Table 2
Survival and recurrence-free survival in 107 patients with cervical adenocarcinoma.

		No. (%)	5-year Survival (%)	Log-rank *P*-value	RFS[a] at 36 months (%)	Log-rank *P*-value
Peritoneal cytology	Negative	91 (85)	87	<0.001	87	<0.001
	Positive	16 (15)	50		53	
Number of positive pelvic lymph nodes	None	79 (73)	91	<0.001	91	<0.001
	1-4	16 (15)	56		60	
	≧5	6 (6)	17		17	
	Not resected	6 (6)	83		83	
Lymph-vascular space invasion	Negative	46 (43)	98	<0.001	98	<0.001
	Positive	61 (57)	69		70	
Tumor size (mm)	≤40	73 (68)	90	<0.001	90	<0.001
	>40	34 (32)	62		90	
Depth in cervical wall	<1/3	32 (30)	94	0.017	97	0.021
	1/3-2/3	26 (24)	84		84	
	>2/3	49 (46)	71		71	
Pathological parametrial involvement	Negative	85 (80)	86	<0.001	88	<0.001
	Positive	14 (13)	50		43	
	Not resected	8 (7)	88		88	
Infiltration to vagina	No	88 (82)	85	0.001	86	0.002
	Yes	19 (18)	62		63	
Ovarian metastasis	Negative	103 (96)	83	<0.001	83	0.010
	Positive	4 (4)	25		33	
Histological subtype	Mucinous	65 (60)	78	0.833	81	0.160
	Endometrioid	36 (34)	86		89	
	Others	6 (6)	83		50	
Histological grade	Well	76 (71)	87	0.023	87	<0.001
	Moderately	16 (15)	81		87	
	Poorly	13 (12)	51		62	
	Unclassified	2 (2)	51		0	

[a] Recurrence-free survival.

and were analyzed using univariate analysis. Among these series, only Takeshima et al. [4] described patients with FIGO stage IB to IIB cervical non-squamous cell carcinoma including adenocarcinoma (52%, 69/132) and adenosquamous carcinoma (48%, 63/132) separately, and survival analysis was performed using multivariate analysis adjusted for other clinical and pathological variables. In their report, all 132 enrolled patients underwent radical hysterectomy, and postoperative adjuvant external irradiation was administered to those patients with pelvic lymph node metastasis. The 3-year disease-free survival rate was 57.8% among patients with positive cytology, while it was 80.7% among patients with negative cytology, and the difference was significant. However, Takeshima et al. [4] presented their Cox model adjusting for age, lymph node status, lymph-vascular space invasion, muscle invasion, ovarian metastasis, parametrial invasion, and clinical stage, and it revealed that positive cytology was not an independent prognostic factor. In addition, peritoneal recurrence was not correlated with the presence of cancer cells in the peritoneal fluid, and they concluded that peritoneal cytology is of little value in treatment planning. The findings of the present study are contrary to those of this previous report. This discrepancy between these two retrospective studies may be mainly due to the small numbers of subjects and adverse events, and the results may have been affected by differences in clinical and pathological variables. Additionally, Takeshima et al. [4] analyzed patients with adenocarcinoma (52%) together with patients with adenosquamous carcinoma (48%).

Table 3
Multivariate analysis of prognostic factors for survival in 107 patients with cervical adenocarcinoma (with a stepwise method, forward selection).[a]

	Hazard ratio	95% Confidence interval	*P*-value
Peritoneal cytology			
Negative	1.00		
Positive	6.27	2.13–18.41	0.001
No. of positive lymph nodes			
None	1.00		
1-4	6.20	1.87–20.57	0.003
≥5	20.86	5.56–78.20	<0.001
Not resected	1.76	0.20–14.91	0.602
Histological grade			
Well differentiated	1.00		
Moderately differentiated	0.57	0.14–2.27	0.430
Poorly differentiated	5.97	2.00–17.78	0.001
Unclassified	10.53	1.20–91.94	0.033
Ovarian metastasis			
Negative	1.00		
Positive	5.20	1.18–22.82	0.029

[a] The analysis was adjusted for peritoneal cytology, number of positive nodes, degree of lymph-vascular space invasion, tumor size, depth in cervical wall, pathological parametrial involvement, infiltration to vagina, ovarian metastasis, and histological grade.

Table 4
Multivariate analysis of prognostic factors for recurrence-free survival in 107 patients with cervical adenocarcinoma (with a stepwise method, forward selection).[a]

	Hazard ratio	95% Confidence interval	*P*-value
Peritoneal cytology			
Negative	1.00		
Positive	4.58	1.48–14.16	0.008
No. of positive lymph nodes			
None	1.00		
1-4	7.61	2.69–21.54	<0.001
≥5	13.46	3.63–49.72	<0.001
Not resected	1.37	0.16–11.26	0.767
Histological grade			
Well differentiated	1.00		
Moderately differentiated	0.54	0.11–2.45	0.426
Poorly differentiated	6.13	2.14–17.77	0.001
Unclassified	31.57	5.82–171.18	<0.001

[a] The analysis was adjusted for peritoneal cytology, number of positive nodes, degree of lymph-vascular space invasion, tumor size, depth in cervical wall, pathological parametrial involvement, infiltration to vagina, ovarian metastasis, and histological grade.

