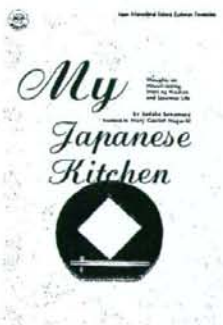
JICEF BOOKS

The Japan International Cultural Exchange Foundation (JICEF) hopes to improve human culture and promote world peace through international cultural exchange activities.



MY JAPANESE KITCHEN

by Sadako Sawamura
translated by Mary Goebel Noguchi
192 pages, ¥2,100

This book is a collection of essays on a wide range of topics related to a traditional Japanese kitchen. These essays, penned by a woman born in the Meiji Era, an actress and essayist, invite us to step behind the screen to see and feel what the everyday customs, concerns and cares of Japanese women used to be.

The English translation is beautifully done. It is as easy and enjoyable to read as the Japanese original. This should be of interest not only to English-speaking readers in general but also to specialists in search of the essence of Japanese culture.

Noriko Matsui, Professor of English
Rikkyo University, Tokyo, Japan

SOICHIRO HONDA : The Endless Racer

by Masajiro Ikeda
translated by Kazunori Nozawa
168 pages, ¥1,890

This book gives the reader an in-depth, multi-faceted look at the founder of Honda Motors, Soichiro Honda. The author, Masajiro Ikeda, describes Soichiro based on his personal interactions with him, but the reader is also afforded vivid glimpses into the life of the playboy-genius through the eyes of Soichiro's employees, his colleagues, his son and even his rivals.

This informative and entertaining narrative traces the life of Soichiro Honda and the ensuing Honda Motors in a way never done before. A generous sprinkling of humor presented in Soichiro's analysis of the Sengoku Period, his views on un-smiling warriors as well as his life sayings make this a must-read book for history buffs, Japanophiles, and auto industry followers alike.

Laura M.Kimoto
Lecturer in Japanese
University of Hawaii at Hilo

Correspondence

Gross features of lobular endocervical glandular hyperplasia in comparison with minimal-deviation adenocarcinoma and stage Ib endocervical-type mucinous adenocarcinoma of the uterine cervix

DOI: 10.1111/j.1365-2559.2008.03095.x

Sir: Lobular endocervical glandular hyperplasia (LEGH) was first described as a benign mimic of minimal-deviation adenocarcinoma (MDA), or 'adenoma malignum'.[1,2] Histopathological criteria for LEGH have well been established,[3,4] but the distinction between LEGH and MDA in imaging studies is still challenging for diagnostic radiologists. Appearance of a multicystic lesion on computed tomography and magnetic resonance imaging has been considered to be diagnostic for MDA,[5–9] but some authors have questioned this view, pointing out that cyst formation is rather uncommon in cases of MDA, but seems to be indicative of LEGH.

In order to elucidate the characteristic topological features of LEGH, we examined haematoxylin and eosin (H&E)-stained glass slides of cervical lesions in hysterectomy specimens from 31 patients, comprising 15 cases of LEGH, six cases of MDA and 10 cases of FIGO stage Ib common endocervical-type mucinous adenocarcinoma (EMA). On representative sagittal sections of these 31 cases, we determined the greatest longitudinal length and depth of the lesion, lesion location and the size and number of the cystic components and calculated the average values and standard deviation (Figures 1 and 2). The mean values were compared between groups by the Mann–Whitney *U*-test.

The mean longitudinal length and depth of MDA (62.3 and 21.8 mm, respectively) were obviously greater than those of LEGH (29.5 and 13.7 mm, respectively) ($P = 0.0022$ and 0.010) or common EMA (26.6 and 13.1 mm, respectively) ($P = 0.0048$ and 0.064) (Table 1). Indeed, all six MDAs extended widely from the vagina to the uterine corpus, occupying the entire uterine cervix.

The tumour location was estimated from measurements of the distance between the distal extremity of the tumour and the squamo-columnar junction (SCJ) [lower distance (LD)] and the distance between the proximal extremity of the tumour and the fundus [upper distance (UD)] (Figure 2). The mean LD and UD differed significantly between LEGH (3.2 and 16.7 mm, respectively) and EMA (−3.7 and 10.6 mm, respectively) ($P = 0.024$ and 0.019). The LD was −8 mm in one MDA, but was not measurable

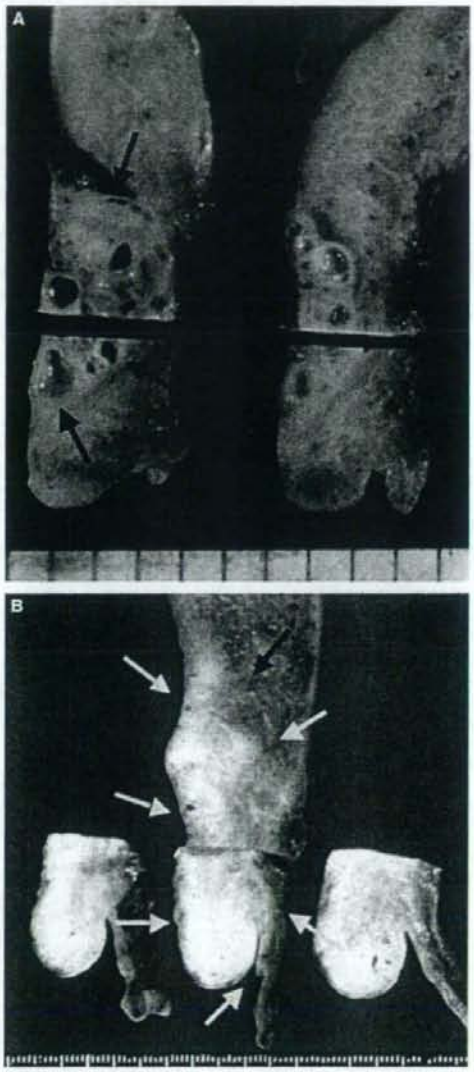


Figure 1. Gross features of surgically resected specimens of lobular endocervical glandular hyperplasia (LEGH) (A) and minimal deviation adenocarcinoma (B). Arrows indicate the area of tumours.

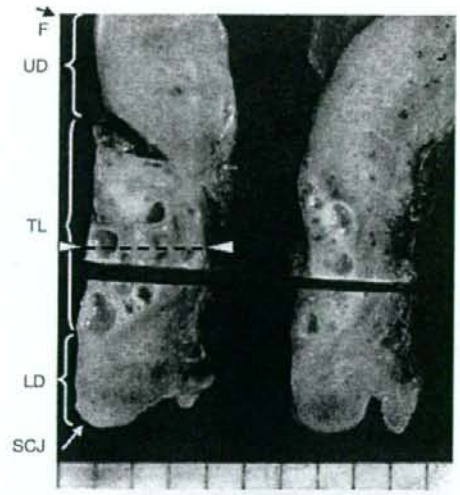


Figure 2. Measurement of longitudinal length, depth and location of a cervical lesion (LEGH). F, fundus of uterine cavity; SCJ, squamo-columnar junction; TL, tumour length; LD, distance between the distal extremity of the tumour and the SCJ; UD, distance between the proximal extremity of the tumour and the uterine fundus. A broken line encompassed by arrowheads indicates the tumour depth. The distance from the SCJ toward the uterine body was expressed as a positive number, and that from the SCJ toward the vagina was expressed as a negative number.

in other cases. The mean UD (18.8 mm) in five informative cases of MDA was smaller than those of LEGH ($P = 0.020$) or EMA ($P = 0.0040$) (Table 1).

Lesions localized in the uterine cervix were classified into high (H) and low (L) types. The L type was defined as a lesion in which the distal extremity of the tumour extended beyond the SCJ or nearly reached the SCJ with a LD of ≤ 3 mm. The H type was defined as a lesion with a LD of > 3 mm. Of 14 informative cases of LEGH, eight and six were classified as H and L types, respectively. Between the H and L types, the mean LD (8.1 and −3.5 mm, respectively) differed significantly ($P = 0.019$), but tumour length, depth and UD were not significantly different (Table 2). In contrast, nine of 10 common EMAs were L type, and only one was H type.

The numbers of cysts measuring ≥ 3 mm and ≥ 2 mm were counted on a representative sagittal cut surface of the tumour. In addition, the diameters of the three largest cysts, including those continuous with, or constituting the lesion, were measured on all available H&E sections.

The average number of cysts measuring ≥ 3 mm, as well as that of cysts measuring ≥ 2 mm, differed significantly between LEGH (4.0 and 7.7, respectively) and MDA (1.3 and 2.5, respectively) ($P = 0.017$ and

Table 1. Comparison of parameters among lobular endocervical hyperplasia (LEGH), minimal deviation adenocarcinoma (MDA) and stage Ib endocervical-type mucinous adeno-carcinoma (EMA)

Parameter	Mean (range, standard deviation) LEGH	MDA	Stage Ib EMA	*P*
Patient age, tumour size and location				
Age	44.0 (22–65, 11.7)	52.8 (44–76, 12.3)	39.6 (33–64, 9.2)	*
Longitudinal length of lesion (mm)	29.5 (8–42, 9.9)	62.3 (37–110, 25.9)	26.6 (11–53, 13.0)	†
Depth of lesion (mm)	13.7 (6–20, 4.3)	21.8 (15–25, 4.1)	13.1 (3–28, 8.4)	‡
LD (lower distance) (mm)	3.2 (−9 to 14, 6.8)	NM	−3.7 (−12 to 0, 4.2)	§
UD (upper distance) (mm)	35.5 (4–50, 12.0)	18.8 (0–35, 12.5)	49.8 (30–64, 12.6)	¶
Cystic components				
Number of cysts ≥ 3 mm	4.0 (1–9, 2.7)	1.3 (0–3, 1.0)	1.0 (0–4, 1.5)	**
Number of cysts ≥ 2 mm	7.7 (1–16, 4.5)	2.5 (1–5, 1.6)	2.4 (0–6, 2.6)	††
Diameter of three largest cysts (mm)	8.5 (3–17, 3.7)	6.8 (2.5–27, 5.8)	4.4 (1–13, 3.2)	‡‡

NM, Not measurable. *$P = 0.067$ between MDA and EMA; †$P = 0.0022$ between LEGH and MDA, and 0.0048 between MDA and EMA; ‡$P = 0.010$ between LEGH and MDA, and 0.064 between MDA and EMA; §$P = 0.024$ between LEGH and EMA; ¶$P = 0.020$ between LEGH and MDA, 0.019 between LEGH and EMA, and 0.004 between MDA and EMA; **$P = 0.017$ between LEGH and MDA, and 0.0026 between LEGH and EMA; ††$P = 0.011$ between LEGH and MDA, and 0.0053 between LEGH and EMA; ‡‡$P = 0.029$ between LEGH and MDA, < 0.0001 between LEGH and EMA, and 0.017 between MDA and EMA.

