(hypermethylation in cancer)-1 are located in the 17p13 region. p53 is a very well-characterized tumor-suppressor gene that has been reported to be deleted and/or mutated in approximately half of all malignant tumors[13,14]. Likewise, HIC-1 is a tumor-suppressor gene located on 17p13.3, distal to p53 on 17p13.1 that has been reported to be deleted in breast cancer[15,40,41]. However, the relation between the tumorigenesis and progression of endometrial adenocarcinoma and the frequent deletions of 1p or 17p in endometrial cancers and precancerous lesions are still unclear and will remain the focus of investigation in the future.

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Clinical Characteristics of Prognostic Factors in Poorly Differentiated (G3) Endometrioid Adenocarcinoma in Japan

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Background: It has been reported that prognosis is less favorable in poorly (G3) differentiated endometrioid adenocarcinoma than in well (G1) or moderately (G2) differentiated endometrioid adenocarcinoma. The goal of this study is therefore to analyze the prognosis of G3 endometrioid adenocarcinoma and various factors that may predict a favorable prognosis.
Method: This study included 699 Japanese cases of endometrioid adenocarcinoma at the International Federation of Gynaecology and Obstetrics (FIGO) surgical stages I–IV (including 74 G3 cases). We investigated the G1–G3 survival rates of endometrioid adenocarcinoma cases and the G2 and G3 disease-free periods. We also examined the clinicopathological characteristics of G3 endometrioid adenocarcinoma.
Result: The prognosis was poor in stages III and IV in G3 and in G2 cases, but recurrence was observed more frequently in G3 cases than in G2 cases. Adnexal metastasis and high pre-surgery CA602 values showed significantly low *P*-values for survival.
Conclusions: We suggest that the risk of late recurrence is higher in G3 than in G2 cases. The absence of adnexal metastasis and low pre-surgery CA19-9 values may suggest a relatively favorable prognosis in G3 endometrioid adenocarcinoma.

Key words: poorly differentiated type – G3 – endometrioid adenocarcinoma

INTRODUCTION

Endometrial carcinoma has a high morbidity in the advanced countries of Western Europe and the USA and also in Japan, where its morbidity has increased in recent years. In 1970, endometrial carcinoma constituted ~3% of total uterine cancers in Japan, but the ratio increased to ~40% in 1998. Therefore, it has become increasingly important to understand the oncogenic mechanisms and prognostic factors in endometrial cancer.

It was previously reported that grade of differentiation is one of the critical prognostic factors in endometrial carcinoma (1–4). Creasman et al. (5) reported that the 5-year survival rate was 92.0% for G1 endometrial carcinoma cases and 86.9% and 74.0%, respectively, for G2 and G3 cases. This suggested a significantly poorer prognosis for carcinomas of lower differentiation grades. Delaloye et al. (6) investigated the rates of local recurrence, metastasis, disease-free survival and overall survival according to differentiation grade for stage I endometrial adenocarcinoma cases, and showed that the lower the grade was, the higher the metastasis rate was and the lower the disease-free survival rate and overall survival rate were.

It has been suggested that there are two types of endometrial cancer based on oncogenic pathology. One type develops in women with signs of high-estrogen conditions such as obesity, hyperlipidemia, anovular bleeding, infertility, delayed menopause and proliferation of the ovarian stroma or endometrium. Another type develops in women without these signs. Many cases of the former type have the G1 or G2 differentiation grade with shallow muscle invasion, a high sensitivity to hormone therapy and a relatively favorable prognosis (7–9). The latter group, in many cases, has the G3 differentiation grade, with deep muscle invasion, high probability of lymph node metastasis, and shows a poor sensitivity to hormone therapy and a poor prognosis (8). Therefore, it is important to examine clinical characteristics of G3 endometrial carcinoma cases separately from highly differentiated cases.

Endometrioid adenocarcinoma constitutes 70% of endometrial carcinomas (5), and those with other tissue types such as clear cell adenocarcinoma and serous adenocarcinoma show a

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significantly poorer prognosis compared with endometrioid adenocarcinoma (5,10–14). Therefore, in this study, we limited the subjects to endometrioid adenocarcinoma patients. Specifically, we compared the prognosis of G3 endometrioid adenocarcinoma with G2 and examined the prognostic factors of G3.

SUBJECTS AND METHODS

Of the 890 endometrial carcinoma cases treated at the Keio University Hospital from 1975 to 2002, this study included 699 patients with endometrioid adenocarcinoma (including adenoacanthoma and adenosquamous cell carcinoma) for whom surgery had been performed. The breakdown was as follows: 405 G1 cases, 220 G2 cases and 74 G3 cases. The age at the start of treatment was 22–86 years (mean 54.8 years). The follow-up period was 1–302 months (mean 93.6 months). Patient backgrounds are summarized in Table 1. We had obtained informed consent to analyze prognostic factors from G3 endometrioid adenocarcinoma patients.

The standard surgical method in endometrial cancer in our department is modified radical hysterectomy for clinical stage I cases, radical hysterectomy for stage II cases, modified radical hysterectomy for stage III cases and total hysterectomy for stage IV cases. Pelvic lymphadenectomy is performed in all stages (I–IV). In modified radical hysterectomy, we dissect the anterior layer of the vesicouterine ligament, remove the ureter to the lateral side, dissect part of the posterior layer of vesicouterine ligament and part of the cardinal ligament and then deliver the uterus with about 1 cm of vaginal wall. Para-aortic lymphadenectomy is performed for: (i) patients with invasion to more than half of the myometrium; (ii) those with metastasis to the pelvic lymph nodes or the adnexas (diagnosed by the intraoperative frozen section); and (iii) those with G3 endometrioid adenocarcinoma (or specific pathological types such as serous adenocarcinoma and clear cell adenocarcinoma).

Table 1. Patients' backgrounds

Variables	Grade of differentiation		
	G1	G2	G3
Stage			
Stage I	307	140	32
Stage II	31	18	5
Stage III	62	54	29
Stage IV	5	8	8
Treatment			
Surgery alone	278	98	20
Surgery and radiotherapy	38	25	12
Surgery and chemotherapy	50	65	33
Surgery and MPA* treatment	17	16	1
Surgery and combination of multiple therapies#	22	16	8

*Methoxyprogesterone acetate.
#Radiotherapy, chemotherapy, and MPA treatment.

Adjuvant therapy after surgery is selected according to the protocol (the first to the fifth editions) of the Japan Gynecological Oncology Group (JGOG).

The G1–G3 survival rates of endometrioid adenocarcinoma cases and the G2–G3 disease-free periods (defined as the period from surgery to recurrence) were investigated. The survival rates and disease-free survival rates were calculated by the Kaplan–Meier method and statistical tests were performed with the log-rank method.

Univariate analysis was performed with the 5-year survival rate and disease-free survival rate of 74 cases of G3 endometrioid adenocarcinoma, to examine the relationships between clinicopathological factors and prognosis. The following 12 factors were examined: vessel permeation, muscle invasion (>1/3 versus ≤1/3), cervical involvement, lymph node metastasis, ascites cell analysis, parametrium invasion, adnexal metastasis, CA125 pre-surgery values (>35 U/ml versus ≤35 U/ml), CA602 pre-surgery values (>63 U/ml versus ≤63 U/ml), CA19-9 pre-surgery values (>37 U/ml versus ≤37 U/ml), the age at the start of the first treatment (age >60 versus age ≤60), and a family history of cancer or multiple cancers. This analysis was performed with the chi-square test. SAS Re16.12 TS060 was used for statistical analysis.

RESULTS

We first investigated the survival rates separately for each differentiation grade (G1–G3) of endometrioid adenocarcinoma in our hospital. The 5-year survival rates were 97.0% for G1, 86.0% for G2 and 78.6% for G3, clearly showing the poorest prognosis in G3 cases. The 10-year survival rate was 95.1% for G1, 82.2% for G2 and 78.6% for G3. In G1 and G3, the survival rate decreased for 5 years and stabilized in the following 5 years whereas the survival rate appeared to decrease steadily for 10 years in G2 cases (Fig. 1).

When the survival rate was compared separately in each surgical stage of G2 and G3 cases, the 5-year survival rate was 93.9% for stage I, 86.9% for stage II, 71.9% for stage III

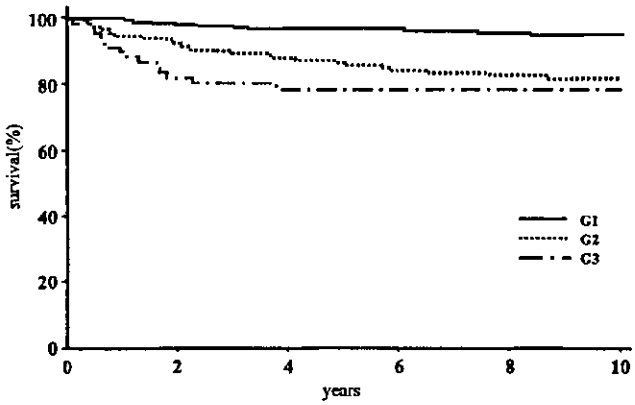

Figure 1. Survival by differentiation grade in 699 cases of endometrioid adenocarcinoma.