One of the limitations of the present study was that it was a retrospective study, and the number of outcomes was small for independent variables that were subjected to statistical analyses. Several rare histological subtypes were included in the present study, and the distribution of these tumors was not uniform between the positive cytology and negative cytology groups. These tumors may have affected the spread pattern or survival, because their clinical behaviors are still not well known. The proportion of patients who received adjuvant chemotherapy in the positive cytology group was larger than that in the negative cytology group, although our standard adjuvant therapy was irradiation to the whole pelvis. This difference may also have affected the outcome. Additionally, few previous reports on the prognostic significance of peritoneal cytology in cervical adenocarcinoma have been published [4,5,8,9,11,12,14]. Considering the above fact, further investigation and multi-institutional studies may be needed to reach a definitive conclusion. If positive peritoneal cytology truly reflects the potential of peritoneal spread and affects survival adversely, additional aggressive postoperative chemotherapy may be proposed as an adjuvant therapy.

In the present study, patients with macroscopic *or microscopic* extrauterine disease disseminating over the surface of the peritoneum or other organs in the abdominal cavity at the primary surgery were excluded, and it is unknown from where cancer cells were derived in these cases. While there have been no definitive data to reach a conclusion, as in the case of endometrial carcinoma, the following speculations are deduced from the literature: (1) lymphatic metastasis to the peritoneal cavity; (2) direct extension of cancer cells through the cervical myometrium; (3) result of transtubal transport, especially in cases in which the tumor extends toward the upper uterine cavity; (4) reflection of multifocal peritoneal occult spread [2,17,18].

Currently, we believe that the presence of positive peritoneal cytology is an independent adverse prognostic risk factor in surgically treated patients with FIGO stage IB to IIB cervical adenocarcinoma, and that it seems to reflect the potential of peritoneal spread. Nonetheless, further investigation and multi-institutional studies with greater numbers of patients are needed.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Radical hysterectomy for FIGO stage IIB cervical cancer: Clinicopathological characteristics and prognostic evaluation

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ABSTRACT

Objective. To clarify the clinicopathological features and prognostic factors of patients with FIGO stage IIB cervical cancer who were treated with radical hysterectomy.

Methods. One hundred thirty-nine FIGO stage IIB patients with squamous or adenosquamous cell carcinoma (median age, 51 years) who were treated with primary radical hysterectomy were examined retrospectively. Sixty-six FIGO stage IIB patients who were treated with primary radiotherapy (median age, 70 years) were included for comparison of survival.

Results. Fifty percent (70/139) of the patients had pathological parametrial involvement. Among them, the positive rate of pelvic lymph nodes was 71% (50/70). Ninety-nine percent (138/139) of the tumors were completely removed, and the pelvic control rate was 88%. Major complications requiring surgery were found in 2.9% (4/139). Significant differences in survival were found among patients in subgroups according to pathological parametrial involvement, pelvic lymph node status, tumor size, lymph-vascular space invasion, and depth of myometrial invasion (log-rank test, $P<0.05$). Of these, the Cox proportional-hazard model revealed that parametrial involvement ($P=0.001$, 95% CI 1.992–6.297) and lymph node metastasis ($P=0.042$, 95% CI 1.023–3.298) were independent prognostic factors. The 5-year survival rate and relapse-free survival at 36 months were 69% and 72% among the radical hysterectomy group, and 69% and 75% among the radiotherapy group. The Cox model adjusted for age showed no significant differences in survival and relapse-free survival between these two groups.

Conclusion. Pathological parametrial involvement and positive nodes were prognostic factors for surgically treated patients with FIGO stage IIB cervical cancer.

Introduction

International Federation of Gynecology and Obstetrics (FIGO) stage IIB cervical cancer is recognized as a locally advanced-stage disease, and radiotherapy has been widely accepted as the standard treatment of choice. The FIGO Annual Report reported that 72% (2320/3233) of patients with stage IIB disease were treated with radiotherapy, and 11% (340/3233) were treated with surgery as the first therapy between 1996 and 1998 [1]. The U.S. National Institutes of Health recommends radiotherapy with concurrent cisplatin-containing chemotherapy as the primary treatment option in stage IIB patients [2]. These recommendations are based on randomized control phase III trials showing an overall survival advantage of concurrent chemo-radiotherapy in comparison with radiotherapy alone [3–7]. However, one trial did not show a benefit of adding concurrent weekly cisplatin to radical radiotherapy on either pelvic control or survival [8]. To our knowledge, no randomized control trial showed a difference in survival between patients who received concurrent chemo-radiotherapy and those who received radical hysterectomy among stage IIB patients.

