

# Retrospective Analysis of Uterine Sarcoma Cases Managed by a Single Institute

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## ABSTRACT

**Background & Objective:** This study aims to analyze the survival outcomes and prognostic factors of patients with uterine sarcoma in the Department of Gynaec-Oncology, between June 2015 and December 2022.

**Materials & Methods:** The study population consists of patients with histopathologically confirmed uterine sarcoma. The oncological data collected includes stage, pathological report, date and type of surgery, adjuvant therapy, recurrence, and mortality. Kaplan-Meier analysis used to estimate survival.

**Results:** We identified 58 eligible uterine sarcoma patients: 13 leiomyosarcoma (22.4%), nine endometrial stromal sarcoma (15.5%), 32 carcinosarcoma (55.2%), two adenosarcoma (3.4%) and another two were undifferentiated sarcoma (3.4%). Mean age was 56.1 (SD=12.03) and 56% of patients were postmenopausal. Majority of patients presented in stage III and IV (53.4%) and only 22 patients (37.9%) in stage I. Adjuvant radiotherapy was given to 21 patients (36.2%); eight patients (13.8%) received chemotherapy, and nine patients (15.5%) received both radiotherapy and chemotherapy. The median follow-up period was 13.5 months (range: 73 months) and total of 35 patients (60.3%) had recurrence with median time to recurrence of 6.0 months (range: 35). Death occurred in 21 patients (36.2%) with median time to death 5.0 months (range: 36 months). Progression free survival (PFS) among all patients was 26.64 (range: 4.32) months with significant correlation with stage of disease. Overall survival (OS) in patients received surgery only, radiotherapy and combined radiotherapy and chemotherapy were 23.3, 54.8 and 62.4 months respectively (P. value 0.03).

**Conclusion:** Uterine sarcoma is a relatively rare tumor type with poor survival. Multimodality adjuvant treatments were shown to improve prognosis in those patients.

**Keywords:** Leiomyosarcoma, Carcinosarcoma, Progression-free Survival, Kaplan-Meier Estimate



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## 1. Introduction

Uterine cancers contribute to 4.6% of cancers among Malaysian women, and majority are carcinoma (1). Uterine sarcomas constitute a rare and heterogeneous group of mesenchymal neoplasms, and they account for 3% to 7% of all uterine cancers (2). Uterine sarcomas were classified histologically into carcinosarcomas (CS), leiomyosarcomas (LMS), endometrial stromal sarcomas (EES) and undifferentiated sarcomas (US). Later, carcinosarcoma has been reclassified, due to its metastatic pattern, as an undifferentiated or most bizarre form of endometrial carcinoma (3). However, carcinosarcoma is still included in the majority of retrospective analysis of uterine sarcomas as it behaves more aggressively than the typical type of endometrial carcinoma. In 2014 World Health Organization (WHO) classification,

carcinosarcoma was listed in a separate section of “mixed epithelial and mesenchymal tumors” (4).

Use of adjuvant treatment remains controversial as there is lack of prospective research on the options. Adjuvant therapy reported being used in uterine sarcoma include radiotherapy, chemotherapy, immunotherapy. The role of adjuvant radiotherapy in uterine sarcoma (RT) has been a subject of discussions for many years, yet there is no consensus among various authorities (5).

This retrospective study aims to analyze the survival outcomes and prognostic factors of uterine sarcoma patients who had been operated on in the Department of Gynecology-Oncology of this institution between June 2015 and December 2022.

## 2. Materials and Methods

### Patients

This was a retrospective study of patients diagnosed with uterine sarcoma who were under treatment in the Gynaecology Department of this institute. The study population consists of patients with histopathologically diagnosed and confirmed to have uterine sarcoma, including leiomyosarcoma, endometrial stromal sarcoma, carcinosarcoma, adenosarcoma, and undifferentiated sarcoma.

Patients list was extracted from operation theatre list and cross-checked with histopathological record. The inclusion criteria for this study were undergoing primary surgery for uterine malignancy in this institution and a histopathological report of uterine sarcoma. We excluded patients with incomplete medical record and those diagnosed with another primary malignancy. Medical records retrieved from the hospital information system were assessed and reviewed. Demography and oncological data collected includes age, parity, menopausal status, FIGO stage, pathological report, date and type of surgery, type of adjuvant therapy, time of recurrence, and mortality.

### Definitions of variables

Overall survival (OS) was measured from the date of first operation to date of death or last follow-up for censored patients. Progression-free survival (PFS) was measured from the date of the first operation to the date of the first recurrence, death or date of last follow-up for censored patients.

### Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA). Estimation of OS and PFS were calculated using the Kaplan-Meier method with two-sided log-rank test. Univariate analyses were performed using the Cox proportional hazard model. A  $p$ -value  $<0.05$  was considered for statistical significance.

### Ethical approval

This study was approved by Medical Research and Ethics Committee of Malaysia (MREC) with MREC ID: NMRR ID-23-00768-S7A (IIR).

## 3. Results

During the study period, 58 eligible patients were identified from the archive of the institute. Mean age at diagnosis was 56.5 years; SD=54 (range: 30-84 years). Among them, 44 patients (75.9%) were parous, and 10 patients (17.2%) were nulliparous. The majority of them (56.9%) were post-menopausal (33 patients). Presenting symptoms include postmenopausal bleeding (50%), Abnormal uterine bleeding (27.6%), pain (6.9%) and abdominal distension or mass detection (5.2%).

For oncological characteristics, HPE subtypes were Carcinosarcomas (55.2%), Leiomyosarcomas (22.4%), Endometrial stromal sarcomas (15.5%), Adenosarcomas (3.4%) and Undifferentiated sarcomas (3.4%).

All patients were operated (total / radical hysterectomy with/without oophorectomy and pelvic lymph node dissection). The majority of them presented with stage III and IV disease (36.2% and 17.2%, respectively). Only 37.9% of patients were presented in stage I. Among them, 65.5% received adjuvant treatments; 36.2% received radiotherapy, 13.8% received chemotherapy and 15.5% received both radiotherapy and chemotherapy. Clinical features and oncological characteristics were summarized in [Table 1](#).

[Table 2](#) shows the crosstabulation of treatment received and stage of disease according to different HPE subtype. Leiomyosarcomas in our cohort tend to be present in stage I whereas majority of Carcinosarcomas patients presented in stage III and IV. The majority of patients receiving adjuvant therapies were carcinosarcomas subtype and all patients receiving both chemotherapy and radiotherapy were carcinosarcomas.

The median follow up period was 14.5 months (range: 73). Recurrence occurred in 35 patients (60.3%) and median time to recurrence was 8.0 months (range: 35). Total of 21 patients (36.2%) died during follow up with median time to death was 8.0 months (range: 37).

The 2-year OS and PFS for all patients were 63.3% and 36.6%, respectively. Median PFS was 11 months (Std error: 2.67) and mean OS was 45.6 months (S.D.: 4.74).

### HPE Subtype

We exclude cases of undifferentiated sarcomas and adenosarcomas from the analysis due to there being only two cases for each type. There was no statistically significant difference in OS and PFS between the remaining groups, however patients with endometrial stromal sarcomas tend to perform better (mean OS: 47.64 months; S.E.: 10.85 and mean PFS: 44.66 months; S.E.: 11.30). [Figure 1](#) shows the difference in OS (1A) and PFS (1B) according to different histopathological subtypes.

### Treatment Groups

[Figure 2 \(A\)](#) shows the difference in OS according to different treatment groups. Patients receiving radiotherapy and combined radiotherapy + chemotherapy had significantly longer mean OS; 62.8 months (SD=5.54) and 55.52 months (SD=7.09), respectively; compared to surgery alone (26.14 months (SD=5.91). (log rank comparison;  $p$  value = 0.025)

[Figure 2 \(B\)](#) shows the difference in PFS according to different treatment groups. Patients receiving

radiotherapy and combine radiotherapy + chemotherapy had longer median PFS; 11.0 months (SE=3.56) and 27.0 months (SE=10.43), respectively; compared to surgery alone (9.0 months (SE=11.73)) however the difference was not statistically significant. (log rank comparison;  $p$  value = 0.332).

#### Stage

[Figure 3 \(A\)](#) shows the difference in OS according to stages of disease. Patients diagnosed at stage I had mean survival of 66.41 months (S.E.: 5.13), while those in stage II, III and IV had shorter mean survival; 51.00 months (S.E.: 16.33) 34.57 months (S.E.: 6.45), and 18.47 months (S.E.: 7.63) respectively. The difference was significance ( $p$  value <0.001) and patients in stage IV had a hazard ratio for mortality of 16.14 ( $p$  value 0.01) compared to those in stage I; as shown in [Table 3](#).

