Clinical characteristics and treatment outcomes of women with recurrent uterine leiomyosarcoma

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Abstract

Objective To determine the clinical characteristics and treatment outcomes of women with recurrent uterine leiomyosarcoma (uLMS). Methods We conducted a retrospective cohort study to evaluate the clinical characteristics and survival of women with recurrent uLMS and identify prognostic factors. Results Overall, 71 patients with first recurrence of uLMS were included in our study. 19 patients (26.8%) received systematic therapy and 52 patients (73.2%) received secondary cytoreductive surgery (SCS). In SCS subgroup (n=52), a complete resection with no residual disease was reported in 47 patients (90.4%). 38.5% (20/52) patients received non-genital organ surgeries. 10 (19.2%) patients had received thoracic surgery because of lung-only recurrences. Bowel, bladder surgery was performed in 8 (15.4%), 3 (5.8%) patients, respectively. 1 (1.9%) patient had received liver surgery. The median follow-up duration was 38.7 months (range: 2.7-317.6 months). 41 (57.7%) patients died during follow-up. 5-year OS for the entire cohort was 52.9%. Patients experienced first recurrence after initial diagnoses within 12 months (n=24) had a worse 5-year OS than those after 12 months (n=47) (17.0% vs 69.1%, P<0.001). 5-year OS for the SCS and non-SCS subgroup was 62.0% and 28.0%, respectively (P<0.001). Multivariate analysis showed time to fist recurrence within 12 months (HR=4.60, 95% CI: 1.49-14.4, P = 0.008) was an independent predictor of decreased 5-year OS in SCS subgroup. Conclusion SCS is an important treatment choice for recurrent uLMS and seems to have benefited patients. Time to fist recurrence within 12 months is an independent predictor of decreased 5-year OS in SCS subgroup.

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Results

Overall, 71 patients with first recurrence of uLMS were included in our study. 19 patients (26.8%) received systematic therapy and 52 patients (73.2%) received secondary cytoreductive surgery (SCS). In SCS subgroup (n=52), a complete resection with no residual disease was reported in 47 patients (90.4%). 38.5% (20/52) patients received non-genital organ surgeries. 10 (19.2%) patients had received thoracic surgery because of lung-only recurrences. Bowel, bladder surgery was performed in 8 (15.4%), 3 (5.8%) patients, respectively. 1 (1.9%) patient had received liver surgery.

The median follow-up duration was 38.7 months (range: 2.7-317.6 months). 41 (57.7%) patients died during follow-up. 5-year OS for the entire cohort was 52.9%. Patients experienced first recurrence after initial diagnoses within 12 months (n=24) had a worse 5-year OS than those after 12 months (n=47) (17.0% vs 69.1%, P<0.001). 5-year OS for the SCS and non-SCS subgroup was 62.0% and 28.0%, respectively (P<0.001). Multivariate analysis showed time to fist recurrence within 12 months (HR=4.60, 95% CI: 1.49-14.4, P = 0.008) was an independent predictor of decreased 5-year OS in SCS subgroup.

Conclusion

SCS is an important treatment choice for recurrent uLMS and seems to have benefited patients. Time to fist recurrence within 12 months is an independent predictor of decreased 5-year OS in SCS subgroup.

Keywords

recurrent uterine leiomyosarcoma clinical characteristics treatment outcomes

INTRODUCTION

Uterine sarcomas account for approximately 3%-7% of all uterine cancers.(Mbatani *et al* , 2018) The most common histologic types of uterine sarcomas are leiomyosarcomas (LMS, 63%), endometrial stromal sarcomas (ESS, 21%), adenosarcomas (6%), undifferentiated sarcoma (5%), and smooth muscle tumors of uncertain malignant potential (STUMP).(Kurman RJ, Carcanigiu ML, Herrington S, Young RH.) Most women with uterine leiomyosarcoma (uLMS) are diagnosed in their 50s and the vast majority present with disease confined to the uterine.(Kapp*et al* , 2008) Preoperative diagnosis of leiomyosarcoma is difficult and often only made at time of surgical resection. Uterine leiomyosarcoma is an aggressive malignant tumor with a high rate of recurrence.(Takehara *et al* , 2020) Though the majority (60%) are diagnosed at an early stage, uLMS is still associated with a poor prognosis. (Roberts *et al* , 2018)The 5-year overall survival rates for stage I, II, III, and IV uLMS were 55.4%, 32.6%, 24.6%, and 13.1%, respectively.(Seagle *et al* , 2017) Recurrence rate has been reported to be 45-73% in uLMS.(Giuntoli *et al* , 2007) Time to first recurrence varies widely and the median intervals are estimated around 12–24 months.(Bartosch *et al* , 2017) The disease of most patients recurs within the pelvis and upper abdominal. And metastasis to the lungs is also common.

Very few patients with recurrent or metastatic uLMS can be curatively treated. The prognosis of patients with recurrent/persistent uLMS is poor and the 5-year post-relapse survival rate was 15%.(Rauh-Hain*et al* , 2014) Due to their rarity, the management strategy for patients with recurrent uLMS has not been well established. Treatment choice for recurrent disease is dependent on previous therapy, the site of the recurrent tumor, time to recurrence, and the patient's performance status.(Rauh-Hain *et al* , 2014)

These tumors are relatively chemo and/or radio-resistant. Optimal surgical resection for recurrent uLMS may provide an opportunity for long-term survival in a select patient population.(Leitao *et al* , 2002) Patients presenting after a prolonged progression-free interval with an isolated site of recurrence amenable to complete resection are the best candidates for attempted surgical resection.(Giuntoli *et al* , 2007) Secondary

cytoreduction to no residual disease is an option that may be proposed in recurrent uterine leiomyosarcoma.(Bizzarri*et al* , 2019) Modern multimodal therapy or combining chemotherapy with aggressive surgery in selected patients may be significant in prolonging survival of women with this fatal disease.(Bernstein-Molho*et al* , 2010)

We therefore conducted a retrospective cohort study to evaluate the clinical characteristics and treatment outcomes of women with recurrent uterine leiomyosarcoma and identify prognostic factors.

MATERIALS AND METHODS

Patients

Following Institutional Review Board approval, we performed a retrospective analysis of all patients diagnosed with recurrent uLMS who presented to our institution from January 1, 2001 to January 1, 2020. All patients had previously undergone either total hysterectomy or radical hysterectomy or myomectomy at our center or an outside institution and diagnosed with uLMS after primary surgery which confirmed by an experienced gynecologic pathologist in our hospital. Only patients with first recurrent uLMS were included. Patients received treatment in the Department of Gynecological Oncology of Cancer Hospital, Chinese Academy of Medical Sciences, National Cancer Center.

The cohort was divided into two subgroups according to whether receive secondary cytoreductive surgery (SCS) for recurrent uLMS: the SCS subgroup, and non-SCS subgroup. The patients' full medical records were included in this study. Clinical and pathologic variables, treatment modalities, and outcomes were assessed. Stage was retrospectively assigned using the International Federation of Gynecology and Obstetrics (FIGO) 2008 staging system for uterine sarcomas.

