ORIGINAL CONTRIBUTION

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ANALYSIS OF FACTORS INFLUENCING TREATMENT OUTCOMES OF UTERINE SARCOMAS

Background. Uterine sarcoma (US) is a rare type of tumor characterized by aggressive clinical behavior and high recurrence rate. Its histopathological heterogeneity has led to a lack of consensus regarding risk factors that could guide the selection of optimal treatment strategies for this pathology. **Aim.** To investigate the factors influencing treatment outcomes of US. **Materials and Methods.** We conducted a retrospective analysis of the treatment outcomes of 107 women diagnosed with stage I—II US from 2010 to 2023. The follow-up period ranged from 1.0 to 156.0 months. Kaplan — Meier survival curves were used for the analysis of overall survival (OS) and recurrence-free survival (RFS) rates. The correlation between the studied parameters was analyzed including relative risk (odds ratio, OR) and correlation coefficient. **Results.** The assessment of OR allowed us to identify the following prognostic factors with a negative impact on the 5-year OS and RFS of patients with US: differentiation grade G3, necrotic areas in tumor tissue, lymphovascular invasion, high mitotic activity (11 or more mitoses per 10 HPF), nuclear atypia 4+, negative ER and PR statuses, and high Ki-67 expression. **Conclusions.** Survival of patients with US depends on tumor grade, necrosis, and lymphovascular invasion of tumor tissue; mitotic activity and nuclear atypia; ER and PR statuses; and the level of Ki67 expression.

Keywords: sarcoma, disease prognosis, surgery, risk factors, treatment, long-term treatment outcomes.

Uterine sarcoma (US) is a rare type of tumor, accounting for only 1% of all malignant gynecological diseases and 3—7% of all malignant tumors of the uterus, with an incidence of approximately 0.4 per 100,000 women. It is characterized by an aggressive course and poor prognosis [1, 2]. Information on the incidence of US is not available in the International Agency for Research on Cancer of the World Health Organization, the European Network of Cancer Registries, the American Cancer Society's estimates, and the National Cancer Registry of Ukraine [3].

Despite various approaches to radical treatment, sarcoma remains a tumor with a poor prognosis, often leading to local and distant recurrences [4]. The most significant prognostic factor for five-year survival is the stage of the disease. In stage I, the five-year survival rate is 50%—70%, while for stages II, III, and IV, it drops to 0—20% [5].

There are three most common types of US: leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), and undifferentiated uterine sarcoma (UUS). A significant risk factor for US development is

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a history of radiation therapy, especially at a young age [6—8]. US can also be part of genetic syndromes such as retinoblastoma (due to *RB1* gene deletion) and Li — Fraumeni syndrome (caused by *TP53* gene mutation) [9, 10]. The most frequently mutated genes in LMS include *TP53* (30%), *ATRX* (25%), and *MED12* (20%) [11].

Uterine LMS accounts for 1% of all malignant uterine neoplasms and 35%—40% of all US cases, making it the most common type of gynecological sarcoma [12]. LMS originates from smooth muscle cells, is highly aggressive, and grows rapidly. There is a hypothesis that LMS arises from abnormal myometrial stem cells [13—16]. However, the exact cell of origin is yet to be determined [17]. The exact cause of LMS development remains unknown [18].

The pathogenesis of ESS is unclear, but prolonged use of tamoxifen and estrogens and conditions such as polycystic ovary syndrome have been implicated in its development [19, 20]. Recently, a specific translocation t(7;17) (p15;q21) has been described in most cases of ESS. *BCOR* gene abnormalities characterize high-grade ESS [21—24]. A high Ki-67 level indicates rapid tumor growth and is a prognostic factor for aggressive disease progression [25]. *TP53* mutations are associated with aggressive disease behavior and an increased risk of metastasis [26, 27].

The aim of the study was to investigate the factors influencing treatment outcomes of uterine sarcomas.

Materials and Methods

The treatment outcomes of 107 women diagnosed with (US stage I—II (T1-2N0M0) who underwent surgical intervention from 2010 to 2023 were analyzed. The effectiveness of treatment was evaluated based on the recurrence-free survival (RFS) rates throughout the follow-up period, as well as the frequency of tumor recurrence and metastasis. The follow-up period ranged from 1.0 to 156.0 months.