Table 2. Comparison of size and location between H type and L type of lobular endocervical hyperplasia (LEGH)

Parameter	Mean (range minimum–maximum, standard deviation)			
	LEGH total	H type	L type	*P*
Longitudinal length of lesion (mm)	29.5 (8–42, 9.9)	25.5 (8–37, 8.7)	30.2 (28–42, 6.7)	
LD (lower distance, mm)	3.2 (–9 to 14, 6.8)	8.1 (4–14, 3.0)	–3.5 (–9 to 1, 3.6)	*
UD (upper distance, mm)	35.5 (4–50, 12.0)	34.2 (4–50, 16.4)	36.8 (33–48, 6.7)	
Depth of lesion (mm)	13.7 (6–20, 4.3)	13.6 (6–20, 5.2)	14.0 (10–17, 2.9)	

*P = 0.019 between H and L types.

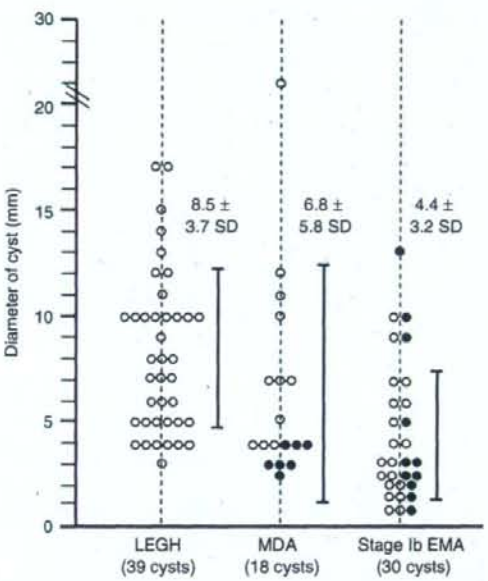


Figure 3. The distribution of the mean diameter of the largest three cysts per tumour in lobular endocervical glandular hyperplasia (LEGH), minimal deviation adenocarcinoma (MDA), and stage Ib common endocervical-type mucinous adenocarcinoma (EMA). An open circle stands for a benign cyst, e.g. nabothian cyst or component of LEGH. A closed circle stands for a malignant cyst delineated by adenocarcinoma cells. The vertical bars indicate the range of standard deviation (SD). Numbers stand for mean ± SD.

0.011). These average numbers were lower in EMA (1.0 and 2.4, respectively) than in LEGH (P = 0.0026 and 0.0053). The mean diameter of the largest three cysts per tumour was 8.5, 6.8 and 4.4 mm in LEGH, MDA and common EMA, respectively, all being significantly different from each other (Table 1, Figure 3). In the 15 cases of LEGH, the three largest cysts were always components of the lesion. In cases of MDA, cysts > 4 mm in size were always components of coexisting LEGH or nabothian cysts, whereas seven of 10 cysts measuring ≤ 4 mm in MDA were malignant cysts (Figure 3).

In summary, LEGH shows a characteristic location and architecture distinct from MDA. LEGH tends to be located in the higher part of the uterine cervix, whereas MDA is usually found at a locally advanced stage involving the SCJ. In LEGH there are two types (H and L) that differ in location. Both LEGH and MDA are associated with grossly visible cysts that can be demonstrated by imaging studies, but the number and size of these cysts in LEGH are greater than those in MDA and larger cysts in MDA appear to be benign components of the tumour. These findings may be of value in establishing criteria enabling distinction of LEGH from malignancy in imaging studies as well as pathological assessment.

ACKNOWLEDGEMENTS

Supported in part by a grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare, Japan, and by a grant-in-aid from the Foundation for Promotion of Defence Medicine, Japan.

Y Sasajima[1]
Y Mikami[2]
T Kaku[3]
T Kiyokawa[4]
Y Ohishi[5]
T Hamada[4]
T Sasaki[6]
H Fujita[6]
T Moriya[7]
T Kasamatsu[8]
H Tsuda[1,9]

[1]*Pathology Section, Clinical Laboratory Division, National Cancer Centre Hospital, Tokyo,* [2]*Laboratory of Diagnostic Pathology, Kyoto University Hospital, Kyoto,* [3]*Department of Health Sciences, Graduate School of Medicinal Sciences, Kyushu University, Fukuoka and* [4]*Department of Pathology, Faculty of Medicine, The Jikei University, Tokyo,* [5]*Department of Anatomic Pathology, Graduate School of Medicinal Sciences, Kyushu University, Fukuoka,* [6]*Department of Gynaecology, Hokkaido Cancer Society, Sapporo,* [7]*Department of Pathology, Kawasaki Medical University, Kurashiki,* [8]*Division of Gynaecology, National Cancer Centre Hospital, Tokyo and* [9]*Department of Basic Pathology, National Defence Medical College, Tokorozawa, Japan*

1. Nucci MR, Clement PB, Young RH. Lobular endocervical glandular hyperplasia, not otherwise specified: a clinicopathologic analysis of thirteen cases of a distinctive pseudoneoplastic lesion and comparison with fourteen cases of adenoma malignum. *Am. J. Surg. Pathol.* 1999; **23**; 886–891.
2. Mikami Y, Manabe T. Lobular endocervical glandular hyperplasia represents pyloric gland metaplasia? *Am. J. Surg. Pathol.* 2000; **24**; 323–326.
3. Tsuda H, Mikami Y, Kaku T *et al.* Interobserver variation in the diagnosis of adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. *Pathol. Int.* 2003; **53**; 440–449.
4. Tsuda H, Mikami Y, Kaku T *et al.* Reproducible and clinically meaningful differential diagnosis is possible between lobular endocervical glandular hyperplasia and 'adenoma malignum' based on common histopathological criteria. *Pathol. Int.* 2005; **55**; 412–418.
5. Doi T, Yamashita Y, Yasunaga T *et al.* Adenoma malignum: MR imaging and pathologic study. *Radiology* 1997; **204**; 39–42.
6. Tsuruchi N, Tsukamoto N, Kaku T, Kamura T, Nakano H. Adenoma malignum of the uterine cervix detected by imaging methods in a patient with Peutz-Jeghers syndrome. *Gynecol. Oncol.* 1994; **54**; 232–236.
7. Yamashita Y, Takahashi M, Katabuchi H, Fukumatsu Y, Miyazaki K, Okamura H. Adenoma malignum: MR appearances mimicking nabothian cysts. *Am. J. Roentgenol.* 1994; **162**; 649–650.
8. Oguri H, Maeda N, Izumiya C, Kusume T, Yamamoto Y, Fukaya T. MRI of endocervical glandular disorders: three cases of a deep nabothian cyst and three cases of a minimal-deviation adenocarcinoma. *Magn. Reson. Imaging* 2004; 22; 1333–1337.
9. Bardsley M, Pather S, Neesham D *et al.* Benign endocervical cystic glandular change mimicking minimal deviation adenocarcinoma of the cervix on magnetic resonance imaging: a case report. *Aust. NZ J. Obstet. Gynaecol.* 2004; **44**; 358–359.

Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma

SHIN NISHIO[1,3], NORIYUKI KATSUMATA[1], KOJI MATSUMOTO[1], HIROSHI TANABE[1], KAN YONEMORI[1], TSUTOMU KOHNO[1], CHIKAKO SHIMIZU[1], MASASHI ANDO[1], TAKAHIRO KASAMATSU[2] and YASUHIRO FUJIWARA[1]

Departments of [1]Medical Oncology and [2]Gynecologic Oncology, National Cancer Center Hospital, Tokyo 104-0045, Japan

Received July 23, 2007; Accepted October 22, 2007

Abstract. The aim of this study was to evaluate the clinicopathological prognostic factors in patients with stage IVb cervical carcinoma (CC). All patients with stage IVb CC included in the study were diagnosed from 1997 to 2006 at the National Cancer Center Hospital. We retrospectively examined clinicopathological parameters in these patients, including the efficacy of chemotherapy. Survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using a Cox's proportional hazard model. Thirty-six patients (median age 54 years) were diagnosed with stage IVb CC. The median progression-free survival and overall survival were 3.8 and 11.1 months, respectively. As initial treatment, 4 patients underwent hysterectomy, 13 received chemotherapy, 17 received radiotherapy, and the remaining 2 patients refused treatment. A total of 21 patients received chemotherapy, of which 13 were initial cases, 7 were persistent/recurrence cases, and 1 was a postoperative adjuvant case; 15 patients were never treated with chemotherapy. On univariate analysis, poor performance status (PS) and non-chemotherapy groups were considered poor prognostic factors, respectively. On multivariate analysis, poor PS (p=0.007; hazard ratio, 2.64) and non-chemotherapy (p=0.016; hazard ratio, 6.03) were independent prognostic factors of survival, respectively. Poor PS and non-chemotherapy groups were found to have poor prognosis in patients with stage IVb CC. Chemotherapy may improve the survival for stage IVb CC.

Correspondence to: Dr Shin Nishio, [3]*Present address*: Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
E-mail: nishio_shin@hotmail.com

Key words: stage IVb cervical carcinoma, prognostic factor, chemotherapy, performance status

Introduction

Cervical carcinoma is the main cause of death in females throughout the world, despite the fact that a useful screening method has been established (1). In stage I/II patients, conventional treatments such as surgery and radiotherapy have achieved good results. In stage III/IV patients, various treatments such as the combination of surgery and radiotherapy, radiotherapy, and chemoradiation therapy are being examined, though their long-term results are still poor (2,3). The 5-year survival of stage IVb patients ranges from 0 to 44%, and approximately 50% of these patients show a fatal outcome within 1 year (4-6). No standard therapy has been established, and palliative surgery, radiotherapy, and best supportive care (BSC) have been performed as initial treatment. However, since stage IVb cervical carcinoma is a systemic disease, surgery and radiotherapy are useful for local control, but are insufficient. In addition, BSC is not effective for the severe local pain characteristic of this disorder (7). Since 1990, chemotherapy has been employed as a type of BSC in patients with good general condition and organ function (8). However, as this therapy targets the relief of symptoms and improvements in quality of life (QOL), regimens with less toxic low-dose agents were initially administered (9). No randomized comparative study has examined whether chemotherapy for stage IVb cervical carcinoma prolongs survival compared to BSC.

