Uterine Sarcomas in Siriraj Hospital (1991-2005)

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ABSTRACT

Objective: To study the incidence, clinical characteristics, treatments and outcomes in patients with uterine sarcomas at Siriraj Hospital.

Methods: A medical record search of patients treated at Siriraj Hospital from January 1991 to December 2005 was performed for clinical characteristics and treatments. Survival curves were generated using Kaplan-Meier method.

Results: Sixty uterine sarcomas were diagnosed during a 15-year period. The mean age was 49.3 years (range 27-74; SD 10.6). Abnormal bleeding was the most common presenting symptom (40%). Only 11.7% of the cases could be diagnosed preoperatively. Of 60 patients, 37 (61.6%) had leiomyosarcoma (LMS), 9 (15%) had malignant mixed mullerian tumor (MMMT), and 14 (23.3%) had endometrial stromal sarcoma (ESS). The distribution by FIGO staging was as follows: stage I: 47.5%, stage II: 15%, stage III: 17.5%, and stage IV: 20%. The treatment was mainly hysterectomy with adjuvant chemotherapy. The median follow-up time was 25 months. The five-year survival rate was 55.4%.

Conclusion: The incidence of uterine sarcoma at Siriraj Hospital was 4.4% of uterine malignancies. The most common histologic type was leiomyosarcoma (61.6%). The common presenting symptoms were uterine bleeding and pelvic mass. In most cases, the treatment modality was surgery combined with chemotherapy. The overall 5-year survival rate of the studied group was 55.4%.

Keywords: Endometrial stromal sarcoma; Leiomyosarcoma; Malignant mixed mullerian tumor; Uterine sarcoma

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Uterine sarcomas are rare mesodermal tumors that account for approximately 3% of uterine cancer[1] with a worldwide annual incidence between 0.5 and 3.3 cases per 100,000 women.[2] The annual incidence of uterine sarcoma in a large cancer registry in the United Kingdom was 1/100,000 women; 87% (367/423) of these were mixed mesodermal tumors and leiomyosarcomas.[3] These tumors arose primarily from two distinct tissues: 1) leiomyosarcoma from myometrial muscle; and, 2) mesodermal (mullerian) and stromal sarcomas from endometrial epithelium. The histologic diversity of the disease leads to several systems of classification. The Gynecologic Oncology Group classified the neoplasm into 5 subgroups as follows: leiomyosarcomas, endometrial stromal sarcomas, mixed homologous mullerian sarcomas (carcinosarcoma), mixed heterologous mullerian sarcomas (mixed mesodermal sarcomas) and other sarcomas.[4,5] Pelvic radiation is thought to predispose to the subsequent development of uterine sarcomas.[6]

Because of the heterogenous nature of the tumors, and individual experience with each lesion is limited, the treatment protocols are not standardized and there are few controlled studies evaluating different therapeutic approaches. Most patients with uterine sarcoma often undergo hysterectomy for a presumed diagnosis of leiomyoma or central pelvic mass. When the diagnosis of sarcoma is established and hysterectomy is technically feasible, surgical resection of the primary tumor should be attempted. Such surgery may be curative if the tumor is only confined to the uterus. There is no firm evidence from any prospective study that the adjuvant chemotherapy or radiation therapy is beneficial to patients with uterine sarcoma.[7] However, because the risk of disease recurrence is high even with localized presentations, many physicians have considered the use of adjuvant chemotherapy or radiation therapy.[8]

The objective of this study was to describe the incidence, clinical characteristics, treatment and outcomes in patients diagnosed with uterine sarcoma at Siriraj Hospital.

MATERIALS AND METHODS

During January 1991 to December 2005, a total of 60 patients diagnosed with uterine sarcoma were treated at Siriraj Hospital. Medical records were retrospectively

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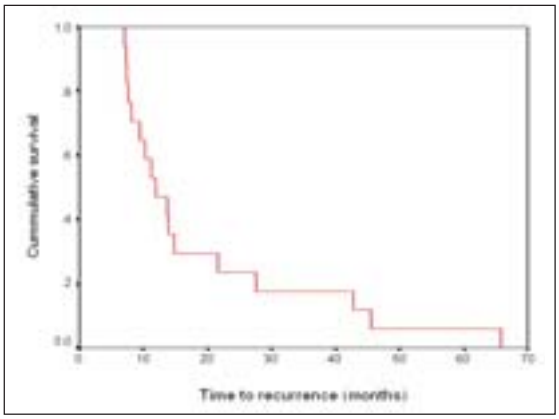