On the other hand, Okabayashi [9] in Japan introduced a surgical procedure for the treatment of cervical cancer in 1921 that was more radical than the conventional Wertheim operation. After Okabayashi introduced his method, gynecologic oncologists in Japan studied and modified his procedure, and radical hysterectomy came to be adopted as one of the standard treatments for stage IIB disease. Based on this historical background, when our division was started in 1962, both primary radiotherapy and radical surgery were employed as treatment options for stage IIB cervical cancer. Generally, we have recommended radical surgery for patients 65 years and under, and radiotherapy for patients over 65 years, based on empirical observations at that time. Few reports on the clinical features of patients with pathologically confirmed findings of stage IIB cervical cancer treated with radical hysterectomy have been published [10]. Clarifying the clinicopathological features of surgically treated stage IIB cervical cancer is useful for discussing the treatment strategy of not only the surgical procedure, but also chemo-radiotherapy for stage IIB disease. We analyzed the clinicopathological characteristics and prognostic factors of stage IIB patients who underwent radical hysterectomy.

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We also studied stage IIB patients who underwent primary radiotherapy for comparison of survival and complications.

Materials and methods

Patients

We reviewed the medical records and pathological materials obtained from 1189 patients with stage IB–IVA primary cervical cancer treated at the Gynecology Division of the National Cancer Center Hospital, Tokyo, Japan, between 1984 and 2003. This study included patients who met the following criteria: the patient had FIGO stage IIB disease; the patient underwent (a) primary surgery consisting of radical hysterectomy with pelvic lymphadenectomy, or (b) primary radiotherapy; and the patient had a histological subtype of squamous cell carcinoma including adenosquamous cell carcinoma. Patients who received preoperative chemotherapy or radiotherapy were excluded. Patients with stage IIB disease who received primary radiotherapy were included in this study to make a critical comparison of survival and complications.

Patients were staged according to the FIGO staging system. Pathological classification of the resected specimens was performed according to the International Union Against Cancer TNM classification of malignant tumors [11]. Histological typing was performed according to the criteria of the World Health Organization International Histological Classification of Tumors [12].

Treatment

Our standard treatment for stage IIB patients was either radical hysterectomy or concurrent chemo-radiotherapy. The choice of treatment modality depended on the age of the patient, presence of comorbid conditions, and distribution of the tumor. Generally, we recommended radical hysterectomy for patients 65 years and under, and radiotherapy for patients over 65 years, as mentioned earlier. Our technique of radical hysterectomy was based on Kobayashi's technique and the Tokyo method [13–15]. In this technique, the surgeon first widened the paravesical and pararectal spaces and broadened the visibility in order to be able to clearly view the pelvic anatomy and facilitate dissection and hemostasis. Next, pelvic lymphadenectomy was performed. All regional lymph nodes including the common iliac, external iliac, internal iliac, obturator, parametrial, and suprainguinal lymph nodes were removed. Then, the anterior, medial, and posterior retinacula were divided and cut along the pelvic side wall. The pelvic autonomic nerve bundle under the cardinal ligament was preserved except in advanced tumors. Paravaginal tissue was widely removed, and the vaginal canal was cut a length of at least 3 to 4 cm. Then, the uterus was removed en masse. In patients with pelvic lymph node metastasis or parametrial involvement proven by pathological examination following surgery, adjuvant postoperative irradiation to the whole pelvis was administered. The field of external irradiation was placed as follows: superior margin at the fifth lumbar vertebra, inferior margin at the obturator foramen, and lateral margin 2 cm lateral to the internal pelvic wall [16]. If the common iliac node was positive for metastasis, the superior margin was placed at the third lumbar vertebra. A daily dose of 2 Gy, 5 fractions a week, was given using a linear accelerator. The total dose for the whole pelvis was 50 Gy with an opposed anterior and posterior field, or a 4 fields anterior–posterior and lateral technique. Concurrent chemotherapy was not employed with postoperative radiotherapy in any patient.

Primary radiotherapy consisted of external-beam plus high-dose-rate intracavitary irradiation. A remote after-loading system of 192Ir with tandem and ovoid applicators was employed according to the Manchester system. A combination of external and intracavitary irradiation was tailored based on the size and distribution of the tumor [16]. For patients with small-size tumor, intracavitary irradiation was performed at 1 fraction dose of 6 Gy (point A) per week, for a total of 5 fractions. External irradiation with a central shielding block was administered with a total dose of 50 Gy. For patients with large-size tumor, intracavitary irradiation was performed at 1 fraction dose of 6 Gy (point A) per week, for a total of 4 fractions. External irradiation to the whole pelvis was administered with a total dose of 20 Gy, and external irradiation with a shielding block was administered with a total dose of 30 Gy. From 2001, concurrent chemo-radiotherapy with cisplatin was administered. Cisplatin was given at a dose of 40 mg/m^2 once a week for up to six doses.

