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Favorable factors affecting the prognosis of recurrent uterine leiomyosarcoma

재발성 자궁 평활근육종의 예후 인자 분석

2021년 8월

서울대학교 대학원

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지도교수 김 희 승

이 논문을 의학석사 학위논문으로 제출함
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위 원 장 서 정 화

부위원장 김 희 승

위 원 이 마 리 아

Abstract

Favorable factors affecting the prognosis of recurrent uterine leiomyosarcoma

Introduction: To evaluate favorable prognostic factors related to the prognosis of recurrent uterine leiomyosarcoma (uLMS).

Materials and Methods: The database searched those diagnosed at Seoul national university hospital for recurrent uLMS between January 2000 and December 2020. Prognostic factors related to the treatment-free interval (TFI), treatment-related survival (TRS), and overall survival (OS) were evaluated by using the Kaplan and Meier and Cox proportional hazard analyses.

Results: A total of 43 patients with recurrent uLMS were included, and 25 (58.1%) underwent secondary cytoreductive surgery (CRS). Secondary CRS improved TFI (median, 8.1 vs. 4.6 mons; P=0.001), which was favorable factor affecting TFI (HR, 0.298; 95% CI 0.137-0.646; P=0.002). Moreover, prior treatment-free interval (PTFI) longer than six months was related with better TRS (median, 9.84 vs. 22.28 mons; P <0.001) and OS (median, 16.99 vs. 51.09 mons; P <0.001), which was also a factor improving TRS (HR, 0.298; 95% CI 0.133-0.667; P=0.003) and OS (HR, 0.184; 95% CI 0.069-0.489; P=0.001). In 15 patients of multiple recurrences, secondary CRS showed better TFI with borderline significance (P=0.059).

Conclusion: These data suggest that secondary CRS is a favorable factor for TFI, and PTFI longer than six months may be important for improving TRS and OS in recurrent uLMS. After maximal CRS in multiple recurrences, it is expected that the TFI can be delayed.

주요어: Uterine neoplasm, recurrent leiomyosarcoma, prognosis, cytoreductive surgery, survival

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Chapter 1. Introduction

1.1. Study background

Mesenchymal uterine tumors are rare, and uterine sarcomas account for only 1–3% of uterine malignancies (1). Among them, uterine leiomyosarcoma (uLMS) accounts for the highest proportion of uterine sarcomas (70%) and a significant proportion of uterine cancer deaths (2, 3). So far, total hysterectomy with/without oophorectomy is the standard treatment for uLMS. Adnexal or lymphatic spread only occurs in about 3% of early-stage, and adnexectomy and lymphadenectomy turn out not to be independent prognostic factors (4, 5). Although uLMS is usually diagnosed in the early stages, it shows high recurrence rates in all stages despite surgery and adjuvant treatment (6, 7). Despite aggressive treatment, the recurrent rate is more than half (approximately 53% to 71%) (8).

In recurrent disease, there is no choice but palliative care. Patients with recurrence may consider secondary surgery, but neither chemotherapy nor radiation therapy improves outcomes with recurrent uLMS (9). Secondary cytoreductive surgery (CRS) improves disease-specific survival from the first recurrence (9–11). So, if the recurrent disease is surgically resectable, CRS with the goal of no gross residual disease should be considered (12). Some retrospective studies showed the surgical resection for recurrent uLMS would provide a survival benefit. However, some studies have even reported that surgical treatment is not so important because uLMS shows early hematogenous and rare lymphatic metastasis (13, 14). Recently, adjuvant treatment such as chemotherapy and radiation therapy has not presented a noticeable survival benefit (7). Like this, there is no ideal treatment option for recurrent uLMS.

The stage is the most important prognostic factor of uLMS, and most cases are diagnosed in the early stage. But, it is hard to

prepare for the recurrence and even more challenging to predict the prognosis of recurrent uLMS.

