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ORIGINAL ARTICLE

# P53 as an Adverse Prognostic Factor in Patients with Uterine Sarcoma: A Retrospective Study of 113 Patients

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**ABSTRACT**

**Objective**: Uterine sarcoma is an aggressive malignancy with poor prognosis. This study aimed to identify prognostic factors for this rare cancer.

**Methods**: A retrospective study involved 113 patients with uterine sarcomas was performed, including 61 cases identified by systematic computer-based searches of the literature and 52 patients diagnosed with uterine sarcomas at the SYSUCC. Immunohistochemical analyses of p53, p27, CD146 and Ki-67 were performed in tissue samples collected from the 52 patients in this institution, and for p53 in 45 cases from the literature.

**Results**: Median survival was 30.7 months for all 113 patients . The 5-year overall survival (OS) and disease-free survival (DFS) rates were 44% and 46%, respectively. Patient age, disease stage, histological type, tumor size and p53 were significant prognostic indicators for survival. Positive expression of p53 was significantly correlated with adverse OS, FIGO stage, premenopause, age <50 years, tumor size >5 cm, negative lymph node metastasis and negative expressions of p27 and CD146. Cox regression analysis showed that FIGO stage and p53 were independent prognostic factors for OS and DFS.

**Conclusions**: Our results indicated that P53 is a potential, novel prognostic marker for patients with uterine sarcoma and serves to guide treatment strategies.

## INTRODUCTION

Uterine sarcoma, a rare and heterogeneous malignant tumor, accounts for only 3% of all uterine malignancies [1,2], with an annual incidence rate of less than 2 per 100,000 females [3]. According to traditional classification systems, there are three main subtypes of uterine sarcomas, including leiomyosarcoma (LMS), P53 is a nuclear phosphoprotein that can regulate cell proliferation and suppress tumor growth [6]. *P53* gene mutations occur in approximately half of all tumors from a wide range of human malignancies, and its overexpression is associated with poor prognosis [7–12]. Although there are several reports of p53 overexpression in uterine LMS, CS and ESS [13,14], most studies limited to the small sample size of available cases due to the rarity of this disease. Consequently, randomized, controlled clinical trials to determine optimal therapies and draw conclusions on overall management are difficult to perform.

In this study, we compiled data from patients diagnosed with uterine sarcomas from both our institution and those reported in the literature. This enabled us to perform a more comprehensive analysis of

potential prognostic factors for this rare tumor. Based on our findings, p53 was identified as a novel, independent prognostic biomarker in uterine sarcoma.

## MATERIALS AND METHODS

### Patient selection and treatment

This study involved 113 cases of uterine sarcoma, included 61 cases identified by systematic computer-based searches of the PubMed database and Chinese journals, and a further 52 patients who had received histological and clinical diagnoses between 1996 and 2011 at the Sun Yat-Sen University Cancer Center (SYSUCC), Guangzhou, China. Paraffin-embedded tissue samples were collected from these 52 patients. The study protocol was approved by the Medical Ethics Committee of SYSUCC.

Of the 61 cases identified in the literature, 47/61 (77.0%) had been diagnosed with malignant ESS and 14/61 (23.0%) with LMS. Of the 52 patients selected from SYSUCC, 25 (48.1%) had been diagnosed with malignant ESS, 16 (30.8%) with LMS, 7 (13.5%) with CS and 4 (7.7%) with other malignant histopathological subtypes. The patients' clinicopathological characteristics are given in Table 1, including age at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, histopathological subtypes, surgical procedure, postoperative adjuvant therapy, pelvic lymphadenectomy, lymph node involvement, tumor size, depth of stromal invasion, distant metastasis and recurrence and immunohistochemical staining patterns of p53, p27, CD146 and Ki-67.

The patients from SYSUCC were selected according to the following criteria: diagnosed with uterine sarcomas classified as LMS, CS or ESS according to the 2003 WHO diagnostic criteria; absence of preoperative anti-tumor treatment; without previous malignant disease or second primary tumors; and had complete clinicopathological and follow-up data. A total of 84 cases who did not meet these criteria were excluded. Patients were examined at 2-month intervals for the first 2 years, at 6-month intervals for the next 3 years and once a year thereafter. The median follow-up period was 63.3 months (range, 1–272.1 months). The primary end-point was any cancer-related death. Pathological diagnoses were conducted by experienced pathologists to ensure the accuracy of diagnosis. Clinical data was retrieved from medical records maintained in institutional databases. The follow-up data were updated in August, 2013.

