Prognostic factors and adjuvant therapy in uterine carcinosarcoma

T.I. Wu[1], *M.D.*; **K.H. Hsu**[2], *Ph.D.*; **H.J. Huang**[1], *M.D.*; **S. Hsueh**[3], *M.D.*; **H.H. Chou**[1], *M.D.*; **C.S. Tsai**[4], *M.D.*; **K.C. Ho**[5], *M.D.*; **A. Chao**[1], *M.D., Ph.D.*; **T.C. Chang**[1], *M.D., M.P.H.*; **C.H. Lai**[1], *M.D.*

[1]Department of Obstetrics and Gynecology, [2]Department of Health Care Management, [3]Department of Pathology, [4]Department of Radiation Oncology, [5]Department of Nuclear Medicine, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan (Taiwan)

Summary

Purpose of investigation: The objective of this retrospective study was to investigate prognostic variables and impact of adjuvant therapy in uterine carcinosarcoma. *Methods:* The clinical information and pathological confirmation were reviewed for cases with uterine carcinosarcoma from 1984 to 2005. A total of 45 patients were eligible for analysis. *Results:* The median follow-up for survivors was 84 months. Five-year overall survival and progression-free survival (PFS) rates were 36.5% and 33.8%, respectively for Stage I-IV. Distant site metastasis with/without pelvic failure occurred in 83.3% of those with recurrence/progression. By multivariate analysis, older age ($p = 0.001$) and more than half of myometrial invasion ($p = 0.002$) were significant predictors of death, while only myometrial invasion ($p = 0.022$) was significantly associated with PFS. Stratified analyses demonstrated a monotonic trend of chemotherapy or chemoradiation to decrease death. *Conclusions:* Our results suggested that age and depth of myometrial invasion were significant prognostic factors, and chemotherapy or chemoradiation seemed to be beneficial for uterine carcinosarcoma.

Key words: Uterine carcinosarcoma; Chemotherapy, Chemoradiation , Malignant mixed müllerian tumor, Prognostic factor.

Introduction

Uterine carcinosarcoma (CS) is an aggressive neoplasm of the female genital tract, which comprises 4% of malignancies of the uterine corpus. According to a study of Surveillance, Epidemiology, and End Results from the United States, the incidence of CS (or malignant mixed müllerian tumor) was 1.71, 4.28 and 0.99 per 100,000 women/years in white, black or the other races, while a population-based study from Norway showed a trend of increasing incidence and mortality in CS over time [1, 2]. This malignancy has biphasic epithelial and mesenchymal components. The histogenesis remains unclear, but recent immunohistochemical and molecular genetic studies have attributed CS to a metaplastic carcinoma [3]. CS has been recognized as an aggressive subtype of endometrial cancer, and the carcinomatous component seems to be the driving force of malignant behavior [3, 4].

Clinical Stage I or II CS (grossly confined to the uterus) are often upstaged (30-61%) at the time of comprehensive surgical staging. The rates of pelvic or paraaortic lymph node metastasis ranges from 13.2% to 90% according to clinical stage. The prognosis has been poor even in early stage (44-74% of 5-year overall survival [OS] in International Federation of Gynecology and Obstetrics (FIGO) Stage I/II), and 5-year OS ranges from 6-38% in Stage I-IV [4-9]. The outcome is disappointing with currently available chemotherapeutic agents or radiotherapy (RT) [10]. Moreover, efforts to improve outcome of uterine CS are hindered by its rarity.

In this study, we aimed to investigate the prognostic factors of CS and evaluate the impact of adjuvant therapy on survival in CS from the 21-year experience of a tertiary referral medical center in Taiwan.

Materials and Methods

Patients

We retrospectively reviewed the hospital medical records and pathological slides, through a search of the disease code database (International Classification of Diseases of Oncology [ICDO]) and Systematized Nomenclature of Medicine (SNOMED) code in Chang Gung Memorial Hospital from June 1984 to January 2005. The diagnosis of CS was based on the World Health Organization's classification, and all primary uterine CS contained malignant elements of both epithelial and stromal light microscopic appearance [11].

