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Survival analysis of patients with rare tumors of the uterine corpus – carcinosarcomas

Analiza preživljavanja bolesnika sa retkim tumorima tela materice – karcinosarkomima

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Abstract

Background/Aim. Uterine carcinosarcoma (UCS), formerly known as malignant mixed Müllerian tumor, is a rare, aggressive malignancy of the female genital tract. The aim of this study was to analyze the most important clinical and pathohistological characteristics of UCSs on operated patients, as well as to determine which of those factors are affecting progression-free survival (PFS) and overall survival (OS) of patients. **Methods.** The study was conducted as a retrospective analysis of medical data documentation of patients with a diagnosis of UCS who were surgically treated at the Department of Gynecology, Clinic for Operative Oncology, Oncology Institute of Vojvodina, Sremska Kamenica, Serbia, in 10 years' period (from the beginning of 2009 to the end of 2018). The analysis included data for a total of 31 patients. **Results.** Of all the examined parameters (age of the patient, clinical stage of the disease, histological grade, depth of myometrial invasion, and lymphovascular invasion – LVI), the greatest influence on the choice of therapeutic procedure had a histological tumor grade. **Conclusion.** Our research showed the joint influence of the examined clinical and pathohistological factors on PFS and OS of patients with UCS. The only independent parameter that showed a statistically significant impact on survival is LVI.

Key words:
carcinosarcoma; progression-free survival; risk factors; survival analysis; uterine neoplasms.

Apstrakt

Uvod/Cilj. Karcinosarkom materice (KSM), ranije poznat kao maligni mešoviti Milerov tumor, je redak i agresivan malignitet ženskog genitalnog trakta. Cilj rada bio je da se analiziraju najvažnije kliničke i patohistološke karakteristike KSM operisanih bolesnica, kao i da se utvrde faktori značajni za preživljavanje bez progresije (PBP) bolesti i ukupno preživljavanje (UP) obolelih. **Metode.** Studija je rađena kao retrospektivna analiza dokumentacije medicinskih podataka bolesnica sa dijagnozom KSM, koje su hirurški lečene na Odeljenju ginekologije Klinike za operativnu onkologiju Instituta za onkologiju Vojvodine, Sremska Kamenica, Srbija, u periodu od 10 godina (od početka 2009. do kraja 2018. godine). Analizirani su podaci ukupno 31 bolesnice. **Rezultati.** Od svih ispitivanih parametara (starost bolesnica, klinički stadijum bolesti, histološki gradus, dubina invazije miometrijuma i limfovaskularna invazija – LVI), najveći uticaj na izbor terapijske procedure imao je histološki stepen tumora. **Zaključak.** Naše istraživanje pokazalo je zajednički uticaj ispitivanih kliničkih i patohistoloških faktora na PBP bolesti i UP bolesnica sa KSM. Jedini nezavisni parametar koji je pokazao statistički značajan uticaj na preživljavanje je LVI.

Ključne reči:
karcinosarkom; preživljavanje, bez progresije; faktori rizika; preživljavanje, analiza; materica, neoplazme.

Introduction

After several decades of scientific debate, it is known today that uterine carcinosarcoma (UCS), a malignant neoplasm, has both an epithelial and a mesenchymal part [1–4]. Incidence ranges from 0.5 to 3.3 cases *per* 100,000 women; depending on the studies, they make up from 1–2% to 5% of all uterine malignancies. These are highly aggressive tumors whose contribution to the total mortality from uterine malignancies is about 16.4% [1, 5–7]. According to the recent find-

