# The prognostic relevance of histological type in uterine sarcomas: a Cooperation Task Force (CTF) multivariate analysis of 249 cases

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**Summary**

*Purpose of investigation:* The objective of this retrospective multicenter study was to assess the prognostic relevance of histologic type in uterine sarcomas.

*Methods:* The hospital reports of 249 patients with uterine sarcomas were reviewed. Surgery was the initial therapy for all patients. Histologic type was leiomyosarcoma in 95 cases, low-grade endometrial stromal sarcoma (ESS) in 19, high-grade ESS in 34, and carcinosarcoma in 101. Postoperative treatment was given without well-defined protocols. Median follow-up of survivors was 97 months.

*Results:* In the whole series 2-year, 5-year, and 10-year survival rates were 53.5%, 41.6%, and 35.8%, respectively, and median survival was 31 months. At univariate analysis survival was significantly related to stage (p = 0.0001), mitotic count (p = 0.0001), and histologic type (low-grade ESS vs leiomyosarcoma vs carcinosarcoma vs high-grade ESS, median: not reached vs 27 months vs 21 months vs 16.5 months, p = 0.0011), but not to postoperative therapy and patient age. The Cox model revealed that tumor stage, mitotic count and histologic type were independent prognostic variables for survival. In detail, the risk of death was significantly lower for low-grade ESS (risk ratio [RR] = 0.257; 95% confidence interval [CI] = 0.071-0.931) and carcinosarcoma (RR = 0.509; 95% CI = 0.324-0.799) when compared to leiomyosarcoma. Conversely, no significant difference in survival was found between leiomyosarcoma and high-grade ESS.

*Conclusions:* Histologic type is an independent prognostic variable for survival in uterine sarcomas. Low-grade ESS has the best clinical outcome, whereas leiomyosarcoma has the poorest one. It is noteworthy that, when adjusting for stage and mitotic count, leiomyosarcoma has a significantly worse prognosis than carcinosarcoma.

*Key words:* Uterine sarcoma; Leiomyosarcoma; Low-grade endometrial stromal sarcoma; High-grade endometrial stromal sarcoma; Carcinosarcoma; Prognosis.

## Introduction

Sarcomas of the uterus account for 1-5% of all uterine malignancies [1-4]. The most common histologic types are represented by leiomyosarcoma, endometrial stromal sarcoma (ESS) and carcinosarcoma [1, 5].

According to the data from nine US population-based cancer registries (1973-1981), the annual incidence of leiomyosarcoma, ESS and carcinosarcoma is 0.64/100,000, 0.19/100,000, and 0.82/100,000 women, respectively [6]. As suggested by Norris and Taylor [7], ESSs can be separated into low-grade and high-grade categories according to the maximal mitotic count (less or more than 10 mitoses per 10 high-power fields [HPF]). This classification system has persisted as the worldwide standard [8-11]. However other authors [12, 13] suggested that the separation into low- and high-grade ESS should be based not only on the mitotic count, but on a combination of pathologic features, including also degree of cytologic atypia, vascular architecture, pattern of myometrial infiltration, and presence or absence of tumor necrosis and hemorrhage.

Revised manuscript accepted for publication March 15, 2002

Uterine sarcomas generally have an aggressive clinical behaviour, with a great tendency to local recurrence, and, even more, to distant spread. Several clinical, pathological and biological variables have been assessed as predictors of survival, but the prognostic influence of the different factors has not been well-defined largely because uterine sarcomas are rare and no single institution has a wealth of experience with these malignancies.

In detail, the prognostic relevance of histologic type is still debated [1, 2, 14-20].

The aim of this retrospective study was to assess whether the histologic type is an independent prognostic variable for survival in a series of 249 patients with uterine sarcomas treated in five different Italian gynecologic oncology centers.

## Materials and Methods

We reviewed the hospital reports, including surgical notes and pathologic reports, of 249 patients with uterine sarcomas treated at the Departments of Gynecology and Obstetrics of the University of Brescia, Milan-Bicocca, Padua, Pisa, and Turin between 1980 and 1994. These patients had been included in previous papers, which assessed in detail the pattern of treat-

ment failures [21-23]. The histological material was reviewed by the same pathologist in each center.

Leiomyosarcoma was defined histologically as a smooth-muscle tumor with cytologic atypia and five or more mitoses per 10 HPF.

ESSs were separated into low-grade and high-grade categories according to the criteria suggested by Norris and Taylor [7]. The diagnosis of carcinosarcoma was based on the histologic criteria established by Kempson and Bari [5].

Surgery was the initial therapy for all patients. Patients were staged retrospectively according to a modification of the International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer, as suggested by Berchuck *et al.* [24]. Staging information was derived from surgical notes and pathologic reports.

Postoperative therapy was given without well-defined protocols.