1.2. Purpose of research

We conducted a retrospective study to evaluate favorable prognostic factors related to the prognosis of recurrent uLMS. We purposed to figure out the favorable factors for the treatment-free interval (TFI), treatment-related survival (TRS), and overall survival (OS) in patients with recurrent uLMS.

Chapter 2. Body

2.1. Material and methods

Patients and methods

This study was approved by the Institutional Review Board in advance (No. 2101-100-1189). We reviewed the medical records of 43 patients with recurrent uLMS diagnosed from January 2000 to December 2020. Clinicopathologic data including age, the initial International Federation of Gynecology and Obstetrics (FIGO) stage, mitotic counts per 10 high power field (HPF), nuclear atypia and tumor necrosis at initial diagnosis, types of treatment, residual disease after primary CRS, recurrence pattern (localized versus distant), and survival were collected.

Prior treatment-free interval (PTFI) was defined between the time of completion of the primary treatment and the first recurrence. Treatment-free interval (TFI) was defined between the time of the diagnosis of the first recurrence and the time of the diagnosis of the second recurrence. Moreover, treatment-related survival (TRS) was defined as the time between the diagnosis of recurrence and the patients' death or last follow-up. Overall survival (OS) was defined as the time from the diagnosis to the end for disease or last follow-up.

Statistical analysis

Cox proportional hazards model was used for univariate and multivariate analyses to evaluate the prognostic significance of clinicpathologic features for TFI, TRS, and OS. Survival was estimated using the Kaplan–Meier method with the Log-rank test. A P-value of 0.05 was considered statistically significant. For the statistical analysis, we used SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA).

2.2. Results

A total of 43 patients with recurrent uLMS were included during the study period. Their clinicopathologic characteristics are presented in Table 1. The duration of median follow-up was 100 months. The median age was 51 (range, 27-75) years, mostly (55.8%) was stage I. The median mitotic count was 31 (/10 HPF), mostly showed necrosis (86%) and severe atypia (65.1%) at initial diagnosis. All patients received surgery in the initial treatment, and most of them (81.4%) got no residual disease after primary surgery. Twenty-five patients (58.1%) were found to be longer than six months of PTFI, and the same number of patients (58.1%) received secondary CRS. The rates of distant metastasis were relatively high in first recurrence or second recurrence, respectively (60.5%, 65.1%).

Univariate and multivariate analyses were carried out to verify favorable prognostic factor for TFI, TRS, and OS. First, only secondary CRS improved TFI (median, 8.1 vs. 4.6 mons; P=0.001) (Figure 1), which was favorable factors affecting TFI (HR, 0.298; 95% CI 0.137-0.646; P=0.002) (Table 2). And, only PTFI longer than six months was a significant variable for TRS (HR, 0.298; 95% CI 0.133-0.667; P=0.003) (Table 3), and OS (HR, 0.184; 95% CI 0.069-0.489; P=0.001) (Table 4). It improved TRS (median, 9.84 vs. 22.28 mons; P <0.001) (Figure 2A), and OS (median, 16.99 vs. 51.09 mons; P <0.001) (Figure 2B).

There was a total of 15 patients with multiple recurrences among recurrent uLMS patients. Among them, secondary CRS showed better TFI with borderline significance (P=0.059). There was no statistically significant difference in the survival rate (Figure 3). Among the recurrent uLMS patients with multiple recurrences, a total of 9 patients received secondary CRS. We analyzed whether residual tumor after secondary CRS affected TFI, OS, and TRS in these patients, and there was no statistical significance (Figure 4).

2.3. Conclusion

Despite appropriate primary treatment (almost all primary CRS), uLMS shows an aggressive disease pattern with a high risk of recurrence and poor clinical outcome. Standard therapy for recurrent disease is not fixed. So, the goal of this investigation was to evaluate the favorable prognostic factors in recurrent uLMS.

This study's retrospective analysis of 43 patients with recurrent uLMS demonstrated possible prognostic factors for TIF, TRS, and OS. Secondary CRS was associated with a significant improvement in TFI. In other words, if the recurrent disease is surgically resectable, CRS with the goal of no gross residual disease should be considered to extend the period until the secondary recurrence.