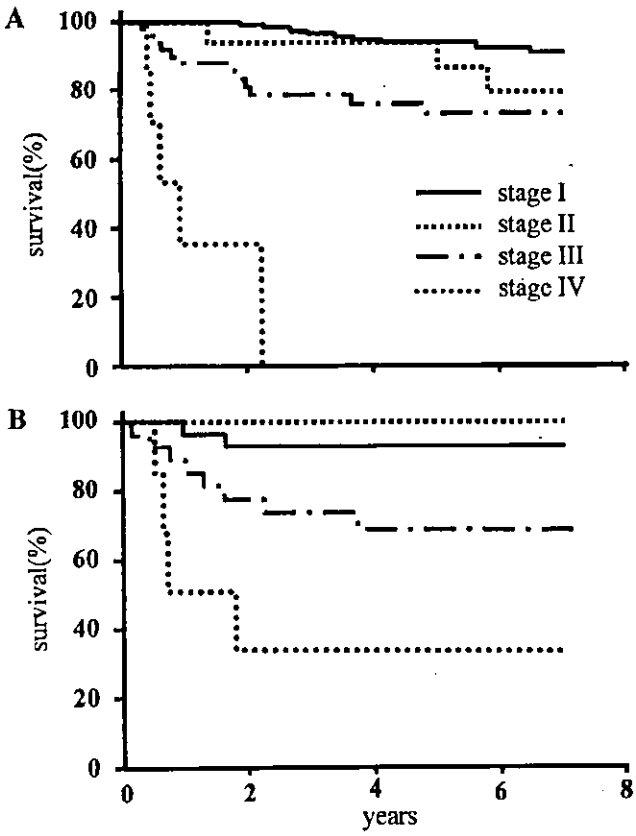

Figure 2. Survival by surgical stage for (A) G2 and (B) G3 endometrioid adenocarcinoma patients.

and 0% for stage IV G2 cases, and 93.2% for stage I, 100% for stage II, 68.9% for stage III and 34.3% for stage IV G3 cases. This clearly shows a poor prognosis in stages III and IV, even in G2 cases (Fig. 2).

When the G2–G3 disease-free periods were compared, there were recurrences in many cases within 5 years after surgery and some late recurrences after more than 10 years in G3 cases. In G2 cases, recurrences were observed steadily until 8 years after surgery, but not after 8 years (Fig. 3).

In the univariate analysis of the 5-year survival rate of 74 cases of G3 endometrioid adenocarcinoma, adnexal metastasis ($P = 0.0027$) and high pre-surgery CA19-9 values ($P = 0.020$) showed significantly low P-values for survival (Table 2). Cervical involvement ($P = 0.063$) and high pre-surgery CA602 values ($P = 0.070$) showed relatively low P-values, although they were not statistically significant. The 5-year survival rate, as analyzed separately by the presence or absence of these four factors, was 63.1% in the presence and 87.9% in the absence of cervical involvement, 61.9% in the presence or 87.9% in the absence of adnexal metastasis, 34.3% with high CA602 values and 87.5% with low CA602 values, and 50.8% with high CA19-9 values and 100% with low CA19-9 values (Fig. 4).

DISCUSSION

We examined the prognosis and the prognostic factors of G3 endometrioid adenocarcinoma in this study. First, we analyzed the 10-year survival rates for all grades. The rate decreased steadily for 5 years but remained steady without further

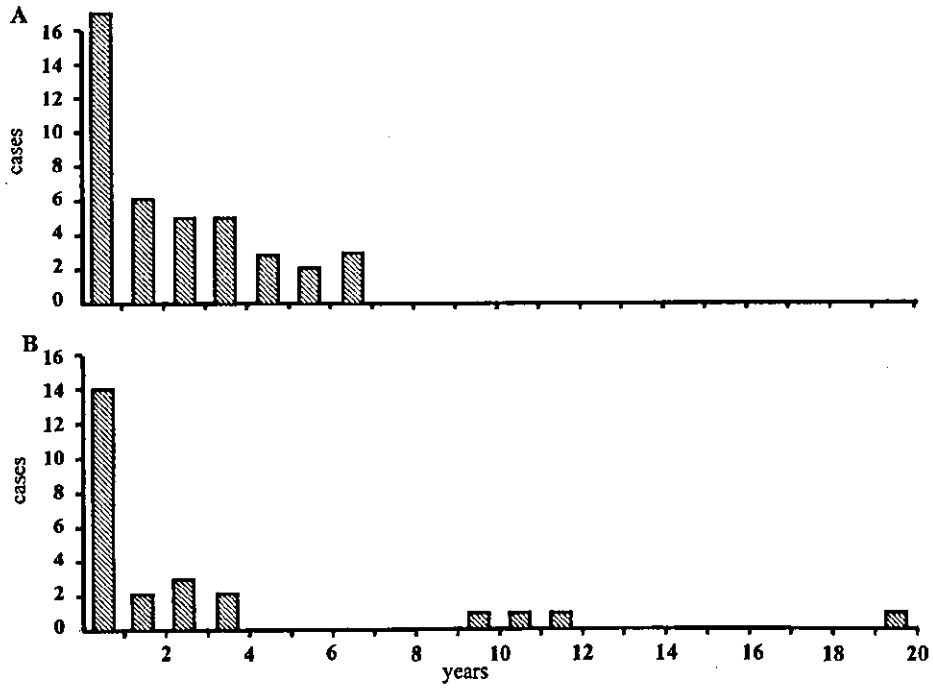

Figure 3. Disease-free periods for (A) G2 and (B) G3 endometrioid adenocarcinoma patients.

Table 2. Univariate analysis of G3 endometrioid adenocarcinoma

Clinicopathological factor	Number of cases (positive/negative or over/under)	5-year survival (*P*-value)	Disease-free survival (*P*-value)
Vessel permeation	51/20	0.39	0.058
Muscle invasion (>1/3 versus ≤1/3)	53/20	0.16	0.069
Cervical involvement	24/49	0.063	0.0058
Lymph node metastasis	7/42	0.48	0.20
Ascites cell analysis	20/8	0.11	0.25
Parametrium invasion	12/62	0.77	0.57
Adnexal metastasis	16/58	0.0027	0.00026
CA125 value (>35 U/ml versus ≤35 U/ml)	11/18	0.11	0.22
CA602 value (>63 U/ml versus ≤63 U/ml)	9/8	0.070	0.062
CA19-9 value (>37 U/ml versus ≤37 U/ml)	9/11	0.020	0.025
Age at start of the first treatment (age >60 versus ≤60)	64/10	0.20	0.072
Family history of cancer or multiple cancers	11/63	0.81	0.73

