN gene				P
	Negative		Positive		
	Abs.	%	Abs.	%	
Hormonodependent (I)	37	74,0	12	24,0	$\chi2$=0,574; GL=1; p>0.05
Autonomous (II)	1	2,0	-	-	

The number of patients with the c.389G>A mutation (p.R130Q) *of the PTEN gene in the pathogenetic variant I of the EC prevailed over the number of patients with* PTEN in the case of variant II (18% and 0%), which probably explains the more favorable evolution in variant I. Based on this, it can be assumed that the presence of mutations in the phosphatase tensine-type domain region of the PTEN suppressor gene *may cause a favorable course of the disease.*

We analyzed the relationship between the presence of a c.389G>A mutation (p.R130Q) *of the PTEN gene and* morphological prognostic factors - the histological structure of the tumor and the degree of its differentiation, as well as the level of tumor invasion in the myometrium. Thus, in the presence of a highly differentiated tumor, the c.389G>A (p.R130Q) mutation of the *PTEN* gene was absent in all study groups. With increasing degree of tumor malignancy, the frequency of mutations of the *PTEN gene* in each of the studied groups also increases. The results of determining the c.389G>A mutation (p.R130Q) of the *PTEN* gene according to the degree of tumor differentiation in patients with EC are presented in Table 4.7.

Table 4.7. Dependence of c.389G>A mutation (p.R130Q) of PTEN gene on degree of differentiation in patients with EC stages I-II by risk group (abs.)

Degree of differentiation	Risk group								P
	Low		Intermediate		Intermediate-high		High		
	PTEN -	*PTEN* +	*PTEN* -	*PTEN* +	*PTEN* -	*PTEN* +	*PTEN* -	*PTEN* +	
Low	16	1	3	-	-	3	-	8	$\chi2$=15,698; gl=2; p<0.001
Moderate	1	1	5	1	3	3	-	-	$\chi2$=1,659; gl=2; p>0.05
High	-	-	-	-	2	1	2	-	$\chi2$=2,359; GL=1; p>0.05

The c.389G>A (p.R130Q) mutation of the *PTEN* gene was most common in poorly differentiated tumors. Thus, 100% of low-grade tumors in the high-risk group had a c.389G>A (p.R130Q) mutation of the *PTEN gene*. The c.389G>A (p.R130Q) mutation of the *PTEN* gene was also observed in 15.7% of moderately differentiated tumors and 13.3% of highly differentiated tumors.

PTEN gene mutations were significantly more commonly observed in tumors invading more than half the thickness of the myometrium in all groups studied. Thus, in tumors with myometrium invasion up to half its thickness in the low-risk group, only 1 in 12 tumors were *PTEN* positive (13.6%); whereas tumors with invasion over half the thickness of the myometrium were observed in 6 out of 8 cases (87.5%) of the high-risk group.

Table 4.8. Dependence of *PTEN* expression on depth of myometrial invasion in patients with stage I-II EC by risk group (abs.)

Depth of invasion in myometrium	Risk group								P
	Low		Intermediate		Intermediate-high		High		
	PTEN -	*PTEN* +	*PTEN* -	*PTEN* +	*PTEN* -	*PTEN* +	*PTEN* -	*PTEN* +	
Infiltrate < 50%	17	1	-	-	3	1	-	2	$\chi 2$=7,619; gl=2; p<0.05
Infiltrate > 50%	-	1	8	1	2	6	2	6	$\chi 2$=7,525; gl=2; p<0.05

When analyzing the data obtained, it was found that when the invasion of endometrial cancer in the myometrium is less than 0.5 cm, the c.389G>A (p.R130Q) mutation of the *PTEN* gene is detected in 11% of cases. In a widespread tumor process, the c.389G>A (p.R130Q) mutation of the *PTEN gene* is detected much more often (57%). Thus, the analysis of the obtained data revealed that the frequency of c.389G>A mutation (p.R130Q) of the *PTEN gene* in patients with CE depends on the degree of tumor differentiation, the stage of the tumor process and the depth of tumor invasion. The rate of presence of the c.389G>A (p.R130Q) mutation of *the PTEN* gene was highest expressed in the high-risk group, which is an important feature.

When studying microsatellite instability (MI) in 50 patients with EC in stages I - II, aged between 30 and 80 years, showed that in stage I CE the frequency of detection of MI was 20%. Taking into account the age factor, the following was detected (Table 4.10): the frequency of tumors with microsatellite instability has a clear pattern - it increases during menopause, reaching 30.0% at the age of 50-59 years and 50.0% of cases at 60-69 years, and decreases in the age periods 70-79 years, ie postmenopausal.

Table 4.9. Distribution of EC patients by age and presence of MLH1 epimutation

Age range	MLH1 *presence*	
	Abs.	%
30—39 years	-	-
40—49 years	2	20,0
50—59 years	3	30,0
60—69 years	5	50,0
70—79 years	0	0

In postmenopausal women, MI is rarely detected, although the number of gene mutations generally increases with age. Our data point to a possible relationship between age-related hormonal disorders and CE, as postmenopausal adenocarcinoma often develops from atrophic endometrium. Analysis of the results obtained showed that in patients with CE, the presence of *MLH1* epimutation was significantly higher in stage I disease. MLH1 epimutation was observed in 22.0% of stage I patients.

Table 4.10. Dependence of *MLH1* epimutation on disease stage in patients with stage I-II endometrial cancer

Stage of the disease	*MLH1*				P
	Negative		Positive		
	Abs.	%	Abs.	%	
I	34	68,0	8	22,0	$\chi 2$=0,001; GL=1; p>0.05
II	6	8,1	2	4	

The results of determining the epimutation of *the MLH1* gene according to the degree of tumour differentiation in EC patients are presented in Table 4.11.

Table 4.11 Dependence of MLH1 epimutation on degree of tumor differentiation in patients with stage I-II endometrial cancer by risk group (abs.)

Degree of differentiation	Risk group								P
	Low		Intermediate		Intermediate-high		High		
	MLH1-	*MLH1+*	*MLH1-*	*MLH1+*	*MLH1-*	*MLH1+*	*MLH1-*	*MLH1+*	
Low	-	1	3	2	3	2	3	4	$\chi 2$=1,480; gl=2; p>0.05
Moderate	14	1	3	-	5	-	2	-	$\chi 2$=2,806; gl=2; p>0.05
High	4	-	1	-	-	-	2	-	$\chi 2$=0,231; GL=1; p>0.05

When analysing the results, it was revealed that in patients with CE, the absence of *MLH1* epimutation was more often observed in patients with low- and moderate-differentiating adenocarcinoma (4% and 12%). There were no significant differences, but a trend was observed – with increasing degree of differentiation of the tumor, the frequency of detection of *MLH1* epimutation decreases. We studied the presence *of MLH1* epimutation according to the depth of tumor invasion in EC patients in all risk groups.

Table 4.12. Dependence of *MLH1* epimutation on depth of myometrial invasion in endometrial cancer patients by risk group (abs.)