Sectioning of the resected specimen and pathological examination

The removed cervix was sectioned along the longitudinal axis, and the deepest myometrial invasion and maximum horizontal extension of the tumor were examined microscopically. The resected parametrium was cut into three parts: the proximal portion, center portion and distal portion. Parametrial lymph node metastasis was classified as positive pelvic lymph nodes, and lymph–vascular space invasion found in parametrial tissue was classified as parametrial involvement.

Statistical methods

Survival curves were obtained by the Kaplan–Meier method, and were compared by nonparametric survival analysis (log-rank test). $P<0.05$ was considered to indicate statistical significance. Variables that showed a significant association with survival were included in multivariate analysis based on the Cox proportional-hazard model with a stepwise method (forward selection). $P<0.05$ was adopted as inclusion criteria, and $P>0.10$ was adopted as exclusion criteria for the forward selection. Fisher's exact test was used for statistical analysis of categorical variables, and the independent sample t-test was used for statistical analysis of continuous variables. Patients who died of other causes were included as deaths in the survival analysis. Follow-up continued through December 31, 2007. All statistical analyses were performed with the statistical software package SPSS for Windows (version 11.0J; SPSS Inc., Chicago, Illinois, U.S.A.).

Results

Patient characteristics

Among the 243 patients with stage IIB cervical cancer who were treated in our division during the study period, 205 patients met the study criteria. Reasons for exclusion were adenocarcinoma or other uncommon histological subtype ($n=34$), having received preoperative radiotherapy ($n=2$), having received preoperative chemotherapy ($n=1$), and nonradical hysterectomy ($n=1$). Among the 205 patients, 139 patients (age, median 51 years, range 24–78 years) underwent radical hysterectomy, and 66 patients (median 70 years, range 26–84 years) received primary radiotherapy. The patients who underwent radical hysterectomy were significantly younger than those who underwent primary radiotherapy ($p<0.001$). Eight patients (12%, 8/66) received primary concurrent chemo-radiotherapy. The patients were followed for 3 to 288 months (median, 96 months), including until death, and no patient was lost to follow-up.

Among the 139 patients treated with radical hysterectomy, 5 patients (3%) were over 65 years of age. Three 66-year-old patients strongly desired surgery. In the remaining two patients, before the operation, cervical biopsies had revealed uncommon non-squamous cell carcinoma, and it was considered to be a radioresistant lesion in both cases. In these two cases, pathologic examination of the resected specimens revealed that the histological subtypes were squamous cell carcinoma and adenosquamous cell carcinoma.

Among the 66 patients who received primary radiotherapy, 22 patients (33%) were 65 years of age or younger. The reasons for

Table 1
Patient characteristics of the 139 patients with FIGO stage IIB cervical cancer who underwent radical hysterectomy.

Histological subtype	Squamous cell carcinoma	$n=129$ (93%)
	Adenosquamous cell carcinoma	$n=10$ (7%)
Pathological stage (pTNM)	pT1b	$n=33$ (24%)
	pT2a	$n=36$ (26%)
	pT2b	$n=70$ (50%)
Positive rate of pelvic lymph node metastasis	pT1b	27% ($n=9/33$)
	pT2a	36% ($n=13/36$)
	pT2b	71% ($n=50/70$)
Lymph-vascular space invasion	Positive	$n=122$ (88%)
Tumor size (mm)	Horizontal extension	4–90 (median, 45)
	Myometrial invasion	3–40 (median, 20)
Ovarian metastasis	Positive	$n=5$ (4%)
Postoperative radiotherapy	Done	$n=91$ (65%)

employing radiotherapy in these 22 patients were as follows: patients refused surgery even though their tumors were resectable ($n=12$); uncontrolled comorbid internal disease ($n=3$); vaginal involvement that nearly reached the lower third of the vagina, and severe urinary incontinence was predicted following surgery ($n=3$); severe anterior extension of the tumor imaged by CT and MRI, and incomplete resection of the tumor during the operation was predicted ($n=3$); and metastasis in multiple para-aortic nodes as proven by pathologic examination of frozen sections of materials obtained at exploratory laparotomy ($n=1$). No patient underwent the alternate procedure based on only tumor size or degree of parametrial involvement.

The characteristics of the 139 patients who underwent radical hysterectomy are summarized in Table 1. Among the 70 patients with pathological parametrial involvement (pT2b), 48 (69%) had parametrial involvement in the proximal portion of the parametrium, 13 (18%) in the center portion, and 9 (13%) in the distal portion. All tumors were completely removed except in one case in which the vaginal surgical cut margin was positive microscopically. The median number of resected pelvic lymph nodes was 30 (range, 9 to 81). Among the 72 patients with pelvic lymph node metastasis, 20 patients (29%) had positive common iliac nodes. Ninety patients (65%, 90/139) received postoperative adjuvant radiotherapy, and one patient received radiotherapy to control microscopic residual tumor in the vaginal stump.