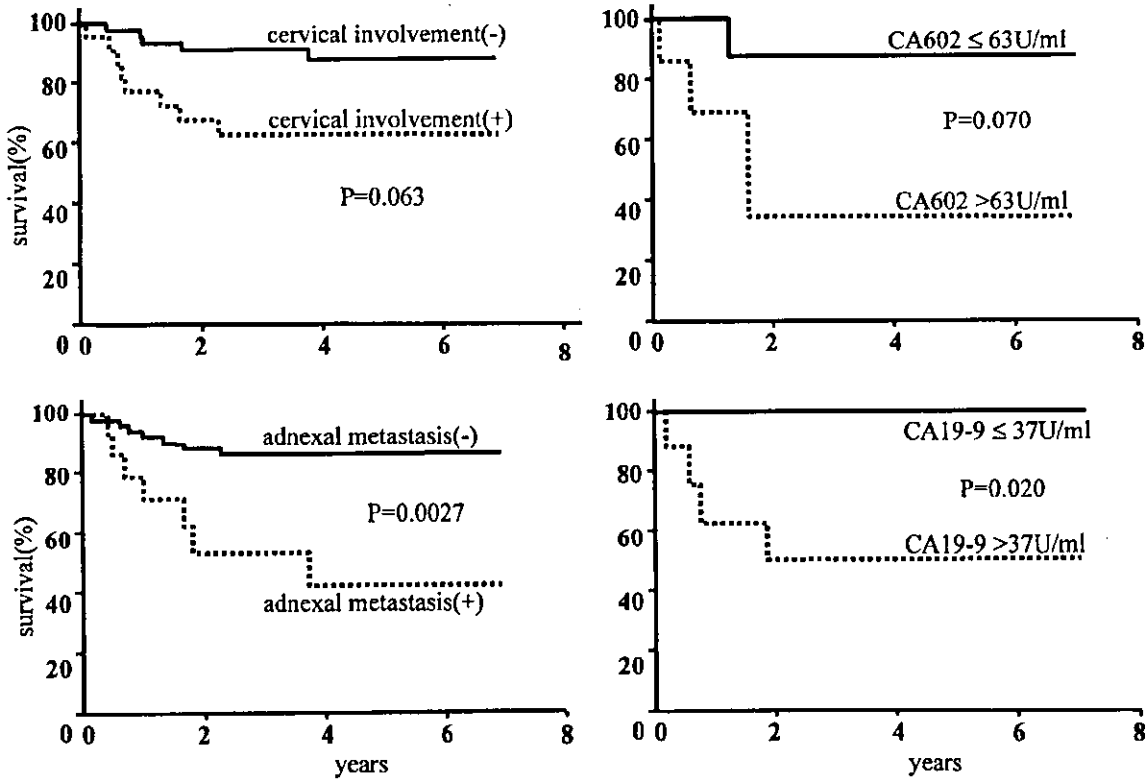

Figure 4. Survival by clinicopathological factors (cervical involvement, adnexal metastasis, and CA602 and CA19-9 pre-surgery values) in 74 cases of G3 endometrioid adenocarcinoma.

decreases in G1 and G3, suggesting that recurrence was rare during the 5–10-year period. In G2 cases, on the other hand, the survival rate decreased steadily for 10 years, but there were recurrences in many cases after 5 years. Compared with G1, both G2 and G3 showed poor prognosis, and the 10-year G2 survival rate was similar to that of G3.

Next, we analyzed the survival rate for each surgical stage of the G2 and G3 grades. Since the prognosis of G1 cases was much more favorable than that of G2 or G3 cases (as shown in Fig. 1), we limited the subjects to G2 and G3 cases. It was found that, in both G2 and G3 cases, prognosis was favorable in stages I and II, but poor in stages III and IV (Fig. 2). We

could not find any critical difference between G2 and G3 from this analysis.

We subsequently examined the disease-free period for G2 and G3 cases (Fig. 3), and showed that in G2 recurrences were observed steadily for 8 years after surgery, but there was no recurrence after 8 years. In G3, recurrences were often observed within 5 years after surgery and some late recurrences were also observed after 10 years. It was thus found that in G3 cases, recurrence occurred relatively early, quickly leading to death, but that late recurrences could also occur. We suggest that the high risk of late recurrence is one of the most significant features of G3 cases. Careful follow-up observation is important over a long period after surgery in G3 endometrioid adenocarcinoma.

In clinical practice we sometimes encounter G3 patients whose prognosis is rather favorable. In order to determine what factors might predict a favorable outcome, we analyzed 12 clinicopathological prognostic factors for G3 endometrioid adenocarcinoma. Most of the factors that we examined in this analysis proved to have a significant effect on the prognosis of endometrioid adenocarcinoma (1,15–17). However, we initially conjectured that the grade of differentiation might be so critical a prognostic factor that it could be expected that none of the other clinicopathological factors would be significant in our G3 case analysis. In fact, in the univariate analysis of clinicopathological prognostic factors in G3 endometrioid adenocarcinoma cases, adnexal metastasis and high pre-surgery CA19-9 values were the only factors that showed significantly low *P*-values for the 5-year survival. Of the other 10 factors, cervical involvement and high pre-surgery CA602 values showed relatively low *P*-values. Therefore, the absence of adnexal metastasis and cervical involvement, and low pre-surgery CA19-9 and CA602 values suggest relatively favorable prognosis in G3 endometrioid adenocarcinoma cases.

We examined the prognosis and the prognostic factors of G3 endometrioid adenocarcinoma. Although the prognosis of G2 and G3 cases was significantly poorer than that of G1, we could not find any critical difference between the G2 and G3 survival rates. We suggest that the high risk of late recurrence is one of the most significant features of G3 endometrioid adenocarcinoma. The univariate analysis of prognostic factors showed that the absence of adnexal metastasis and cervical involvement, and low pre-surgery CA19-9 and CA602 values had some favorable effect on the prognosis of G3 endometrioid adenocarcinoma.

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● 原 著 ●

進行子宮体癌に対するPaclitaxel, Doxorubicin, Cisplatin併用化学療法の臨床的検討

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〔*Jpn J Cancer Chemother* 31(4): 549-553, *April*, 2004〕

A Pilot Study of Combined Chemotherapy with Paclitaxel, Doxorubicin and Cisplatin for Endometrial Cancer: Hiroyuki Honma, Satoru Sagae, Katsuhiko Terasawa, Ryouichi Tanaka, Manabu Chida, Hisanobu Mizumoto, Shinichi Ishioka, Tsuyoshi Saito and Ryuichi Kudo (*Dept. of Obstetrics and Gynecology, School of Medicine, Sapporo Medical University*)

Summary

A pilot trial of combined chemotherapy with paclitaxel, doxorubicin and cisplatin was conducted in patients with advanced endometrial cancer. Between June 2000 and March 2002 8 patients were treated with combined chemotherapy, consisting of paclitaxel, 135mg/m^2; doxorubicin, 30mg/m^2; and cisplatin, 50mg/m^2 (TAP therapy). Patients received 3 to 5 courses of TAP therapy every 4 weeks. The major adverse effect was myelosuppression. All patients had grade 3 or 4 neutropenia, but did not have any severe infection with uncontrollable fever. Only 1 patient discontinued additional therapy due to grade 3 thrombocytopenia after 3 cycles. Grade 2 neurotoxicity occurred in 5 patients, but grade 3 was not observed. Among 5 patients with measurable tumors, 4 achieved partial response and 1 had no change of tumor size, indicating a response rate of 80.0%. We found that TAP therapy was feasible with G-CSF support and shows potential for high efficacy in advanced endometrial cancer.

Key words: Endometrial cancer, Paclitaxel, Doxorubicin, Cisplatin (*Received Feb. 26, 2003/Accepted Oct. 1, 2003*)

要旨 進行子宮体癌に対しpaclitaxel (PTX), doxorubicin (DXR), cisplatin (CDDP) 併用化学療法 (TAP療法) を行った。2000年6月から2002年3月までの間に当科で診断, 治療した子宮体癌8症例を対象とした。組織型は類内膜腺癌5例, 未分化型腺癌1例, 漿液性腺癌1例, 腺扁平上皮癌1例である。投与法はPTX 135 mg/m^2 (3時間), CDDP 50 mg/m^2, DXR 30 mg/m^{2}をday 1に投与し4週ごとに3～5コース施行した。有害事象では顆粒球減少はgrade 3以上が全コースでみられたが, 重篤な感染の合併はみられなかった。grade 3の血小板減少がみられた1例は3コースで治療中止となったが, 残りの7症例については治療を完遂できた。また, PTX投与により生じる末梢神経障害はgrade 2が5例にみられた。抗腫瘍効果は, 評価可能病変のある5例中4例でPR, 漿液性腺癌の1例がNCであった。以上よりTAP療法は進行子宮体癌に対しG-CSF投与を必要とするが, 安全に行うことが可能で, かつ効果も期待できる治療法と考えられた。今後, さらに症例を重ね多数の症例での臨床比較試験が必要である。

はじめに

子宮体癌は本邦において近年増加傾向にあり, 早期癌は比較的予後良好といわれているが, 進行癌は依然として予後不良である。そのため有用な寛解導入化学療法や術後補助化学療法が必要とされている。子宮体癌に対して単剤で有効とされている主な薬剤はcisplatin (CDDP), carboplatin, doxorubicin (DXR), epirubicin (EPI), paclitaxel (PTX) などがあり, 多剤併用化学療法としてはcyclophosphamide (CPA), DXR, CDDPの3剤併用するCAP療法が最も広く行われており, 31～56%と高い奏効率が確認されている[1]。しかし奏効期間が短く, 生存期間の延長に必ずしも貢献しないなどの問題点も指摘されている[2]。

欧米では, 術後の追加治療として化学療法よりも放射線療法が積極的に行われているが, どちらの治療がよいかという臨床的な疑問への明確な回答は得られていない。現在GOG # 122[3]でIII, IV期進行子宮体癌に対する術