Depth of invasion in myometrium	Risk group								P
	Low		Intermediate		Intermediate-high		High		
	MLH1-	*MLH1+*	*MLH1-*	*MLH1+*	*MLH1-*	*MLH1+*	*MLH1-*	*MLH1+*	
Infiltrate < 50%	18	2	1	-	-	-	-	1	$\chi 2$=2,424; gl=2; p>0.05
Infiltrate > 50%	-	-	6	2	8	2	7	3	$\chi 2$=1,293; gl=2; p>0.05

When analyzing the data obtained, the presence of *MLH1 epimutation in 40% of cases is detected in patients with EC invasion in the myometrium less than 0.5 cm. In a widespread tumor process, epimutation of* MLH1 *is detected much more often (60%).*

5. SIGNIFICANCE OF CLINICAL-MORPHOLOGICAL AND MOLCEULAR-GENETIC PROGNOSTIC FACTORS IN PATIENTS WITH ENDOMETRIAL CANCER IN STAGES I-II

In our study, three-year overall survival for stage I EC patients was observed in 201 (93.5%; I 95% [90.0-96.6]) patients. At the same time, this indicator for patients with stage IA and IB was 94.2% (95% CI [89.0-98.1])and 92.7% (95% CI [87.1-97.3]), respectively. As shown by the data presented, there is a trend of improvement in long-term outcomes in patients with stage IA EC compared to stage IB (p>0.05). Follow-up periods in the low-risk group from 3 to 6 months, from 6 to 9 months and from 9 to 12 months went without "event" recording 100% in overall survival; In the high-risk

group, the period from 3 to 6 months and the interval of 6–9 months went without "event", constituted 98.7% and, respectively, 9–12 months – 97.4%. At 12–18 months, overall survival was 97.3% in the low-risk group compared to 91.0% in the high-risk group; 18–24 months – 98.9% in the low risk group versus 87.2% in the high risk group; 24–30 months – 98.9% in the low risk group, compared to 78.2% in the high risk group; At 30–36 months, overall survival was 98.7% in the low-risk group and 71.8% in the high-risk group. The Equality of Survival Distributions test for different levels of the risk group according to the Log Rank method (Mantel-Cox) showed a higher survival of patients with endometrial cancer in stages I-II in the intermediate risk group $\chi 2=20,420$; gl=3; $p<0.001$.

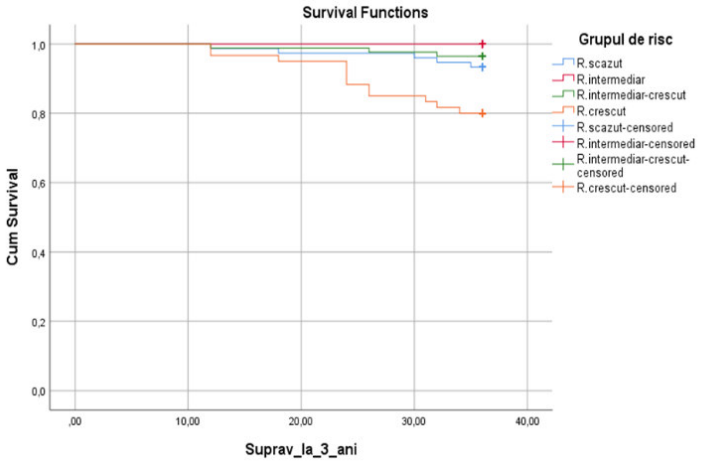

Fig. 5.1. Overall three-year survival of patients with stage I-II endometrial cancer

In our study, overall three-year survival for stage I EC patients was observed in 205 (93.5%; I 95% [90.0-96.6]) patients. At the same time, this indicator for patients with stage IA and IB was 94.2% (95% CI [89.0-98.1]) and 92.7% (95% CI [87.1-97.3]), respectively. As shown by the data presented, there is a trend of improvement in long-term outcomes in patients with stage IA CE compared to stage IB ($p> 0.05$). Because 60 (93.5%; 95% CI [90.0-96.6]) patients with stage II EC were presented by the high-risk group, it should be noted that in stage II the 3-year survival rate was less than 60% and constituted 74.2% (95% CI [71.0-79.6]).

Table 5.1. Overall survival of EC patients at stages I-II by risk group

Stage of the disease	Risk group							
	Low		Intermediate		Intermediate-high		High	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Stage IA	47	94,00	20	100,0	20	100,0	11	78,6
Stage IB	12	92,3	23	100,0	44	93,6	24	85,7
Stage II	0	0	0	0	17	100,0	13	72,2

Of the 269 patients with stage I-II EC included in the study, relapses and metastases were observed in 20 (7.4%; I 95% [4.3-10.6]) patients. Of these, 3 (1.1%; 95% [0.0-2.4]) patients were diagnosed with disease relapses, 17 (6.3%; 95% CI [3.4-9.2]) - metastases. As follows from the above, in patients with EC in stages I-II, metastases occurred 5.7 times more often than relapses. Patients with disease progression were distributed as follows: stage IA - 7 (21.8%), IB - 10 (36.4%) patients (Table 5.2).

Table 5.2. Distribution of patients with EC in stages I-II by frequency of relapses and metastases

	Stage IA	Stage IB	Stage II	P
Relapses	2	1	-	$\chi 2=0,667$; gl=2; $p>0.05$
Metastases	5	9	3	$\chi 2=4,94$; gl=2; $p>0.05$

In stage IA of EC relapse was detected only in 2 patients, which is almost 2.5 times lower than the number of detected metastases - in 5 patients. In stage IB of CE, disease relapse was diagnosed in 1 patient, and metastases – in 9 patients. Metastases in lymph nodes (GL) were recorded in 6 patients, in one patient the iliac region was affected, in 5 paraaortic region. Metastases to the liver were diagnosed in 2 patients, to the lungs - to 3, to the brain - to 1 and multiple - to 5 patients (Table 5.3).

Table 5.3. Distribution of patients with EC in stages I-II by risk group and location of relapses and metastases (abs.)

Groups of relapses and metastases	Localization	Risk group				P
		Low	Intermediate	Intermediat e-high	High	
Loco-regional	Vaginal abutment	2	1	-	-	$\chi2$=2,322; gl=3; p>0.05
	Metastases in lymph nodes	2	2	2	-	$\chi2$=2,632; gl=3; p>0.05
Remote metastases	Liver	1	-	1	-	$\chi2$=1,405; gl=3; p>0.05
	Lungs	-	-	2	1	$\chi2$=2,795; gl=3; p>0.05
	Brain	-	-	1	-	$\chi2$=2,211; gl=2; p>0.05
Mixed		-	1	3	1	$\chi2$=2,789; gl=2; p>0.05

The average duration of metastases was 17.0±1.59 (95% CI [13.8–20.2]) months, metastases in lymph nodes – 21.6±0.87, lungs – 10.5±0.62, liver – 18.5±0.52, multiple – 17.2±0.89. When analyzing the distribution of patients with progression of CE in stages I-II depending on the depth of tumor invasion in the myometrium, it was found that in 1 (12,5%) case, the tumor was located in the endometrium, and in 2 (25%) cases, the depth of invasion was 1 cm; with metastases, these indicators were 2 (8.3%), 1 (4.2%), 7 (29.2%) and 7 (58.3%), respectively (Table 5.4).

