GYNAECOLOGY

Prognostic Factors and Survival Outcome of Uterine Sarcoma Patients: 21 Years Experience at Ramathibodi Hospital

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ABSTRACT

Objectives: To evaluate the prognostic factors that may affect the survival outcome of patients with uterine sarcoma.

Materials and Methods: In this retrospective study, various clinicopathologic factors and treatment of 58 patients with uterine sarcoma treated between January 1987 and December 2007 at Ramathibodi Hospital were reviewed. Univariated and multivariated logistic regression model were used to evaluate the prognostic factors for statistical significance. The survival was assessed by Kaplan-Meier method and proportional hazards method.

Results: During the study period, 58 uterine sarcoma patients met the inclusion criteria. The median follow up time was 19.8 month. Fifty-three patients had primary surgery and then received adjuvant therapies which were radiation in 21 cases (36.2%) and chemotherapy in 26 cases (44.8%). The 5-year overall survival rate was 46%. The median survival time was 21 months. The overall death rate was 14/1000/month. The univariate analysis showed that residual tumor, age $\geq$ 50 years, advanced stage undergoing bilateral salpingo – oophorectomy (BSO) and carcinosarcoma were significant with poor survival. Patients who underwent hysterectomy were associated with longer survival time than those who did not (Median survival time (MST) 31.1 vs 7.1 months, p = 0.02). The multivariate analysis showed that residual tumor after surgery and age $\geq$ 50 years were significantly associated with poor survival. Hysterectomy was significantly associated with good survival.

Conclusion: The overall survival of uterine sarcoma patients was rather short. The unfavorable prognostic factors were residual tumor after surgery and age $\geq$ 50 years. The favorable prognostic factor was undergoing hysterectomy.

Keywords: uterine sarcoma, prognostic factors

Introduction

Uterine sarcomas are rare tumors that account for 1-3 % of all malignancies in the female genital tract[1] and 3-5% of all malignancies in the uterus[2]. The worldwide incidence rate is between 0.5-3.3 cases per 100,000 women per year[3]. These malignancies are aggressive and progress rapidly. The most common histologic types are carcinosarcoma and leiomyosarcoma

which account for approximately 85% of all cases and endometrial stromal sarcoma which account for 15% of cases[1,2,4].

Treatment of uterine sarcomas are hysterectomy with or without bilateral salpingo-oophorectomy (BSO) and pelvic lymph nodes sampling[5]. The role of adjuvant therapies is controversial. Radiation seems to improve local control but not survival[1]. Adjuvant chemotherapy does not decrease the risk of metastatic spread or improve survival[4,6]. Endometrial stromal sarcoma is the only uterine sarcoma that responds to hormonal manipulation[7].

The prognosis of uterine sarcoma patients are poor. Overall 5-year survival has been between 17.5-54.7%[8]. Prognostic factors vary such as stage, age, tumor size, parity, residual tumor and adjuvant treatment[8,9].

The aim of our study was to evaluate, retrospectively, clinical data of uterine sarcoma treated in Ramathibodi Hospital between January 1987 and December 2007. Prognostic factors and survival outcome of uterine sarcoma patients were evaluated.

Materials and Methods
Patients

The present study included uterine sarcoma patients who were treated at the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Ramathibodi Hospital. Those who had uncertain malignant potential tumors were excluded.

Methods

The present study was conducted after approval of the Institution Ethics Committee. Between January 1987 and December 2007, patients with uterine sarcoma who received treatment in our institution were identified. Those who met the inclusion criteria were recruited in the present study. Patients' clinical and pathological data were collected from the patients' charts. Data of age, menopausal status, International Federation of Gynecology and Obstetrics (FIGO) stage[10], tumor histological cell type and grade, the type of primary surgery include residual tumor, the type and dose of radiation, the type of chemotherapy and the disease response were collected. Status at last contact was noted. The responses were defined as following: complete response was defined when there was no clinical evidence of tumor after treatment, partial response was defined when tumor reduction was $\geq$ 50% and stable disease when a tumor that was unchanged in size or had decreased < 50% or increased < 25%. Progressive disease was defined as an increase in tumor size $\geq$ 25% or development of new lesion[11]. Response of abdominal disease was evaluated by CT scan or ultrasound. CT chest and chest x-ray were used in lung metastasis.