Fig 1. Kaplan-Meier analysis of progression free survival

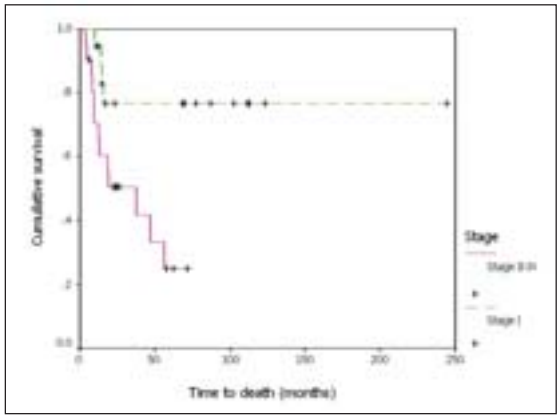

Fig 3. Kaplan-Meier analysis of overall survival stratified by staging

reviewed and all relevant clinical and pathologic data were extracted. Data of adjuvant therapy were also recorded. The histopathologic criteria for the diagnosis of leiomyosarcomas (LMS) included tumors with more than 10 mitoses/10 high power fields (HPF) or tumors with 5-9 mitoses/10 HPF with atypical neoplastic cells. Endometrial stromal sarcoma (ESS) were sub-classified into low-grade ESS with less than 10 mitoses/10 HPF and high-grade ESS with 10 or higher/10 HPF. The tumors were designated as malignant mixed mullerian tumor (MMMT) when they comprised an admixture of both sarcomatous and carcinomatous components.[1]

Using modified International Federation of Gynecology and Obstetrics (FIGO) criteria for endometrial carcinoma, staging was retrospectively assigned on the basis of surgical and pathological findings.[9] The patients were assigned stage I if the disease was confined to the corpus; stage II if the disease extended to the cervix; stage III if the disease was confined to the pelvis and retroperitoneal nodes; and, stage IV if there was a distant spreading. In case of incomplete surgical staging, stage was assigned on the basis of available pathologic findings with unevaluated areas were considered negative.

Most of the patients were scheduled for post-operative follow-up every 3 months for 2 years, and then every 6 months afterward. Descriptive statistics were presented as percentage, mean and standard deviation. The time of diagnosis was considered the date of the primary surgical procedure. The time to recurrence and death or latest contact was determined. Survival analysis was calculated using Kaplan-Meier method.

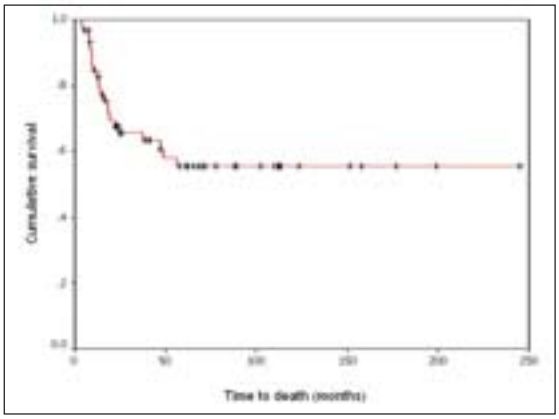

Fig 2. Kaplan-Meier analysis of overall survival

RESULTS

During the period of this study, there were 60 cases of uterine sarcoma treated at Siriraj Hospital. The hospital-based incidence of the disease was 4.4% of all uterine malignancies (60/1,368). The characteristics of the patients are shown in Table 1. The mean age at diagnosis was 49.3 years (SD 10.6). At the time of primary surgical treatment, 45% of patients (27/60) were post-menopause. Grand multiparity (> 5) was seen in 4 cases, while 9 were nulliparous. Abnormal bleeding was the most common presenting symptom and was reported in 40% of the patients (24/60). Diagnostic curettage was performed in 9 patients with abnormal bleeding and correct pre-operative diagnosis was established in only 77.7% of cases (7/9). Pelvic mass and pelvic pain were reported in 33.3% (20/60) and 10% (6/60) of the patients, respectively. None of the patient in our series had any previous history of pelvic radiation therapy.

Of 60 patients, 37 (61.6%) had leiomyosarcoma (LMS), 9 (15%) had malignant mixed mesodermal tumor (MMMT), and 14 (23.3%) had endometrial stromal sarcoma (ESS). According to the modified FIGO staging, 19 (47.5%) were in stage I; 6 (15%) stage II; 7 (17.5%) stage III; and 8 (20%) stage IV. The distribution of the stages is demonstrated in Table 1. The stage of the other 20 cases could not be determined due to the lack of data.

