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.

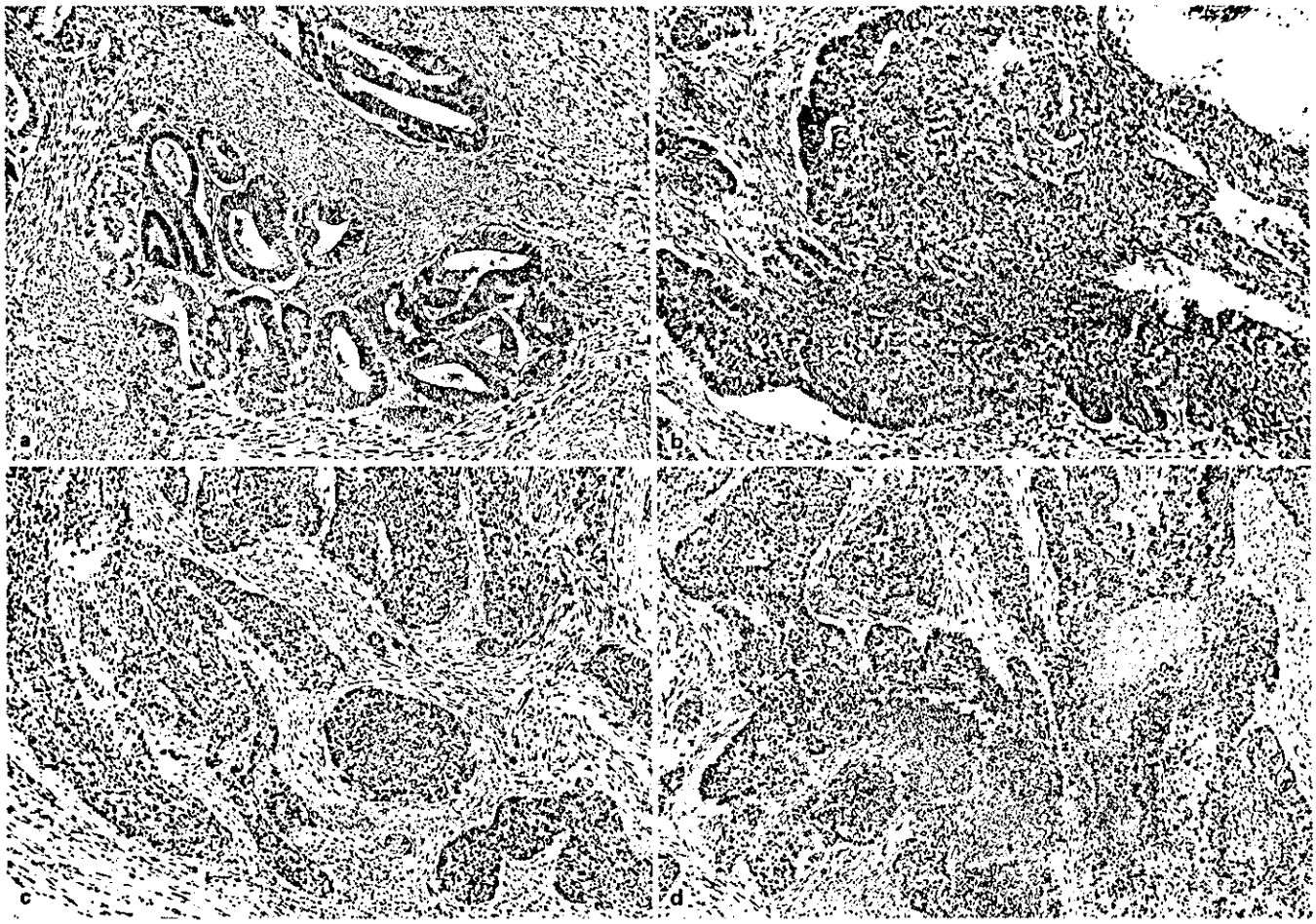

Fig. 1. Low-grade and high-grade endometrial carcinoma (H&E; original magnification, × 100). **a** Low-grade endometrioid carcinoma. The tumor manifests a well-differentiated glandular architecture, with expansive growth pattern and no necrosis. **b** Low-grade endometrioid carcinoma. The tumor has a 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