A few studies on the prognostic factors related to surgical resection for recurrent uLMS have previously been published (10, 15–22). According to them, prolonged time to recurrence (longer than six or twelve months) was frequently raised prognostic factor. Other mentioned factors are optimal resection, initial FIGO stage, site of recurrence, and the number of recurrences. Probably, time to recurrence is an implied factor of tumor biology, in line with what is discussed in ovarian cancer. For epithelial ovarian cancer, one of the most dependent on surgical factors in gynecologic cancers, a disease–free interval greater than six months is associated with improved survival outcomes.

Our data demonstrated that PTFI longer than six months was the strongest factor associated with a better outcome. It showed improvement of TRS and OS. And, after maximal CRS in multiple recurrences, it is expected that the TFI can be delayed even if there is no significant difference in the survival regardless of residual tumors.

This study has some limitations. The analysis was done based on retrospectively collected data, with the small number of cases and missing data on treatments related to prognosis. Despite the shortcoming of this study, we have drawn some meaningful

conclusions. This study suggested favorable prognostic factors for TFI, TRS, and OS. It would be better to increase the number of cases through multicenter research or through meta-analysis to increase the reliability of the study in the future.

Conclusively, we demonstrated that secondary CRS are favorable factors for TFI, and longer than six months of PTFI may be important for improving TRS and OS in recurrent uLMS. Even in multiple recurrences, secondary CRS can help delay the second recurrence. This result may be helpful in counseling patients with recurrent uLMS. Despite some limitations, these results provide useful messages to patients with recurrent uLMS and physicians.

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국문 초록

재발성 자궁 평활근육종의 예후 인자 분석

배경: 자궁육종암은 대부분 조기에 진단됨에도 불구하고 매우 높은 재발률을 보이며, 적극적인 치료를 하더라도 절반 이상에서 재발을 하는 것으로 알려져 있다. 치명률이 높고 재발을 잘하지만 유병률이 낮아서 재발성 자궁평활근육종에 대한 치료 및 예후 인자에 대한 연구가 많지 않은 실정이다. 이에 재발성 자궁 평활근육종의 예후와 관련된 인자를 분석하고자 하였다.

방법: 2000년 1월부터 2020년 12월까지 서울대학교병원에서 재발성 자궁 평활근육종 진단 및 치료를 받은 사람을 데이터베이스로 검색하여 질병의 재발과 생존에 영향을 미칠 수 있는 예후 인자를 추출하여 분석하였다. 무 치료 기간, 치료 관련 생존기간, 전체 생존기간에 영향을 줄 수 있는 예후 인자를 Kaplan-Meier의 방법과 Cox 비례 위험 회귀 분석을 사용하여 분석을 수행하였다.

결과: 총 43 명의 재발성 자궁평활근육종 환자가 확인되었고, 이 중 25명 (58.1%)이 2차 종양감축 수술을 받았다. 2차 종양감축술은 무 치료 기간의 개선에 관련이 있었고, (중앙값, 8.1 vs. 4.6 개월; P=0.001)으로 유의한 개선을 보여주었다. 여러 변수들 중에서 이전 치료로부터 재발까지의 기간이 6개월보다 긴 경우만 치료 관련 생존기간 (HR, 0.298; 95% CI 0.133-0.667; P=0.003) 및 전체 생존 기간 (HR, 0.184; 95% CI 0.069-0.489; P=0.001)에 유의한 변수였다. 이 경우, 치료 관련 생존기간 (중앙값, 9.84 vs. 22.28 개월, P <0.001)와 전체 생존 기간(중앙값, 16.99 vs. 51.09 개월, P <0.001)을 각각 개선하였다. 다발성 재발을 보인 15명의 환자에서 2차 종양감축 수술은 무 치료기간의 연장 가능성을 보였다 (P=0.059).