For treatment, radical surgery usually consisted of total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. For patients with suspected common iliac or para-aortic lymph node involvement, para-aortic lymph node dissection was performed. Omentectomy was performed for patients with stage III ESS. Adjuvant radiotherapy and/or adjuvant chemotherapy was administered in patients with the following pathological risk factors: incomplete resection for late-stage cases, positive pelvic lymph nodes, vascular and lymphatic permeation, and high-grade ESS. Radiotherapy consisted of external pelvic irradiation (18 MV X-rays) using the multiportal technique. Daily fractions of 1.8–2.0 Gy were administered over 5–6 weeks for a total dose of 50 Gy. Chemotherapy mainly consisted of DDP (**cisplatin;** 60–75 mg/m$^2$, d1) + adriamycin (40–50 mg/m$^2$, d1) + DTIC (dacarbazine; 200 mg/m$^2$, d1–5) as the primary drugs and was administered in 3–5 courses over a 3-week period [15].

### Immunohistochemistry

Formalin-fixed and paraffin-embedded (FFPE) tumor tissue samples were used for immunohistochemical analysis. Sections (thickness, 4 μm) containing the area of the tumor with the highest grade of atypia and the least necrosis were cut from the paraffin block. The sections were mounted on slides and deparaffinized in xylene, ethanol and distilled water. Following incubation with 3% hydrogen peroxide in methanol for 10 min, the slides were boiled in citrate buffer solution (pH 6) for 10 min using a domestic pressure cooker. The sections were incubated overnight at 4°C with p53, p27, Ki-67 and CD146 antibodies (Zhongshan Golden Bridge Biotechnology, Beijing, China) at a dilution of 1:100. They were then washed with phosphate-buffered saline (PBS) and incubated for 30 min at 37°C with biotinylated goat anti-mouse secondary antibody (Lab Vision Corporation, Fremont, CA, USA) at a dilution of 1:25. All the slides were stained with 3,3' diaminobenzidine and scored for immunoreactivity based on the percentage of positive tumor cells (percent positivity) and the staining intensity (weak, moderate, strong). Slides with scores of (−) or (+) were recorded as negative; slides with scores of (++) and (+++) were recorded as positive. All results were confirmed by two experienced pathologists in a double-blind analysis. Of the 61 cases selected from the literature, 45 included immunohistochemical data for p53 that had been acquired by the same or similar immunohistochemical methods as above [16].

### Statistical analysis

Statistical analyses were performed using SPSS v. 16.0 software (SPSS Inc., Chicago, IL, USA). Prognosis was determined by overall survival (OS) and disease-free survival (DFS). OS was calculated from the time of histopathological diagnosis to the time of death or last recorded event. DFS was calculated from the time of surgical resection to the first evidence of recurrence or death from any cause. Life tables were used to calculate the survival rates and the median survival time. Survival curves were obtained by the Kaplan-Meier method. Log-rank tests were used for statistical comparison of curves. Univariate and multivariate Cox regression methods were adapted to evaluate potential prognostic factors, giving hazard ratios (HRs) and 95% confidence in-

tervals (CIs). *P* values <0.05 were considered statistically significant.

## RESULTS

### Clinicopathological features

The combined characteristics of the 113 patients are summarized in Table 2. The mean age was 48.3 years, and the median age was 47.5 years (range, 20–81 years). The clinical features were as follows: 14/113 (12.4%) had irregular menstrual bleeding; 36/113 (31.9%) had postmenopausal or abnormal vaginal bleeding; 13/113 (11.5%) had pelvic mass; 18/113 (15.9%) had abdominal pain; 32/113(28.3%) were diagnosed by accidentally. The histological subgroups were 72/113 (63.7%) ESS, 30/113 (26.5%) LMS, 7/113 (6.2%) CS and 4/113 (3.5%) other malignant histopathological types. FIGO staging showed that 63/113 (55.8%) of the tumors were at stage I–II, and 35/113 (30.9%) were at stage III–IV, while 15/113 (13.3%) samples had no available stage.

