**Neuroendocrinology Letters** Volume 36 No. 8 2015
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
*Web of Knowledge / Web of Science:* Neuroendocrinol Lett
*Pub Med / Medline:* Neuro Endocrinol Lett

ORIGINAL ARTICLE

# Survival and risk factors associated with uterine sarcomas and carcinosarcomas in stage I and II

**Jozef Visnovsky [1], Erik Kudela [1], Pavol Slavik [2], Milan Krkoska [1], Pavol Buocik [1], Peter Szepe [2], Jan Danko [1]**

1 Department of Gynecology and Obstetrics, Jessenius Faculty of Medicine, University Hospital Martin, Slovak Republic
2 Department of Pathologic Anatomy, Jessenius Faculty of Medicine, University Hospital Martin, Slovak Republic

*Correspondence to:* Erik Kudela, MD.
Jessenius Faculty of Medicine
Department of Obstetrics and Gynecology
Kollarova 2 , 03601, Martin, Slovakia.
TEL: +421 902 300 017; FAX: +421 43 4203 242; E-MAIL: kudela.erik@gmail.com

*Submitted: 2015-11-03 Accepted: 2015-12-18 Published online: 2015-01-23*

*Key words:* **uterine sarcoma; carcinosarcoma risk factor; survival; lymphadenectomy**

Neuroendocrinol Lett 2015; **36**(8):750–757 **PMID:** 26921575 NEL360815A06 

## Abstract

**OBJECTIVE:** Uterine sarcomas are rare mesodermal malignant tumors with an incidence between 0.5 and 3.3 cases per 100,000 females per year. Most sarcomas are aggressive tumors leading to poor overall survival rates and only limited therapeutic options. The aim of this study was to evaluate the risk factors for uterine sarcomas and carcinosarcomas, and to identify the factors influencing the survival rate.
**SUBJECTS AND METHODS:** We conducted a retrospective study with twenty-nine patients who were diagnosed with uterine sarcoma and thirty-four patients with carcinosarcoma between the years 1990 and 2006 at the Oncogynecologic center at the University Hospital in Martin, Slovakia. We focused on the analysis of the risk factors and survival rate of early stages I and II.
**RESULTS:** We confirmed highly statistically significant values for the inverse correlation between survival and tumor size, positive lymph nodes, high mitotic activity, vascular invasion, positive peritoneal cytology, elevated CA-125, smoking and BMI in sarcoma and carcinosarcoma group ($p<0.001$ for all factors). The use of lymphadenectomy had no effect on survival of all patients.
**DISCUSSION:** Sarcomas and carcinosarcomas are aggressive tumors leading to poor overall survival rates and only limited therapeutic options. As there is no consensus on specific treatment, an individual approach based on evaluation of known risk factors is essential.

**Abbreviations:**

| | |
|---|---|
| ESS | - endometrial stromal sarcoma |
| LMS | - leiomyosarcoma |
| AS | - adenosarcoma |
| CS | - carcinosarcoma |
| OS | - overall survival |
| HR | - hazard ratio |
| FIGO | - International Federation of Gynecology and Obstetrics |
| BMI | - body mass index |
| HMA | - high mitotic activity |

## INTRODUCTION

Uterine sarcomas are rare mesodermal malignant tumours with an incidence between 0.5 and 3.3 cases per 100,000 females per year (American Cancer Society 2012). The overall annual incidence rate in Slovakia in 1999–2003 was 1.1 per 100000 females in the population per year, accounting for 2.4% of all uterine corpus malignancies (Klacko *et al.* 2012). They were classified in four main categories: carcinosarcomas 40%, leiomyosarcomas (LMS) 40%, endometrial stromal sarcomas (ESS) 10–15%, "other" sarcomas 5–10%. Carcinosarcomas have recently been reclassified as either a differentiated or metaplastic form of endometrial carcinoma. Despite such reclassification, carcinosarcoma is still included in most retrospective studies of uterine sarcomas as well as in the 2003 World Health Organization (WHO) classification (D´Angelo *et al.* 2012). As far as the staging system is concerned, a new International Federation of Gynaecology and Obstetrics (FIGO) classification was designed in 2009 (Prat 2010).

All the causes for the majority of the uterine sarcomas are unclear. However, some risk factors were identified. Pelvic radiation therapy used to treat other malignancies is connected with the development of uterine sarcomas. Nevertheless, the linkage to radiation is difficult, since the uterine sarcoma may be diagnosed 5–25 years after the exposure. Uterine sarcomas are also twice as common in Afro-American women when compared to Caucasian or Asian women. The most common genetic abnormalities found in CS and LMS are p53, KRAS and PTEN mutations. These mutations are missing in low-grade ESS, but nuclear β-catenin expression is seen in up to 40% of ESS tumors (Kildal *et al.* 2009).

The aim of this study was to further evaluate and compare the risk factors for uterine sarcomas and carcinosarcomas, as well as to identify the factors influencing the survival rate.