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表 1 症例

症例	年齢	Stage	手術	組織	Grade	転移
1	53	III a	MRH	Endometrioid	G 1	Ovary
2	47	IV b	TAH+BSO	Adenosquamous	G 3	Lung, liver
3	53	IV b	TAH+BSO	Undifferenciated	G 3	Vulva
4	72	IV b	MRH	Endometrioid	G 2	Liver
5	56	III c	MRH	Endometrioid	G 3	Pelvic lymphnode
6	43	III c	MRH	Serous papillary	G 3	Para-Aortic lymphnode
7	48	I b	RH	Endometrioid	G 3	—
8	53	III a	MRH	Endometrioid	G 3	Ovary

RH: radical hysterectomy, MRH: modified radical hysterectomy, TAH+BSO: total abdominal hysterectomy+bilateral salpingo-oophorectomy

後放射線療法（全骨盤照射）と化学療法（DXR 60 mg/m²+CDDP 50 mg/m²）についての無作為比較試験が行われており，この結果が待たれるところである（ASCO 2003 にて発表予定）。

近年，PTX を含む多剤併用化学療法が子宮体癌でもいくつか報告されている。藤田ら[4]は PTX+EPI+carboplatin が 5 例中 5 例に有効とし，Fleming ら[5]は PTX+DXR+CDDP（以下 TAP 療法）で 46.2%の奏効率を報告した。また，現在 GOG # 177[6]では III，IV期または再発子宮体癌症例において AP 群（DXR 60 mg/m²+CDDP 50 mg/m²）と TAP 群（DXR 60 mg/m²+CDDP 50 mg/m²+PTX 160 mg/m²）の比較が行われている。また，GOG # 184[7]では子宮全摘出術＋両側付属器摘出術を受けた III，IV期進行子宮体癌症例において，全骨盤照射後に AP 群（DXR 45 mg/m²+CDDP 50 mg/m²）または TAP 群（DXR 45 mg/m²+CDDP 50 mg/m²+PTX 160 mg/m²）を追加する第III相試験が進行中である。

以上の報告をもとに，われわれは進行子宮体癌症例に対し TAP 療法の pilot 試験を計画し，これまで 8 症例に施行した。今回，これらの症例に対する副作用と臨床的効果を報告する。

I．対象と方法

2000 年 6 月から 2002 年 3 月までの間に当科で診断，治療した子宮体癌 8 症例を対象とした。表 1 に全症例の特徴を示す。

わが国における婦人科癌化学療法共同研究会の子宮体癌に対する，5-FU と CAP 療法の第III相比較試験での CAP 療法の用量は CPA 500 mg/m²，DXR 30～40 mg/m²，CDDP 50～60 mg/m²と設定されている。また，GOG # 111[8]において CPA (750 mg/m²)+CDDP と PTX (135 mg/m²)+CDDP の第III相比較試験が行われた。以上の用量を参考に，今回われわれは PTX 135 mg/m²，DXR 30 mg/m²，CDDP 50 mg/m²と用量を設定した。症例の

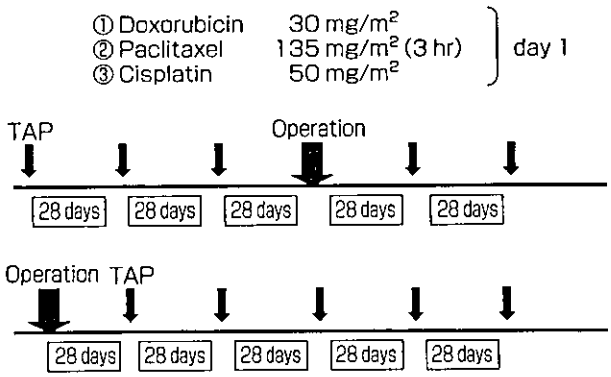

図 1 治療法

年齢は 43～72 歳（平均 51 歳），performance status はすべて 0，1 であり，いずれも肝，腎機能に異常なく，骨髄機能の低下なども認められていない。

手術による臨床進行期は I b 期 1 例，IIIa 期 2 例，IIIc 期 2 例，IVb 期 3 例であった。I b 期の 1 例は，子宮頸部腺癌の診断で TAP 療法を術前化学療法として 3 コース施行後手術を行い，術後病理組織診断にて子宮体部からの頸部浸潤と判断され子宮体癌の最終診断となった症例である。

組織型は類内膜腺癌が 5 例，未分化型腺癌が 1 例，漿液性腺癌が 1 例，腺扁平上皮癌 1 例だった。

1．治療内容

初回治療として手術的治療が困難な進行症例に対しては，術前化学療法として TAP 療法（PTX 135 mg/m² (3 時間)，DXR 30 mg/m²，CDDP 50 mg/m² day 1）を 4 週ごとに 3 コース行い，術後 1 か月以内に追加治療としてさらに 1～2 コース行った。初回手術可能症例においては，術後 1 か月以内に TAP 療法を 3～5 コース行った（図 1）。

2．評価方法

治療効果の判定は，日本癌治療学会の婦人科がん化学療法の直接効果判定基準[9]に基づいて，副作用に関しては日本癌治療学会薬物有害判定基準に基づいて判定された。

表 2 抗腫瘍効果

症例	術後診断	治療回数	効果	測定可能病変-効果	全奏効期間（月）	転帰
2	pT3aN1M1	3(術前)+2(術後)	PR	Lung-CR, Liver-PR, Primary Carcinoma-NC	5	DOD
3	pT3aN1M1	3(術前)+2(術後)	PR	Vulva-CR, Primary Carcinoma-PR	8.3	DOD
4	pT2aN0M1	5 (術後)	PR	Liver-PR, Primary Carcinoma-NC	7.6	DOD
6	pT3aN1M0	5 (術後)	NC	Lymph node-NC, (CA 125-CR)	7.1*	AWD
7	pT1bN0M0	3(術前)+2(術後)	PR	Primary Carcinoma-PR	16.4+	NED

NED: no evidence of disease, AWD: alive with disease, DOD: die of disease, *: CA 125

表 3 副 作 用

	grade					grade≧3
Toxicity	0	1	2	3	4	%of patients
Vomitting	1	2	5	0	0	0%
Diarrhea	5	3	0	0	0	0%
Alopecia	0	2	6	—	—	0%
Fatigue	0	4	4	0	0	0%
Neurotoxicity	1	2	5	0	—	0%
Hemoglobin	0	3	3	2	—	25%
Granulocytes	0	0	0	3	5	100%
Platelets	6	1	0	1	0	13%
Infection	5	2	1	0	0	0%

II. 結　果

治療効果と転帰について表2に示す。全8症例のうち3症例は術後補助化学療法症例であり効果判定病変がなく，残りの5症例について治療効果判定を行った。その結果，測定可能病変を有し画像による治療効果判定可能な5例中4例がPRであり，1例がNCであり，奏効率は80.0%であった。ちなみにNCの1例の組織型は漿液性腺癌だった。また，全奏効期間は手術と化学療法を合わせての奏効期間を示した。このうち手術前投与症例を具体的に説明すると，以下のごとくである。

症例2は，入院時にみられた癌性胸膜炎，胸水，肺転移の所見もTAP療法2コース後にはほぼ消失した。肝転移も2コース終了時には50%以上の縮小を認め，3コース終了時にはほぼ消失，原発巣は3コース終了時にはMRI上65%程度の縮小を認め，以上の所見より総合的にPRと判断した。その後，3コース終了後に原発巣の縮小目的に腹式子宮全摘出術＋両側付属器摘出術施行。しかし，術後TAP療法1コース終了後に脳転移を来しそれが増悪したため，他院にてガンマナイフなどの治療を行ったが腫瘍のコントロールできず，TAP療法開始後8か月で亡くなった。

症例3は外陰部への転移を認めIVb期と診断された。TAP療法2コース終了時には外陰部の転移は消失，原発巣も50%以上縮小し，手術前よりPRの状態であった。3コース終了後に開腹手術にて原発巣が切除できたが，術後TAP療法2コース終了時に肝転移出現し，治療法を変更し化学療法を継続したが効果がみられず原癌死となった。

また，症例7は子宮頸部腺癌Ib2期，類内膜腺癌の診断にて，術前にTAP療法3コースを行った。2コース終了時にはMRI上原発巣の50%以上の縮小を認め，3コース終了時には画像上では腫瘍は消失したため，広汎子宮全摘術を施行したところ，術中所見では肉眼的に病変を認めなかった。しかし，術後病理組織診断にて子宮体癌の頸部浸潤と診断され，さらに子宮頸部間質内に15×5 mmの残存腫瘍を認めたためPRと判断した。