Survival analysis was performed using the Kaplan — Meier method. This method evaluates the

Clinical characteristics of patients

Patients with US (n = 107)				
FIGO	Group I Stage I without adjuvant therapy (n = 45)	Group II Stage I with adjuvant therapy (n = 38)	Group III Stage II without adjuvant therapy (n = 6)	Group IV Stage II with adjuvant therapy (n = 18)
Age at diagnosis (years)	50.4 ± 2.2	56.2 ± 1.6	62.2 ± 4.4	56.4 ± 2.1
Average body weight (kg)	81.3 ± 3.4	83.1 ± 3.0	84.8 ± 5.8	81.0 ± 4.3
Histological type				
LMS	40 (88.9%)	26 (68.4%)	6 (100%)	12 (66.7%)
Grade				
G1	24 (53.3%)	8 (21.1%)	1 (16.7%)	2 (11.1%)
G2	10 (22.2%)	10 (26.3%)	3 (50%)	7 (38.9%)
G3	6 (13.3%)	8 (21.1%)	2 (33.3%)	3 (16.7%)
Histological type				
ESS	5 (11.1%)	12 (31.6%)		6 (33.3%)
Grade				
G1	1 (2.2%)	3 (7.9%)		2 (11.1%)
G2	2 (4.5%)	3 (7.9%)		1 (5.5%)
G3	2 (4.5%)	6 (15.7%)		3 (16.7%)
Other parameters				
Burdened cancer history	8 (17.2%)	5 (13.2%)	0	2 (11.1%)
History of uterine leiomyoma	24 (53.3%)	25 (65.8%)	0	10 (55.6%)

likelihood of survival at a given time point after the initial event and accounts for censored data (e.g., on patients lost to follow-up).

Morphological evaluation of US was carried out according to the Brigham criteria (Chapel D et al., *American Journal of Surgical Pathology*, 2021). The study results were assessed by classifying patients according to key prognostic factors: disease stage, tumor histotype, differentiation grade (G), the number of mitoses per 10 HPF, presence of necrotic fields, presence of lymphovascular invasion, nuclear atypia of the tumor (graded as 1+, 2+, 3+, or 4+), presence of estrogen receptors (ER) and progesterone receptors (PR), and Ki-67 expression in the tumor tissue.

We analyzed the correlation between the studied parameters, including the relative risk (odds ratio — OR) and the correlation coefficient. Relative risk and OR were used to assess associations between qualitative variables, enabling the evaluation of changes in risk across groups and the relationship between a specific outcome and a risk factor.

The correlation coefficient was used to analyze relationships involving at least one quantitative or semi-quantitative variable. The statistical significance of differences between survival curves was evaluated using the Gehan — Wilcoxon test (GWT) for early events, and the log-rank test (LRT) for long-term outcomes. The correlation between mortality/survival and various factors was assessed using Spearman's correlation coefficient. For processing numerical data, Fisher's exact test, contingency tables, and tests for comparing two proportions were applied.

Results and Discussion

Five-year recurrence-free and overall survival rates in uterine sarcoma patients. Patients with US were retrospectively divided into four groups (I—IV) based on the administration of adjuvant therapy (Table).

Among patients with US stage I, 45 underwent surgery alone (Group I), while 38 received adjuvant therapy following surgery (Group II).

The data on the follow-up of patients of Groups I and II who were included in this study were partially analyzed in our previous paper [28]. 3-year OS in Group I was 85% compared to 67.5% in Group II and 5-year OS was 76.6% vs. 53.2%.

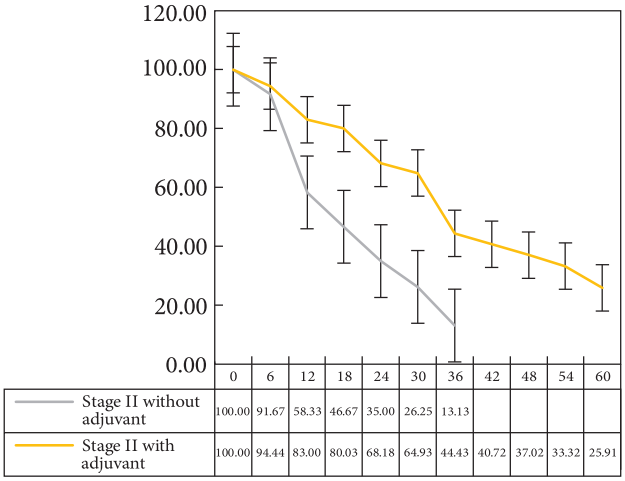
Additionally, RFS rates in patients with US of stage I were analyzed as well. 3-year RFS in patients of group I was 82.4 compared to 51.7% in group II. 5-year RFS rates were 71.4% in group I vs. 39.8% in group II [28].