Several studies have investigated single-agent chemotherapy for cervical carcinoma, and reported that the response rates to cisplatin, ifosfamide, paclitaxel, vinorelbine and topotecan of 20-30% (5,8,10-12), 14-40% (13-15), 17% (16), 15% (17,18) and 12-19% (19,20), respectively. Cisplatin has been the most frequently used agent, and has achieved the highest response rate. Therefore, cisplatin has been employed as a key drug for more than 20 years. However, the response to single-agent cisplatin has been limited, and combination chemotherapy with other agents has been administered to achieve improvement in prognosis, exceeding the enhancement of its toxicity. Result of recent phase III studies have indicated that combination regimens with cisplatin/paclitaxel (21) or cisplatin/topotecan (22) are more effective than single-agent cisplatin.

A few studies have reported that factors affecting the prognosis of stage IVb cervical carcinoma include main organ

metastases, multiple lymph node metastases, poor performance status (PS), and non-squamous cell carcinoma (23-29). According to some studies, the results of surgery combined with radiotherapy or radiotherapy alone are relatively good in stage IVb cervical carcinoma patients with para-aortic lymph node metastases alone (30-33). However, chemotherapy for stage IVb patients with cervical/mediastinal lymph node or main organ metastases, without surgery and radiotherapy, has been reported to have only slight effect.

In this study, we retrospectively investigated the clinicopathological features of stage IVb cervical carcinoma, and evaluated the efficacy of chemotherapy for this stage of cancer.

Patients and methods

Patients with stage IVb cervical carcinoma were diagnosed and treated in the National Cancer Center Hospital between April 1997 and March 2006. Stage was evaluated according to the FIGO staging. We rectrospectively reviewed the medical chart of these patients.

Treatment. Therapeutic strategies were selected for individual patients. For surgery, total hysterectomy (radical hysterectomy in some patients) and bilateral salpingo-oophorectomy were performed. Pelvic and/or para-aortic lymphadenctomy were performed in some patients. For radiotherapy, the area of external irradiation was established as the entire pelvic region from the closed pore to the L4/5 lumbar vertebrae, with a radiation dose of 2 Gy per treatment (total dose, 50-60 Gy). When the cumulative dose reached 20-30 Gy, external irradiation was combined with high-dose intra-cavity irradiation, with a central shield, at a radiation dose of 5 Gy (total dose, 20-25 Gy). When imaging findings suggested para-aortic lymph node metastases, biopsy was performed. After a definitive diagnosis of metastases was made, the irradiation field was extended to include the para-aortic node. For chemotherapy, eligible patients participated in a phase II clinical study with an in-house protocol that we previously reported, including paclitaxel (PTX)/carboplatin (CBDCA) therapy (Kitagawa R, *et al*, Proc ASCO 22: abs. 5048, 2004) (PTX, 175 mg/m^2, CBDCA AUC5, day 1, every 3 weeks for 6 cycles), and carboplatin (CBDCA)/irinotecan (CPT) therapy (Hori S, *et al*, Proc ASCO 21: abs. 835, 2002) (CBDCA AUC5, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles). For patients with PS of 3, weekly PTX/CBDCA therapy (PTX 80 mg/m^2, CBDCA AUC2, continuous administration for 20 weeks) was administered. In 1 patient with small cell carcinoma, cisplatin (CDDP)/CPT therapy (CDDP, 60 mg/m^2, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles) was administered as postoperative adjuvant therapy.

Best supportive care (BSC) was defined as treatment targeting the relief of symptoms without surgery, radiotherapy or chemotherapy, as described above.

Evaluation. Pretreatment clinical evaluation was repeated before each treatment cycle with the exception of radiography or CT/MRI imaging, which was repeated at least every other treatment cycle. Treatment was continued until disease progression or adverse effects precluded further administration. The response to treatment, in terms of the best response achieved in a given patient, was assessed using standard clinical criteria. A complete response (CR) was defined as the disappearance of all gross evidence of disease for at least 4 weeks. A partial response (PR) was defined as a >50% reduction in the product of perpendicular diameters obtained from the measurement of each lesion, sustained for at least 4 weeks. Progressive disease (PD) was defined as a >50% increase in the product of perpendicular diameters of any lesion documented within 2 months of study entry or the appearance of any new lesion within 8 weeks of study entry. Stable disease (SD) was any condition not meeting any of the above three criteria. Overall survival was measured as the observed length of life from protocol entry to death or (for living patients) date of last contact. Progression-free survival was measured from the date of initiation of protocol to the first progression or death, or to the date of last contact for patients who were alive and progression-free.

Persistent disease was defined as carcinoma at a pelvic site known to be previously involved within 6 months of staging. Recurrent disease was classified as a new tumor in the extrapelvic area or pelvic disease >6 months after staging in a location previously tumor-free. Persistent or recurrent disease was documented by surgical exploration, biopsy or progression on imaging studies. The time of recurrence or death was calculated from the date of original staging. The end of the follow-up period was March 2006.

Statistical analysis. Statistical analysis was performed using SPSS. The impact of clinical and pathologic risk factors on survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using Cox's proportional hazard model. P-values <0.05 were considered significant.

Results

Thirty-six patients were treated between April 1997 and March 2006. Table I shows the patient characteristics. The median age was 54 years. In 34 patients, PS was almost 0, 1 or 2. In the remaining 2 patients, PS was 3. As initial treatment, surgery was performed in 4 patients, radiotherapy in 17, and chemotherapy in 13. BSC was performed in two patients who did not wish to receive aggressive treatment. Histopathologically, 18 patients had squamous cell carcinomas, 16 had adenocarcinomas and 2 had small cell carcinomas. The median primary tumor diameter was 4.1 cm, with a maximum of 7.7 cm. In addition, a bulky mass was detected in 28 patients. In 13 patients, hydronephrosis was noted, with 8 of these having bilateral hydronephrosis. The number of distant metastases was 1 in most patients, but 3 or 4 in some patients. The metastatic lesion sites included the para-aortic node in 7 patients and the main organs in 8 patients. Table II shows the sites of distant metastases (including duplicating patients). In the abdominal cavity, para-aortic lymph node metastases were detected in 18 patients (50%), comprising the highest percentage. In the extraperitoneal region, supraclavian lymph node metastases were detected in 13 patients (36%). Among main organ metastases, liver metastases were detected in 7

Table I. Patient characteristics.

Age (year), median (range)	54 (28-77)
PS 0/1/2/3	5/18/11/2
No. of patients	36
Initial treatment	
Surgery	4
Radiotherapy	17
Chemotherapy	13
Best supportive care	2
Pathology	
Squamous cell carcinoma	18
Adenocarcinoma	16
Small cell carcinoma	2
Primary tumor size (cm), median (range)	4.1 (2.1-7.7)
Bulky mass >4 cm	
Negative	8
Positive	28
Hydronephrosis	
Negative	23
Unilateral	5
Bilateral	8
No. of distant metastases	
1	20
2	13
3	2
4	1
Site of distant metastases	
Para-aortic lymph node only	7
Distant lymph node only	7
Organ metastases only	1
Para-aortic lymph node + Distant lymph node	10
Para-aortic lymph node + Organ metastases	1

Table II. Distant metastases in patients.

Metastatic sites	n (%)
Intra-abdominal metastases	
Para-aortic lymph node	18 (50)
Liver	7 (19)
Spleen	2 (5.5)
Small intestine	1 (2.7)
Extra-abdominal metastases	
Lung	4 (11)
Bone	2 (5.5)
Supraclavicular lymph node	13 (36)
Mediastinal lymph node	2 (5.5)
Inguinal lymph node	2 (5.5)

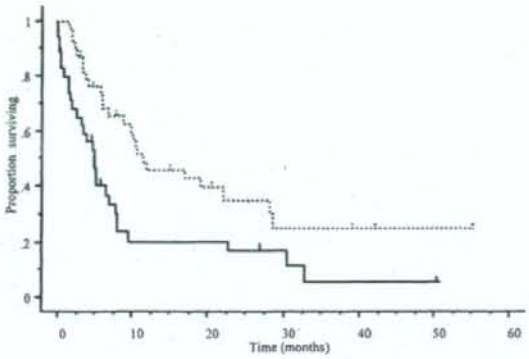


Figure 1. Kaplan-Meier analysis of progression-free survival (solid line) and overall survival (dotted line). Vertical bars indicate censored cases.

Table III. Characteristics of 21 patients with chemotherapy.

	n=21
Indication for therapy	
Initial case	13
Persistent/recurrence case	7
Postoperative case	1
Regimens	
Paclitaxel/carboplatin	9
Irinotecan/carboplatin	9
Weekly paclitaxel/carboplatin	2
Irinotecan/cisplatin	1

patients, comprising the highest percentage, followed by lung metastases in 4 patients. The median progression-free survival and overall survival were 3.8 months and 11.1 months, respectively (Fig. 1).

We examined the effects of chemotherapy on stage IVb cancer (Table III). Chemotherapy was administered to 21 patients, 13 of whom were undergoing initial treatment, 7 of whom had persistent/recurrence, and 1 of whom was undergoing postoperative therapy. The regimens consisted of paclitaxel/carboplatin in 9 patients, irinotecan/carboplatin in 9, weekly paclitaxel/carboplatin in 2, and cisplatin/irinotecan in 1. In 2 patients, including 1 undergoing postoperative adjuvant therapy, chemotherapy was discontinued due to adverse effects. For lesions that could be measured, the response rate was 61.9% (95% CI, 41.1-82.6) including 4 patients with CR and 9 patients with PR (Table IV).

We compared survival in the chemotherapy and non-chemotherapy groups. The median survivals of the chemotherapy and non-chemotherapy groups were 11.1 and 5.1 months, respectively, with a significant difference (p=0.0055) (Fig. 2).

We also compared survival between initial chemotherapy and initial other treatment groups. The median survivals in the initial chemotherapy and initial other treatment groups

Table IV. Response rate of chemotherapy (n=21).

Response (%)					
CR	PR	SD	PD	NE	RR
4	9	4	1	3	61.9%
					(95% CI, 41.1-82.6%)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; RR, response rate.

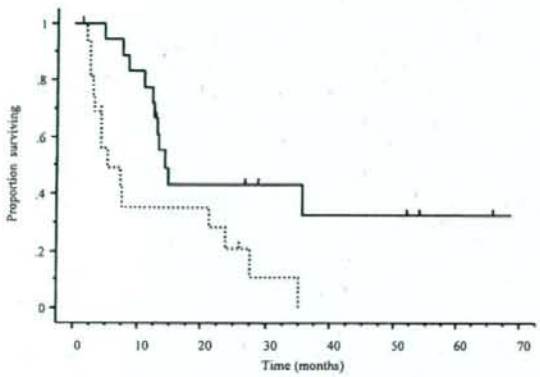


Figure 2. Kaplan-Meier analysis of overall survival according to with/without chemotherapy in stage IVb cervical carcinoma. Chemotherapy group (solid line) is significantly better prognosis (p=0.0055) than non-chemotherapy group (dotted line). Vertical bars indicate censored cases.