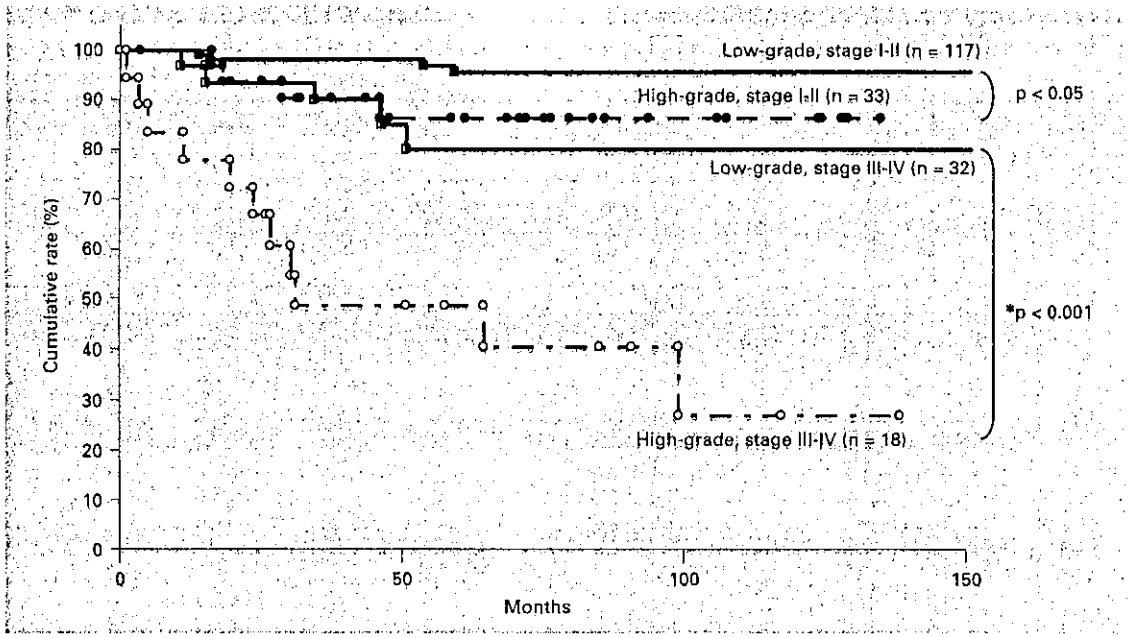

Fig. 2. Kaplan-Meier survival curves for low-grade and high-grade endometrioid carcinomas stratified into stage I–II and stage III–IV.

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.
© 2004 Elsevier Inc. All rights reserved.

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[c]		5/41[c]			

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] $P < 0.0001$.
[c] 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.

III. 子宮体癌

子宮体癌の治療
化学療法—概論—

Recent outline to chemotherapy for uterine endometrial cancer

渡部　洋
星合　昊

Key words　endometrial cancer, chemotherapy, clinical trial

はじめに

子宮体癌に対する化学療法は，骨盤・傍大動脈リンパ節転移陽性例や腹腔洗浄細胞診陽性例などのextra uterine spreadが認められる症例，あるいは脈管侵襲や深部筋層浸潤を有する進行例，更に再発例といった全身疾患ととらえられるべき病態を有する症例に対して予後改善が期待されている．

しかし，これまで進行体癌におけるadjuvant therapyの主体は放射線療法と考えられており，実際にNational Comprehensive Cancer Network (NCCN) practice guidelineでは，完全手術が遂行されたFIGO stage I，II例に対するadjuvant therapyの適応は摘出組織の組織分化度にもよるが放射線治療が推奨されており，化学療法はFIGO stage IIIa以上の症例に対する選択肢としてchemotherapy(±radiation therapy)と記載されているにすぎない．

体癌の大部分がchemosensitiveと考えられる類内膜腺癌であるのにもかかわらず化学療法が治療optionの一策にとどまっている原因には，歴史的に放射線治療への信頼性が高いこと，あるいは体癌化学療法に関する臨床試験が単剤phase II studyを中心に行われてきたため，卵巣癌において展開されてきた系統的な大規模phase III studyによる新規regimenの検証や移行が行われてこなかったことなどがある．現実的に我が国においても体癌に保険適応を有する薬剤が少ないため，体癌化学療法は各種regimenの有効性の比較検証が行われないまま卵巣癌化学療法の変遷に準じた治療regimenが適応されてきた感は否めない．しかし近年国内外において体癌化学療法に対するregimen検証の気運が高まっており，特に卵巣癌に対して良好な治療成績を有するタキサン系抗癌剤を中心とした効果的な新規薬剤の出現によって，我が国においても新たな臨床試験が進行してきている．

そこで本稿においては近年に至る体癌化学療法の動向と現況および今後の方向性について概説する．

1. Single-agent chemotherapy

体癌に対してはphase II studyからanthracycline系薬剤特にadriamycin(doxorubicin)の有効性が報告されており，国内外においてadriamycin(ADM)が体癌化学療法のkey-drugとして用いられてきている．anthracycline系薬剤の単剤phase II studyではADMに37%[1]と最も高い奏効率が得られており，一方anthracyclin analogではepirubicinで26%[2]，pirarubicinでは10%とやや低率である結果が報告されてい

Yoh Watanabe, Hiroshi Hoshiai: Department of Obstetrics and Gynecology, Kinki University School of Medicine
近畿大学医学部産科婦人科

0047-1852/04/¥50/頁/JCLS

る．また近年新規anthracycline系薬剤として注目されているpegylated liposomal doxorubicinについても既にphase II studyが行われており，paclitaxel/platinumあるいは放射線治療歴を有する進行体癌を対象としたstudyであるにもかかわらず，奏効率21%[3]と良好な成績が示されていることから，今後卵巣癌のみならず体癌に対する早期適応が期待されている．このようにADMの体癌化学療法におけるkey-drugとしての優位性は広く認知されてきたが，近年卵巣癌を中心として良好な治療成績が確認されているタキサン系抗癌剤の体癌に対する有効性検証の期待が高まってきた．paclitaxelについては，既にGynecologic Oncology Group(GOG)および欧州において単剤phase II studyが行われており，奏効率36-37%[4,5]とADMとほぼ同等の治療成績が示されている．我が国においてもpaclitaxel，docetaxelの両タキサン系抗癌剤について体癌治療に関する保険適応を望む声が多いが，2003年には既に両薬剤ともに保険収載のためのphase II studyが終了しており，有効性と安全性の解析を待って早晩保険適応が認められる見込みである．