Median follow-up of survivors was 97 months (25% quantile, Q1= 60 months; 75% quantile, Q3= 148 months).

Age, histologic type, tumor stage, mitotic count and postoperative therapy were related to survival.

The cumulative probability of survival from the time of surgery was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of survival functions across strata defined by categories of prognostic variables.

A multiple regression analysis based on the Cox proportional hazard model was used to jointly test the relative importance of variables as predictors of survival.

## Results

Median age of patients was 59 years (range, 21-84 years). Histologically, 95 patients had a leiomyosarcoma, 19 had a low-grade ESS, 34 had a high-grade ESS, and 101 had a carcinosarcoma (Table 1). Tumor stage was I in 140 patients, II in 14, III in 49, and IV in 46. Mitotic count was < 10 mitoses per 10 HPF in 57 cases, between 11 and 20 mitoses per 10 HPF in 78, and > 20 mitoses per 10 HPF in 114.

Table 1. — *Tumor stage by histologic type.*

| Histologic type | Stage I | II | III | IV |
|---|---|---|---|---|
| Leiomyosarcoma | 63 (66.3%) | 2 (2.1%) | 13 (13.7%) | 17 (17.9%) |
| Low-grade-ESS | 13 (68.4%) | 1 (5.3%) | 3 (15.8%) | 2 (10.5%) |
| High-grade-ESS | 18 (52.9%) | 1 (2.9%) | 8 (23.5%) | 7 (20.6%) |
| Carcinosarcoma | 46 (45.5%) | 10 (9.9%) | 25 (24.8%) | 20 (19.8%) |

Note: ESS: endometrial stromal sarcoma.

Table 2. — *Variables predictive of survival by Cox proportional hazard model.*

| Variable | Wald Chi-Square | Risk ratio | 95% Confidence Limits | p value |
|---|---|---|---|---|
| Stage | | | | |
| I | | 1 | | |
| II | 1.58242 | 1.680 | 0.749-3.768 | 0.2084 |
| III | 16.04944 | 2.586 | 1.625-4.117 | 0.0001 |
| IV | 38.90724 | 4.613 | 2.853-7.457 | 0.0001 |
| Mitotic count (mitoses per 10 HPF) | | | | |
| < 10 | | 1 | | |
| 11-20 | 3.07388 | 1.887 | 0.928-3.837 | 0.0796 |
| > 20 | 12.69189 | 3.346 | 1.722-6.502 | 0.0004 |
| Histologic type | | | | |
| Leiomyosarcoma | | 1 | | |
| High-grade-ESS | 0.04206 | 0.951 | 0.586-1.543 | 0.8375 |
| Carcino-sarcoma | 8.59031 | 0.509 | 0.324-0.799 | 0.0034 |
| Low-grade-ESS | 4.2778 | 0.257 | 0.071-0.931 | 0.0386 |

Note: ESS: endometrial stromal sarcoma.

Surgery consisted of total abdominal hysterectomy with or without monolateral salpingo-oophorectomy in 24 patients, total abdominal hysterectomy with bilateral salpingo-oophorectomy in 145, total abdominal hysterec-

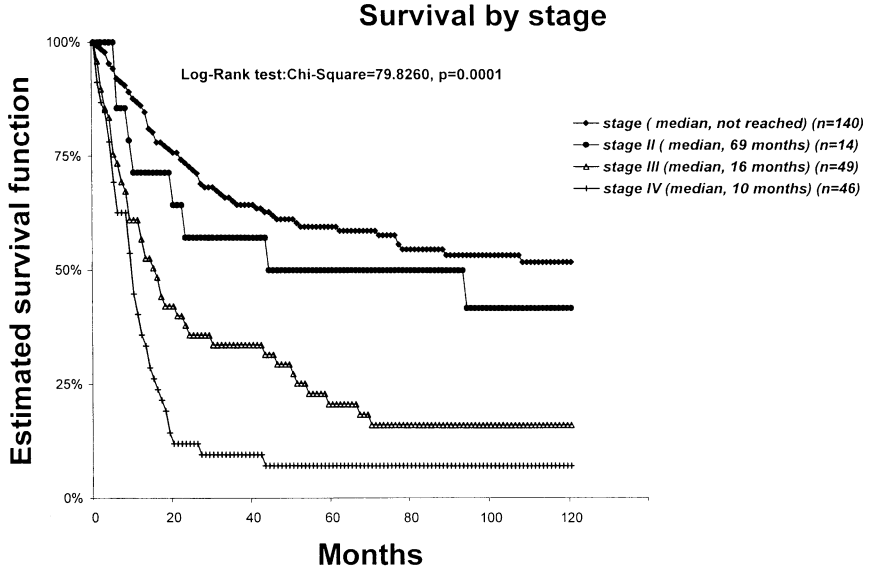


Figure 1. — Survival of patients with uterine sarcoma by stage.