術後補助化学療法を施行した4症例については，stage IVbである症例4は原癌死となったが，残りの3症例については現在も再発兆候を認めていない。

次に副作用について表3に示す。主な副作用は骨髄抑制であり，他に脱毛，嘔吐などは必発であった。顆粒球減少については，全症例でG-CSF製剤を必要としたが重篤な感染症の合併はみられなかった。症例8ではコースごとのgrade 4の顆粒球減少に加え，grade 3の血小板減少も出現し，3コースで投与中止となった。表4に全症例におけるコースごとの顆粒球減少の推移を示す。術前投与例，術後投与例，ともに連続した化学療法による明らかな副作用の蓄積は認められないが，全37コース中でのgrade 3以上の副作用出現の割合は92%と高率に

表 4 顆粒球減少の推移

術後投与症例

症例	顆粒球減少 (grade)				
	1コース	2コース	3コース	4コース	5コース
1	2	3	3	4	—
4	4	4	3	3	4
5	3	4	2	3	3
6	3	2	3	3	3
8	4	4	4	—	—

術前投与症例

症例	顆粒球減少 (grade)				
	1コース	2コース	3コース	4コース	5コース
2	4	3	4	3	4
3	3	3	3	4	4
7	3	4	3	3	4

認められた。

III. 考. 察

PTX は DXR, CDDP に交叉耐性がなく[10], 乳癌では PTX+DXR の奏効率が非常に高いと報告[11]され, 卵巣癌においては PTX+CDDP が既存の化学療法に比較し, 生存に寄与すると報告[8]されている。一方, PTX はその特徴的な副作用として, 末梢神経障害が指摘されている。今回, われわれは進行子宮体癌に対して PTX を含む多剤併用化学療法を行い, 特にその副作用を中心に検討した。

藤田ら[4]は TAC 療法 (PTX 150 mg/m², EPI 50 mg/m², carboplatin AUC=4) を 4 週ごとに 3~6 コース行い, 最も重篤な副作用は顆粒球減少であり, grade 3 は 18%, grade 4 は 82% と全症例で grade 3 以上の副作用が認められた。しかし, 連続した化学療法による副作用の蓄積はなく, 重篤な副作用による治療の中止, 薬剤減量などはみられなかったと述べている。治療効果としては 100% で, 5 例中 2 例に CR, 3 例に PR がみられた。

また, Fleming ら[5]は TAP 療法の第 I 相試験において, PTX 160 mg/m², DXR 45 mg/m², CDDP 60 mg/m²が第II相試験での推奨投与量であり, 用量規制毒性は G-CSF が使用されたならば, 末梢神経障害であったと述べている。また, 彼らは末梢神経障害を予防するため PTX と CDDP の同日投与, 心毒性減少のため PTX と DXR の同日投与を避け, day 1 に DXR, CDDP を投与し, day 2 に PTX を投与したとも述べている。治療効果は測定可能病変をもつ 13 例に対し CR 2 例, PR 4 例であった。

さらに, 2002 年の ASCO において GOG #177 (再発または進行子宮体癌に対する AP 群と TAP 群の第III相試験) の中間報告があり[6], grade 3 の末梢神経障害が TAP 群で 12% にみられたが, 奏効率では AP 群 33% に対して TAP 群では 57%, また 1 年生存率においても AP 群 50% に対し TAP 群 59% と, TAP 群で優れた成績が認められた。Lissoni ら[12]は進行・再発子宮頸部腺癌, 子宮体癌症例に対し, CEP 療法 (CDDP 50 mg/m², EPI 70 mg/m², PTX 175 mg/m²) を 3 週ごとに行い, 子宮体癌において奏効率は 73%, 副作用の点では grade 3 以上の顆粒球減少は 61%, 軽度の末梢神経障害は 46% に出現したと述べている。

自験例においても上記の報告と同様に, 主な副作用は骨髄抑制であった。なかでも顆粒球減少はほぼ全コースにおいて G-CSF の投与が必要であったが, 重篤な感染の合併はみられなかった。grade 3 の血小板減少がみられた 1 例は 3 コースで治療中止せざるを得なかったが, 残りの 7 症例については治療を完遂できた。次に投与間隔の延長では, 予定どおりの投与が可能であったのが 33 コースであり (89%), 1 週間までの延長は 4 コース (11%) にみられた。

以上より TAP 療法は海外では 3 週ごとの投与間隔とする報告もあるが, われわれは骨髄抑制の点より困難であり, 4 週ごとの投与間隔が妥当ではないかと考えている。また, PTX 投与により生じると考えられた末梢神経障害は, grade 2 が 5 例と治療を中断または中止するには至らなかった。われわれの行った TAP 療法は PTX 135 mg/m², DXR 30 mg/m², CDDP 50 mg/m² と, 海外からの報告に比べると投与量が少ないとの印象を受ける。しかし, 国内では藤田ら[4]の投与量と比較してもほぼ同等であり, また Onda などが卵巣癌においての TAP 療法の第 I, II相試験[13]の報告をしているが, 推奨投与量は PTX 110 mg/m², DXR 50 mg/m², CDDP 75 mg/m² であり, 用量規制毒性は好中球減少で, やはり全症例において grade 3 以上の好中球減少が認められている。副

作用，特に顆粒球減少の点から考えると，これ以上の投与量の増量は困難であると考えられる。また，骨髄抑制だけでなく，その他の副作用軽減のためにも，PTXの第2日目投与[5,6]，投与量の変更，あるいはより毒性の低い薬剤への変更なども検討する必要があると考えられる。

今回われわれが行ったTAP療法は，症例数は少ないが高い奏効率を示しており，副作用の点においてもG-CSFの投与は必要であるものの，比較的安全に行え，進行子宮体癌に有効な治療法であると考えられる。今後はさらに症例を重ね，安全で治療効果の高い治療法として確立する必要があるであろう。術後化学療法については，子宮体癌においてもさらにPTXを含んだ研究が中心となると考える。

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Preoperative Diagnosis and Treatment Results in 106 Patients with Uterine Sarcoma in Hokkaido, Japan

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Key Words
Preoperative diagnosis · Residual disease · Adjuvant therapy · Survival · Uterine sarcoma

Abstract
Objective: The aim of this study was to evaluate the clinicopathological features of uterine sarcoma in Hokkaido, Japan, between 1990 and 1999, and to identify prognostic factors of patients with such malignancies in this area and period. ***Methods:*** One hundred and six patients with histologically proven uterine sarcoma were evaluated retrospectively. ***Results:*** 93.5% of the patients with carcinosarcoma (CS) were diagnosed as having malignant disease preoperatively, while 65% of those with leiomyosarcoma (LMS) and 75% of those with endometrial stromal sarcoma (ESS) were preoperatively diagnosed as benign leiomyoma. When patients had no residual disease postoperatively, 5-year survival rates in patients with CS and LMS were 78.8 and 73.0%, respectively. ESS cases had a better prognosis (94.7% for stage I cases). In patients with early-stage sarcoma, pelvic lymphadenectomy and adjuvant chemotherapy, with or without cis-diamminedichloroplatinum, failed to show a survival benefit in both CS and LMS cases. Distant metastasis, myometrial invasion, and no residual disease at surgery were significantly associated with risk of death or recurrence in CS and LMS cases. ***Conclusion:*** Accurate preoperative diagnosis of uterine sarcoma was difficult, and no residual disease at surgery was the most important prognostic factor in patients with this disease. Postoperative adjuvant therapy had little effect on survival , especially in early-stage disease.

The following institutions participated in this study; the principal investigators are shown in parentheses: Asahikawa Red Cross Hospital (T. Hasegawa); Asahikawa Medical University Hospital (T. Yamashita); Asahikawa Kousei Hospital (H. Sato); Asahikawa City General Hospital (K. Yoshiaki); Hokkaido University Hospital (N. Sakuragi); Japan Railway Hokkaido Hospital (A. Tamagawa); Kin-I-kyo Central Hospital (K. Sakamoto); Kitami Red Cross Hospital (M. Mizunuma); Kushiro Rousai Hospital (T. Yamazaki); National Sapporo Hospital (K. Yamashita, Director of the Hokkaido Gynecologic Cancer Chemotherapy Group; T. Kanemoto, former Director of the Hokkaido Gynecologic Cancer Chemotherapy Group); H. Hayashi, Nikkou Memorial Hospital (H. Hayashi); Nippon Telegraph and Telephone East Japan Hospital (T. Sato); Sapporo Kousei Hospital (M. Nishiya); Sapporo City General Hospital (H. Hareyama).

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Introduction

Uterine sarcomas consist of carcinosarcoma (CS), leiomyosarcoma (LMS), and endometrial stromal sarcoma (ESS) [1]. They are rare mesodermal tumors that account for approximately 3% of uterine cancers, and they usually have a poor prognosis [2]. Recently, the incidence of these tumors has been reported to be increasing [3]. However, little is known regarding the epidemiology of these tumors because of their rarity [4].