また体癌は一般的にestrogen dependentと考えられているため，anti-estrogenic activityを有する薬剤を用いたhormonal therapyについてもphase II studyが行われている．これらの薬剤では，特にmedroxyprogesterone acetate(MPA)に良好な奏効性が認められているが，他の薬剤には有効な奏効性は認められていない．したがってhormonal therapyはsteroid hormone receptorの発現レベルによって有効性が異なる可能性を有することや，多剤併用療法への適応においてsynergic effectsを発現させる薬理学的根拠が得難いことなどから，現時点ではtumor dormancyによるlong-term no change(long NC)を目的としたsalvage therapyへの応用が主と考えられている．

表1に主な薬剤の体癌に対するphase II studyの成績を示したが，現在のところ単剤で30%を越す奏効率が得られている薬剤はADMとpaclitaxelのみであり，併用化学療法への移行における認容性を考慮すると体癌化学療法のkey-drugは将来的にADMからタキサン系抗癌剤へ移行していくものと考えられる．

表1　体癌に対する単剤化学療法の直接効果

agent	response rate (%)
doxorubicin	37
epirubicin	26
pirarubicin	10
pegylated liposomal doxorubicin	21
cisplatin	20
carboplatin	24
cyclophosphamide	14
ifosfamide	15
vincristine	18
vinblastine	8
etoposide(oral)	14
topotecan	20
medroxyprogesterone acetate	25
tamoxifen	10
danazol	0(SD: 27)
leuprolide	0(SD: 32)
paclitaxel	36-37

2. Combination chemotherapy

体癌に対する多剤併用化学療法では前述のごとくADMがkey-drugと考えられており，更に多癌種における化学療法の中心的薬剤であるcisplatin(CDDP)が単剤で20%[6]の奏効率が得られていることから，主にADMとCDDPを含むregimenあるいはADMの認容性が考慮されたADMとcyclophosphamide(CPA)の併用regimen(AC)の検討が行われてきた．ただし実際に使用されるregimenは，欧米ではAP(ADM+CDDP)が広く用いられているが，我が国においては卵巣癌化学療法において経験の多いCAP(CPA+ADM+CDDP)が一般的に用いられている．

これらADM-base併用regimenの治療成績は，APで奏効率33-81%[7]，ACで31-46%[8]，一方CAPでは31-56%[9]と報告されているが，ADM単剤(60mg/m²)とのphase III studyによる比較

表2 体癌に対する併用化学療法の直接効果

regimen	response rate (%)
ADM-base	
doxorubicin+cisplatin (AP)	33-81
doxorubicin+cyclophosphamide (AC)	31-46
doxorubicin+cyclophosphamide+cisplatin (CAP)	31-56
taxane-base	
paclitaxel+doxorubicin (TA)	43
paclitaxel+doxorubicin+cisplatin (TAP)	57
paclitaxel+cisplatin (TP)	67
paclitaxel+carboplatin (TJ)	78
others	
vinorelbine+cisplatin (VP)	57
etoposide+5-FU+cisplatin	41
methotrexate+5-FU+carboplatin+MPA	74
methotrexate+vinblastine+doxorubicin+cisplatin	67
doxorubicin+5-FU+etoposide+cisplatin	45

試験ではAC(A; 60 mg/m^2+CPA; 500 mg/m^2)[10], AP(A; 60 mg/m^2+CDDP; 50 mg/m^2: GOG 107) いずれのregimenにおいても併用療法に奏効率あるいは生存期間がやや良好である結果が得られているものの，併用化学療法に明らかな統計学的優位性は証明されてはこなかった．更に近年The European Organization of Research and Treatment of Cancer(EORTC)からも化学療法感受性の進行・再発体癌を対象としたADM単剤とAPのcomparative phase III study(EORTC 55872)の結果が報告されたが[11]，これまでの報告と同様にAPはADM単剤に比較して有意に奏効率が高率であるが，生存については有意差を認めなかったとされている．

またAPについては1993年に米国GOGのphase II studyからcircadian-timed chemotherapyの有効性が報告され注目されたが，近年のphase III study(GOG 139)によってそのbenefitについては否定[12]されている．

このようにADM-baseの併用化学療法が生存においてADM単剤化学療法を凌駕できない現状から，現在は単剤化学療法と同様にタキサン系抗癌剤をbaseとした新規regimenの設定と検証が望まれている．既に，paclitaxelを用いた併用化学療法の有効性については幾つかのphase II，III studyが進行しており，近年のphase II studyではpaclitaxel 175 mg/m^2+CDDP 75 mg/m^{2}の併用(TP)で奏効率67%[13]，一方paclitaxel 175 mg/m^2+carboplatin AUC=5-7の併用(TJ)では奏効率78%[14]という驚異的な成績が報告されている．