Surgical and postoperative treatment

Although this retrospective study spanned two decades, it has been our policy that all patients with histologically confirmed CS should undergo surgery unless an unresectable situation is clinically obvious. Limited distant nodal or upper abdominal metastasis did not preclude an initial surgical intervention. If medically feasible, surgical staging consisting of washing cytology, abdominal total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection with/without paraaortic lymph node (PALN) dissection, omentectomy, and appendectomy were performed. In the case of incomplete surgical staging, stage was assigned on a basis of available pathologic findings, and unevaluated areas were considered negative. For patients with deep myometrial invasion, cervical extension,

Supported by research grants from Chang Gung Memorial Hospital (CMRPG340011 and CMRPG340081).

Revised manuscript accepted for publication December 6, 2007

or retroperitoneal nodal metastasis usually received postoperative RT, and chemotherapy (CT) was given concurrently or sequentially preceding RT. Adjuvant CT alone might be recommended to Stage IA-B. CT regimens usually involved combinations of ifosfamide, cisplatin or doxorubicin. Hormone or molecular targeted therapy has been used in recent years for inoperable cases according to molecular diagnosis of targeted protein and gene expression studies.

Statistical analysis

Survival curves (OS and progression-free survival [PFS]) were generated using the Kaplan-Meier method. Cox's proportional hazard model was used to implement multivariable analysis while variables were screened by univariate analysis in advance. Hazard ratio (HR) of factors associated with death or recurrence/progression was calculated by incidence density ratio with a 95% confidence interval (CI). The cut-off point of a continuous variable was determined by receiver operating curve (ROC) analysis to get optimal differentiation between groups. Dummy variables were designed for those independent categorical variables in the Cox regression analysis. A test of monotonic trend was performed to examine an increasing pattern of variables from the lowest to the highest relative risk. A p value of less than 0.05 was considered statistically significant [12, 13].

Results

Patient characteristics and treatment

A total of 45 patients were eligible for analysis. The median age of the study population was 58 years old (range 36-85), and the most common initial manifestation (86.8%) was abnormal vaginal bleeding or postmenopausal bleeding. Nineteen (43.2%) of the 44 study patients whose FIGO Stage could be assigned were in Stage I, two in Stage II (4.5%), 15 in Stage III (34.1%), and eight were in Stage IV (18.2%). A total of 45.5% (15/33) cases with lymph node metastasis, 26.7% (4/15) cases with PALN metastasis, 30% (12/40) with adnexal involvement, and 73.8% (31/42) with more than half of myometrial invasion were recorded (Table 1).

Treatment

Of the 45 study patients, 42 received primary surgery, and for the remaining three imaging studies confirmed the diagnosis from endometrial sampling (apparently with advanced disease - unresectable IVB). Adjuvant CT, RT or both was administered in 14 (31.8%), six (13.6%) and 12 (27.3%) of all patients, while the remaining 12 did not receive adjuvant therapy and one unknown adjuvant therapy (Table 2). Among the 21 Stage I/II patients, seven did not receive adjuvant therapy, ten received CT, one received RT, two received CT-RT, and one unknown adjuvant therapy. Of the 21 Stage III/IV patients receiving primary surgery, 18 received postoperative adjuvant therapy.

Clinical outcome and pattern of failure

The median follow-up for survivors was 84 months (range, 6-215). Median time to recurrence/progression was eight months (range, 0-68). The 5-year OS and PFS was 36.6% and 33.8% in the whole series, and 59.7% and 60.1% in Stage I/II, respectively. A single Stage IA

Table 1. — *Characteristics of patients with uterine carcinosarcoma.*

Characteristic	Number of patients	(%)
Age (years)		
Mean ± SD		58.6 ± 10.8
Median, range		58, 36-85
< 58	22	(48.9%)
≥ 58	23	(51.1%)
Stage	44	(100%)
I	19	(43.2%)
II	2	(4.5%)
III	15	(34.1%)
IV	8	(18.2%)
Unknown	1	
Lymph node metastasis	33[a]	(100%)
No	18	(54.6%)
Yes	15	(45.4%)
Pelvic lymph node metastasis	33[a]	(100%)
No	21	(63.6%)
Yes	12	(36.4%)
Para-aortic lymph node metastasis	15[b]	(100%)
No	11	(73.3%)
Yes	4	(26.7%)
Adnexal involvement	42[c]	(100%)
No	30	(71.4%)
Yes	12	(28.6%)
Differentiation	45	(100%)
Homologous	32	(71.1%)
Heterologous	13	(28.9%)
Lymphovascular permeation	42[c]	(100%)
No	21	(50%)
Yes	21	(50%)
Myometrial invasion	42[c]	(100%)
Endometrium only	2	(4.8%)
Inner half	9	(21.4%)
Outer half	31	(73.8%)
Preoperative CA-125 (U/ml)	25[d]	(100%)
≤ 35	13	(52%)
> 35	12	(48%)

[a]Thirty-three patients underwent pelvic with or without paraaortic lymphadenetomy. [b]Only 15 patients underwent paraaortic lymphadenetomy. [c]Three patients with missing data did not receive surgery. [d]Twenty-five patients had preoperative serum CA-125 records.