[Figure 3 \(B\)](#) shows the difference in PFS according to stages of disease. Patients diagnosed at stage I had a mean PFS of 40.36 months (S.E. 6.45), while those in stage II, III and IV had shorter mean PFS; 24.47 months (S.E. 14.23), 20.31 months (S.E. 4.47), and 8.20 months (S.E. 3.21) respectively ( $p$  value 0001).

#### COX Univariate Regression Analysis

[Table 3](#) shows COX regression analysis for OS and OFS among all patients. We did another analysis after excluding patients in stage I disease ( $n=36$ ) and the difference was statistically significant with comparison using Breslow test showed  $p$ -value of 0.028 for PFS and <0.001 for OS (as shown in [Table 4](#)). Patients receiving both chemotherapy and radiotherapy have significantly lower probability for recurrence as shown in Hazard Ratio of 0.20 compared to those undergone surgery alone (95% CI, 0.05 – 0.72) and significantly lower hazard ratio for mortality; HR 0.03 (95% CI: 0.01 – 0.27).

**Table 1.** Clinical characteristics of patients

N		58
Age at diagnosis (years),		
Median (range)		56.5 (54)
Mean (SD)		56.1 (12.03)
Parity		n (%)
• Nulliparous		10 (17.2)
• Parous		44 (75.9)
• Missing		4 (6.9)
Menopausal status		n (%)
• Pre-menopausal		21 (36.2)
• Post-menopausal		33 (56.9)
• missing		4 (6.9)
Presenting symptom		n (%)
• postmenopausal bleeding		29 (50.0)
• AUB (menorrhagia)		16 (27.6)
• Pain		4 (6.9)
• Abdominal mass / distension		3 (5.2)
• missing		6 (10.3)
HPE type		n (%)
• Leiomyosarcoma		13 (22.4)
• Endometrial stromal sarcoma		9 (15.5)
• Carcinosarcoma (MMMT)		32 (55.2)
• Adenosarcoma		2 (3.4)
• Undifferentiated sarcoma		2 (3.4)

<b>N</b>	<b>58</b>
<b>FIGO Stage</b>	<b>n (%)</b>
• I	22 (37.9)
• II	5 (8.6)
• III	21 (36.2)
• IV	10 (17.2)
<b>Treatment received</b>	<b>n (%)</b>
• Surgery only	20 (34.5)
• Surgery + Adjuvant Radiotherapy	21 (36.2)
• Surgery + Adjuvant chemotherapy	8 (13.8)
• Surgery + Adjuvant Radiotherapy & Chemotherapy	9 (15.5)
<b>Recurrence</b>	
<b>n (%)</b>	<b>35 (60.3)</b>
<b>Death</b>	
<b>n (%)</b>	<b>21 (36.2)</b>
<b>Follow up period (months)</b>	
<b>Median (range)</b>	<b>14.5 (73)</b>
<b>Mean (SD)</b>	<b>22.8 (21.58)</b>
<b>Time to recurrence (months)</b>	
<b>Median (range)</b>	<b>8.0 (35)</b>
<b>Mean (SD)</b>	<b>10.77 (8.8)</b>
<b>Time to death (months)</b>	
<b>Median (range)</b>	<b>8.0 (37)</b>
<b>Mean (SD)</b>	<b>11.57 (11.49)</b>

\*AUB: Abnormal uterine bleeding; HPE: Histopathological Examination; SD: Standard Deviation

**Table 2.** Crosstabulation of disease stage and treatment group against different HPE subtype

Type of HPE	Stage					Treatment group				
	I	II	III	IV	<u>Total</u>	Surgery only	Adj RT	Adj chemo	Both RT & chemo	<u>Total</u>
<b>Leiomyosarcoma</b>	8	1	2	2	13	5	4	4	0	13
<b>Endometrial stromal sarcoma</b>	4	1	3	1	9	6	2	1	0	9
<b>Carcinosarcoma</b>	8	3	15	6	32	7	13	3	9	32
<b>Undifferentiated sarcoma</b>	0	0	1	1	2	2	0	0	0	2
<b>Adenosarcoma</b>	2	0	0	0	2	0	2	0	0	2
<b>Total</b>	22	5	21	10	58	20	21	8	9	58