결론: 이러한 결과는 재발성 자궁 평활근육종에서 2차 종양 감축 수술이 무 치료기간의 연장, 즉 재발까지의 기간을 늘리는데 호재라는 것을 보여주었다. 또한, 치료로부터 재발까지의 기간이 6개월보다 긴 경우가 치료 관련 생존기간, 전체 생존기간 개선에 중요한 요인일 수 있음을

확인할 수 있었다. 또한, 다발성 재발을 보인 경우에서도 최대 종양감축 수술은 무 치료기간의 연장에 지연 효과가 있을 수 있음을 확인하였다.

주요어: 자궁 신생물, 재발성 평활근육종, 예후, 종양감축술, 생존률
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Tables

Table 1. Clinical and pathological characteristics of the patients

Characteristics No. of patients (% of patients)	All patients (n=43)
Age (median, range, mons)	51 (27−75)
FIGO stage	
I	24 (55.8)
II	4 (9.3)
III	4 (9.3)
IV	11 (25.6)
Mitotic count (median, range, /10 HPF)	31 (7−137)
Necrosis at initial diagnosis	
Yes	37 (86)
No	3 (7)
Atypia at initial diagnosis	
Mild	0 (0)
Moderate	10 (23.3)
Severe	28 (65.1)
Treatment at initial diagnosis	
Surgery alone	11 (25.6)
Surgery+Chemotherapy	27 (62.8)
Surgery+Radiotherapy	4 (9.3)
Surgery+Chemotherapy+Radiotherapy	1 (2.3)
Residual disease after primary surgery	
Yes	7 (16.3)
No	35 (81.4)
Prior treatment−free interval (PTFI)	
≤ six months	18 (41.9)
> six months	25 (58.1)
Recurrence pattern (1st recurrence)	
Localized	15 (34.9)
Distant	26 (60.5)
Treatment at 1st recurrences	
Surgery alone	3 (7)
Surgery+Chemotherapy	19 (44.2)
Surgery+Radiotherapy	1 (2.3)
Surgery+Chemotherapy+Radiotherapy	2 (4.7)
Chemotherapy±Radiotherapy	16 (37.2)
Secondary cytoreductive surgery (CRS)	

Yes No	25 (58.1) 18 (41.9)
Recurrence pattern (2nd recurrence) Localized Distant	 8 (18.6) 28 (65.1)
Duration of follow up (median, range, mons)	100 (15-298)

FIGO, International Federation of Gynecology and Obstetrics; HPF, high power field;

Table 2. Factors affecting treatment-free interval in 43 patients with recurrent uterine leiomyosarcoma

Variables	Treatment-free interval			
	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age (≤50 vs. >50)	0.887 (0.454-1.732)	0.726	-	-
FIGO stage (I vs. II-IV)	1.213 (0.618-2.381)	0.574	-	-
Mitotic counts (≤30 vs. >30 / 10 HPF)	1.896 (0.943-3.812)	0.073	-	-
Tumor necrosis (No vs. Yes)	1.207 (0.364-4.001)	0.759	-	-
Atypia (moderate vs. severe)	1.888 (0.758-4.704)	0.172	-	-
Residual disease after primary CRS (No vs. Yes)	2.069 (0.842-5.082)	0.113	-	-
1st recurrence pattern (localized vs. distant)	1.619 (0.663-3.953)	0.290	-	-
Secondary CRS (No vs. Yes)	0.318 (0.152-0.665)	0.002	0.298 (0.137-0.646)	0.002
PTFI (≤ six vs.> six months)	0.450 (0.228-0.886)	0.021	-	-

HR, hazard ratio; CI, confidential interval; FIGO, International Federation of Gynecology and Obstetrics; HPF, high-power field; CRS, cytoreductive surgery; PTFI, Prior treatment-free interval

Table 3. Factors affecting treatment-related survival in 43 patients with recurrent uterine leiomyosarcoma