The best diagnostic method would be curettage of the uterus, but a histological diagnosis of uterine sarcoma is often made after surgery for benign uterine myoma [5]. Given the poor prognosis and propensity of uterine sarcoma to spread hematogenously [6], it is unclear whether surgical staging provides accurate prognostic information or guides appropriate adjuvant radiotherapy and chemotherapy. Generally, the most common treatment modality for uterine sarcoma is surgical removal of the uterus and extrauterine metastatic lesions [2]. The most extensively discussed prognostic factors in uterine sarcoma are disease stage, patient's age, and mitotic activity of the tumor [7–10]. There have also been reports on various factors that indicate worse biologic behavior of the tumors, such as histologic grade of differentiation, myometrial invasion, lymphovascular space invasion, and residual disease at surgery [11, 12], but these findings remain controversial.

This is the first collaborative retrospective study of the Hokkaido Gynecologic Cancer Chemotherapy Group to identify intrinsic pathological factors associated with extrauterine disease, recurrence, and survival in patients with uterine sarcoma. Another aim of this study was to examine the accuracy of preoperative diagnosis and the effect of adjuvant therapy on recurrence and survival in patients with uterine sarcoma.

Materials and Methods

A total of 115 patients with uterine sarcoma were evaluated. Among the 115 cases, 41 were LMS, 22 were ESS, and 52 were CS. Five cases were excluded because they occurred outside the study period (1990–1999): 2 occurred before 1990, 3 after 1999. After pathological verification, 4 cases were excluded because the organ of origin was unclear. In each histological group, 2 cases were classified into other histological groups. At the end of the review, 9 cases were excluded from the study, and the final total was 106 cases: 46 with CS [homologous in 32; heterologous in 14 (rhabdomyosarcoma in 6; chondrosarcoma in 8)], 40 with LMS, and 20 with ESS.

As characteristics of patients with each histological type, the following were examined: age, gravida status, parity, premenopausal status, past history of double cancers; existence of uterine enlargement; results of cervical or endometrial cytology, results of ultrasound, CT, and MR imaging examinations, and preoperative diagnosis.

At laparotomy, macroscopic findings were evaluated as to tumor dissemination, ascites, and myometrial invasion. Pathological study also evaluated tumor dissemination, myometrial invasion, cervical invasion, pelvic lymph node metastasis, para-aortic lymph node metastasis, washing cytology, and ascitic fluid cytology. The diagnosis of each histological type of uterine sarcoma was established according to the routine textbook guidelines [13]. Currently, there are no official staging systems for uterine sarcoma, but it is usual to apply the FIGO system for endometrial cancers [14]. The postoperative TNM classification, such as pT, pN, and pM, was established using the criteria of the UICC classification [15].

As to treatment modalities, surgery was evaluated as the presence of residual disease, with or without lymphadenectomy. Radiotherapy was assessed. Chemotherapy was examined, including the regimen, number of courses, and total drug doses. Chemotherapy, radiotherapy, and surgery were also examined as treatments for recurrent disease.

Overall survival was evaluated by univariate or multivariate analysis with the Cox proportional hazard model using relative risk and the confidence interval. Survival data were evaluated using the SAS system [16], including distribution analysis, χ^2 testing, and residual analysis of prognostic factors. Survival was calculated by the Kaplan-Meier method [17], and survival between groups was compared using the log-rank test [18]. Deaths due to causes other than uterine sarcoma were censored in the analysis. Multiple predictors of survival were compared using Cox regression analysis [19].

Results

As shown in table 1, in the CS group (n = 46), the average patient age was 58.0, which was significantly older compared with the other groups. Parity was 1.9, and was detected as a significant prognostic factor by multivariate analysis. Five cases had a history of double cancer. Patients in the LMS group (n = 40) were older compared with the ESS group. The most significant symptom was uterine enlargement, as in the ESS group. The ESS group (n = 20) had the youngest average patient age, with 70% premenopausal patients. Distribution analysis using the SAS statistical system was conducted on the following factors: patient age, parity, and menopausal status among the three groups. Patients in the ESS group were significantly younger ($p < 0.05$) compared with the CS group, and the percentage of premenopausal women in the ESS group was significantly higher ($p < 0.05$) than in the CS group.

As preoperative diagnosis of uterine sarcoma, the CS group showed positive cytological results from the endometrial cavity in 64.9% of cases. Ultrasound and CT scans in the CS group showed higher percentages of abnormal findings compared with other groups. How-

ever, MR imaging showed no difference among the three groups. In the CS group, the suspected preoperative diagnosis was malignant disease in 93.5% of the cases. In the LMS group, cytological abnormalities were rarely detected. Ultrasound showed no abnormal findings, except for uterine enlargement. Therefore, examinations by CT and MR imaging were seldom performed in this group. The preoperative diagnosis in the LMS group was leiomyoma in 65% of the cases, and malignant disease in 35%. This tendency was similar in the ESS group, in which both cytological examination and ultrasound detected only few abnormalities. In the ESS group, only 25% of cases were preoperatively diagnosed as having malignant disease.

In the CS group, muscle invasion at a level beyond half the depth (pT1c) was significantly associated with patient prognosis. Pelvic or para-aortic lymph node involvement was found at a relatively higher percentage in the CS group, compared with the other groups. Ascites was detected in 28 cases, 10 of which were positive for malignant cells. Surgical staging was significantly related to patient prognosis in all three pTNM classifications. In the LMS group, muscle invasion at a level beyond one-half of the depth was found in 29 of 39 cases. Pelvic or para-aortic lymphadenectomy was not performed routinely, although a few cases were positive for lymph node metastasis. Ascites was detected in 13 cases, 2 of which were positive for malignant cells. In the LMS group, stage I tumors showed better survival by univariate analysis; distant metastasis was also related to prognosis by univariate and multivariate analyses. In the ESS group, muscle invasion with a depth of greater than one half was found in 9 of 20 cases. Pelvic and para-aortic lymphadenectomies were performed only in 7 cases and 1 case, respectively, and all of them were negative for metastasis. Ascites was detected in 7 cases, and all of them were negative for malignant cells. All of the ESS group cases were diagnosed as stage I disease, and all were negative for lymph node metastasis or distant metastasis.

Therapeutic modalities for the uterine sarcomas in the present study are shown in table 2. As surgery in the CS group, simple hysterectomy was performed in 20 cases, and radical hysterectomy in 23. Only 7 of these 43 were present with residual disease. In the LMS group, simple total hysterectomy was the most common treatment modality. Total resection was performed in 80% of the present cases, with statistical significance regarding the prognosis. All cases in the ESS group received simple total hysterectomy. The significance of pelvic lymphadenectomy and chemotherapy with the cis-diamminedichloro-

Table 1. Characteristics of the women with uterine sarcomas

Characteristics	CS	LMS	ESS
Cases entered	46	40	20
Age, mean, years	58[1]	53.8[2]	48.2
Parity	1.9[3]	2.2	1.9
Premenopause	14/46	14/40	14/20[4]
Uterine enlargement	29/46 (63%)	38/40 (95%)[3]	20/20 (100%)
Endometrial cytology			
Normal	13	16	8
Abnormal	24[4]	6	1
Not specified	9	18	11
US			
Normal	3	12	13
Abnormal	35[4]	18	5
Not specified	8	10	2
CT			
Normal	1	4	3
Abnormal	26[4]	9	4
Not specified	9	27	13
MRI			
Normal	20[4]	3	3
Abnormal	8	12	5
Not specified	18	25	12
Preoperative diagnosis			
Leiomyoma	3 (6.5%)	26[4]	15
Cancer	32 (69.6%)	5	1
Sarcoma	11 (23.9%)	9	4
Myometrial invasion			
<1/2	29	10	11
>1/2	15[2,3]	29[4]	9
Not specified	2	1	0
Pelvic lymph node involvement			
No	24	11	7
Yes	8	1	0
Not determined	14	28	13
pT			
I	26[1]	30[2]	20
II	5	1	0
III	11	5	0
IV	4	4	0
pN			
No	23[1]	7	7
Yes	9	4	0
Not determined	13	29	13
pM			
No	40	34	20
Yes	4[2]	6[2,3]	0
Not determined	2	0	0

[1] Statistically significant factor by χ^2 and residual analysis in each group ($p < 0.01$).
[2] Statistically significant factor by univariate analysis in each group.
[3] Statistically significant factor by multivariate analysis in each group.
[4] Statistically significant factor by χ^2 and residual analysis in each group ($p < 0.05$).