またphase III studyでは1996年にGOGにおいてAP(A; 60 mg/m^2+CDDP 50 mg/m^2)とADM+paclitaxel(A; 50 mg/m^2+paclitaxel 150 mg/m^2, 24 h)の比較試験(GOG 163)が行われたが，奏効率および生存期間のいずれについても両群間に有意差が認められなかった．更に1998年から同様にGOGにおいて，ADM+paclitaxel+CDDP(A; 45 mg/m^2+paclitaxel 160 mg/m^2, 3 h+CDDP 50 mg/m^2: TAP)とAP(A; 60 mg/m^2+CDDP 50 mg/m^2)の比較試験(GOG 177)が行われ，奏効率はAP 33.3%，TAP 56.7%とTAPが勝ったもののtoxicityによるoff treatmentがAPにおいては9.8%であったのに対してTAPでは23.9%に認められたため，現時点では認容性の面からTAPの臨床適応性を疑問視する意見が多い．なお，APとTAPの比較については現在EORTCにおいてもGOGと同様のcomparative phase III study(EORTC 55984)が進行しており，体癌に対するTAPの有効性および認容性の再

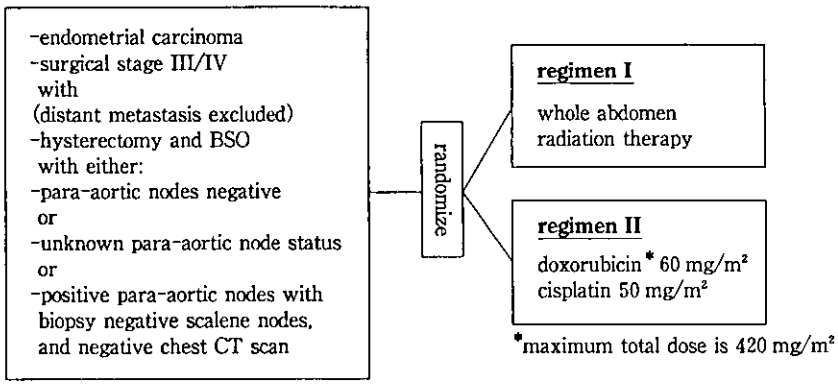

図1 GOG 122

検証結果が待たれる.

表2に体癌に対する主な併用化学療法の奏効率を示した. 各regimenの成績をみると, 現在のところ併用regimenではpaclitaxel+platinumの有効性が期待されるが, 将来的にAP, CAPなどのADM-base併用regimenあるいはTAPとのcomparative phase III studyによる有効性の検証が必要となるであろう.

また体癌に対するtaxanes-based併用regimenの有効性の検討については, 我が国でも2003年末より婦人科悪性腫瘍化学療法研究機構(Japan Gynecologic Oncology Group: JGOG)によって, 進行・再発体癌を対象としたpaclitaxel+carboplatin(paclitaxel 180 mg/m²+carboplatin AUC=6: TJ), docetaxel+carboplatin(docetaxel 60 mg/m²+carboplatin AUC=6: DJ), docetaxel+CDDP(docetaxel 70 mg/m²+CDDP 60 mg/m²: DP)の3-arm randomized comparative phase II study(JGOG 2041)がactivateされている. 本試験は体癌に対して, 複数のタキサン系抗癌剤と複数の白金錯体系抗癌剤を用いた各regimenの有効性を検証するものであり, 我が国から体癌に対する新たな治療regimenの発信が期待される興味深いstudyである.

3. Adjuvant chemotherapy

近年, 進行体癌に対するadjuvant chemotherapyの有効性について放射線療法との比較から検証したphase III studyがGOGによって行われ(GOG 122, 図1), 既に389人の症例集積が完了しAmerican Society of Clinical Oncology(ASCO)のannual meetingにおいて早期解析結果が報告された. 本試験はstage III/IVの進行体癌に対する術後adjuvant therapyとしてのchemotherapy(doxorubicin 60 mg/m²+CDDP 50 mg/m²: AP)とradiation therapy(whole abdominal irradiation: WAI)の有効性を比較検証した興味深いclinical trialであり, 現時点ではAPがWAIをprogression free survival, overall survivalともに勝るとする報告が行われたため注目を浴びている.

GOG statistical reportによると, hematologic toxicityがAPに高いことやWAIにおいて肺・脳・脊椎への再発の多い傾向などが報告されている. ただし, 治療関連死が9人(AP: 5, WAI: 4)に認められたため, GOGでは現在本試験の最終解析を行うとともに, platinum-agentをEORTCの単剤phase II studyから24%[15]の奏効率が得られているcarboplatinへ変更の可能性についても検討を行っている模様である. いずれにせよ本試験は進行体癌治療における化学療法の優位性が証明される可能性のある興味深いstudyであり, EORTCの試験結果を含めた最終解析結果が待たれる.

また頸癌については米国National Cancer InstituteからCDDP concurrent chemoradiationの有効性についてclinical announcementが行われ, 我が国においても実地臨床に応用され始めて

いるが，体癌についてはまだphase IIを含めてclinical trialは行われていない．化学療法と放射線療法のいずれもが体癌治療の標準的治療として広く応用されてきたことを考慮すると，併用薬剤の検討を含めたconcurrent chemoradiationの有効性の検討は，体癌に対するadjuvant therapyの一法として将来的な検証が必要となるかもしれない．

おわりに

NCCN practice guidelineでは体癌のsalvage chemotherapyの項に，推奨される薬剤の記載に加えて'strongly encourage clinical trial'と記載されており，現時点における体癌化学療法は効果的な新規薬剤の開発と系統的なregimenの検証が望まれる未知の分野といえる．