Table 5.4. Distribution of EC patients in stages I-II with progression by risk group and depth of tumor invasion in myometrium (abs.)

Depth of tumor invasion in myometrium	Risk group							
	Low		Intermediate		Intermediate-high		High	
	I recid.	Metast.	I recid.	Metast.	I recid.	Metast.	I recid.	Metast.
Within the limits of the endometrium	-	-	-	-	-	-	1	-
Up to 50% myometrium (п=48)	-	2	-	3	-		2	1
More than 50% myometrium(п=52)	-	-	-	3	-	2	-	1
Full thickness	-	-	-	3	-	1	-	1

Thus, the prevalence of patients whose depth of tumor invasion was >1 cm, and the highest this indicator was in patients with metastases. It should be noted that the mean depth of myometrial invasion in patients with relapses and metastases was 10.8±0.63 mm versus 7.2±0.52 mm in the absence of disease progression. At stages IA-IB, these indicators were 7.9±1.4 and 6.2±0.9 mm, and at stage II - 11.7±1.3 mm, respectively. The level of cell proliferation marker, Ki-67, estimated in the immunohistochemical examination in 50 patients with EC in stages I-II, was imposed by predictive value on survival, so that with its increase the survival rate decreases. In patients with an imminent

level of Ki-67 proliferative activity of 0-33%, the overall survival rate was 80.8±3.3%, and at a proliferative activity greater than 34%, the overall survival rate depreciated to 57.9±5.4% during the 3-year surveillance period. The Log Rank Survival Distribution Equality Test (Mantel-Cox) showed that increased proliferative activity (49% or more) had no effect on outcomes $\chi 2=2.620$; gl=1; p=0.105.

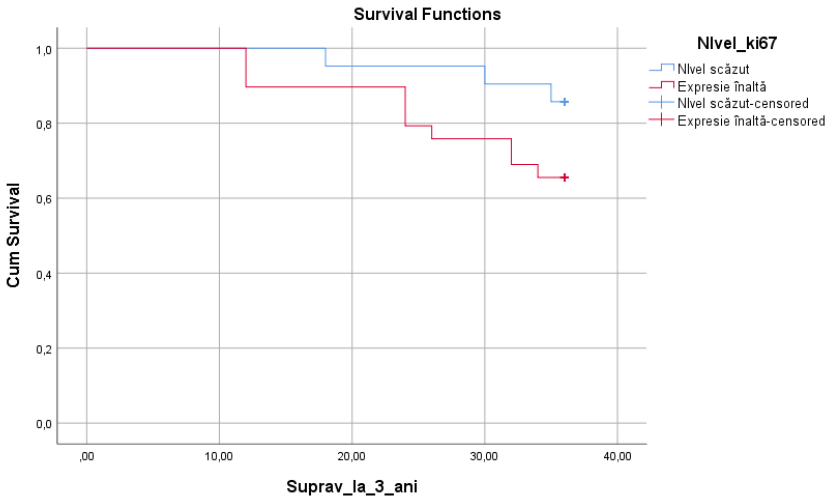

Figure 5.2. Overall survival at 3 years in patients with EC in stages I-II, depending on the expression of the Ki-67 proliferation index

High expression of proliferation factor Ki-67 reduces relapse-free survival to 15.3±2.21 (95% CI [11.1–19.7]) months. The mean time to progression in high-risk patients was 13.5±4.50 months (95% CI [9.0-18.0]), 15.8±3.36 months in low-risk patients (95% CI [10.5-23.0]) (F=0.066; p=0.937), which may indicate the prognostic value of this indicator for early signs of progression. At the same time, our main task was to study the effect of the presence of genetic mutations on treatment outcomes. The results of the analysis of overall survival in patients in study groups by presence of MLH1 epimutation showed that 71% of women with *MLH1 epimutation and 92.5% without* MLH1 *epimutation* achieved survival at 3 years. Survival at 3 years without relapse was recorded in 6 patients with EC with the presence of epimutation in the *MLH1 gene*. The mean time to CE progression in patients with *MLH1* epimutation was 14.6±2.54 (95% CI [11.1-19.7]) months. The mean time to progression in patients in the low-risk group was 16.3±5.5 (95% CI [9.0-28.0]) months. At the same time, the mean time to CE progression in patients with *MLH1* epimutation in the high-risk group was 10.5±1.11 (95% CI [9.0-12.0]) months (F=0.305; p=0.750). Thus, the analysis of the obtained results showed that in patients with CE, the presence of the tumor IMS phenotype significantly affects survival without relapse at three years, regardless of stratification of risk groups. Overall 3-year survival rates in EC patients who are carriers of *MLH1* epimutation in different risk groups are shown in Fig. 5.3. The Log Rank Survival Distribution Equality Test (Mantel-Cox) showed greater survival of patients not carrying *MLH1 promoter epimutation* $\chi 2=15.974$; gl=1; p<0.001.

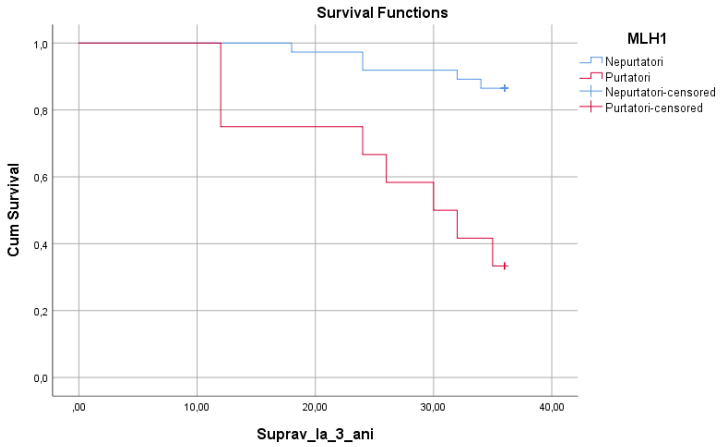

Figure 5.3. Overall survival in EC patients carrying *MLH1* epimutation in different risk groups

As for the influence *of mutation in the PTEN gene in patients with CE on the time of progression in different risk groups, it also demonstrates the correlation of the presence of* PTEN mutation with survival rate in patients with endometrial cancer. The mean time to CE progression in patients with *the PTEN* mutation was 15.7±1.89 (95% CI [11.3-20.5]) months (95% CI 7 to 15 months), which did not differ (F=0.005; p=0.943) from mean time to progression in patients without mutations – 16.0±3.97 (95% CI [12.0-28.0]). Thus, the mean time to progression in patients with the *PTEN* gene mutation in the low-risk group was 13.5±3.37 (95% CI [9.0-18.0]) months , significantly different from that in high-risk patients – 15.8±3.34 (95% CI [10.5-23.0]) months (F=16.2; p=0.891), which may indicate the prognostic significance of this indicator for detecting early signs of relapse (Fig. 5.7). The Log Rank Survival Distribution Equality Test (Mantel-Cox) showed higher survival of patients not carrying the mutation in the *PTEN gene* $\chi 2$=9.214; gl=1; p=0.002.