**Table 3.** Cox Univariate Analysis for OS and PFS among all patients

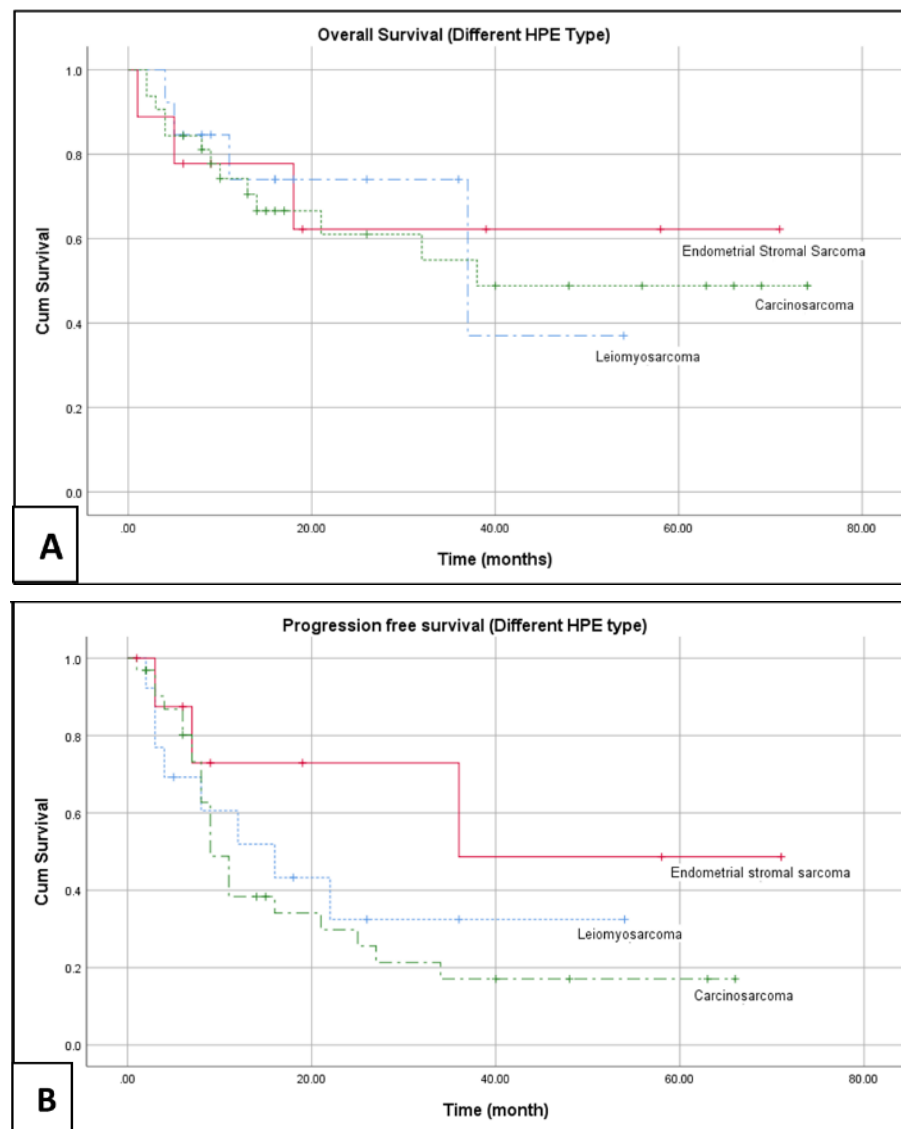
	Mean OS (months)	p-value*	HR (mortality)	Mean PFS (months)	p-value*	HR (recurrence)
	SE		(95% CI)	SE		(95% CI)
<b>Menopause</b>						
<b>No (n=21)</b>	51.37 6.58	0.246	1	41.74 7.06	0.018	1
<b>Yes (n=33)</b>	42.72 6.40		1.76 (0.66 – 4.66)	17.02 3.37		2.43 (1.11 – 5.33)
<b>Stage</b>						
<b>I</b>	66.41 6.133	0.000	1	40.36 6.45	0.001	1
<b>II</b>	51.00 16.33		2.63 (0.24 – 29.08)	24.67 14.24		2.03 (0.55 – 7.54)
<b>III</b>	34.57 6.45		6.74 (1.49 – 30.43)	20.31 4.47		2.18 (0.95 – 4.99)
<b>I V</b>	18.47 7.63		16.14 (3.30 – 78.85)	8.20 3.21		5.35 (2.03 – 14.11)
<b>Treatment group</b>						
• <b>Surgery only</b>	26.13 5.913	0.025	1	26.70 6.79	0.332	1
• <b>Adj Radiotherapy</b>	55.52 7.09		0.29 (0.12 – 0.85)	28.36 6.58		0.892 (0.38 – 2.09)
• <b>Adj Chemotherapy</b>	20.27 5.69		0.83 (0.26 – 2.26)	11.55 4.38		1.83 (0.68 – 4.97)
• <b>Both RT &amp; chemo</b>	62.80 5.54		0.10 (0.01 - 0.82)	30.40 7.53		0.76 (0.27 – 2.16)
<b>HPE type (n=54)</b>						
• <b>All (exclude adenosarcoma &amp; undifferentiated)</b>	45.37 4.86			26.34 4.05		
• <b>Leiomyosarcoma</b>	35.54 6.70	0.702	1	23.94 6.36	0.437	1
• <b>ESS</b>	47.64 10.85		1.00 (0.22 – 4.51)	44.66 11.30		0.49 (0.13 – 1.88)
• <b>Carcinosarcoma</b>	43.99 6.16		1.21 (0.39 – 3.73)	20.98 4.21		1.21 (0.54 – 2.72)