Statistical analyses

The differences of clinicopathologic characteristics between SCS and non-SCS subgroups were performed using the Pearson χ^2test or the Fisher exact test. For the survival analyses, overall survival (OS) was defined as the time from the date of diagnosis to death for which uLMS was the primary or underlying cause. Survival was estimated using the Kaplan–Meier product-limit method, and differences were tested for statistical significance using the log-rank test. Cox proportional hazards regression models were used to identify the prognostic factor [HR and 95% confidence intervals (CI)]. Two-sided P values less than 0.05 were considered to be statistically significant. All analyses were performed using the SPSS Statistics20.0 software.

RESULTS

1. Patient characteristics

Overall, 71 patients with first recurrent of uLMS were included in our study. Patients median age at diagnosis was 48 years (range: 26-69 years). More than half of them were initially diagnosed before 50 years (54.9%). The FIGO 2008 distribution by stage at initial presentation was: stage I in 55 patients (77.5%), stage II in 8 patients (11.3%), stage III in 3 patients (4.2%) and stage IV in 5 patients (7.0%) (Table 1). Primary surgical treatment consisted of a total hysterectomy in 51 (71.8%) of the patients, 17 (23.9%) underwent a myomectomy, 3 (4.2%) had a radical hysterectomy (Table 1). Of these patients, 45 (63.4%) received adjuvant chemotherapy, and 3 (4.2%) received adjuvant radiotherapy (Table 1).

2. Recurrent pattern

The median time from the initial diagnoses to first recurrence was 16.3 months (range: 1.0-161.9 months). 33.8% (24/71) patients experienced recurrence after initial diagnoses within 12 months. And other 66.2% (47/71) patients had first recurrence after 12 months (Table 1).

The most common location of first recurrence was the abdominal/pelvic peritoneum, diagnosed in 47 (66.2%) patients, followed by lung metastases in 24 (33.8%) patients, abdominal wall metastases in 13 (18.3%), bone metastases in 5 (7.0%) patient, vaginal cuff metastases in 6 (8.5%) patients (Table 2).

In the entire cohort, multiple metastases in different locations were found in 18 (25.4%) patients. And 31 (43.7%) patients only had abdominal/pelvic peritoneum recurrence, 16 (22.5%) patients only had lung metastases, 3 (4.2%) patients only had abdominal wall metastases, 2 (2.8%) patients only had vaginal cuff metastases, 1 (1.4%) patient only had bone metastasis (Table 3).

3. Patient characteristics in different subgroup

In the entire cohort, 19 patients (26.8%) received systematic therapy and 52 patients (73.2%) received secondary cytoreductive surgery (SCS). Patients who treated with SCS were younger than those with non-SCS. 63.5% and 31.6% patients were initially diagnosed before 50 years in the SCS and non-SCS subgroup, respectively (P=0.017, Table1). More patients received myomectomy in SCS subgroup (32.7% vs 0.0%, P=0.003, Table1). The majority of patients were assigned to stage I at the time of original diagnosis in SCS subgroup than in non-SCS subgroup (86.5% vs 52.6%, P=0.008, Table1). More patients experienced first recurrence after 12 months since diagnosis in SCS subgroup than in non-SCS subgroup (73.1% vs 47.4%, P=0.043, Table1).

The recurrent pattern was different in SCS and non-SCS subgroup. Patients treated with SCS were more likely to experience recurrence in isolated sites (36.5% vs 5.3%, P=0.009, Table1), and less likely to recurred in multiple locations (17.3% vs 47.4%, P=0.015, Table1). Patients treated with SCS were more likely to experience recurrence in abdominal/pelvic peritoneum (71.2%), abdominal wall (21.2%) and vaginal cuff (9.6%) (Table 2). Of patients received systematic treatment, 68.4% and 21.1% had lung metastases and bone metastases, respectively (Table 2).

4. Secondary cytoreductive surgery treatment

Of the 52 patients undergoing secondary cytoreductive surgery, a complete resection with no residual disease was reported in 47 patients (90.4%) (Table 4). 69.2% patients had a tumor larger than 5 cm found at secondary cytoreduction. 38.5% (20/52) patients received non-genital organ surgeries. 10 (19.2%) patients had received thoracic surgery because of lung-only recurrences. Bowel, bladder surgery was performed in 15.4%, 5.8% of the cases, respectively. 1 (1.9%) patient had received liver surgery because of liver recurrence. 34.6% patients had estimated blood loss more than 500 ml (Table 4).

5. Adjuvant therapy after SCS

35 (67.3%) patients received adjuvant chemotherapy after SCS (Table 4). The most common chemotherapy regimen was doxorubicin-based treatment, followed by gemcitabine/docetaxel regimen. 1 (1.9%) patient with vaginal cuff recurrent received pelvic radiotherapy. 1 (1.9%) patient received pazopanib treatment. 16 (30.8%) patients did not receive any adjuvant therapy after SCS.

6. Non-secondary cytoreductive surgery treatment

Among patients received non-secondary cytoreductive surgery treatment, 14 (73.7%) patients received chemotherapy, 2 (10.5%) patients received chemotherapy and pelvic radiotherapy, 1 (5.3%) patient received anlotinib treatment, and 2 (10.5%) patients refused cancer treatment (Table S1). 16 patients died during follow-up.

7. Survival analysis

The median follow-up duration was 38.7 months (range: 2.7-317.6 months). 41 (57.7%) patients died during follow-up. 5-year OS for the entire cohort was 52.9% (Figure S1). Stage-specific 5-year OS were as follows: stage I—60.7%, stage II-IV—27.8% (P=0.001; Figure S2). Patients experienced first recurrence after initial diagnoses within 12 months had a worse 5-year OS than those after 12 months (17.0% vs 69.1%, P<0.001, Figure 1A). 5-year OS for the SCS and non-SCS subgroup was 62.0% and 28.0%, respectively (P<0.001; Figure S3). Patients who recurred at isolated site associated had a better survival (5-year OS: 73.5% vs 44.0%, P=0.045; Figure S4). Patients who developed recurrence in multiple locations had a significantly worse survival (5-year OS: 58.4% vs 34.7% P=0.039, Figure 2).

Of the 52 patients undergoing SCS, patients experienced first recurrence after initial diagnoses within 12 months had a worse 5-year OS than those after 12 months (28.5% vs 72.8%, P=0.001, Figure 1B). Patients with residual tumors after cytoreductive surgery had a tendency towards a worse survival than those without (5-year OS: 20.0% vs 67.7%, P=0.082; Figure S5). Patients who received non-genital organ surgeries had a non-significantly worse survival than those who did not receive (5-year OS: 51.5% vs 69.8%, P=0.057; Figure S6). And patients with lung-only recurrence (n=10) had a tendency towards better 5-year OS than those without (n=42) (77.8%% vs 57.8%, P=0.938; Figure S7).

Multivariate analysis showed time to fist recurrence within 12 months (HR=4.60, 95% CI: 1.49-14.4, P = 0.008, Table 5) was an independent predictor of decreased 5-year OS after adjusted time to fist recurrence, diameter of largest mass found at SCS, isolated site recurrence, multiple locations, non-genital organ surgeries, residual tumor, adjuvant chemotherapy.