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ings, the greatest role in the clinical behavior and prognosis of this malignancy is attributed to the epithelial component due to a higher mitotic index, the frequent presence of lymphovascular invasion (LVI), and expression of endothelial growth factors [3, 4, 8–13]. In addition to age, other risk factors for its occurrence were observed, such as obesity, previous tamoxifen therapy, long-term exposure to estrogen, previous therapeutic irradiation of the pelvis, nulliparity, positive BRCA1 gene mutation, socioeconomic factor in African American women, etc. [12, 14, 15]. In patients with tumors in the early stages of the disease, in stage I according to the International Federation of Gynecology and Obstetrics (FIGO), survival reaches up to 50%, which is still significantly lower than the five-year survival rate in early endometrioid carcinoma, which exceeds 80% [16]. In the last stage of the disease (FIGO IV), the five-year survival rate is below 10%, and the occurrence of recurrence is less frequent locally compared to the occurrence of distant metastases [17, 18]. For now, the most significant prognostic predictors are the stage and histological grade of the disease, the depth of myometrial invasion, LVI, and the age of the patient [5]. Surgical treatment remains the most effective and commonest treatment for patients with localized disease, and chemotherapeutics commonly used are ifosfamide, cisplatin, carboplatin, paclitaxel, and doxorubicin [18, 19].

Methods

The study was conducted as a retrospective analysis of medical data documentation of patients with a diagnosis of UCS who were surgically treated at the Oncology Institute of Vojvodina, Serbia, in a period of 10 years, from the beginning of 2009 to the end of 2018. The research was approved on December 23, 2021, by the Ethics Committee of the Oncology Institute of Vojvodina (No. 4/21/2-4093/2-4).

The analysis of medical records included a total of 31 female patients. For one patient it was not possible to find information about the FIGO stage of the disease and she could not be included in the presented results regarding the spread of the disease and survival depending on the FIGO stage of the disease.

From the pathohistological parameters of the tumor, data were collected on: a) histological grade, whereby grades 1 and 2 were considered as well differentiated, while grade 3 was considered as poorly differentiated carcinosarcoma; b) histological type, depending on the characteristics of the sarcoma component – homologous and heterologous; c) presence or absence of LVI; d) the thickness of the involvement of the myometrium by tumor tissue (more or less than ½ of total thickness of the myometrium); e) tumor size in the largest diameter measured in mm.

Data were also collected on the applied therapeutic procedures. Survival of patients was analyzed based on progression-free survival (PFS), as well as the overall survival (OS) of the patient, expressed in months from surgery to death or until the end of 2021. Every patient was followed for at least three years from the moment of the operation.

Statistical analysis

Descriptive statistics were performed separately for continuous and ordinal variables. Age data were classified into two categories, with patients divided into two age groups (younger than the median value and older than the median value). For other categorical variables (homologous/heterogenous type, LVI, depth of invasion, lymphadenectomy, additional therapy, PFS code, OS code, three-year survival), frequency analysis was performed. A Cox regression model was used to test the significance of predictors on OS and PFS. This model determines the significance of the influence of individual predictor variables on the dependent variable (univariate analysis) and their joint influence (multivariate analysis). The cumulative survival of patients was shown using the Kaplan-Meier analysis. IBM-SPSS 21 and Statistica 14.0.0.15 software were used for statistical data processing; a significance threshold of 0.05 was used.

The aim of this study was to analyze the most important clinical and pathohistological characteristics of UCSs on operated patients, as well as to determine which of those factors are affecting PFS and OS of patients.

Results

Analyzing the ages of the patients showed that the youngest patient at the time of the operation was 50, and the oldest was 76 years old. The median age of patients was 67 years.

At the time of surgery, 80% of patients were in the early stages of the disease (FIGO I and II), of which the largest number were in the first stage of the disease (56.7%) (Table 1).

Table 1

Stage of the spread of the disease according to the FIGO classification

FIGO stage	Value
I	17 (56.70)
II	7 (23.30)
III	5 (16.70)
IV	1 (3.30)
Total	30 (100.00)

FIGO – International Federation of the Gynecology and Obstetrics.
All values are given as numbers (percentages).

Observing the histological grade of the tumors, more than 3/4 (78.6%) of patients in the observed group had poorly differentiated tumor grades 2 and 3 (high grade) (Figure 1a). Regarding the histological type of the tumor, 4/5 (80.8%) was homologous (made of tissues native to the uterus) and 1/5 (19.2%) was heterologous (made of tissues non-native to the uterus) (Figure 1b).

The tumor size ranged from 35 to 90 mm, while the median value was 61 mm.

LVI was present in 55.2% of patients (Figure 1c). Myometrial invasion of more than 50% was observed in 2/3 (73.3%) of patients (Figure 1d).