Variables	Treatment-related survival			
	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age (≤50 vs. >50)	0.990 (0.508-1.929)	0.976	-	-
FIGO stage (I vs. II-IV)	1.636 (0.829-3.231)	0.156	-	-
Mitotic counts (≤30 vs. >30 / 10 HPF)	1.853 (0.927-3.704)	0.081	-	-
Tumor necrosis (No vs. Yes)	1.688 (0.503-5.662)	0.396	-	-
Atypia (moderate vs. severe)	1.209 (0.531-2.750)	0.651	-	-
Residual disease after primary CRS (No vs. Yes)	2.575 (0.990-6.700)	0.053	-	-
1st recurrence pattern (localized vs. distant)	3.728 (1.252-11.102)	0.018	-	-
Secondary CRS	0.406 (0.198-0.834)	0.014	-	-
PTFI (≤ six vs.> six months)	0.223 (0.103-0.483)	< 0.001	0.298 (0.133-0.667)	0.003

HR, hazard ratio; CI, confidential interval; FIGO, International Federation of Gynecology and Obstetrics; HPF, high-power field; CRS, cytoreductive surgery; PTFI, Prior treatment-free interval

Table 4. Factors affecting overall survival in 43 patients with recurrent uterine leiomyosarcoma

Variables	Overall survival			
	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age (≤50 vs. >50)	1.412 (0.692-2.878)	0.340	-	-
FIGO stage (I vs. II-IV)	1.661 (0.837-3.297)	0.147	-	-
Mitotic counts (≤30 vs. >30/ 10 HPF)	2.030 (1.011-4.076)	0.047	-	-
Tumor necrosis (No vs. Yes)	1.203 (0.363-3.987)	0.762	-	-
Atypia (moderate vs. severe)	1.486 (0.648-3.404)	0.349	-	-
Residual disease after primary CRS (No vs. Yes)	2.849 (1.078-7.531)	0.035	-	-
1^{st} recurrence pattern (localized vs. distant)	0.388 (0.195-0.772)	0.007	-	-
Secondary CRS	0.113 (0.046-0.274)	< 0.001	-	-
PTFI (≤ six vs.> six months)	2.030 (1.011-4.076)	0.047	0.184 (0.069-0.489)	0.001

HR, hazard ratio; CI, confidential interval; FIGO, International Federation of Gynecology and Obstetrics; HPF, high-power field; CRS, cytoreductive surgery; PTFI, Prior treatment-free interval

Figures

Figure 1. Comparison of treatment-free interval (TFI) between secondary cytoreductive surgery (CRS) and chemotherapy or radiotherapy alone for 43 patients with recurrent uterine leiomyosarcoma

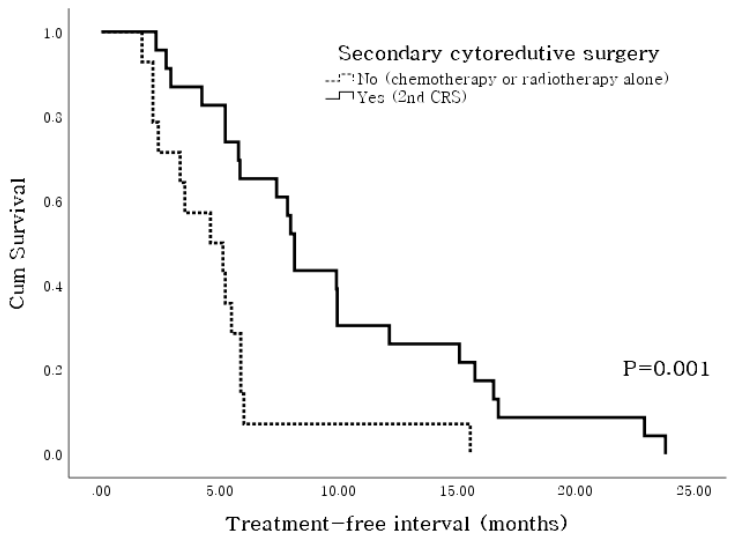
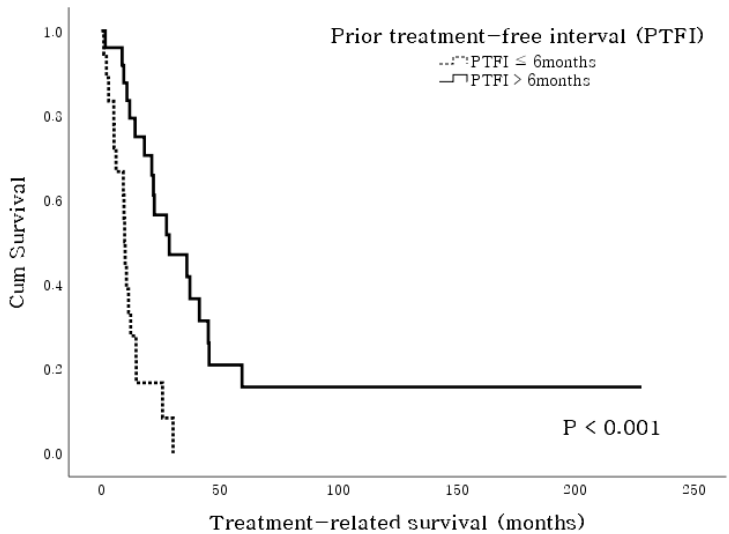


