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。

文　献

1) Hoskins WJ, Perez CA and Young RC: Corpus: Epithelial tumors in principles and practice of gynecologic oncology, 2nd ed, Lippincott-Raven, Philadelphia, 1997.
2) Burke TW, Stringer CA, Morris M, *et al*: Prospective treatment of advanced or recurrent endometrial carcinoma with cisplatin, doxorubicin, and cyclophosphamide. *Gynecol Oncol* **40**: 264-267, 1991.
3) Randall ME, Spirtos NM and Dvoretsky P: Whole abdominal radiotherapy versus combination chemotherapy with doxorubicin and cisplatin in advanced endometrial carcinoma (phase III): Gynecologic Oncology Group Study No. 122. *J Natl Cancer Inst Monogr* **19**: 13-15, 1995.
4) 藤田征己，榎本隆之，中村隆文・他: 進行または再発子宮体癌に対するTaxol＋Epirubicin＋CBDCA併用療法. *Oncol Chemother* **16**: 162-166, 2000.
5) Fleming GF, Fowler JM and Waggoner SE: Phase I trial of escalating doses of paclitaxel combined with fixed doses of cisplatin and doxorubicin in advanced endometrial cancer and other gynecologic malignancies: a Gynecologic Oncology Group study. *J Clin Oncol* **19**: 1021-1029, 2001.
6) Fleming GF, Brunetto VL, Mundt AJ, *et al*: Randonized trial of doxorubicin (dox) plus cisplatin (CIS) versus DOX plus CIS plus paclitaxel in patients with advanced or recurrent endometrial carcinoma: Gynecologic Oncology Group (GOG) trial. *Proc ASCO* (*abstr*): 202 a, 2002.
7) http://www.gog.fccc.edu/document/protocols/pdf/0184. PDF
8) McGuire WP, Hoskins WJ, Brady MF, *et al*: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* **334**: 1-6, 1996.
9) 日本産婦人科学会・編: 卵巣腫瘍取扱い規約. 第2部付1. 婦人科がん化学療法の直接効果判定基準，金原出版，東京，1997.
10) 野田起一郎，池田正則，工藤隆一・他: Paclitaxel (BMS-181339) の卵巣癌患者に対する臨床第II相試験 (3時間点滴静注). 癌と化学療法 **23** (3): 317-325, 1996.
11) Sledge GW Jr: Phase III trial of doxorubicin (A) versus paclitaxel (I) versus doxorubicin＋paclitaxel (A＋T) as first-line therapy for metastatic breast cancer (MBC): An Intergroup Trial. ASCO 17: #2 Plenary Session, 1997.
12) Lissoni A, Gabriele A, Gorga G, *et al*: Cisplatin-, epirubicin-and paclitaxel-containing chemotherapy in uterine adenocarcinoma. *Ann Oncol* **8**: 969-972, 1997.
13) Onda T, Katumata N, Yasugi T, *et al*: Cisplatin, paclitaxel and escalating dose of doxorubicin (TAP) in advanced ovarian cancer. A phase I-II trial. *Proc ASCO* (*abstr*) **21**: 217 a, 2002.

Clinical Study

Oncology

Oncology 2004;67:33–39
DOI: 10.1159/000080283

Received: August 4, 2003
Accepted after revision: January 12, 2004

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

Satoru Sagae[a,d] Kohki Yamashita[d] Shinichi Ishioka[a] Yoshihiro Nishioka[a] Katsuhiko Terasawa[a] Mitsuru Mori[b] Katsushige Yamashiro[c] Toshitaka Kanemoto[d] Ryuichi Kudo[a]

Departments of [a]Obstetrics and Gynecology and [b]Public Health, Sapporo Medical University, School of Medicine, Sapporo, [c]Department of Pathology, National Sapporo Hospital, Sapporo, [d]Hokkaido Gynecologic Cancer Chemotherapy Group, Sapporo, Japan

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).

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0030–2414/04/0671–0033$21.00/0

Accessible online at:
www.karger.com/ocl

Satoru Sagae, MD, PhD, Associate Professor
Department of Obstetrics and Gynecology
Sapporo Medical University, School of Medicine
South 1 West 16, Chuou-ku Sapporo, 0606-0061 (Japan)
Tel. +81 11 611 2111, ext. 3373, Fax +81 11 614 0860, E-Mail sagaes@sapmed.ac.jp

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

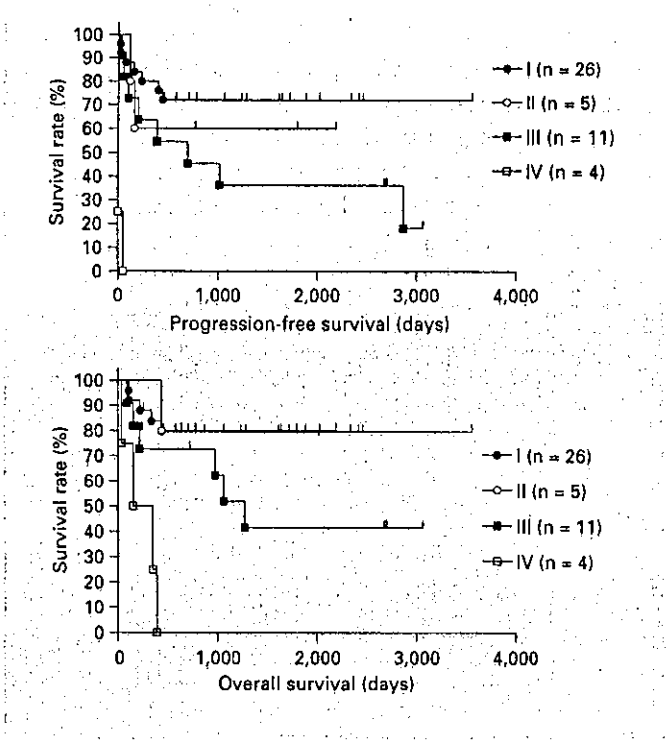

Fig. 1. Progression-free interval and overall survival in CS.

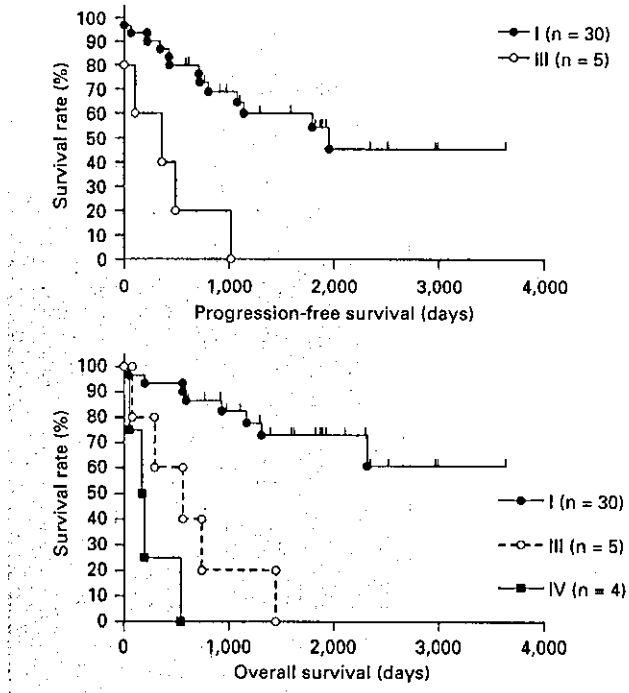

Fig. 2. Progression-free interval and overall survival in LMS.