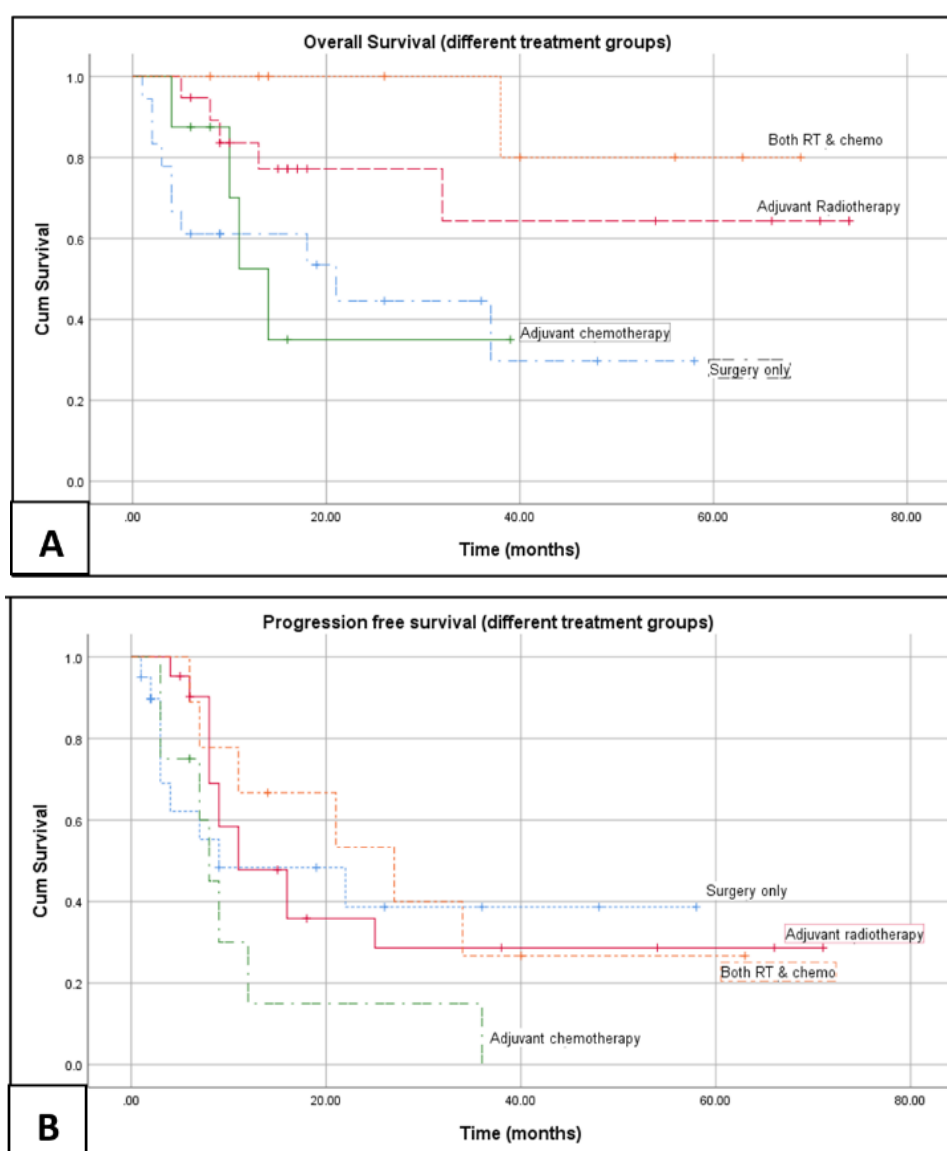
\*Log Rank (Mantel Cox) test for overall comparison

