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Importance of p53, bcl-2 genes in uterine body cancer and their role in prediction

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Abstract---Uterine body cancer (UBC) makes up 7.1% of malignant tumors in women and ranks 6th in the structure of the incidence of malignant tumors in women in the world after breast cancer, cervical cancer, colorectal cancer, lung and thyroid cancer. In developed countries, it is the most common malignant tumor of the female genital organs. The study included 105 patients with a diagnosis of stage I uterine body cancer, the patients were divided into 2 groups: I - the main group consists of 60 patients who received preoperative brachytherapy (Total focal dose (TFD) = 16-20Gy). Control group II consisted of 45 patients who, after curettage of the uterine cavity, were immediately operated on in the volume of extirpation of the uterus with appendages and routinely received combined radiation therapy: from distance gamma therapy (DGT) TFD = 44 Gy, from brachytherapy TFD = 20 Gy. All biological materials obtained during curettage of the uterine cavity and as a result of surgery in both groups were subjected to immunohistochemistry. The mutant p53

gene and the apoptosis regulator bcl-2 were studied by immunohistochemical method. With a decrease in the expression of the mutant gene p53 after radiation therapy in patients with poorly differentiated endometrioid adenocarcinoma, the overall and relapse-free three-year survival rate was 69.7 ± 7.2 and $68.8 \pm 7.4\%$, while, as with maintaining the positive status of p53, these indicators decreased to $66, 5 \pm 9.5$ and $64.9 \pm 7.3\%$ ($p < 0.01$). A statistically significant decrease in both overall and disease-free survival was noted in patients in whom the bcl-2 gene expression did not change after brachytherapy, regardless of the histological type. During the initial treatment of patients during the verification of the disease, in addition to the histological type and degree of differentiation, we recommend that the expression of the p53 and bcl-2 genes be specified. With high gene expression and in combination with rare forms of UBC, such as serous - papillary adenocarcinoma, glandular squamous cell carcinoma, and with low differentiation of endometrioid adenocarcinoma, treatment should be started with preoperative radiation therapy.

Keywords---brachytherapy, immunohistochemistry, p53, bcl-2, endometrial cancer.

Introduction

Worldwide, the incidence of cancer among women of reproductive age and menopause is increasing. Currently, the incidence rate of endometrial cancer is 19.5 per 100,000 female population; over the past 30 years, the incidence of UBC has increased threefold (Axel, 2012). In recent years, there has been a tendency for an increase in the incidence of cancer of the uterine body (UBC), which can be explained by an increase in average life expectancy and an increase in the frequency of such "diseases of civilization" as anovulation, chronic hyperestrogenism, infertility, uterine fibroids and endometriosis, their combination with disorders of endocrine function and metabolism (obesity, diabetes mellitus, hyperinsulinemia, hyperlipidemia) leads to the development of a syndrome of disorders in the reproductive, metabolic and adaptive systems of the body (Gordeladze, Andreev, 2002). There is a steady increase in the proportion of young women among patients with endometrial cancer - in reproductive and perimenopausal ages, accounting for almost 40% of the total number of patients. The early manifestation of symptoms of the disease in the form of various bleeding from the genital tract and good visualization of the tumor using ultrasound diagnostic methods make it possible to detect UBC at stages I - II in almost 80% of patients. At the same time, mortality from the progression of the disease has remained stable over the past 10 years (Atakhanova, Almuradova, et al., 2020). A number of studies are being carried out in the world aimed at maintaining the health of the population, preventing and timely treatment of UBC. In this regard, special attention is paid to early diagnosis and improvement of treatment methods. The lack of uniform standardized criteria, the variety of clinical manifestations determines the relevance and importance of the study. The priority is the development of a set of measures aimed at studying the incidence,

prevalence and prognosis of uterine cancer, justification of their use, determination of indications and contraindications. Of great importance is the development of a complex of health-improving measures aimed at developing proposals, taking into account immunohistochemical signs, for the treatment of patients with UBC (Blokhin, 2011).

Cancer of the body of the uterus accounts for about 5% and 2% of the global cancer morbidity and mortality among women. In 2012, uterine cancer was the 6th most common cancer among women worldwide and the 14th leading cause of cancer death, with 319,600 cases and 76,200 deaths identified according to analyzes (Creasman, Odicino, Maisonneuve, 2006). The highest rates of uterine cancer are found in North America and Eastern Europe, while the highest death rates are found in Melanesia, Eastern Europe and the Caribbean. Incidence rates are usually higher in high-income countries than in middle-income countries, due to the high incidence of metabolic syndrome and hormonal disorders in the population of these countries (Brinton, Lacey, Devesa, 2004). Most of the risk factors for endometrial cancer are hormone-related. These include overweight, estrogen therapy during menopause, early age at menarche and late menopause, infertility, polycystic ovary syndrome, and the use of tamoxifen (Crosbie, Zwahlen, Kitchener, 2010). Overweight alone is estimated to account for about 34% of uterine cancers worldwide. Other risk factors include Lynch syndrome and diabetes. Factors that reduce risk include pregnancy, use of oral contraceptives and intrauterine devices, and physical activity (Lee, Kim, Choi, Lee, Kim, 2010). Trends in uterine cancer incidence are primarily influenced by changes in the prevalence of overweight and reproductive / hormonal factors such as the number of births and hormonal therapy in menopause (Ebina, Katabuchi, Mikami, Nagase, 2016). According to GLOBOCAN (2018), data on new cases of morbidity and mortality from the most common malignant tumors of 36 localizations in 2018 were analyzed. Cancer of the body of the uterus ranked 17th on this list and accounted for 382,069 new cases, 89,929 deaths. Endometrial cancer among women ranked sixth and accounted for 4.4% of all malignant neoplasms (Bray, Ferlay, 2018). Pathogenetic type I of UBC is characterized by high or moderate tumor differentiation, superficial myometrial invasion, with a favorable prognosis and combination with diseases such as obesity, diabetes mellitus, hypertension, menstrual irregularities caused by prolonged hyperestrogenism, estrogen-secreting ovarian formations, sclerocystic ovarian tumor syndrome, hyperplasia of endometrium (Kozachenko, 2016). On the contrary, with UBC of pathogenetic type II, tumors with low differentiation, deep invasion of the myometrium are usually observed, occur against the background of endometrial atrophy and have a poor prognosis, and there are no clinical and morphological signs of hyperestrogenism (Artoshina, 2010). UBC type I in more than 80% of cases is represented by endometrioid tumors; UBC type II usually reveals clear cell, serous or undifferentiated cancer (Gordeladze, Andreev, 2002.). The authors describe numerous prognostic factors in UBC, which creates some difficulties in their application in clinical practice (Ebina, Katabuchi, Mikami, Nagase, 2016). The overwhelming majority of these factors are morphological, and information about them is obtained by standard histological examination. This information is used to assess the risk of metastases in the lymph nodes, to predict the progression and life of patients with UBC, and to plan postoperative