Table 2. Treatment modalities of the women with uterine sarcomas

	CS		LMS		ESS
	all	early only	all	early only	
Surgery					
Simple	20		28[1]		20
Radical	23		7		0
Others	0		5		0
Not done	3		0		0
Residual disease at surgery					
None	36		32[2,3]		20
Present	7		7		0
Not determined	3		1		0
Lymphadenectomy					
Not done	11	7	28	23	13
Done	32[1]	24	11	9	7
Not determined	3		1		0
Chemotherapy[4]					n.s.
Not done	7	11	13	10	13
Done	39	20	27	22	7
Regimen[4]					n.s.
Platinum	30	15	17	12	5
Non-platinum	9	5	10	10	2

[1] Statistically significant factor by χ^2 and residual analysis in each group ($p < 0.05$).
[2] Statistically significant factor by univariate analysis in each group.
[3] Statistically significant factor by multivariate analysis in each group.
[4] Not significant.

platinum (CDDP) or the non-CDDP regimen was examined for survival benefit, especially in early-stage disease. Among 46 cases in the CS group, 24 of 31 patients with early-stage disease received pelvic lymphadenectomy, and 20 of 31 received chemotherapy, including 15 with the CDDP regimen, and 5 cases with a non-CDDP regimen. In the LMS group, 9 of 32 patients with early-stage disease received pelvic lymphadenectomy, and 22 of 32 received chemotherapy, including 12 with the CDDP regimen, and 10 with the non-CDDP regimen. In both groups, none of those therapies was significantly related to patient prognosis.

χ^2 testing and residual analysis of prognostic factors among the three groups were also used. In the CS group, positive cervical cytology, positive endometrial cytology, abnormality in medical electronic (ME) diagnoses, ovarian metastasis, and pelvic lymphadenectomy were prognostically different from the other groups, with statistical significance at $p < 0.01$, as were age over 50 years, pN status, ovarian metastasis, and pT status at $p < 0.05$. In the LMS group, uterine enlargement, diagnosis of myoma, myometrial invasion, and simple hysterectomy were significantly different regarding prognosis from the other groups at $p < 0.01$, as was the presence of ascites at $p < 0.05$. In the ESS group, only the number of patients that died and premenopausal status were significantly different from the other groups regarding prognosis ($p < 0.01$).

Univariate analyses were used with the Cox proportional hazards model. In the CS group, univariate factors with a relative risk of more than 2.0 were distant metastasis, preoperative diagnosis, pN status, age over 50 years, surgically inoperable status, simple hysterectomy, and myometrial invasion, in which distant metastasis and myometrial invasion were statistically significant at $p < 0.01$. In the LMS group, univariate factors with a relative risk of more than 2.0 were distant metastasis, surgically inoperable status, pT status, and age over 50 years, in which distant metastasis and surgically inoperable status were statistically significant at $p < 0.01$. In the ESS group, univariate analysis was not performed because of the small number of deaths in survival analysis.

Multivariate analysis by variable regression methods using the Cox proportional hazards model was also used for ten variables: gravida status, parity, double cancer, myometrial invasion, lymph node metastasis, presence of ascites, pT status, pM status, apparent residual disease after surgery, and chemotherapy in tables 1 and 2. In the CS group, parity and myometrial invasion were the most important factors associated with patient survival. In the LMS group, distant metastasis was the most important factor associated with patient survival.

In our series, adjuvant radiotherapy was seldom performed, except as palliative therapy for recurrent cases. And adjuvant chemotherapy was given to 84.8% of CS, 67.5% of LMS, and 35% of ESS patients. Adjuvant chemotherapy for early-stage uterine sarcoma was also given to 48.4% of CS and 37.5% of LMS patients. However, no adjuvant treatment showed a statistical benefit for patient survival compared with surgery alone.

The progression-free interval and overall survival in the uterine sarcomas were also compared, using the Kaplan-Meier method and the log-rank test. In the CS group ($n = 46$), 28 patients (61%) are alive at present, but 43.5% of the patients have had recurrences. Treatment at recurrence yielded favorable results only in 15% of the patients treated, and eventually a total of 18 patients (39%) died. The 5-year progression-free intervals were 70.8% for stage I disease, 60% for stage II, 36.8% for stage III, and 0% for

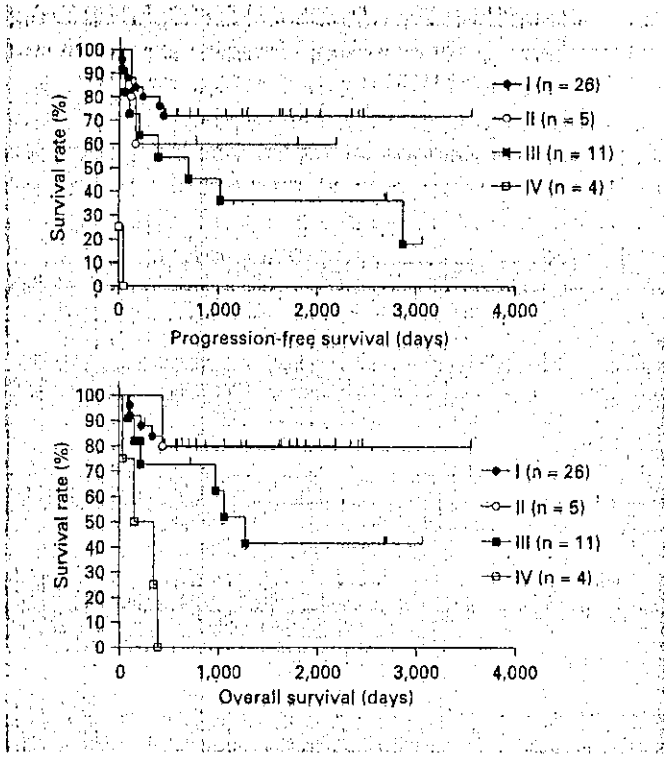

Fig. 1. Progression-free interval and overall survival in CS.

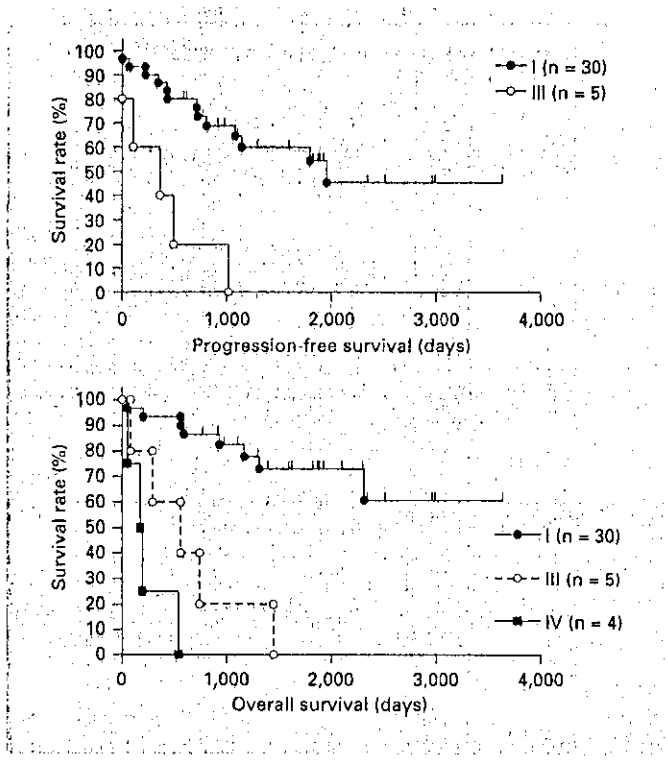

Fig. 2. Progression-free interval and overall survival in LMS.

stage IV. The 5-year overall survival rates were 78.8% for stage I disease, 80% for stage II, 41.6% for stage III, and 0% for stage IV (fig. 1).

In the LMS group (n = 40), 23 patients (58%) are alive at present, but 60% of the patients in this group had recurrences. Treatment at recurrence yielded favorable results in only 20% of the cases, and eventually a total of 17 patients (42%) died. The 5-year progression-free intervals were 54.5% for stage I disease, 100% for stage II, 0% for stage III, and 0% for stage IV. The 5-year overall survival rates were 73.0% for stage I disease, 100% for stage II, 0% for stage III, and 0% for stage IV (fig. 2).

In the ESS group (n = 20), 18 patients (90%) are alive at present, but 30% of the patients in this group had recurrences. However, treatment at recurrence yielded favorable results in 80% of those treated, and eventually a total of 2 patients (10%) died. The 5-year progression-free interval was 74.0% for stage I disease, and the 5-year overall survival was 94.7% for stage I disease (fig. 3).