**Table 4.** Cox Univariate Analysis for OS and PFS among patients in stage II, III and IV according to different treatment groups

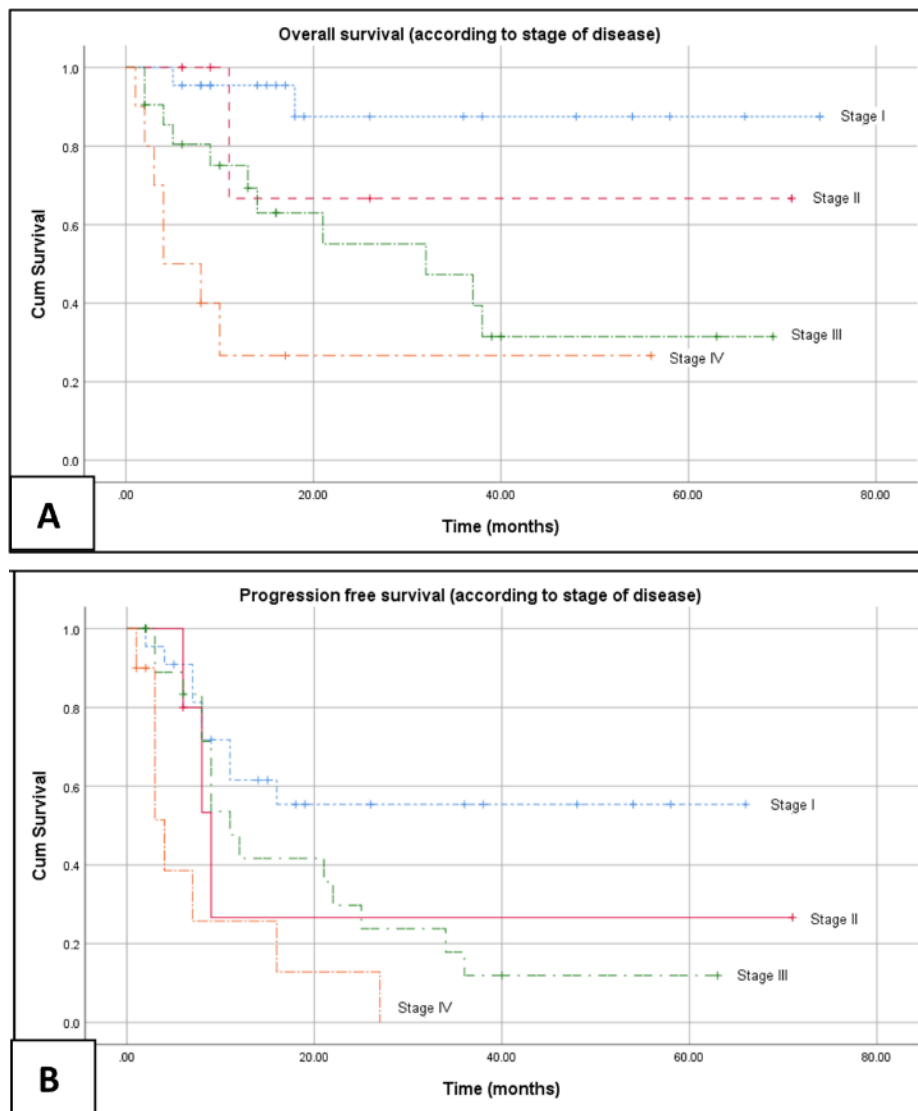
	Mean OS (months)	p-value*	HR (mortality)	Mean PFS (months)	p-value*	HR (recurrence)
	SE		(95% CI)	SE		(95% CI)
<b>OVERALL, exclude Stage 1 (n=36)</b>	33.01 5.46			18.28 3.81		
• Surgery only	8.48 3.83	0.000	1	7.364 3.35	0.028	1
• Adj Radiotherapy	35.95 11.23		0.19 (0.05 – 0.64)	17.686 6.73		0.43 (0.14 – 1.29)
• Adj Chemotherapy	20.27 5.69		0.26 (0.07 – 0.86)	11.550 4.38		0.57 (0.18 – 1.75)
• Both RT & chemo	62.80 5.54		0.03 (0.01 – 0.27)	32.143 8.06		0.20 (0.05 – 0.72)

\* Breslow (Generalized Wilcoxon) test for Overall comparison

**Figure 1.** Overall survival (1A) and Progression free survival (1B) in patients according to different HPE type.



**Figure 2.** Overall survival (2A) and Progression free survival (2B) in patients according to different treatment group.