treatment. As with many other malignant neoplasms, the main prognosis factor for UBC is the stage (Nechushkina, Morkhov, Kuznetsov, 2011).

In approximately 10% of patients with endometrial cancer, histological examination reveals malignant epithelial tumors, which are characterized by an unfavorable clinical course: serous-papillary cancer (incidence 4-10%), clear cell carcinoma (1-6%), mixed adenocarcinoma (0.3-0.5%), as well as undifferentiated (1-2%) and glandular squamous cell carcinoma (0.1-0.2%) (Galaeva, 2010). The five-year overall survival rate for serous-papillary cancer is 40-60%, for clear cell carcinoma - 30-75% (Laktionov, Abdullaeva, Anurova, 2008). The detection rate of stages III-IV in serous and clear cell carcinoma of the uterine body is 41 and 33%, respectively, compared with 14% in endometrioid cancer (Olkin, Bokina, Mustafina, Barinov, Bokin, 2013). The high (40-70%) frequency of the exit of serous-papillary cancer cells outside the uterus explains the need to perform all stages of determining the surgical stage of the disease (Ulrich, 2002)

In case of damage to the p53 protein gene, in 50% of cases, oncological growth - tumors develop, since the malfunctioning of this protein makes possible cell division even with DNA damage (Huh, Powell, Leath, 2010). As a result, the genetic instability of the cell increases and the frequency of mutations increases, which leads to the accumulation of defective, defective tumor suppressors and oncogenes (Banno, Kisu, Yanokura, Tsuji, 2012). With the so-called "Gain of function" mutations, mutant p53 can also acquire additional oncogenic properties and inactivate normal p53 (wild-type p53) (Wang, Zhao, Wu, 2015). p53 is a nuclear protein that detects and identifies a genetic defect and triggers cell repair mechanisms. If it is impossible to restore the damaged DNA, this protein, instead of starting the repair mechanisms, triggers apoptosis (programmed cell death), and thus prevents the replication of the damaged DNA. In case of mutation of the p53 gene, this protein can lose its abilities (Kanwar, Kamalapuram, Kanwar, 2011). Mutated p53 has a longer half-life compared to other proteins, therefore it accumulates and collects in the cell nucleus. According to N.E. Langlois et al., overexpression of p53 correlates with patient survival. In their study, overexpression of p53 was predominantly observed in patients with more common forms and was practically absent in patients with localized forms of the disease (Langlois, Eremin, Heys, 2000).

Members of the Bcl-2 family of proteins are required to maintain homeostasis in most organ systems. Mutations that damage these genes play an important role in carcinogenesis. Proteins of the Bcl-2 family regulate apoptosis at the mitochondrial level (Levine, 2013). The apoptosis-preventing members of this large family include Bcl-2 itself, as well as Bcl-w, Bcl-xL, Mcl-1, A1, and Boo; proapoptotic proteins - Bad, Bax, Bok, Bcl-xS, Bak, Bik, Bim, Krk, Bid and Mtd. (Banno, Kisu, Yanokura, Tsuji, 2012). Increased expression of Bcl-2 leads to blocking of cell apoptosis in the body, triggered by various factors, such as depletion of growth factors, radiation, c-myc, or anticancer drugs. (Nikolaidou, Apostolaki, Tserkezoglou, 2012)

The aim of the study

To improve the results of treatment of uterine body cancer in patients by developing a differentiated approach in combined treatment and to determine the role of p53 and bcl-2 genes in predicting the disease.

Materials and Methods

The material of the study was outpatient records of patients (form 025/y), case histories (form 003/y), control cards of dispensary observation (form 030/y), patient radiation cards (form 051/y), conclusion of histological and immunohistochemical studies of patients present on examination and treatment in the Tashkent city branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology in 2015-2017yy. The criterion for selecting patients for inclusion in the study was a morphologically verified diagnosis of UBC stage I. According to the hospital city cancer registry, during this period, the city branch received outpatient or inpatient treatment: 2015 - 976 patients, 2016 - 880 patients, 2017 - 918 patients with UBC stages I-IV, however, after the initial study of medical documentation and revision of histological findings 105 patients with stage I were included in the studies depending on the methods of treatment. The patients were divided into 2 groups: I - the main group consists of 60 patients who received preoperative brachytherapy in the Moulti Sources BEBIG apparatus (TFD = 16-20Gy) and operated on for 48-72 hours in the volume of extirpation of the uterus with appendages. Subsequently, the patients received combined radiation therapy: brachytherapy TFD = 30 Gy (from 2 stages) and distance gamma therapy (TERABALT apparatus) TFD = 44-46 Gy, in total, the total focal dose = 85 Gy per point A is equivalent. The control group II consisted of 45 patients who, after curettage of the uterine cavity, were immediately operated in the volume of extirpation of the uterus with appendages and routinely received combined radiation therapy: from distance gamma therapy TFD = 44 Gy, from brachytherapy TFD = 20 Gy.