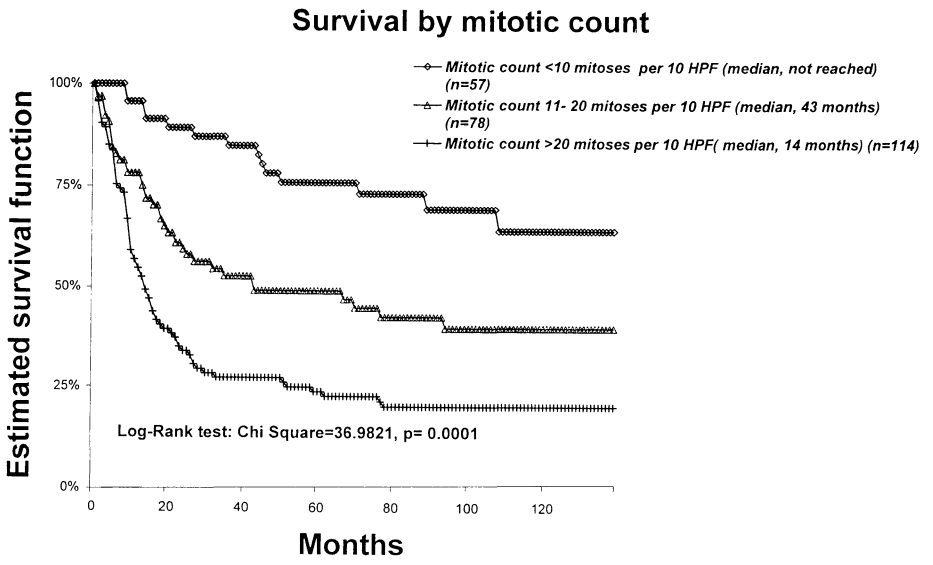


Figure 2. — Survival of patients with uterine sarcoma by mitotic count.

tomy with bilateral salpingo-oophorectomy and pelvic and/or para-aortic selective lymphadenectomy in 48, total abdominal hysterectomy with bilateral salpingo-oophorectomy and tumor debulking in 23, and explorative laparotomy in nine. Postoperative treatment was as follows: external pelvic irradiation in 69 patients, chemotherapy in 59, external pelvic irradiation plus chemotherapy in six, progestins in four, and no further therapy in 111.

In the whole series 2-year, 5-year, and 10-year survival rates were 53.5%, 41.6%, and 35.8% respectively, and median survival was 31 months.

At univariate analysis survival was significantly related to tumor stage (p = 0.0001) (Figure 1), mitotic count (p = 0.0001) (Figure 2), and histologic type (p = 0.0011) (Figure 3), but not to postoperative therapy (any treatment versus no further treatment) or patient age (< 59 versus > 59 years) (data not shown).

Cox model showed that tumor stage, mitotic count and histologic type were independent prognostic variables for survival (Table 1). The risk of death was significantly lower for low-grade ESS and carcinosarcoma when compared to leiomyosarcoma, whereas no significant difference in survival was found between leiomyosarcoma and high-grade ESS.

## Discussion

The prognostic relevance of tumor stage, mitotic count and histologic type in uterine sarcomas has been widely investigated. All authors agree that the extent of tumor at

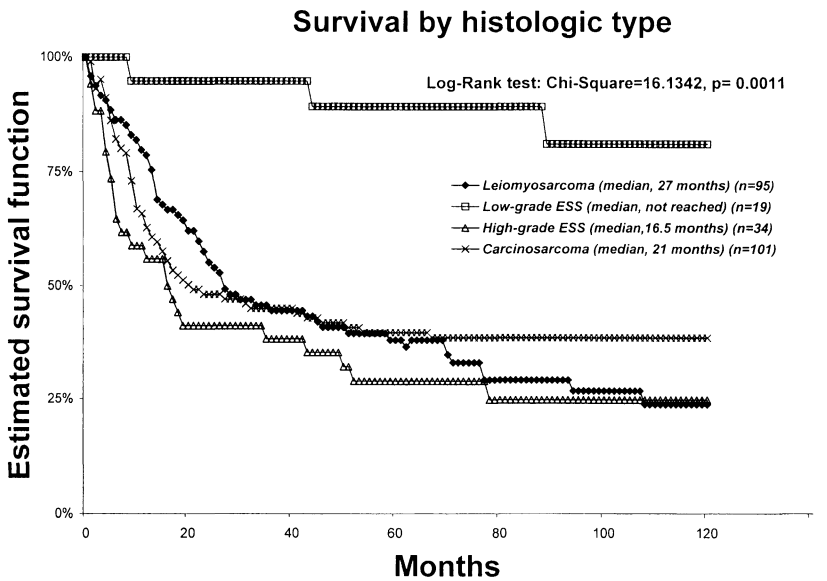


Figure 3. — Survival of patients with uterine sarcoma by histologic type.

diagnosis is a strong predictor of survival [3, 14-16, 20, 25-27]. For instance, in the study of Wolfson *et al.* [20], including 62 uterine sarcomas, median survival for stages I, II, III, and IV was 126, 43, 19, and 7 months, respectively ($p = 0.00004$).