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

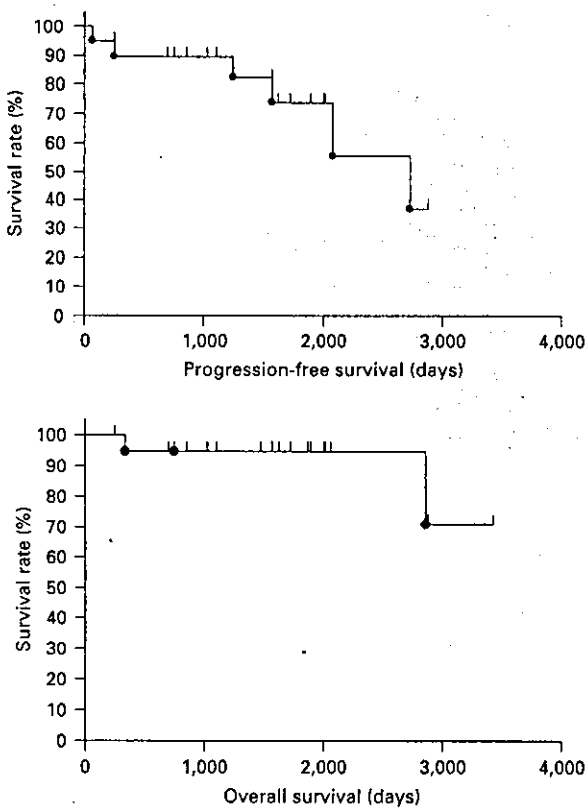

Fig. 3. Progression-free interval and overall survival in ESS.

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.

References

1 Zaloudek C, Norris HJ: Mesenchymal tumors of the uterus; in Kurman RJ (ed): Balustein's Pathology of the Female Genital Tract, ed 4. New York, Springer, 1994, pp 487–528.
2 Berek J, Hacker N: Practical Gynecologic Oncology, ed 3. Baltimore, Williams & Wilkins, 2000, pp 441–446.
3 Nordal RR, Thoresen SO: Uterine sarcomas in Norway 1956–1992: Incidence, survival and mortality. Eur J Cancer 1997;33:907–911.
4 Schwartz SM, Thomas DB: A case-control study of risk factors for sarcomas of the uterus. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Cancer 1989;64:2487–2492.
5 Leibsohn S, d'Ablaing G, Mishell DR Jr, Schlaerth JB: Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. Am J Obstet Gynecol 1990; 162:968–976.
6 Rose PG, Piver MS, Tsukada Y, Lau T: Patterns of metastasis in uterine sarcoma. An autopsy study. Cancer 1989;63:935–938.
7 Wolfson AH, Wolfson DJ, Sitttler SY, et al: A multivariate analysis of clinicopathologic factors for predicting outcome in uterine sarcomas. Gynecol Oncol 1994;52:56–62.
8 Mayerhofer K, Obermair A, Windbichler G, Petru E, Kaider A, Hefler L, Czerwenka K, Leodolter S, Kainz C: Leiomyosarcoma of the uterus: A clinicopathologic multicenter study of 71 cases. Gynecol Oncol 1999;74:196–201.
9 Gadducci A, Landoni F, Sartori E, Zola P, Maggino T, Lissoni A, Bazzurini L, Arisio R, Romagnolo C, Cristofani R: Uterine leiomyosarcoma: Analysis of treatment failures and survival. Gynecol Oncol 1996;62:25–32.
10 Pautier P, Genestie C, Rey A, Morice P, Roche B, Lhomme C, Haie-Meder C, Duvillard P: Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of a grading score validated for soft tissue sarcoma. Cancer 2000;88:1425–1431.
11 Arrastia CD, Fruchter RG, Clark M, et al: Uterine carcinosarcomas: Incidence and trends in management and survival. Gynecol Oncol 1997;65:158–163.
12 Silverberg SG, Major FJ, Blessing JA, Fetter B, Askin FB, Liao S-Y, Miller A: Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus: A Gynecologic Oncology Group pathologic study of 203 cases. Int J Gynecol Pathol 1990;9:1–9.
13 Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson EJ: World Health Organization international histological classification of tumours: Histological typing of female genital tract tumours, ed 2. Springer, Berlin, 1994.
14 Pecorelli S, Benedet JL, Creasman WT, Shepherd JH: FIGO staging of gynecologic cancer: 1994–1997 FIGO Committee on Gynecologic Oncology. International Federation of Gynecology and Obstetrics. Int J Gynaecol Obstet 1999;65:243–249.
15 Sobin LH, Wittekind C: TNM classification of malignant tumours. UICC, ed 6. New York, Wiley, 2002, pp 147–151.
16 SAS Institute Inc: SAS Procedures Guide, ed 8. Cary, SAS Institute Inc, 2000.
17 Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
18 Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1977; 35:1–39.
19 Cox DR: Regression models and life tables. J R Stat Soc 1972;34:187–220.
20 Bodner K, Boner-Adler B, Obermair A, et al: Prognostic parameters in endometrial stromal sarcoma: A clinicopathologic study in 31 patients. Gynecol Oncol 2001;81:160–165.
21 Kvale G, Heuch I, Ursin G: Reproductive factors and risk of cancer of the uterine corpus: A prospective study. Cancer Res 1988;48:6217–6221.
22 Kobayashi K, Sagae S, Kudo R, Saito H, Koi S, Nakamura Y: Microsatellite instability in endometrial carcinomas: Frequent replication errors in tumors of early onset and/or of poorly differentiated type. Genes Chromosomes Cancer 1995;14:128–132.
23 Parker WH, Fu YS, Berek JS: Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol 1994;83:414–418.
24 Wang X, Khoo US, Xue WC, Cheung AN: Cervical and peritoneal fluid cytology of uterine sarcomas. Acta Cytol 2002;46:465–469.
25 Goto A, Takeuchi S, Sugimura K, Maruo T: Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. Int J Gynecol Cancer 2002;12;354–361.
26 Umesaki N, Tanaka T, Miyama M, Kawamura N, Ogita S, Kawabe J, Okamura T, Koyama K, Ochi H: Positron emission tomography with ^{18}F-fluorodeoxyglucose of uterine sarcoma: A comparison with magnetic resonance imaging and power Doppler imaging. Gynecol Oncol 2001;80:372–377.
27 Covens AL, Nisker JA, Chapman WB, Allen HH: Uterine sarcoma: An analysis of 74 cases. Am J Obstet Gynecol 1987;56:370–374.
28 Major FJ, Blessing JA, Silverberg SG, et al: Prognostic factors in early-stage uterine sarcomas. A Gynecologic Oncology Group study. Cancer 1993;71:1702–1709.
29 Goff BA, Rice LW, Fleischhacker D, et al: Uterine leiomyosarcoma and endometrial stromal sarcoma: Lymph node metastases and sites of recurrence. Gynecol Oncol 1993;50:105–109.

Clinical Study

Oncology

Oncology 2004;67:344–350
DOI: 10.1159/000082917

Received: February 4, 2004
Accepted: April 23, 2004

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

Satoru Sagae[a] Tsuyoshi Saito[a] Masaaki Satoh[b] Tatsuru Ikeda[b]
Sachiko Kimura[b] Mitsuru Mori[c] Noriyuki Sato[b] Ryuichi Kudo[a]

Departments of [a]Obstetrics and Gynecology, [b]Pathology and [c]Public Health, Sapporo Medical University, School of Medicine, Sapporo, Japan

Key Words
Reproducibility, prognosis · Binary tumor grading system · Endometrial endometrioid carcinoma · FIGO grading system, nuclear grading

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 ($\kappa = 0.57$; percent agreement: 82% and $\kappa = 0.62$; 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

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0030–2414/04/0676–0344$21.00/0

Accessible online at:
www.karger.com/ocl

Assoc. Prof. Satoru Sagae, MD, PhD
Department of Obstetrics and Gynecology
Sapporo Medical University, School of Medicine, South 1 West 16, Chuou-ku
Sapporo 060-0061 (Japan)
Tel. +81 11 611 2111 ext 3373, Fax +81 11 614 0860, E-Mail sagaes@sapmed.ac.jp

the final tumor grade, in which case tumors that are architecturally grade 1 or 2 are elevated to grade 2 or 3, respectively, if apparent nuclear atypia is present [2].