Table 1. Distribution of patients depending on the treatment

Types of treatment	Control group (45 patients)	Main group (60 patients)
Preoperative radiation therapy	Was not performed	TFD 20Gy (single focal dose (SFD) 5-7.5Gy)
Operation	Extirpation of the uterus with appendages	Extirpation of the uterus with appendages
DGT "TERABALT"	TFD 46Gr (SFD 2Gr)	TFD 46Gr (SFD 2Gr)
Brachytherapy "Moulti Sources BEBIG"	TFD 20Gr (SFD 5Gy)	TFD 30Gy (from 2 stages)

Source: [Compiled by the authors]

All biological materials obtained during curettage of the uterine cavity and as a result of surgery in both groups were subjected to immunohistochemistry. The mutant p53 gene and the apoptosis regulator bcl-2 were studied by immunohistochemical method. Based on the literature data on prognostic factors in UBC, a codifier was compiled, which included 55 items. It reflected information

about patients obtained from case histories and outpatient cards, and included passport data, obstetric and gynecological anamnesis data, information about past diseases, clinical picture, diagnosis and treatment of the underlying disease, morphological findings and results of observation of patients. General clinical studies included a detailed collection of anamnesis, including the individual characteristics of the woman's body, behavioral and environmental factors, complaints with the definition of the time of their occurrence, assessment of menstrual and generative function. All patients underwent examinations as ultrasound of the abdominal cavity and small pelvis. According to this study, the endometrium was thickened in 42 (70.0%) patients in group I, in 32 (71.1%) patients in group II. The median M-echo was 11.8 mm (8.5-15.1 mm). Chest fluoroscopy was performed in all patients, rectaromanoscopy was performed in 58 (96.7%) patients in the main group and in 42 (93.3%) patients in the control group, the rest of the patients in both groups underwent irrigoscopy - 2 (3, 3%) and 3 (6.7%) patients, respectively. 93 (88.5%) patients underwent MRI examination of the small pelvis, of which 59 (98.3%) patients were from the main group.

In our study, all biological materials obtained during curettage of the uterine cavity and as a result of surgery in both groups were subjected to immunohistochemical analysis. The mutant p53 gene and the apoptosis regulator bcl-2 were studied by immunohistochemical method. Immunohistochemical studies were carried out in "PREMIUM DIAGNOSTICS" LLC, "Medical Center" clinic (Certificate No. 004973-01 dated 02/08/2012 by the registration authority of the Khokimiyat of the Uchtepa district; License No. 1260-00 Series A No. 005951 dated 03/26/2012 Ministry of Health of the Republic of Uzbekistan; Registration certificate of the main department for quality control of medicines and medical equipment of the Republic of Uzbekistan No. 0058/03/2015 dated 03/13/2015). For immunohistochemical studies, reagents were used - Dako Denmark A / S. Daniya Produktionvej 42. Dako, DK - 2600.

Immunohistochemical (IHC) study of the tumor was carried out according to a standardized technique using serial paraffin sections placed on adhesive glasses coated with polysin (Menzel-Glaser, Germany) and DAKO reagents with monoclonal antibodies (MAB). In the immunohistochemical assessment of mtp53 expression, we used murine anti-p53 mAb, clone DO-7, IgG2b (M7001 "Dako Cytomation") at a dilution of 1: 100 with an exposure time of 60 min. Bcl-2 was detected using mAb to Bcl-2, clone Bcl-2/124 (M0887 "Dako Cytomation"), at a 1:80 dilution with incubation for 60 min.

The intensity of IHC staining for p53 was assessed as negative (no staining), weakly positive (<5% stained cells), moderately positive (> 5% average staining intensity), and strongly positive (> 5% high staining intensity). When evaluating bcl-2, a semi-quantitative method was used: 0 points - no dyeing; + (1 point) - more than 20% of cells with a weak intensity of staining of the cytoplasm; ++ (2 points) - moderate staining of the cytoplasm; +++ (3 points) - intense staining of the cytoplasm.

Research Results

The youngest patient included in the study was 30 years old, the oldest - 87 years old, the median age of the patients was 58.5 years (53.1-65.3 years). The most numerous was the age group 51-60 years old (31 patients; 51.6% in the main group and 18 patients; 40% in the control group). When detecting serous-papillary, clear cell, squamous, undifferentiated or mixed cancer during postoperative histological examination or during histological examination of scraping from the uterine cavity was diagnosed pathogenetic type II of UBC. The same can be said about the development of UBC against the background of endometrial atrophy. With the development of cancer against the background of endometrial hyperplasia was diagnosed pathogenetic type I. Data on the state of the endometrium were obtained from postoperative histological findings. Endometrial hyperplasia was observed in 46 (76.7%) patients, atrophy - in 14 (23.3%) patients in the main group. In the control group, 11 (24.4%) patients had endometrial atrophy, the remaining 34 (75.6%) patients had endometrial hyperplasia. In the absence of the above signs, they were guided by clinical data. In the presence of obesity and diabetes mellitus (or impaired glucose tolerance) or all three signs of the "clinical triad" they spoke of pathogenetic type I, in the absence of these signs - of II. As a result, pathogenetic type I was diagnosed in 42 out of 60 (70%) patients included in the study, II - in 18 (30%); in the control group, pathogenetic type was detected in 32 (71.1%), in group II - in 13 (28.9%) patients.

In 41 (68.4%) patients in the main group was diagnosed endometrial adenocarcinoma, of which highly differentiated adenocarcinoma was observed in 19 (31.7%), moderately differentiated in 16 (26.7%), poorly differentiated in 6 (10.0%) sick, respectively. Also, rare forms of cancer of the uterine body were observed, such as glandular squamous cell carcinoma in 9 (15%), serous-papillary carcinoma in 10 (16.7%) patients, respectively. In the control group, the histological distribution of patients was as follows: endometrial adenocarcinoma - 27 (60%), of which highly differentiated endometrioid adenocarcinoma in 20 (44.5%), moderately differentiated endometrioid adenocarcinoma in 5 (11.1%) patients, low-grade adenocarcinoma in 2 (4.4%) patients from rare forms of uterine cancer, glandular-squamous cell carcinoma was found in 11 (24.4%), serous-papillary carcinoma in 7 (15.6%) patients, respectively.