**Table 1: Patients' clinical and histopathological characteristics (n = 113)**

| Characteristics | Missing case | Sun Yat-Sen University Cancer Center | Chen Y, et al | Mao SQ, et al | Blom R, et al | Zhai YL, et al |
|---|---|---|---|---|---|---|
| **Age (years)** | 0 | | | | | |
| <50 | | 29 | 7 | 11 | 7 | 5 |
| ≥50 | | 23 | 8 | 4 | 10 | 9 |
| **Histologic type** | 0 | | | | | |
| ESS | | 25 | 15 | 15 | 17 | / |
| LMS | | 16 | / | / | / | 14 |
| CS | | 7 | / | / | / | / |
| Others | | 4 | / | / | / | / |
| **FIGO stage** | 15 | | | | | |
| I | | 28 | 8 | / | 12 | 10 |
| II | | 2 | 2 | / | 0 | 1 |
| III | | 17 | 3 | / | 2 | 2 |
| IV | | 5 | 2 | / | 3 | 1 |
| **Depth of muscular invasion** | 59 | | | | | |
| <1/2 | | 16 | / | / | 8 | / |
| ≥1/2 | | 23 | / | / | 7 | / |
| **Surgical procedure** | 39 | | | | | |
| TAH ± BSO/OT/PL/PLND | | 6 | 0 | / | 4 | / |
| TAH + BSO ± /PL/OT | | 21 | 11 | / | 10 | / |
| TAH + BSO+ PL± OT ± PLND | | 5 | 1 | / | 0 | / |
| Hysterectomy | | | | | | |
| With BSO | | 4 | 1 | / | 0 | / |
| Without BSO | | 8 | 2 | / | 1 | / |
| **Pelvic lymphadenectomy** | 37 | | | | | |
| Yes | | 8 | 1 | / | 0 | / |
| No | | 38 | 14 | / | 15 | / |
| **Postoperative adjuvant therapy** | 16 | | | | | |
| Chemotherapy | | 17 | 7 | 15 | 0 | / |
| Radiotherapy | | 1 | 1 | 0 | 5 | / |
| Hormonal therapy | | 1 | 0 | 0 | 1 | / |
| Chemotherapy and radiotherapy | | 13 | 1 | 0 | 3 | / |
| Chemotherapy and hormonal therapy | | 2 | 0 | 0 | 0 | / |
| Radiotherapy and hormonal therapy | | 1 | 0 | 0 | 0 | / |
| No adjuvant therapy | | 15 | 6 | 0 | 8 | / |
| **Distant metastasis and recurrence** | 32 | | | | | |
| Pelvic | | 8 | 1 | / | 2 | / |
| Pelvic and liver/ lung | | 4 | 0 | / | 3 | / |
| Lung | | 3 | 0 | / | 3 | / |
| Other parts | | 5 | 0 | / | 0 | / |
| Without | | 29 | 14 | / | 9 | / |
| **P53** | 16 | | | | | |
| Positive | | 19 | / | 11 | 5 | 9 |
| Negative | | 33 | / | 4 | 12 | 4 |
| **Ki67** | 61 | | | | | |
| Positive | | 15 | / | / | / | / |
| Negative | | 37 | / | / | / | / |
| **CD146** | 61 | | | | | |
| Positive | | 25 | / | / | / | / |
| Negative | | 27 | / | / | / | / |
| **P27** | | | | | | |
| Positive | 62 | 10 | / | / | / | / |
| Negative | | 41 | / | / | / | / |

**TAH**: total abdominal hysterectomy; **BSO**: **bilateral salpingo-oophorectomy; OT**: omentectomy; **PL**: pelvic lymphadenectomy; **PLND**: para-aortic lymph node dissection; **missing cases**: data was not present in the literature.