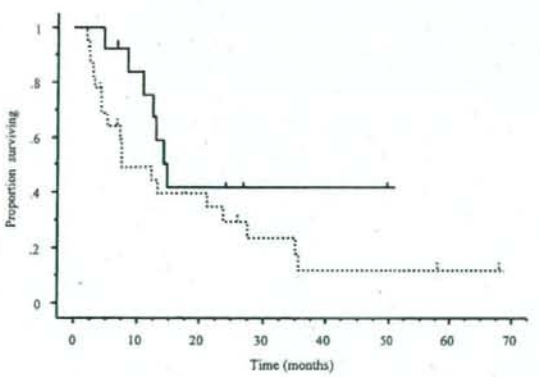


Figure 3. Kaplan-Meier analysis of overall survival according to with/without initial chemotherapy in stage IVb cervical carcinoma. There are no statistical differences (p=0.09) between initial chemotherapy group (solid line) and other initial treatment group (dotted line). Vertical bars indicate censored cases.

were 13.2 and 7.5 months, respectively, but it did not reach statistical significant (p=0.09) (Fig. 3). Two patients treated by chemotherapy alone as an initial treatment have survived

Table V. Prognostic factors of overall survival.

Factor	Univariate P-value	Multivariate P-value	HR	95% CI
Age ≥50	0.171	0.506	1.36	0.54-3.43
PS (0 and 1 vs. 2 and 3)	0.005	0.007	2.64	1.42-4.91
Pathology (SCC vs. non-SCC)	0.638	-	-	-
Organ metastases (0 vs. ≥1)	0.792	-	-	-
No. of distant metastases (1 vs. ≥2)	0.109	0.546	1.22	0.63-2.35
Bulky mass	0.478	-	-	-
Chemotherapy	0.011	0.016	6.03	1.97-18.37

disease-free for 51.8 and 68.6 months, respectively. One patient had stage IVb CC with para-aortic lymph node metastases while the other had stage IVb CC with subclavian lymph node metastases and mediastinal lymph node metastases. Both patients were administered paclitaxel/carboplatin for 6 cycles. After 6 cycles, the primary lesion and metastatic site exhibited complete response.

We analyzed chemotherapy, age, PS, histological type, main organ metastases, number of distant metastases, and bulky masses as prognostic factors. On univariate analysis, poor PS and non-chemotherapy groups were prognostic factors. On multivariate analysis, a poor PS (p=0.007; hazard ratio, 2.64; 95% CI, 1.42-4.91) and non-chemotherapy groups (p=0.016; hazard ratio, 6.03; 95% CI, 1.94-18.37) also affected overall survival (Table V).

Discussion

The prognosis of stage IVb cervical carcinoma is poor in patients with systemic metastases. No treatment has been established. In the NCI-PDQ, it is described that therapeutic strategies for this stage of cancer include palliative radiotherapy, chemotherapy as a regimen designed by a clinical study, and chemotherapy with cisplatin, which has previously been reported (34).

In stage IVb patients with para-aortic lymph node metastasis alone, surgery with postoperative radiotherapy and extended radiotherapy achieved a 5-year survival rate of 50% (30-33), and radical surgery may also be an option. However, since most metastases involve the main organs, it is difficult to control them by local treatment, and chemotherapy is indicated for most patients (4).

Various regimens of chemotherapy for this stage of cancer, including single-agent, have been investigated. In particular, cisplatin has most frequently been employed, and yields the highest response rate as a single-agent. It has therefore been

used as a key drug for more than 20 years (5,8,10-12). However, since the efficacy of cisplatin as a single-agent persists for only 6 months, combination regimens have been administered to improve in the prognosis to an extent exceeding the enhancement of its toxicity. In the 1990s, many phase II clinical studies investigated combination regimens with 2-4 agents including cisplatin. Cisplatin with ifosfamide (IFM) yielded the second highest response rate, and bleomycin (BLM), which has commonly been employed to treat other cancers due to its similar high response rate and low toxicity. The usefulness of IP (IFM + CDDP) (35) and BIP (BLM + IFM + CDDP) (36) regimens has also been examined. Some regimens have achieved a response rate of 60% or higher; however, these regimens for the non-advanced and locally advanced stages are quite toxic and shorten the survival of some patients. In addition, no comparative study has been conducted, and the evaluation of each regimen has been insufficient. In the latter half of the 1990s, combination regimens with new agents were designed, and the need for a standard therapy was emphasized.

Recently, carboplatin (37-39), topotecan (19,20) and paclitaxel (40-42) have also been reported to be tolerable and efficacious. Complete responses have also been observed with topotecan and paclitaxel. However, topotecan has greater toxicity than carboplatin or paclitaxel. Therefore, palliation with single-agent cisplatin, carboplatin, paclitaxel or topotecan is a reasonable approach in patients with recurrent disease. A phase II study evaluating the effectiveness of docetaxel in patients who have persistent or recurrent cervical cancer is ongoing (GOG-0127S).

Cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel (21) and cisplatin/topotecan (22) have been extensively investigated in clinical studies. A randomized phase III study comparing paclitaxel and cisplatin versus cisplatin alone showed that the two-drug combination yielded a higher response rate (36 versus 19%) and improved progression-free survival (4.8 versus 2.8 months; $p<0.001$), although no improvement has been seen in median survival (21). Another randomized phase III GOG study investigated the combination of cisplatin and topotecan versus cisplatin alone for persistent/recurrent cervical cancer. In this study of 294 eligible patients, the topotecan combination regimen was superior to single-agent cisplatin with respect to overall response rate (27 versus 13%; $p=0.004$), progression-free survival (4.6 versus 2.9 months; $p=0.014$), and median survival (9.4 versus 6.5 months; $p=0.017$) (22). A phase II study assessed cisplatin and gemcitabine in patients with advanced, persistent/recurrent cervical cancer; 17 patients were evaluated (43). The response rate was 57% in patients who had not previously received radiotherapy, and there was 1 complete response of 14 months. Paclitaxel and carboplatin have recently been assessed for recurrent or persistent cancer of the cervix; 4 of 15 patients had a complete response and 5 showed a partial response for an overall response rate of 60% (39). The median survival of all 15 patients treated was 17 months (range, 4-39 months). The combination of vinorelbine and cisplatin has also been assessed in 42 patients with recurrent or metastatic cervical cancer; the overall response rate was 48% (44). The GOG is currently conducting a phase III trial (GOG204) to assess 4 cisplatin-doublet regimens in patients with advanced metastatic or recurrent cancer (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisiplatin/vinorelbine).

In our hospital, we conducted an in-house clinical study. For eligible patients, paclitaxel/carboplatin or irinitecan/carboplatin therapy was administered. Adverse effects were within the permissible ranges, and there were no treatment-related deaths, as reported in other studies. Response rate as an end-point was also similar to or exceeded that previously reported, suggesting the usefulness of these treatment options in chemotherapy for cervical carcinoma. In patients with poor PS, weekly paclitaxel/carboplatin therapy was safe. Several reports have indicated that the hematological toxicity of this therapy is lower than that of tri-weekly therapy, and that the therapeutic effects of these two regimens are similar (45,46). Weekly paclitaxel/carboplatin therapy may be useful for treating stage IVb cancer patients with poor PS.

In patient with this stage of cancer, nephropathy is frequent, making cisplatin administration difficult in many cases. Carboplatin can be administered to patients with nephropathy, without hydration. Considering the adverse effects, less toxic agents should be reviewed.

In this study, two patients treated by chemotherapy alone as an initial treatment have survived disease-free for 51.8 and 68.6 months, respectively. For patients with recurrence who desired sequential treatment, chemotherapy was administered when we considered them eligible. Considering that the prognosis was significantly better than that in the non-chemotherapy group, chemotherapeutic intervention may be useful in stage IVb patients who have undergone initial treatment and in those with persistent/recurrent metastases.

Eligible, consenting patients should be enrolled in clinical trials employing new drugs and/or strategies. Since there is as yet no evidence for the curative potential of chemotherapy in cervical cancer and no established survival benefit, and uncertainty exists as to how often response translates into symptom relief ('palliation'), non-protocol therapy should not be encouraged. Nevertheless, for a patient who is ineligible or unwilling to participate in a study but who wants treatment, there may still be an indication for chemotherapy giving 'psychological support' or hope. When such a patient insists on treatment and seeks untested remedies rather than a hospice if orthodox chemotherapy is not offered, single-agent cisplatin or carboplatin may be justified, with due attention being paid to contraindications and the toxic side effects. An interval response assessment and finite period of treatment are indicated. Objective benefit is possible, but not likely.

Prognostic factors for stage IVb cervical carcinoma include PS, age, histological type, main organ metastases, and distant metastases (23-29). In this study, univariate and multivariate analysis revealed that non-chemotherapy and poor PS influenced prognosis. In patients with poor PS, it is difficult to continue treatment, and chemotherapy may exceed cancer control due to systemic disease. However, we can not conclude the efficacy of chemotherapeutic intervention, as this study was a retrospective study and involved only a small number of patients. Previously, surgery and radiotherapy have been selected for this stage of cancer. The results of chemotherapy for initial treatment were similar to those for conventional treatment, suggesting the efficacy of chemotherapy as initial

treatment. However, a randomized comparative study should be conducted to demonstrate its efficacy.

In conclusion, the prognosis of stage IVb cervical carcinoma remains poor. Chemotherapy may improve the survival of patients with stage IVb CC.

Acknowledgments

This work was supported by The Supporting Fund of Obstetrics and Gynecology Kurume University.