When studying scrapings from the uterine cavity by the immunohistochemistry (IHC) method 43 (71.6%) patients were positive with bcl-2 from 60 patients in the main group, of which 19 (31.6%) were highly differentiated, 10 (16.7%) were moderately differentiated, 4 (6.7%) poorly differentiated adenocarcinomas, 6 (10%) glandular squamous cell carcinomas, 4 (6.7%) serous-papillary carcinomas. At the same time, the expression of mutant p53 was detected in 48 (80%) patients. The distribution of these 48 p53 expressed patients was as follows: 10 (16.7%) - highly differentiated, 14 (23.3%) - moderately differentiated, 6 (10%) - poorly differentiated adenocarcinoma, 9 (15%) - glandular squamous cell carcinoma, 9 (15%) - serous-papillary carcinoma.

In the control group of 45 patients with bcl-2, 31 (68.9%) patients with endometrial adenocarcinoma were positive, of which 17 (37.8%) were highly

differentiated, 2 (4.4%) were moderately differentiated, 2 (4.4%) - poorly differentiated adenocarcinoma. 4 (8.9%) patients were with glandular squamous cell carcinoma and 6 (13.3%) patients with serous-papillary carcinoma. The expression of mutant p53 was detected in 39 (86.7%) patients and the distribution of these patients by histological forms was as follows: 14 (31.1%) - highly differentiated, 5 (11.1%) - moderately differentiated, 2 (4.4%) - poorly differentiated adenocarcinoma. 11 (24.5%) patients were with glandular squamous cell carcinoma and 7 (15.6%) patients with serous papillary carcinoma. We can note that in both groups, patients with high expression of bcl-2 and p53 genes prevailed in groups with highly differentiated and moderately differentiated adenocarcinoma, it was also noted that a relatively high percentage was the positive status of genes in rare forms of cancer of the uterine body - glandular squamous cell and serous papillary carcinoma.

A study of the expression of the bcl-2 and p53 genes revealed a direct correlation between the expression level and tumor differentiation. Thus, all patients with highly differentiated endometrial adenocarcinoma had a "+" level of bcl-2 and p53 expression, while rare forms of UBC and poorly differentiated endometrial adenocarcinoma had a high expression of these genes: "+++".

Table 2. Distribution of patients depending on the level of bcl-2 gene expression

Expression level of the bcl-2 gene	Number of patients in the main group (n = 43)	Number of patients in the control group (n = 31)
+	19 (31,7%)	15 (33,3%)
++	10 (16,7%)	4 (8,9%)
+++	14 (23,3%)	12 (26,7%)

Source: [Compiled by the authors]

Table 3. Distribution of patients depending on the level of p53 gene expression

Expression level of the p53 gene	Number of patients in the main group (n = 48)	Number of patients control group (n = 39)
+	10 (16,7%)	14 (31,1%)
++	14 (23,3%)	5 (11,1%)
+++	24 (40%)	20 (44,4%)

Source: [Compiled by the authors]

Surgical treatment in the volume of extirpation of the uterus with appendages as a component of the combined treatment was carried out in all 105 patients (100%), while 60 patients from the main group underwent preoperative radiation therapy (brachytherapy). Preoperative brachytherapy was performed on a BEBIG Multi Source HDR (60Co) apparatus. The median TFD from brachytherapy was 12.1 Gy (8.2-16.1 Gy), the median number of fractions was 1 (1-2).

Postoperative combined radiation therapy included distance gamma therapy (DGT) (TFD 40-44 Gy) and intracavitary radiation therapy (for patients who received preoperative brachytherapy, TFD was 30 Gy from 2 stages, and for patients from the control group, the total focal dose (TFD) was 20 Gy on the dome

of the vaginal stump). DGT was carried out on the "TERABALT" apparatus (60Co). The volume of external beam radiation therapy: Stage 1 - for the entire volume of the pelvis, the lower border - the middle of the bosom, the upper border - at the level of the bifurcation of the common iliac arteries; Stage 2 - irradiation of the pelvic lymph nodes and lymphatic collectors within the above boundaries. The fractionation regime was as follows: distance gamma therapy - stage 1 - daily 5 times a week, one fraction at 24h, SFD2Gr, TFD 30-36Gy; distance gamma therapy - stage 2 - daily 5 times a week, one fraction at 24 hours, SFD 2-2.4 Gy, TFD 44-46 Gy from both stages;

When studying the analysis of postoperative materials, it was revealed that after preoperative brachytherapy in 15 patients (15.0%) with highly differentiated, in 8 patients (13.3%) with moderately differentiated, in 3 (5.0%) with poorly differentiated adenocarcinoma, and in all patients with rare forms of uterine cancer, the expression of the bcl-2 gene disappeared. Also, the absence of expression of the mutant p53 gene was found in 70% of patients after brachytherapy. Negative expression of the mutant p53 gene was observed in 10 patients (16.7%) with highly differentiated, in 14 patients (23.3%) with moderately differentiated, in 4 (6.7%) with poorly differentiated adenocarcinoma, in 8 (13.3%) with glandular squamous cell carcinoma and 6 (10.0%) patients with serous-papillary carcinoma ($p \leq 0.05$).