**Table 2**: **Relationship between overexpression of p53 and survival analysis in patients with uterine sarcoma (n = 113)**

| Variable | No | P53 | | | | OS | | | | DFS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MC | (+) | (-) | P value | 2-year (%) | 5-year (%) | median survival (weeks) | P value | 2-year (%) | 5-year (%) | median survival (weeks) | P value |
| **Age (years)** | | | | | | | | | | | | | |
| ＜50 | 59 | 7 | 34 | 18 | | 65 | 52 | 200 | | 74 | 49 | 139.5 | |
| ≥50 | 54 | 9 | 19 | 26 | **0.039** | 34 | 34 | 65.31 | **0.006** | 39 | 39 | 39.68 | **0.026** |
| **Histologic type** | | | | | | | | | | | | | |
| ESS | 72 | 15 | 20 | 37 | | 63 | 52 | 200 | | 68 | 49 | 138.5 | |
| LMS | 30 | 0 | 19 | 11 | | 29 | | 36.19 | **0.011** | 35 | | 30.63 | **0.011** |
| CS | 7 | 1 | 3 | 3 | | 56 | | 120 | | 56 | | 120 | |
| Other | 4 | 0 | 2 | 2 | 0.104 | 45 | | 36.67 | | 50 | | 140 | |
| **FIGO stage** | | | | | | | | | | | | | |
| I-II | 63 | 10 | 20 | 33 | | 65 | 65 | 200 | | 68 | 68 | 200 | |
| III-IV | 35 | 6 | 13 | 16 | **0.001** | 23 | 11 | 35.34 | **0.0001** | 44 | 22 | 52.19 | 0.062 |
| **Menopause status** | | | | | | | | | | | | | |
| Postmenopause | 52 | 7 | 14 | 31 | | 60 | 50 | 200 | | 70 | 50 | 139.98 | |
| Permenopause | 35 | 6 | 15 | 14 | **0.002** | 34 | 34 | 60.64 | 0.054 | 36 | 36 | 44.73 | 0.077 |
| **Tumor grade** | | | | | | | | | | | | | |
| HG | 25 | 9 | 3 | 13 | | 56 | 42 | 127.93 | | 85 | 85 | 160 | |
| LOW | 23 | 4 | 5 | 14 | **0.0001** | 64 | 64 | 160 | 0.528 | 36 | | 45 | **0.013** |
| **Tumor size** | | | | | | | | | | | | | |
| ＜5cm | 15 | 0 | 4 | 11 | | 92 | 92 | 140 | | 93 | 93 | 140 | |
| ≥5cm | 32 | 0 | 13 | 19 | 0.074 | 43 | 43 | 70.02 | **0.013** | 46 | 46 | 47.62 | **0.008** |
| **Lymph node metastasis** | | | | | | | | | | | | | |
| Positive | 9 | 2 | 6 | 1 | | 58 | | 80 | | 60 | | 80 | |
| Negative | 67 | 23 | 18 | 26 | **0.026** | 63 | 49 | 138.57 | 0.992 | 67 | 52 | 200 | 0.974 |
| **Depth of stromal invasion** | | | | | | | | | | | | | |
| <1/2 | 24 | 0 | 6 | 18 | | 57 | 57 | 200 | | 62 | 62 | 200 | |
| ≥1/2 | 30 | 1 | 10 | 19 | **0.043** | 49 | 49 | 117.38 | 0.407 | 55 | 55 | 160 | 0.469 |
| **P53** | | | | | | | | | | | | | |
| Positive | 44 | | | | | 20 | | 63.81 | | 41 | | 43.08 | |
| Negative | 53 | | | | | 63 | 55 | 200 | **0.007** | 65 | 52 | 200 | 0.099 |
| **Ki67** | | | | | | | | | | | | | |
| Positive | 15 | 0 | 2 | 13 | | 25 | | 17.19 | | 53 | | 15.01 | |
| Negative | 37 | 0 | 31 | 6 | 0.191 | 71 | 55 | 50 | 0.056 | 76 | 59 | 50 | **0.046** |
| **P27** | | | | | | | | | | | | | |
| Positive | 10 | 0 | 3 | 7 | | 40 | | 52.12 | | 38 | | 50.88 | |
| Negative | 41 | 0 | 30 | 11 | **0.031** | 67 | 52 | 200 | 0.435 | 70 | 55 | 200 | 0.572 |
| **CD146** | | | | | | | | | | | | | |
| Positive | 25 | 0 | 15 | 10 | | 49 | 49 | 79.27 | | 57 | 57 | 135.54 | |
| Negative | 27 | 0 | 18 | 9 | **0.024** | 71 | | 135.02 | 0.931 | 73 | 44 | 200 | 0.893 |
| **Distant metastasis and recurrence** | | | | | | | | | | | | | |
| Yes | 29 | 1 | 9 | 19 | | 24 | 12 | 53.59 | | 27 | | 24.43 | |
| No | 52 | 12 | 14 | 26 | **0.007** | 78 | 78 | 200 | **0.0001** | 84 | 84 | 200 | **0.0001** |

**OS:** overall survival; **DFS**: disease-free survival; **PL**: pelvic lymphadenectomy; **MC**: missing cases; data was not present in the literature.