## SUBJECTS AND METHODS

Between the years 1990 to 2006 twenty –nine patients with uterine sarcoma and thirty-four patients with carcinosarcoma were diagnosed in stage I and II at the Oncogynecologic center for Northern and Central Slovakia at the University Hospital in Martin, Slovakia.. The results of monitoring for this period were evaluated retrospectively with ethical committee approval for the study. The period of the follow-up was 5 years.

Uterine sarcomas were restaged according to the new FIGO classification from 2009. ESS were divided into the two subgroups: endometrial stromal sarcomas (2 patients) and high-grade undifferentiated sarcomas (4 patients). The size of sarcoma was measured in the biggest diameter of the tumor by CT scan and histopathological evaluation. Positive lymph node status was defined as the histopathologic confirmation of lymph node metastases obtained during pelvic lymphadenectomy. High mitotic activity/index was considered positive when more than 10 mitoses per 10 high-power fields were found. CA-125 was considered to be positive at a level greater than 35 mg/ml.

Data were analyzed using PASW Statistics version 18 (IBM, New York, USA). Quantitative variables were compared using the T-test, and categorical variables were compared with the $\chi^2$ test. Survival rates and hazard ratios (HR) were analyzed using the Kaplan-Meier method and Cox regression model analysis. The $p$-values <0.05 were considered to be statistically significant.

## RESULTS

From 816 patients treated for uterine cancer treated in the Oncogynecologic center in Martin, sarcomas accounted for 4.9% of cases (29 cases in stage I and II, 11 cases in stage III and IV). The mean age at the time of the diagnosis was 54.95±9.85 (range 41–84). Carcinosarcomas were represented by 34 patients (4.2% of uterine cancer cases). Leiomyosarcomas were the most common type of uterine sarcoma– 21 patients (72.4%) The remaining sarcomas were ESS (6 patients – 20.7%) and adenosarcomas (AS) (2 patients – 6.9%) (Table 1).

Every variable was compared as far as LMS and CS are concerned. We did not do an analysis of AS and ESS because of the small number of patients in both groups. Highly statistically significant values were confirmed for the inverse correlation between survival and tumor size, positive lymph nodes, high mitotic activity, vascular invasion, positive peritoneal cytology, elevated CA-125, smoking and BMI ($p$<0.001) in CS and LMS group. The age of the patients correlated with the tumor size ($p$<0.01), high mitotic index ($p$<0.05), vascular invasion ($p$<0.01), positive peritoneal cytology ($p$<0.05) and elevated CA-125 ($p$<0.05). Histopathology variables also correlated between each other ($p$<0.05) in both groups.

Primary treatment option for LMS group was hysterectomy with bilateral adnexectomy in 61.9% cases (13 patients). In carcinosarcoma group the lymphadenectomy was performed in 28 patients (82.4%) according to the recommendations. 3-year/5-year survival rate in different groups of tumors was as followed: CS 30/15 patients (88.2%/44.1%), LMS 17/8 (80.9%/38.1%), ESS 4/2 (66.7%/33.3%) and AS 2/1 (100%/50%). Using the Kaplan-Meier method, we considered the strongest factors related to patient survival (Figures 1–4). The use of lymphadenectomy as a therapeutic procedure is also analyzed. In the end we calculated the hazard ratio for each risk factor using the Cox regression test. The highest values of HR were associated with tumor size, lymph node status, mitotic index, vascular invasion and age. Significant values were also found in the association with BMI and smoking (Table 2).