In the three-tiered FIGO tumor grading system, architectural tumor grade is a sensitive predictor of tumor spread by either direct invasion or lymph node metastasis [3]. There appears, however, to be no clear linearity of risk using the three-grade system. The intermediate grade lesion (grade 2) may lead to some ambivalence in assigning risk for recurrence, and in subsequent recommendation for postoperative treatment. In fact, determining whether solid nonsquamous growth comprises less than or greater than 5% of the tumor (that is, distinguishing grade 1 from grade 2 tumors) is often problematic and arbitrary.

Further, nuclear atypia is subject to wide subjective interpretation, as there are no precise criteria for assigning nuclei to a certain grade. There are several reports that nuclear grading is superior to FIGO tumor grading [4, 5], while other investigators have not confirmed this [6]. As a prognostic factor in many papers, tumor grade has been well described as two-tiered grouping, such as grade 1 and 2 versus grade 3, or grade 1 versus grade 2 and 3, since grade 2 is questionably diagnosed architecturally or atypically in the FIGO tumor grading system.

Under these circumstances, tumor grading has recently become a subject of debate [7–9] for determining patient prognosis. Taylor et al. [7] found only moderate interobserver agreement between two pathologists using the FIGO tumor grading system. This was especially due to the difficulty in consistent nuclear grading. A two-tiered system was proposed by Lax et al. [8], which divides tumors into poorly differentiated and well-differentiated tumors. This system showed greater inter- and intraobserver reproducibility, and had a better correlation with the clinical outcome.

Our analysis was done to reconfirm the usefulness of a proposed binary systematic grading, compared with the FIGO and nuclear grading systems for predicting prognosis; and to compare the intra- and interobserver reproducibility of the three grading systems.

Methods

Patient Selection

Hysterectomy Specimens from a total of 218 patients with uterine endometrial endometrioid carcinoma were selected at random from the surgical pathology files of the departments of pathology of Sapporo Medical University Hospitals, for the period 1980–1999. A surgical pathologist at our institute reviewed all the slides, and selected two representative tumor slides from each patient, for the evaluation of grade by five investigators. The five investigators had no knowledge of clinical data at evaluation, including stage and follow-up. The FIGO staging (including tumor grading) [1] was determined based on review of operative and surgical pathology reports and histological slides. Information on treatment and outcome was obtained from patient records, and sufficient follow-up information was available on 200 patients. Eighteen patients were excluded from this study: 3 patients had sample errors, 5 had serous adenocarcinoma, 1 had clear cell adenocarcinoma, 3 had squamous cell carcinoma, 2 had carcinosarcoma, 1 had primary ovarian cancer, and 3 had primary cervical cancer.

Grading

Grading was performed by five investigators, who recorded the grading on diagnostic sheets independently using three different systems: (1) the novel binary grading [8], (2) the FIGO tumor grading [1, 2], and (3) nuclear grading [10].

Using the binary grading system, tumors are graded as either low or high (fig. 1), based on the description of Lax et al. [8]. A tumor was classified as high grade if it had at least two of the following items: solid growth of more than 50%, a diffusely infiltrative or expansive growth pattern, or tumor cell necrosis. For tumors that were confined to the endometrium, only the percentage of solid growth and tumor necrosis in the myometrium were used for assessment. Tumor cell necrosis was defined as areas of necrotic tumor immediately adjacent to the viable tumor.

The FIGO tumor grading [2] was based on the amount of solid nonsquamous growth as follows: grade 1, 5% or less; grade 2, 6–50%; and grade 3, more than 50%. If marked nuclear atypia was present, the FIGO tumor grade was elevated by one grade.

Nuclear grading [2, 10] was based on nuclear size and shape, chromatin distribution, and the size of the nucleoli.

Assessment of Intra- and Interobserver Reproducibility

To minimize bias, assessment of inter- and intraobserver agreement was started with the second round of randomly redistributed slides, 6 months after the initial investigation of all slides. In addition, all slides were coded using serial numbers on new labels. The five investigators independently graded the 200 tumors of our patients according to the three different tumor grading systems. To evaluate interobserver reproducibility, the grading procedure was repeated by all five investigators, 6 months after completion of the first round.

Statistical Analysis SAS

All statistical calculations were performed using the SAS system [11]. Inter- and intraobserver agreement was assessed by the percentage of agreement and κ statistics [12]. As a measurement of agreement, κ values are interpreted as follows: 0.00–0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.80–1.00, almost perfect. Survival analysis was performed based on Kaplan-Meier estimates of survival [13]. Tumors of various grades were stratified into two groups for analysis: FIGO stages I–II (early-stage), and FIGO stages III and IV (advanced stage). The probability of survival was compared between different groups using the log-rank test [14]. Because age and stage represent strong prognosticators for endometrial carcinoma, grade was tested as a predictor of survival independent from age and stage in multivariate analysis using Cox proportional hazard analysis with their 95% confidence [15]. A p value of <0.05 was considered significant.