A total of 76/113 (67.3%) patients accepted surgical treatment, including 28/76 (36.8%) complete resections and 48/76 (63.2%) incomplete resections (partial or complete hysterectomy). Adjuvant radiotherapy was administered to 73/113 (64.6%) patients, chemotherapy to 37/113 (32.7%) patients, adjuvant radiotherapy plus chemotherapy to 17/113 (15.0%) patients and hormone therapy with megestrol acetate to 4/113 (3.5%) patients. Lymphovascular space invasion and lymph node metastasis was observed in 7/113 (6.2%) patients. A total of 29/113 (25.7%) patients developed recurrence, and 19/113 (16.8%) patients died during the follow-up. The locations of recurrence were as follows: pelvic recurrence, 11/29 (37.9%), extrapelvic recurrence,11/29 (37.9%); both pelvic and extrapelvic recurrences, 7/29(29.2%).

### Overexpression of p53 protein and survival analysis in patients with uterine sarcoma

Immunohistochemical data was acquired from a total of 97/113 (85.8%) cases in this study, including 52 tissue specimens collected from SYSUCC and 45 analyses reported in the literature. Overexpression of p53 was identified in 44/97 (45.4%) cases, including

19/44 (43.2%) LMS, 19/44 (43.2%) ESS, 4 (9.1%) CS, 1/44 (2.3%) undifferentiated sarcoma and 1/44 (2.3%) uterine adenosarcoma. The remaining 53/97 (54.6%) cases stained negative for p53. The breakdown of the 52 specimens from SYSUCC showed that 19/52 (36.5%) stained positive for p53, and 33/52 (63.5%) stained negative for p53. Statistical analysis confirmed that p53 was a significant prognostic factor for uterine sarcoma. Figure 1 shows the immunohistochemical staining patterns for p53 protein, demonstrating that overexpression of p53 is associated with uterine sarcoma. Additional immunohistochemical analyses were performed for p27, CD146 and Ki-67 for the 52 specimens collected in this institution. The results are described below.

Survival analysis showed that positive p53 staining significantly correlated with worse overall survival in patients aged <50 years ($P$ = 0.039), those with depth of muscular invasion ≥1/2 ($P$ = 0.043), premenopause ($P$ = 0.002), low FIGO stage ($P$ = 0.0001), negative lymph node metastasis ($P$ = 0.026), negative staining of p27 ($P$ = 0.031) and negative staining of CD146 ($P$ = 0.024). Furthermore, survival analysis showed that p53 was an important prognostic factor in patients with either early-stage or late-stage uterine sarcoma. Recurrent patients with positive p53 staining had worse prognosis compared to those with negative for p53 ($P$ = 0.007). These results are summarized in Table 2.

**Expression of p27, CD146 and Ki-67 proteins in patients with uterine sarcoma**

Further immunohistochemical analyses for additional proteins, p27, CD146 and Ki-67, were performed in the 52 uterine sarcoma tissue specimens collected from SYSUCC. The results were as follows:

In all, 10/52 (19.2%) patients were positive for p27, and 41/52 (78.8%) were negative for p27. One paraffin tissue suffered from date missing. The 2-year DFS and 2-year OS rates in patients positive for p27 expression were 38% and 40%, respectively; the 2-year DFS and 2-year OS rate in patients negative for p27 expression were 70% and 67%, respectively. The corresponding median DFS and OS rates ($P$ = 0.572; $P$ = 0.435, respectively) are presented in Table 2.

In addition, 25/52 (48.1%) patients were positive for CD146, and 27/52 (51.9%) were negative for CD146. The 2-year DFS and 2-year OS rate in the patients with positive expression of CD146 were 57% and 49% respectively; the 2-year DFS and 2-year OS rate in the patients with negative CD146 expression were 73% and 71%, respectively. The corresponding median DFS and OS rates ($P$ = 0.893; $P$ = 0.931, respectively) are presented in Table 2.