**Tab. 1.** Basic risk factors, tumour characteristics and treatment.

| | CS (34) | LMS (21) | ESS (6) | AS (2) |
|---|---|---|---|---|
| Age | 55.29±11.25 | 53.57±8.8 | 58.67±5.43 | 52.5±2.12 |
| survival (5-year period) | 49.91±11.59 | 48.33±11.33 | 48±11.51 | 57±4.24 |
| stage T | | | | |
| T1 | 22 (64.7%) | 15 (71.4%) | 3 (50%) | 2 |
| T2 | 12 (35.3%) | 6 (28.6% ) | 3 (50%) | 0 |
| stage N | | | | |
| N0 | 22 (64.7%) | 4 (57.1%) | 3 (50%) | 1 |
| N1 | 12 (35.3%) | 3 (42.9%) | 3 (50%) | 1 |
| High mitotic activity | | | | |
| Absent | 23 (67.6%) | 10 (47.6%) | 3 (50%) | 2 |
| Present | 11 (32.4%) | 11 (52.4%) | 3 (50%) | 0 |
| Lymphovascular invasion | | | | |
| Absent | 19 (55.9%) | 10 (47.6%) | 6 (100%) | 1 |
| Present | 15 (44.1%) | 11 (52.4%) | 0 | 1 |
| Tumour size | 2.48±0.84 | 6.61±3.42 | 1.93±0.87 | 1.85±0.92 |
| CA-125 | 29.4±14.72 | 21.4±9.76 | 31.87±13.31 | 33.35±10.68 |
| Peritoneal cytology | | | | |
| Absent | 26 (76.5%) | 18 (85.7%) | 6 (100%) | 2 |
| Present | 8 (23.5%) | 3 (14.3%) | 0 | 0 |
| Menopausal status | | | | |
| premenopausal | 17 (50%) | 9 (42.9%) | 2 (33.3%) | 2 |
| postmenopausal | 17 (50%) | 12 (57.1%) | 4 (66.67%) | 0 |
| Smoking | | | | |
| non-smokers | 22 (64.7%) | 13 (61.9%) | 4 (66.67%) | 1 |
| Smokers | 12 (35.3%) | 8 (38.1%) | 2 (33.3%) | 1 |
| Body mass index (BMI) | 29.74±2.32 | 29.53±2.7 | 30.63±2.88 | 31.35±3.61 |
| Parity | | | | |
| Nullipara | 19 (55.9%) | 8 (38.1%) | 3 (50%) | 1 |
| Multipara | 15 (44.1%) | 13 (61.9%) | 3 (50%) | 1 |
| Uterine bleeding | | | | |
| Absent | 21 (61.8%) | 12 (57.1%) | 2 (33.3%) | 0 |
| Present | 13 (38.2%) | 9 (42.9%) | 4 (66.67%) | 2 |
| Abdominal pain | | | | |
| Absent | 22 (64.7%) | 13 (61.9%) | 3 (50%) | 1 |
| Present | 12 (35.3%) | 8 (38.1%) | 3 (50%) | 1 |
| No symptoms | | | | |
| No | 27 (79.4%) | 16 (76.2%) | 4 (66.67%) | 2 |
| Yes | 7 (20.6%) | 5 (23.8%) | 2 (33.3%) | 0 |
| Lymphadenectomy | | | | |
| LAE- | 6 (17.6% ) | 13 (61.9%) | 0 | 0 |
| LAE+ | 28 (82.4%) | 8 (38.1%) | 6 (100%) | 2 |
| Chemotherapy | | | | |
| CHT- | 21 (61.8%) | 9 (42.9%) | 2 (33.3%) | 1 |
| CHT+ | 13 (38.2%) | 12 (57.1%) | 4 (66.67%) | 1 |
| Radiotherapy | | | | |
| RT- | 6 (17.6% ) | 6 (28.6%) | 0 | 0 |
| RT+ | 28 (82.4%) | 15 (71.4%) | 6 (100%) | 2 |

(CS- carsinocarcoma, LMS – leiomyosarcoma, ESS – endometrial stromal sarcoma, AS – adenosarcoma, LAE- without lymphadenectomy, LAE+ with lymphadenectomy, CHT- without chemotherapy, CHT+ with chemotherapy, RT- without radiotherapy, RT+ with radiotherapy)

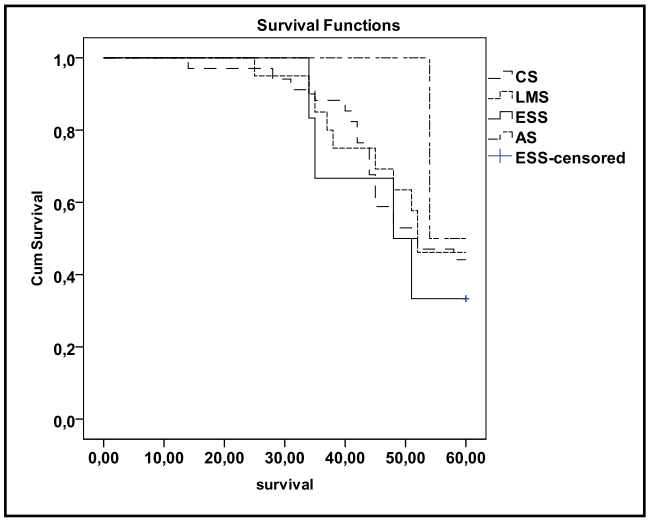


**Fig. 1.** 5-year survival analysis (numbers in months) – types of tumours, insignificant p value (CS – carcinosarcoma, LMS – leiomyosarcoma, ESS – endometrial stromal sarcoma, AS – adenosarcoma).

## DISCUSSION

Sarcomas are rare tumors accounting for 3–7% of uterine cancer. In our study the ratio of uterine sarcomas was 4.9%, which corresponds with the literature facts. Because of their incidence there is no consensus on prognostic and risk factors. Treatment strategies – the use of lymphadenectomy, chemotherapy and radiotherapy and their appropriate combination are also questionable.

*Leiomyosarcomas*

Leiomyosarcomas usually arise *de novo* from uterine smooth muscle, although rarely they may arise in a pre-existing leiomyoma (Wilkinson *et al.* 2001). They occur mainly in the 45–55 years age group. In our group of patients the mean age was 53.57±8.81. ESS and LMS appear in patients of younger ages than MMMT and