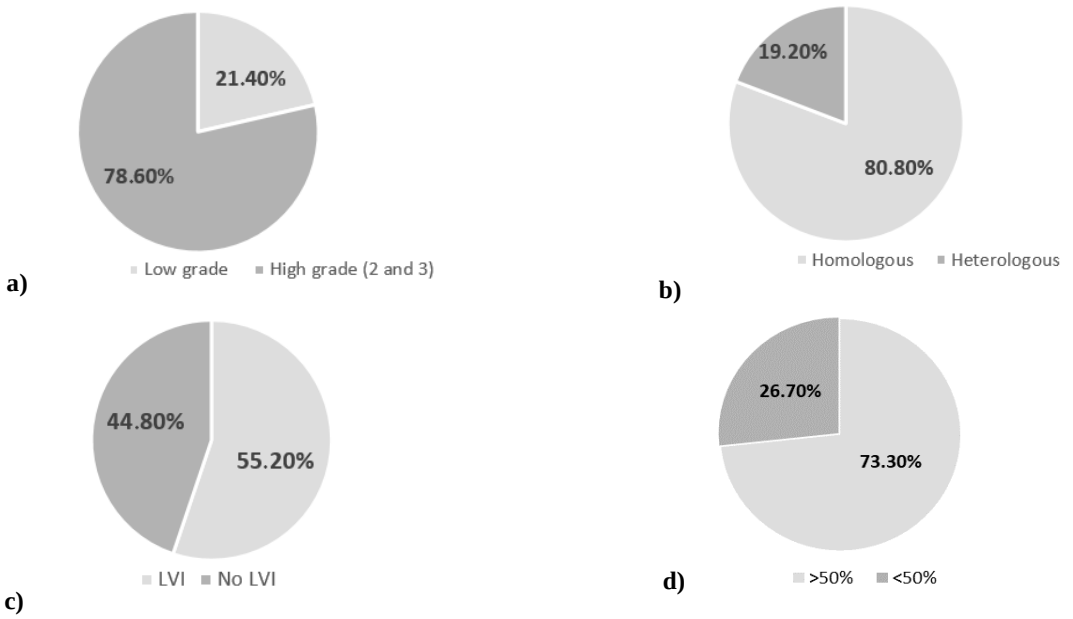

Fig. 1 – a) Histological grade of the tumor; b) Histological tumor subtype; c) Presence of lymphovascular invasion (LVI); d) Thickness of myometrium.

The median value of progression-free survival (PFS) in all stages of the disease was 28 months, while the median value of OS was 39 months (Table 2).

Median length of PFS and OS depended on whether the disease was in early (FIGO I and II) or advanced stages (FIGO III and IV) (Table 3).

Half (51.6%) of the patients experienced disease progression during the follow-up period, while three-year survival was 64.3%. At the end of 2021, 41.9% of those treated died (Figure 2).

Only in 16.1% of patients, all of whom were in the FIGO I stage of the disease, no adjuvant therapy was

Table 2

Parameters of progression-free survival and overall survival

Survival (months)	Mean	Med	Min–Max	SD
Progression-free survival	40.94	28.00	2.00–138.00	36.07
Overall survival	45.61	39.00	3.00–138.00	35.08

Med – median; Min–Max – minimum-maximum; SD – standard deviation.

Table 3

Parameters of progression-free survival and overall survival depending on the stage of the disease

Survival (months)/Stage	n	Mean	Med	Min–Max	SD
Progression-free survival					
FIGO I and II	24	45.17	45.50	2.00–138.00	38.98
FIGO III and IV	6	29.17	23.50	11.00–59.00	19.32
Overall survival					
FIGO I and II	24	48.88	50.00	3.00–138.00	36.88
FIGO III and IV	6	37.67	28.00	11.00–91.00	28.55

n – number of patients. For other abbreviations, see Tables 1 and 2.