DISCUSSION

In the present study, the clinical characteristics and treatment outcomes of 71 patients with recurrent uterine leiomyosarcoma treated at our institution were analyzed. To our knowledge, the current study is one of the largest studies to evaluate the clinical characteristics and treatment outcomes of women with recurrent uLMS in a single center to data. We found that secondary cytoreductive surgery is an important treatment choice for recurrent uLMS and time to fist recurrence within 12 months is an independent predictor of decreased 5-year OS in patients who received SCS. These findings suggested that it's important to identify the suitable candidate for SCS.

Uterine leiomyosarcoma is the most frequent malignant gynecologic mesenchymal tumor, often develops distant metastases and local recurrence.(Mbatani *et al* , 2018) Because of their low incidence and the lack of prospective studies, it is very difficult to reach conclusions as to the best disease management recommendations for recurrent uLMS. Treatment recommendations are made according to the site and nature of the recurrence for recurrent uLMS. Emerging evidence suggested that optimal surgical resection for recurrent uLMS may provide an opportunity for long-term survival in a select patient population.(Leitao *et al* , 2002; Giuntoli *et al* , 2007; Bacalbasa *et al* , 2015; Villalaín-González *et al* , 2017; Nakamura *et al* , 2018; Bizzarri *et al* , 2019; Cybulska*et al* , 2019) The survival advantage was seen not only in patents with pulmonary metastases but also patients with extrapulmonary metastases.(Giuntoli *et al* , 2007) In the present study, we found secondary cytoreduction surgery in patients with first recurrent uLMS was associated with a significant improvement in overall survival. Recently, some studies showed cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) was a promising treatment modality for uterine sarcoma patients with peritoneal dissemination.[6–8] It's important to identify the suitable candidate for SCS.

The time to first recurrent since initial diagnosis affects the survival. Patients with uLMS who experience longer time to recurrence may have improved survival outcomes following metastasectomy.(Leitao *et al* , 2002) In the present study, patients experienced first recurrence after initial diagnoses within 12 months had a significantly worse 5-year OS than those after 12 months, which was an independent predictor of worse survival.

Site governs local control, distant recurrence-free and disease-specific survival for completely resected locally recurrent sarcoma without metastasis.(Stojadinovic *et al* , 2002) Patients with single site recurrence are more likely to receive SCS and achieve a complete resection with no residual disease than those with multiple sites recurrences. We found patients with multiple recurrent locations were more likely to receive systematic therapy and had a worse survival, which in accordance with other studies. Similarly, patients with residual tumors after cytoreductive surgery had a tendency towards a worse survival than those without in the present study.

Furthermore, Bartosch et al found the most frequent distant metastatic sites were lung (67.7%).(Bartosch *et al* , 2017) We found lung was also the most common distant metastatic site in our study. But it's not that bad for some patients, especially for those with lung-only recurrence. We found patients with lung-only recurrence had a tendency towards better 5-year OS than those without.

uLMS also have a high tendency for local recurrent in pelvic and abdominal cavity after initial treatment. Since it is difficult to discriminate between benign uterine fibroids and uterine sarcomas preoperatively, most uterine sarcomas are often found incidentally after primary hysterectomy or myomectomy.(Hosh *et al* , 2016) Tumor fragmentation/morcellation might be used which was associated with significantly higher risk of recurrence and a nearly 4-fold increase in peritoneal recurrence.(Pedra Nobre *et al* , 2021) Since nearly all patients received primary myomectomy in other centers, we could not determining how many patients received morcellation clearly in the present study.

Radiotherapy can be recommended for patients with recurrent uterine sarcoma based on tumor resectability and patients' prior radiotherapy exposure. For patients with local recurrent, all recurrences are localized either in the vagina or in or directly proximal to the vaginal stump that is negative for distant metastatic disease. Radiotherapy or surgery treatment are reasonable choices. Concurrent radiotherapy shows good local effectiveness with a good long-term survival for local recurrence.(Kortmann *et al* , 2006) A combined modality approach with perioperative EBRT, surgery, and IORT for locally advanced or recurrent uterine sarcoma resulted in excellent local disease control with acceptable toxicity, even in patients with positive resection margins. (Barney *et al* , 2012) 8.5% patients had vaginal cuff recurrent in our study and 3 of them received pelvic radiotherapy in our study.

Further adjuvant systemic therapy should be considered for patients with recurrent leiomyosarcoma after initial surgical treatment or radiotherapy. Systemic therapy is also important medical choice for patients with distant metastasis.

Leoimyosarcoma is extremely aggressive and responds poorly to traditional chemotherapeutics. Docetaxel/gemcitabine, doxorubicin, and ifosfamide are all reasonable options for advanced or recurrent disease with response rates ranging from 17% to 36%.(Seddon *et al* , 2017; Mbatani *et al* , 2018) Gemcitabine and docetaxel have demonstrated the highest objective response rates as first-line or second-line treatment for metastatic disease, with an OS of 14.7 months in second-line treatment.(Hensley *et al* , 2008) Gemcitabine-docetaxel remains a standard first-line treatment for uLMS.(Hensley *et al* , 2015) Recently, new drugs such as trabectedin and eribulin have showed promising therapeutic effect for patients with recurrent uLMS. (Pautier *et al* , 2015; Schöffski*et al* , 2016) The most common chemotherapy regimens for recurrent uLMS were doxorubicin-based regimens and docetaxel/gemcitabine in our study.

Target therapy are important choice for patients with recurrent sarcoma. In recent years, targeted therapies such as pazopanib and olaratumab achieved a highly significant improvement in survival for patients with metastatic uLMS.(van der Graaf*et al* , 2012; Tap *et al* , 2016) Larotrectinib is highly active treatment especially for patients with TRK fusions.(Hong *et al* , 2020) The potential role of immunotherapy is being assessed in current uLMS clinical trials. Doxorubicin in combination with pembrolizumab is a promising combination worthy of further study, especially in certain sarcoma subtypes.(Pollack *et al* , 2020; Livingston *et al* , 2021) Endocrine therapy is also an important treatment for recurrent sarcoma. Aromatase inhibitors can be considered for ER/PR-expressing uLMS.(George *et al* , 2014)

There are two limitations to our study. The current study was retrospective, and the primary treatment was not assigned at randomized. All patients with recurrent uLMS in this study came from our single center. Therefore, caution is required when interpreting our results.

CONCLUSION

Recurrent uLMS are a rare group of tumors with an aggressive behavior and poor outcomes. The current study shows that secondary cytoreductive surgery is an important treatment choice for these patients and seems to have benefited patients. Time to fist recurrence within 12 months is an independent predictor of decreased 5-year OS in SCS subgroup. It's important to identify the suitable candidate for SCS. A prospective large study is warranted to validate these findings.

Disclosure of interests:

The authors declare that they have no competing interests.