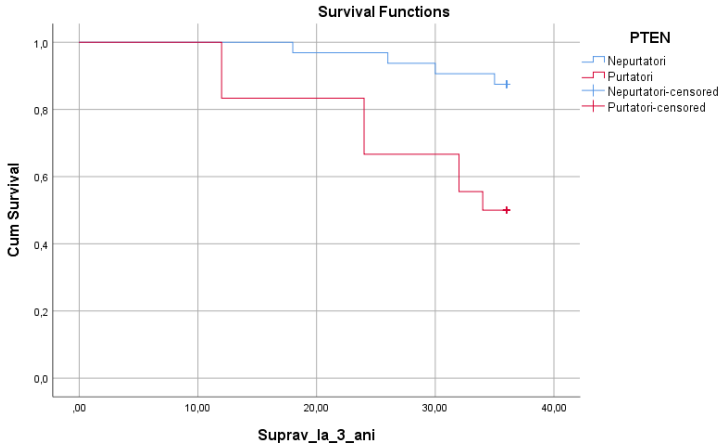

Figure 5.4. Overall survival in EC patients in stages I-II carrying *PTEN* mutation in different risk groups

6. PROGNOSIS OF ENDOMETRIAL CANCER EVOLUTION

The results of the multivariate analysis (IBM SPSS Statistics 26.0 software) regarding the estimation of the prognostic value of the clinical-morphological and molecular-genetic parameters regarding the overall survival and without relapse at a distance of 3 years of the 269 patients with EC in stages I-II included in the study are presented. The indices used in this context are: age, BMI, stage of disease, degree of differentiation of the tumor, histological subtype of tumor, depth of invasion in the myometrium and cervical canal, presence of perilymphovascular infiltration, presence of perineural infiltration, presence of foci of necrosis, Ki-67 expression level, presence of c.389G>A mutation (p.R130Q) *of the PTEN* gene and hypermethylation of the promoter *MLH1*. It is noted that disease stage is a statistically significant factor in the overall 3-year survival of patients with CE, and so indicate how the degree of differentiation and the level of the Ki-67 marker are statistically significant predictors of survival without relapse at the same surveillance period. Also, the results of

cluster discriminant analysis are reported, meant to highlight from a group of 14 indices clinical, morphological, and genetic factors with predictive value on the distant diagnosis and prognosis of patients with EC in stages I-II. As a result of the complex investigations carried out in the previous chapters, we determined the value of decisive risk factors in the prognosis of EC evolution, presented in Table 6.1.

Table 6.1. Decisive risk factors included in the model to assess the prognosis of disease progression in patients with EC stages I and II

Name of risk factors	Lambda Wilks	Tolerance	p
Age	0,65137	0,77346	0,00015
Depth of invasion in myometrium	0,57698	0,88573	0,01619
Degree of differentiation	0,56283	0,90336	0,04465
Primary tumor size	0,59191	0,83085	0,00589
INL Index	0,59657	0,79819	0,00433
Age of menopause	0,59707	0,85419	0,02034
Infertility	0,58378	0,84414	0,01830
Duration of menstrual cycle disorder	0,57504	0,84660	0,01312
Stage of the disease	0,61638	0,77200	0,00123
Perilymphovascular invasion	0,57541	0,7865	0,00234
Perineural invasion	0,59309	0,67421	0,00970
PTEN	0,55544	0,90359	0,02835
MLH 1	0,55329	0,86420	0,00978
Ki 67	0,54165	0,92120	0,02494

The following linear discriminating functions were obtained:
Y1=0.556*X1+2,774*X2+0,145*X3+13,438*X4+0,177*X5+6,526*X6+9,938*X7+36,150*X8+(-0,881)*X9 +3,589*X10+3,817*X11+0,012*X12-407,350
Y2=-2,179*X1+1,987*X2+0,186*X3+14,173*X4+0,027*X5+6,846*X6+9,622*X7+38,367*X8+(-1,094)*X9 +1,756*X10+3,399*X11+0,005*X12-416,584, where
X1 - age (1- reproductive, 2 - perimenopausal, 3 - menopausal, 4 - postmenopausal)
X2 - depth of invasion in the myometrium (1 - up to 50%, 2 - over 50%)
X3 - degree of differentiation (1 - G1, 2 - G2, 3 - G3)
X4 - size of the primary tumor (1 – up to 2 cm, 2-from 2-5 cm, 3-more than 5 cm)
X5 - INL index
X6 - age of menopause
X7 - infertility (0 - absent, 1 - present)
X8 - duration of menstrual cycle disorders
X9 - stage of the disease (1 - stage I, 2 - stage II)
X10 - *PTEN* 1.0 (0 - absent, 1 - present)
X11- *MLH1* 1.0 (0 - absent, 1 - present)
X12 - proliferation index Ki 67 (1 - up to 49, 2 - over 49)
X13 - perilymphovascular invasion (0 - absent, 1 - present)
X14 - perineaural invasion (0 - absent, 1 - present)

When calculating discriminant functions, the object (patient with EC in stages I and II) was assigned to one of the classes. If Y1>Y2, then the object belongs to the first class (unfavorable prognosis) with a level of significance $p<0.05$, which means that the risk of developing a poor outcome in this patient is 95%. If Y1<Y2, then the object belongs to the second class (favorable prognosis) with a level of significance $p<0.05$, which means that the risk of developing a favorable outcome is 95%. The quality of functions achieved was assessed in 20 patients not included in the main sample. The sensitivity and specificity of the developed mathematical model were 87% and 89%. The application of the mathematical model for highlighting the predictors algorithm was done in the context of 2 groups of patients: (1) with favorable prognosis and (2) unfavorable survival without relapse at the postoperative distance of 3 years.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

1. Conclusions

1. The results of the complex study conducted on a group of 269 patients with EC in stages I-II revealed clinical-morphological predictors of the occurrence of relapses and metastases: clear cell carcinoma, glandular squamous cells, serous papillary cancer, invasion of more than 50% in the myometrium, depth of tumor invasion in myometrium >1 cm and stroma >0.5 cm, moderate and increased degree of cellular and nuclear anaplasia of the tumor, the presence of lymphovascular invasion and the presence of foci of necrosis in the tumor.

2. The level of cell proliferation marker, Ki-67, estimated in the immunohistochemical examination in 50 patients with EC in stages I-II, was imposed by predictive value on survival, so that with its increase the survival rate decreases. In patients with an imminent level of Ki-67 proliferative activity of 0-33%, the survival share was 80.8%, and in proliferative activity greater than 34%, the survival share depreciated to 57.9% during the 3-year surveillance period.

3. DNA testing in 50 patients with EC in stages I-II detected mutations in the *MLH1* gene in 10 (20%) cases and will be used to determine the risk of disease recurrence. The analysis of the results obtained showed that in patients with EC the presence of *MLH1* epimutation significantly affects survival without relapse regardless of stratification of risk groups. The mean time to CE progression in patients with MLH1 epimutation was 14.6±2.54 (95% CI [11.1-19.7]) months.

4. The c.389G>A (p.R130Q) mutation of the *PTEN* gene was detected in 12 (24%) patients. More frequently, *PTEN* mutation was detected in the high-risk group in 8 (66%) cases. Dynamic observation of patients (n=12) carrying the c.389G>A mutation (p.R130Q) of the *PTEN* gene for 3 years, regardless of risk group, revealed an unfavorable prognosis of the disease, which was manifested either by recurrence of endometrial adenocarcinoma (n=8) or by metastases (n=4).