References

1. Sasieni PD, Cuzick J and Lynch-Farmery E: Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Coordinating Network for Cervical Screening Working Group. Br J Cancer 73: 1001-1005, 1996.
2. Wong LC, Ngan HY, Cheung AN, Cheng DK, Ng TY and Choy DT: Chemoradiation and adjuvant chemotherapy in cervical cancer. J Clin Oncol 17: 2055-2060, 1999.
3. NCI Clinical Alert Urges New Standard of Care for Invasive Cervical Cancer, URL:http://www.nci.nih.gov/clinicaltrials/developments/cervical-cancer-alert0600.
4. Omura GA: Current status of chemotherapy for cancer of the cervix. Oncology 6: 27-32, 1992.
5. Omura GA: Chemotherapy for stage IVb or recurrent cancer of the uterine cervix. J Natl Cancer Inst Monogr 21: 123-126, 1996.
6. Lea JS, Sheets EE, Wenham RM, Duska LR, Coleman RL, Miller DS and Schorge JO: Stage IIB-IVB cervical adenocarcinoma: prognostic factors and survival. Gynecol Oncol 84: 115-119, 2002.
7. Cleeland CS: Pain assessment in cancer. In: Effect of Cancer on Quality of Life. Osoba D (ed). CRC Press, Boston, MA, pp293-306, 1991.
8. Thigpen T: The role of chemotherapy in the management of carcinoma of the cervix. Cancer J 9: 425-432, 2003.
9. Thigpen JT, Vance R, Puneky L and Khansur T: Chemotherapy as a palliative treatment in carcinoma of the uterine cervix. Semin Oncol 22: 16-24, 1995.
10. Thigpen T, Shingleton H, Homesley H, Lagasse L and Blessing J: Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II trial of the Gynecologic Oncology Group. Cancer 48: 899-903, 1981.
11. Bonomi P, Blessing J, Stehman FB, DiSaia PJ, Walton L and Major FJ: Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 3: 1079-1085, 1985.
12. Thigpen JT, Blessing JA, DiSaia PJ, Fowler WC Jr and Hatch KD: A randomized comparison of rapid versus prolonged (24 h) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. Gynecol Oncol 32: 198-202, 1989.
13. Coleman RE, Harper PG, Gallagher C, *et al*: A phase II study of ifosfamide in advanced and relapsed carcinoma of the cervix. Cancer Chemother Pharmacol 18: 280-283, 1986.
14. Meanwell CA, Mould JJ, Blackledge G, Lawton FG, Stuart NS, Kavanagh JJ, Latief TN, Spooner D and Chetiyawardana AD: Phase II study of ifosfamide in cervical cancer. Cancer Treat Rep 70: 727-730, 1986.
15. Sutton GP, Blessing JA, McGuire WP, Patton T and Look KY: Phase II trial of ifosfamide and mesna in patients with advanced or recurrent squamous carcinoma of the cervix who had never received chemotherapy: a Gynecologic Oncology Group study. Am J Obstet Gynecol 168: 805-807, 1993.
16. McGuire WP, Blessing JA, Moore DH, Lentz SS and Photopulos G: Paclitaxel has moderate activity in squamous cervix cancer: a Gynecologic Oncology Group study. J Clin Oncol 14: 792-795, 1996.
17. Morris M, Brader KR, Levenback C, Burke TW, Atkinson EN, Scott WR and Gershenson DM: Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix. J Clin Oncol 16: 1094-1098, 1998.
18. Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB and Menzin A: Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 92: 639-643, 2004.
19. Bookman MA, Blessing JA, Hanjani P, Herzog TJ and Anderson WA: Topotecan in squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 77: 446-449, 2000.
20. Muderspach LI, Blessing JA, Levenback C and Moore JL Jr: A phase II study of topotecan in patients with squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 81: 213-215, 2001.
21. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF and Rocereto TF: Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 22: 3113-3119, 2004.
22. Long HJ III, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA and Fiorica JV: Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol 23: 4626-4633, 2005.
23. Leath CA III, Straughn M Jr, Kirby TO, Huggins A, Partridge EE and Parham GP: Predictors of outcomes for women with cervical carcinoma. Gynecol Oncol 99: 432-436, 2005.
24. Kastritis E, Bamias A, Efstathiou E, Gika D, Bozas G, Zorzou P, Sarris K, Papadimitrou C and Dimopoulos MA: The outcome of advanced or recurrent non-squamous carcinoma of the uterine cervix after platinum-based combination chemotherapy. Gynecol Oncol 99: 376-382, 2005.
25. Sommers GM, Grigsby PW, Perez CA, Camel HM, Kao MS, Galakatos AE and Lockett MA: Outcome of recurrent cervical carcinoma following definitive irradiation. Gynecol Oncol 35: 150-155, 1989.
26. Yamamoto K, Yoshikawa H, Shiromizu K, Saito T, Kuzuya K, Tsunematsu R and Kamura T: Pulmonary metastasectomy for uterine cervical: a multivariate analysis. Ann Thorac Surg 77: 1179-1182, 2004.
27. Brader KR, Morris M, Levenback C, Levy L, Lucas KR and Gershenson DM: Chemotherapy for cervical carcinoma: factors determining response and implications for clinical trial design. J Clin Oncol 16: 1879-1884, 1998.
28. Potter ME, Hatch KD, Potter NY, Shingleton HM and Baker VV: Factors affecting the response of recurrent squamous cell carcinoma of the cervix to cisplatin. Cancer 63: 1283-1286, 1989.
29. Seki M, Nakagawa K, Tsuchiya S, Matsubara T, Kinoshita I, Weng SY and Tsuchiya E: Surgical treatment of pulmonary metastases from uterine cervical cancer. Operation method by lung tumor size. J Thorac Cardiovasc Surg 104: 876-881, 1992.
30. Lovecchio JL, Averette HE, Donato D and Bell J: Five-year survival of patients with periaortic nodal metastases in clinical stage IB and IIA cervical carcinoma. Gynecol Oncol 34: 43-45, 1989.
31. Varia MA, Bundy BN, Deppe G, Mannel R, Averette HE, Rose PG and Connelly P: Cervical carcinoma metastatic to para-aortic nodes: extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: a Gynecologic Oncology Group Study. Int J Radiat Oncol Biol Phys 42: 1015-1023, 1998.
32. Grigsby PW, Lu JD, Mutch DG, Kim RY and Eifel PJ: Twice-daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of the cervix with positive para-aortic lymph nodes: phase II study of the RTOG 92-10. Int J Radiat Oncol Biol Phys 41: 817-822, 1998.
33. Grigsby PW, Heydon K, Mutch DG, Kim RY and Eifel P: Long-term follow-up RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. Int J Radiat Oncol Biol Phys 51: 982-987, 2001.
34. NCI Cancer Topics Cervical Cancer (PDQ®): Treatment URL: http://www.nci.nih.gov/cancertopics/pdq/treatment/health-professional/.
35. Omura GA, Blessing JA, Vaccarello L, Beman ML, Clarke-Pearson DL, Mutch DG and Anderson B: Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. J Clin Oncol 15: 165-171, 1997.
36. Bloss JD, Blessing JA, Behrens BC, Mannel RS, Rader JS, Sood AK, Markman M and Benda J: Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. J Clin Oncol 20: 1832-1837, 2002.

37. McGuire WP, Arseneau J, Blessing JA, DiSaia PJ, Hatch KD, Given FT Jr, Teng NN and Creasman WT: A randomized comparative trial of carboplatin and iproplatin in advanced squamous carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol 7: 1462-1468, 1989.
38. Higgins RV, Naumann WR, Hall JB and Haake M: Concurrent carboplatin with pelvic radiation therapy in the primary treatment of the cervix cancer. Gynecol Oncol 89: 499-503, 2003.
39. Sit AS, Kelley JL, Gallion HH, Kunschner AJ and Edwards RP: Paclitaxel and carboplatin for recurrent or persistent cancer of the cervix. Cancer Invest 22: 368-373, 2004.
40. Papadimitriou CA, Sarris K, Moulopoulos LA, Fountzilas G, Anagnostpoulos A, Voulgaris Z, Gika D, Giannakoulis N, Diakomanolis E and Dimopoulos MA: Phase II trial of paclitaxel and cisplatin in metastatic and recurrent carcinoma of the uterine cervix. J Clin Oncol 17: 761-766, 1999.
41. Rose PG, Blessing JA, Gershenson DM and McGehee R: Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 17: 2676-2680, 1999.
42. Tinker AV, Bhagat K, Swenerton KD and Hoskins PJ: Carboplatin and paclitaxel for advanced and recurrent cervical carcinoma: The British Columbia Cancer Agency experience. Gynecol Oncol 98: 54-58, 2005.
43. Burnett AF, Roman LD, Garcia AA, Muderspach LI, Brader KR and Morrow CP: A phase II study of gemcitabine and cisplatin in patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix. Gynecol Oncol 76: 63-66, 2006.
44. Gebbia V, Caruso M, Testa A, Mauceri G, Borsellino N, Chiarenza M, Pizzardi N and Palmeri S: Vinorelbine and cisplatin for the treatment of recurrent and/or metastatic carcinoma of the uterine cervix. Oncology 63: 31-37, 2002.
45. Schuette W, Blankenburg T, Guschall W, Dittrich I, Schroeder M, Schweisfurth H, Chemaissani A, Schumann C, Dickgreber N, Appel T and Ukena D: Multicenter randomized trial for stage IIIb/IV non-small-cell lung cancer using every-3-weeks versus weekly paclitaxel/carboplatin. Clin Lung Cancer 7: 338-343, 2006.
46. Van der Burg ME, van der Gaast A, Vergote I, Burger CW, van Doorn HC, De Wit R, Stoter G and Verweij J. What is the role of dose-dense therapy? Int J Gynecol Cancer 15 (Suppl. 3): S233-S240, 2005.

ARTICLE IN PRESS

Available online at www.sciencedirect.com

ScienceDirect

ELSEVIER

Pathology – Research and Practice ▮ (▮▮▮▮) ▮▮▮–▮▮▮

PATHOLOGY
RESEARCH AND PRACTICE

www.elsevier.de/prp

ORIGINAL ARTICLE

Clinicopathological significance of cervical adenocarcinoma associated with lobular endocervical glandular hyperplasia

Shin Nishio[a,b,*], Hitoshi Tsuda[a,c], Naoki Fujiyoshi[b], Shun-Ichiro Ota[b], Kimio Ushijima[b], Yuko Sasajima[c], Takahiro Kasamatsu[d], Toshiharu Kamura[b], Osamu Matsubara[a]

[a]*Department of Basic Pathology, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan*
[b]*Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan*
[c]*Pathology Section, Clinical Laboratory Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*
[d]*Department of Gynecologic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*

Received 2 June 2008; received in revised form 29 November 2008; accepted 2 December 2008

Abstract

Lobular endocervical glandular hyperplasia (LEGH) is usually assumed to be a benign tumor-like lesion of the glands of the uterine cervix. However, LEGH has been associated with obvious cervical adenocarcinoma. The clinicopathological significance of coexistence of LEGH with adenocarcinoma remains unclear. We microscopically examined the presence or absence of LEGH components in 95 stage Ib cervical adenocarcinomas. Gastric mucin was detected with the use of clone HIK1083. Associations of the coexistence of LEGH components with clinicopathological variables were analyzed. LEGH components were present in 16 cases (16.8%). Gastric mucin was positive in all 16 LEGH components, as compared with only 6 of the 95 adenocarcinoma components. Of the 16 adenocarcinomas with LEGH components, 15 were well-differentiated mucinous adenocarcinomas, and one was poorly differentiated adenocarcinoma. The mortality rate of tumor recurrence was 25% (4 of 16) in patients whose tumors had LEGH components, and 21.5% (17 of 79) in those whose tumors had no LEGH components. There was no significant difference in survival. Early cervical adenocarcinoma was relatively frequently associated with LEGH components. LEGH may be one of the factors related to the development of cervical adenocarcinoma, but adenocarcinoma with LEGH components does not necessarily develop into a highly aggressive "adenoma malignum."