Table 4. Distribution of patients in whom the expression of bcl-2 and p53 positive genes became negative after preoperative radiation therapy

The result of histopathological study	bcl-2		p53	
	Number of patients	Proportion of patients (%)	Number of patients	Proportion of patients (%)
Highly differentiated endometrioid adenocarcinoma	15 (19)*	25%	10 (10)*	16,7%
Moderately differentiated endometrioid adenocarcinoma	8 (10)	13,3%	14 (14)	23,3%
Poorly differentiated endometrioid adenocarcinoma	3 (4)	5%	4 (6)	6,7%
Glandular squamous cell carcinoma	6 (6)	10,0%	8 (9)	13,3%
Serous-papillary adenocarcinoma	4 (4)	6,7%	6 (9)	10,0%
Total	36 (43)	60 (71,6)%	42 (48)	70 (80)%

* - in scrapings the number of patients with positive expression of bcl-2, p53

Source: [Compiled by the authors]

When studying postoperative materials in the control group, it was found that the value of bcl-2 and mutant p53 remained the same as in endometrial scraping, i.e. without changes.

Data on the results of observation of patients included in the study were obtained from outpatient records, responses to inquiries to oncology offices in polyclinics and address bureaus at the place of residence of patients. The observation period for patients was 36 months, during this period 54 out of 60 (90.0%) patients in the study group and 38 out of 45 (84.4%) patients in the control group included in the study were alive. The median follow-up period was 3 years, which made it possible to analyze the 3-year survival rate.

At the time of receipt of the latest information (January 2019), 45 out of 60 (75.0%) patients in group I, 27 out of 45 (60%) patients in group II were alive without signs of UBC progression. 9 (15.0%) patients in the main group, 11 (24.4%) patients in the control group are alive in the presence of UBC manifestations. 2 (3.3%) patients died from the progression of UBC, 4 (6.7%) patients in group I from non-oncological pathology. In the control group, all 7 patients (15.5%) died of progression.

Table 5. Results of combined treatment of patients

Outcome treatment (observation period 36 months)	Main group		Control group	
	Number of patients	Proportion of patients (%)	Number of patients	Proportion of patients (%)
Alive with no signs of progression	45	75%	27	60%
Alive in the presence of UBC manifestations	9	15%	11	24,4%
Death from progression of UBC	2	3,3%	7	15,6%
Fatal outcome from non- oncological pathology	4	6,7%	---	---
Total	60	100%	45	100%

Source: [Compiled by the authors]

The progression of UBC is observed in 11 out of 60 (18.3%) patients in the main group, 18 of 45 (40.0%) in group II, respectively. The median of the relapse-free period was 21.05 months (6.1-36.0 months) for the main group of patients, and 13.75 months (3.2 - 24.3 months) for the patient's control group. For the subsequent analysis of risk factors of different progression options, we allocated local, regional and remote progression, as well as their combination. In the main group in 3 of 11 (5.0%) patients with progression, it was local character (relapse in the cult of vagina, metastases in the vagina, parameter infiltrates), in 2 (3.3%) - regional (metastasis in pelvic and lumbar lymphatic nodes), 3 (5.0%) of patients revealed remote metastases. The frequency of combined progression options was distributed the same. The combination of remote metastases and lesions of regional lymph nodes (in 1 patient, 1.7%), a combination of local and remote progression (in 1 patient, 1.7%), as well as a combination of local and regional progression (in 1 patient, 1.7 %).

In the control group, 6 of 18 (13.3%) patients were local progression (recurrence in the vaginal cult, metastases in the vagina, parameter infiltrates), 3 (6.7%) -

regional (metastases in pelvic and lumbar lymph nodes), 4 (8.9%) patients revealed remote metastases. The combination of remote metastases and lesions of regional lymph nodes was in 2 patients, 4.4%. The combination of local and remote progression was observed in 2 patients, 4.4%, as well as a combination of local and regional progression in 1 patient, 2.2%.

Table 6. Distribution of patients under progression

The outcome of treatment	Main group		Control group	
	Number of patients	Proportion of patients (%)	Number of patients	Proportion of patients (%)
Local progression	3	5%	6	13,3%
Regional progression	2	3,3%	3	6,7%
Remote progression	3	5%	4	8,9%
The combination of remote metastases and lesions of regional lymph nodes	1	1,7%	2	4,4%
Combination of local and distant progression	1	1,7%	2	4,4%
Combination of local and regional progression	1	1,7%	1	2,2%
TOTAL	11	18,5%	18	39,9%

Source: [Compiled by the authors]

Thus, in the I group as a whole, local progression was observed in 5 out of 60 (8.3%) patients, regional - in 4 (6.7%), remote - in 5 (8.3%), in group II, local progression was observed in 9 of 45 (20%) patients, regional - in 5 (11.1%), remote - in 8 (17.8%). The effectiveness of the treatment is estimated by the study of the overall and disease-free survival of patients. Analysis of the survival of patients showed a significant advantage of patients with the main group. Three-year-old overall survival was in the I group of $87.1 \pm 9.3\%$, in group II $82 \pm 5.8\%$. Three-year disease-free survival in the control group was $69 \pm 8.6\%$, while in the main group it was $74 \pm 6.9\%$, respectively ($p \leq 0.05$). Separately illustrated the total and disease-free three-year survival of patients according to the method of Kaplan-Meyer (Fig. 1 and 2).

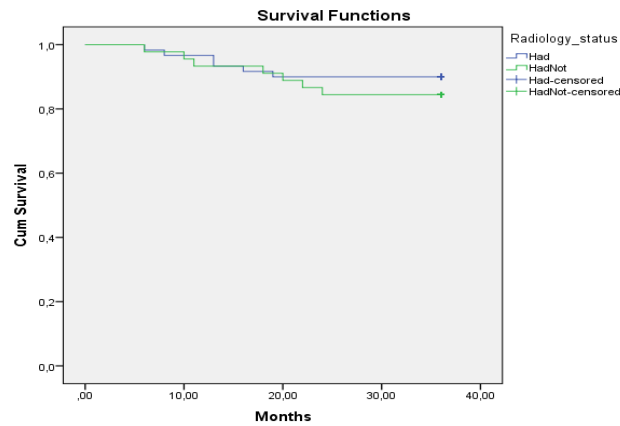


Figure 1. Common survival rate of patients of the main and control group.
Source: [Compiled by the authors]

