Thai Journal of Obstetrics and Gynaecology
September 1997, Vol. 9, pp. 189-195

GYNAECOLOGY

Uterine Leiomyosarcoma : Multivariate Analysis of Survival Determinants

Sarikapan Wilailak MD,*
Dwight D Im MD,**
Robert E Bristow MD,**
Surinda Kuntolbutra Msc,***
Neil B Rosenshein MD.**

* *Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Bangkok 10400, Thailand*

** *Division of Gynaecologic Oncology, The Johns Hopkins University, School of Medicine,*

*** *Department of Epidemiology, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland 21205, U.S.A.*

ABSTRACT

Objective Our purpose was to study the relationship between clinicopathologic findings and survival of uterine leiomyosarcoma (LMS).

Design Retrospective study.

Setting Johns Hopkins Hospital, U.S.A.

Subjects Thirty-four uterine LMS patients admitted between March 1984 and October 1993.

Main outcome measures Survival of the patients

Results In univariate analysis, positive prognostic factors were the age ≤ 50 years, Caucasian race, premenopausal status, disease free interval ≤ 6 months, mitotic activity < 10/10 high power fields, absence of abnormal mitotic figure, nuclear grades 1 or 2 and the presence of fascicular architecture. By multivariate analysis, if the patient's race was Caucasian, the histopathology of tumour showed absence of abnormal mitotic figures, or the patients had disease free interval ≥ 6 months, the survival rate was longer.

Conclusion The Caucasian race, disease free interval ≥ 6 months and absence of abnormal mitotic figures were independent prognostic factors for prolonged survival. The addition of chemotherapy or radiation to surgery in the primary treatment of the tumour does not seem to prolong survival.

Key words : uterine leiomyosarcoma, survival, clinicopathology

Uterine leiomyosarcoma (LMS) is a rare neoplasm with an estimated annual incidence of 0.5 to 3.0 per 100,000 women.[1-4] Uterine LMS accounts for approximately 45% of all uterine sarcomas.[5-8] Although it represents only 1.3% of all uterine malignancies,[9] it is considered one of the most lethal malignancies of the uterus with a 5-year survival rate of 17-62%.[10] The problem of relapse of disease after the initial treatment often confronts the physician.[3,11-15] The purpose of this retrospective study was to relate clinical and pathologic findings to survival of uterine LMS.

Materials and Methods

The hospital charts, surgical pathologic files and the tumour registry data were used to identify all patients admitted to the Johns Hopkins Hospital between March 1984 and October 1993 with the diagnosis of uterine LMS. Thirty-four cases of uterine LMS were identified. Nineteen cases had primary treatment at Johns Hopkins. Other 15 cases had primary treatment from outside and referred to Johns Hopkins. All data needed were obtained from the patients' files or direct contact. All haematoxylin & eosin slides and pathologic reports on these cases were reviewed. The following gross and microscopic features were analyzed. The presence or absence of haemorrhage or necrosis, tumour margin, mitotic activity, and nuclear grade were noted. The tumour margin was classified as either circumscribed or infiltrated. Mitotic activity was evaluated by counting mitotic figures (MF) in 50 high power fields (HPF) of the most active areas. The tumours were then grouped into those with 5-9 MF/10 HPF or those with 10 MF/10 HPF or greater. The presence of abnormal MF was also noted. Nuclear atypia was based on the degree of nuclear pleomorphism, hyperchromasia and coarse chromatin pattern and was graded as mild (grade 1), moderate (grade 2), or severe (grade 3). The fascicular architecture was noted as to the presence or absence of muscle bundle characteristics.

Prognostic variables studies included : (1) age at diagnosis (age ≤ or > 50 years), (2) race (Caucasian or African American), (3) menopausal status (premenopausal or postmenopausal), (4) concomitant disease such as cardiovascular or endocrine diseases (absent or present), (5) family history of cancer within first generation relatives (absent or present), (6) presenting symptoms (associated with mass or vaginal bleeding or discharge), (7) stage (modified FIGO staging)[16] : stage I (tumour within uterine corpus) or II-IV (tumour beyond uterine corpus), (8) disease interval (≥ 6 months or < 6 months), (9) primary treatment (surgery alone or surgery and chemotherapy or surgery and radiation), (10) haemorrhage/necrosis (absent or present), (11) mitotic activity (5-9 or ≥ 10 MF/10 HPF), (12) abnormal mitotic figures (absent or present), (13) nuclear grade (nuclear grade 1, 2 or grade 3), (14) fascicular architecture (present or absent), (15) tumour margin (circumscribed or infiltrated).