Mitotic count has a strong prognostic significance for leiomyosarcoma [15, 28]. Kahanpaa *et al.* [15] found that a high mitotic activity was predictive of poor clinical outcome in ESS, whereas De Fusco *et al.* [10] observed no significant relationship between the number of mitoses and survival in patients with this malignancy. Most authors reported that the degree of mitotic activity of the sarcomatous component is not helpful in predicting the outcome of carcinosarcomas [15, 25, 27, 28]. In the present investigation both tumor stage and mitotic count are independent prognostic factors for survival in uterine sarcomas.

The prognostic value of histologic type has not yet been defined.

Some authors failed to detect significant differences in the outcome according to this variable [3, 4, 16-18, 20]. For instance, in a series of 74 patients, Covens *et al.* [4] noted no significant difference in survival according to histologic type, with the exclusion of low-grade ESS which experienced an excellent prognosis. Malmstrom *et al.* [18] found that 5-year survival probability was 0.38 for leiomyosarcoma, 0.50 for ESS, and 0.21 for carcinosarcoma ($p = 0.56$). Similarly histologic type failed to yield prognostic significance for survival in the study of George *et al.* [16] including 209 patients treated in 13 French oncology centers. Kahanpaa *et al.* [15] observed that 5- and 10-year survival rates were 39% and 27%, respectively, for the 51 patients with leiomyosarcoma, 61% and 37%, respectively, for the 23 patients with ESS, and 33% and 14%, respectively, for the 45 patients with carcinosarcoma. Ten-year survival rates were significantly worse ($p < 0.05$) in carcinosarcoma than in the other two histologic types, whereas no significant difference in 10-year survival was found between leiomyosarcoma and ESS. Salazar and Dunne [14] reported a 5-year survival of 40% for leiomyosarcoma, 39% for ESS and 23% for carcinosarcoma. These authors suggested that the better outcome of leiomyosarcoma was probably due to the higher incidence of stage I disease at presentation. In fact, stratifying patients by stage, all histologic types had similar survival rates.

In the study of Olah *et al.* [19], median survival was 17 months for the 215 patients with leiomyosarcoma, 13 months for the 152 patients with carcinosarcoma, 30 months for the 26 patients with ESS, and nine months for the 30 patients with other sarcomas. Although the log-rank test revealed no significant difference in survival by histologic type, multivariate analysis demonstrated that leiomyosarcoma had a poorer prognosis than carcinosarcoma when adjusting for stage, age and grade. In fact the risk ratio (RR) of death among patients with leiomyosarcoma compared to those with carcinosarcoma was 1.45 (95% confidence interval [CI] = 1.25-1.68, $p = 0.013$). In agreement with Olah *et al.* [19], the present study showed that carcinosarcoma has a lower risk of death (RR = 0.509; 95% CI = 0.324-0.799) when compared to leiomyosarcoma. On the other hand, according to recent insights carcinosarcomas are regarded as poorly differentiated endometrial carcinomas (27, 29, 30). Silverberg *et al.* [29] reported that among 40 carcinosarcoma cases with metastases, 30 showed carcinoma, six showed carcinoma and sarcoma, and four showed pure sarcoma. Therefore the carcinomatous element may be the driver that influences the biological behaviour of these tumors. Moreover the relatively high incidence of lymph nodal involvement [23, 28] and the sensitivity to cisplatin-based chemotherapy [23, 31-36] seem to suggest that carcinosarcomas behave like carcinomas rather than like soft tissue sarcomas.

Most papers assessing the prognostic role of histologic type in uterine sarcomas include ESS as a single category. In the present investigation low-grade ESS has been analyzed separately from high-grade ESS, since these tumors have completely different biological aggressiveness and clinical behavior [7, 9, 10, 13, 14, 37, 38). The present data confirmed that low-grade ESS has the best prognosis, with a significantly lower risk of death (RR = 0.257; 95% CI = 0.071-0.931) when compared to leiomyosarcoma, whereas there is no significant difference in survival between high-grade ESS and leiomyosarcoma.

## Conclusion

Histologic type is an independent prognostic variable for survival in uterine sarcomas. Low-grade ESS has the best clinical outcome, whereas leiomyosarcoma has the poorest one. It is noteworthy that, when adjusting for stage and mitotic count, leiomyosarcoma has a significantly worse prognosis than carcinosarcoma.

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