**Table 3: Cox regression analysis of clinical factors associated with overall survival and disease-free survival in patients with uterine sarcoma**

| Clinical variable | Subset | Hazard ratio (95% CI) | P value |
|---|---|---|---|
| **Overall survival** | | | |
| **Univariate analysis** | | | |
| Age (year) | ≥50 VS <50 | 2.46 (1.20-5.08) | 0.015 |
| Histologic type | ESS VS LMS VS CS VS other | 1.62 (1.15-2.30) | 0.007 |
| FIGO stage | I-II VS III-IV | 3.32 (1.62-6.79) | 0.001 |
| Menopause status | Postmenopause VS premenopause | 1.05 (0.46-2.39) | 0.913 |
| Tumor grade | HG VS LG | 0.79 (0.25-2.48) | 0.681 |
| Depth of muscular invasion | ≥1/2 VS <1/2 | 1.22 (0.48-3.11) | 0.671 |
| Tumor size | ≥5cm VS <5cm | 8.95 (1.18-67.88) | 0.034 |
| Lymph node metastasis | Positive VS negative | 1.34 (0.38-4.71) | 0.650 |
| P53 | Positive VS negative | 2.77 (1.26-6.10) | 0.011 |
| **Multivariate analysis** | | | |
| FIGO stage | I-II VS III-IV | 2.87 (1.37-6.07) | 0.006 |
| P53 | Positive VS negative | 3.45 (1.58-7.55) | 0.002 |
| **Disease-free survival** | | | |
| **Univariate analysis** | | | |
| Age (year) | ≥50 VS <50 | 2.32 (1.17-4.60) | 0.016 |
| Histologic type | ESS VS LMS VS CS VS other | 1.48 (1.05-2.09) | 0.024 |
| FIGO stage | I-II VS III-IV | 3.28 (1.69-6.38) | 0.000 |
| Menopause status | Postmenopause VS premenopause | 1,74 (0.87-3.50) | 0.118 |
| Tumor grade | HG VS LG | 0.11 (0.41-3.17) | 0.803 |
| Depth of muscular invasion | ≥1/2 VS <1/2 | 1.71 (0.63-4.63) | 0.294 |
| Tumor size | ≥5cm VS <5cm | 9.47 (1.24-72.28) | 0.030 |
| Lymph node metastasis | Positive VS negative | 1.03 (0.23-4.56) | 0.974 |
| P53 | Positive vs. Negative | 2.27 (1.12–4.61) | 0.023 |
| **Multivariate analysis** | | | |
| FIGO stage | I-II vs. III-IV | 2.70 (1.36–5.37) | 0.005 |
| P53 | Positive vs. negative | 2.68 (1.33–5.46) | 0.006 |

**ESS:** endometrial stromal sarcoma; **LMS**: leiomyosarcoma; **CS**: carcinosarcoma; **FIGO**: International Federation of Gynecology and Obstetrics; **CI**: confidence interval.

The proliferation indices for Ki-67 expression were <30% in 37/52 (71.2%) cases and ≥30% in 15/52 (28.8%) cases. The 2-year DFS rate of patients with positive Ki-67 expression and a proliferation index ≥30% were 53% vs. 76% in those with negative Ki-67 expression and a proliferation index <30% ($P$ = 0.046). The 2-year OS rates were 25% vs. 71% ($P$ = 0.056) in patients with positive Ki-67 expression and negative Ki-67 expression, respectively. Although positive staining for Ki-67 indicated a trend towards adverse survival times, the results were not statistically significant (Table 2).

**Survival analysis**

The median survival time of the 113 patients with uterine sarcomas in this study was 30.7 months (range, 1–271 month). The 2-year and 5-year OS rates were 51% and 44%, respectively. The 2-year and 5-year DFS rates were 57% and 46%, respectively.