Discussion

Epidemiological analyses have been unclear regarding uterine sarcoma. In our series, the mean age was younger in the ESS group compared with the LMS and CS groups [20]. Parity was significantly related to patient prognosis by multivariate analysis for the CS group. This is similar to the report by Kvale et al. [21]. Premenopausal status had a higher rate in the ESS group. A history of other cancers (double cancer) had a higher rate in the CS group compared with the other sarcoma groups, which was similar to the tendency seen with endometrial cancer. Considering familial accumulation of genetic abnormalities, endometrial cancer is regarded as a disease within the syndrome of hereditary nonpolyposis colon cancer (HNPCC) [22]. Carcinosarcoma also might be related to the genetic environments.

A precise preoperative diagnosis of uterine sarcoma is generally difficult, and in most cases, patients usually receive surgery for presumed leiomyoma [5, 23]. As shown in table 1, many of our LMS (65.0%) and ESS cases (75.0%) were identified as being sarcoma by postoperative examination of a uterus excised for leiomyoma. The

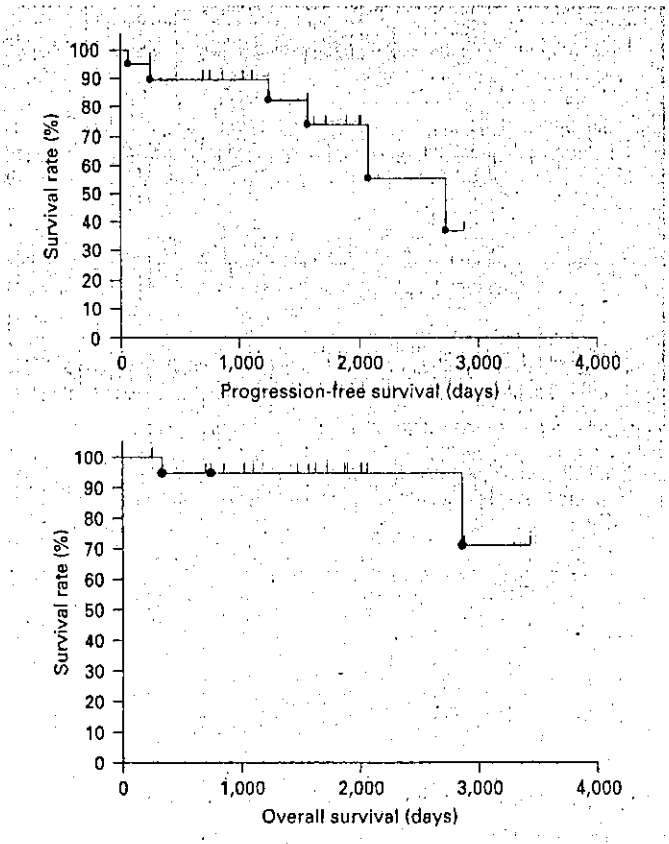

Fig. 3. Progression-free interval and overall survival in ESS.

only symptom for those patients was uterine enlargement, which would be an indication for surgical treatment as a benign disease, such as uterine leiomyoma [23]. Actually, in our series, 95% of LMS and 100% of ESS cases were detected and diagnosed as uterine enlargement by ME devices, with a fairly low rate of subjective symptoms. Preoperative cytological detection of sarcomatous lesions is also very difficult to achieve by cervical and endometrial cytology, or peritoneal cytology at surgery [24]. Diagnostic imaging techniques, such as ultrasound, CT, and MR imaging, have been developing in the field of abdominal tumors [25]. As a new imaging tool, positron emission tomography has been used to diagnose uterine sarcoma [26], but such use is still experimental. At the final preoperative diagnosis, 93.5% (43/46) of CS cases were diagnosed as having malignant disease, because of symptomatic genital bleeding and positive endometrial sampling. Strikingly, 65% of LMS cases and 75% of ESS cases were diagnosed as benign leiomyomas, as described earlier. When performing surgical treatment for 'rapidly growing' uterine tumors, clinicians should suspect the presence of uterine sarcoma [23]. Though its incidence is very low, it is slightly increasing, as reported earlier [5]. For early-stage sarcoma, the most important factor related to patient survival is no residual disease after surgery [1]. Therefore, more precise and conventional diagnostic tools will be required to improve patient survival.

There is a strong consensus that surgery is the mainstay of treatment for uterine sarcoma. The standard procedure is total abdominal hysterectomy, bilateral salpingo-oophorectomy, and the sampling of pelvic lymph nodes. No residual disease after surgery is the most important prognostic factor, as described in our data. The survival benefit of additional pelvic or para-aortic lymphadenectomy [27–29] is still unclear. Further, there are no clear guidelines for recommending adjuvant radiotherapy or chemotherapy following definitive surgery and staging for uterine sarcoma, because of the absence of randomized trials to address the role of adjuvant radiotherapy or chemotherapy.

Various prognostic factors for uterine sarcoma, such as myometrial invasion, pelvic or para-aortic lymph node metastasis, the presence of ascites, and pTNM, has been well described in many reports using univariate or multivariate analyses. However, the clinical usefulness of such prognostic factors remains controversial. Our series included too few patients with ESS to analyze for prognostic factors; almost all of them had low-grade tumors, and are still alive [3, 10]. Therefore, the other 2 groups of uterine sarcoma: CS and LMS, were analyzed by univariate and multivariate survival analyses with the Cox proportional hazards model. In the CS group, by univariate and multivariate survival analysis, distant metastasis, parity and myometrial invasion were significantly associated with risk of death or recurrence. These data are very similar to those for endometrial cancer, except for parity, as described earlier. Myometrial invasion [12] and extrauterine lesions [3, 7, 11, 28] have been most extensively discussed. In the LMS group, multivariate analysis for this group showed distant metastasis and presence of residual disease [7–9] to be significantly associated with risk of death or recurrence. These data seem reasonable, because both presence of residual disease and distant metastasis were directly related to prognosis. Therefore, it is very important for clinicians to try to resect a tumor as completely as possible, and this appears to be the only way to improve patient survival with LMS.

In this regional study in Hokkaido, Japan, it is concluded that CS and LMS are often fatal diseases, especial-

ly in advanced stages, as described above. However, ESS is a type of uterine sarcoma with a relatively good prognosis. Future prospective studies are necessary to (1) establish more accurate preoperative procedures for uterine sarcoma, (2) establish useful adjuvant therapies with no residual disease after surgery, and (3) enter prospective randomized trials, collaborating with some international clinical trial groups, such as the Gynecologic Oncology Group (GOG) or the European Organization for Research and Treatment of Cancer (EORTC), in the West.

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The Reproducibility of a Binary Tumor Grading System for Uterine Endometrial Endometrioid Carcinoma, Compared with FIGO System and Nuclear Grading

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Abstract
Objective: A binary grading system has been proposed to assess the amount of solid growth, the pattern of invasion, and the presence of necrosis, and thereby divide endometrial endometrioid carcinomas into low- and high-grade tumors. We analyzed this system for predicting the prognosis, with respect to inter- and intraobserver reproducibility and treatment modalities. ***Methods:*** A total of 200 endometrial carcinomas, based on hysterectomy specimens, were graded according to the binary grading system, for comparison against The International Federation of Gynecology and Obstetrics (FIGO) system and nuclear grading. ***Results:*** Both inter- and intraobserver agreement using the binary grading system (κ = 0.57; percent agreement: 82% and κ = 0.62; 84%) were superior compared with the FIGO system (0.50; 60% and 0.62; 73%) and the nuclear grading (0.23; 49% and 0.43; 65%). Patients with early-stage low-grade tumors had a 98% rate for 5-year survival (5YS). Patients with early-stage high-grade tumors, and those with advanced-stage low-grade tumors, had respectively 86% to 87% rates for 5YS. But patients with advanced-stage high-grade tumors had a 49% rate for 5YS. In binary low-grade early-stage tumors, the patient outcome was better with no adjuvant therapy and chemotherapy, compared with other therapies. ***Conclusion:*** A binary grading system was superior to others in permitting greater reproducibility and predicting the prognosis of endometrial cancer patients.

Introduction

The International Federation of Gynecology and Obstetrics (FIGO) tumor grading system [1] is the most widely used for endometrial carcinoma. For endometrioid endometrial carcinomas, the FIGO grading system is a three-tiered system for nonsquamous architectural grading, in which grade 1 has a 5% or less solid growth pattern, grade 2 has between a 6 and 50% solid growth pattern, and grade 3 has a greater than 50% solid growth pattern. In addition to the extent of nonsquamous solid growth, a markedly atypical nuclear pattern can increase

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