Survival estimates were obtained for each covariate using the method of Kaplan and Meier.[17] Statistical significance between survival curves was assessed using the log-rank test. Multivariate analysis was performed to assess the importance of each variable in the presence of other variables. The proportional hazards model of Cox[18] was used to assess the importance of the various variables on survival and to construct a multivariate model to assess the independent favourable effect of the important prognostic factors relative to one another. The DBASE IV and SAS statistical software packages were used to perform the analysis.

Table 1. Uterine LMS : a univariate analysis of prognostic factors

Variables	No. of Patients (n = 34)	Median survival (mo.)	P value
Age			
≤ 50 years	16	78	
> 50 years	18	22	0.036*
Race			
Caucasian	22	86	
African American	12	31	0.049*
Menopausal status			
Premenopausal	15	78	
Postmenopausal	18	22	0.006*
Unknown	1		
Concomitant disease			
Absent	10	78	
Present	23	48	0.487
Unknown	1		
Family history of cancer			
Absent	20	65	
Present	13	76	0.778
Unknown	1		
Presenting symptoms			
Associated with mass	22	65	
Vaginal bleeding or discharge	12	48	0.431
Stage			
I	19	76	
II-IV	15	55	0.062
Disease free interval			
≥ 6 mo.	21	92	
> 6 mo.	12	13	0.0004*
Free of disease	1		
Primary treatment			
Surgery alone	19	78	
Surgery & Chemotherapy or surgery & radiation	15	55	0.778
Haemorrhage/necrosis			
Absent	13	65	
Present	19	48	0.626
Unknow	2		
Mitotic activity (/10 HPF)			
5-9	13	86	
≥ 10	21	48	0.044*
Abnormal mitotic figure			
Absent	14	86	
Present	18	28	0.029*
Unknown	2		
Nuclear grade			
1. 2	21	78	
3	11	26	0.033*
Unknown	2		
Fascicular architecture			
Present.	28	86	
Absent	4	15	0.025*
Unknown	2		
Tumour margin			
Circumscribed	20	86	
Infiltration	12	65	0.141
Unknown	2		

* Statistical significance (P < 0.05)

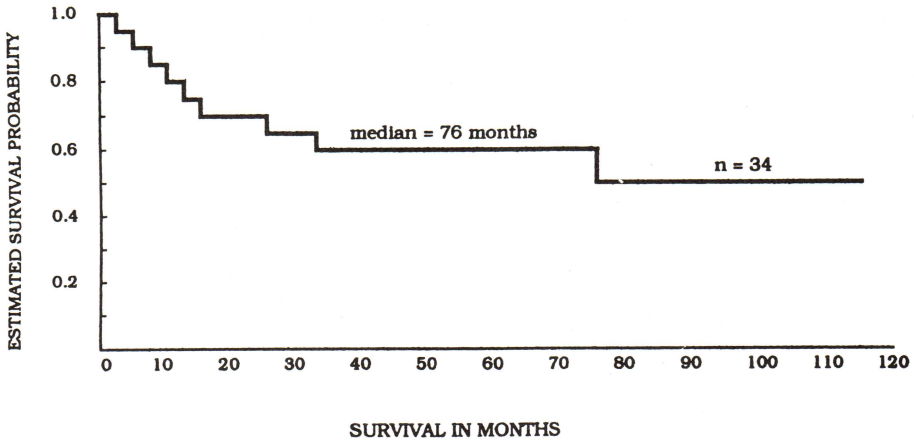

Fig. 1. Survival curve of patients with uterine leiomyosarcoma.

Results

Of the 34 patients, the mean age at diagnosis was 53.2 years with the range of 18-77 years (SD = 12.8). Twenty-one patients had 10 MF/10 HPF or greater and 13 patients had 5 to 9 MF/10 HPF and contained cytologically atypical neoplastic cells. The mean parity was 2.1 with the range of 0-6 (SD = 1.7). The median follow-up time of the study patients was 63 months with the range of 2-115 months. The primary treatment was surgery alone in 19 cases, surgery and chemotherapy or surgery and radiation in 15 cases. Surgical procedures included total abdominal hysterectomy, bilateral salpingo-oophorectomy and tumour debulking. Only one patient (2.9%) was still free of disease after 52 months of follow-up. Fourteen patients died with a median survival of 23.5 months. Twenty patients are still alive with a median follow-up time of 75 months. The survival curve of uterine LMS patients is shown in Fig. 1. The estimated median survival time was 76 months. The 2-year and 5-year survival rate for these patients were 68% and 58% respectively.