Figure 2. Comparison of treatment-related survival (TRS) (A) and overall survival (OS) (B) between less than six months and more than six months of prior treatment-free interval (PTFI) in 43 patients with recurrent uterine leiomyosarcoma

A



B

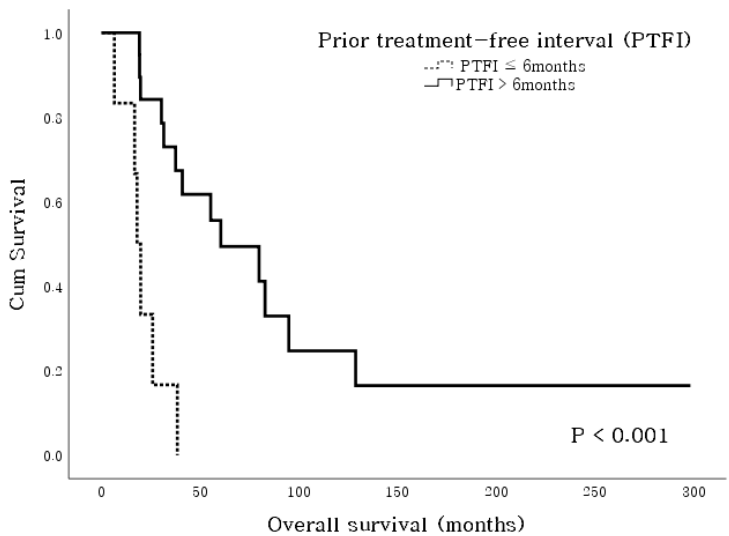
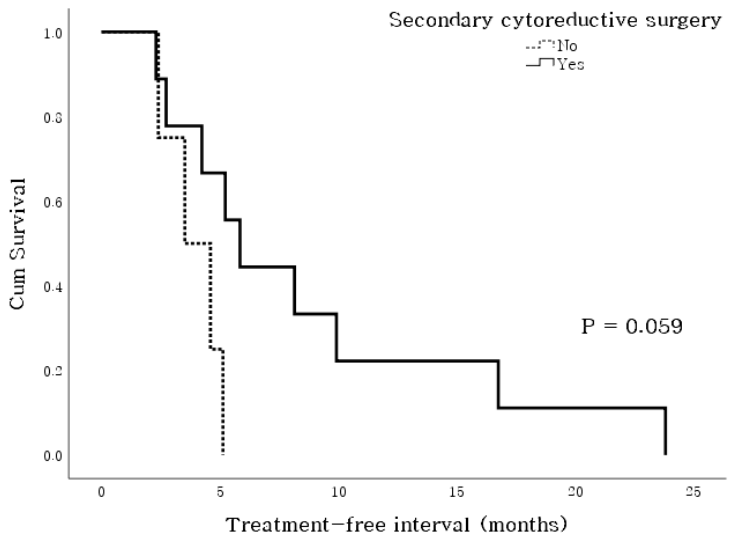
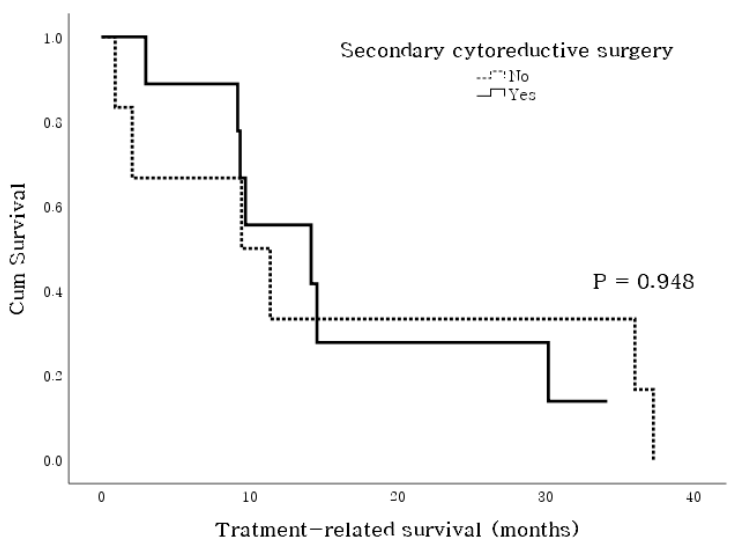