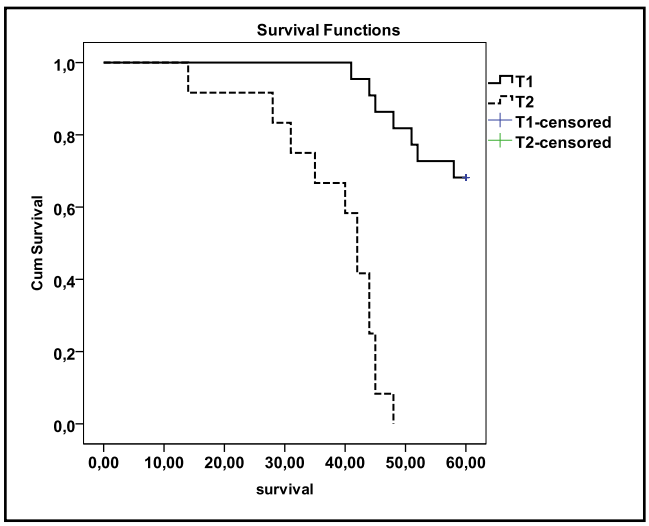


**Fig. 2a.** 5-year survival analysis (numbers in months) for tumor stage T (T1, T2), $p<0.001$ in CS group.

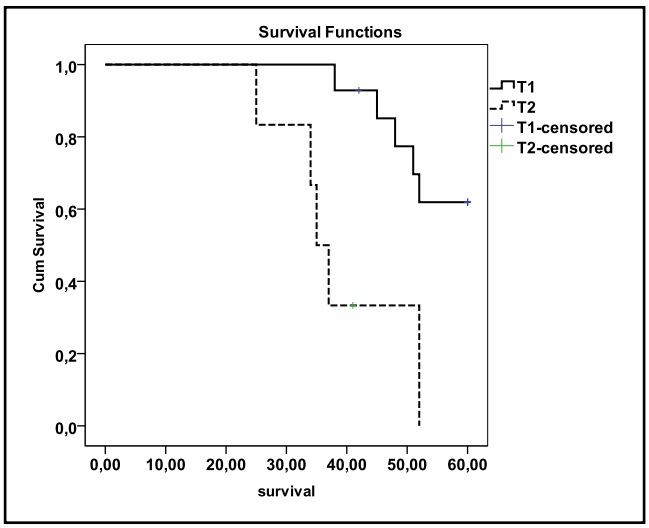


**Fig. 2b.** 5-year survival analysis (numbers in months), for tumor stage T (T1, T2), $p<0.001$ in LMS group.

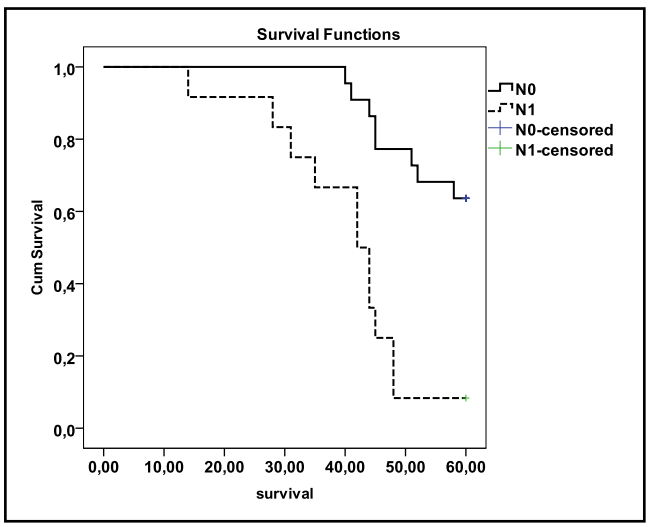


**Fig. 3a.** 5-year survival for lymph node status (N0, N1), $p<0.001$ in CS group.

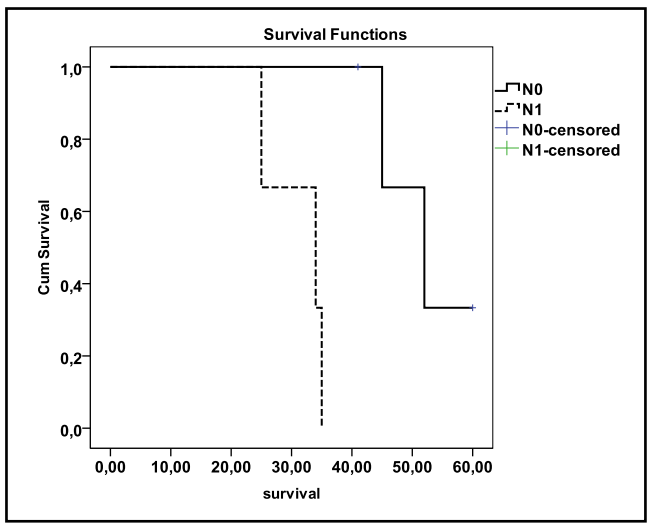


**Fig. 3b.** 5-year survival for lymph node status (N0, N1), $p<0.001$ in MS group.

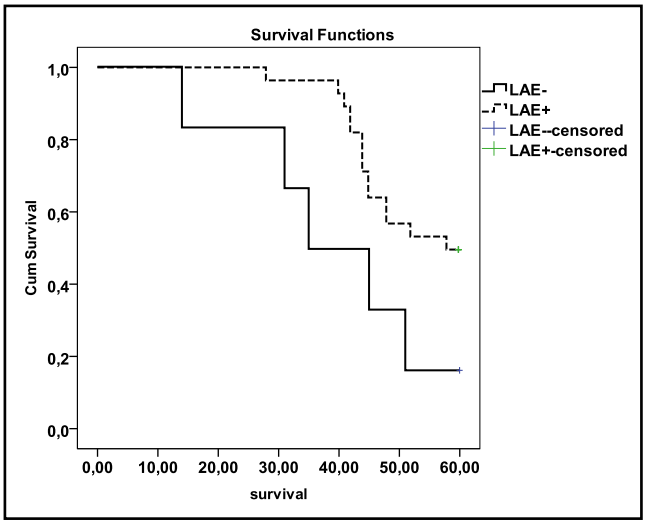


**Fig. 4a.** Effect of lymphadenectomy (LAE) on survival in CS group – p value insignificant (LAE- without lymphadenctomy, LAE+ with lymphadenectomy).

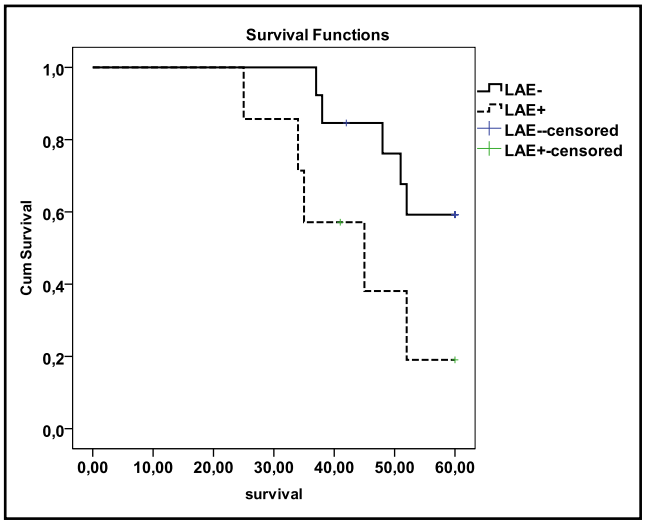


**Fig. 4b.** Effect of lymphadenectomy (LAE) on survival in LMS group – p value insignificant (LAE- without lymphadenctomy, LAE+ with lymphadenectomy).

**Tab. 2.** Hazard ratios for risk factors.

| variable | CS | | | LMS | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *p*-value | Hazard ratio | 95% CI | *p*-value |
| age <60;≥60 | 4.41 | 3.08–22.99 | $p<0.001$ | 8.42 | 1.95–36.31 | $p<0.01$ |
| smoking | 0.87 | 0.33–2.28 | $p=0.771$ | 5.11 | 1.61–16.23 | $p<0.01$ |
| menopausal status | 1.83 | 0.74–4.57 | $p=0.194$ | 10.66 | 2.27–50.05 | $p<0.01$ |
| BMI <30; ≥30 | 2.8 | 1.09–7.24 | $p<0.05$ | 1.51 | 0.48–4.71 | $p=0.479$ |
| parity | 0.5 | 0.19–1.33 | $p=0.166$ | 0.36 | 0.12–1.09 | $p=0.072$ |
| bleeding | 0.2 | 0.06–0.67 | $p<0.05$ | 1.21 | 0.40–3.60 | $p=0.738$ |
| abdominal pain | 1.04 | 0.41–2.64 | $p=0.940$ | 2.63 | 0.87–7.97 | $p=0.088$ |
| no symptoms | 1.26 | 0.42–3.81 | $p=0.678$ | 0.99 | 0.27–3.60 | $p=0.985$ |