A univariate analysis of clinical and histopathologic prognostic factors was done using survival as the end point (Table 1). Significant prognostic factors for a longer survival period were (1) age ≤ 50 years (P = 0.036), (2) race : Caucasian (P = 0.049) (3) premenopausal (P = 0.006), (4) disease free interval ≥ 6 months (P = 0.0004), (5) mitotic activity < 10 MF/10 HPF (P = 0.0044), (6) absence of abnormal mitotic figures (P = 0.029), (7) nuclear grade 1, 2 (P = 0.0033) and (8) presence of fascicular architecture (P = 0.025).

All significant variables were then considered as possible independent predictors of survival in the Cox proportional hazards model. The result of the multivariate analysis is shown in Table 2, the Caucasian race (P = 0.045), disease free interval ≥ 6 months (P = 0.014) and absence of abnormal mitotic figures (P = 0.027) were independent prognostic factors for prolonged survival.

Discussion

Our study population, consisting of a very high rate of relapse due to case referral, does not represent the general population of uterine LMS. However, the 58% five-year survival rate of patients in this study is comparable to other

Table 2. Prognostic variables for survival-multivariate analysis

Variable	X^2	P Value
Race	3.996	0.045
Disease free interval	5.971	0.014
Abnormal mitotic figure	4.879	0.027

studies (17-62%).[3,11-15] The mean age at diagnosis of uterine LMS in this study was 53.2 years. The reported mean age of uterine LMS ranges from 43-56 years with an age range of 20-83 years.[19-22] Analysis of prognostic factors has been reported in uterine LMS and has provided guidelines for separation of good-and poor-risk subgroups. In the univariate analysis of this study, the factors that predicted a longer survival were an age ≤ 50 years, Caucasian race, premenopausal status, disease free interval ≥ 6 months, mitotic activity 5-9 MF/10 HPF, absence of abnormal mitotic figures, nuclear grades 1 and 2 and the presence of fascicular architecture.

Christopherson et al reported a poorer prognosis in African American.[2] Silverberg did not find a higher incidence or racial predilection for this malignancy.[23] In Steinhorn's series,[24] after adjustment for the significant factors, prognosis was equally poor for African American patients and Caucasian patients.

Premenopausal patients were reported to have a better prognosis than postmenopausal patient.[4,25-27] Bartsich[21] and Hart and Billman[28] emphasized that the improved survival rate in premenopausal patients may be due to the inclusion of cellular myomas in the tumours diagnosed as LMS. Hart and Billman and other groups have found no differences in the survival rates between pre-and postmenopausal women, when the tumour was carefully classified.[28-30]

A factor commonly related to prognosis is the mitotic count of the tumour.[5,10,15,23,27,30] However, some investigators did not find significant differences in the survival rates of patients with different mitotic counts.[14,29,31] Some series used 10 MF/10 HPF, some used 20 MF/10 HPF as the cut off point. In our series we used mitotic count of < and ≥ 10 MF/10 HPF as the cut off point because only few cases have > 2 MF/10 HPF.

Using Silverberg's grading system,[23] Hunnigan and Gomez[32] found that the histologic grade correlated with the clinical outcome. This finding is also supported by two studies using a different grading system.[5,27]

When these significant variables were included in multivariate analysis, race, disease free interval ≥ 6 months and absence of abnormal mitotic figure were independent prognostic factors for longer survival.

Several studies found that the clinical extent of the tumour or its stage was related to the prognosis, but in this study, the stage of the tumour was not among the prognostic factors (P = 0.062). This may be attributed to the small number of cases in our study. The addition of chemotherapy or radiation to surgery in the primary treatment of the tumour does not seem to prolong survival (P = 0.778).

In summary, the univariate analysis of the uterine LMS showed that positive prognostic fac-

tors were an age ≤ 50 years, Caucasian race, premenopausal status, disease free interval ≥ 6 months, mitotic activity less than 10/10 HPF, absence of abnormal mitotic figures, nuclear grades 1 or 2, and the presence of fascicular architecture. The multivariate analysis indicated that positive prognostic factors were caucasian race, absence of abnormal mitotic figures, and disease free interval ≥ 6 months. The addition of chemotherapy or radiation to surgery in primary treatment of the tumour does not seem to prolong survival.

Acknowledgement

The authors are grateful to the Tumour Registry of the Johns Hopkins Hospital for providing information for this study, and to Dr. Robert J. Kurman and the staff members of Pathology Division for providing assistance.

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