Age, FIGO stage, histological type, tumor size, p53 expression and surgical procedure were statistically significant prognostic factors for OS in patients with uterine sarcomas. The median survival times were as follows: 50.0 months and 16.3 months in patients aged <50 years and ≥50 years, respectively ($P$ = 0.006); 50.0 months and 8.8 months for stage I–II and stage III–IV, respectively ($P$ = 0.000); 50.0 months, 9.1 months and 30.0 months for ESS, LMS and CS, respectively ($P$ = 0.01); and 35.0 months and 17.5 months for tumor sizes <5 cm and ≥5 cm, respectively ($P$ = 0.01). In addition, the difference in survival times between patients with positive and negative expression for p53 was significant ($P$ = 0.007): the 2-year OS rate was 20% and 63%, respectively; the corresponding 2-year DFS rates were 41% and 65%, respectively. The 2-year DFS rate for patients who underwent complete resection was 70% compared to 38% for those who underwent incomplete resection.

The following factors were not significant prognostic indicators for survival: menopause status ($P$ = 0.054), muscular invasion depth ($P$ = 0.407), tumor grade ($P$ = 0.528), lymph node metastasis ($P$ = 0.992), p27 positivity ($P$ = 0.435), CD 146 positivity ($P$ = 0.931) and Ki-67 positivity ($P$ = 0.056).

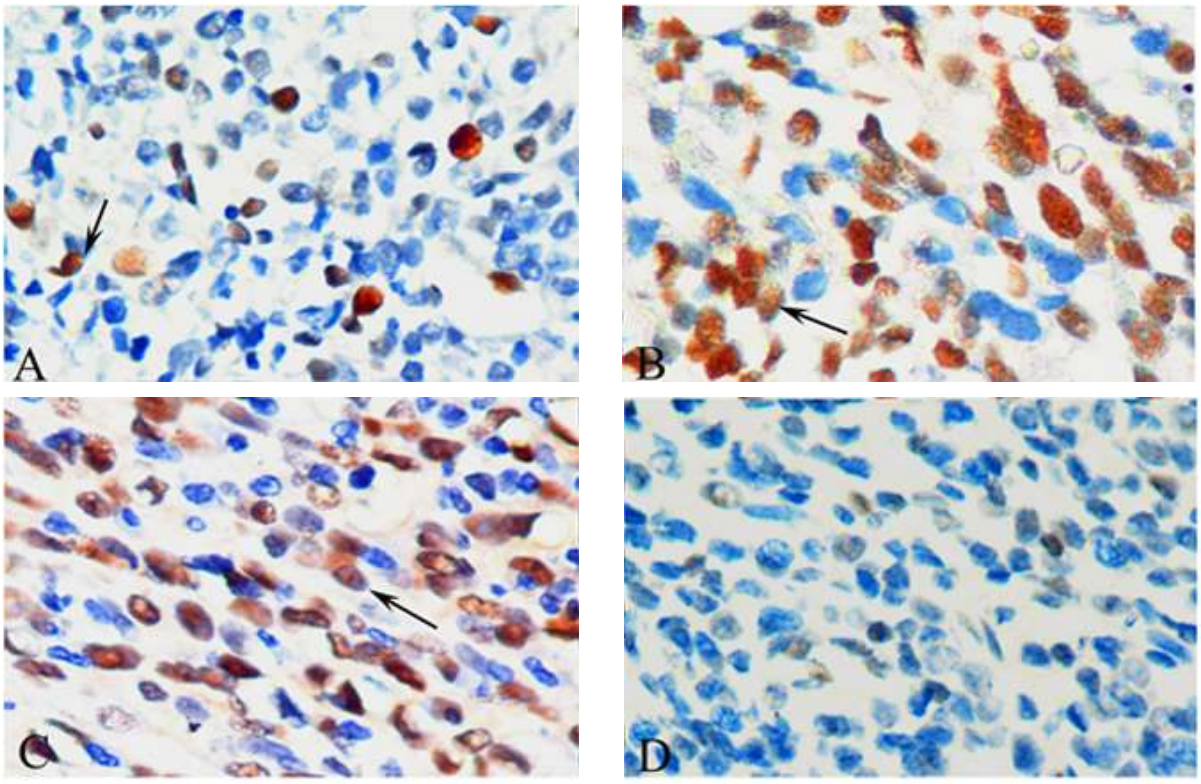


**Fig. 1.** (A–C) Immunohistochemical staining shows overexpression of p53 in endometrial stromal sarcoma, leiomyosarcoma and carcinosarcoma, respectively; (D) This shows no expression of p53 and therefore represents a negative control.