The median length of hospital stay of the patients who underwent surgery without radiotherapy was 27 days (range, 17–52 days). During the hospitalization, all patients who underwent surgery learned to compensate for the sensory and motor loss and the bladder returned to near normal function (less than 50 ml of residual urine volume). The median length of hospital stay of the patients who received both surgery and adjuvant radiotherapy was 63 days (range, 49–122 days).

Survival

The 5-year survival rate among the 139 patients who underwent radical hysterectomy was 69% [95% confidence interval (95% CI), 62–77%], and the median survival time was 262 months (95% CI, 199–325 months). The relapse-free survival (RFS) rate at 36 months was 72% (95% CI, 64–79%). Survival was assessed in six clinicopathological subgroups, and significant differences in survival were found among patients in subgroups according to pathological parametrial involvement, lymph node status, tumor size, lymph-vascular space invasion, and depth of myometrial invasion (log-rank test, $P<0.05$) (Table 2). Multivariate analysis for differences in survival among the subgroups of pathological parametrial involvement, lymph node status, tumor size, lymph-vascular space invasion, and depth of myometrial invasion was performed. The Cox proportional-hazard model with a forward stepwise method identified that parametrial involvement and lymph node metastasis were independent prognostic factors

Table 2
Survival of the 139 patients with FIGO stage IIB cervical cancer who underwent radical hysterectomy.

Characteristic	*n* (%)	5-year survival rate	Log-rank *P*-value
Parametrial involvement			
Negative	69 (50)	85%	<0.001
Positive	70 (50)	53%	
Pelvic lymph node status			
Negative	67 (48)	82%	<0.001
Positive	72 (52)	58%	
$n=1$–4	49	82%	
$n=5$–9	12	40%	
$n\geq 10$	11	27%	
Tumor size			
≤40 mm	58 (42)	81%	0.017
>40 mm	81 (58)	61%	
Lymph-vascular space invasion			
Absent or a few	52 (37)	81%	0.007
Several or many	87 (63)	63%	
Myometrial invasion			
<1/3	5 (4)	100%	<0.001
<2/3	16 (11)	88%	
<3/3	58 (42)	75%	
≥3/3[a]	60 (43)	56%	
Age			
<40 years	29 (21)	66%	0.4542
≥40 years	110 (79)	71%	

[a] Tumor involved all of the myometrium or invaded directly into the parametrium.

(Table 3). Among the patients with both pathological parametrial involvement and lymph node metastasis (pT2bN1), the 5-year survival rate was 45% (95% CI, 32–59%), and the median survival time was 53 months (95% CI, 23–84 months). Among the patients with parametrial involvement and no lymph node metastasis (pT2bN0), the cumulative 5-year survival rate was 74% (95% CI, 54–94%), and the median survival time was 230 months (95% CI, 169–292 months). There was a significant difference in survival between these two groups (log-rank test, $P=0.039$).

The 5-year survival rate among the 66 patients who received primary radiotherapy was 69% (95% CI, 57–80%), and the median survival time was 112 months (95% CI, 83–140 months). RFS at 36 months was 75% (95% CI, 64–85%). Survival was significantly longer in patients who underwent radical hysterectomy than in those who received primary radiotherapy by Kaplan–Meier analysis ($P=0.007$). There was no difference in RFS between these two groups ($P=0.676$, Kaplan–Meier method). To adjust the age distribution, the Cox proportional-hazard model of testing for differences in survival and RFS among the subgroups of treatment modality and age was performed. After adjustment for age, the Cox model showed that there were no significant differences in survival and RFS between the radical hysterectomy group and radiotherapy group (Table 4).

Failure sites

Among the 139 patients who were treated with radical hysterectomy, 46 patients (33%) suffered tumor recurrence at a median

Table 3
Multivariate proportional-hazard model for survival in patients with FIGO stage IIB cervical cancer treated with radical hysterectomy (stepwise method, forward selection).

	P-value	Hazard ratio	95% CI[a]
Parametrial involvement			
Negative		1.000	
Positive	0.001	3.542	1.992–6.297
Pelvic lymph node status			
Negative	1.00		
Positive	0.042	1.873	1.023–3.298

[a] 95% Confidence interval.

Table 4
Multivariate proportional-hazard model for survival and relapse-free survival in patients with FIGO stage IIB cervical cancer treated with radical hysterectomy or primary radiotherapy.