**Figure 3.** Overall survival (3A) and Progression free survival (3B) in patients according to different stages of disease.

#### 4. Discussion

Almost half of our patients were menopausal during the diagnosis of uterine sarcoma and univariate analysis showed being menopausal is a poor prognostic factor for recurrence with a hazard ratio of 2.43 compared to pre-menopausal. Other studies had reported that menopausal status is associated with poorer prognosis and poor histopathological type (6, 7). Age being more than 52 years old had been reported to be one of significant prognostic factors and lead to shorter PFS and OS (8, 9). Apart from higher association with poor histopathological type, older age is associated with higher prevalence of co-morbidities and poorer performance status that may affect the choice of adjuvant treatment and its toxicities. With increasing life expectancy, we will see increasing incidence of uterine sarcoma, hence the need for better understanding and number of research in this subject (10).

Half of our patients were presented with postmenopausal bleeding and another 27.6% had abnormal uterine bleeding (pre-menopausal). The finding of per-vaginal bleeding as the commonest presentation in uterine sarcoma is consistent worldwide. Previous studies reported vaginal bleeding occurred in 45.2% - 95% of uterine sarcoma cases (11) and 17-37% presented with pelvic mass (12, 13). In the Thai study, almost all CS (23 patients or 92%) presented with abnormal uterine bleeding (12). Similarly in endometrial carcinoma, the most common presentation is postmenopausal bleeding, although contrary to uterine sarcoma, they are usually presented in early stage (14). A vigilant approach should always be taken in patients presented with postmenopausal bleeding, even though the probability of uterine cancers as the cause is small in majority of cases.

In our study, the majority of carcinosarcoma presented at stage 3, while LMS tend to present at stage



1. This finding concurs with the study by Durnali et al (15) who reported 56% of their CS patients were in stage 3 while 48.1% of LMS were in stage 1 (15). For all sarcoma patients, Potikul et al (12) reported the commonest stage was stage 1, followed by stage 3 and the least common was stage 2 (12). Previous studies reported that stage at presentation and surgery is a significant prognostic factor, both in OS and PFS of uterine sarcoma patients (15, 16).

For HPE type, 55% of our patients had carcinosarcoma. This finding was consistent with previous studies in Thailand (12), U.S. SEER Database (17), Canary Island (13), China (6) and Spain (11) which found carcinosarcoma in 54.3%, 53%, 48%, 47% and 44% of their uterine sarcoma patients respectively. In contrast, Ebner et al (18) and Morice et al (19) Momtahan et al (9) found most of their patients had LMS (44-46% - 54.7%) while Yu et al (5) found equal proportion of CS (20), LMS (21) and EES (22). A study by Kyriazoglou et al (23) did not include carcinosarcoma under their uterine sarcoma analysis and found LMS counted for 50% of their cohort of 61 patients (23). The difference in the findings might be caused by exaggerated proportion of each pathological type, due to small number of patients in each individual and different population characteristic being studied, such as age and race. The finding of better survival in EES group had been reported in an Iranian cohort by Behtash and Akhavan (24).

In our study, among 32 carcinosarcoma patients, 22 received radiotherapy as adjuvant treatment. The use of adjuvant radiotherapy in carcinosarcoma patients was higher than reported in the literature (48 – 60%) (11, 15, 20, 21). In general, carcinosarcoma is regarded as carrying higher risk and presented at relatively higher stage as shown in our series (almost 50% in stage 3). This may explain the higher rate of radiotherapy given to carcinosarcoma patients. Hosh M et.al. had reported that their carcinosarcoma patients receiving adjuvant radiotherapy had significantly better survival than those who underwent surgery alone (17).

For all patients, adjuvant radiotherapy plus chemotherapy showed a longer overall survival as compared to patients without adjuvant treatment. Patients receiving chemotherapy only post-surgery had shorter OS of 20 months compared to 26 months for surgery only. However, if we exclude patients with stage 1, all adjuvant treatment groups showed better OS compared to surgery only with combination of radiotherapy and chemotherapy lead to significantly lower hazard ratio (0.03) of mortality and longest OS of 62 months. Durnali et al (15) found that sequential adjuvant treatment with chemotherapy and radiotherapy had significant longer overall survival for leiomyosarcoma subtype (15). Momtahan et al (9) reported no benefit of adjuvant radiotherapy plus chemotherapy, in which their survival was 50%, like those receiving surgery alone (9). This may be due to

their patient selection, where the combination treatment is given to those in higher stage of disease.