Keywords: LEGH; Cervical adenocarcinoma; Prognostic factor

Introduction

Adenocarcinoma is detected in approximately 10% of all uterine cervix cancers. Among these lesions, minimal deviation adenocarcinoma (MDA), initially described by Gusserow in 1870, is characterized by a watery vaginal discharge clinically, an extremely

*Corresponding author at: Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan. Tel.: +81 942317573; fax: +81 942350238.
E-mail address: shinshin@med.kurume-u.ac.jp (S. Nishio).

0344-0338/$ - see front matter © 2008 Elsevier GmbH. All rights reserved.
doi:10.1016/j.prp.2008.12.002

well-differentiated adenocarcinoma histologically, and high-grade malignancy biologically [1–3,15]. Indeed, MDA is usually associated with metastasis and dissemination at the time of diagnosis and poorly responds to treatment, resulting in poor outcomes.

In 1999, Nucci et al. [13] proposed a new disease entity called lobular endocervical glandular hyperplasia (LEGH) to describe a benign disease closely akin to MDA. Of the 13 reported cases, 4 had watery vaginal discharge, a characteristic symptom of MDA. Their report clearly distinguished LEGH from MDA: all affected glands appeared to be benign in LEGH, whereas MDA consistently had some regions that were clearly cancerous within the affected area. Subsequently, it was questioned whether LEGH could be accurately differentiated from MDA. However, recent studies have provided compelling evidence that MDA can be clearly distinguished from LEGH, and that LEGH and MDA are distinct disease entities [5,9,16,17].

The natural history of LEGH is still poorly understood. Some investigators have suggested that LEGH is a precancerous lesion, based on the occasional coexistence of LEGH and obvious adenocarcinoma [8,10]. However, it is not known how often adenocarcinoma develops from LEGH, and the biological characteristics of such cases need to be clarified. The present study was designed to clarify the frequency and the clinicopathological significance of LEGH components in early (stage Ib) cervical adenocarcinoma.

Patients and methods

Patients

The study group comprised 95 patients with stage Ib cervical adenocarcinoma (Ib1: 65 cases, Ib2: 30 cases) according to the diagnostic criteria proposed by the International Federation of Gynaecology and Obstetrics (FIGO). All cases were diagnosed and treated surgically at the Kurume University Hospital and National Cancer Center Hospital between 1989 and 2004. Postoperative radiotherapy was administered to patients who had lymph node metastasis, lymphovascular invasion, a tumor-invasion depth of more than two thirds (>2/3 invasion) of the cervical stroma, or poorly differentiated tumors. The resected tissue specimens were processed into formalin-fixed, paraffin-embedded sections for pathological examination, and sections containing a representative part of the tumor were studied.

Table 1 summarizes the characteristics of the adenocarcinomas studied. The histopathological factors suggesting high-grade malignancy were poor differentiation in 9 cases, a longitudinal tumor size of >4 cm in 30 cases, >2/3 invasion of the cervical stroma in 44 cases, lymphovascular invasion in 48 cases, and lymph node metastasis in 20 cases. The histological subtypes of adenocarcinoma were endocervical-type mucinous in 60 cases, endometrioid in 20 cases, intestinal-type mucinous in 10 cases, serous in 3 cases, and clear cell in 2 cases.

Table 1. Characteristics of 95 patients with stage Ib cervical adenocarcinoma.

Age (years) median (range)	47 (28–74)
<35	15
35–50	44
⩾50	36
FIGO stage	
Ib1	65
Ib2	30
Tumor diameter (mm) median (range)	25 (4–118)
Depth of stromal invasion (mm) median (range)	10 (1.5–25)
Differentiation	
Well	82
Moderate	4
Poorly	9
Histopathology	
Endocervical-type mucinous	60
Intestinal-type mucinous	10
Endometrioid type	20
Serous	3
Clear cell	2

Histopathological evaluation

The presence or absence of LEGH was judged by two histopathologists (SN and HT). Cases that met the following criteria on examination of sections stained with hematoxylin and eosin (HE) were classified as adenocarcinoma with LEGH components: (1) the tumor is composed of a distinct area of LEGH and one area of obvious adenocarcinoma, e.g., endocervical-type mucinous, intestinal-type mucinous, endometrioid, serous, or clear cell adenocarcinoma. (2) The LEGH component shows the following characteristics: glands are arranged in certain directions and grow towards the musculature in a compressive manner while retaining the lobular structure; growth of the cervical glands is associated with scant evidence of nuclear atypia; glands assume a circular or oval form, with a regular margin; and clear demarcation from the surrounding musculature and no evidence of stromal invasion [9,13]. (3) The LEGH component shows the following characteristics: cells

Please cite this article as: S. Nishio, et al., Clinicopathological significance of cervical adenocarcinoma associated with lobular endocervical glandular hyperplasia, Pathol. Res. Practice (2009), doi:10.1016/j.prp.2008.12.002

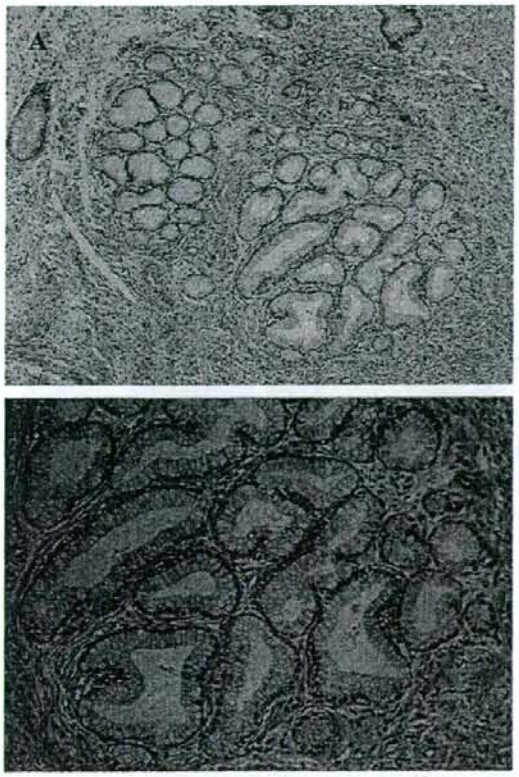


Fig. 1. Histological findings of the lobular endocervical glandular hyperplasia (LEGH) component in obvious cervical adenocarcinoma. (A) Lobular proliferation of small-to-medium-sized rounded glands surrounding larger glands. (B) Hyperplastic glandular lesions are arranged in a lobular fashion, without desmoplastic stomal reactions. These features are identical to those of pure LEGH. HE stain. Original magnification: (A) × 100; and (B) × 200.

with small nuclei (circular or oval) relatively uniform in size; nuclear chromatin not dense; minimal or no nucleoli; basally located nuclei, with no stratification; and no visible evidence of nuclear division or apoptosis [9,13] (Fig. 1).

Immunohistochemistry

Tissue blocks were cut into 4-μm-thick sections, mounted on silane-coated glass slides, and studied immunohistochemically using the following primary monoclonal antibodies and dilutions: clone HIK1083, recognizing gastric mucin (1:200, Kanto Kagaku, Tokyo, Japan) [6,7,18], and anti-$p16^{INK4a}$ (clone sc-56330, 1:500, Santa Cruz, CA) [4,19]. The tissue sections were deparaffinized, subjected to antigen retrieval by autoclaving in sodium citrate buffer (pH 6.0) for 15 min at 121 °C for clone HIK1083 and anti-$p16^{INK4a}$, and allowed to cool at room temperature. Endogenous peroxidase was blocked with 5% hydrogen peroxide. Non-specific staining was blocked with 2% normal swine serum (Dako, Grostrup, Denmark). The slides were incubated with primary antibodies overnight at 4 °C and then allowed to react with a dextran polymer reagent mixed with secondary antibodies and peroxidase (Envision Plus; Dako) for 1 h at room temperature. Specific antigen–antibody reactions were visualized with 0.2% diaminobenzidine tetrahydrochloride (Muto Chemical, Tokyo, Japan) and hydrogen peroxide. Counterstaining was performed using Mayer's hematoxylin. For HIK1083, cases showing any degree of cytoplasmic immunoreactivity were judged as positive (Fig. 2).

On the basis of the literature [4,19], $p16^{INK4a}$ was regarded as nuclear immunostaining and was classified

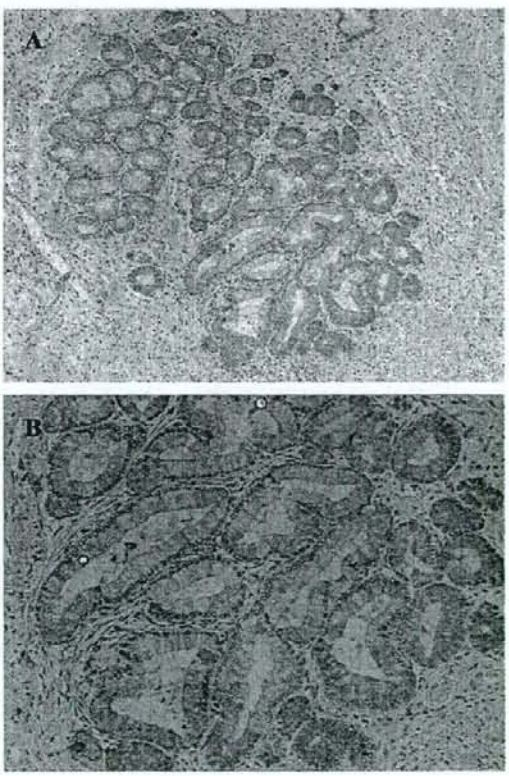


Fig. 2. Gastric mucin expression in lobular endocervical glandular hyperplasia (LEGH) components, detected on immunostaining with HIK1083. (A, B) Gastric mucin is diffusely positive in the cytoplasm of the LEGH component. Immunoperoxidase stain. Original magnification: (A) × 100; (B) × 200.