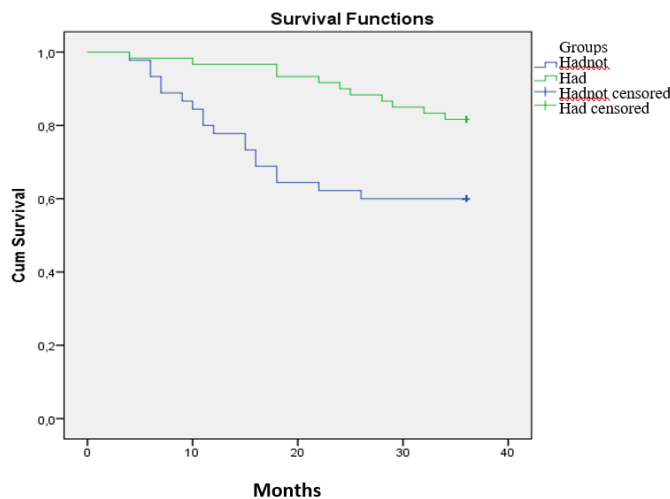


Figure 2. The disease-free survival of patients in both groups
Source: [Compiled by the authors]

The results obtained, on the one hand, confirm the high efficiency of preoperative brachytherapy, but it should be noted about the importance of choosing the dose of radiation therapy, which requires additional research for the widespread introduction of neoadjuvant radiation therapy into clinical practice. Separately analyzed the total and disease-free three-year survival of patients with highly, moderately and low-differentiated endometrioid adenocarcinoma and rare body cancer for the uterus. In patients with low-differentiated endometrioid adenocarcinoma and glandular squamous cell carcinoma, the overall and disease-free survival was almost the same: $69.5 \pm 3.4\%$ and $69.2 \pm 4.1\%$; $68.7 \pm 5.4\%$ and $67.7 \pm 6.6\%$. The high indicators of overall and disease-free survival were in a group with highly differentiated endometrioid adenocarcinoma $90.0 \pm 5.4\%$ and $82.7 \pm 6.7\%$. The lowest indicators of general and disease-free survival were in

patients with serous-papillary adenocarcinoma. So in the main group of patients, the overall survival was $63.7 \pm 4.6\%$, the disease-free survival $61.9 \pm 3.8\%$, in the control group 60.2 ± 9.1 and $57.9 \pm 7.4\%$, respectively.

Table 7. The overall and disease-free survival rate of patients with UBC depending on the histological type of tumor

Histological type		N (main group)	3-year survival rate	N (control group)	3-year survival rate
Endometrioid adenocarcinoma:	Highly differentiated	19 (31,7%)	90,0±5,4* 82,7±6,7	20 (44,5%)	85,5±6,1* 80,5±4,5
	Moderately differentiated	16 (26,7%)	85,7±10,9 79,8±5,9	5 (11,1%)	80,9±5,6 74,5±7,6
	Low differentiated	6 (10,0%)	69,5±13,4 68,7±9,4	2 (4,4%)	69,4±7,2 66,2±8,2
Glandular squamous carcinoma	9 (15,0%)	69,2±9,1 67,7±6,6	11(24,4%)	65,8±8,1 62,6±7,1	
Serous papillary carcinoma	10 (16,7%)	63,7±10,6 61,9±7,8	7 (15,6%)	60,2±9,1 57,9±7,4	

Source: [Compiled by the authors]

Note: * in the numerator is the indicator of overall, in the denominator - disease-free survival $p \leq 0.05$

The overall and disease-free survival rates of patients in whom the expression of the mutant p53 and bcl-2 genes were destroyed was analyzed separately. After radiation therapy, 36 (60%) of 43 bcl-2 expressed patients showed no expression of this gene. Three-year overall survival was the highest in patients with highly differentiated adenocarcinoma and amounted to $84.5 \pm 7.5\%$, relapse-free three-year survival - $81.9 \pm 4.9\%$. Low rates of overall and disease-free three-year survival after the destruction of bcl-2 expression were in the group of patients with poorly differentiated adenocarcinoma and serous-papillary carcinoma: (low-grade adenocarcinoma 73.7 ± 8.2 and $70.9 \pm 9.4\%$, serous-papillary carcinoma 70.9 ± 6.8 and $66.4 \pm 7.5\%$).

Table 8. Overall and disease-free survival of patients in whom bcl-2 positive genes were not expressed after preoperative radiation therapy

Histological type	The number and % of patients (in whom the expression of the bcl-2 gene has disappeared)	Overall 3-year survival rate	Disease-free 3-year survival
Highly differentiated endometrioid adenocarcinoma	15 (25%)	84,5 ± 7,5	81,9 ± 4,9
Moderately differentiated endometrioid adenocarcinoma	8 (13,3%)	78,5 ± 7,6	76,6 ± 7,6

Poorly differentiated endometrioid adenocarcinoma	3 (5%)	73,7 ± 8,2	70,9 ± 9,4
Glandular squamous cell carcinoma	6 (10%)	72,5 ± 8,1	68,5 ± 4,1
Serous - papillary adenocarcinoma	4 (6,7%)	70,9 ± 6,8	66,4 ± 7,5
Total	36 (60%)	P <0,05	

Source: [Compiled by the authors]

A statistically significant decrease in both overall and relapse-free survival was observed in patients in whom the bcl-2 gene expression remained unchanged after radiation therapy (brachytherapy), regardless of the degree of differentiation of endometrioid adenocarcinoma. Thus, with highly differentiated adenocarcinoma overall and relapse-free survival was 81.3 ± 4.9% and 79.4 ± 5.5%, with moderately differentiated adenocarcinoma 77.3 ± 6.7% and 75.2 ± 8.2%, poorly differentiated endometrioid adenocarcinoma 72.0 ± 2.3 and 68.0 ± 3.5%, respectively.