Table 2. — *Treatment in patients with uterine carcinosarcoma (n = 45).*

Treatment	Total (n)	Stage I (n)	Stage II (n)	Stage III (n)	Stage IV (n)	Stage unknown (n)
Hysterectomy	45					
No	3	0	0	0	2	1
Yes	42	19	2	15	6	
Lymphadenectomy	45					
No	12	5	0	2	4	1
Yes	33	14	2	13	4	
Adjuvant Therapy	45	19[a]	2	15	8	
No adjuvant	12	5	1	2	3	1
Chemotherapy	14	10	1	2	1	
Radiotherapy	6	1	0	4	1	
CT-RT	12	2	0	7	3	
Unknown	1	1	0	0	0	

CT-RT, chemotherapy and radiotherapy; a One patient had part of her medical record missing, therefore adjuvant therapy was unknown.

Table 3. — *Recurrence/progression rates and pattern by stage and adjuvant treatment (n = 44)* [a].

	Total	Patients with recurrence/progression	Site of recurrence/progression[b]			
	No. of pts.	N (%)	Pelvic N (%)	Distant N (%)	Pelvic + Distant N (%)	Unknow N (%)
Stage I & II						
Adjuvant Therapy						
No	7	3 (42.9%)	1		2	
Chemotherapy	10	5 (50%)	1	2	2	
Radiotherapy	1	1 (100%)		1		
CT-RT	2	0				
Unknown	1	1 (100%)			1	
Total	21 (100%)	10 (47.6%)	2 (20%)	3 (30%)	5 (50%)	
Stage III & IV						
Adjuvant Therapy						
No	5	5 (100%)			3	2
Chemotherapy	3	3 (100%)			2	1
Radiotherapy	5	5 (100%)		1	2	2
CT-RT	10	7 (70%)	2	3	1	1
Total	23 (100%)	20 (87%)	2 (10%)	4 (20%)	8 (40%)	6 (30%)

CT-RT, chemotherapy and radiotherapy. [a] One unstaged patient unlisted here had no adjuvant therapy and expired 4 months later.
[b]Abdomen (n = 9), lung (n = 7), vagina (n = 5), PALN (n = 5), liver (n = 3), neck (n = 2), inguinal lymph nodes (n = 1), and bone (n = 1) recurrences were recorded.

patient receiving surgery without adjuvant therapy was recurrence-free at six months. One of the three (33.3%) Stage IB patients who received surgery only experienced recurrence, while two of the remaining seven (28.7%) with Stage IB relapsed despite postoperative CT. One each of Stage IC patients receiving surgery alone or adjuvant RT had a recurrence and died, as did two of the other three (66.7%) receiving CT. The ages of the three deceased Stage IB patients were 64, 58, and 76 years, respectively. Two Stage IC patients received CT-RT and remained alive and recurrence-free. Twenty-one of the 22 (95.5%) Stage IC-IV patients without adjuvant CT-RT failed. Of the known 24 sites of failure, 83.3% involved distant sites with/without local recurrence/progression (Table 3).

Among the four patients with PALN metastasis, two cases received adjuvant CT and extended field RT according to institutional guidelines. One of them has no evidence of disease 29 months later, while the other died of cancer with the failure site unknown. The remaining two did not receive prescribed adjuvant treatment because of rapid progression and the other died from hepatic failure after the third CT. Of the 17 patients receiving pelvic RT, only six failed in the pelvis and none failed in the vagina. In contrast, those with PALN recurrence/progression (n = 5) did not undergo adjuvant extended field RT. Only one patient with recurrence was salvaged successfully. The single survivor after CS relapse was a Stage IIIC patient who encountered recurrence in a left supraclavicular node one month after adjuvant RT, and she remained with no evidence of disease for 83 months after salvage RT.