Please cite this article as: S. Nishio, et al., Clinicopathological significance of cervical adenocarcinoma associated with lobular endocervical glandular hyperplasia, Pathol. Res. Practice (2009), doi:10.1016/j.prp.2008.12.002

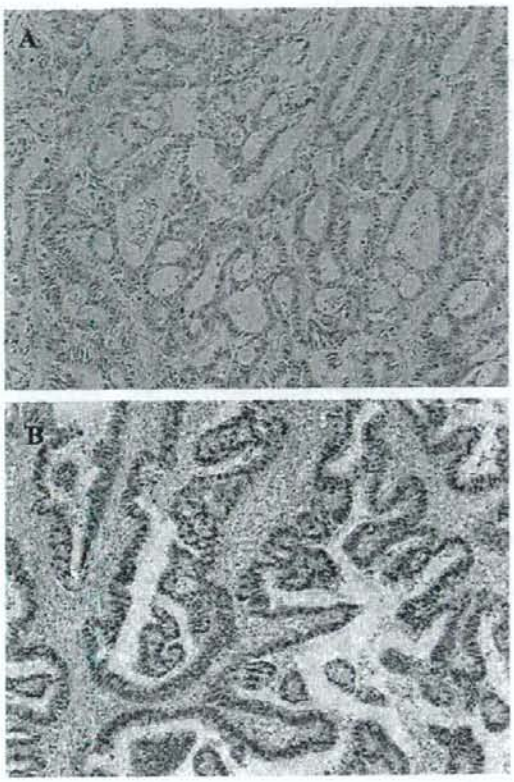


Fig. 3. $p16^{INK4a}$ expression in obvious cervical adenocarcinoma. (A) More than 10% of carcinoma cells show weak nuclear immunoreactivity, scored as 1+. (B) More than 10% of carcinoma cells show strong nuclear immunoreactivity, scored as 3+. Immunoperoxidase stain. Original magnification: (A) ×100; (B) ×200.

as +1 if less than 1% of the cells showed positive staining, as +2 if 1–10% of the cells showed positive staining, and as +3 if more than 10% of the cells showed positive staining. Scores of 0, 1+, or 2+ were defined as negative staining, whereas a score of 3+ was defined as positive staining.

As positive controls, we used gastric mucosal tissue for HIK1083 and a case of squamous cell carcinoma for $p16^{INK4a}$. As negative controls, the primary antibodies were omitted from the respective reactions (Fig. 3).

Statistical analysis

Correlations between the presence of LEGH components and clinicopathological characteristics were analyzed using the chi-square test or Fisher's exact test. Cumulative survival curves were drawn by the Kaplan–Meier method, and differences between curves were tested by the log-rank test. Prognostic significance was computed by univariate and multivariate analyses with a Cox proportional-hazards model. Independent effects of the following variables were assessed by multivariate analysis: presence/absence of LEGH, $p16^{INK4a}$, tumor differentiation, tumor size, invasion depth of the cervical stroma, lymphovascular invasion, and lymph node metastasis.

Results

The patients' characteristics are shown in Table 1. The median follow-up time was 66.3 months. At the time of analysis, tumor recurrence had been diagnosed in 21 patients, and 19 had died. Microscopic examination of HE-stained specimens revealed the presence of LEGH in 16 cases (16.8%). LEGH was localized to defined area(s) and did not intermingle with obvious adenocarcinoma components (Fig. 4). The mean maximal diameter of the LEGH component was 27 mm, ranging from 8 to 42 mm (standard deviation 8.01). The ratios of the area of the LEGH component in the 16 tumors ranged from 1% to 80%, with an average of 18.6% and a standard deviation of 24.92. The $p16^{INK4a}$ scores were 0, 1+, 2+, and 3+ in 13, 12, 10, and 63 cases, respectively. When classified according to the criteria used in this study, 63 cases (66.3%) with components of adenocarcinoma were positive for $p16^{INK4a}$. Staining for $p16^{INK4a}$ was positive in 5 (31.2%) of the 16 cases with LEGH components and in 58 (73.4%) of the 79 cases without LEGH components. Of the 16 cases with LEGH components, the cancer component was well-differentiated adenocarcinoma in 15 and poorly differentiated adenocarcinoma in one. The presence of LEGH components correlated with

Fig. 4. Histological findings of cervical adenocarcinoma. Apparent cellular atypia (left upper side) is seen in carcinoma cells, and atypical small glands (right lower side) are part of LEGH. Original magnification: ×20.

Please cite this article as: S. Nishio, et al., Clinicopathological significance of cervical adenocarcinoma associated with lobular endocervical glandular hyperplasia, Pathol. Res. Practice (2009), doi:10.1016/j.prp.2008.12.002

Table 2. Clinicopathological characteristics of 95 stage Ib cervical adenocarcinomas associated with or without lobular endocervical glandular hyperplasia (LEGH) components.

Variable	No. of patients (%)			*P* value
	Total	LEGH component		
		Present	Absent	
Patient age (years old)				
<50	40	8	32	0.15
≥50	55	8	47	
$p16^{INK4a}$				
Positive	63	5	58	0.026
Negative	32	11	21	
Maximal tumor diameter (cm)				
<4.0	65	10	55	0.56
≥4.0	30	6	24	
Cervical stromal invasion				
<2/3 in depth	51	9	42	0.99
≥2/3 in depth	44	7	37	
Lymphovascular space invasion				
Negative	47	7	30	0.78
Positive	48	9	39	
Lymph node metastasis				
Negative	75	13	62	0.99
Positive	20	3	17	
Differentiation of adenocarcinoma component				
Well/moderate	86	15	71	0.99
Poorly	9	1	8	
Histological type of adenocarcinoma component				
Endocervical/intestinal-type	79	16	63	0.048
Other histological type	16	0	16	

$p16^{INK4a}$ ($P = 0.026$) and histological type ($P = 0.048$), respectively (Table 2).

In all 16 cases with LEGH components, immunoreactivity with clone HIK1083 was positive in the LEGH component. In 7 cases, HIK1083 immunoreactivity was also positive in the adenocarcinoma component. In 72 cases without LEGH components, immunoreactivity to HIK1083 was negative in the adenocarcinoma component.

In the study group as a whole, median disease-free survival was 61 months, and median overall survival was 62.1 months. Of the 16 patients who had cervical adenocarcinoma with LEGH, 4 died of tumor recurrence, and the remaining 12 were alive without recurrence. Of the 79 patients who had cervical adenocarcinoma without LEGH, 17 died. The survival curves did not differ significantly according to the presence or absence of LEGH.

Univariate analyses of prognostic factors potentially related to OS revealed that the following factors were associated with poorer clinical outcome: tumor size of >4 cm ($P = 0.0002$), >2/3 invasion of the cervical stroma ($P = 0.0052$), lymphovascular invasion ($P = 0.0018$), lymph node metastasis ($P < 0.0001$), and poor differentiation ($P = 0.039$). In a multivariate analysis, including those five factors as well as the presence of LEGH and $p16^{INK4a}$, lymph node metastasis ($P = 0.0018$, hazard ratio: 8.45, 95% confidence interval: 2.21–32.3) and poor differentiation ($P = 0.0049$, hazard ratio: 5.74, 95% confidence interval: 1.33–24.7) were associated with poor outcomes (Table 3). The presence/absence of LEGH was not an independent prognostic indicator.

Discussion

Several cases of adenocarcinoma in association with LEGH have been reported [8,10]. Kondo et al. [8] analyzed 4 cases of endocervical adenocarcinoma coexisting with LEGH. In our study, a LEGH component was detected in a relative percentage (16.8%) of stage Ib cervical adenocarcinomas. The LEGH component was contiguous with the adenocarcinoma component and comprised part of the tumor. However, the LEGH and adenocarcinoma components were sharply demarcated.

The coexistence of LEGH and adenocarcinoma in a tumor may arise through two mechanisms: one possibility is that adenocarcinoma develops from LEGH in a multistep manner. The relatively frequent coexistence of LEGH components and stage Ib cervical adenocarcinoma components in the same tumor supports the mechanism of LEGH giving rise to cervical adenocarcinoma. However, many cases of LEGH grow into large tumors without malignant components. The relative risk of LEGH as a precancerous lesion thus remains unclear.

The other mechanism is that the adenocarcinoma component arises in the vicinity of LEGH, where common environmental factors promote the development of both LEGH and adenocarcinoma. However, such environmental factors have yet to be identified. In cervical cancer, human papillomavirus (HPV) infection induces $p16^{INK4a}$ expression [12]. LEGH has been shown to be associated with $p16^{INK4a}$ expression, but

Please cite this article as: S. Nishio, et al., Clinicopathological significance of cervical adenocarcinoma associated with lobular endocervical glandular hyperplasia, Pathol. Res. Practice (2009), doi:10.1016/j.prp.2008.12.002

Table 3. Impact of variables on overall survival of patients with stage Ib cervical adenocarcinoma, computed by univariate and multivariate analyses.

Factor	Univariate	Multivariate		
	P value	Hazard ratio	95%CI	*P* value
LEGH component (absent vs. present)	0.96	1.95	0.47–8.08	0.35
$p16^{INK4a}$ (positive vs. negative)	0.14	0.47	0.14–1.52	0.20
Tumor diameter (≥4 cm vs. <4 cm)	0.0002	1.91	0.55–6.57	0.30
Cervical stromal invasion (≥2/3 vs. <2/3)	0.0052	1.82	0.40–8.32	0.43
Lymphovascular invasion (positive vs. negative)	0.0018	1.62	0.27–9.69	0.59
Lymph node metastasis (positive vs. negative)	<0.0001	8.45	2.21–32.3	0.0018
Tumor differentiation (poorly vs. well/moderate)	0.049	5.74	1.33–24.7	0.0189

LEGH, lobular endocervical glandular hyperplasia; CI, confidence interval.

not with HPV [4,19]. In our series, $p16^{INK4a}$ expression in the adenocarcinoma component correlated with the presence of an LEGH component.

Before LEGH became an established clinical entity, adenocarcinoma with LEGH components might have been included in MDA, because the LEGH component was believed to constitute malignant glands. In our previous studies, both true MDA and adenocarcinoma with LEGH components were included in MDA [5,17]. True MDA, extremely well-differentiated mucinous adenocarcinoma, is composed mainly of well-formed glands resembling LEGH. Foci of obvious adenocarcinoma are sparsely distributed among the LEGH-like glands and the tumor infiltrates into the cervical stroma [5].

The 16 cases of adenocarcinoma with LEGH components in the present study were stage Ib cases, and tumor extension was limited to the uterine cervix. In contrast, MDA is usually a widespread lesion, with a mean maximal tumor diameter of 62 mm (range 37–110 mm) in 6 cases and extension to the uterine corpus and vagina [14]. After surgery, the clinical outcomes of patients with MDA were poor, whereas the clinical outcomes of adenocarcinoma with LEGH components were slightly better than those of adenocarcinoma without LEGH components. These findings suggest that LEGH-associated cervical adenocarcinoma could differ from MDA with respect to the biological aggressiveness of tumor cells.