	Survival			Relapse-free survival		
	P-value	Hazard ratio	95% CI[a]	*P*-value	Hazard ratio	95% CI[a]
Treatment modality						
Radical hysterectomy		1.000			1.000	
Primary radiotherapy	0.063	1.670	0.973–2.867	0.590	1.210	0.605–2.423
Age						
≤65 years		1.000			1.000	
>65 years	0.831	1.064	0.602–1.881	0.211	0.595	0.264–1.342

[a] 95% Confidence interval.

interval of 13 months (range, 1–126 months). Among the 46 patients, the initial recurrent site was located outside the pelvis in 30 patients (65%), inside the pelvis in 12 patients (26%), and both inside and outside the pelvis in the remaining 4 patients (9%). The pelvic control rate was 88% (123/139). Among the total of 41 distant metastatic sites, the most frequent site was a distant lymph node (54%), followed by the lung (19%), bone (15%), liver (7%) and peritoneal spread (5%). Among the total of 22 lymph nodes with distant metastasis, 46% were para-aortic nodes, 46% were cervical nodes, 4% were in the mediastinum, and 4% were inguinal nodes. Among these 46 patients who suffered recurrence, 27 patients received radiotherapy, 7 patients received chemotherapy, 3 patients underwent surgery, and 8 patients received only palliative care.

Among the 66 patients who were treated with primary radiotherapy, 20 patients (30%) suffered tumor recurrence at a median interval of 12 months (range, 3–106 months). The initial recurrent site was located outside the pelvis in 10 patients (50%), inside the pelvis in 8 patients (40%), both inside and outside the pelvis in 1 patient (5%), and unknown in the remaining 1 patient. The pelvic control rate was 86% (57/66). Among these 20 patients who recurred, 12 patients received radiotherapy, 3 patients received chemotherapy, 1 patient underwent surgery, and 4 patients received only palliative care.

Among the 139 patients who underwent radical hysterectomy, 48 patients did not receive postoperative radiotherapy. Of these 48 patients, 6 patients (12.5%) developed local recurrence (4 patients had central recurrence, 2 patients had pelvic side wall recurrence). All 6 patients received radiotherapy as salvage therapy at the time of recurrence, and 2 patients with central recurrence survived. Of the remaining 157 patients including the 66 patients in the primary radiotherapy group and the 91 patients who received postoperative radiotherapy, 14 patients (8.9%) developed local recurrence (7 patients had central recurrence, 7 patients had lateral recurrence). Among the 14 patients, 3 patients received chemotherapy, 4 patients received palliative radiotherapy, 2 patients underwent surgery, and 5 patients received only palliative care. All 14 patients died of the disease.

Complications

Major complications requiring surgery following radical hysterectomy occurred in 4 patients (2.9%, 4/139) in the late phase, and details were as follows: a vesicovaginal or ureterovaginal fistula ($n=2$), small bowel obstruction ($n=1$), and rupture of the bladder ($n=1$). Among these 4 complications, 3 occurred in patients who received postoperative irradiation to the whole pelvis. Late adverse events requiring surgery after primary radiotherapy occurred in one patient with rectovaginal fistula (1.5%, 1/66). There was no difference in the rate of major complications requiring surgery between the radical hysterectomy group and primary radiotherapy group (Fisher's exact test, $P=1.000$). Treatment-related death did not occur in any patient. Other complications not requiring surgical intervention after radical hysterectomy were hydronephrosis ($n=1$), abscess formation in a lymph cyst requiring drainage ($n=1$), urethral fistula ($n=1$), small bowel obstruction ($n=1$), and severe bladder atony requiring temporary self-catheterization ($n=1$). Pulmonary embolism, thrombophlebitis, or marked lymphedema that developed into infectious lymphangitis did not occur in any patient. The median volume of blood loss during radical hysterectomy was 1188 ml ($n=139$; range, 304–6074 ml), and 65% of the patients received blood transfusion (median volume 600 ml; range, 240–3600 ml).

Discussion

In eight reports in the literature since 1980 including the present study, the incidence of parametrial involvement proven pathologically among patients with FIGO stage IIB disease ranged between 21.5 and 55% [17–23]. Assessment of parametrial involvement is important because discriminating the true pathological extent of the tumor from inflammatory change, adhesion, fibrosis, and irregular-shaped, large-size cervical tumor is difficult in the FIGO staging system. It is also difficult to make this discrimination by CT and MRI. In the present study, assessment of FIGO staging was performed by at least 2 gynecologists and a consensus diagnosis was reached, and no stage IIB patient who had massive parametrial extent of the tumor received radiotherapy. The survival rate of stage II B patients treated with chemo-radiotherapy in previous studies may have been affected by the number of enrolled patients with true pathological invasion of the parametrium.

Seven studies analyzed prognostic factors of stage IB–II cervical cancer treated with radical hysterectomy using multivariate analysis [22–28]. In these series, pathological parametrial involvement, vaginal invasion, number of positive nodes, lymph–vascular-space invasion, and non-squamous cell carcinoma were identified as independent prognostic factors. These seven studies included both patients with squamous cell carcinoma and patients with non-squamous cell carcinoma (13–29%), and six series analyzed stage IIB disease together with stage IB and IIA diseases. Only Kamura et al. [22] described stage IIB patients separately, and positive pelvic lymph node was the only independent prognostic factor.