Univariate and multivariate analysis

Older age, lower parity, advanced stage, adnexal metastasis, heterologous element, lymphovascular permeation, deeper myometrial invasion and no adjuvant CT were significant adverse factors for OS by univariate analysis (Table 4). However, only older age (HR: 9.84 [95% CI,

Table 4. — *Univariate analysis of prognostic factors in uterine carcinosarcoma.*

Characteristic	N	5-year PFS	p (log rank)	5-year OS	p (log rank)
Age (years)					
Continuous			0.192	49.9%	0.004
< 58	22	39.8%	0.341	23.0%	0.045
≥ 58	23	28.1%			
Parity (0-9)	34		0.033		0.026
Stage			< 0.001		0.007
I-II	21	66.9%		66.4%	
III-IV	23	13.3%		17.8%	
Lymph node metastasis			0.05		0.098
No	18	52.6%		52.6%	
Yes	15	19.1%		25.7%	
Adnexal involvement			0.003		0.005
No	30	48.1%		51.4%	
Yes	12	24 mo		30 mo	
Differentiation			0.023		0.009
Homologous	32	44.7%		49.3%	
Heterologous	13	7.7%		7.7%	
Lymphovascular permeation			0.008		0.037
No	17	52.3%		37.5%	
Yes	21	17.9%		26.5%	
Myometrial invasion					
No	2	13 mo	0.002	30 mo	0.008
Inner half	9	77.9%	0.001	77.8%	0.003
Outer half	31	17.4%	(No/inner vs outer half)	27.7%	(No/inner vs outer half)
Preoperative CA-125					
Continuous			0.017		< 0.001
≤ 35	13	59.2%	0.042	46.2%	0.153
> 35	12	32.6%		26.4%	
Adjuvant chemotherapy			0.001		0.014
No	18	13.0%		21.4%	
Yes	26	45.5%		44.4%	
Adjuvant radiotherapy			0.821		0.686
No	26	36.5%		37.9%	
Yes	18	26.7%		31.3%	
Adjuvant CT-RT			0.235		0.610
No	32	29.4%		33.9%	
Yes	12	61.7%		38.9%	

PFS: progression-free survival; OS: overall survival; CT-RT: chemotherapy and radiotherapy.

2.43-39.87], p = 0.001) and deeper than half of myometrial invasion (HR: 7.87 [1.39-44.59], p = 0.002) were significant predictors of death under the Cox proportional hazards model (Table 5). Advanced Stage (III-IV vs I-II, HR: 3.71 [95% CI, 0.95-14.50], p = 0.059) revealed only marginal statistical significance for death.

Likewise, decreased parity, advanced stage, lymph node metastasis, adnexal involvement, heterologous element, lymphovascular permeation, and deeper myometrial invasion were adversely associated with PFS and adjuvant CT was favorably related to PFS in univariate analysis (Table 4). Among multivariate analyses, only deep myometrial invasion (outer half vs no/inner half, HR: 11.81 [1.42-97.92], p = 0.022) showed independent prognostic significance, while adjuvant CT was marginally associated with improved PFS (p = 0.074) (Table 5).

Preoperative increased CA-125 serum level was significantly associated with poor OS (p < 0.001) and PFS (p = 0.017) as a continuous variable although we could not define a cut-off point with the ROC curve with this limited sample size (n = 25). Patients with preoperative CA-125 >35 U/ml (normal upper limit in general) had a worse PFS as compared with those with ≤ 35 U/ml by univariate analysis (Table 4). However, it was not selected by multivariate analysis.

Table 5. — *Multivariate analysis of overall and progression-free survival evaluation of prognostic factors in uterine carcinosarcoma.*

	HR	95% CI	p value
Overall survival			
Age (≥ 58 vs < 58)	9.84	2.43-39.87	0.001
Stage (III-IV vs I-II)	3.71	0.95-14.50	0.059
Myometrial invasion (outer half vs no/inner half)	7.87	1.39-44.59	0.002
Progression-free survival			
Myometrial invasion (outer half vs no/inner half)	11.81	1.42-97.92	0.022
Adjuvant chemotherapy (yes vs no)	0.261	0.06-1.14	0.074

HR: hazard ratio; CI: confidence interval.