Thus, both 3-year and 5-year OS and RFS rates were significantly higher in patients with US of stage I who did not undergo adjuvant therapy.

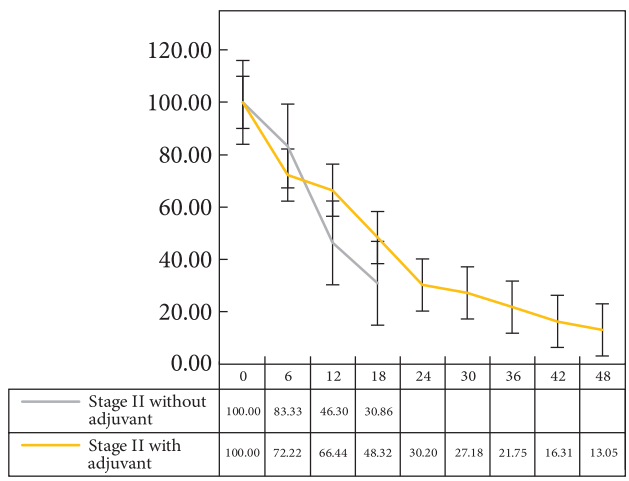
Among patients with US of stage II, 6 underwent surgery alone (Group III), while 18 received adjuvant therapy after surgery (Group IV). The OS and RFS with US of stage II (Groups III and IV) were analyzed (Fig. 1).

The 3-year OS rate in Group III was only 13.1%, compared to 44.4% in Group IV. Among the patients of Group III, there were no 5-year survivors. In contrast, the 5-year OS in Group IV was 25.9%.

Thus, the OS rate during the 60-month observation period was higher in Group IV patients compared to Group III patients.



a



b

Fig. 1. OS (*a*) and RFS (*b*) of patients with US of stage II depending on treatment