In our study, the area of LEGH components associated with adenocarcinoma showed an immunoreactivity pattern to HIK1083 that was identical to that of pure LEGH [6,7,8]. Therefore, the mucin profile in the LEGH components of our 16 cases of adenocarcinoma might be consistent with that of pure LEGH.

Mikami et al. attempted to differentiate LEGH and MDA on the basis of immunohistochemical properties of stromal cells [11]. Their findings suggested that MDA is characterized by positive immunoreactivity of stromal cells to alpha-smooth muscle actin and by weak or no response to estrogen receptor. Perhaps LEGH can be distinguished from MDA on the basis of these properties [11].

In conclusion, our study showed that early cervical adenocarcinomas were relatively frequently associated with LEGH. Cervical adenocarcinomas with LEGH components were almost always well-differentiated tumors and had no significantly better clinical outcomes than cervical adenocarcinomas without LEGH. Our findings suggested that LEGH may serve as a basis for the development of cervical adenocarcinoma, but obvious adenocarcinomas with LEGH components appear to differ from MDA because the former is not destined to develop into a highly aggressive "adenoma malignum."

Acknowledgment

This work was supported by The Supporting Fund of Obstetrics and Gynecology, Kurume University.

References

[1] P.F. Caminski, H.J. Norris, Minimal deviation carcinoma (adenoma malignum) of the cervix, Int. J. Gynecol. Pathol. 2 (1983) 141–152.
[2] C.B. Gilks, R.H. Young, P. Aguire, R.A. DeLellis, R.E. Scully, Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunochemical analysis of 26 cases, Am. J. Surg. Pathol. 13 (1989) 717–729.
[3] A.L.S. Gusserow, Über sarcome des uterus, Arch. J. Gynaekol. 1 (1870) 240–251.
[4] A. Hashi, J.Y. Xu, T. Kondo, K. Hashi, T. Yuminamochi, M. Nara, S. Murata, R. Katoh, K. Hoshi, p16INK4a Overexpression independent of human papillomavirus infection in lobular endcervical glandular hyperplasia, Int. J. Gynecol. Pathol. 25 (2006) 187–194.

Please cite this article as: S. Nishio, et al., Clinicopathological significance of cervical adenocarcinoma associated with lobular endocervical glandular hyperplasia, Pathol. Res. Practice (2009), doi:10.1016/j.prp.2008.12.002

[5] I. Hayashi, H. Tsuda, T. Shimoda, A. Maeshima, T. Kasamatsu, T. Yamada, R. Tsunematsu, Difference in cytoplasmic localization pattern of neutral mucin among lobular endocervical glandular hyperplasia, adenoma malignum, and common adenocarcinoma of the uterine cervix, Virchows Arch. 443 (2003) 752–760.
[6] K. Ishii, N. Hosaka, T. Toki, M. Momose, E. Hidaka, S. Tsuchiya, T. Katsuyama, A new view of the so-called adenoma malignum of the uterine cervix, Virchows Arch. 432 (1998) 315–322.
[7] K. Ishii, T. Katsuyama, H. Ota, T. Watanabe, I. Matsuyama, S. Tsuchiya, T. Shiozawa, T. Toki, Cytologic and cytochemical features of adenoma malignum of the uterine cervix, Cancer 87 (1999) 245–253.
[8] T. Kondo, A. Hashi, S. Murata, T. Nakazawa, T. Yuminamochi, M. Nara, K. Hoshi, R. Katoh, Endocervical adenocarcinomas associated with lobular endocervical glandular hyperplasia: a report of four cases with histochemical and immunohistochemical analyses, Mod. Pathol. 18 (2005) 1199–1210.
[9] Y. Mikami, S. Hata, J. Melamed, K. Fujiwara, Lobular endocervical glandular hyperplasia is a metaplastic process with a pyloric gland phenotype, Histopathology 39 (2001) 364–372.
[10] Y. Mikami, T. Kiyokawa, S. Hata, K. Fujiwara, T. Moriya, H. Sasano, T. Manabe, J. Akahira, K. Ito, T. Tase, N. Yaegashi, I. Sato, H. Tateno, H. Naganuma, Gastrointestinal immunophenotype in adenocarcinoma of the uterine cervix and related glandular lesions: a possible link between lobular endocervical glandular hyperplasia/pyloric gland metaplasia and 'adenoma malignum', Mod. Pathol. 17 (2004) 962–972.
[11] Y. Mikami, T. Kiyokawa, T. Moriya, H. Sasano, Immunophenotypic alteration of the stromal component in minimal deviation adenocarcinoma (adenoma malignum) and endocervical glandular hyperplasia: a study using oestrogen receptor and α-smooth muscle actin double immunostaining, Histopathology 46 (2005) 130–136.
[12] N. Missaoui, S. Hmissa, L. Frappart, A. Trabelsi, A. Ben Abdelkader, C. Traore, M. Mokni, M.T. Yaecoubi, S. Korbi, p16INK4A overexpression and HPV infection in uterine cervix adenocarcinoma, Virchows Arch. 448 (2006) 597–603.
[13] M.R. Nucci, P.B. Clement, R.H. Young, Lobular endocervical glandular hyperplasia, not otherwise specified: a clinicopathologic analysis of thirteen cases of a distinctive pseudoneoplastic lesion and comparison with fourteen cases of adenoma malignum, Am. J. Surg. Pathol. 23 (1999) 866–891.
[14] Y. Sasajima, Y. Mikami, T. Kaku, T. Kiyokawa, Y. Ohishi, T. Hamada, T. Sasaki, H. Fujita, T. Moriya, T. Kasamatsu, H. Tsuda, Gross features of lobular endocervical glandular hyperplasia in comparison with minimal-deviation adenocarcinoma and stage Ib adenocarcinoma of the uterine cervix, Histopathology 53 (2008) 487–490.
[15] S.G. Silverberg, G. Hurt, Minimal deviation adenocarcinoma (adenoma malignum) of the cervix. A reappraisal, Am. J. Obstet. Gynecol. 121 (1975) 971–975.
[16] H. Tsuda, Y. Mikami, T. Kaku, F. Akiyama, T. Hasegawa, S. Okada, I. Hayashi, T. Kasamatsu, Interobserver variation in the diagnosis of adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix, Pathol. Int. 53 (2003) 440–449.
[17] H. Tsuda, Y. Mikami, T. Kaku, T. Hasegawa, F. Akiyama, Y. Ohishi, Y. Sasajima, T. Kasamatsu, Reproducible and clinically meaningful differential diagnosis is possible between lobular endocervical glandular hyperplasia and 'adenoma malignum' based on common histopathological criteria, Pathol. Int. 55 (2005) 412–418.
[18] K. Utsugi, Y. Hirai, N. Takeshima, F. Akiyama, S. Sakurai, K. Hasumi, Utility of the monoclonal antibody HIK1083 in the diagnosis of the adenoma malignum of the uterine cervix, Gynecol. Oncol. 75 (1999) 345–348.
[19] J.Y. Xu, A. Hashi, T. Kondo, T. Yuminamochi, M. Nara, K. Hashi, Absence of human papillomavirus infection in minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia, Int. J. Gynecol. Pathol. 24 (2005) 296–302.

Please cite this article as: S. Nishio, et al., Clinicopathological significance of cervical adenocarcinoma associated with lobular endocervical glandular hyperplasia, Pathol. Res. Practice (2009), doi:10.1016/j.prp.2008.12.002

Image of the Month

A Case of Diffuse Retroperitoneal Lymphangioma with Endometrial Cancer

A 46-year-old female patient was referred to our hospital for further evaluation and treatment of endometrial cancer. The curettage specimen revealed moderately-differentiated endometrioid adenocarcinoma of the uterine corpus. Computed tomography and magnetic resonance imaging showed the diffuse proliferation of soft tissue in the retroperitoneal area, spreading from the level of common iliac vessels up to renovascular level (Fig. 1), and extending along the inferior mesenteric artery (Fig. 2, white arrow head). The present neoplasm was not typical for the lymph node metastasis of endometrial cancer, and it raised the possibility of malignant lymphoma. We conducted surgical treatment for both endometrial cancer and exploration of retroperitoneal neoplasm.

She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and biopsy of the retroperitoneal neoplasm. The endometrial cancer had superficial myometrial invasion macroscopically in the resected uterus, but in the retroperitoneal space the yellowish soft tissue adhered to the abdominal aorta, the inferior vena cava and the common iliac vessels. It also extended into the mesentery of the sigmoid colon. However, frozen section of the soft tissue revealed no malignancy, so she did not undergo resection of the retroperitoneal neoplasm.

The final pathological diagnosis was lymphangioma (Fig. 3). Lymphangioma is a rare benign neoplasm of the lymphatic system, and retroperitoneal lymphangioma accounts for 1% of all lymphangiomas. Although the retroperitoneal lymphangioma is a benign neoplasm, it may cause significant morbidity because of its invasive character and size. The patient has to be followed up carefully not only for endometrial cancer but also for retroperitoneal lymphangioma.

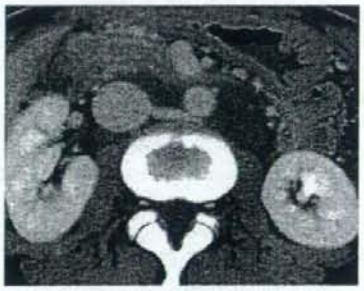


Figure 1.

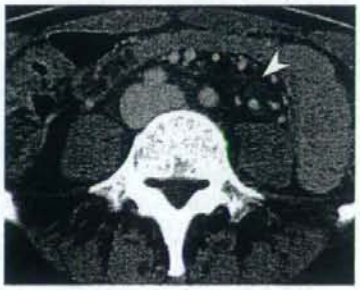


Figure 2.

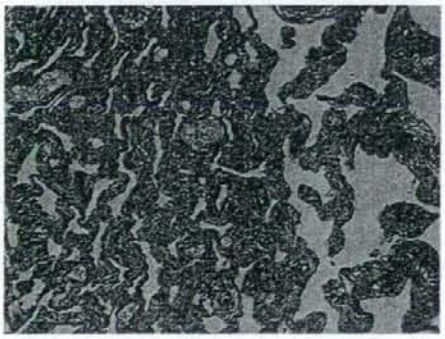


Figure 3.

Michihiro Tanikawa and Takahiro Kasamatsu
Gynecology Division
National Cancer Center Hospital
Tokyo, Japan
doi:10.1093/jjco/hyn051