| T stage (T1 vs T2) | 14.19 | 4.30–46.85 | $p<0.001$ | 5.46 | 1.77–16.89 | $p<0.01$ |
| N stage (N0 vs N1) | 5.72 | 2.19–14.93 | $p<0.001$ | * | * | * |
| HMA | 7.6 | 2.93–19.72 | $p<0.001$ | * | * | * |
| Vasc. Invasion | 5.37 | 1.99–14.50 | $p<0.01$ | 6.03 | 1.63–22.30 | $p<0.01$ |
| T. size <3 cm; ≥3 cm | 7.63 | 2.72–21.43 | $p<0.001$ | 1.32 | 0.17–10.27 | $p=0.790$ |
| peritoneal cytology | 3.54 | 1.36–9.19 | $p<0.01$ | 1.34 | 0.36–4.96 | $p=0.660$ |
| CA-125 <35.0; ≥35.0 | 3.29 | 1.27–8.51 | $p<0.05$ | * | * | * |

(all sarcomas, CS - carcinosarcomas, LMS – leiomyosarcomas, HMA – high mitotic activity, T.size – tumor size, BMI – body mass index, vasc. Invasion – vascular invasion, * - absent data for LMS category)

adenosarcomas (Benito *et al.* 2009). However, we did not find any difference between the different types of tumors. In our study, the average age of the patients was highest with leiomyosarcomas, but the value was not significant when compared with the others. The strongest prognostic factor is the stage of the tumor (Gadducci *et al.* 1996). In stage I, the 5-year overall survival (OS) in our study was 64.3% (27/42) and in stage II 4.8% (1/21), $p<0.001$ (Figure 2a,3a). The highest average tumor size was in the leiomyosarcoma group – 6.61±3.42 cm, ($p<0.05$) (Table 1). The prognostic value of histological type is also not clear (Figure 1) and has been long debated, with the exception of low-grade endometrial stromal sarcoma, which has excellent prognosis (Gaducci *et al.* 1996). The highest survival rates were in the group of leiomyosarcomas, but the difference between the LMS group and those with the other types of tumours was small.