Stratified analysis

We performed stratified analyses using the monotonic trend in OS from the different risk groups (age) selected by multivariate analysis under the presence or absence of adjuvant CT or CT-RT. Myometrial invasion was excluded for stratified analysis due to the strong correlation with adjuvant CT. According to the optimal stratification of age (< 58 vs ≥ 58 years) in different models, a monotonic trend toward increased death in these patients with uterine CS not receiving adjuvant CT (p = 0.005) or CT-RT (p = 0.006) was noted (Table 6).

Table 6. — *Stratified analysis of adjuvant chemotherapy or chemoradiation in age groups on overall survival.*

		Death (n)	Total follow-up time (days)	HR	(95% CI)	p
Model 1						
Age (years)		CT				0.005[a]
< 58	Yes	2	569	1.00		
	No	1	194	0.61	(0.05-6.92)	0.689
≥ 58	Yes	8	474	3.93	(0.81-19.16)	0.090
	No	6	72	6.84	(1.24-37.86)	0.027
Model 2						
Age (years)		CT-RT				0.006[a]
< 58	Yes	6	293	1.08	(0.29-3.97)	0.909
	No	5	768	1.00		
≥ 58	Yes	1	111	1.00	(0.11-9.14)	0.997
	No	16	768	4.23	(1.36-13.21)	0.013

HR: hazard ratio; CI: confidence interval; CT: chemotherapy; CT-RT: chemoradiation. [a]Test for monotonic trend from lowest to highest groups.

Discussion

Uterine CS is one of the most aggressive uterine tumors, with a high potential of hematogenous and lymphatic spread resulting in poor survival. Despite multimodality treatment, the 5-year survival in various reports ranges from 6-38% [4-9]. Therefore, it is very important to identify prognostic variables and appropriate adjuvant therapy for this highly lethal malignancy.

A large Gynecologic Oncology Group (GOG) prospective surgical-pathological study of 453 clinical Stage I-II uterine sarcomas found that histologic type (homologous vs heterologous), adnexal spread, lymph node metastasis, and grade of sarcomatous component were significant prognostic factors for CS (n = 301) based on multivariate analysis [5]. An Italian multicenter retrospective study (n = 118) identified surgical stage, depth of myometrial invasion, and lymphovascular space involvement as significant predictors of outcome [8].

Our data indicated that 45.5% of the patients who underwent LN dissection had pelvic node metastasis and 26.7% had PALN metastasis. In addition, 20 of 24 (83.3%) patients with recurrence/progression involved a distant failure. Because of the high probability of lymphatic and hematogenous metastasis in uterine CS, it is imperative that adjuvant systemic therapy be utilized after surgery. Older age and deeper myometrial invasion were independent predictors of death, and only myometrial invasion was significantly correlated with PFS by multivariate analysis. Our results are similar to previous series except for older age, which might reflect the worse tumor biology, poor performance status and treatment intolerance [5-8].

The role of adjuvant therapy in uterine CS has not been clearly established. Several retrospective reports demonstrated favorable local control with no influence on survival benefit from adjuvant RT. Gerszten *et al.* reported that both decreased local and distant failure rates were found in Stage I/II uterine CS receiving adjuvant RT compared to surgery alone [14]. In contrast, Callister *et al.* noted that adjuvant pelvic RT decreased pelvic recurrences, but no survival benefit in a large retrospective series of Stage I-III CS (n = 300) [15]. Manolitsas *et al.* reported a 5-year survival rate of 74% with postoperative CT-RT for 38 clinical Stage I-II CS [16]. Menczer *et al.* reported that 41 of 49 (83.7%) uterine CS with Stage I-

IV had postoperative adjuvant treatment including CT (n = 10), RT (n = 21) and sequential CT-RT (n = 10). Sequential CT-RT had a significant decrease in mortality when compared to CT alone (p = 0.049) but was not significant compared to whole pelvic RT alone (p = 0.4) after controlling for stage [17]. Sutton *et al.* reported a 5-year OS of 62% for Stage I-II CS with adjuvant CT alone using ifosfamide and cisplatin. Although the regimen seemed tolerable, pelvic relapse remained problematic [18].

In our study, adjuvant CT revealed a marginal progression-free survival benefit in multivariate analysis. Stratified analyses demonstrated a monotonic trend of CT or CT-RT in various risk groups to decrease death. Adjuvant CT could be useful for Stage IB in younger age (< 58 years), while CT or RT alone was obviously inadequate for Stage IC (3 of 4 died). Indeed, 21 of the 22 (95.5%) Stage IC-IV patients without adjuvant CT-RT failed.