Trend of better prognosis for those receiving adjuvant treatment was also evidenced in significantly longer PFS among stage 2 to 4 patients. Patients in radiotherapy plus chemotherapy group had significantly lower hazard ratio of recurrence (0.2 compared to those who underwent surgery only). This observation had been reported in a previous study by Durnali et al (15) that reported in multivariate analysis, sequential adjuvant treatment with chemotherapy and radiotherapy had longer relapse-free survival (HR of 0.17, p value 0.002) for all subtypes and significantly longer overall survival for leiomyosarcoma subtype (15).

Regarding adjuvant radiotherapy without chemotherapy, our series showed significantly better OS in all patients and better PFS in stage 2-4 patients compared to surgery alone. This observation had been shown in previous reports (9, 17, 25). However, in the study by Hosh et al (17) it was reported that in localized uterine sarcoma, patients underwent surgery alone showed significantly better survival compared to those receiving radiotherapy after surgery (17). Other studies had reported the survival benefit of radiotherapy as adjuvant being shown only in carcinosarcoma patients, not in other subtypes (5). It has been reported that radiotherapy in EES patients lead to worse survival compared to those who underwent surgery alone (22). Adjuvant radiation shown to lead to better local control in a study (16).

Patients in chemotherapy group had worse outcomes compared to those underwent surgery only. Huss et al (8) reported the same observation; patients with no chemotherapy had significantly longer OS and PFS (8). This might be due to patients' profile, comorbidities and performance status, preventing them from being a suitable candidate for adjuvant radiotherapy. Another possible explanation are complication of chemotherapy and choice of more toxic drugs. We did not analyze further regarding the patients' selection and choice of chemotherapy drugs for this study. Huss et al (8) also reported their observation as a compounding factor, as the association was unable to be confirmed in multivariate analysis (8). Several studies investigating the use of chemotherapy in uterine sarcoma had many biases and limiting factors, hence concluded that the role of adjuvant chemotherapy in these case remains controversial. The challenges in designing a big randomized controlled trial in uterine sarcoma are due to the rarity of the disease (26).

Overall prognosis of our sarcoma patients was poor. In our study, the 2-year OS and PFS for all patients were 63.3% and 36.6%, respectively. Median PFS was 11 months, and mean OS was 45.6 months, comparative to a Korean study with 5-year OS of 64.2% (5). Potikul et al (12) reported in a Thai study of 46 patients, the 2-year OS and PFS was 48.3% and 45.2% respectively with shorter median time to

recurrence of 5.8 months (12). In our patients, 60% of patients had recurrence. This is concordant with other studies which found recurrences ranging from 37% to 63% (13, 18, 20, 27).

In our study, univariate analysis showed menopausal status is a significant prognostic factor for PFS but not for OS. Only stage of disease and receiving radiotherapy were found to be a significant prognostic factor in our cohort. Other pathological factors that had been reported to affect survival outcome in other studies include tumor size (7), progesterone receptor negativity (8), residual disease / surgical margins (7, 8, 28), presence of recurrence (7), tumor morcellation (18), lymph node involvement (7) and pre-operative neutrophil / lymphocyte ratio (6, 29). Interestingly, Blay et al (30) found in their study that multidisciplinary team management and discussion in tumor board are significant predictors for better survival in uterine sarcoma patients (30).

## 5. Conclusion

In this study, we did not analyze different regimes of chemotherapy and radiotherapy, the pattern and management of recurrence, multiple surgical characteristics such as lymph node dissection, residual disease, surgical route, tumor size and tumor grading. Further analysis of these aspects may lead to a better understanding of the disease pattern and survival in Malaysian populations. Our data support the use of adjuvant radiotherapy and chemotherapy in uterine sarcoma patients, especially in stage 2 to 4 patients; and to avoid chemotherapy only as adjuvant treatment in stage 1 disease. Significant prognostic factors include menopausal status and stage of disease. Further

analysis involving pathological characteristics and recurrence pattern is warranted and may give positive insight into understanding of this relatively rare disease.

## 6. Declarations

### Acknowledgments

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### Ethical Considerations

This study was approved by Medical Research and Ethics Committee of Malaysia (MREC) with MREC ID: NMRR ID-23-00768-S7A (IIR).

### Authors' Contributions

All authors contributed to methodology development and reviewed the manuscript. The corresponding author performed the data analysis and wrote the original draft.

### Conflict of Interest

The authors declare no conflict of interest.

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