癌化学療法には，奏効率および生存率の改善を含む高い治療効果の達成，有害事象の抑制による認容性の改善，および2剤あるいは3剤併用を原則としたよりsimpleなregimenの設定が求められる．これらの諸点を考慮し，これまでの体癌に対するclinical trialの成績をみると，今後体癌化学療法はtaxanes+platinumの併用regimenを中心とした検証が進行するものと考えられる．

文献

1) Thigpen JT, et al: Phase II trial of adriamycin in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Cancer Treat Rep 63: 21-27, 1979.
2) Caiero F, et al: Epirubicin in advanced endometrial adenocarcinoma: a phase II study of the Grupo Ginecologico Espanol para el Tratamiento Oncologico (GGETO). Eur J Cancer 27: 864-866, 1991.
3) Escobar PF, et al: Phase 2 trial of pegylated liposomal doxorubicin in advanced endometrial cancer. J Cancer Res Clin Oncol 129: 651-654, 2003.
4) Ball HG, et al: A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 62: 278-281, 1996.
5) Lissoni A, et al: Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol 7: 861-863, 1996.
6) Thigpen JT, et al: Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 33: 68-70, 1989.
7) Pasmanitier MW, et al: Treatment of advanced endometrial carcinoma with doxorubicin and cisplatin on both untreated and previously treated patients. Cancer Treat Rep 69: 539-542, 1985.
8) Campora E, et al: Treatment of advanced or recurrent adenocarcinoma of the endometrium with doxorubicin and cyclophosphamide. Eur J Gynecol Oncol 11: 181-183, 1990.
9) Hancock KC, et al: Use of cisplatin, doxorubicin, and cyclophosphamide to treat advanced and recurrent adenocarcinoma of the endometrium. Cancer Treat Rep 70: 789-791, 1986.
10) Thigpen JT, et al: A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. J Clin Oncol 12: 1408-1414, 1994.
11) Aapro MS, et al: Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomized study (55872) by the EORTC Gynecological Cancer Group. Ann Oncol 14: 441-448, 2003.
12) Gallion HH, et al: Randomized phase III trial of standard timed doxorubicin plus cisplatin versus circadian timed doxorubicin plus cisplatin in stage III and IV or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 21: 3808-3813, 2003.
13) Dimopoulos MA, et al: Paclitaxel and cisplatin in advanced or recurrent carcinoma of the endometrium: long-term results of a phase II multicenter study. Gynecol Oncol 78: 52-57, 2000.
14) Hoskins PJ, et al: Paclitaxel and carboplatin, alone or with irradiation, in advance or recurrent endometrial cancer: a phase II study. J Clin Oncol 15: 4048-4053, 2001.
15) Van Wijk FH, et al: Phase II study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the EORTC Gynecological Cancer Group. Eur J Cancer 39: 78-85, 2003.

II. 子宮頸癌

子宮頸癌の治療
血中ヘモグロビン値と再発率

Hemoglobin level and recurrent rate of uterine cervical cancer

上田晴彦
渡部　洋
星合　昊

Key words　子宮頸癌，血中ヘモグロビン値，tumor hypoxia

はじめに

子宮頸癌の予後因子についてはこれまでに数多くの検討が行われ，臨床進行期をはじめとした年齢などの患者因子，組織型・腫瘍体積・リンパ管侵襲あるいはリンパ節転移などの病理組織学的因子，血清腫瘍マーカー・血管新生因子活性などの生理学的因子，更にはp53，c-erb B2などの遺伝子学的因子など種々の予後因子の有用性が報告されてきた．更に近年では，腫瘍の低酸素状態(tumor hypoxia)が固形癌における腫瘍進展や治療抵抗性と関連する新たな予後因子として注目されており，子宮頸癌においてもtumor hypoxiaの予後因子としての有用性[2-4]が精力的に検討されてきている．特に患者血中ヘモグロビン値はtumor hypoxiaを簡便に反映する臨床的因子[1]であるとされ，治療前あるいは治療中に生じる血中ヘモグロビン値の低下は治療反応性および長期予後の改善の視点から綿密な管理が必要とされている．

そこで本稿では，子宮頸癌患者における血中ヘモグロビン値の予後因子としての意義について基礎・臨床の両面から，教室の成績および文献的考察を交えて解説する．

1. 腫瘍低酸素状態(tumor hypoxia)と腫瘍増殖・進展

近年の研究によると低酸素状態におかれた腫瘍は，hypoxia-inducible factor(HIF)-1 alphaあるいはHIF-2 alphaといった生理活性因子の発現を生じ，特にHIF-1 alphaはvascular endothelial cell growth factor(VEGF)，platelet-derived endothelial cell growth factor(PDECGF)などの血管新生因子(angiogenetic factors)発現の促進[2,3]や腫瘍細胞のapoptosisの抑制[4]を惹起するため，腫瘍発育や進展と有意な関連性を有することが報告されている．また実験動物を用いた研究から，慢性貧血によってHIF-1 alphaの発現が誘導されることやHIF-1 alphaの過剰発現がerythropoietin geneの発現や組織への酸素運搬および酸素低下に対する組織適合性に関連する遺伝子の発現を抑制することが確認されており，血中ヘモグロビン値の低下はtumor hypoxiaによるHIF-1 alphaの過剰発現を介して腫瘍増殖に間接的に関与するものと推定されている．