Statistical analysis

Patients' characteristics were described by means [+ standard deviations (SDs)] or median (range) in continuous data and by frequency in group data. Survival time was defined as length of time from date of initial diagnosis of uterine sarcoma to either the date of death or last follow-up. The Kaplan-Meier test was used to estimate the overall probability of survival. The log-rank test was used to compare the median survival time among factors. The cox's proportional hazard model was used to estimate hazard ratio of prognostic factors. A p < 0.05 was considered statistically significant.

Results

Between January 1987 and December 2007, 58 uterine sarcoma patients who were diagnosed and treated at Ramathibodi Hospital were identified. As shown in Table1, the mean age of the patients was 52.5 years. The median follow-up time was 19.8 months (range 0.4-187.2 months). Twenty four patients (41.4%) were in the premenopausal state. With regard to the histological type, 26 cases were diagnosed as carcinosarcoma, 22 cases as leiomyosarcoma and 10 cases as endometrial stromal sarcoma. The first line treatment was surgery in 53 patients (91.4%). The primary operation was hysterectomy in 53 patients. Bilateral salpingo-oophorectomy (BSO) was performed in 42 of the 53 patients. Lymphadenectomy, omentectomy

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and peritoneal washing was performed in 14 of the 53, 27 of the 53 and 24 of the 53 patients, respectively. Hysterectomy was not performed in 5 cases. The diagnosis were from fractional curettage in 2 cases, cervical biopsy in 1 case, tissue found in vagina in 1 case and from myomectomy specimen in 1 case. Chemotherapy was given in advanced and recurrent disease. Chemotherapy was given to 26 patients (41.4%). The first line chemotherapy regimens were cisplatin combined with adriamycin, cisplatin combined with ifosfamide, single agent adriamycin or ifosfamide. Pegylated liposomal doxorubicin, pacitaxel and oral etoposide were used in salvage therapy. Cisplatin combined with adriamycin was the most common used regimen. Tamoxifen was used in only one patient. Radiation was given in stage II-IV and recurrent disease. Radiation was given to 21 patients (36.2%). Most patients underwent whole pelvic irradiation dose 50-50.4 Gy, 180-200 cGy/fraction. Five patients had additional brachytherapy 500-650 cGy/fraction, 1-3 times. Palliative radiation 30 Gy (10Gy/fraction) at bone, paraaortic nodes and supraclavicular nodes was used in five patients. At the end of follow up 17 cases (29.3%) were alive, 37 cases (63.8%) were died and 4 cases (6.9%) lost to follow-up.

Kaplan-Meier survival curve was generated to evaluate overall survival as shown in Fig. 1. The 5-year overall survival rate was 46 %. The median survival time (MST) was 21 months (carcinosarcoma 11.5 months, leiomyosarcoma 66.8 months and endometrial stromal sarcoma 59.7 months). The overall death rate was 14/1000/months.

The results of univariate analysis of relationships between factors and death were shown in Table 2. Residual tumor, age $\geq$ 50 years, advanced stage, undergoing BSO and carcinosarcoma were significant with poor survival. Patients who underwent hysterectomy were associated with longer survival time than those who did not (MST 31.1 vs 7.1 months, p = 0.02). However, lymphadenectomy, omentectomy, peritoneal washing and adjuvant chemotherapy or radiation were not significantly associated with survival.

Table 3 shows multivariate analysis of relationships between risk factors and death. Residual tumor after surgery and age $\geq$ 50 years were significantly associated with poor survival. Hysterectomy was significantly associated with good survival.

Table 1. Baseline Characteristics

Characteristics	N (%)
Mean age; years (SD)	52.5 ($\pm$14.7)
Postmenopause	
Yes	34 (58.6)
No	24 (41.4)
Cell types	
Carcinosarcoma	26 (44.8)
Leiomyosarcoma	22 (37.9)
Endometrial stromal sarcoma	10 (17.3)
Stage	
I	23 (39.7)
II	5 (8.6)
III	14 (24.1)
IV	15 (25.9)
Unstage	1 (1.7)

Table 1. Baseline Characteristics (cont.)