Complete surgical staging was only performed in 7 cases who were pre-operatively diagnosed as uterine sarcoma from curettage. The procedure consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph nodes sampling, infracolic omentectomy and peritoneal washing. Simple hysterectomies were performed in other 52 cases due to pre-operative diagnosis of leiomyoma. There was only 1 case that underwent myomectomy. Adjuvant chemotherapy was given in 55 cases except 2 cases who had low grade, stage I leiomyosarcoma and endometrial stromal sarcoma and 3 cases in whom hysterectomy was performed from other hospitals after being diagnosed as leiomyoma. Table 1 also shows data on adjuvant chemotherapy. Thirty-five cases received platinum and ifosfamide as adjuvant chemotherapy (58.3%), platinum plus doxorubicin were used in 5 cases (8.3%). The other 15 cases (25%) received other chemotherapy regimens including platinum alone, platinum, doxorubicin plus cyclophosphamide, and etc. but the response rates, disease free intervals and overall survival were not different between one group of treat-

TABLE 1. Demographic data of 60 patients with uterine sarcoma

Characteristics	Number	Percent
Menopausal status		
Pre-menopause	27	45
Post-menopause	33	55
Parity		
Nulliparous	9	15
1-4	47	78.3
>5	4	6.7
Presenting symptoms		
Abnormal bleeding	24	40
Pelvic mass	20	33.3
Pelvic pain	6	10
No data	10	16.7
Histologic types		
LMS	37	61.7
MMMT	9	15
ESS	14	23.3
Staging (40 cases)		
I	19	47.5
II	6	15
III	7	17.5
IV	8	20
Adjuvant chemotherapy		
No	5	8.3
Platinum Ifosfamide	35	58.3
Platinum doxorubicin	5	8.3
Others	15	25

ment to the other.

In this study, 52 cases achieved best response as complete response (86.7%), 3 showed stable disease (5%) and 5 had progressive disease (8.3%) as shown in Table 2. All stable cases eventually progressed and died. Seventeen cases had recurrence after complete response (32.7%) with the median time to recurrence of 15 months (7-66 months) (Fig 1). All cases with recurrence received second-line chemotherapy but only 6 cases were still alive without evidence of disease with the follow-up times of 6, 60, 60, 88, 108, and 111 months. Other 35 cases were also alive. The overall follow-up time ranged from 4-245 months, the median follow-up time was 25 months (Fig 2). In the patients who did not receive chemotherapy, 3 cases in whom hysterectomy was performed from other hospitals, 2 of them had recurrence in 13 and 14 months. They received salvage chemotherapy and progressed to death. The other case was still alive without evidence of disease with the follow-up time of 60 months that similar to the 2 cases with low grade, stage I leiomyosarcoma and endometrial stromal sarcoma (the follow-up time of 68 and 40 months, respectively).

Using Kaplan-Meier survival analysis, the overall 5-year survival rate was 55.4%. The survival rate declined most rapidly during the first 2 years after treatment and was stable after the fourth year. Comparing menopausal status, histopathology, and type of adjuvant chemotherapy, no difference in disease free interval and overall survival was found. The only factor that effected survival was the stage of disease. Stage I has better survival than stage II-IV, as shown in Fig 3. (p=0.008).

TABLE 2. Outcome of 60 patients with uterine sarcoma

Response	Number	Percent
Complete response	52	86.7
Partial response	0	0
Stable disease	3	5
Progressive disease	5	8.3

DISCUSSION

Uterine sarcoma is a rare gynecologic neoplasm. In this study, we reported the incidence of 4.4% of uterine malignancies admitted. A decade ago, a worldwide report ranked LMS as the most common subtype,[4,10-12] but more recent data revealed MMMT the most common, followed by LMS and ESS.[13-17] In this series, however, the most common subtype is LMS which accounted for more than 50% of cases. The next most common is ESS (23.3%) while only 15% of patients having MMMT. These proportions are similar to the series reported from Ramathibodi Hospital.[12] Most reports revealed a mean age of 55-60 years among patients with uterine sarcoma.[11,14,18] 7.2% of patients were post-menopausal.[11,18] The mean age for LMS is usually around 45-55 years which is 10-15 years younger than MMMT patients.[10,11,16,18] The mean age in our series is 49.3 years with 45% of patients are post-menopausal.

The two most common presenting symptoms are abnormal uterine bleeding and pelvic mass, which are similar to other series.[1,2,10-12,15,18] The most common pre-operative diagnosis is leiomyoma. Correct diagnosis could be established in 77.7% of the patients who underwent diagnostic curettage for abnormal bleeding other than hypermenorrhea. This rate is consistent with other reports.[11,19] These data still warrant the value of uterine curettage among patients with abnormal uterine bleeding. None of the patients in our series had any history of pelvic radiation, which was the only documented etiologic factor for uterine sarcoma. Others reported the incidence of 0-29%.[2,10,18] The majority of our patients were diagnosed with stage I (47.5%) which is comparable to other studies.[15,18] The early symptomatic characters of the disease might be contributed to such early detection.