A recent GOG phase III study found that adjuvant CT (cisplatin, ifosfamide, and mesna [CIM]) reduced the recurrence rate and marginally significantly prolonged OS in optimally debulked uterine Stage I-IV CS patients as compared to whole abdominal irradiation (WAI). However, due to a high relapse rate (CIM 49%, WAI 55%) and poor OS, CT-RT is at least what can be done before the emergence of new effective systemic therapies [19].

With regard to the selection of CT regimens, three GOG randomized phase III trials with CT including uterine sarcoma or CS have been reported [20-22]. The earlier studies showed that combination arms (adriamycin with dimethyl triazenoimidazole carboxamide or cisplatin with ifosfamide) had better response rates than single agent adriamycin or cisplatin but no survival benefit [20, 21]. However, a recent phase III trial demonstrated that ifosfamide with paclitaxel compared with ifosfamide alone decreased 31% HR of death (13.5 vs 8.4 months, p = 0.03) and 29% HR of progression (5.8 vs 3.6 months, p = 0.03) in advanced, persistent or recurrent uterine CS [22]. Other agents such as topotecan appeared disappointing (response rate of 10%) [23]. Conventional cytotoxic and radiotherapeutic options have brought about limitation and challenges for clinical investigators toward uterine CS, thus exploring novel targeted therapies is necessary [24, 25].

The limitations of our study series are the retrospective nature, small sample size, long time span, and heterogeneous chemotherapeutic regimens. Nevertheless, the current study has added to the literature of results of consecutive uterine CS patients diagnosed and treated under the same surgical policy and principle of selecting adjuvant therapy in a tertiary referral medical center. Fighting a rare disease, every piece of deliberately collected information should be valued to support future prospective studies.

Conclusion

Age and depth of myometrial invasion were significant prognostic factors for CS, and adjuvant CT or CT-RT might be beneficial for outcome. This retrospective study suggests that all Stage IC-IV CS need adjuvant CT-RT, while optimal treatment for Stage IA-IB should be further elucidated. Prospective studies are warranted to validate the role of adjuvant therapy and to identify optimal CT regimens as well as novel targeted agents to overcome the high lethality of uterine CS.

References

[1] Brooks S.E., Zhan M., Cote T., Baquet C.R.: "Surveillance, Epidemiology, and End Results analysis of 2677 cases of uterine sarcoma 1989-1999". *Gynecol. Oncol.*, 2004, *93*, 204.

[2] Nordal R.R., Thoresen S.Ø.: "Uterine sarcomas in Norway 1956-1992: incidence, survival and mortality". *Eur. J. Cancer,* 1996, *33,* 907.

[3] McCluggage W.G..: "Malignant biphasic uterine tumours: carcinosarcomas or metaplastic carcinomas?". *J. Clin. Pathol.*, 2002, *55,* 321.

[4] Silverberg S.G., Major F.J., Blessing J.A., Fetter B., Askin F.B., Liao S.Y. *et al.*: "Carcinosarcoma (MMMT) of the uterus: a GOG pathologic study of 203 cases". *Int. J. Gynecol. Pathol.*, 1990, *9,* 1.

[5] Major F.J., Blessing J.A., Silverberg S.G., Morrow C.P., Creasman W.T., Currie J.L. *et al.*: "Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study". *Cancer,* 1993, *71* (suppl.), 1702.

[6] Iwasa Y., Haga H., Konishi I., Kobashi Y., Higuchi K., Katsuyama E. *et al.*: "Prognostic factors in uterine carcinosarcoma: a clinicopathologic study of 25 patients". *Cancer,* 1998, *82,* 512.

[7] Yamada D.S., Burger R.A., Brewster W.R., Anton D., Kohler M.F., Monk B.J.: "Prognostic variables and adjuvant therapy as predictors of recurrence and survival for patients with surgically evaluated carcinosarcoma of the uterus". *Cancer,* 2000, *88,* 2782.

[8] Sartori E., Bazzurini L., Gadducci A., Landoni F., Lissoni A., Maggino T. *et al.*: "Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study". *Gynecol. Oncol.*, 1997, *67,* 70.