Contribution to authorship:

Conceptualization: Y.H.W., Y.H.; Methodology: Y.H.W., Y.H.; Validation: Y.H., L.N.; Formal analysis and investigation: Y.H.W., L.N., Y.H.; Resources and data curation: Y.H.; Writing - original draft preparation: Y.H.W., Y.H.; Writing - review and editing: Y.H.W., L.N., Y.H.; Supervision: Y.H.W., L.N., Y.H.; Project administration: Y.H.W., Y.H.; Funding acquisition: Y.H. All authors have read and approved the manuscript.

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Written informed consent was obtained from all individuals.

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Details of ethics approval:

This study was approved by the Cancer Hospital, Chinese Academy of Medical Sciences Institutional Review Board (IRB). This study was performed in accordance with the Declaration of Helsinki.

Conflicts of Interest

No potential conflicts of interest were disclosed.

References

Bacalbasa N, Balescu I, Dima S, Brasoveanu V, Popescu I (2015) Prognostic factors and survival in patients treated surgically for primary and recurrent uterine leiomyosarcoma: a single center experience. *Anticancer Res* **35** : 2229–2234.

Barney BM, Petersen IA, Dowdy SC, Bakkum-Gamez JN, Haddock MG (2012) Long-term outcomes with intraoperative radiotherapy as a component of treatment for locally advanced or recurrent uterine sarcoma. *Int J Radiat Oncol Biol Phys* **83** : 191–197, doi:10.1016/j.ijrobp.2011.06.1960.

Bartosch C, Afonso M, Pires-Luís AS, Galaghar A, Guimarães M, Antunes L, Lopes JM (2017) Distant Metastases in Uterine Leiomyosarcomas: The Wide Variety of Body Sites and Time Intervals to Metastatic Relapse.*Int J Gynecol Pathol* **36** : 31–41, doi:10.1097/PGP.0000000000000284.

Bernstein-Molho R, Grisaro D, Soyfer V, Safra T, Merimsky O (2010) Metastatic uterine leiomyosarcomas: a single-institution experience.*Int J Gynecol Cancer* **20** : 255–260, doi:10.1111/IGC.0b013e3181c9e289.

Bizzarri N, Ghirardi V, Di Fiore GLM, De Iaco P, Gadducci A, Casarin J, Perrone AM, Pasciuto T, Scambia G, Fagotti A (2019) Secondary cytoreductive surgery in recurrent uterine leiomyosarcoma: a multi-institutional study. *Int J Gynecol Cancer* **29** : 1134–1140, doi:10.1136/ijgc-2019-000355.

Cybulska P, Sioulas V, Orfanelli T, Zivanovic O, Mueller JJ, Broach VA, Long Roche KC, Sonoda Y, Hensley ML, O'Cearbhaill RE, Chi DS, Alektiar KM, Abu-Rustum NR, Leitao MM (2019) Secondary surgical resection for patients with recurrent uterine leiomyosarcoma. *Gynecol Oncol***154** : 333–337, doi:10.1016/j.ygyno.2019.05.015.

Díaz-Montes TP, El-Sharkawy F, Lynam S, Harper A, Sittig M, MacDonald R, Gushchin V, Sardi A (2018) Efficacy of Hyperthermic Intraperitoneal Chemotherapy and Cytoreductive Surgery in the Treatment of Recurrent Uterine Sarcoma. *Int J Gynecol Cancer* **28** : 1130–1137, doi:10.1097/IGC.0000000000001289.

George S, Feng Y, Manola J, Nucci MR, Butrynski JE, Morgan JA, Ramaiya N, Quek R, Penson RT, Wagner AJ, Harmon D, Demetri GD, Krasner C (2014) Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. *Cancer* **120** : 738–743, doi:10.1002/cncr.28476.

Giuntoli RL, Garrett-Mayer E, Bristow RE, Gostout BS (2007) Secondary cytoreduction in the management of recurrent uterine leiomyosarcoma.*Gynecol Oncol* **106** : 82–88, doi:10.1016/j.ygyno.2007.02.031.

van der Graaf WTA, Blay J-Y, Chawla SP, Kim D-W, Bui-Nguyen B, Casali PG, Schöffski P, Aglietta M, Staddon AP, Beppu Y, Le Cesne A, Gelderblom H, Judson IR, Araki N, Ouali M, Marreaud S, Hodge R, Dewji MR, Coens C, Demetri GD, Fletcher CD, Dei Tos AP, Hohenberger P, EORTC Soft Tissue and Bone Sarcoma Group, PALETTE study group (2012) Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* **379** : 1879–1886, doi:10.1016/S0140-6736(12)60651-5.

Hensley ML, Blessing JA, Mannel R, Rose PG (2008) Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol* **109** : 329–334, doi:10.1016/j.ygyno.2008.03.010.

Hensley ML, Miller A, O'Malley DM, Mannel RS, Behbakht K, Bakkum-Gamez JN, Michael H (2015) Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic Oncology Group study. *J Clin Oncol* **33** : 1180–1185, doi:10.1200/JCO.2014.58.3781.

Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM, Rohrberg KS, van Tilburg CM, Nagasubramanian R, Berlin JD, Federman N, Mascarenhas L, Geoerger B, Dowlati A, Pappo AS, Bielack S, Doz F, McDermott R, Patel JD, Schilder RJ, Tahara M, Pfister SM, Witt O, Ladanyi M, Rudzinski ER, Nanda S, Childs BH, Laetsch TW, Hyman DM, Drilon A (2020) Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol* **21** : 531–540, doi:10.1016/S1470-2045(19)30856-3.

Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B (2016) Uterine Sarcoma: Analysis of 13,089 Cases Based on Surveillance, Epidemiology, and End Results Database. *Int J Gynecol Cancer* **26** : 1098–1104, doi:10.1097/IGC.0000000000000720.

Jimenez WA, Sardi A, Nieroda C, Gushchin V (2014) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of recurrent high-grade uterine sarcoma with peritoneal dissemination. *Am J Obstet Gynecol* **210** : 259.e1-8, doi:10.1016/j.ajog.2013.11.002.

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** : 820–830, doi:10.1002/cncr.23245.

Kortmann B, Reimer T, Gerber B, Klautke G, Fietkau R (2006) Concurrent radiochemotherapy of locally recurrent or advanced sarcomas of the uterus. *Strahlenther Onkol* **182** : 318–324, doi:10.1007/s00066-006-1491-2.

Kurman RJ, Carcanigiu ML, Herrington S, Young RH. World Health Organization classification of tumours of the female reproductive organs. IARC, Lyon, 2014.

Leitao MM, Brennan MF, Hensley M, Sonoda Y, Hummer A, Bhaskaran D, Venkatraman E, Alektiar K, Barakat RR (2002) Surgical resection of pulmonary and extrapulmonary recurrences of uterine leiomyosarcoma. *Gynecol Oncol* **87** : 287–294, doi:10.1006/gyno.2002.6840.