Although most authorities regard surgery as the primary treatment in uterine sarcoma,[2,4] the optimal management has yet to be defined. The minimal standard procedure is total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH with BSO). One series reported that, patients with ovarian preservation had no significant difference in disease specific survival compare with those who underwent BSO.[20] Peritoneal washings and pelvic/para-aortic lymph nodes sampling were reported to be useful in predicting prognosis,[21] but did not improve overall survival.[2] The roles of adjuvant/adjunctive radiotherapy or chemotherapy are also still controversial and most series showed benefit only among the high risk or advanced disease.[2,15,18] Most of the patients in this series had undergone at least TAH for primary treatment (59/60), and 91.7% (55/60) received post-operative chemotherapy. Also, the roles of adjuvant radiotherapy or chemotherapy are still controversial and most series showed benefit only among high risk or advanced diseases.[2,15,18] At our institute, chemotherapy is the preferred adjuvant treatment in this group of patients.

Most series reported 5-year overall survival rates of 32-42%.[11,15,18,19] Our series, however, reports a 5-year survival rate of 55.4%. The relativity better prognosis might be due to the higher proportions of stage I patients. We found that stage I disease is the only factor that improves the survival and overall survival.

In conclusion, the incidence of uterine sarcoma in Siriraj Hospital is 4.4% of uterine malignancies. The most

common histologic type is leiomyosarcoma (61.6%). The common presenting symptoms are uterine bleeding and pelvic mass. In most cases, the treatment modality is surgery combined with chemotherapy. The overall 5-year survival rate of the studied group is 55.4%.

REFERENCES

1. Zaloudex CJ, Noris HJ. Mesenchymal tumors of the uterus. In: Engolio C, Wolft M, eds. Progress in Surgical Pathology. Vol .3, New York: Masson, 1981:1-35.
2. Curtin TP, Silverberg SG, Thigpen JT, Spanos WJ Jr. Corpus: mesenchymal tumors. In: Hoskins WJ, Perez CA, Young RC, eds. Principles and Practice of Gynecologic Oncology. Philadelphia: Lippincott-Raven, 1997: 897-918.
3. Olah KS, Dunn JA, Gee H. Leiomyosarcomas have a poorer prognosis than mixed mesodermal tumours when adjusting for known prognostic factors: the result of a retrospective study of 423 cases of uterine sarcoma. Br J Obstet Gynecol 1992;99: 590-4.
4. DiSaia PJ, Creasman WT. Clinical gynecologic oncology. St. Louis: Mosby, 1997:169-79.
5. Creasman WT. Cancer of the uterine corpus. In: Holzman GB, ed. Prosis, oncology: an update in obstetrics and gynecology. Washington DC: Amerrican college of Obstetrics and Gynecologists, 1998:31-7.
6. Noris HJ, Taylor HB. Postirradiation sarcomas of the uterus. Obstet Gynecol 1965;26:685-93.
7. Omura GA, Blessing JA, Major F, Lifshitz S, Ehrlich CE, Mangan C, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group Study. J Clin Oncol 1985;3:1240-5.
8. Kohorn EI, Schwartz PE, Chambers JT, Peschel RE, Kapp DS, Merino M. Adjuvant therapy in mixed mullerian tumors of the uterus. Gynecol Oncol 1986;23:212-21.
9. Benedet JL, Bender H, Jones H, Ngan HY, Percorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynecol Obstet 2000;70:209-62.
10. Wen BC, Tewfik FA, Tewfik HH, Long JP, Anderson B. Uterine sarcoma: a retrospective study. J Surg Oncol 1987;34:104-8.
11. Schwartz Z, Dgani R, Lancet M, Kessler I. Uterine sarcoma in Israel: a study of 104 cases. Gynecol Oncol 1985;20:354-63.
12. Wilailak S, Tansuttiwong A, Tangtrakul S. Uterine sarcomas in Ramathibodi Hospital (1987-1988). Thai J Obstet Gynecol 2000;12:241-6.
13. Harlow BL, Weiss NS, Lofton S. The epidemiology of sarcomas of the uterus. J Natl Cancer Inst 1986;76:399-402.
14. Wolfson AH, Wolfson DJ, Sittler SY, Breton L, Markoe AM, Schwade JG, et al. A multivariate analysis of clinicopathologic factors for predicting outcome in uterine sarcomas. Gynecol Oncol 1994;52:56-62.
15. Echt G, Jepson J, Steel J, Langholz B, Luxton G, Hernandez W, et al. Treatment of uterine sarcomas. Cancer 1990;66:35-9.
16. Major FJ, Blessing JA, Silverberg SG, Morrow CP, Creasman WT, Currie JL, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer 1993;71:1702-9.
17. Silverberg SG, Major FJ, Blessing JA, Fetter B, Askin FB, Liao SY, et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. Int Gynecol Pathol 1990;9:1-19.
18. Piura B, Rabinovich A, Yanai-Inbar I, Cohen Y, Glezerman M. Uterine sarcoma in the south of Israel: study of 36 cases. J Surg Oncol 1997;64:55-62.
19. Kahanpaa KV, Wahlstrom T, Grohn P, Heinonen E, Nieminen U, Widholm O. Sarcomas of the uterus: a clinicopathologic study of 119 patients. Obstet Gynecol 1986;67:417-24.
20. Giuntoli RL, Metzinger DS, DiMacro CS, Cha SS, Sloan JA, Keeney GL, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol 2003;89:460-9.
21. Rose PG, Piver MS, Tsukada Y, Lau T. Patterns of metastasis in uterine sarcoma. An autopsy study. Cancer 1989;63:935-8.