Characteristics	N (%)
TAH	
Yes	53(91.4)
No	5(8.6)
BSO	
Yes	42 (72.4)
No	16 (27)
Lymphadenectomy	
Yes	14(24.1)
No	44(75.9)
Omentectomy	
Yes	27(46.5)
No	31(53.6)
Peritoneal washing	
Yes	24(41.4)
No	34(58.6)
Chemotherapy	
Yes	26(44.8)
No	32(55.2)
Radiation	
Yes	21(36.2)
No	37(63.8)
Response of treatment	
complete response	17(29.3)
partial response	1(1.7)
stable disease	1(1.7)
progressive disease	39(67.3)
Status at the end of follow-up	
Alive	17(29.3)
Death	37(63.8)
Loss to follow-up	4(6.9)

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Table 2. Factors associated with death after diagnosis of uterine sarcoma: Univariate analysis

Factors	Total subject	No. of death	Death rate /1000/month	Median survival time (month)	p-value
Residual tumor					
Yes	11	11	169	5.5	<0.001
No	47	26	10	60.9	
Age					
<50 (yrs.)	22	7	4	-	
≥50 (yrs.)	36	30	35	11.5	<0.001
Stage					
I	23	8	4	-	
II	5	3	26	14.5	<0.001
III	14	11	19	19.2	
IV	15	15	74	6.2	
TAH					
Yes	53	33	13	31.1	0.02
No	5	4	101	7.1	
BSO					
Yes	42	31	20	14.2	0.02
No	16	6.0	5	-	
Lymphadnectomy					
Yes	14	10	22	14.5	
No	44	27	12	21.1	0.52
Omentectomy					
Yes	27	19	18	20.2	
No	31	18	11	31.1	0.29
Peritoneal washing					
Yes	24	15	13	30.4	
No	34	22	15	19.4	0.6
Radiation					
Yes	21	14	22	19.2	
No	37	23	11	31	0.45
Chemotherapy					
Yes	26	21	21	14.5	
No	32	16	9	66.8	0.15
Histologic type					
Carcinosarcoma	26	21	31	11.5	
Leiomyosarcoma	22	10	8	66.8	
Endometrial stromal sarcoma	10	6.0	8	59.7	0.02