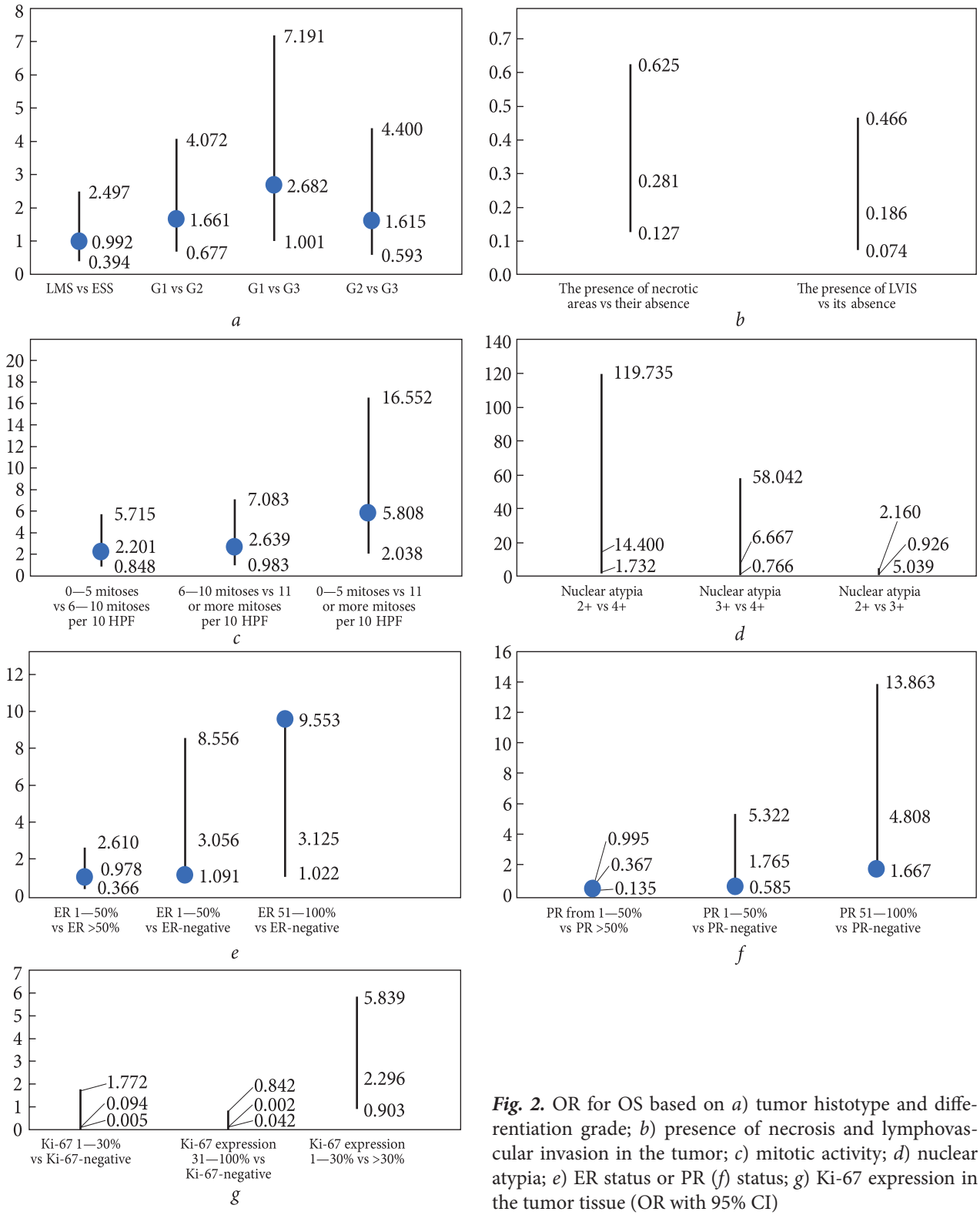


Fig. 2. OR for OS based on *a*) tumor histotype and differentiation grade; *b*) presence of necrosis and lymphovascular invasion in the tumor; *c*) mitotic activity; *d*) nuclear atypia; *e*) ER status or PR (*f*) status; *g*) Ki-67 expression in the tumor tissue (OR with 95% CI)

When analyzing RFS from 12 months onward, the rates were significantly higher in patients of group IV compared to group III. At the 42-month follow-up point, only 1 patient remained in Group III, and by 48 months, no patients remained in Group III (Fig. 1, *b*). Therefore, both 3-year and 5-year OS and RFS rates were significantly higher in patients with stage II US who received adjuvant therapy.

The OR analysis revealed that the 5-year OS did not depend on the histological type of the tumor (ESS or LMS) and increased along with