Figure 3. Comparison of treatment-free interval (TFI) (A), treatment-related survival (TRS) (B), and overall survival (OS) (C) between secondary cytoreductive surgery (CRS) and chemotherapy or radiotherapy alone in 15 patients with multiple recurrences of recurrent uterine leiomyosarcoma

A



B



C

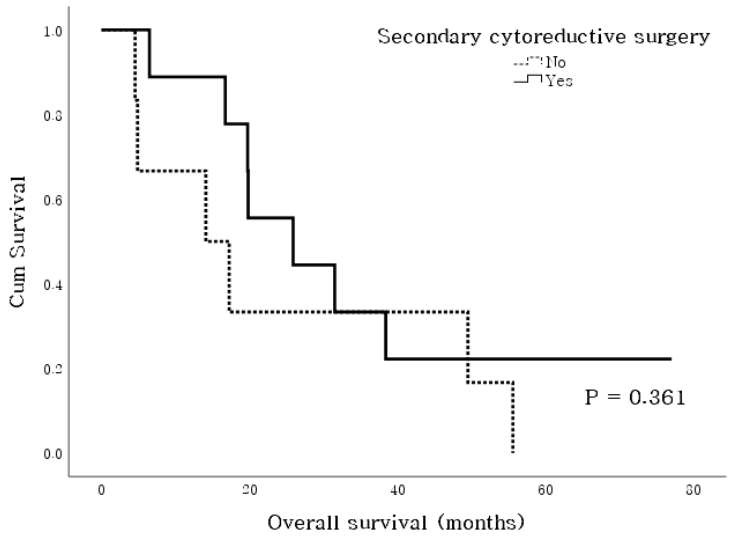
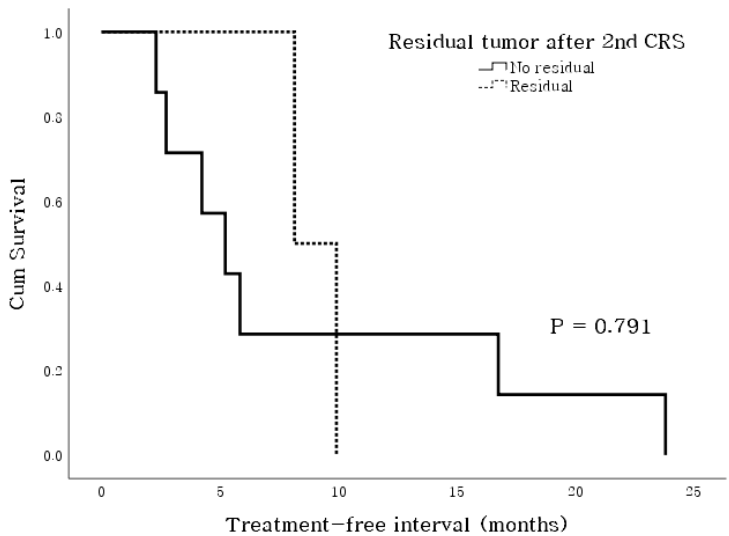
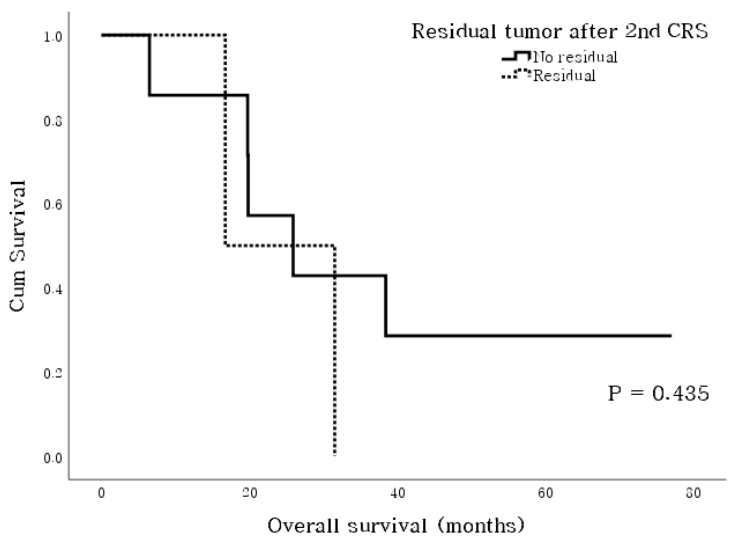

Secondary cytoreductive surgery
No
Yes
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