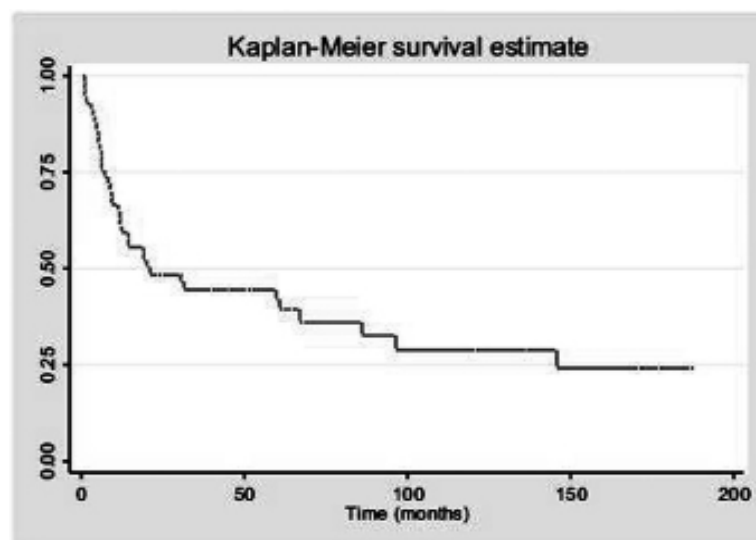TAH = total abdominal hysterectomy

BSO = bilateral salpingo-oophorectomy

Table 3. Prognostic factors of death for uterine sarcoma: multivariate analysis

Factors	HR (95% CI)	Standard error	p-value
Residual tumor			
Yes	5.6 (2.0-15.6)	2.92	0.001
No	1	-	
Age			
<50	1	-	0.034
≥50	3.3(1.1-10.2)	1.9	
Stage			
I	1	-	
II	1.1(0.2-5.1)	0.9	0.099
III	2.0(0.8-5.4)	1.0	0.152
IV	2.5(0.8-7.5)	1.4	0.970
Histologic type			
Carcinosarcoma	0.4(0.1-1.3)	0.2	0.1
Leiomyosarcoma	0.4(0.1-1.3)	0.2	0.1
Endometrial	1	-	
stromal sarcoma			
TAH			
Yes	0.6(0.0-0.4)	0.06	0.006
No	1	-	
BSO			
Yes	2.85(0.57-14.15)	2.3	0.2
No	1	-	

Median survival time = 21 months

Probability of survival

Fig. 1. Overall survival curve for the study patients (n=58)

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Discussion

Uterine sarcomas are rare and aggressive neoplasms of the female genital tract. From the previous study of our institution, the incidence of uterine sarcomas were 7.5% of uterine malignancy patients admitted (26/346) and 10.7/10,000 gynecologic admissions (total gynecologic admissions = 24,357)[12].

Distribution of sarcoma subtypes were as follows: carcinosarcoma 44.8%, leiomyosarcoma 37.9% and endometrial stromal sarcoma 17.3%. This proportions are similar to many recent literature[8,13]. Surgery is the primary treatment of uterine sarcomas. Hysterectomy and BSO are the standard treatment for uterine sarcomas[5,8]. From our study, hysterectomy was performed in 53 patients (91.4%). BSO and lymphadenectomy were performed in 42 patients (72.4%) and 14 patients (24.1%) respectively. From univariate and multivariate analysis, hysterectomy was significantly associated with prolonged survival [HR=0.14(95%CI=0.04-0.40),p=0.001] and hysterectomy reduced death rate by 86%. From univariate analysis, BSO was significantly associated with poor survival. But in multivariate analysis, BSO was not associated with survival outcome. This result is similar to a study by Park et al, 47 of 127 uterine sarcoma patients who did not undergo BSO did not have significantly different disease free interval and overall survival time than patients who underwent this procedure[9]. Kapp et al, reported that there was no statistically significant difference in 5-year survival for leiomyosarcoma patients without oophorectomy versus patient who underwent oophorectomy at time of their initial cancer surgery (72.3% vs 66.2%, p=0.15)[14]. However, some studies showed that BSO was associated with an improved prognosis[15,16]. In our study, there was no survival benefit in the lymphadenectomy group. Koivisto-Korander et al, studied in 100 uterine sarcoma patients, lymphadenectomy was reported to have no benefit in improving survival[8]. In a series described by Sagae et al, survival in cases of early stage leiomyosarcoma and carcinosarcoma did not improve with pelvic lymphadenectomy[6]. Univariate and multivariate analysis showed that the group of no residual tumor after surgery had good survival outcome when compared to the group with residual tumor (HR=7.25). Park et al, reported that complete resection is important for favorable treatment outcomes[9]. Although advanced stage did not show significant survival benefit in our study, Koivisto-Korander et al concluded that stage was proven to have independent influence on overall survival. In the same result Park et al. concluded that advanced stage was associated with poor prognosis[8,9]. Univariate analysis showed that when comparing histology, carcinosarcoma had significant poor prognosis. However, with multivariate analysis, histologic types were not associated with survival outcome. This result is similar to a study by Park et al, that histologic type does not impact survival[9].

Adjuvant chemotherapy and radiation were used in 26 cases (44.8%) and 21 cases (36.2%). Adjuvant treatments were not significantly associated with survival in the present study. Similar results by Koivisto-Korander et al, showed that disease specific survival was not significantly better among patients who were treated with adjuvant chemotherapy. The study of Wilailak et al, in 34 uterine leiomyosarcoma patients showed that additional radiation to surgery in primary treatment does not seem to prolong survival[17]. The review by Wilailak et al showed no survival gain in uterine sarcoma receiving radiotherapy after surgery[18]. Recently, the European Organization for Research and Treatment (EORTC) randomized study for stages I and II uterine sarcomas confirmed that external pelvic radiation decreases pelvic relapse but does not improve overall survival for carcinosarcoma[19]. Park et al, revealed that adjuvant therapy has little impact on the management of uterine sarcoma, especially in early stage disease[9].