Livingston MB, Jagosky MH, Robinson MM, Ahrens WA, Benbow JH, Farhangfar CJ, Foureau DM, Maxwell DM, Baldrige EA, Begic X, Symanowski JT, Steuerwald NM, Anderson CJ, Patt JC, Kneisl JS, Kim ES (2021) Phase II Study of Pembrolizumab in Combination with Doxorubicin in Metastatic and Unresectable Soft-Tissue Sarcoma. *Clin Cancer Res*doi:10.1158/1078-0432.CCR-21-2001.

Mbatani N, Olawaiye AB, Prat J (2018) Uterine sarcomas. *Int J Gynaecol Obstet* **143 Suppl 2** : 51–58, doi:10.1002/ijgo.12613.

Nakamura K, Kajiyama H, Utsumi F, Suzuki S, Niimi K, Sekiya R, Sakata J, Yamamoto E, Shibata K, Kikkawa F (2018) Secondary cytoreductive surgery potentially improves the oncological outcomes of patients with recurrent uterine sarcomas. *Mol Clin Oncol* **8** : 499–503, doi:10.3892/mco.2018.1560.

Pautier P, Floquet A, Chevreau C, Penel N, Guillemet C, Delcambre C, Cupissol D, Selle F, Isambert N, Piperno-Neumann S, Thyss A, Bertucci F, Bompas E, Alexandre J, Collard O, Lavau-Denes S, Soulié P, Toulmonde M, Le Cesne A, Lacas B, Duffaud F, French Sarcoma Group (2015) Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. *Lancet Oncol* **16** : 457–464, doi:10.1016/S1470-2045(15)70070-7.

Pedra Nobre S, Hensley ML, So M, Zhou QC, Iasonos A, Leitao MM, Ducie J, Chiang S, Mueller JJ, Abu-Rustum NR, Zivanovic O (2021) The impact of tumor fragmentation in patients with stage I uterine leiomyosarcoma on patterns of recurrence and oncologic outcome. *Gynecol Oncol***160** : 99–105, doi:10.1016/j.ygyno.2020.10.020.

Pollack SM, Redman MW, Baker KK, Wagner MJ, Schroeder BA, Loggers ET, Trieselmann K, Copeland VC, Zhang S, Black G, McDonnell S, Gregory J, Johnson R, Moore R, Jones RL, Cranmer LD (2020) Assessment of Doxorubicin and Pembrolizumab in Patients With Advanced Anthracycline-Naive Sarcoma: A Phase 1/2 Nonrandomized Clinical Trial.*JAMA Oncol* **6** : 1778–1782, doi:10.1001/jamaoncol.2020.3689.

Rauh-Hain JA, Hinchcliff EM, Oduyebo T, Worley MJ, Andrade CA, Schorge JO, George S, Muto MG, del Carmen MG (2014) Clinical outcomes of women with recurrent or persistent uterine leiomyosarcoma. *Int J Gynecol Cancer* **24** : 1434–1440, doi:10.1097/IGC.0000000000000221.

Roberts ME, Aynardi JT, Chu CS (2018) Uterine leiomyosarcoma: A review of the literature and update on management options. *Gynecol Oncol***151** : 562–572, doi:10.1016/j.ygyno.2018.09.010.

Sardi A, Sipok A, Baratti D, Deraco M, Sugarbaker P, Salti G, Yonemura Y, Sammartino P, Glehen O, Bakrin N, Díaz-Montes TP, Gushchin V (2017) Multi-institutional study of peritoneal sarcomatosis from uterine sarcoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol* **43** : 2170–2177, doi:10.1016/j.ejso.2017.08.011.

Schöffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, Grignani G, Camargo V, Bauer S, Rha SY, Blay J-Y, Hohenberger P, D'Adamo D, Guo M, Chmielowski B, Le Cesne A, Demetri GD, Patel SR (2016) Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet* **387** : 1629–1637, doi:10.1016/S0140-6736(15)01283-0.

Seagle B-LL, Sobecki-Rausch J, Strohl AE, Shilpi A, Grace A, Shahabi S (2017) Prognosis and treatment of uterine leiomyosarcoma: A National Cancer Database study. *Gynecol Oncol* **145** : 61–70, doi:10.1016/j.ygyno.2017.02.012.

Seddon B, Strauss SJ, Whelan J, Leahy M, Woll PJ, Cowie F, Rothermundt C, Wood Z, Benson C, Ali N, Marples M, Veal GJ, Jamieson D, Küver K, Tirabosco R, Forsyth S, Nash S, Dehbi H-M, Beare S (2017) Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol***18** : 1397–1410, doi:10.1016/S1470-2045(17)30622-8.

Stojadinovic A, Yeh A, Brennan MF (2002) Completely resected recurrent soft tissue sarcoma: primary anatomic site governs outcomes. *J Am Coll Surg* **194** : 436–447, doi:10.1016/s1072-7515(02)01120-1.

Takehara K, Yamashita N, Watanabe R, Teramoto N, Tsuda H, Motohashi T, Harano K, Nakanishi T, Tokunaga H, Susumu N, Ueda Y, Yokoyama Y, Saito T (2020) Clinical status and prognostic factors in Japanese patients with uterine leiomyosarcoma. *Gynecol Oncol* **157** : 115–120, doi:10.1016/j.ygyno.2020.01.022.

Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, Agulnik M, Cooney MM, Livingston MB, Pennock G, Hameed MR, Shah GD, Qin A, Shahir A, Cronier DM, Ilaria R, Conti I, Cosaert J, Schwartz GK (2016) Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet* **388** : 488–497, doi:10.1016/S0140-6736(16)30587-6.

Villalaín-González C, Tejerizo-García Á, Lopez-Garcia P, López-González G, Oliver-Perez MR, Jiménez-López JS (2017) Vaginal metastasis as the initial presentation of leiomyosarcoma: a case report. *BMC Cancer***17** : 503, doi:10.1186/s12885-017-3484-1.

Table 1. Clinicopathological characteristics of SCS and non-SCS patients in the entire cohort

Clinical Characteristics		**All**
		n
N		71
Median age (Range), years		48(26-69)
Age at diagnosis (y)		
<50		39
50		32
Parity		
0		4
1		41
>1		23
BMI		
<24		39
24		32
Pathologic Stage (FIGO 2009)	**Pathologic Stage (FIGO 2009)**	**Pathologic Stage (FIGO 2009)**
I		55
II		8
III		3
IV		5
Surgical route of primary surgery	**Surgical route of primary surgery**	**Surgical route of primary surgery**
Hysterectomy		51
Myomectomy		17
Radical hysterectomy		3
Initial adjuvant chemotherapy	**Initial adjuvant chemotherapy**	**Initial adjuvant chemotherapy**
Yes		45
No		26
Initial adjuvant radiotherapy	**Initial adjuvant radiotherapy**	**Initial adjuvant radiotherapy**
Yes		3
No		68
Time to fist recurrence	**Time to fist recurrence**	**Time to fist recurrence**
12 months		47
<12 months		24
Isolated site*		
Yes		20
No		51
Multiple locations#		
Yes		18
No		53

Abbreviations: SCS, secondary cytoreduction surgery; non-SCS, non- secondary cytoreduction surgery; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.

Notes: * Patients who had a recurrence at only 1 site.# Patients who had a recurrence at 2 or more locations were considered to have multiple locations of recurrence.