5. The evolution of EC excels by increasing the level of neutrophils / lymphocytes dispensable from the stratification of risk groups with impaired survival without relapse at 3 years, which indirectly correlates with the average time of occurrence of CE progression. The data of our study demonstrated that in patients with INL<2.43 the trigger time for EC progression is 16.2±2.75 (95% CI [14.5-18.4]) months, it is reduced to 15.3±2.21 (95% CI [11.1-19.7]) months in patients with INL (2.43-5.0) and reaches a minimum value of 9.1±3.32 (95% CI [6.7-12.7]) months in patients with INL>5.0. Remarkably, in patients with the c.389G>A (p.R130Q) mutation of the *PTEN* gene, the INL level was significantly higher compared to the prototype inherent in patients without this mutation (5.2 versus 3.7; $p<0.05$).

6. The scientific problem solved in the thesis consists in that research based on clinical-morphological and molecular-genetic studies has detected novel pathogenetic mechanisms and predictors of EC exacerbation, such as the presence of c.389G>A mutation (p.R130Q) *of the PTEN* gene, hypermethylation of the promoter *of the MLH1 gene, the* proliferation marker Ki-67, the increase of INL, which allowed the elaboration of a mathematical model for predicting the evolution of the disease in patients with EC from different risk groups over the period of 3 years.

2. Practical recommendations

System level

1. The results of the study on the detection of clinical-morphological and molecular-genetic prognostic factors in endometrial cancer are feasible for estimating the risk of relapse at 3 years and can serve as benchmarks for developing the personalized treatment algorithm in patients with EC in stages I-II.

2. Review of the National Clinical Protocol: Endometrial Cancer by the working group of the Ministry of Health of the Republic of Moldova, consisting of representatives of IMSP Institute of Oncology of the Republic of Moldova. It is necessary that the National Protocol be developed in accordance with current international guidelines on endometrial cancer and will serve as a basis for the development of the institutional protocol.

Medical institution level

3. The manager of IMSP IO is responsible for reviewing the institutional protocol in endometrial cancer, implementing clinical and molecular-genetic criteria, such as determining the

c.389G>A mutation (p.R130Q) of the *PTEN* gene, methylation of the promoter *of the MLH1* gene, the proliferation marker Ki-67 and the neutrophil/lymphocyte index. The application of these criteria can be widely used to estimate the risk of recurrence in patients with EC stages I-II.

4. In the clinical activity of the Cancer Biology Laboratory of IMSP, Institute of Oncology, elaboration and implementation of molecular-genetic research programs of CE with the establishment of the molecular subtype of the tumor. Thus, the estimation of the evolution of endometrial cancer in stages I-II will be streamlined, which will allow its application in accordance with the developed criteria.

Level of family doctors, oncologists, gynecologists, surgeons and oncology specialists

5. The implementation in everyday practice of the mathematical model, which includes in itself 14 clinical-morphological and molecular-genetic parameters, would be useful for estimating the evolution of the disease in patients with EC in stages I-II from different risk groups for a period of up to 3 years.

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ADNOTARE

Teza pentru gradul științific de doctor habilitat în medicină cu tema „Factorii molecular-genetici de prognostic al cancerului endometrial în stadiile I-II" a fost elaborată de către Tripac Irina în cadrul Instituției Medico-Sanitare Publice Institutul Oncologic, Chișinău, 2023. Structura tezei: introducere, 6 capitole, concluzii și recomandări practice, bibliografie din 206 titluri, 5 anexe, 161 pagini de text de bază, 32 figuri, 62 tabele. Rezultatele obținute sunt publicate de către autor în 55 de lucrări științifice.

Cuvinte-cheie: factori de prognostic, factori clinico-morfologici, factori molecular-genetici, model de prognostic, cancer endometrial.

Domeniul de studiu: Oncologie și radioterapie.

Scopul studiului: determinarea factorilor clinico-morfologici și molecular-genetici de prognostic al cancerului endometrial (CE) în stadiile I-II pentru elaborarea modelului matematic de predicție a recidivelor și supraviețuirii pacientelor pe o perioada de până la 3 ani.

Obiectivele lucrării: stabilirea criteriilor clinice, morfologice, imunohistochimice ca factorii de prognostic ai CE; estimarea corelației datelor imunohistochimice și molecular-genetice în funcție de caracteristicile clinice și morfologice ale cancerului de endometru; estimarea profilului molecular al tumorii la pacientele lotului de studiu; analiza multifactorială al complexului criteriilor de prognostic stabilite cu determinarea valorii de prognostic pentru fiecare factor aparte la pacientele cu CE în stadiile I-II; crearea modelului matematic al evaluării complexe de prognostic al CE în stadiile I-II în funcție de grupurile de risc și de factorii de prognostic.

Noutatea și originalitatea științifică: pentru prima dată a fost cercetată interfața biomarkerilor evenimentelor fiziopatologice principale ce se referă la declanșarea și evoluția cancerului endometrial în stadiul I și II. S-a estimat rolul echilibrului între procesele extreme iminente CE, cum ar fi apoptoza celulară și proliferarea celulară în contiguitate cu angiogeneza tumorii pentru a consolida markerii cu valoare predictivă asupra prognosticului patologiei.

Problema științifică soluționată în teză: problema științifică soluționată în teză constă în aceea, că cercetarea bazată pe studii clinico-morfologice și molecular-genetice a decelat mecanisme patogenetice inedite și predictori ai exacerbării CE, cum ar fi prezența epimutației c.389G>A (p.R130Q) a genei *PTEN*, metilării promotorului genei *MLH1*, markerului de proliferare Ki-67, creșterea indicelui neutrofile/limfocite, fapt ce a permis elaborarea unui model matematic pentru prezicerea evoluției bolii la pacientele cu CE din diferite grupuri de risc.

Semnificația teoretică: prin dovezile concludente obținute este completat conceptul și suportul teoretic al cancerului endometrial. La această formă este importantă decantarea aportului mutației c.389G>A a genei *PTEN*, creșterii activității proliferative a ciclului mitotic evaluată prin intermediul creșterii antigenului Ki-67, mutației genei *TP53* rezultante în deprecierea raportului Bax/Bcl2. Totodată, este evidențiat rolul inflamației în promovarea CE, iar majorarea indicelui neutrofile/limfocite este nu numai un mecanism patogenetic, dar și un predictor fezabil al prognosticului tumorii. Este conceptual importantă legătura notabilă a CE cu creșterea masei corporale, precum și absența legăturii între CE vizavi de riscul recurenței pe o parte și caracteristicile menstruației, numărului de nașteri și avorturi spontane pe de altă parte. Valoare predictivă asupra creșterii riscului de recurențe la pacientele cu CE este atribuită unor factori inerenți patologiei organelor reproductive, cum ar fi chistul ovarian, miomul uterin și mastopatia fibrochistică. Rata adenocarcinomul papilar seros în lotul pacientelor cu CE cu stadiul II este în medie cu 44-48% mai mare comparativ cu indicele stadiului IA și IB. Gradul diferențierii tumorale are impact concludent asupra riscului recurenței, astfel că gradul scăzut de diferențiere se estimează în 95% la pacientele de risc crescut, iar gradul înalt de diferențiere este caracteristic riscului scăzut (80%). Remarcabil, că