**Univariate and multivariate analyses of prognostic factors for survival**

Clinicopathological characteristics were evaluated to identify potential prognostic factors for survival in patients with uterine sarcoma (Table 3). Univariate analysis revealed that OS was significantly associated with age (HR, 2.46; 95% CI, 1.20–5.08; $P$ = 0.015); histological type (HR, 1.62; 95% CI, 1.15–2.30; $P$ = 0.007), FIGO stage (HR, 3.32; 95% CI, 1.62–6.79; $P$

= 0.001), tumor size (HR, 8.95; 95% CI, 1.18–67.88; $P$ = 0.034) and p53 (HR, 2.77; 95% CI, 1.26–6.10; $P$ = 0.011). DFS was associated with age (HR, 2.32; 95% CI, 1.17–4.60; $P$ = 0.016), histological type (HR, 1.48; 95% CI, 1.05–2.09; $P$ = 0.024), FIGO stage (HR, 3.28; 95% CI, 1.69–6.38; $P$ = 0.0001), tumor size (HR, 9.47; 95% CI, 1.24–72.28; $P$ = 0.030) and p53 (HR, 2.27; 95% CI, 1.12–4.61; $P$ = 0.023). Furthermore, multivariate Cox regression analysis revealed that FIGO stage and overexpression of p53 were significant independent predictors of OS and DFS ($P$ = 0.006 and $P$ = 0.002; $P$ = 0.005 and $P$ = 0.006, respectively).

## DISCUSSION

Uterine sarcomas have an aggressive clinical behavior and a poor prognosis [3]. The majority of reports on the prognosis of uterine sarcoma relate to the stage, surgical treatment, tumor grade, histological type and mitotic index [17–20]. Our findings were consistent with these reports. Furthermore, our results showed that FIGO stage and p53 expression were independent prognostic factors, and that patient age was also a significant prognostic factor in patients with uterine sarcomas. The median 2-year OS rate was 51% for all the patients assessed in this study; this rate was higher (65%) in those aged <50 years than in those aged ≥50 years (34%). In addition, the survival outcome of patients with tumor size <5 cm was better than those with tumor size ≥5 cm.

The histological type of uterine sarcoma has also been reported to play an important role in survival outcome [21]. In this study, we found that patients with ESS had better OS and improved local control than those with other histological types. However, in contrast to other studies [22–24], we found no significant difference in OS between patients with low- and high-grade ESS. This may be due to merely two patients were diagnosed with high-grade cases in this study (two cases with one lost during follow-up).

The low incidence rate of uterine sarcoma means that it is difficult to recruit a sufficient number of patients for conclusive research. As such, the number of reports on protein expression in uterine sarcoma is low. In this study, we were able to analyze data from 113 cases of uterine sarcoma, which comprises the largest number of cases studied to date. These included 97 immunohistochemical analyses of p53 expression, allowing us to explore the relationship between overexpression of p53 and clinical significance in uterine sarcoma. However, it was unavailable to fully qualify the data reported in the literature.

Szukala et al. reported p53 overexpression in both epithelial and stromal elements of carcinosarcoma in 18/19 (95%) cases that had previously been found to have *P53* mutations [25]. Several other studies have shown that p53 overexpression in endometrial carcinomas was associated with poor prognosis [26–34]. In agreement with these studies, our data showed that overexpression of p53 was adversely correlated with OS. Furthermore, univariate and multivariate analyses revealed that p53 was an independent prognostic factor for uterine sarcoma, with 2-year OS rates of 20% and 63% in patients with positive and negative expression of p53, respectively. We also found that p53 was positively correlated with disease stage, premenopause, patient age, tumor size, lymph node metastasis, recurrence, and negative p27 and CD146 expression. Consistent with previous studies showing that Ki-67 expression was associated with prognosis in uterine sarcoma [35], we observed distinctive differences in the 2-year survival rates between patients with positive and negative Ki-67 expression; however, the difference was not reach statistical significance ($P$ = 0.056). This may be due to the low number of cases involved in this study.

This study has demonstrated that prognosis in uterine sarcoma is significantly associated with patient age, FIGO stage, histological type, tumor size and overexpression of p53. Furthermore, p53 was identified as an independent prognostic factor in uterine sarcoma, and may therefore serve as a novel prognostic marker for this disease. These findings may enable more accurate evaluation of prognosis and guide treatment strategies in patients with uterine sarcoma.

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