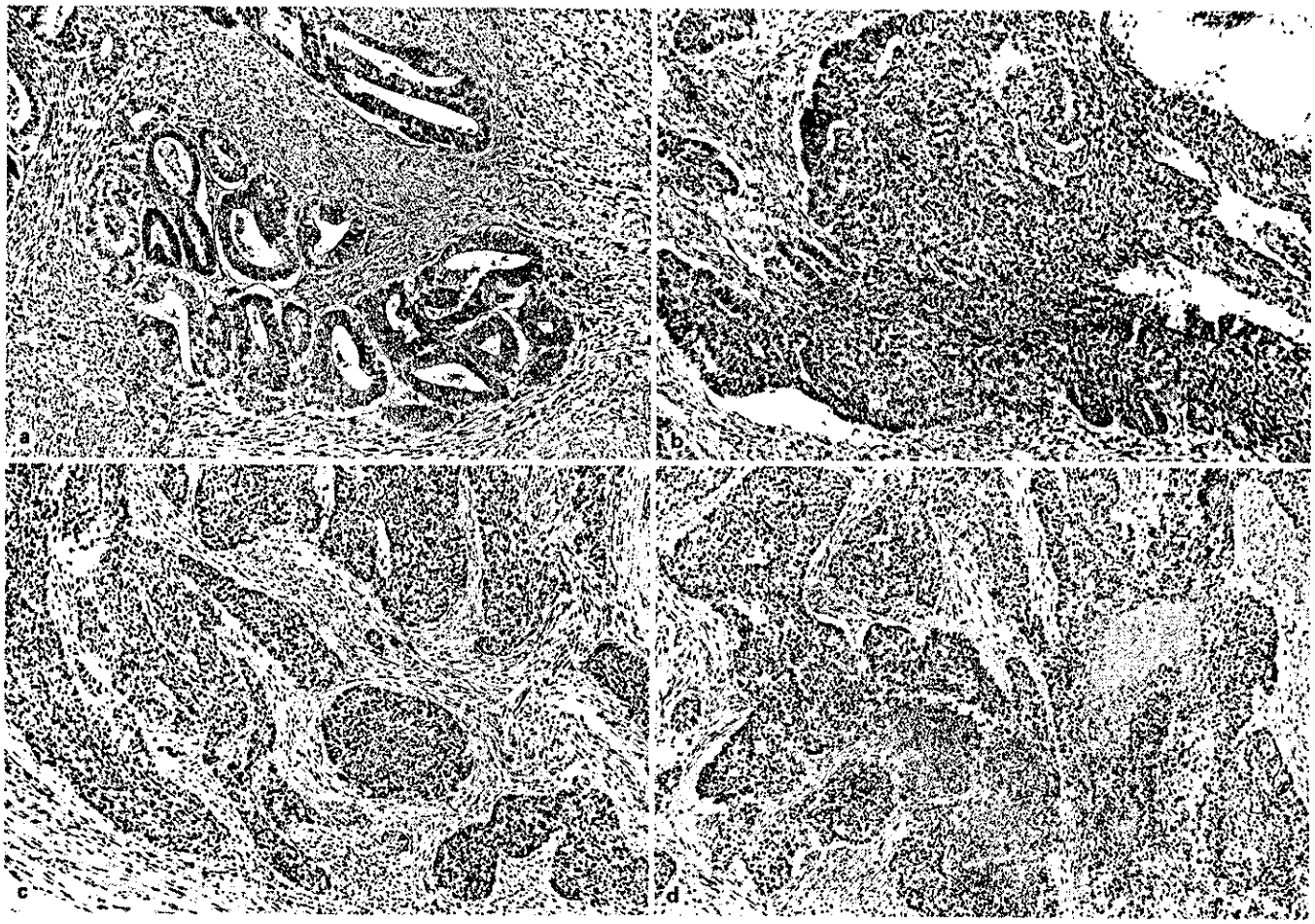

Fig. 1. Low-grade and high-grade endometrial carcinoma (H&E; original magnification, × 100). **a** Low-grade endometrioid carcinoma. The tumor manifests a well-differentiated glandular architecture, with expansive growth pattern and no necrosis. **b** Low-grade endometrioid carcinoma. The tumor has a solid architecture, without infiltrative pattern and no necrosis. **c** High-grade endometrioid carcinoma. The growth pattern is infiltrative without any glandular architecture. **d** High-grade endometrioid carcinoma. The tumor shows solid architecture and apparent necrosis.

Results

A total of 200 patients were included in the survival analysis. Age and FIGO stage distributions for the cases grouped according to the three tumor grading systems are shown in table 1. Binary high grade was seen in older patients, and there was a statistically significant relationship between binary grade and stage distribution ($p < 0.01$). However, the FIGO tumor grading showed no statistical difference. Nuclear grading showed a statistically significant difference ($p < 0.05$).

Survival Analysis

By the binary grading system, patients with low-grade tumors of all stages had a significantly better outcome than those with high-grade tumors (fig. 2 and table 2). The 5-year survival (5YS) rate for patients with stages I and II low-grade tumors was 98%, compared with 87% for those with stage I and II high-grade tumors ($p = 0.04$). The 5YS rate for patients with advanced-stage low-grade tumors was 86%, compared with 49% for those with advanced-stage high-grade tumors ($p < 0.001$). The 5YS rate for patients with advanced-stage low-grade tumors was similar to that of patients with early-stage high-grade tumors (86 and 87%, respectively). Subclassification of stage I tumors into IA through IC showed no difference in the outcome of low-grade and high-grade tumors in our present series, and no tendency was seen for a poorer prognosis with stage IC tumor. Within each stage, the 5YS rates correlated highly with the FIGO tumor grade. Stages I and II FIGO grade 1

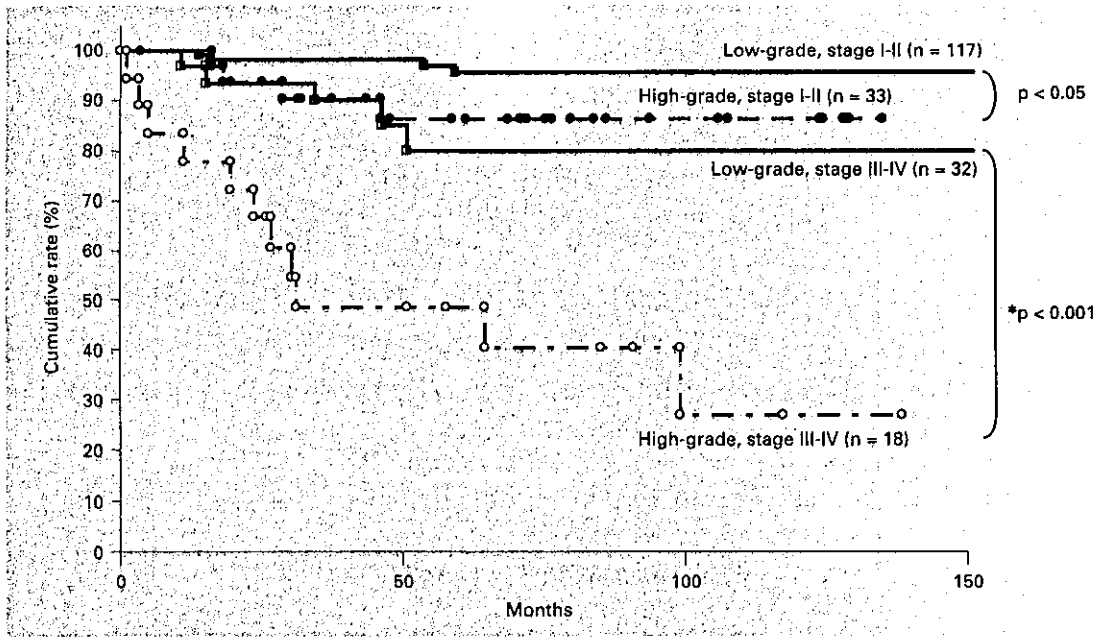

Fig. 2. Kaplan-Meier survival curves for low-grade and high-grade endometrioid carcinomas stratified into stage I–II and stage III–IV.

Table 1. Age and FIGO stage distribution of 200 endometrioid carcinomas for each of the three grading systems

	Cases	Age (range)	FIGO stage				p
			I	II	III	IV	
Binary grade							
Low	149	55 (22–78)	109	8	32	0	
High	51	61 (24–80)	27	6	14	4	0.001
FIGO grade							
1	93	53 (22–77)	68	8	17	0	
2	64	58 (35–80)	44	3	16	1	
3	43	61 (24–77)	24	3	13	3	0.078
Nuclear grade							
1	20	52 (22–77)	16	1	3	0	
2	148	56 (28–80)	100	13	34	1	
3	32	63 (24–78)	20	0	9	3	0.021

tumors had a better prognosis than stage I and II FIGO grade 2 and stage I and II FIGO grade 3 tumors, but the differences were not significant (p = 0.2557). Advanced-stage FIGO grade 1 and 2 tumors had a significantly better prognosis than advanced-stage FIGO grade 3 tumors (p = 0.0051). Nuclear grading did not correlate well with 5YS for stages I and II tumors. Nuclear grade 1 tumors behaved better than nuclear grade 2 and nuclear grade 3 tumors, but failed to show any significant difference because of the small number of patients (p = 0.0650).