Leiomyosarcomas are characterised by hypercellularity, severe nuclear atypical and a high mitotic rate

exceeding 15 mitotic figures per 10 high-power fields (Rauh-Hain *et al.* 2013). There is also high positivity of immunohistochemistry markers Ki67, p53 and p16 (Chen & Yang 2008). The spread of leiomyosarcomas is mainly haematogenous, with the dominant pattern appearing outside the small pelvis. This type of tumour is significantly larger than the other sarcomas (Benito *et al.* 2009). Because of the tumour size, a common symptom is abdominal pain caused by distension (38.1% in our LMS group). Another common symptom is uterine bleeding (42.9% in our LMS group). There was no significant difference between the subgroups of sarcomas and carcinosarcomas as far as the bleeding was concerned; it was present in 44.4% of patients. Interestingly, uterine bleeding was associated with better survival $p<0.05$. No similar observation appears in the literature. One possible answer is that bleeding forces the patient to visit a doctor, leading to appropriate management. Asymptomatic sarcomas can grow continuously without the patient ever knowing about them. Cure rates range from 20–60%, and the recurrence rate is approximately 70% for stage I and stage II disease (Feng *et al.* 2013). In our study the survival rate (5-year OS) of LMS is 47.6%. . In the Norwegian series (Abeler *et al.* 2009) patients with leiomyosarcomas limited to the uterus had a poor prognosis, with a 5-year overall survival rate of 51% at stage I and 25% at stage II. The main criteria used to determine treatment and prognosis are the mitotic count, necrosis and nuclear atypia (Gaducci *et al.* 1996, Feng *et al.* 2013). In a study by Kapp *et al.* involving 1,396 patients with uterine leiomyosarcomas, the independent predictors of disease-free survival (DFS) included age, race, stage, grade and primary surgery (Kapp *et al.* 2008).

When we evaluated the hazard ratios of the risk factors we found that the risk of death was increased by 8.42-times in the group of patients older than 60. In their study, Wu *et al.* revealed an 11.07-fold increase in the risk of death in women older than 50 compared with younger patients (Wu *et al.* 2006). A similar increase was evaluated in a group of smokers (HR: 5.11), postmenopausal women (HR: 10.66) and BMI over 30 (HR: 1.51). As far as tumour size is concerned, with tumors larger than 3 cm HR was 1.3 (univariate analysis –Table 3).

Standard surgical treatment consists of abdominal hysterectomy and bilateral salpingoophorectomy (Gaducci *et al.* 1996, Feng *et al.* 2013), but oophorectomy was not found to have an independent impact on survival (Kapp *et al.* 2008). Pelvic and/or paraaortic lymphadenectomy (LAE) is not indicated unless macroscopic changes are present. Lymph nodal status has a limited prognostic relevance (Kapp *et al.* 2008, Major *et al.* 1993) because of low-risk lymph node involvement (4%) (Fong *et al.* 1993), which is why pelvic lymphadenectomy is not a part of primary therapy. We performed lymphadenectomy in only 7 patients at the beginning of the study, and the percentage of positive lymph nodes is very high; however, a small group of patients cannot be evaluated in this way (Figure 4a). A gynaecological oncological group (GOG) study of 59 patients reported positive lymph nodes in only 3.5% of patients.

There is no proven benefit of any adjuvant treatment, and only two randomised trials have even explored the benefit of such treatment (Omura *et al.* 1985, Reed *et al.* 2008). We also confirmed this fact, finding no difference in OS. Reed *et al.* investigated 103 patients – through either observation or pelvic radiation (51Gy in 28 fractions) – and there was no benefit for patients receiving radiotherapy. Similar results occurred with the use of chemotherapy – doxorubicin – with recurrence in 11 of 25 patients in the doxorubicin group and 14 of 23 in the control group (Reed *et al.* 2008).

*Carcinosarcomas*
*(malignant mixed Müllerian tumours – MMMT)*

These highly malignant mixed tumors were previously considered the most common uterine sarcomas. Now it is widely accepted that carcinosarcomas either arise from a common pluripotential cell with divergent differentiation and sarcomatous component develops from carcinomatous component by a metaplastic process or dedifferentiation. Our study is retrospective that is why we evaluate also this group of tumors as a part of sarcomas.