บทคัดย่อ

Uterine Sarcomas ในโรงพยาบาลศิริราช (พ.ศ. 2534 - 2548)

อรรถพล ใจชื่น พ.บ., มณฑา แห่งทรัพย์เจริญ พย.ม., มงคล เบญจาภิบาล พ.บ., ดิฐกานต์ บริบูรณ์ทิรัญสาร พ.บ., ปร.ด., บุญเลิศ วิริยะภาค พ.บ., อิสสระชา สู่พานิช วท.บ.

ภาควิชาสูติศาสตร์-นรีเวชวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กทม 10700, ประเทศไทย

วัตถุประสงค์: เพื่อศึกษาอุบัติการณ์, ลักษณะทางคลินิก, การรักษาและผลการรักษาของผู้ป่วย uterine sarcoma ในโรงพยาบาลศิริราช

วิธีการ: ศึกษาจากรายงานผู้ป่วย uterine sarcoma ที่มารับการรักษาในโรงพยาบาลศิริราชตั้งแต่ เดือนมกราคม 2534 ถึงธันวาคม 2548

ผลการศึกษา: ในช่วงเวลา 15 ปีดังกล่าวมีผู้ป่วย uterine sarcoma ทั้งหมด 60 คน อายุเฉลี่ย 49.3 ปี (27-74, SD 10.6) อาการที่นำผู้ป่วยมาโรงพยาบาลมากที่สุดคือ เลือดออกผิดปกติทางช่องคลอด (ร้อยละ 40) มีเพียงร้อยละ 11.7 ที่สามารถให้การวินิจฉัยได้ก่อนผ่าตัด จากผลการตรวจทางพยาธิวิทยาพบว่าเป็น leiomyosarcoma (LMS) 37 คน (ร้อยละ 61.6), mixed malignant mullerian tumor (MMMT) 9 คน (ร้อยละ 15) และ endometrial stromal sarcoma (ESS) 14 คน (ร้อยละ 23.3) โดยพบว่าร้อยละ 47.5 อยู่ในระยะที่ 1, ร้อยละ 15 อยู่ในระยะที่ 2, ร้อยละ 17.5 อยู่ในระยะที่ 3 และร้อยละ 20 อยู่ในระยะที่ 4 การรักษาส่วนใหญ่คือการตัดมดลูกร่วมกับการให้ยาเคมีบำบัด โดยที่มีมัธยฐานระยะเวลาในการมาตรวจติดตาม 25 เดือน อัตราการอยู่รอด 5 ปีคิดเป็นร้อยละ 55.4

สรุป: อุบัติการณ์ของ uterine sarcoma ในโรงพยาบาลศิริราชคิดเป็นร้อยละ 4.4 ของมะเร็งทุกชนิดของมดลูก ผลตรวจทางพยาธิวิทยาที่พบมากที่สุดคือ LMS (ร้อยละ 61.6) อาการที่นำผู้ป่วยมาโรงพยาบาลที่พบบ่อยได้แก่เลือดออกผิดปกติทางช่องคลอดและก้อนในอุ้งเชิงกราน การรักษาส่วนใหญ่คือการตัดมดลูกร่วมกับการให้ยาเคมีบำบัด อัตราการอยู่รอดที่ 5 ปีในการศึกษานี้คิดเป็นร้อยละ 55.4