2. 放射線治療と血中ヘモグロビン値

tumor hypoxiaは子宮頸癌に対する放射線治療の治療抵抗性因子[5,6]としても報告されており，

Haruhiko Ueda, Yoh Watanabe, Hiroshi Hoshiai: Department of Obstetrics and Gynecology, Kinki University School of Medicine　近畿大学医学部産科婦人科

0047-1852/04/¥50/頁/JCLS

腫瘍内酸素濃度の直接測定を行って放射線の治療効果と比較検討した研究によると，$\%P_{O_2}$ <5mmHgを示す頸癌では放射線治療後の予後が有意に不良であると報告されており，tumor hypoxiaの有効な管理の必要性が示唆されている．

前述のごとく血中ヘモグロビン値の低下はtumor hypoxiaを簡便に反映する因子とされており，Grinskiら[7]によると放射線治療が行われた進行子宮頸癌を対象とした検討成績では，血中ヘモグロビン値10g/dlを境界値として予後と相関し，更に放射線治療中に輸血によって予後の改善が認められたと報告している．またThomasら[8]も同様の検討から，血中ヘモグロビン値12g/dlを境界値として予後との相関性が認められ，更に治療前の血中ヘモグロビン値(base line hemoglobin value)よりも治療週ごとの平均最低ヘモグロビン値(average weekly hemoglobin nadir)がより有意な関連性を有すると報告している．

このように放射線治療を行う進行頸癌における血中ヘモグロビン値は簡便な治療効果推定因子と考えられていたが，実際的な放射線治療中の血中ヘモグロビン値の有効な管理法については不明であった．しかし近年recombinant erythropoietin(r-HuEPO)により放射線治療中の血中ヘモグロビン値が効果的に改善するとの報告[11]が行われ，臨床的な有用性が注目されている．更に報告では200U/kg/dayのr-HuEPO投与群は非投与群に比較して有意に血中ヘモグロビン値の改善とともに治療効果，局所再発率，生存率のいずれもが良好であるとされており，現在Gynecologic Oncology Group(GOG)においてもcisplatin concurrent chemoradiationを行う進行頸癌に対するr-HuEPOを用いた血中ヘモグロビン値の管理について生存への寄与効果をphase III randomized comparative study (GOG 191)で検証が行われている．

3. 放射線治療における血中ヘモグロビン値と再発率

教室において放射線単独療法が行われた子宮頸癌における血中ヘモグロビン値と再発率について，stage IIIb扁平上皮癌22例を対象にretrospectiveに検討を行った．この結果，治療前の平均血中ヘモグロビン値(base line hemoglobin value)では10g/dlを境界値として再発率(57.1% vs 33.3%)に有意差($p<0.001$)が認められ，また治療中の血中ヘモグロビン最低値(nadir hemoglobin)との関連性では9g/dlを境界値として再発率(60.0% vs 35.3%)に有意差($p<0.001$)が認められた．一方，最も予後との関連性が深いとされる，治療週における最低ヘモグロビン値(average weekly hemoglobin nadir)での検討では再発率に一定の関連性は認められなかった(表1)．更に再発症例における再発までの期間(time to relapse)と血中ヘモグロビン値の関連性についても検討を行ったが，base line hemoglobin value，nadir hemoglobin，average weekly hemoglobin nadirのいずれの因子を用いた検討でも再発までの期間との有意な関連性は認められなかった．本検討はretrospective studyであり症例数の関係からmultivariate analysisが行えなかったため，血中ヘモグロビン値の放射線治療頸癌における再発推定因子としての有用性を論ずるにはまだ不十分ではあるが，血中ヘモグロビン値は進行頸癌における新たな予後因子である可能性が推察された．

表1 血中ヘモグロビン値と再発率

factor	recurrent rate	p value
base line Hb value		
<10.0g/dl	57.1%(4/ 7)	p<0.001
10.0g/dl≦	33.3%(5/15)	
nadir Hb		
<9.0g/dl	60.0%(3/ 5)	p<0.001
9.0g/dl≦	35.3%(6/17)	
average weekly Hb nadir		
<10.0g/dl	42.9%(3/ 7)	NSD
10.0g/dl≦	40.0%(6/15)	
<9.0g/dl	50.0%(1/ 2)	NSD
9.0g/dl≦	40.0%(8/20)	

Hb: hemoglobin

おわりに

子宮頸癌の予後因子としての血中ヘモグロビン値の有用性および臨床応用についてはまだ明らかとはいえないが，教室における検討結果や諸報告における成績をみると，少なくとも子宮頸癌においては積極的に血中ヘモグロビン値の管理を行うことが必要であると考えられる．近年tumor hypoxiaを画像診断を用いて診断する試みも始まっており，Cooperら[9]はgadoliniumを用いたenhanced MRIにより，Krishnaら[10]はOxo 63を用いたenhanced MRIによってtumor hypoxiaの画像診断が可能であると報告している．これらの方法はまだ実験段階の域を出ないが，今後臨床応用が可能となれば子宮頸癌の新たな予後因子の確立について有用な情報を与えるものと考えられる．