They appear more frequently in postmenopausal women. Clinical symptoms include vaginal bleeding and uterine enlargement (D´Angelo *et al.* 2010); 37% of patients with carcinosarcomas have a history of pelvic irradiation (Silverberg *et al.* 1990). Mesenchymal component is either homologous or heterologous tissue. The heterologous forms include embryonal rhabdomyosarcoma and malignant skeletal muscle. The tumour protrudes like a polyp through the cervical channel in half of the patients (Gadducci *et al.* 1996, Feng *et al.* 2013).

Patients with carcinosarcomas made up 4.2% of all fiagnosed endometrial malignancies in our center. The incidence is again similar to that in the literature. Factors associated with a poor prognosis include stage, grade, adnexal spread and lymph node metastasis. The most important prognostic factor, as in the LMS group, is tumour stage (Major *et al.* 1993, Sartori *et al.* 1997) (Figure 2b, 3b). Relevant prognostic factors of CS and LMS also include high mitotic activity of the tumour (HMA or HMI – high mitotic index), positive peritoneal cytology, lymphovascular invasion and positive oncomarker CA-125 (Table 4).The HR for tumour size and T stage is 7.63 and 14.19, respectively. These results are even more crucial than in the LMS group. The 5-year OS was 68.2% (15/22) for stage I and 0% (0/12) for stage II; $p<0.001$. In the retrospective analysis by Bosquet *et al.* (Gonzales Bosquet *et al.* 2010), the 5-year DFS was 59% for stages I–II.

Surgical treatment should consist of exploratory laparotomy, total abdominal hysterectomy, bilateral salpingoophorectomy, omentectomy, aspiration of abdominal fluid for cytological evaluation, pelvic and paraaortic

lymph node dissection and tumour debulking (Gadducci *et al.* 1996, Benoit *et al.* 2005). There is also a high incidence of lymph node metastasis (Temkin *et al.* 2007). In our study lymphadenectomy was performed on 28 of the 34 patients. In the group with lymphadenectomy we found a significant difference ($p<0.05$) regarding OS (16.7% 5-year OS without LAE vs. 50.0% 5-year OS with LAE) (Figure 4b). Positive lymph nodes were present in 12 patients (35.3%). Women with either pelvic or paraaortic lymph-node metastasis had a significantly greater failure rate than those without metastasis (Rauh-Hain *et al.* 2013). Moreover, we did not find any correlation between adjuvant therapy and the OS of patients. A recent European Organisation for Research and Treatment of Cancer (EORTC) randomised study confirmed that while external pelvic radiation decreases pelvic relapse it does not improve overall survival for carcinosarcomas (Wilkinson & Rollason 2001).

*Endometrial stromal sarcomas*

according to the latest WHO classification, endometrial stromal malignancies include endometrial stromal sarcomas and undifferentiated or poorly differentiated endometrial sarcomas (Rauh-Hain *et al.* 2013, De Fusco *et al.* 1989) . ESS contributes to 15–25% of uterine sarcomas (Chang *et al.* 1990). Our study contained only 6 patients in ESS group (9.5%); thus statistical analysis cannot be performed correctly, as the results would be impaired. Most patients are in the age range of 42–53 years. These tumours are more commonly seen in premenopausal women, but in our sample all of the patients were postmenopausal. Typical symptoms include vaginal bleeding, abdominal pain and uterine enlargement (Chang *et al.* 1990).

The 5-year survival rate is 80–100%, but 37–60% of patients show recurrence after a long period of time and 15–25% die (Gadducci *et al.* 1996). Recurrence usually occurs locally, and patients benefit from aggressive cytoreductive surgery to remove cell macroscopic sites of disease. The standard treatment for ESS is a hysterectomy with bilateral salpingoophorectomy. If the parametria are involved, a radical hysterectomy is the best choice. Lymphadenectomy in ESS does not improve survival. In the work of Chan *et al.* (Chan *et al.* 2008), nodal involvement was 6.0% in grade I and 8.9% in grade 2. We performed lymphadenectomy on all 6 patients with ESS with 5-year survival 33.3%.

*Other risk factors for the development of CS, LMS and ESS*

Obesity is a potential risk factor for uterine sarcomas (Schwartz *et al.* 1996). Schwartz and co-workers reported elevated risks of CS, LMS and ESS among patients with a body mass index over 27 kg/m$^2$. The average BMI for CS group was 29.74±2.32; 29.53±2.7 for LMS group and 30.63±2.88 for ESS group and was associated with a higher death rate in all groups (Table 3). Logically, a high BMI index is associated with a spectrum of other diseases, which is why we cannot include obesity as an independent risk factor for uterine sarcomas and OS. No specific association was found between either type of uterine sarcoma and smoking. The incidence of US has been described as being higher among women who have never been married than in women who have been married, and it has been explained by nulliparity among never-married women (Schwartz *et al.* 1991). We found no correlation between parity and other sarcoma tumor characteristics, but the hazard ratio for death rate was decreased.