Table 2. Locations of the first relapse disease in the entire population

Recurrent locations	All	All	SCS	SCS	Non-SCS	Non-SCS
	n	%	n	%	n	%
Abdomen/pelvis*	47	66.2	37	71.2	10	52.6
Lung	24	33.8	11	21.2	13	68.4
Abdominal wall	13	18.3	11	21.2	2	10.5
Vaginal	6	8.5	5	9.6	1	5.3
Bone	5	7.0	1	1.9	4	21.1

Abbreviations: SCS, secondary cytoreduction surgery; non-SCS, non- secondary cytoreduction surgery.

Notes: * Some patients recurred in 2 or multiple locations, and patients might be included in more than 1 category.

Table 3. Recurrent patterns of first relapse disease in the entire population

Recurrent locations	All	All	SCS	SCS	Non-SCS	Non-SCS
	n	%	n	%	n	%
Abdomen/pelvis only	31	43.7	28	53.8	3	15.8
Lung only	16	22.5	10	19.2	6	31.6
Abdominal wall only	3	4.2	3	5.8	0	0.0
Vaginal only	2	2.8	2	3.8	0	0.0
Bone only	1	1.4	0	0.0	1	5.3
Multiple locations*	18	25.4	9	17.3	9	47.4

Abbreviations: SCS, secondary cytoreduction surgery; non-SCS, non- secondary cytoreduction surgery.

Notes: * Patients who had a recurrence at 2 or more locations were considered to have multiple locations of recurrence.

Table 4. Details of cytoreduction surgery in patients who received SCS

Clinical Characteristics	
Diameter of largest mass found at secondary cytoreduction (cm)	**Diameter of largest mass found at second**
<5	
5	
Thoracic surgery	
Yes	
No	
Liver surgery	
Yes	
No	
Bowel resection	
Yes	
No	
Bladder surgery	
Yes	
No	
Residual tumor	
No	

Clinical Characteristics		
Yes		
Estimated blood loss		
<500ml		
500ml		
Adjuvant therapy after SCS		**Adjuvant therapy after SCS**
None		
Target therapy		
Chemotherapy		
Chemotherapy+ Radiotherapy		Chemotherapy+ Radiotherapy

Abbreviations: SCS, secondary cytoreduction surgery.

Table 5. Univariate and m ultivariate analyses of OS in SCS subgroup (n=52).

Clinical Characteristics	Clinical Characteristics	Univariate ana
		HR
Time to fist recurrence (months)	**Time to fist recurrence (months)**	**Time to fist re**
<12 vs [?]12		3.91
FIGO stage		
II-IV vs I		2.64
Diameter of largest mass found at SCS (cm)	**Diameter of largest mass found at SCS (cm)**	**Diameter of la**
5 vs <5		1.23
Isolated site*		
No vs Yes		1.57
Multiple locations		
Yes vs No		2.07
Non-genital organs surgeries	**Non-genital organs surgeries**	**Non-genital or**
Yes vs No		2.12
Residual tumor		
Yes vs No		2.54
Adjuvant chemotherapy	**Adjuvant chemotherapy**	**Adjuvant chem**
No vs Yes		1.26

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; SCS, secondary cytoreduction surgery.

Table S1. Treatment for non-SCS patients

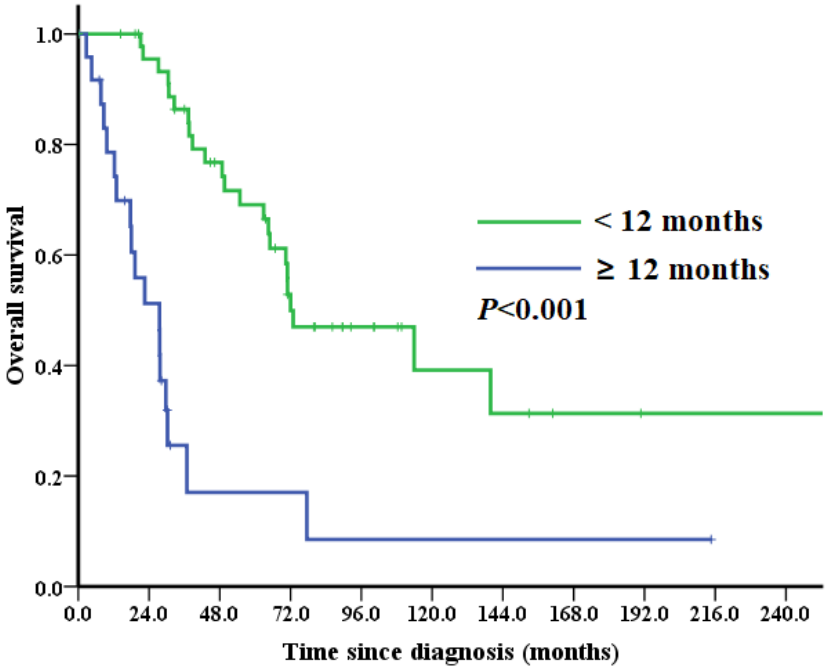
Treatment		n	%
None		2	10.5
Chemotherapy		14	73.7
Chemotherapy+ Radiotherapy	Chemotherapy+ Radiotherapy	2	10.5
Target therapy		1	5.3

Abbreviations: Non-SCS, non secondary cytoreduction surgery.

Figure 1. Overall survival (OS) analyses by the Kaplan–Meier method according to the time to first

recurrence after initial diagnoses in (A) the entire subgroup (n=71) and (B) the SCS subgroup (n=52).

A.



B.

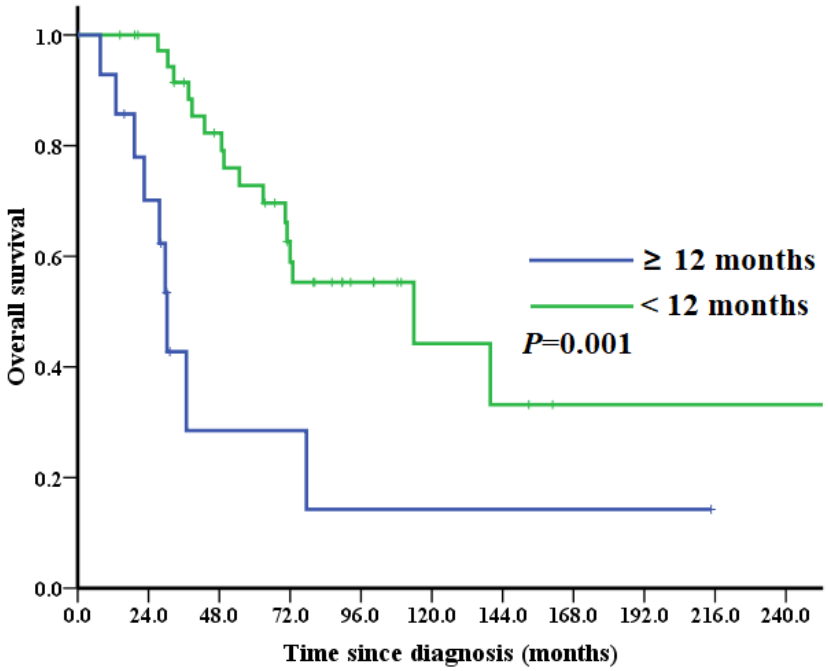


Figure 2. Overall survival (OS) analyses by the Kaplan–Meier method according to whether or not had the multiple locations recurrence in the entire cohort (n=71).