Inter- and Intra-Observer Agreement

Both inter- and intraobserver agreement were moderate and substantial for the binary grading system (κ = 0.57 and 0.62, respectively) compared with the FIGO grading system (tables 3 and 4), which demonstrated the same agreement (κ = 0.50 and 0.62, respectively). For nuclear grading, inter- and intraobserver agreement were poor and fair, respectively (κ = 0.23 and 0.43). The percent agreement was greatest for the binary system (82% combined for the two rounds), whereas the percent agreement

Table 2. Comparison of 5-year cumulative survival for FIGO stage I–II and stage III–IV tumors using binary, FIGO, and nuclear grading systems

	Stage I–II tumors		Stage III–IV tumors	
	cases	survival %	cases	survival %
Binary grade				
Low	117	98	32	86
High	33	87	18	49
	p = 0.04		p = 0.0006	
FIGO grade				
1	76	97	17	100
2	47	98	17	65
3	27	88	16	55
	p = 0.2557		p = 0.0051	
Nuclear grade				
1	17	93	3	100
2	113	96	35	78
3	20	95	12	50
	p = 0.9817		p = 0.0650	

was substantially less for the FIGO and nuclear grading systems (60 and 49%, respectively).

Among each item of the binary grading system, intraobserver agreement showed little difference, such as solid growth, infiltrative pattern, and necrosis, at 0.75, 0.60, and 0.58, respectively. The diagnosis of necrosis showed fair agreement among the three criteria.

Clinicopathological Factors

The frequency of lymph node metastases showed no statistical difference between low-grade and high-grade tumors. Further, the frequency of extrauterine disseminations (adnexa, lymph node, and distant metastases) was correlated with the binary grading system, in which high-grade tumors showed much more frequent extrauterine disseminations, with statistical significance (p = 0.0002).

The frequency of adenocarcinoma or adenosquamous carcinoma for each of the three grading systems was also examined, due to the diagnostic difference between binary and FIGO grading of having versus not having a squamous component in the tumor. Both binary and FIGO grading systems showed statistically significant differences between adenocarcinoma and adenosquamous carcinoma, except in nuclear grading. Binary and FIGO grading systems themselves were not different in the point of counting the presence of squamous lesions.

Table 3. Interobserver agreement for the three grading systems (κ values with percent agreement)

Method	Round 1*	Round 2*	Round 1 + 2*
Binary	0.53 (79%)	0.61 (85%)	0.57 (82%)
Growth	0.66 (87%)	0.72 (90%)	0.69 (88%)
Pattern	0.48 (74%)	0.45 (72%)	0.46 (73%)
Necrosis	0.40 (72%)	0.43 (77%)	0.41 (74%)
FIGO	0.48 (59%)	0.51 (61%)	0.50 (60%)
Nuclear	0.26 (51%)	0.20 (46%)	0.23 (49%)

In table 5, we compared the cumulative 5YS by adjuvant treatment modality for the patients at all stages. Binary low-grade and FIGO grade 1 and 2 patients showed statistically significant differences ($p < 0.01$) between each of a no-adjuvant-therapy group, an adjuvant chemotherapy group with radiation, a chemotherapy group, and a radiation group. Patients with other prognostic factors, such as myometrial invasion, lymph node metastasis, etc., received adjuvant chemotherapy or radiation therapy, or both, showing poorer outcomes with more aggressive therapy. But this phenomenon occurred only in low binary grading and FIGO 1 or 2 grading groups. In other words, patients with high binary grade or FIGO grade 3 or higher nuclear grade, all have poorer survival, despite adjuvant treatment.

Discussion

In this study, the binary grading was done by the most experienced pathologist, MS, one of the authors, and three kinds of tumor grading systems were compared, twice, at different periods, with the correlation of clinicopathological factors among 200 cases with endometrial cancer. And in the same manner, the other four doctors performed the slide examination for tumor grading twice, at different periods.

Inter-observer agreement was moderate for both the binary grading system (κ = 0.57) and the FIGO grading system (κ = 0.50). However, for nuclear grading, inter-observer agreement was poor (κ = 0.23). In the original report [8], inter-observer agreement using the binary grading system (κ = 0.65) was superior compared with the FIGO grading system (κ = 0.55) and nuclear grading (κ = 0.22). Inter-observer agreement itself was less different between the binary and FIGO grading systems, probably due to the unfamiliarity of the novel binary grading in our study. However, the percent agreement was superior for

Table 4. Intra-observer agreement for the three grading systems (κ values with percent agreement)

Method	MD 1	MD 2	MD 3	MD 4	MD5	Overall
Binary	0.56 (83%)	0.56 (82%)	0.72 (90%)	0.70 (89%)	0.58 (80%)	0.62 (84%)
Growth	0.64 (87%)	0.66 (87%)	0.76 (92%)	0.90 (97%)	0.77 (90%)	0.75 (91%)
Pattern	0.54 (81%)	0.68 (86%)	0.56 (79%)	0.60 (83%)	0.62 (81%)	0.60 (82%)
Necrosis	0.56 (81%)	0.51 (79%)	0.56 (86%)	0.72 (87%)	0.54 (77%)	0.58 (82%)
FIGO	0.56 (73%)	0.58 (67%)	0.69 (79%)	0.71 (77%)	0.59 (70%)	0.62 (73%)
Nuclear	0.37 (63%)	0.38 (61%)	0.35 (56%)	0.56 (83%)	0.47 (63%)	0.43 (65%)

Table 5. Cumulative 5-year survival by adjuvant treatment modality

	Patients	None	Chemo	Radiation	Both	p
Binary grade						
Low	149	98.9% (90)	97.4% (38)	77.8% (9)	83.3% (12)	<0.01
High	51	82.3% (18)	70.4% (17)	71.4% (4)	66.7% (12)	NS
FIGO grade						
1	93	98.2% (58)	100% (25)	100% (4)	83.3% (6)	<0.05
2	64	97.1% (34)	87.5% (16)	75.0% (4)	70.0% (10)	<0.05
3	43	86.7% (16)	70.7% (14)	51.9% (5)	75.0% (8)	NS
Nuclear grade						
1	20	92.3% (15)	100% (4)	-	100% (1)	NS
2	148	96.2% (79)	92.5% (40)	75.6% (13)	87.5% (16)	<0.05
3	32	100% (14)	72.2% (11)		42.9% (7)	<0.05

the binary system (82% combined for the two rounds), whereas it was substantially less for the FIGO and nuclear grading systems (60 and 49%, respectively), as shown in table 3. Differences in inter-observer agreement between the three factors of solid growth, infiltrative pattern, and necrosis were present; their respective κ values and percent agreements were 0.69 (88%), 0.46 (73%), and 0.41 (74%), respectively. Solid growth was almost perfect in percent agreement, but necrosis showed a fair κ value among the three criteria. Diagnosis of necrosis depends on excised uterine materials and the quality of related hematoxylin-and-eosin-stained slides or necrotic findings. As a result, binary grading system was superior in inter-observer agreement, compared with the other grading systems.

Intra-observer agreement for the three tumor grading systems was substantial (κ = 0.62) for both the binary and FIGO grading systems, compared with the nuclear grading (κ = 0.43). Percent agreement was 84% for binary, 73% for the FIGO, and 65% for the nuclear grading. Overall agreements were similar to the original report by Lax et al. [8] Further, intra-observer agreement of each factor in the binary grading showed little difference, such as solid growth, infiltrative pattern, and necrosis, at 0.75 (91%), 0.60 (82%), and 0.58 (82%), respectively. In the binary grading system, agreement of solid growth was almost perfect between the five doctors. Therefore, this new binary grading system was the most superior among the three systems, and also certificated among 200 Japanese patients with endometrial cancer.

Among the prognostic factors in endometrial cancer, tumor grade correlated with age and FIGO stage, and binary high grade showed older age and the most statistically significant relationship between binary grade and stage distribution ($p < 0.01$), but the FIGO grading showed no statistical difference. Nuclear grading showed a statistically significant difference ($p < 0.05$) in table 1. Under the binary grading system, the 5YS rates for patients with stages I and II low- and high-grade tumors were 98 and 87%, respectively. The 5YS rate for patients with advanced-stage low-grade tumors was 86%, compared with 49% for those with advanced-stage high-grade tumors ($p < 0.01$). As a result, 200 patients with endometrial cancer were divided into three groups: low-grade early-stage patients, high-grade early-stage patients and low-grade advanced-stage patients, and finally the most lethal, high-grade advanced-stage patients.