Pelvic lymph node metastasis was found in 35 to 45.8% of the stage IIB patients treated with radical hysterectomy in 10 reports [18–25,28,29]. Three of these 10 series mentioned the rate of positive lymph node status among patients with pathological parametrial involvement (pT2b) and it ranged between 54% and 58% [18,21,29], and when the tumor extended into the parametrial tissue, the rate of nodal metastasis increased significantly [18]. In the present study, we found that parametrial involvement and lymph node metastasis were significant prognostic factors. Therefore, it is important to perform systemic lymphadenectomy and wide dissection of the parametrium during radical hysterectomy for stage IIB disease.

The 5-year survival rate of stage IIB patients treated with radical hysterectomy ranged between 55.2% and 81.1% in 7 studies including the present study [17–19,26,27,30]. Among these, three studies including the present study mentioned the 5-year survival rates of stage IIB patients with pathological parametrial involvement (pT2b) [17,26], and they were 52.0, 53, and 62.3%, respectively. Although

there are few previous studies, an overall 5-year survival rate of over 50% may be achieved in FIGO stage IIB patients with pathological parametrial involvement by performing radical hysterectomy followed by adjuvant radiotherapy. The radicality of our hysterectomy for stage IIB disease corresponds to Classes III and IV of the Piver-Rutledge classification [31]. Consequently, 99% of the tumors in the present study were completely removed and 12% relapsed inside the pelvis. Pelvic control by radical hysterectomy is feasible, and control of distant node and lung metastases by adjuvant therapy should be considered.

To our knowledge, there has been no randomized control trial testing for the difference in survival between radical hysterectomy and radiotherapy for stage IIB disease. The FIGO Annual Report presented the five-year survival rates of stage IIB patients who received various treatments: the 5-year survival rate was 64.3% among 232 patients treated with surgery followed by adjuvant radiotherapy, 64.2% among 1718 patients treated with radiotherapy, and 64.4% among 112 patients treated with chemo-radiotherapy [1]. Yamashita et al. [30] retrospectively compared the survival of stage IIB patients who underwent radical hysterectomy followed by adjuvant radiotherapy and those who underwent radiotherapy. They reported that the 5-year cause-specific survival rate among patients who underwent surgery or radiotherapy was 81.1% and 81.2%, respectively, and the difference was not statistically significant. Ohara et al. [32] also reported no significant difference in cause-specific survival between these 2 groups; the 5-year cause-specific survival rate was 70.5% in the radiotherapy group and 85.2% in the radical hysterectomy group. In the present study, the reason for the better survival of the radical hysterectomy group by univariate analysis may have been that the patients who did not receive radiotherapy as the initial treatment could receive curative radiotherapy when the tumor recurred locally in comparison with the patients who received adjuvant or primary radiotherapy. However, a definitive conclusion cannot be reached, because the number of patients in our study was small and survival after recurrence is affected by the recurrent site (central or lateral) and various other clinical factors. One limitation of the present study was that it was a retrospective study. The selection criteria may have been biased against candidates for surgery. Surgeons may have tended to avoid performing surgery in patients with more advanced tumors because of the risk involved in the operation. This latent selection bias may have affected the better survival of the radical hysterectomy group. Also, primary chemo-radiation which was introduced in 2001, was administered to 8 patients (12%) in the primary radiotherapy group, and this may have affected the survival of the primary radiotherapy group. As the proportion of patients who received chemo-radiation versus radiation increased, the survival of the radiotherapy group may also have increased. Although the present study was a single-center retrospective study and the number of enrolled patients was small, our study and these previously-reported studies suggest that the survival of FIGO stage IIB patients treated with radical hysterectomy and that of patients treated with radiotherapy may be approximately equivalent.

Radical hysterectomy and radiotherapy are essentially different treatment modalities. Generally, radical hysterectomy is suitable for young patients who desire preservation of ovarian function and patients with radioresistant tumors. The advantage of radiotherapy is that it can be administered to elderly patients, patients with comorbid disease, and patients with wide vaginal invasion in whom severe urinary incontinence following surgery is predicted. Potential complications also differ between the two treatment modalities. Complications of radical hysterectomy include lymphocysts, lymphedema, bladder dysfunction, urinary fistula, and hemorrhage. Late complications of radiotherapy are proctitis, cystitis, urinary and rectal fistula, rectal stricture, and small bowel obstruction. If the survival rates following the two treatments are approximately equivalent, the choice of treatment option for patients with FIGO stage IIB disease would be based on the patient and tumor characteristics. Age, comorbid condition, distribution of the tumor, radiosensitivity, lifestyle of the patient, and desire of the patient considering potential complications, are considered. However, adjuvant external irradiation to the whole pelvis is problematic. Because radiotherapy is employed as postoperative adjuvant therapy for patients with pelvic lymph node metastasis or pathological parametrial involvement, consequently, the frequency of adjuvant radiotherapy is higher among patients with FIGO stage IIB disease than among those with FIGO stage IB–IIA disease. While the survival rate was over 80% among those in the radical hysterectomy group with no pathological parametrial involvement and no positive lymph nodes, the proportion of patients who did not require adjuvant radiotherapy was 35%. Radical hysterectomy may have a beneficial effect in about one-third of patients with FIGO stage IIB cervical cancer.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Clinical Studies