P = 0.361
Overall survival (months)

Figure 4. Comparison of treatment-free interval (TFI) (A), treatment-related survival (TRS) (B), and overall survival (OS) (C) according to a residual tumor or not after secondary cytoreductive surgery in 9 patients with multiple recurrences of recurrent uterine leiomyosarcoma

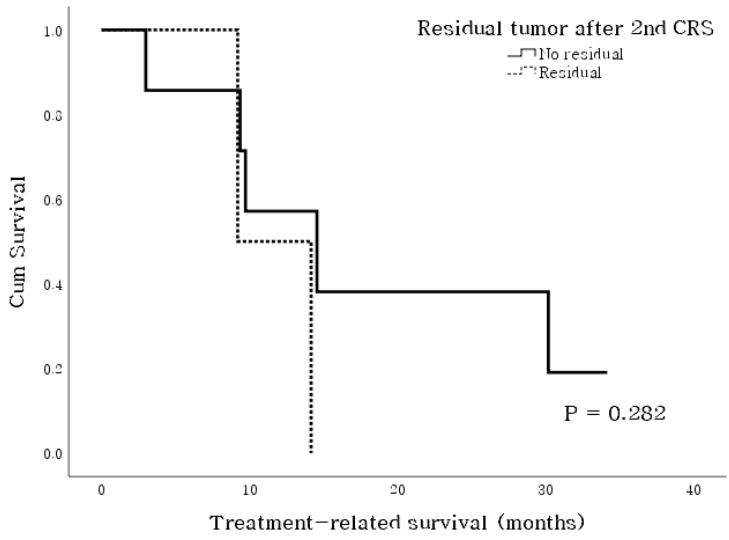
A



B



C


Residual tumor after 2nd CRS
No residual
Residual
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
P = 0.282
Treatment-related survival (months)