The results of the analysis of the overall and disease-free survival of patients with UBC, in whom the expression of the mutant p53 gene disappeared after radiation therapy, are presented in Table 9. According to the results of the study, it was revealed that out of 48 patients who have a high expression of the mutant p53 gene, after preoperative brachytherapy in 42 (70%) patients, this expression became negative. The overall and recurrence-free survival rate of patients with poorly differentiated endometrioid adenocarcinoma (69.7 ± 7.2 and 68.8 ± 7.4%) was statistically significantly that of patients with glandular squamous cell UBC (68.8 ± 10.2 and 66.9 ± 8, 7%).

The overall and recurrence-free survival of patients with unchanged expression of the p53 gene with serous-papillary adenocarcinoma (64.9 ± 5.7 and 63.1 ± 4.4%) was statistically significantly lower than those for poorly differentiated adenocarcinoma and glandular squamous cell carcinoma (66.5 ± 9.5 and 64.9 ± 7.3%; 66.3 ± 7.3 and 65.3 ± 2.8%) (p <0.05).

Table 9. Overall and disease-free survival of patients in whom the expression of mutant p53 genes became negative after preoperative radiation therapy

Histological type	The number and % of patients (in whom the expression of the p53 gene has disappeared)	Overall 3-year survival rate	Disease-free 3-year survival
Highly differentiated endometrioid adenocarcinoma	10 (16,7%)	85,5 ± 4,9	82,4 ± 5,5
Moderately differentiated endometrioid adenocarcinoma	14 (23,3%)	76,9 ± 4,8	75,6 ± 4,6
Poorly differentiated endometrioid adenocarcinoma	4 (6,7%)	69,7 ± 7,2	68,8 ± 7,4
Glandular squamous cell carcinoma	8 (13,3%)	68,8 ± 10,2	66,9 ± 8,7

Serous - papillary adenocarcinoma	6 (10%)	67,6 ± 9,8	65,4 ± 8,5
Total	42 (70%)	P <0,05	

Source: [Compiled by the authors]

We studied the correlations between clinical, morphological and immunohistochemical parameters in cancer of the uterine body after preoperative radiation and radical surgery therapy and also in a group of patients after radical surgery therapy without preoperative radiation therapy. The relationship between indicators was determined using the nonparametric rank correlation coefficient τ (Kendall Tau Correlations). The level of statistical significance was taken as $p < 0.05$. The nature of the correlations between clinical, morphological and immunohistochemical parameters in the main group of patients are presented in Table 10.

Table 10. The character of the correlations using Kendall's test (τ) (Kendall Tau Correlations)

Indicator	Correlation coefficient (τ)	P
Bcl-2 and T	0,469	0,019
p53 and T	0,700	0,001
Bcl-2 and G	0,318	0,041
p53 and G	0,514	0,010
Bcl-2and p53	0,165	0,131

Source: [Compiled by the authors]

Confidence level $p \leq 0.05$

T - the level of tumor invasion

G - the degree of tumor differentiation

As can be seen from the table, a direct correlation was revealed between the expression of bcl-2, p53 and the degree of tumor invasion of the myometrium -T ($\tau = 0.469$ and $\tau = 0.700$; $p < 0.05$). In our study, the increased expression level of bcl-2 and p53 directly correlated with the degree of malignancy of UBC - G ($\tau = 0.318$ and $\tau = 0.514$; $p < 0.05$)

Discussion

The prognostic factors for UBC are numerous. All of them, to one degree or another, affect both the survival rate of patients and the risk of further progression of the disease. R. C. Boronow, in his work with the iconic title "Endometrial cancer: not a benign disease", described four common "myths" about UBC: (Abdullaeva, 2008) UBC is a relatively benign disease; (2) the optimal method of its treatment is known; (Artoshina, 2011) prognostic factors have been identified; (4) the condition of the lymph nodes has little prognostic value (Laktionov, Abdullaeva, Anurova, Gadzhieva. 2010). The overall and relapse-free survival of patients with UBC stage IA (invasion up to $\frac{1}{2}$ myometrium: 89.1 ± 2.5 and $85.4 \pm 1.4\%$) was statistically significantly higher than that of patients with UBC IB and IC (invasion of more than $\frac{1}{2}$ myometrium, invasion up to seroses: 84.8 ± 5.2 and $77.3 \pm 5.2\%$; 80.1 ± 6.4 and 75.1 ± 4.4). The significance of the stage of the disease as one of the main prognosis factors for UBC was noted both

in the FIGO report (Galaeva, 2010) and in the works of other authors (Levine, 2013). The three-year survival rate was analyzed separately depending on the histological forms of the tumor. In patients with poorly differentiated endometrioid adenocarcinoma and glandular-squamous cell carcinoma, overall and recurrence-free survival was almost the same: $69.5 \pm 13.4\%$ and $69.2 \pm 9.1\%$; $68.7 \pm 9.4\%$ and $67.7 \pm 6.6\%$. Data on the prognostic significance of the degree of differentiation in UBC are given by many authors (Gavrish, Berlev, Artemyeva, 2012). High rates of overall and disease-free survival were observed in the group with highly differentiated endometrioid adenocarcinoma, $90.0 \pm 5.4\%$ and $82.7 \pm 6.7\%$. The lowest rates of overall and disease-free survival were in patients with serous-papillary adenocarcinoma. So in the main group of patients the overall survival rate was $63.7 \pm 10.6\%$, relapse-free $61.9 \pm 7.8\%$, in the control group 60.2 ± 9.1 and $57.9 \pm 7.4\%$, respectively. More aggressive clinical course of serous, clear cell carcinoma and mixed adenocarcinoma is well known and noted by many authors (Felix, Weissfeld, Stone, 2011).