■文　献

1) Vaupel P, et al: Oxygen status of malignant tumors: Pathogenesis of hypoxia and significance for tumor therapy. Semin Oncol 28(2): 29-35, 2001.
2) Blancher C, et al: Relationship of hypoxia-inducible factor(HIF)-1 alpha and HIF-2 alpha expression to vascular endothelial growth factor induction and hypoxia survival in human breast cancer cell lines. Cancer Res 60(24): 7106-7113, 2000.
3) Ziemer LS, et al: Hypoxia and VEGF mRNA expression in human tumors. Neoplasia 3(6): 500-508, 2001.
4) Suzuki H, et al: Dephosphorylated hypoxia-inducible factor 1 alpha as a mediator of p53-dependent apoptosis during hypoxia. Oncogene 20(41): 5779-5788, 2001.
5) Fyles AW, et al: Oxygenation predicts radiation response and survival in patients with cervix cancer. Radiother Oncol 48(2): 149-156, 1998.
6) Rofstad EK, et al: Hypoxia-induced treatment failure in advanced squamous cell carcinoma of the uterine cervix is primarily due to hypoxia-induced radiation resistance rather than hypoxia-induced metastasis. Br J Cancer 83(3): 354-359, 2000.
7) Grinski T, et al: Prognostic value of hemoglobin concentrations and blood transfusions in advanced carcinoma of the cervix treated by radiation therapy: results of a retrospective study of 386 patients. Int J Radiat Oncol Biol Phys 16(1): 37-42, 1989.
8) Thomas G, et al: The effect of hemoglobin level on radiotherapy outcomes: the Canadian experience. Semin Oncol 28(2): 60-65, 2001.
9) Cooper RA, et al: Tumour oxygenation levels correlate with dynamic contrast-enhanced magnetic resonance imaging parameters in carcinoma of the cervix. Radiother Oncol 57(1): 53-59, 2000.
10) Krishna MC, et al: Overhauser enhanced magnetic resonance imaging for tumor oximetry: coregistration of tumor anatomy and tissue oxygen concentration. Proc Natl Acad Sci USA 99(4): 2216-2221, 2002.
11) Dusenbery KE, et al: Erythropoietin increases hemoglobin during radiation therapy for cervical cancer. Oncol Biol Phys 29(5): 1079-1084, 2001.

Available online at www.sciencedirect.com

SCIENCE DIRECT

Gynecologic Oncology 94 (2004) 774–778

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Clinical experience with combination paclitaxel and carboplatin therapy for advanced or recurrent carcinosarcoma of the uterus

Masafumi Toyoshima,[a,*] Jun-ichi Akahira,[a] Gen Matsunaga,[b] Hitoshi Niikura,[a] Kiyoshi Ito,[a] Nobuo Yaegashi,[a] and Toru Tase[b]

[a] *Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan*
[b] *Division of Gynecology, Miyagi Prefecture Cancer Research Center, Miyagi, Japan*

Received 9 March 2004
Available online 20 July 2004

Abstract

Objective. The purpose of the study was to evaluate the efficacy of combination chemotherapy with paclitaxel and carboplatin in patients with advanced or recurrent carcinosarcoma of the uterus.

Methods. A retrospective review was carried out at Miyagi Prefecture Cancer Research Center Hospital. Six patients pathologically diagnosed with uterine carcinosarcoma were treated with paclitaxel (175 mg/m^2 given intravenously over 3 h) and carboplatin (dosed at AUC 6) every 3 weeks at our center between 1997 and 2003. Responses and adverse effects were assessed according to Response Evaluation Criteria in Solid Tumors and National Cancer Institute—Common Toxic Criteria, respectively.

Results. All six patients were evaluable for toxicity, and no unacceptably severe toxicities were reported. Grades 3 and 4 hematologic toxicities occurred, but all of them were overcome by adequate treatment with granulocyte colony-stimulating factor and blood transfusions. Five of six patients had measurable disease and thus were evaluable for response: Four patients had a complete response (CR) and the remaining patient had progressive disease (PD). The median progression-free interval (PFI) for all six cases was 18 months, with a median overall survival of 25 months.

Conclusions. Although the number of cases was small, the regimen evaluated in the current study demonstrated higher activity and lesser toxicity than those found in previous studies in patients with advanced or recurrent uterine carcinosarcoma. Additional phase II clinical studies are necessary to evaluate fully the benefits of this regimen.
© 2004 Elsevier Inc. All rights reserved.

Keywords: Uterus; Carcinosarcoma; Malignant mixed mullerian tumor; Chemotherapy; Paclitaxel; Carboplatin

Introduction

Carcinosarcoma (CS) of the uterus, also known as malignant mixed mullerian tumor, is a rare and aggressive neoplasm that contains both carcinomatous and sarcomatous histologic elements. The overall prognosis of uterine CS is extremely poor due to a high tendency to spread and associated with high relapse rate even after local therapy such as surgery, radiation, or both. Although total hysterectomy with surgical staging is regarded as a standard treatment for patients with early-stage disease, 53% of patients with clinical stage I–II uterine CS developed recurrent disease within 5 years of initial therapy [1]. Adjuvant pelvic radiotherapy seems to improve local disease control, but it has not had a significant impact on overall survival due to the propensity of the disease to recur in a distant location [2,3]. These data indicate that up to half of all patients diagnosed with uterine CS are potential candidates for chemotherapy.

Development of systemic chemotherapy against CS is an urgent issue, and some drugs have been examined as single-agent therapy with response rates as follows: 16–19% with adriamycin [4,5], 32–36% with ifosfamide [6,7], 19% with cisplatin [8], and 18% with paclitaxel [9]. Combination regimens have not proven to be more effective than therapy with the single-agent ifosfamide. Only two combination regimens have been reported to be superior to single-agent

* Corresponding author. Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, 1-1, Seiryo-machi, Aoba, Sendai 980-8574, Japan. Fax: +81-22-717-7258.
E-mail address: m-toyo@mail.tains.tohoku.ac.jp (M. Toyoshima).