In patients with early-stage and 'binary low-grade' tumors, we should consider conservative treatment, including minimal invasive surgical treatment and avoidance of adjuvant chemotherapy or radiation therapy. Under the NCCN guideline [16], stage IA and FIGO G1/G2 endometrial cancer is recommended to receive observation, but other stage IB and G3 or stage II endometrial cancers are suggested to receive adjuvant radiation therapy. However, some recent reports have said that there is no need for adjuvant radiation for stage I endometrial cancer [17]. Actually, we showed 98.8% survival among 90 patients, with mainly early-stage disease, who had not received adjuvant therapy, as shown in table 5. In stage I and II endometrial cancer, with less than half of myometrial invasion and binary low grade, only observation might be appropriate, postoperatively.

Patients with early-stage but 'binary high-grade' tumors or advanced-stage with 'binary low-grade' tumors should receive adjuvant therapy, which is usually radiation therapy in Western countries [18] and chemotherapy in Japan [19]. Until now, no prospective randomized study on endometrial cancer has looked at the usefulness, as adjuvant therapy, of radiation versus chemotherapy [20]. A recent prospective randomized study on advanced endometrial cancer compared whole abdominal irradiation and chemotherapy with doxorubicin and cisplatin (GOG122) [21]. It was concluded that the chemotherapy arm was superior in both progression-free and overall survival, compared with the irradiation arm. Further prospective trials of adjuvant radiation or chemotherapy for postoperative or advanced endometrial cancer patients will be required, but chemotherapy, including adriamycin, cisplatin, and paclitaxel, will be actively applied for patients with endometrial cancer.

In summary, under the analyses of three grading systems, the binary grading system was much more reproducible than the FIGO or nuclear grading. Binary high-grade tumors were correlated with older age and more advanced stage, with statistical significance for a worse prognosis compared with low-grade tumors. Binary grading as a prognostic factor was investigated using the efficacy of treatment modalities, such as chemotherapy or radiation therapy. In binary low-grade, early-stage tumors, patient outcome was better with no adjuvant therapy and chemotherapy, compared with giving radiation or both therapies. Diagnosis by binary grading will be useful in deciding which patients should receive adjuvant therapy.

References

1 Announcements: FIGO stages –1988 revision. Gynecol Oncol 1989;35:125–127.
2 Zaino RJ, Kurman RJ, Diana KL, et al: The utility of the revised international federation of gynecology and obstetrics histologic grading of endometrial adenocarcinoma using a defined nuclear grading system. A Gynecologic Oncology Group Study. Cancer 1995;75:81–86.
3 Creasman WT, Morrow CP, Bundy BN, et al: Surgical pathologic spread patterns of endometrial cancer. Cancer 1987;60:2035–2041.
4 Mittal KR, Schwartz PE, Barwick KW: Architectural (FIGO) grading, nuclear grading, and other prognostic indicators in stage I endometrial adenocarcinoma with identification of high-risk and low-risk groups. Cancer 1988;61: 538–545.
5 Hachisuga T, Kawarabayashi T, Iwasaka T, et al: The prognostic value of semiquantitative nuclear grading in endometrial carcinomas. Gynecol Oncol 1997;65:115–120.
6 Zaino RJ, Silverberg SG, Norris HJ, et al: The prognostic value of nuclear versus architectural grading in endometrial adenocarcinoma: A Gynecologic Oncology Group Study. Int J Gynecol Pathol 1994;13:29–36.
7 Taylor RR, Zeller J, Lieberman RW, et al: An analysis of two versus three grades for endometrial carcinoma. Gynecol Oncol 1999;74:3–6.
8 Lax SF, Kurman RJ, Pizer ES, et al: A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. Am J Surg Pathol 2000;24:1201–1208.
9 Scholten AN, Creutzberg CL, Noorduk EM, et al: Long-term outcome in endometrial carcinoma favors a two instead of a three-tiered grading system. Int J Radiat Oncol Biol Phys 2002; 52:1067–1074.
10 Ronnett BM, Zaino RJ, Ellenson LH, et al: Endometrial carcinoma; in Kurman RJ ed: Blaustein's Pathology of the Female Genital Tract. ed 5. New York, Springer, 2001, pp 501–559.
11 SAS Institute Inc: SAS Procedures Guide, Release 8 Edition. Cary, NC: SAS Institute Inc, 2000.
12 Fleiss JJ: Statistical Methods for Rates and Proportions, ed 2. New York, Wiley, 1980, pp 212–236.
13 Kaplan EL, Meier P, Kaplan EL, et al: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
14 Peto R, Pike MC, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1977; 35:1–39.
15 Cox DR: Regression models and life tables. JR Stat Soc 1972;34:187–220.
16 Uterine cancers. NCCN National Comprehensive Cancer Network Clinical practice guidelines in Oncology-v. 1. 2002. http://www.nccn.org/physician+gls/f+guidelines.html
17 Creutzberg CL, van Putten WLJ, Koper PC, et al: The morbidity of treatment for patients with stage I endometrial cancer: Results from a randomized trial. Int J Radiat Oncol Biol Phys 2001;51:1246–1255.
18 Morrow CP, Bundy BN, Kurman RJ, et al: Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: A Gynecologic Oncology Group study. Gynecol Oncol 1991; 40:55–65.
19 Creasman WT, Odicino F, Maisonneuve P, et al: Carcinoma of the corpus uteri. FIGO annual report on the results of treatment in gynecological cancer, vol 24. J Epidemiol Biostat 2001;6: 45–86.
20 Patient reports in 1999 of Gynecologic Cancer Committee. Acta Obstet Gynaecol Jpn 2002; 54:1527–1572.
21 Randall ME, Brunetto G, Muss H, et al: Whole abdominal radiotherapy versus combination doxorubicin-cisplatin chemotherapy in advanced endometrial carcinoma: A randomized phase III trial of the Gynecologic Oncology Group. Proc Am Soc Clin Oncol 2003;22:2.

Available online at www.sciencedirect.com

SCIENCE DIRECT

Gynecologic Oncology 95 (2004) 231–234

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Conservative excisional laser conization for early invasive cervical cancer

Masatsugu Ueda*, Ken Ueki, Masanori Kanemura, Shinji Izuma, Hiroyuki Yamaguchi, Yoshito Terai, Minoru Ueki

Department of Obstetrics and Gynecology, Osaka Medical College, Takatsuki, Osaka 569-8686, Japan

Received 20 May 2004

Abstract

Objective. To investigate the possibility of conservative excisional laser conization for early invasive cervical cancer.

Methods. Four hundred one women with early invasive squamous cell cancer were treated by laser conization and semiradical or radical hysterectomy with pelvic lymphadenectomy. Their histologic findings and clinical outcomes were evaluated retrospectively.

Results. Two hundred Ia1 cases without confluent invasion or vessel permeation receiving only laser therapy had no recurrent disease. There was no lymph node metastasis in 123 Ia1 and 24 Ia2 cases with stromal invasion of under 4 mm in depth regardless of confluent invasion and vessel permeation. However, lymph node metastasis was detected in 1 of 13 Ia2 cases with stromal invasion of over 4 mm in depth and in 5 of 41 Ib1 cases. All of these six cases had vessel permeation in the resected specimens.

Conclusion. Conservative excisional laser conization may be possible for stage Ia cervical cancer with stromal invasion of under 4 mm in depth. However, the risk of lymph node metastasis should be still considered for those lesions with vessel permeation.