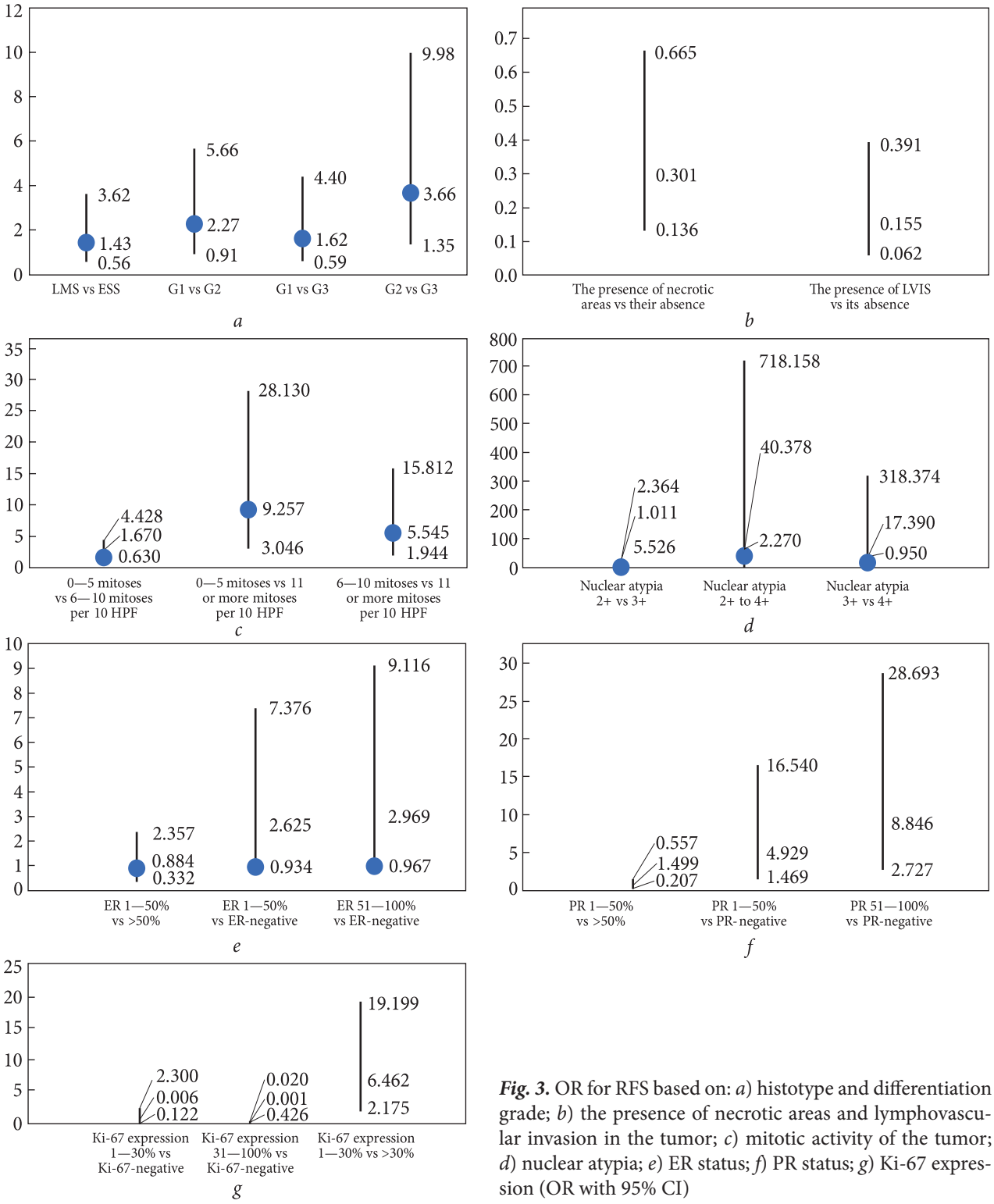


Fig. 3. OR for RFS based on: *a*) histotype and differentiation grade; *b*) the presence of necrotic areas and lymphovascular invasion in the tumor; *c*) mitotic activity of the tumor; *d*) nuclear atypia; *e*) ER status; *f*) PR status; *g*) Ki-67 expression (OR with 95% CI)

the decrease in the tumor differentiation grade (Fig. 2, *a*), however, insignificantly. The presence of necrotic areas or the presence of lymphovascular invasion were linked to a 3.556-fold or 5.375-fold decrease in the 5-year OS, respectively ($p < 0.05$) (Fig. 2, *b*). The low mitotic activity was linked to higher 5-year OS rates compared to the higher mitotic indexes ($p < 0.05$) (Fig. 2, *c*). Nuclear atypia was in direct relation to the 5-year OS, which was the highest in the case of nuclear atypia of 4 ($p < 0.05$) (Fig. 2, *d*). The 5-year OS rates increased depending on positive ER and PR statuses ($p < 0.05$) compared to receptor-negative US cases (Fig. 2, *e*, *f*) but

decreased in reverse relation to Ki-67 expression ($p < 0.05$) (Fig. 2, *g*).

Our analysis showed that the 5-year RFS did not depend significantly on the histological type of tumor (LMS compared to ESS) but was higher for tumors of G1 grade compared to G3 grade ($p < 0.05$) (Fig. 3, *a*). It was negatively affected by the presence of necrotic areas ($p < 0.05$), lymphovascular invasion ($p < 0.05$) (Fig. 3, *b*), and high mitotic activity indices ($p < 0.05$) (Fig. 3, *c*).

The nuclear atypia 2+ compared to 3+ or 2+ compared to 4+ was linked to the significantly increased 5-year RFS ($p < 0.05$). No patients with nuclear atypia 4+ survived for 5 years, so the OR was corrected using Haldane — Anscombe's data (Fig. 3, *d*).