profunzimea invaziei tumorii nu corelează autentic cu creșterea riscului. Prezența focarelor necrotice este un predictor veritabil al riscului crescut. Impactul inflamației se impune prin valori maxime ale raportului neutrofile/limfocite și trombocite/limfocite la pacientele cu CE de risc crescut. Markerul proliferației Ki-67 este în raport direct cu gradul de risc, precum și cu stadiul bolii (nivelul expresiei Ki-67>49% este decelat numai în grupul de risc crescut). Prezența mutației c.389G>A (p.R130Q) a genei *PTEN* este în grupul riscului crescut de 4-8 ori mai mare comparative de riscul intermediar și intermediar-crescut. Important este prezența acestei mutații numai la pacientele cu paternul hormondependent al tumorii în proporție de 36%, dar stadiul II bolii se impune prin reducerea ratei mutației genei *PTEN* versus stadiul I. Epimutația *MLH1* nu demonstrează o legătură atât de concludentă cu evoluția CE comparative cu mutația c.389G>A (p.R130Q) a genei *PTEN*.

Valoarea aplicativă: pe un material clinic probatoriu vast a fost apreciată semnificația clinică a expresiei markerilor biologici moleculari care caracterizează apoptoza, proliferarea celulară și angiogeneza în țesutul tumoral la pacientele cu CE în stadiul I și II. Au fost determinate criteriile clinice, morfologice, imunohistochimice, și genetice precise de diagnostic și prognostic al CE la pacientele cu cancer endometrial în stadiile I-II. Au fost evidențiate caracteristicile imunohistochimice ale CE (expresia Ki-67), prezența mutației c.389G>A a genei *PTEN*, identificarea metilării promotorului genei *MLH1* și corelația în funcție de caracteristicile clinico-morfologice ale cancerului endometrial la pacientele lotului de studiu cu elaborarea profilului molecular al tumorii pentru fiecare pacient. Această abordare permite de a efectua o analiză detaliată a valorii de prognostic pentru fiecare factor aparte, ce va permite identificarea celor mai principali factori de prognostic. A fost elaborat un model propriu de prognostic, care include caracteristici clinice, morfologice, imunologice, imunohistochimice și genetice ale cancerului endometrial. Supraviețuirea pacientelor cu CE pe o perioadă de supraveghere de 3 ani este minimală (72,2%) în rândul celor cu vârsta mai mare de 60 de ani și care fac parte din grupul de risc crescut al recurenței. Rata de supraviețuire fără recidive este de asemenea minimală la aceste paciente (44%). Totodată, rata metastazelor la pacientele cu CE nu corelează inteligibil cu stadiul bolii. Timpul mediu de progresie a CE este în raport indirect cu valoarea raportului neutrofile/limfocite, acesta fiind minimal (6 luni: de la 5 până la 9 luni) la pacientele de risc crescut de recurență ce au un INL > 5,0. Markerul Ki-67 are valoare predictivă certă asupra ratei de supraviețuire și de recidivă la pacientele cu CE, astfel, că activitatea proliferativă sporită (>49%) are impact negativ la distanța de 3 ani. Prezența epimutației *MLH1* de asemenea influențează recidiva bolii la pacientele cu CE la distanța de 3 ani, dată fiind valoarea minimală a timpului mediu până la progresare de 10,5 ani atestat la purtătoarele acestei mutații din grupul de risc crescut.

Implementarea rezultatelor științifice: Rezultatele studiului au fost raportate la 8 foruri naționale și 18 internaționale. Pe marginea cercetării au fost validate: 3 brevete de invenții. Rezultatele studiului vor fi expuse sub forma unor recomandări practice pentru medicii de familie, ginecologi, dar și pentru specialiștii din domeniul oncologiei. În activitatea clinică a Laboratorului Biologia Cancerului a IMSP Institutul Oncologic vor fi elaborate și implementate programe de cercetare molecular-genetică a CE cu stabilirea subtipului molecular al tumorii. Astfel, va fi eficientizată estimarea evoluției cancerului endometrial în stadiile I-II, ceea ce va permite aplicarea acestuia în conformitate cu criteriile elaborate.

РЕЗЮМЕ

Диссертация на соискание ученой степени доктора медицинских наук на тему: «Молекулярно-генетические факторы прогноза рака эндометрия I-II стадии» выполнена Трипак Ириной Евгеньевной в Медико-Санитарном Публичном Учреждении Институт Онкологии, Кишинэу, 2023. Диссертация состоит из введения, 6 глав, выводов и практических рекомендаций. Работа изложена на 161 печатных страницах, содержит 62 таблиц, 32 рисунка. Библиография представлена 206 источниками. Полученные результаты были опубликованы в 55 научных работах.

Ключевые слова: прогностические факторы, клинико-морфологические факторы, молекулярно-генетические факторы, прогностическая модель, рак эндометрия.

Область исследования: Онкология и лучевая терапия.

Цель исследования: определение клинико-морфологических и молекулярно-генетических факторов прогноза рака эндометрия (РЭ) I-II стадий для разработки математической модели прогнозирования рецидивов и выживаемости пациенток на срок до 3 лет.

Задачи исследования: установить клинические, морфологические, иммуногистохимические критерии как прогностические факторы РЭ; оценить корреляции иммуногистохимических и молекулярно-генетических данных по клинико-морфологическим характеристикам рака эндометрия; оценить молекулярный профиль опухоли у пациентов основной группы; провести многофакторный анализ комплекса установленных прогностических критериев с определением прогностического значения каждого отдельного фактора у больных РЭ I-II стадии; создание математической модели комплексной прогностической оценки РЭ I-II стадий.

Научная новизна и оригинальность: впервые исследовано взаимодействие биомаркеров основных патофизиологических событий, связанных с возникновением и развитием рака эндометрия на I и II стадиях. По оценкам, роль баланса между такими процессами РЭ, как клеточный апоптоз и пролиферация в сочетании с опухолевым ангиогенезом, усиливает маркеры, имеющие прогностическое значение для данной патологии.

Решенная научная проблема: в диссертации на основании клинико-морфологических и молекулярно-генетических исследований выявлены новые патогенетические механизмы и предикторы обострения РЭ, такие как наличие эпимутации c.389G>A (p.R130Q) гена *PTEN*, метилирование промотора гена *MLH1*, маркера пролиферации Ki-67, повышение нейтрофильно-лимфоцитарного индекса, что позволило разработать математическую модель для прогнозирования эволюции заболевания у больных РЭ из разных групп риска.