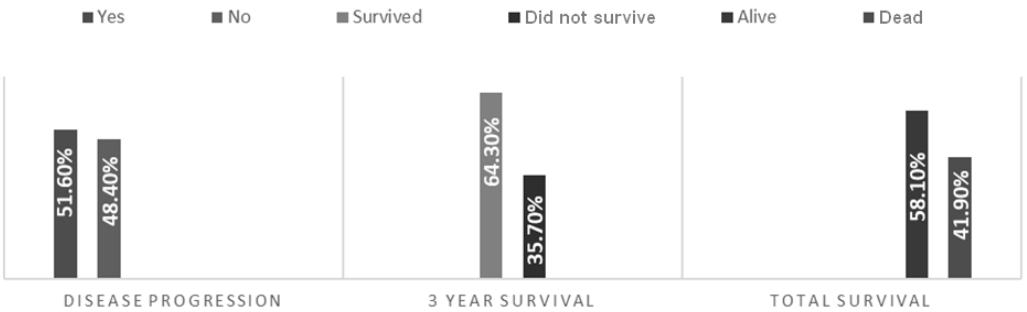

Fig. 2 – Disease progression, 3-year survival, and total survival.

applied in addition to surgery (Table 4).

Lymphadenectomy was performed in 54.8% of patients.

There were 15 (48.39%) patients in the first group (older than median 67 years) and 16 (51.61%) in the second. The results of the performed χ^2 test (Table 5) show the existence of statistically significant differences between younger and older patients when it comes to LVI, which was more often present in the group of younger patients (χ^2 = 3.892, p = 0.049), while in the other examined parameters, no significant differences were found between these two groups.

Of all the examined parameters, the greatest influence on the choice of therapeutic procedure had a histological grade (Table 6).

To evaluate the significance of the impact of individual predictors on PFS and OS, two Cox regression models were formed (Table 7).

When looking at the individual predictors of PFS in the Cox regression analysis, only LVI stands out as a statistically significant predictor ($p < 0.05$). However, the Cox multivariate regression model is overall statistically significant

Table 4

Applied therapeutic procedures

Parameter	Value
Surgery only	5 (16.10)
Adjuvant radiation therapy	4 (12.90)
Adjuvant chemotherapy	10 (32.30)
Adjuvant chemoradiation therapy	12 (38.70)
Total	31 (100.00)

All values are given as numbers (percentages).

Table 5

Differences in observed parameters between younger and older patients

Parameter	χ^2	p
FIGO	1.402	0.705
Histological type	1.704	0.192
Lymphovascular invasion	3.892	**0.049**
Depth of tumor invasion	0.386	0.544
Histological grade	0.039	0.843
Lymphadenectomy	0.457	0.491
Therapeutic procedure	5.707	0.127
Survival without a progression	0.819	0.366
Total survival	1.551	0.213

FIGO – International Federation of the Gynecology and Obstetrics. Bolded value is statistically significant.

Table 6

Influence of observed parameters on the choice of therapeutic procedure

Parameter	χ^2	p
Age (years)	0.068	0.127
FIGO	5.723	0.767
Histological grade	6.410	**0.043**
Depth of tumor invasion	0.697	0.264
Lymphovascular invasion	0.142	0.342

FIGO – International Federation of the Gynecology and Obstetrics. Bolded value is statistically significant.

Table 7

Influence of individual predictors on progression-free survival and overall survival

Parameters	Progression-free survival			Overall survival		
	df/b¤	F-value/SE b♦	p-value	df/b¤	F-value/SE b♦	p-value
FIGO	3	0.64	0.5959	3	0.49	0.6924
FIGO I & II vs. III & IV	1	0.93	0.3419	1	0.48	0.4952
Homologous/heterologous	1	0.71	0.4070	1	0.69	0.4147
Lymphovascular invasion	1	4.98	0.0342	1	3.07	0.0908
Depth of tumor invasion	1	2.81	0.1051	1	2.09	0.1597
Histological grade	1	0.98	0.3321	1	0.41	0.5255
Lymphadenectomy	1	1.71	0.2013	1	1.86	0.1838
Therapeutic procedure	3	0.47	0.7085	3	0.58	0.6318
Age (years)	-0.41¤	1.36♦	0.7629	-0.51¤	1.34♦	0.7115
Tumor size (mm)	-0.13¤	0.53♦	0.8012	-0.15¤	0.52♦	0.7731

FIGO – International Federation of the Gynecology and Obstetrics; ¤ – value of coefficient b; ♦ – standard error (SE) of coefficient b.

