MATHEMATICAL MODELING OF THE SURVIVAL PROGNOSIS OF PATIENTS WITH ENDOMETRIAL CANCER

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Abstract: *Endometrial cancer (EC) is one of the most common malignancies in women and is the most common in developed countries and the second most common in developing countries. It is known that the results of treatment of patients belonging to the same classification subgroup differ from each other, so these signs cannot fully describe how the disease will progress later. Prognostic factors of EC are diverse, they affect to one degree or another the survival of patients and the risk of further disease progression. In order to create a prognostic model, the following article analyzes a set of laws and correlations determined on the basis of important factors. Then, based on them, the diagnostic and treatment algorithm for this disease was improved.*

Key words: *uterine body cancer, mathematical modeling, disease prognosis, overall survival, survival without recurrence.*

By the end of the last century, endometrial cancer (EC) has become a leading oncogynecological pathology in economically developed and developing countries [1]. The main symptom of the modern clinical presentation of endometrial cancer is its aggressiveness, early metastasis to the lymph nodes of the ovary, vagina, and small pelvis. According to literature sources, the recurrence rate is on average 50%, three-year average survival is 57.3%, 5-year average survival is only 30%, in endometrioid cancer this indicator is from 75% increases [2]. Currently, the idea of considering EC as a tumor disease with a favorable course and prognosis has been reconsidered [3]. According to the International Federation of Obstetricians and Gynecologists, 5-year survival in EC is achieved in 67.7% of patients, while 22.4% of patients die of recurrence and tumor metastasis during the 5-year follow-up period. Treatment is ineffective in 1 out of 5 patients [4]. The main prognostic factor of the disease is its stage. In the early stages of EC, progression is observed in 25% of pts. Also, the poor prognostic factors include the patient's age, rare histological types (clear cell carcinoma, serous-papillary carcinoma), low differentiation of the tumor, deep invasion of the myometrium, the growth of the tumor to the cervix, blood and lymphatic vessels. The presence of tumor emboli, the presence of metastases in the ovaries and lymph nodes, the presence of dissemination to the peritoneum, the size of the tumor, the presence of tumor cells in the abdominal fluid, the low level of estrogen and progesterone receptors in the tumor lysis, high expression of apoptosis regulatory genes (p53, bcl-2), tumor aneuploidy. EC metastasis is mainly related to tumor differentiation and myometrial invasion [5]. If highly differentiated endometrioid tumors are superficially invasive, lymphogenous and

implant metastases rarely occur [2,6]. A high level of estrogen and progesterone receptors is a good prognostic sign, while a high level of mutant p53 gene and apoptosis regulator bcl-2 is a bad prognostic sign. The zone of regional metastasis is the iliac and para-aortic lymph nodes. In highly differentiated, non-myometrial cancer, lymphogenous metastasis is <5%. In medium- and low-differentiated adenocarcinomas, in cases with less than 50% invasion of the myometrium, 5-10% metastasize to the pelvic lymph nodes, and 4% to the para-aortic lymph nodes; in poorly differentiated cancer and non-endometrioid carcinoma, in the case of deep invasion and intraperitoneal spread, metastases occur in pelvic lymph nodes in 20-60% of cases, and in para-aortic lymph nodes in 10-30% of cases.

Distant metastases spread to the lungs, lymph nodes and spinal cord, liver, bones, brain [4,7].

Most of the risk factors in the origin of endometrial cancer are related to hormones. These include excess body weight, estrogen therapy during menopause, early menarche and late menopause, infertility, polycystic ovary syndrome, and tamoxifen use [7,8]. Worldwide, 34% of cases of uterine cancer are caused by excess weight. Other factors include Lynch syndrome and diabetes. Risk-reducing factors include pregnancy, oral contraceptives, intrauterine devices, and physical activity. The increase in the incidence of endometrial cancer is primarily influenced by changes in the distribution of excess body weight and the number of births due to reproductive/hormonal factors, hormonal therapy during menopause [9].

Taking into account the above, we studied several factors and performed a mathematical analysis.

A mathematical model is a mathematical representation of reality [10], one of the variants of a model as a system, the study of which allows to obtain information about another system. A mathematical model, in particular, is designed to predict the behavior of a real object, but always represents one or another level of its idealization.

Mathematical modeling refers to both the activity itself and the set of methods and methods adopted for building and studying mathematical models [11].

All natural and social sciences that use mathematical apparatuses are mainly engaged in mathematical modeling: they replace the studied object with its mathematical model and then study the latter. Using mathematical methods, as a rule, an ideal object or process built at the stage of meaningful modeling is described [15]. The connection between the mathematical model and reality is carried out using a chain of empirical laws, hypotheses, idealizations and simplifications.

The most important mathematical models usually have the important property of universality: the same mathematical model can describe fundamentally different real phenomena. For example, a harmonic oscillator describes not only the movement of a spring load, but also other oscillatory processes, often of a completely different nature: small oscillations of a pendulum, a change in the liquid level in a U-shaped container, or a change in the current in an oscillating circuit. Thus, by studying one mathematical model, it is possible to immediately study the entire class of phenomena described by it. This isomorphism of the laws expressed by mathematical models in various segments of

scientific knowledge inspired Ludwig von Bertalanffy to create the "general theory of systems".