Keywords: Laser conization; Conservative management; Cervical cancer

Introduction

Cervical cancer is the second most common cancer in women worldwide, and is both a preventable and a curable disease especially if identified at an early stage. A recent analysis of five long-term studies of the follow-up of conservative treatment for cervical intraepithelial neoplasia (CIN) has shown a reduction in the risk of invasive cervical cancer by 95% for at least 8 years [1]. Conization of the cervix is widely used for the diagnosis and conservative treatment of CIN. Recently, the traditional surgical technique of cold knife conization has been replaced by laser conization and by the loop electrosurgical excisional procedure because of the high incidence of incomplete excision and recurrence with conventional cold conization [2]. The main advantage of these methods over the destructive procedures, such as cryosurgery and laser vaporization, is that they provide histologic information on the depth of invasion and the involvement of the surgical margins. We have performed neodymium-ytlium, argon, gadolinium (Nd-YAG) laser conization for over 2500 cases with cervical neoplasms so far and reported its usefulness as a conservative therapeutic tool for CIN and microinvasive cancer without vessel permeation and bulky invasion [3–6]. However, the number of young patients with more advanced disease has been increasing, and the necessity of conservative therapy for those lesions is now becoming greater to preserve their fertility. In the present study, we sought to find out the clinical and pathological limitation of conservative treatment for early invasive cervical cancer using laser technique.

Patients and methods

In the past 15 years, between 1983 and 1997, we treated 401 women with early invasive squamous cell

* Corresponding author. Department of Obstetrics and Gynecology, Osaka Medical College, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan. Fax: +81 72 681 3723.

E-mail address: gyn017@poh.osaka-med.ac.jp (M. Ueda).

0090-8258/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2004.07.001

cancer of the cervix. Their histologic findings and clinical outcomes were evaluated retrospectively. Nd-YAG laser conization was initially performed for 241 cases who were preoperatively suspected as having microinvasive squamous cell cancer by cytology, colposcopy, and target biopsy. A large dome-like contact laser conization was done and contact vaporization on the surrounding tissue and the ectocervix was added after the conization as described previously [3,4]. A histological examination was done on 16 blocks of each cone specimen stained with hematoxylin–eosin. Stages of the disease were classified according to FIGO classification [7] based on the histologic finding of the cone specimen; stage Ia1, measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm in diameter; Ia2, measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter; Ib1, preclinical lesions greater than stage Ia.

Two hundred of 241 cases who had stage Ia1 disease without confluent invasion (confluent pattern of stromal growth) or vessel permeation (lymph vascular space invasion) received no additional surgical treatment because we previously demonstrated that no lymph node metastasis was observed in those lesions [4]. Forty-one (17%) of 241 cases underwent semiradical or radical hysterectomy and pelvic lymphadenectomy because they had stage Ia1 with confluent invasion or vessel permeation, Ia2 or Ib1 disease on the initial conization. The other 160 patients who were preoperatively suspected as having Ia2 or Ib1 disease by cytology, colposcopy, and target biopsy received radical surgery. Histological specimens of 401 patients enrolled in this study were re-reviewed by pathologists after surgery and were diagnosed as having squamous cell cancers in stage Ia1–Ib1. The depth of stromal invasion in resected specimens was compared with the diameter of stromal invasion and the incidence of confluent invasion, vessel permeation, or lymph node metastasis, and checked by the Mann–Whitney U and chi-square tests. A level of $P < 0.05$ was accepted as statistically significant.

Postoperatively, all patients were followed up every 3 to 6 months in our outpatient clinic with cytology, colposcopy, and/or biopsy until December 2003. The median follow-up time was 117.1 months with a range of 72–240 months.

Results

The operative procedure of laser conization required 12 min on the average. A blood loss of over 30 ml during the operation occurred in 11% and cervical obstruction occurred in 8% during the follow-up period.

Table 1 shows the correlation between depth and diameter of stromal invasion in 401 cases examined. Two hundred (62%) of 323 Ia1 cases without confluent invasion or vessel permeation were treated only by laser conization as described above. One hundred twenty-three (38%) of 323 Ia1 cases underwent abdominal surgery because they were preoperatively suspected as having stage Ia1 with confluent invasion or vessel permeation, Ia2 or Ib1 disease. Thirty-seven Ia2 and 41 Ib1 cases also underwent radical surgery. Increasing depth of stromal invasion was well correlated with increasing diameter.

Table 1
The correlation between depth and diameter of stromal invasion in 401 cases examined

Diameter of stromal invasion	Depth of stromal invasion			
	−3.0 mm (337)	3.1–4.0 mm (30)	4.1–5.0 mm (20)	5.1 mm⁻ (14)
Under 7 mm	Ia1 (323)	Ia2 (24)	Ia2 (13)	Ib1 (3)
Over 7 mm	Ib1[a,b,c] (14)	Ib1[a] (6)	Ib1[b] (7)	Ib1[c] (11)

Two hundred of 323 Ia1 cases without confluent invasion or vessel permeation were treated only by laser conization 123 of 323 Ia1, 37 Ia2, and 41 Ib1 cases underwent semiradical or radical hysterectomy and pelvic lymphadenectomy. ( ): number of cases.
[a] $P = 0.0002$.
[b,c] $P = 0.0001$.

Table 2 indicates the correlation between depth of stromal invasion and incidence of confluent invasion, vessel permeation or lymph node metastasis. Increasing depth of stromal invasion and stages were correlated with increasing incidence of confluent invasion and vessel permeation. In 323 Ia1 cases, the incidence of confluent invasion and vessel permeation was 3.7% (12/323) and 3.1% (10/323), respectively. Two hundred of 323 cases were treated only by laser conization as described above. Lymph node metastasis was not observed in 123 of 323 Ia1 cases who underwent semiradical or radical hysterectomy and pelvic lymphadenectomy. In 24 Ia2 cases with stromal invasion of under 4 mm in depth, the incidence of confluent invasion and vessel permeation was 16.7% (4/24) and 12.5% (3/24), respectively. However, there was no lymph node metastasis in these 24 cases. In contrast, lymph node metastasis was detected in 1 of 13 Ia2 cases with stromal invasion of over 4 mm in depth and in 5 of 41 Ib1 cases. All of these six cases had vessel permeation in the resected specimens.

Of 200 Ia1 cases without confluent invasion or vessel permeation receiving only laser therapy, 11 cases had positive cone margins with CIN I to III. Two cases with CIN III received re-conization and one with CIN III underwent re-vaporization. The other eight cases with CIN I to II experienced spontaneous disappearance of their lesions during follow-up period, which ranged from 9 to 47 months after initial laser conization. All of 200 patients treated only by laser therapy had no recurrent disease. Final pathology results of 41 cases who initially had laser conization followed by hysterectomy were 3 Ia1, 10 Ia2 and 28 Ib1 diseases. One Ia2 and five Ib1 cases with pelvic lymph node metastasis subsequently received an additional radiation therapy and had no recurrent disease. After all,

Table 2
The correlation between depth of stromal invasion and incidence of confluent invasion, vessel permeation or lymph node metastasis in 401 cases examined

Variable	Ia1	Ia2		Ib1			
	−3.0 mm	3.1–4.0 mm	4.1–5.0 mm	−3.0 mm	3.1–4.0 mm	4.1–5.0 mm	5.1 mm⁻
Confluent invasion	12/323[a,b]	4/24	6/13	2/14	3/6	3/7	7/14
		10/37[a]		15/41[b]			
Vessel permeation	10/323[c,d]	3/24	5/13	2/14	4/6	3/7	7/14
		8/37[c]		16/41[d]			
Lymph node metastasis	0/123	0/24	1/13	1/14	0/6	1/7	3/14
		1/37[e]		5/41[e]			

Two hundred of 323 Ia1 cases without confluent invasion or vessel permeation were treated only by laser conization. Lymph node metastasis was not observed in 123 of 323 Ia1 cases who underwent semiradical or radical hysterectomy and pelvic lymphadenectomy.
[a–d] $P < 0.0001$.
[e] Not significant.

none of the 401 patients enrolled in this study have recurred so far during follow-up period.