Patients who developed recurrence in multiple locations had a significantly worse survival (5-year OS: 58.4 vs 34.7 P=0.039).

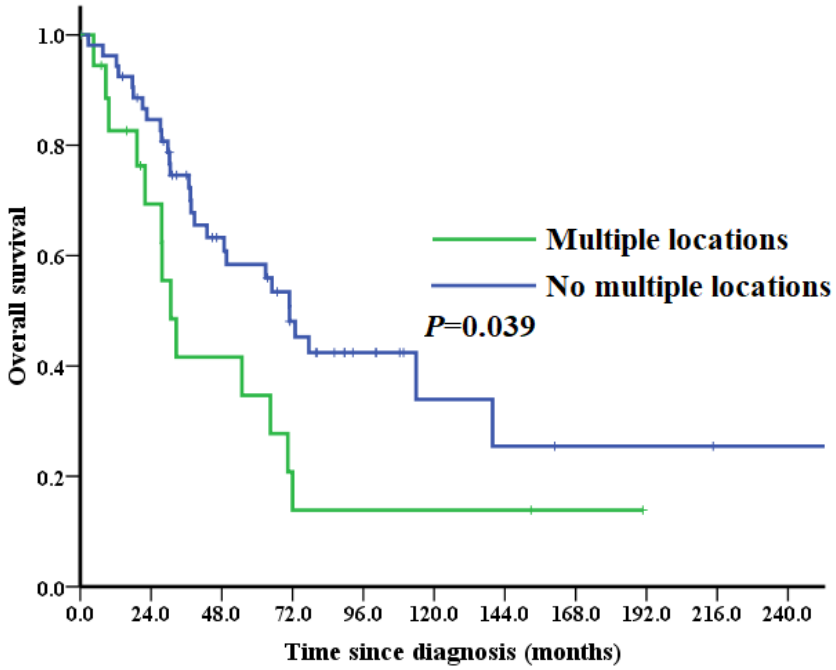


Figure S1. Overall survival (OS) analyses by the Kaplan–Meier method in the entire cohort (n=71).

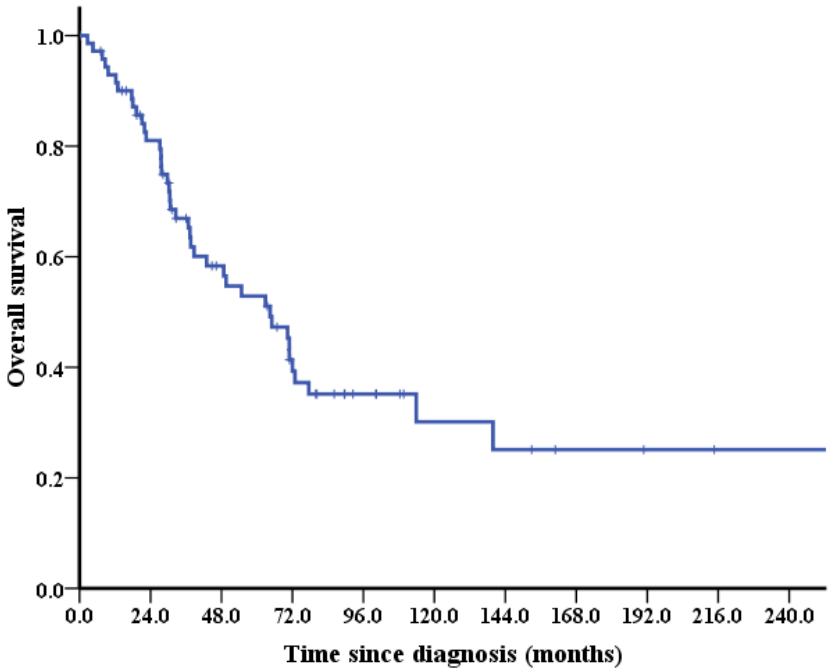


Figure S2. Overall survival (OS) analyses by the Kaplan–Meier method according to the tumor stage in the entire cohort (n=71).

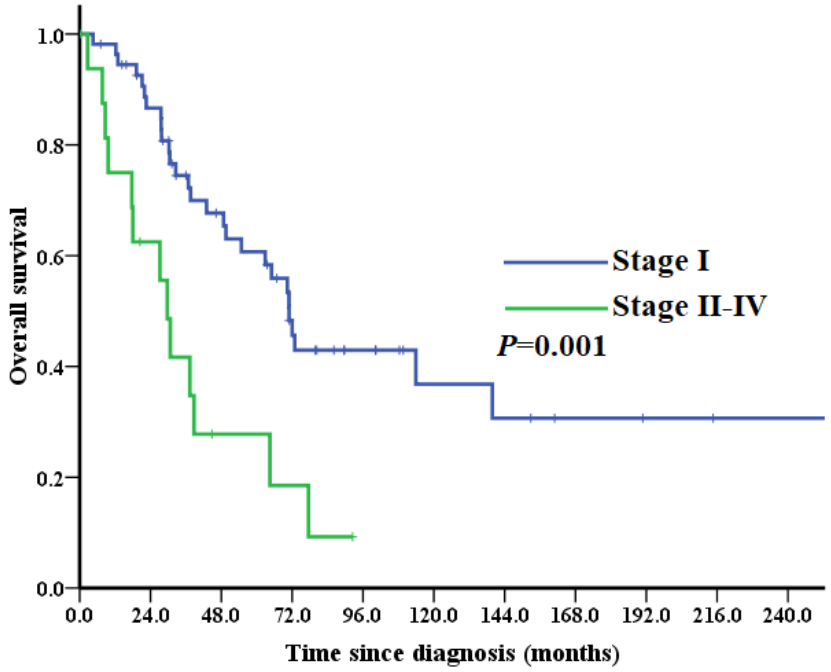


Figure S3. Overall survival (OS) analyses by the Kaplan–Meier method according to whether or not

received SCS for the first recurrence after initial diagnoses in the entire cohort (n=71).