Теоретическое значение: полученные убедительные доказательства дополняют концепцию и теоретическую основу рака эндометрия. На этом этапе важно оценить вклад мутации c.389G>A гена *PTEN*, повышение пролиферативной активности клеток, оцениваемое по увеличению экспрессии антигена Ki-67, приводящий к снижению соотношения Bax/Bcl2. При этом подчеркнута роль воспаления в стимуляции РЭ, а повышение нейтрофильно-лимфоцитарного индекса является не только частью патогенетического механизма, но и возможным предиктором опухолевого прогноза. Прогностическое значение повышенного риска рецидива у пациенток с РЭ следует придавать патологическим процессам репродуктивных органов, таким как киста яичника, миома матки и фиброзно-кистозная мастопатия. Частота серозно-папиллярной аденокарциномы в группе больных со II стадией РЭ в среднем на 44-48% выше показателя IA и IB стадии. Показано, что степень дифференцировки опухоли оказывает решающее влияние на риск рецидива, так, низкая степень дифференцировки определялась в 95% больных высокого риска, а высокая степень дифференцировки характерна в группе низкого риска (80%). Примечательно, что глубина инвазии опухоли на нашем материале не коррелировала с увеличением риска рецидивироания. Наличие очагов некроза является верным предиктором повышенного риска рецидива. Показано, что влияние воспаления проявляется максимальными значениями соотношения нейтрофилы/лимфоциты и тромбоциты/лимфоциты у больных РЭ высокого риска. Маркер пролиферации Ki-67 также напрямую связан со степенью риска, стадией заболевания (уровень

экспрессии Ki-67 >49% выявляется только в группе высокого риска). По нашим данным наличие эпимутации c.389G>A (p.R130Q) гена *PTEN* выявлено в группе высокого риска в 4-8 раз чаще по сравнению с промежуточным и промежуточно-высоким риском. Эпимутация *MLH1* не показала убедительной связи с прогнозом РЭ.

Практическая ценность: разработана собственная прогностическая модель, включающая клинические, морфологические, иммунологические, иммуногистохимические и генетические характеристики рака эндометрия I-II стадии. Выживаемость пациентов с РЭ за 3-летний период наблюдения минимальна (72,2%) среди лиц старше 60 лет и относящихся к группе повышенного риска рецидива. Безрецидивная выживаемость у этих больных также минимальна (44%). Среднее время до прогрессирования РЭ косвенно связано с величиной соотношения нейтрофилов/лимфоцитов, которое минимально (6 мес.: 5-9 мес.) у пациентов с высоким риском рецидива с индексом НЛИ > 5,0. Маркер Ki-67 имеет определенную прогностическую ценность в отношении выживаемости и частоты рецидивов у пациентов с РЭ, так что повышенная пролиферативная активность (>49%) оказывает негативное влияние на протяжении 3 лет. Наличие эпимутации *MLH1* также влияет на рецидив заболевания у больных РЭ на протяжении 3 лет, вне зависимости от стратификации группы риска.

Внедрение научных результатов: Результаты исследования были представлены на 8 национальных и 18 международных форумах, подтверждено 3 патента на изобретения. Результаты исследования будут представлены в виде практических рекомендаций для семейных врачей, гинекологов, а также для специалистов в области онкологии. В клинической деятельности Лаборатории биологии рака Медико-Санитарного Публичного Учреждения Института Онкологии будут разработаны и реализованы программы молекулярно-генетических исследований РЭ с установлением молекулярного подтипа опухоли. Таким образом, будет упрощена оценка эволюции рака эндометрия на I-II стадиях, что позволит применять ее в соответствии с разработанными критериями.

SUMMARY

The dissertation for doctor in philosophy in medicine on topic: "Molecular-genetic factors for the prognosis of endometrial cancer in stages I-II" was elaborated by Tripac Irina in the Public Medico-Sanitary Institution Institute of Oncology, Chisinau, 2023. This work includes an introduction, 6 chapters, conclusions and practical recommendations. The paper contains 161 pages, 62 tables, 32 schemes. The bibliography list includes 206 sources. The results obtained have been published in 55 scientific papers.

Key-words: Prognostic factors, clinical-morphological factors, molecular-genetic factors, prognostic model, endometrial cancer.

Study domain: Oncology and radiotherapy.

The aim of the study: determination of clinical, morphological and molecular genetic factors of endometrial cancer (EC) stages I-II to develop a mathematical model for predicting relapses and patient survival for up to 3 years.

Objectives of the study: To establish the clinical, morphological, immunohistochemical criteria as prognostic factors of the endometrial cancer (EC); estimating the correlation of immunohistochemical and molecular-genetic data according to the clinical and morphological characteristics of endometrial cancer; estimating the molecular profile of the tumour in the patients of the study group; multifactorial analysis of the complex of prognostic criteria established with the determination of the prognostic value for each separate factor in patients with EC in stage I-II; creation of the mathematical model of the complex prognostic evaluation of the EC in stages I-II according to the risk groups and the prognostic factors.

Scientific novelty and originality: The mathematical model allows complex analysis of the prognostic factors of the evolution of endometrial cancer, based on the molecular profile of the tumour and the characteristics that make it possible to predict the response of the tumour to treatment. Determining the expression of Ki-67, PDL1, *MLH1* proteins presents useful information about the biological behaviour of the tumour already in the early stages of EC.

The solved scientific problem: The scientific problem solved in the thesis is that research based on clinical-morphological and molecular-genetic studies has found novel pathogenic mechanisms and predictors of EC exacerbation, such as the presence of c.389G>A epimutation (p.R130Q) of the *PTEN* gene, methylation of the *MLH1* gene promoter, the Ki-67 proliferation marker, the increase of the neutrophil-lymphocyte index, which allowed the development of a mathematical model to predict the evolution of the disease in patients with EC from different risk groups.

Theoretical significance: The conclusive evidence obtained completes the concept and theoretical support of endometrial cancer. At this point, it is important to decant the contribution of the c.389G>A mutation of the *PTEN* gene, the increase of the proliferative activity of the mitotic cycle evaluated by the increase of the Ki-67 antigen, the mutation of the *TP53* gene resulting in the depreciation of the Bax / Bcl2 ratio. At the same time, the role of inflammation in promoting the EC is highlighted, and the increase in the neutrophil / lymphocyte index is not only a pathogenic mechanism, but also a feasible predictor of tumour prognosis. It is conceptually important that the EC has a significant link with the increase in body mass, as well as the absence of a link between the EC with regard to the risk of recurrence on the one hand and the characteristics of menstruation, births and miscarriages on the other. Predictive value on the increased risk of recurrence in patients with EC is attributed to factors inherent in the pathology of reproductive organs, such as ovarian cyst, uterine fibroids and fibrocystic mastopathy. The rate of serous papillary adenocarcinoma in the group of patients with stage II EC is on average 44-48% higher compared to the index of stage IA and IB. The degree of tumour differentiation has a conclusive impact on the risk of recurrence, so that the low degree of differentiation is estimated at 95% in high-risk patients, and the high degree of differentiation is characteristic of low risk (80%). Remarkably, the depth of the tumour invasion does not really correlate with the increase in risk. The presence of necrotic foci is a true predictor of increased risk. The impact of inflammation is imposed by maximum values of the ratio neutrophils / lymphocytes and platelets / lymphocytes in patients with high-risk EC. The marker of Ki-67 proliferation is directly related to the degree of risk as well as to the stage of the disease (the level of