Discussion

We previously suggested that laser conization might be an acceptable conservative therapy for stage Ia1 and selected Ia2 cases without confluent invasion or vessel permeation based on the clinical analysis of 227 patients with early invasive squamous cell cancer of the cervix [6]. Our present results on 401 patients preoperatively suspected as having early invasive cancer demonstrated that there was no lymph node metastasis in 123 Ia1 and 24 Ia2 cancer with stromal invasion of under 4 mm in depth regardless of confluent invasion and vessel permeation. Moreover, none of the 401 patients enrolled in this study including 200 Ia1 cases treated only by laser conization had no recurrent disease during the long follow-up period which ranged from 72 to 240 months with a median time of 117.1 months. Creasman et al. [8,9] reported that conservative therapy was possible for stage Ia1 and some stage Ia2 patients, and Sevin et al. [10] advised that conization for stage Ia patients might be possible but should be performed based not only on depth of invasion but also on vessel permeation. Recently, Elliott et al. [11] demonstrated that stage Ia1 patients could be managed only by conization. However, the clinical and pathological criteria for conservative treatment of stage Ia2 squamous cell cancer of the cervix has not been established yet.

In the conservative therapy for Ia2 cancer, it is quite important to determine the risk of lymph node metastasis. The incidence of pelvic lymph node metastasis in stage Ia2 disease has been reported to be 0/44 (0%) [9], 2/59 (3.4%) [11], 2/28 (7.1%) [12], 7/94 (7.4%) [13], and 2/9 (28.6%) [14]. Lymph vascular space invasion was found in 11/44 (25%) [9], 30/59 (53%) [11], 15/28 (54%) [12], 31/94 (33%) [13], and 7/9 (77.8%) [14], respectively. These previous reports indicated that lymph node metastasis was closely associated with lymph vascular space invasion in resected cervical lesions. In our series, 1 Ia2 and 5 Ib1 patients with pelvic lymph node metastasis also had vessel permeation in the resected specimens. In contrast, the rate of lymph node metastasis in stage Ia1 disease was reported to be 1/679 (0.15%) from a number of literatures [4]. The risk of lymph node metastasis with vessel permeation in Ia2 cancer may be significantly higher than that in Ia1 cancer. NIH consensus statement [15] also suggested that radical surgery with lymphadenectomy is needed for Ia2 cancer because of the high incidence of pelvic lymph node metastasis. In order to preserve the fertility of the patient with stage Ia2 disease on initial conization, laparoscopic lymph node sampling or dissection may be recommended in the present stage [16].

Despite abundant evidences on the correlation between lymph node metastasis and vessel permeation in stage Ia2 cervical cancer, the limit of stromal invasion for conservative excisional laser conization in Ia2 cancer has not been well discussed. Only Zaino et al. [17] reported that lymph node metastasis was strongly associated with the depth of invasion and no lymph node metastasis was found in the cases with stromal invasion of under 4 mm in depth. The present results that no lymph node metastasis was found in stage Ia cervical cancer with stromal invasion of under 4 mm in depth may suggest the possibility of conservative laser therapy for those lesions regardless of confluent invasion and vessel permeation. Although the risk of lymph node metastasis should be still considered for Ia2 cancer with vessel permeation according to the previous literatures, our observations may be helpful for active challenge to conservative management of the patients with early invasive cervical cancer in reproductive age.

Acknowledgments

We are grateful to E Shintani and K Sato for their technical assistance. This work was supported in part by High-Tech Research Program of Osaka Medical College.

References

[1] Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. Invasive cervical cancer after conservative

treatment for cervical intraepithelial neoplasias. Lancet 1997;349: 978–80.
[2] Ueki M, Green GH. Cervical carcinoma in situ after incomplete conization. Asia-Oceania J Obstet Gynaecol 1988;14:147–53.
[3] Ueki M, Kitsuki K, Misaki O, Seiki Y, Ueda M. Clinical evaluation of contact Nd-YAG laser conization for cervical intraepithelial neoplasia of the uterus. Acta Obstet Gynecol Scand 1992;71:465–70.
[4] Ueki M, Okamoto Y, Misaki O, Seiki Y, Kitsuki K, Ueda M, et al. Conservative therapy for microinvasive carcinoma of the uterine cervix. Gynecol Oncol 1994;53:109–13.
[5] Ueki M, Ueda M, Kumagai K, Okamoto Y, Noda S, Matsuoka M. Cervical cytology and conservative management of cervical neoplasias during pregnancy. Int J Gynecol Pathol 1995;14:63–9.
[6] Okamoto Y, Ueki K, Ueki M. Pathological indications for conservative therapy in treating cervical cancer. Acta Obstet Gynecol Scand 1999;78:818–23.
[7] FIGO Cancer Committee. Staging announcement. Gynecol Oncol 1979; 8:353–85.
[8] Creasman WT, Fetter BF, Clarke-Pearson DL, Kaufmann L, Parker RT. Management of Stage IA carcinoma of the cervix. Am J Obstet Gynecol 1985;153:164–72.
[9] Creasman WT, Zaino RJ, Major FJ, DiSaia PJ, Hatch KD, Homesley HD. Early invasive carcinoma of the cervix (3 to 5 mm invasion): risk factors and prognosis. A Gynecologic Oncology Group study. Am J Obstet Gynecol 1998;178:62–5.
[10] Sevin BU, Nadji M, Averette HE, Hilsenbeck S, Smith D, Lampe B. Microinvasive carcinoma of the cervix. Cancer 1992;70:2121–8.
[11] Elliott P, Coppleson M, Russell P, Liouros P, Carter J, MacLeod C, et al. Early invasive (FIGO stage IA) carcinoma of the cervix: a clinico-pathologic study of 476 cases. Int J Gynecol Cancer 2000; 10:42–52.
[12] Ostor AG, Rome RM. Micro-invasive squamous cell carcinoma of the cervix: a clinico-pathologic study of 200 cases with long-term follow-up. Int J Gynecol Cancer 1994;4:257–64.
[13] Buckley SL, Tritz DM, Van Le L, Higgins R, Sevin BU, Ueland FR, et al. Lymph node metastases and prognosis in patients with stage IA2 cervical cancer. Gynecol Oncol 1996;63:4–9.
[14] Roman LD, Felix JC, Muderspach LI, Varkey T, Burnett AF, Qian D, et al. Influence of quantity of lymph-vascular space invasion on the risk of nodal metastases in women with early-stage squamous cancer of the cervix. Gynecol Oncol 1998;68:220–5.
[15] National Institute on Health Consensus Development Conference Statement of Cervical Cancer. Gynecol Oncol 1997;66:351–61.
[16] Koliopoulos G, Sotiriadis A, Kyrgiou M, Martin-Hirsch P, Makrydimas G, Paraskevaidis E. Conservative surgical methods for FIGO stage IA2 squamous cervical carcinoma and their role in preserving women's fertility. Gynecol Oncol 2004;93:469–73.
[17] Zaino RJ, Ward S, Delgado G, Bundy B, Gore H, Fetter G, et al. Histopathologic predictors of the behavior of surgically treated stage IB squamous cell carcinoma of the cervix. Cancer 1992;69:1750–58.