0090-8258/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2004.05.048

ifosfamide in their response rates [7,10], but adverse effects with these combinations were unacceptably severe, and these combinations have not been justified as standard treatment because of toxicity. For all of these reasons, there is a continuing need to identify other active agents and combinations that are effective against this aggressive malignancy.

Recently, convincing evidence has suggested that most cases of uterine CS are monoclonal in original rather than true collision tumors [11,12]. These data indicate that uterine CS may be metaplastic, with the implication that the sarcomatous components of CS are derived from its carcinomatous elements [13]. In this point of view, McCluggage [13] pointed out that chemotherapeutic regimens effective with aggressive high-grade endometrial carcinoma should also be effective with uterine CS. For advanced or recurrent endometrial carcinoma, the combination of doxorubicin and cisplatin is currently considered standard first-line chemotherapy [14]. In addition, Fleming et al. reported that 3-h paclitaxel plus the combination of doxorubicin and cisplatin with granulocyte colony-stimulating factor (G-CSF) produced an improvement in overall survival with the price of additional peripheral neuropathy, compared to the combination of doxorubicin and cisplatin, as reported for the Gynecologic Oncology Group (GOG) protocol #177 (ASCO, 2002). Furthermore, recent studies have reported the efficacy of single-agent paclitaxel [15], and many more cases of combination paclitaxel plus carboplatin for patients with advanced or recurrent endometrial carcinoma are reported [16–19].

With these backgrounds, we examined the efficacy of paclitaxel and carboplatin regimen in patients with advanced CS of the uterus.

Patients and methods

Records for the Department of Gynecology, Miyagi Prefecture Cancer Research Center Hospital, for the years 1997 through 2003 were retrospectively reviewed. We identified six cases with pathologically diagnosed uterine CS: each was to be treated with paclitaxel and carboplatin chemotherapy. All six patients presented advanced or recurrent disease at their first visit to our hospital, and treatments with few side effects were needed for them. Thus, we offered the combination of paclitaxel and carboplatin as first-line chemotherapy, instead of ifosfamide-based therapy.

No patients received any chemotherapy and radiation therapy before paclitaxel and carboplatin. All pathological specimens were reviewed in detail, and none had any heterologous elements. Clinical data are summarized in Table 1.

Five of the six cases were primary and the remaining one (Case 6) represented recurrent disease. Three of the five primary cases (Cases 1, 2, and 3) underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) to reduce tumor burden. In addition, Case 2 underwent radiotherapy against bone metastases, 30 Gy for T6-L1, L4-S1, C5, and right hip bone, respectively, simultaneously with paclitaxel and carboplatin chemotherapy. However, irradiation fields were limited to relatively narrow scope; no dose adjustment were required. The remaining two primary cases (Cases 4 and 5) were initially treated with paclitaxel and carboplatin chemotherapy. Case 4 underwent TAH-BSO 2 weeks after the third course of paclitaxel and carboplatin chemotherapy. Because Case 5 refused surgery, her uterus with vaginal involvement and swollen pelvic lymph nodes were treated with external whole pelvic radiation 50 Gy without center split and 20 Gy with center split, simultaneously with paclitaxel and carboplatin chemotherapy. During whole pelvic radiation, the dose adjustments were needed over three cycles of chemotherapy, to 135 mg/m^2 of paclitaxel and AUC 4 of carboplatin. Her uterine size was continuously reduced while eight courses of paclitaxel and carboplatin were administered. The recurrent case (Case 6) had initially undergone TAH-BSO at another hospital after a diagnosis as stage IIIa disease, but she had not received any adjuvant treatments. Thirteen months after the surgery, she complained of abdominal distention and came to our center diagnosed as recurrent disease.

Table 1
Clinical characteristics, treatments, and results for all six patients

Case	Age (years)	Stage	Initial treatment before TJ	Sites of evaluation	Response (RECIST)			PFI (months)	OS (months)	Chemotherapy (courses)
					TL	NTL	OR			
1	63	IVb	surgery	lungs	CR	none	CR	32	AWN, 32	TJ × 14
2	55	IVb	surgery	lungs, liver	PD	none	PD	0	DOD, 5	TJ × 5
3	57	IIIa	surgery	none	none	none	–	6	DOD, 7	TJ × 6
4	52	IVb	none	lungs	CR	none	CR	16	AWD, 23	TJ × 10
5	58	IVb	none	lungs	CR	none	CR	20	AWD, 30	TJ × 8
6	47	IIIa[a]	none	pelvis, liver	CR	CR[b]	CR	28	AWN, 28	TJ × 10

RECIST: response evaluation criteria in solid tumors.
TL: target lesions; NTL: nontarget lesions; OR: overall response; PFI: progression-free interval; OS: overall survival.
AWN: alive with no evidence of disease; AWD: alive with disease; DOD: died of disease.
TJ: paclitaxel + carboplatin; CR: complete response; PD: progressive disease.
[a] Case 6 had recurrent disease.
[b] Nontarget lesions were ascites and peritonitis carcinomatosa.