From multivariate analysis, age was an important prognostic factor and age ≥ 50 years was a significant unfavorable prognostic factor. The same results with Koivisto-Korander et al, showed that old age (≥50 years) was associated with poor survival. Kapp et al showed that age ≥ 50 years was associated with poor survival in leiomyosarcoma patients[14]. Others have reported that patients younger than age 50 years have significantly longer DFS and OS[13,20].

As a hospital base setting, our study is beneficial in terms of having a set of data for counseling patients about treatment planning and prognosis of disease and aim of treatment. In order to receive the best possible outcome, we propose that everyone who does not have contraindications for surgery should undergo hysterectomy and remove tumor until there is no residual disease.

Limitations of our study are it's retrospective nature, small number of patients and lack of histological review.

In conclusion, the overall survival of uterine sarcoma patients were rather short (median survival time = 21 months). The unfavorable prognostic factors were residual tumor after surgery and age ≥ 50 years. The favorable prognostic factor was undergoing hysterectomy.

References

1. Chauveinc L, Deniaud E, Plancher C, Sastre X, Amsani F, de la Rochefordiere A et al. Uterine sarcomas:the Curie Institut experience. Prognostic factors and adjuvant treatments. Gynecol Oncol 1999;72:232-7.
2. Brooks SE, Zhan M, Cote T, Baquet CR. Survillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma. Gynecol Oncol 2004;93:204-8.
3. Curtin TP, Silverberg SG, Thigpen JP, Spanos WJ Jr. Corpus: mesenchymal tumors. In: Hoskins WJ, Perez CA, Young RC, editors. Principles and practice of gynecologic oncology. Philadelphia: Lippincott-Raven 1997:897-918.
4. Benoit L, Arnould L, Cheynel N, Goui S, Collin F, Fraisse J, et al. The role of surgery and treatment trends in uterine sarcoma. Eur J Surg Oncol 2005;31:434–42.
5. Gadducci A. The management of patients with uterine sarcoma: A debated clinical challenge. Crit Rev Oncol Hematol 2008; 65:129
6. Sagae S, Yamashita K, Ishioka S, Nishioka Y, Terasawa K, Mori M, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. Oncology 2004;67:33–9.
7. Garrett A, Quinn MA. Hormonal therapies and gynaecological cancers. Best Pract Res Clin Obstet Gynaecol 2007; 22:407-21.
8. Koivisto-Korander R, Butzow R, Koivisto AM, Leminen A.Clinical outcome and prognostic factors in 100 cases of uterine sarcoma:Experience in Helsinki University Central Hospital 1990–2001. Gynecol Oncol 2008;111:74-81.
9. Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT et al. Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at a single institution, 1989–2007. J Cancer Res Clin Oncol 2008; 134:1277-87
10. International Federation of Gynecology and Obstetrics. Corpus cancer staging. Int J Gynecol Obstet 1989;28:189-90
11. Miller AB, HoogstratenB, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207-14.
12. Wilailak S, Tansuttiwong A, Tangtrakul S. Uterine sarcomas in Ramathibodi Hospital (1987-1998). Thai J Obstet Gynaecol 2000;12:241-6.
13. Kokawa K, Nishiyama K, Ikeuchi M,Ihara Y, Akamatsu N, Enomoto T, et al. Clinical outcomes of uterine sarcomas: results from 14 years worth of experience in Kinki district in Japan (1990-2003). Int Gynecol Cancer 2006;16:1358-63.
14. Kapp DS, Shin JY, Chan JK. Prognostic Factors and Survival in 1396 Patients With Uterine Leiomyosarcomas. Emphasis on Impact of Lymphadenectomy and Oophorectomy. Cancer 2008;112:820-30.
15. Gadducci A, Sartori E, Landoni F, Zola P, Maggino T, Urgesi A, et al. Endometrial stromal sarcoma: analysis of treatment failures and survival. Gynecol Oncol. 1996;63:247-53.
16. Morice P, Rodrigues A, Pautier P, Rey A, Camatte S, Atallah D, et al. Surgery for uterine sarcoma: review of the literature and recommendations for the standard surgical procedure. Gynecol Obstet Fertil 2003;31:147-50.
17. Wilailak S, Im DD, Bristow RE, Kuntolbutra S, Rosenshein NB. Uterine leiomyosarcoma: multivariate analysis of survival determinants. Thai J Obstet Gynaecol 1997; 9: 189-95.
18. Wilailak S, Rosenshein NB. Uterine leiomyosarcoma. Thai J Obstet Gynaecol 1999; 11: 127-37.
19. Reed NS, Mangioni C, Malmstrom H, Scarfone G, Poveda A, Pecorelli S, et al. Phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: An European Organization for Research and Treatment of Cancer, Gynecological Cancer Group Study. Eur J Cancer 2008;44:808-18.
20. Olah KS, Gee H, Blunt S, Dunn JA, Kelly K, Chan KK. Retrospective analysis of 318 cases of uterine sarcoma. Eur J Cancer 1991;27:1095-9.