The 5-year RFS was positively affected by the positive ER status of US (Fig. 3, *e*) and PR status ($p < 0.05$) (Fig. 3, *f*) but decreased with increasing Ki-67 expression levels ($p < 0.05$) (Fig. 3, *g*).

According to the OR calculations, we have identified the following negative prognostic factors ($p<0.05$):

- Tumor differentiation grade G3;
- Presence of lymphovascular invasion and necrotic areas in the tumor;
- Presence of 11 or more mitoses per 10 HPF;
- Presence of nuclear atypia 3+ and 4+ in the tumor;
- Absence of ER and PR in the tumor tissue;
- Ki-67 expression level of 31%—100%.

Prognosis for women with US depends primarily on the stage of the disease at diagnosis [27, 29]. US is a rare disease, and its histopathological diversity has led to a lack of consensus on risk factors that would guide the optimal treatment approach for this pathology [29, 30].

As shown in [31], the combination of tumor size, mitotic index, Ki-67 expression, and BCL-2 protein expression allowed dividing uterine leiomyosarcomas (ULMS) into two groups with different survival outcomes. Tumors > 10 cm in diameter with a mitotic index of > 20 MF/10 HPF, > 10% nuclear immunoreactivity for Ki-67, and negative BCL-2 expression, have a worse prognosis compared to ULMS with tumors < 10 cm in diameter, a mitotic index <20 MF/10 HPF or lower, and < 10% nuclear immunoreactivity for Ki-67, with either positive or negative BCL-2 expression. A high Ki-67 level indicates a rapid tumor growth and serves as a prognostic factor for aggressive disease progression [32, 33]. However, despite many years of research on US, there is still no comprehensive characterization of prognostic factors such as ER, PR, Ki-67 expression, and histological factors (tumor type, necrosis fields, number of mitoses, lymphovascular invasion, perineural invasion, and degree of nuclear atypia).

In the present study, we have identified the following prognostic factors with a negative impact on the 5-year OS: differentiation grade G3, necrotic areas in tumor tissue, lymphovascular invasion, high mitotic activity (11 or more mitoses per 10 HPF), nuclear atypia 4+, negative ER and PR statuses, and high Ki-67 expression.

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АНАЛІЗ ФАКТОРІВ, ЯКІ ВПЛИВАЮТЬ НА РЕЗУЛЬТАТИ ЛІКУВАННЯ ХВОРИХ НА САРКОМУ МАТКИ

Стан питання. Саркома матки являє собою рідкісний тип пухлини, що характеризується агресивним клінічним перебігом та високою частотою рецидивів. Через значну гістопатологічну гетерогенність цих пухлин немає єдиного уявлення щодо факторів ризику, що дозволило би обрати оптимальну стратегію лікування. **Мета** дослідження полягала у з'ясуванні факторів, які впливають на результати лікування хворих на саркому матки. **Матеріали та методи**. Проведено ретроспективний аналіз результатів лікування 107 хворих із діагнозом саркома матки I—II стадій впродовж 2010—2023 рр. Період спостереження за хворими складав від 1 до 156 місяців. Загальну виживаність та безрецидивну виживаність проаналізовано методом Каплана — Мейєра. Визначали відносний ризик (відношення шансів) та коефіцієнт кореляції між досліджуваними параметрами. **Результати**. Аналіз показників відносного ризику дозволив ідентифікувати наступні прогностичні фактори, які негативно впливають на п'ятирічну загальну та безрецидивну виживаність хворих на саркому матки: ступінь диференціювання G3, наявність некротичних ділянок в пухлині, лімфовасулярна інвазія, висока мітотична активність (11 та більше мітозів у 10 полях зору), ядерна атипія 4+, відсутність експресії естрогенових та прогестеронових рецепторів, високий рівень експресії Ki-67. **Висновки**. Виживаність хворих на саркому матки залежить від таких факторів як ступінь диференціювання пухлинних клітин, наявність некрозу та лімфоваскулярної інвазії, мітотична активність пухлинних клітин, ядерна атипія, наявність експресії естрогенових та прогестеронових рецепторів і рівень експресії Ki-67.

Ключові слова: саркома матки, прогноз, фактори ризику, результати лікування.