($\chi^2 = 21.59$, $p = 0.0103$), which means that all predictors considered together significantly affect PFS. If the selected predictors are observed individually, none of the observed factors is a statistically significant predictor of OS, but in this case, LVI stands out for its predictive significance (Table 7). However, in this case, as well, the multivariate regression model is entirely statistically significant ($\chi^2 = 22.18$, $p = 0.0083$), i.e., all examined parameters considered together significantly affect the overall length of survival.

Discussion

Although UCS was first described in 1852, there is currently no scientific consensus on which one of these factors could be used as a reliable prognostic predictor [4, 20]. The largest number of patients is at the end of the seventh or the beginning of the eighth decade of life [2, 16, 21, 22]. In some studies, age was shown as a bad predicting factor [4]. However, in our study, there was no statistically significant difference between younger and older patients in OS and PFS. The prognostic significance of age was not proven by some other authors either [23]. Traditionally, the stage of the disease, according to the FIGO classification, is one of the most important parameters when making decisions about therapeutic procedures and conclusions about outcomes [12, 24]. In our study, 80% of patients were in the early stages (FIGO I and II), and 20% were in the advanced stages of the disease (FIGO III and IV). Initially, a higher frequency of the early stages of the disease was recorded by some other researchers, although the diagnosis in the advanced stages is much more frequent compared to endometrioid tumors, which is attributed to the aggressive nature of the tumor [19, 24–26]. The high number of patients in the early stages can be partially explained by the early onset of symptoms that bring the patient to the doctor, such as painless postmenopausal bleeding. Most researchers have proven that there are differences in the length of survival depending on the FIGO stage [12, 24]. Hapsari et al. [24] determined even three times higher OS in patients in the early stage of the disease. The results of our study did not show a statistically significant effect of disease stage on the PFS and OS. The same conclusion was reached by Şükür et al. [13]. This can be partially explained by the small number of patients in the advanced stages of the disease, especially in FIGO stage IV in our study group.

In our studied group, the homologous type of tumor was significantly more frequent (80.8%), even though the ratio of these two types was more uniform in some other studies [25]. In the biological behavior of tumors, the mesenchymal component is given less and less importance, which is in accordance with our findings, where there is no significant difference in either OS or PFS depending on the characteristics of this component. The same conclusions were reached by other authors [10]. According to current knowledge, the clinical behavior and prognosis of the disease are primarily attributed to the epithelial component of the neoplasm, which is most often a histologically poorly differentiated carcinoma [10]. In the largest number (78.6%) of cases, a high grade, i.e., poor differentiation, was present in our research. It was similar in other comparative studies [16, 27]. In our study, the histological grade did not prove to be a significant predictor of PFS and OS, which was also the conclusion reached by Pautier et al. [28] and Yilmaz et al. [29]. The aggressive nature of the investigated neoplasm is indicated by the frequent presence of LVI and significant tumor invasion into the myometrium [10, 19], which were also recorded in the patients in our study. Thus, as many as 73.3% of examined patients had myometrial invasion greater than 50% of its total thickness, which is in accordance with the data on the predominance of poorly differentiated tumors in the examined group. The presence of LVI and the greater depth of myometrial invasion by the tumor are attributed in the literature to a greater potential for metastasis and recurrence [4]. In line with this is the fact that the presence of LVI is significantly more frequent in carcinosarcoma compared to other types of endometrial cancer [30]. Although some authors determined that both mentioned parameters are significant predictors of the reduction of PFS and OS length, in our research, statistical significance was proven only when it comes to the existence of LVI [2, 8, 29, 31, 32].