At the same time, it is necessary to remember that the model itself is an object and may have specific characteristics unrelated to the real object being modeled; however, even in prestigious journals, there are publications that specifically examine the properties of complex mathematical models unrelated to the object being modeled.

In order to create a prognostic model, a set of regularities and correlations determined on the basis of significant factors was analyzed. The number of significant factors in their separation was 20.

These factors are listed in the table. Based on them, a questionnaire was created, the spread of one or another sign was evaluated on a point scale.

The important selection criteria were based on the calculation of scale amounts of the forecast in points. Thus, the final interpretation of the data can be obtained by calculating the scores. The forecast can be determined based on the accumulated points:

1. If the sum of points is between 10 and 40, the prognosis for EC patients is good.
2. If the sum of points is between 41 and 70, the prognosis for EC patients is poor.
3. If the sum of points exceeds 70, the prognosis for EC patients is very poor.

The introduction of software for predicting the end of the disease and stratifying patients leads to an increase in labor efficiency, a reduction in the time and costs required for the search and understanding of initial data, and simplifies and balances the work process. Advancement of modern technologies helps doctors spend more time working with patients, making constructive decisions to improve communication.

Table

The prognostic table of the main important parameters in the scoring system of evaluation in EC patients

Prognostic indicator	Incidence Grade	in points
Age:	20-39 years	1 score
	40 – 50 years	2 score
	51 - 60 years	3 score
	>61 years	4 score
Pathogenetic type:	I type	1 score
	II type	2 score
Associated extragenital pathology:	hypertension disease (HD) or diabetes (D) or obesity (O)	1 score
	D + HD or D +O or HD + O	2 score
	HD + D + O	3 score
Histological type:	Highly differentiated endometrioid adenocarcinoma	1 score
	Moderately differentiated endometrioid adenocarcinoma	2 score
	Poorly differentiated endometrioid adenocarcinoma	3 score

	Glandular squamous carcinoma	3 score
	Serous-papillary adenocarcinoma	4 score
Localization of the tumor in the uterus:	Uterine fundus and/or fallopian tube angle	1 score
	Uterus devoir	2 score
	Uterine body lower third	3 score
	Complete destruction of the uterine cavity	3 score
Invasion of the tumor into the myometrium:	At the border of the endometrium	1 score
	up to ½ myometrium	2 score
	Increased to more than ½ myometrium or serous	3 score
Lymphovascular invasion:	There is not	0 score
	There is	1 score
Immunohistochemical level of p53 in blood:	Negative	0 score
	+	1 score
	++	2 score
	+++	3 score
Immunohistochemical level of bcl-2 in blood:	Negative	0 score
	+	1 score
	++	2 score
	+++	3 score
The level of p53 in the immunohistochemical examination of the post-operative material:	Negative	0 score
	+	1 score
	++	2 score
	+++	3 score
The level of bcl-2 in the immunohistochemical examination of the post-operative material:	Negative	0 score
	+	1 score
	++	2 score
	+++	3 score
Type of light therapy:	Preoperative brachytherapy followed by combined radiation therapy	0 score
	combined light therapy	1 score
	Only distance light therapy	2 score
	Not held	3 score
Duration of relapse-free period (in months):	1-6 month	4 score
	6-12 month	3 score
	12-18 month	2 score
	18-24 month	1 score

Risk ratios and confidence intervals (95%) were calculated for each clinical-morphological and immunohistochemical (p53 and bcl-2 gene expression). "The program for predicting the survival rate in patients with uterine cancer stage I based on clinical-morphological, immuno-histochemical signs" was approved for EHM No. -number reference). This program made it possible to increase the efficiency of diagnosis in uterine body cancer, facilitate treatment-diagnostic tactics, prolong the duration of the disease and increase the overall survival rate.

A mathematical model was created taking into account the most important factors for predicting patient survival.

The regression equation was calculated using regression analysis:

Y=1.15 + 0.038X1 - 0.404X2 + 0.297X3 - 0.202X4 - 0.114X5 + 0.211X6 + 0.06X7 - 0.067X8

Here: Y is the amount of regression level;

1.15 regression coefficient amount;

X1 - age (1 - 20-39 years old; 2 - 40-49 years old; 3 - 50-59 years old; 4 - 60 years old and above);

X2 – extragenital diseases (1 – YD or D or O; 2 – HD + D or HD + O or D + O.; 3 – HD + D + O)

Pathogenetic type of X3-EC (1 – I; 2 – II;)

X4 - the location of the tumor in the uterus (1 - the bottom of the uterus and/or the corners of the tube; 2 - the walls of the uterus; 3 - the lower third of the body of the uterus; 4 - the entire cavity of the uterus;)

X5 - invasion of the tumor into the muscle (1 - at the border of the endometrium; 2 - up to ½ of the myometrium; 3 - more than ½ of the myometrium or up to the serous layer;)

X6 – Immunohistochemical examination of p53 and bcl-2 in uterine mucus (1 - +; 2 - ++; 3 - +++;).

X7 - Histological type of tumor (1 - highly differentiated adenocarcinoma; 2 - moderately differentiated adenocarcinoma; 3 - poorly differentiated adenocarcinoma; 4 - rare types of EC)

X8 – immunohistochemical examination of p53 and bcl-2 in the material after surgery (1 - +; 2 - ++; 3 - +++;).

It is worth saying that when $p<0.5$ - the prognosis is unfavorable, $p>0.5$ - the prognosis is good, in which X2 = 639.3.

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