ปัจจัยในการพยากรณ์โรค และ การรอดชีพของมะเร็งมดลูกชนิดซาร์โคมาในโรงพยาบาลรามาธิบดี : ประสบการณ์ 21 ปี ใน รพ.รามาธิบดี

ดาราวดี สัทธาพงศ์, สฤกพรรณ วิไลลักษณ์

วัตถุประสงค์ : เพื่อศึกษาปัจจัยที่มีผลต่อการรอดชีพ (prognostic factors) และ การรอดชีพ (survival) ของผู้ป่วยมะเร็งมดลูกชนิด ซาร์โคมา

วัสดุและวิธีการ : รวบรวมข้อมูลผู้ป่วยมะเร็งมดลูกชนิดซาร์โคมาที่ได้รับการรักษาที่หน่วยมะเร็งวิทยานรีเวช ภาควิชาสูติศาสตร์-นรีเวชวิทยา โรงพยาบาลรามาธิบดี ตั้งแต่เดือนมกราคม พ.ศ. 2530 ถึงเดือนธันวาคม พ.ศ. 2550

ผลการศึกษา : ระหว่างการศึกษามีผู้ป่วยที่ตรงตามเกณฑ์การคัดเลือก จำนวน 58 ราย ค่ากลางของระยะเวลาติดตามผู้ป่วยเท่ากับ 19.8 เดือน ผู้ป่วย 53 รายได้รับการรักษาโดยการผ่าตัด ตามด้วยการฉายแสงใน 21 ราย (ร้อยละ 36.2) และรับเคมีบำบัดจำนวน 26 ราย (ร้อยละ 44.8) มีค่ามัธยฐานของการรอดชีพ 21 เดือน และการรอดชีพ 5 ปี เท่ากับ 48% และ อัตราการเสียชีวิต 14 ต่อ 1,000 คน ต่อเดือน จาก univariate analysis พบว่า การมีก้อนมะเร็งเหลือ, อายุ $\geq$ 50 ปี, ระยะของมะเร็งที่มากขึ้น, การตัดรังไข่ และมะเร็งชนิด carcinosarcoma สัมพันธ์กับการรอดชีพที่สั้น ส่วนการตัดมดลูกนั้นสัมพันธ์กับการรอดชีพที่ยาว นอกจากนี้ multivariate analysis แสดงให้เห็นว่า การที่มีมะเร็งเหลือหลังจากผ่าตัด และอายุ $\geq$ 50 ปี สัมพันธ์กับการรอดชีพที่สั้น และการที่ได้รับการผ่าตัดมดลูก สัมพันธ์กับการรอดชีพที่ยาว

สรุป : ปัจจัยการพยากรณ์โรคที่ไม่ดี คือ การที่มีมะเร็งเหลือหลังจากผ่าตัด และอายุ $\geq$ 50 ปี และการพยากรณ์โรคที่ดีคือ การที่ได้รับ การผ่าตัดมดลูก นอกจากนี้อัตราการรอดชีพของมะเร็งมดลูกนั้นค่อนข้างต่ำ