## CONCLUSION

Most sarcomas and carcinosarcomas are aggressive tumors leading to poor overall survival rates and only limited therapeutic options. As there is no consensus on specific treatment, an individual approach is essential. Our study included only tumors in stage I and II. Here we can see the great malignant potential of sarcomas, because survival dramatically drops even in the first two stages. The only type with a good prognosis is low-grade ESS, which has an OS of 84–100% for stage I. The most important risk factors for leiomyosarcomas and carcinosarcomas according to our results are: age, smoking and body mass index. Tumor size and vascular invasion were connected with the poor survival rate in both groups. On the other hand uterine bleeding in leiomyosarcoma group appeared to be a good prognostic factor (HR 0.2).

## ACKNOWLEDGEMENTS

This work was supported by the project "Molecular diagnostics of cervical cancer" (ITMS: 26220220113), Comenius University Grants 303/2011, 242/2012 and VEGA Grant 1/0271/12.

REFERENCES

1 Abeler VM, Røyne O, Thoresen S, Danielsen HE, Nesland JM, Kristensen GB (2009). Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. Histopathology. **54**(3): 355–64.
2 American Cancer Society (2012). Cancer Facts & Figures 2012. American Cancer Society: Atlanta.
3 Benito V, Lubrano A, Arencibia O, Andújar M, Alvarez E, Medina N, Falcón JM, Falcón O (2009). Clinicopathologic analysis of uterine sarcomas from a single institution in the Canary Islands. Int J Gynaecol Obstet. **107**(1): 44–9.
4 Benoit L, Arnould L, Cheynel N, Goui S, Collin F, Fraisse J, Cuisenier J (2005). The role of surgery and treatment trends in uterine sarcoma. Eur J Surg Oncol. **31**(4): 434–42.
5 Chen L, Yang B (2008). Immunohistochemical analysis of p16, p53, and Ki-67 expression in uterine smooth muscle tumors. Int J Gynecol Pathol. **27**(3): 326–32.
6 D'Angelo E, Prat J (2010). Uterine sarcomas: a review. Gynecol Oncol. **116**(1): 131–9.
7 Feng W (2013). Stages I to II WHO 2003-defined low-grade endometrial stromal sarcoma: how much primary therapy is needed and how little is enough? Int J Gynecol Cancer. **23**(3): 488–93.

8 Fong Y, Coit DG, Woodruff JM, Brennan MF (1993). Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg. **217**(1): 72–7.
9 Gadducci A, Landoni F, Sartori E, Zola P, Maggino T, Lissoni A, Bazzurini L, Arisio R, Romagnolo C, Cristofani R (1996). Uterine leiomyosarcoma: analysis of treatment failures and survival. Gynecol Oncol. **62**(1): 25–32.
10 Gonzalez Bosquet J, Terstriep SA, Cliby WA, Brown-Jones M, Kaur JS, Podratz KC, Keeney GL (2010). The impact of multi-modal therapy on survival for uterine carcinosarcomas. Gynecol Oncol. **116**(3): 419–23.
11 Kapp DS, Shin JY, Chan JK (2008). Prognostic factors and survival in 1396 patients with uterine leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. Cancer. **112**(4): 820–30.
12 Kildal W, Pradhan M, Abeler VM, Kristensen GB, Danielsen HE (2009). Beta-catenin expression in uterine sarcomas and its relation to clinicopathological parameters. Eur J Cancer. **45**(13): 2412–7.
13 Klačko M, Babala P, Mikloš P, Zuzák P, Chorváth M, Ondrušová M, Ondruš D (2012). Sarkómy maternice – prehľad (eng. Uterine sarcomas – a review). Klin Onkol. **25**(5): 340–345.
14 Major FJ, Blessing JA, Silverberg SG, Morrow CP, Creasman WT, Currie JL, Yordan E, Brady MF (1993). Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. **71**(4 Suppl): 1702–9.
15 Omura GA, Blessing JA, Major F, Lifshitz S, Ehrlich CE, Mangan C, Beecham J, Park R, Silverberg S (1985). A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group Study. J Clin Oncol. **3**(9): 1240–5.
16 Prat J (2009). FIGO staging for uterine sarcomas. Int J Gynaecol Obstet. **104**(3): 177–8.
17 Rauh-Hain JA, Oduyebo T, Diver EJ, Guseh SH, George S, Muto MG, del Carmen MG (2013). Uterine leiomyosarcoma: an updated series. Int J Gynecol Cancer. **23**(6): 1036–43.
18 Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, et al. (2008). Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer. **44**(6): 808–18.
19 Sartori E, Bazzurini L, Gadducci A, Landoni F, Lissoni A, Maggino T, Zola P, La Face B (1997). Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study. Gynecol Oncol. **67**(1): 70–5.
20 Silverberg SG, Major FJ, Blessing JA, Fetter B, Askin FB, Liao SY, Miller A (1990). Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. Int J Gynecol Pathol. **9**(1): 1–19.
21 Wilkinson N, Rollason TP (2001). Recent advances in the pathology of smooth muscle tumours of the uterus. Histopathology. **39**(4): 331–41.
22 Wu TI, Chang TC, Hsueh S, Hsu KH, Chou HH, Huang HJ, Lai CH (2006). Prognostic factors and impact of adjuvant chemotherapy for uterine leiomyosarcoma. Gynecol Oncol. **100**(1): 166–72.