Operative treatment, primarily hysterectomy with bilateral salpingo-oophorectomy is still the primary modality of treatment and is used for curative purposes in FIGO stages I-III, while in FIGO stage IV, it is used for palliative purposes [2, 19]. All patients included in our research were treated operatively. Although operative treatment remains the “gold standard”, the high rate of recurrence and metastases, as well as available literature data, indicate the need for multimodal treatment [31]. In our research, adjuvant therapy (radiotherapy, chemotherapy, or their combination) was prescribed for 83.9% of the treated patients, which is more than the data of some other authors, sometimes almost double [19]. In our study, when choosing additional treatment methods, the histological grade of the tumor proved to be the most influential factor. Although in practical work, the stage of the disease remains one of the most significant factors influencing the choice of therapeutic modality, the absence of statistical significance of the influence of this factor in our study can be explained by the significant predominance of patients in the early stages of the disease in the examined group. Data on the effectiveness of radiotherapy differ in the literature and remain a subject of debate [2, 4, 17, 24, 33]. Gunther et al. [34] point out that its application reduces the possibility of local recurrence by as much as 50%. However, Callister et al. [35] point to the absence of significant differences regarding the length of OS of patients. In our research, no significant influence of the application of radiotherapy as the only adjuvant modality on the length of either overall or PFS was proven, as some other authors who dealt with this issue also came to [19, 24, 36]. In our study, no statistically significant relationship between the use of adjuvant chemotherapy and survival parameters was observed. Although the application of adjuvant chemotherapy leads to a prolongation of both PFS and OS according to a large number of authors, in some studies, it was observed that in patients in the FIGO I and II stages (to which our patients mainly belonged), there is no significant prolongation of life regardless of the applied chemothera-

py [19]. Nevertheless, regardless of the contradictory results that the researchers reached in their research, the use of chemotherapy is recommended in all stages of the disease after complete resection of the tumor [31]. The combination of radiotherapy and chemotherapy was the most common treatment modality for patients in our study (38.7%). Today, it is considered that this type of therapy is the most effective, especially in patients with advanced disease, and that it prolongs OS more than any modality used alone [19, 22]. However, both in our research and in the research of some other authors, such conclusions were not confirmed [24]. The role of pelvic and paraaortic lymphadenectomy in patients with UCS is still not completely clear. In our observed group, lymphadenectomy was performed in 54.8% of patients in all FIGO disease stages. This is somewhat lower than the findings of other authors [13, 25]. The performed testing did not show a statistically significant difference in the length of OS and PFS between patients who did and those who did not undergo lymphadenectomy. In the group of observed patients, progression of the disease, i.e., occurrence of metastases or recurrence, occurred in 51.6% of examined patients. This result is consistent with the findings of other studies, according to which recurrence rates are usually between 47–67% [4]. The median value of the follow-up period in which disease progression did not occur in our study group was 28 months. Some authors also recorded significantly shorter periods. Thus, in the study by McEachron et al. [22], the median PFS was only 13 months, while it should be considered that the proportion of patients with advanced disease in their study group was triple higher than in our study group. Patients in the early stages of the disease (FIGO I and II) had the median PFS in the follow-up period of 45.5 months, while in the late stages (FIGO III and IV), it was 23.5 months. Other authors also found significant differences in PFS depending on the stage of the disease. In their study, Hapsari et al. [24] recorded a median PFS of 39 months in FIGO I and II, while it was only nine months in FIGO III and IV. The median value of OS of all patients during the follow-up period is 39 months. In the early stages of the disease (FIGO I and II), the median OS was 50 months, while in the late stages (FIGO III and IV), the median OS was 28 months. Data on OS in the literature vary, depending on the length of the follow-up period and the proportion of patients in different stages of the disease in the examined samples. Kurnit et al. [25] recorded a length of total medial OS of 39 months, the same as in our study, while some researchers recorded lower values, i.e., 23 months in the study by Matsuzaki et al. [37]. The three-year survival of patients in our study was 35.7%, which is slightly higher than the values obtained in other studies, but within the expected values considering the predominant presence of early stages of the disease in the examined sample. By the end of the follow-up period, 41.9% of patients died, which shows data similar to those recorded by other authors. Thus, Yilmaz et al. [29], for example, recorded a mortality rate of 35% within the follow-up period.

Conclusion

Our research showed the joint influence of the examined clinical and pathohistological factors parameters on PFS and OS of patients with UCS. The only independent parameter that showed a statistically significant impact on survival is LVI. In order to improve the survival of patients suffering from UCS, additional multicenter randomized trials are needed to reach a consensus regarding therapeutic methods and prognostic parameters.

Conflict of interest

The authors declare no conflict of interest.

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