Analysis of the expression of genes responsible for apoptosis revealed a regular decrease in the overall and disease-free survival rate of patients with UBC as it increases. The adverse effect of the combination of overexpression of these genes and poorly differentiated endometrioid adenocarcinoma and rare forms of UBC on the likelihood of death from UBC was confirmed by an analysis of UBC-determined survival. Thus, with poorly differentiated endometrioid adenocarcinoma in the absence of disappearance of bcl-2 and p53 expression, the overall three-year survival rate was 72.0 ± 2.3 and $66.5 \pm 9.5\%$, the relapse-free three-year survival rate was 68.0 ± 3.5 and $64.9 \pm 7.3\%$, respectively. Similar data are presented in the literature (Apostolou, Apostolou, Biteli, 2014).

Multivariate analysis of life prognosis and progression revealed a significant role of factors such as rare histological types of uterine cancer, poorly differentiated form of endometrioid adenocarcinoma, the presence of lymphovascular tumor invasion, tumor localization in the lower third of the uterus with involvement of the isthmus, the presence of mutant p53 and bcl-2 in tumor cells and the absence of cleavage of these genes after radiation therapy. At the same time, factors such as the duration and onset of the menstrual cycle, concomitant gynecological pathology, the size of the uterus and the thickness of the endometrium at the initial treatment of the patient have lost their prognostic value.

In summary, we would like to return to the quote presented at the beginning of the chapter. Undoubtedly, UBC is characterized by a fairly high survival rate. According to the literature, despite frequent comorbidities and the elderly age of patients, the 5-year overall survival rate is $76.0 \pm 1.2\%$, regardless of the stage and method of treatment and the 10-year survival rate is $62.6 \pm 1.4\%$, with a median life expectancy - 17.3 ± 0.7 years.

The tactics of treating this pathology over the past decades have undergone significant changes, however, the rate of progression of stage I UBC, regardless of the methods of treatment used, is still 15.9%, stage II - 30.1%. Not a single oncogynecological pathology has described such a number of significant prognostic factors as with UBC. A number of risk assessment systems have been

developed that can be used to determine the indications for neoadjuvant and adjuvant RT. An in-depth analysis of the treatment results depending on the expression of the mutant p53 and bcl-2 gene makes us take a fresh look at its tactics. It seems that the final conclusion on the choice of the volume of combined treatment for early stage UBC is possible only after analyzing the expression of genes responsible for apoptosis, taking into account different histological types of the disease, since the task of modern gynecological oncology is to ensure high 15- and 20-year survival rates and an adequate quality of life.

Conclusions

Three-year overall survival after the standard volume of combined treatment was $82 \pm 5.8\%$, relapse-free $69 \pm 8.6\%$ ($p \leq 0.05$), while these indicators were $87.1 \pm 9.3\%$ and $74 \pm 6.9\%$ ($p \leq 0.05$) in the group of patients where preoperative brachytherapy was added to the volume of combined treatment in patients with UBC stage I, depending on the expression of the p53 and bcl-2 genes. There is an aggressive course and low survival rates of stage I UBC in patients with poorly differentiated adenocarcinoma, glandular squamous cell and serous-papillary carcinoma. Almost the same indicators of overall and relapse-free survival were observed in patients with poorly differentiated endometrioid adenocarcinoma and glandular squamous cell carcinoma: $69.5 \pm 3.4\%$ and $69.2 \pm 4.1\%$; $68.7 \pm 5.4\%$ and $67.7 \pm 6.6\%$ ($p \leq 0.05$). High rates of overall and disease-free survival were in the group with highly differentiated adenocarcinoma ($90.0 \pm 5.4\%$ and $82.7 \pm 6.7\%$ ($p \leq 0.05$)), while the lowest rates were in patients with serous papillary adenocarcinoma ($63.7 \pm 4.6\%$ and $61.9 \pm 3.8\%$ ($p \leq 0.05$)).

In the main group bcl-2, 43 (71.6%) patients were positive, in the control group, 21 (46.7%) patients. The mutant p53 gene was expressed in 48 (80%) patients and 39 (86.7%) patients, respectively. When studying the analysis of postoperative materials, it was revealed that after preoperative brachytherapy, in 36 (60%) of 43 patients, the tumor became bcl-2 negative, in 42 (70%) of 48 patients, the mutant p53 gene became negative, which indicates a change in gene expression after radiation therapy, with a median life expectancy.

A direct correlation was found between the expression of bcl-2, p53 and the degree of tumor invasion of the myometrium - T ($\tau = 0.469$ and $\tau = 0.700$; $p < 0.05$) and the degree of malignancy of UBC - G ($\tau = 0.318$ and $\tau = 0.514$; $p < 0.05$). This fact makes it possible to draw a conclusion about the aggressive course of UBC when these prognostic factors are combined with high expression of the apoptosis regulator bcl-2 and the mutant p53 gene.

Taking into account the main clinical and morphological factors, the independent risk factors for death in patients with UBC were age over 50 years, pathogenetic type II, concomitant extragenital pathology of diabetes mellitus + hypertension, grade III obesity, histological forms of UBC, tumor localization and depth of invasion, high expression of the mutant p53 gene and bcl-2, preservation of gene expression after preoperative RT. The analysis of the dependence of the overall and disease-free survival of patients with UBC on the expression of the p53 and bcl-2 genes revealed the risk ratio (RR) and the confidence interval (CI). The RR and 95% CI when calculating overall survival for loss of p53 expression after RT

was 3.67 (2.31-5.82), while for bcl-2 this indicator was 2.67 (1.98-4.95) ... This indicates an improvement in the long-term outcome of UBC patients with the volume of combined treatment with preoperative radiation therapy.

Combination therapy of UBC should begin with preoperative radiation therapy followed by surgical and combined radiation components, depending on the expression of p53 and bcl-2 and the histological type of tumor. During the initial treatment of patients during the verification of the disease, in addition to the histological type and degree of differentiation, we recommend that the expression of the p53 and bcl-2 genes be specified. With high gene expression and in combination with rare forms of UBC, such as serous - papillary adenocarcinoma, glandular squamous cell carcinoma, and with low differentiation of endometrioid adenocarcinoma, treatment should be started with preoperative radiation therapy.

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