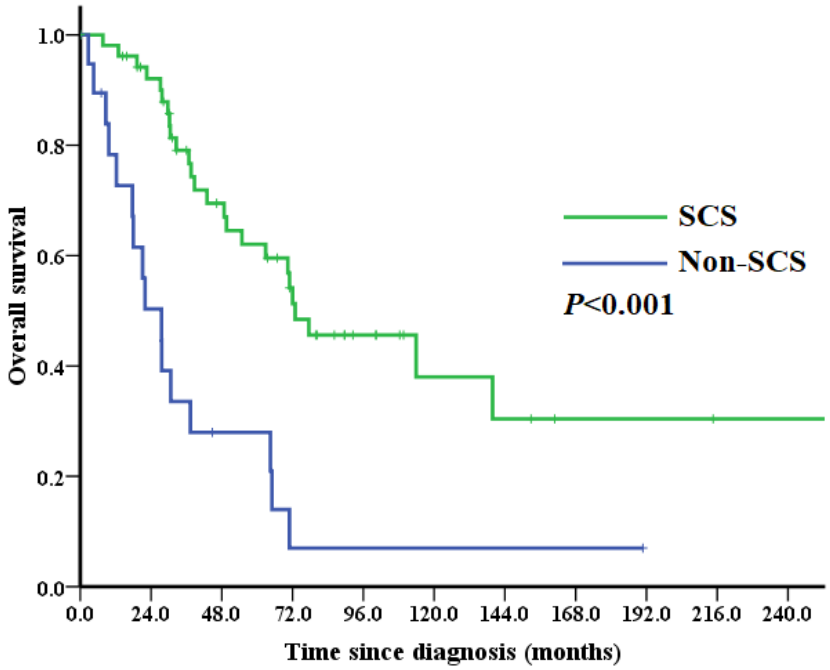


Figure S4. Overall survival (OS) analyses by the Kaplan–Meier method according to whether or not had the isolated recurrent site in the entire cohort (n=71).

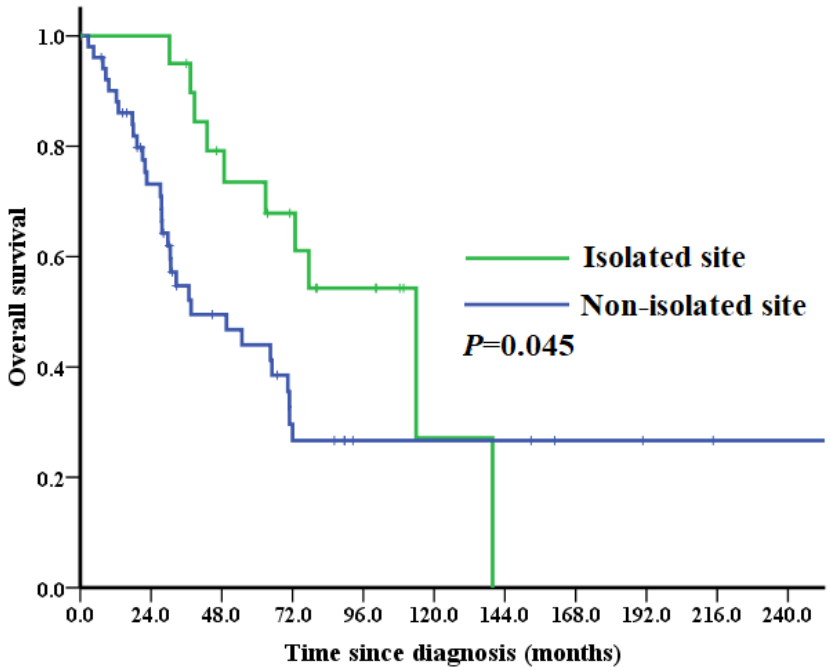


Figure S5. Overall survival (OS) analyses by the Kaplan–Meier method according to residual tumors status in the SCS subgroup (n=52).

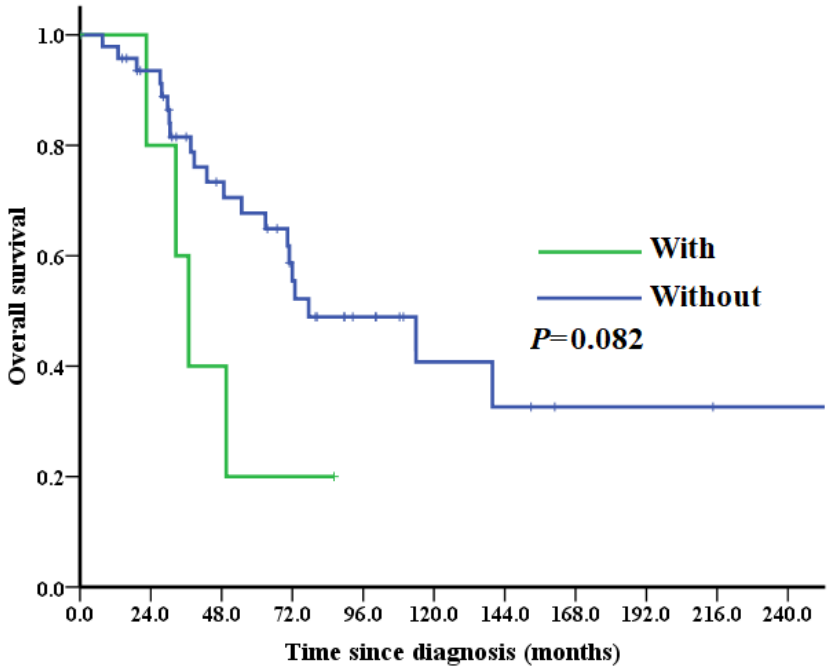


Figure S6. Overall survival (OS) analyses by the Kaplan–Meier method according to whether or not had received non-genital organ surgeries in the SCS subgroup (n=52).

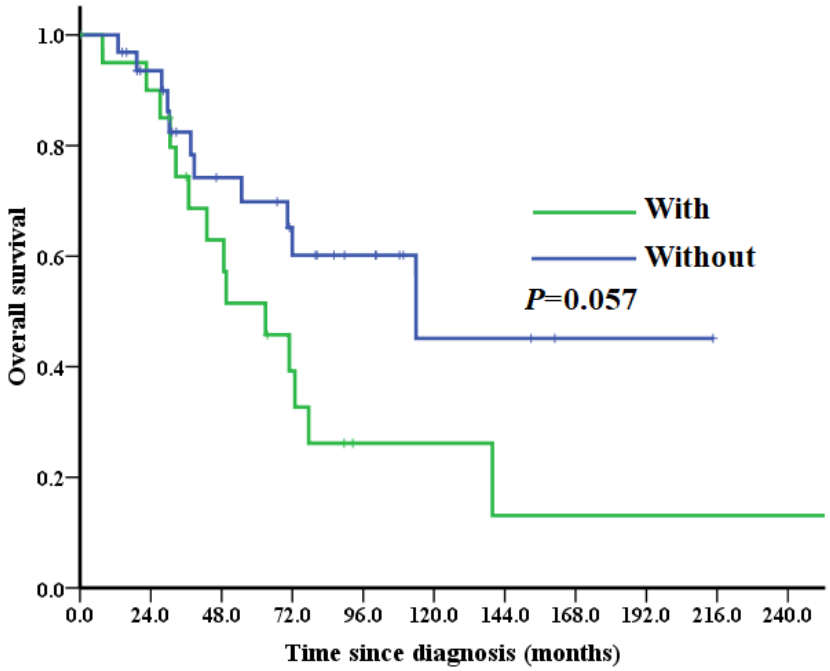


Figure S7. Overall survival (OS) analyses by the Kaplan–Meier method according to lung recurrence status in the SCS subgroup (n=52).