[9] Amant F., Cadron I., Fuso L., Berteloot P., Jonge E., Jacomen G. *et al.*: "Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk endothelial endometrial cancer". *Gynecol. Oncol.,* 2005, *98,* 274.

[10] Kanjeekal S., Chambers A., Fung M.F.K., Verma S.: "Systemic therapy for advanced uterine sarcoma: a systematic review of the literature". *Gynecol. Oncol.,* 2005, *97,* 624.

[11] McCluggage W.G., Haller U., Kurman R.J.: "Mixed epithelial and mesenchymal tumours". In: Tavassoli F.A., Decilee P. (eds.).World Health Organization Classification of Tumours. Pathology & Genetics of Tumours of the Breast and Female Genital Organs. Lyon, IARC Press, 2003, 245.

[12] SPSS for windows, Rel 11.0.1. Chicago, SPSS. Inc., 2001.

[13] SAS Statistical Package, Version 8.1. Cary, NC: SAS Institute, Inc., 2000.

[14] Gerszten K., Faul C., Kounelis S., Huang Q., Kelly J., Jones M.W.: "The impact of adjuvant radiotherapy on carcinosarcoma of the uterus". *Gynecol. Oncol.,* 1998, *68,* 8.

[15] Callister M., Ramondetta L.M., Jhingran A., Burke T.W., Eifel P.J.: "Malignant mixed mullerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome". *Int. J. Radiat. Oncol. Biol. Phy.,* 2004, *58*, 786.

[16] Manolitsas T.P., Wain G.V., Willians K.E., Freidlander M., Hacker N.F.: "Multimodality therapy for patients with clinical Stage I and II malignant mixed müllerian tumors of the uterus". *Cancer,* 2001, *91,* 1437.

[17] Menczer J., Levy T., Piura B., Chetrit A., Altaras M., Meirovitz M. *et al.*: "A comparison between different postoperative treatment modalities of uterine carcinosarcoma". *Gynecol. Oncol.,* 2005, *97,* 166.

[18] Sutton G., Kauderer J., Carson L.F., Lentz S.S., Whitney C.W., Gallion H.: "Adjuvant ifosfamide and cisplatin in patients with completely resected Stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncologic Group study". *Gynecol. Oncol*., 2005, *96,* 630.

[19] Wolfson A.H., Brady M.F., Mannel R.S., Lee Y., Futoran R.J., Cohn D. *et al.*: "A Gynecologic Oncology Group randomized trial of whole abdominal irradiation (WAI) vs cisplatin-ifosfamide+mesna (CIM) in optimally debulked Stage I-IV carcinosarcoma (CS) of the uterus". *Gynecol. Oncol.,* 2007, *107*, 166.
[20] Omura G.A., Major F.J., Blessing J.A., Sedlacek T.V., Thigpen J.T., Creasman W.T. *et al.*: "A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas". *Cancer,* 1983, *52*, 626.
[21] Sutton G., Brunetto V.L., Kilgore L., Soper J.T., McGehee R., Olt G. *et al.*: "A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group study". *Gynecol. Oncol.*, 2000, *79,* 147.
[22] Homesley H.D., Filiaci V., Markman M., Bitterman P., Eaton L., Kilgore L.C. *et al.*: "Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study". *J. Clin. Oncol.,* 2007, *25*, 526.
[23] Miller D.S., Blessing J.A., Schilder J., Munkarah A., Lee Y.C.: "Phase II evaluation of topotecan in carcinosarcoma of the uterus: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 2005, *98,* 217.
[24] Carmen M.G., Fuller A.F., Matulonis U., Horick N.K., Goodman A., Duska L.R. *et al.*: "Phase II trial of anastrozole in women with asymptomatic müllerian cancer". *Gynecol. Oncol.,* 2003, *91,* 596.
[25] Kuo D.Y.S., Timmins P., Blank S.V., Fields A.L., Goldberg G.L., Murgo A. *et al.*: "Phase II trial of thalidomide for advanced and recurrent gynecologic sarcoma: a brief communication from the New York phase II consortium". *Gynecol. Oncol.,* 2006, *100,* 160.

Address reprint requests to:
C.H. LAI, M.D.
Department of Obstetrics and Gynecology,
Chang Gung Memorial Hospital,
5 Fu-Shin St. Kueishan,
Taoyuan 333 (Taiwan)
e-mail: sh46erry@ms6.hinet.net