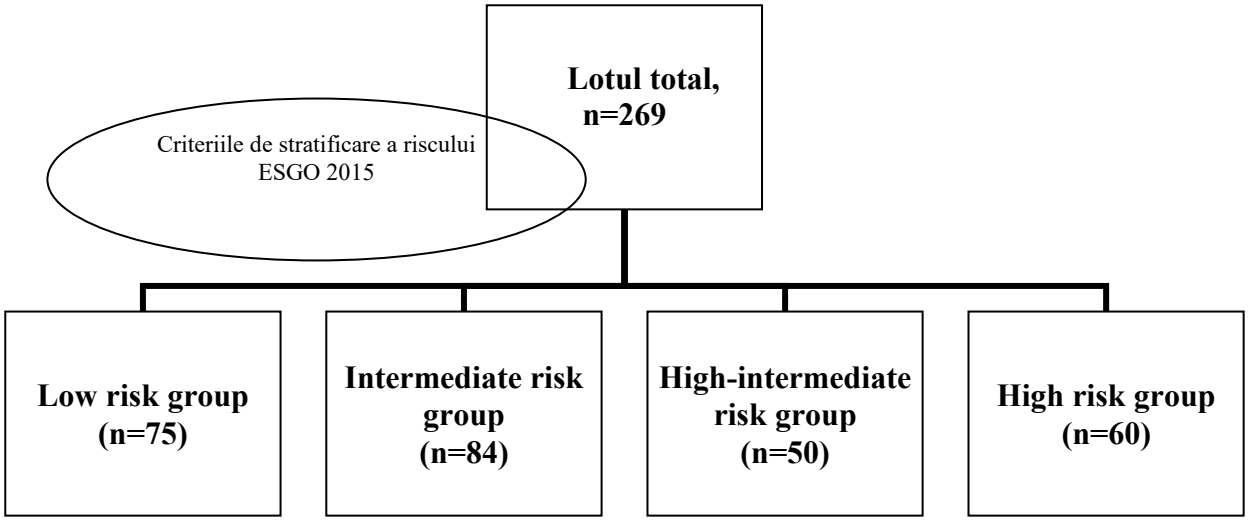
Ki-67 expression> 49% is detected only in the high risk group). The presence of the c.389G>A mutation (p.R130Q) of the *PTEN* gene is in the 4-8 times higher risk group compared to the intermediate and intermediate-increased risk. Important is the presence of this mutation only in patients with a hormone-dependent pattern of tumour in 36%, but stage II disease is required by reducing the rate of *PTEN* gene mutation vs. stage I. *MLH1* epimutation does not show such a conclusive link with EC c.389G>A (p.R130Q) of the *PTEN* gene.

Practical value of the study. The clinical significance of the expression of molecular biological markers that characterize apoptosis, cell proliferation and angiogenesis in tumour tissue in patients with stage I and II EC has been assessed on a wide range of clinical evidence. Precise clinical, morphological, immunohistochemical, and genetic criteria for EC diagnosis and prognosis in patients with stage I-II endometrial cancer have been determined. The immunohistochemical characteristics of EC (Ki-67 expression), the presence of the c.389G>A mutation of the *PTEN* gene, the identification of the methylation of the *MLH1* gene promoter and the correlation according to the clinical-morphological characteristics of endometrial cancer in patients of the study group with molecular profile were highlighted of the tumour for each patient. This approach allows to perform a detailed analysis of the prognostic value for each particular factor, which will allow the identification of the main prognostic factors. Its own prognostic model has been developed, which includes clinical, morphological, immunological, immunohistochemical and genetic characteristics of endometrial cancer. The survival of patients with EC over a 3-year surveillance period is minimal (72.2%) among those older than 60 years and belonging to the high risk group of recurrence. The relapse-free survival rate is also minimal in these patients (44%). At the same time, the rate of metastases in patients with EC is not intelligibly correlated with the stage of the disease. The mean time to progression of the EC is indirectly related to the value of the neutrophil/ lymphocyte ratio, which is minimal (6 months: 5 to 9 months) in patients at high risk of recurrence with an INL index>5.0. The Ki-67 marker has a definite predictive value on the survival and recurrence rate in patients with EC, so that increased proliferative activity (>49%) has a negative impact at a distance of 3 years. The presence of *MLH1* epimutation also influences the recurrence of the disease in patients with EC at a distance of 3 years, given the minimum value of the mean time to progression of 10.5 years attested to the carriers of this mutation in the high risk group.

Implementation of scientific results: The results of the study were reported to 8 national and 18 international forums. On the research side, 3 invention patents were validated. The results of the study will be presented in the form of practical recommendations for family doctors, gynecologists, but also for oncology specialists. In the clinical activity of the Cancer Biology Laboratory of the IMSP Oncological Institute, EC molecular-genetic research programs will be developed and implemented with the establishment of the molecular subtype of the tumor. Thus, the estimation of the evolution of endometrial cancer in stages I-II will be streamlined, which will allow its application in accordance with the elaborated criteria.

ANNEX 1.

Study Design



First stage - assessment of clinical, histopathological features (location, tumour size, shape of growth, degree of tumour differentiation, depth of tumour invasion, presence of perilimmovascular invasion, presence of perineural invasion) and markers of inflammation (neutrophil/lymphocyte index, trombocyte/lymphocyte index)

↓

Second stage - study of molecular-genetic and immunohistochemical features (determination of Ki-67 marker, c.389G>A mutation of PTEN gene, hypermethylation of MLH1 gene promoter)
Molecular profiling and determination of the molecular subtype of the tumour.

↓

Multifactor analysis of the complex of established prognostic criteria with estimation of the predictive value for each separate criterion.

↓

Development of mathematical model of complex prognostic assessment of EC in stages I-II

ABBREVIATIONS

IMSP IO CCD - Diagnostic Advisory Centre of the IMSP Cancer Institute

CCNPE - hereditary non-polyposis colorectal cancer

CRC - colorectal cancer

EC - endometrial cancer

MGC - mammary gland cancer

CM - breast cancer

CO - ovarian cancer

FGC - cancer of the female genital organs

DZ - diabetes mellitus

ESGO - European Society of Gynaecological Oncology

ESMO - European Society for Medical Oncology

ESTRO - European Society for Radiotherapy & Oncology

FIGO - International Federation of Obstetricians and Gynaecologists

Gy - Gray

IDF - International Diabetes Federation

IM - microsatellite instability

IMSP IO - Institution of Public Health Medical Oncology Institute

INL - neutrophil/lymphocyte index

ITL - trombocyte/lymphocyte index

CI - confidence interval

gg/l - lymph nodes

MS - microsatellite stability

MSI - microsatellite instability

MSMPS - Ministry of Health, Labour and Welfare

WHO - World Health Organization PTEN - phosphatase and tensin homologue

MRI - magnetic resonance imaging

RTE - external radiotherapy

RTIC - intracavitary radiotherapy

RTOG - Radiation Therapy Oncology Group

SFR - relapse-free survival

OS - overall survival

MS - metabolic syndrome

CT - computed tomography

USG - ultrasonography

TRIPAC IRINA

MOLECULAR-GENETIC PROGNOSTIC FACTORS ENDOMETRIAL CANCER IN STAGES I-II

321.20 – ONCOLOGY AND RADIOTHERAPY

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