Radical hysterectomy for FIGO stage I–IIB adenocarcinoma of the uterine cervix

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A retrospective analysis was carried out to identify risk factors for survival and relapse in patients with FIGO stage I–IIB cervical adenocarcinoma (AC), who underwent radical hysterectomy, and to compare outcome and spread pattern with those of squamous cell carcinoma (SCC). One hundred and twenty-three FIGO stage I–IIB patients with AC and 455 patients with SCC, who all underwent primary radical hysterectomy, were reviewed. Among the patients with AC, Cox model identified tumour size (95% CI: 1.35–30.71) and node metastasis (95% CI: 5.09–53.44) as independent prognostic factors for survival, and infiltration to vagina (95% CI: 1.15–5.76) and node metastasis (95% CI: 6.39–58.87) as independent prognostic factors for relapse. No significant difference was found in survival or relapse between the AC and SCC groups, after adjusting for other clinicopathological characteristics using Cox model. No significant difference was found in the positive rates of lymph nodes or location of initial failure sites between the two groups, but ovarian metastatic rate was significantly higher in patients with pathologic stage IIB AC ($P = 0.02$). Positive node is a common independent prognostic factor for survival and relapse of patients with AC. FIGO stage I–IIB patients with AC or SCC, who underwent radical hysterectomy, have similar prognosis and spread pattern, but different ovarian metastasis rates.
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Keywords: radical hysterectomy; adenocarcinoma; uterine cervix; FIGO stage I–IIB

At present, standard treatment options for patients with invasive carcinoma of the uterine cervix are as follows: radical hysterectomy followed by adjuvant radiotherapy or primary radiotherapy with concurrent cisplatin-containing chemotherapy, for the patients with the International Federation of Gynecology and Obstetrics (FIGO) stage IB–IIA disease, with equivalent results; and primary radiotherapy with concurrent chemotherapy for the patients with FIGO stage IIB–IVA disease. These therapeutic strategies have been widely accepted. On the other hand, approximately 85% of the patients with carcinoma of the uterine cervix have squamous lesions, and most of the remaining 10% have adenocarcinoma (AC) lesions (Benedet *et al*, 2003). To our knowledge, no practice guideline has referred to the treatment option based on the difference of histological types between AC and squamous cell carcinoma (SCC) It is not clear whether these histological types influence outcome or spread pattern, and there is still controversy, as conflicting results have appeared in the literature because of potential limitations of small cohorts of patients with AC. The question whether standard treatment for patients with SCC is also suitable for patients with AC remains unanswered. Additionally, over the last decade, the proportion of AC relative to SCC has doubled, and the rate of AC per population at risk has also increased (Smith *et al*, 2000). To establish a framework for designing therapeutic strategies, the present retrospective study was undertaken firstly to clarify the clinicopathological features of the surgically treated patients with common type of AC and to identify prognostic factors. Secondly, comparisons of outcomes and spread pattern were made between patients with AC and SCC. Our study will support the design of therapeutic strategies, including surgery, radiotherapy, and chemotherapy, that will be more suitable for different disease types.

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PATIENTS AND METHODS

Patients

We reviewed the medical records and pathological materials that had been obtained from 1189 patients with the FIGO stage IB–IVA invasive carcinoma of the uterine cervix, who were treated at the Gynecology Division of the National Cancer Center Hospital, Tokyo, Japan, between 1984 and 2003. This study included patients who met the following criteria: the patients had (a) common histological subtypes of endometrioid AC and endocervical type AC or (b) SCC; the patients had FIGO stage I–IIB disease; and the patients underwent primary surgery consisting of radical hysterectomy with pelvic lymphadenectomy. Patients who received preoperative chemotherapy or radiotherapy were excluded. Patients with uncommon histological subtypes of AC (adenoma malignum, villoglandular, intestinal type, clear cell, serous, or mesonephric AC), and those who had other epithelial carcinoma (adenosquamous, glassy cell, adenoid cystic, adenoid basal, small cell, or undifferentiated carcinoma) were also excluded. Patients with SCC were included in this study for critical comparison of spread pattern, recurrence, and survival.

All of the patients were staged according to the FIGO staging system. Postoperative pathological classification was carried out according to the International Union Against Cancer (UICC) TNM classification of malignant tumours. Histological typing was evaluated according to the criteria of the World Health Organization International Histological Classification of Tumours.

Treatment

The radicality of hysterectomy in this study corresponded to classes III and IV of the Piver–Rutledge classification (Piver *et al*, 1974). In patients with pelvic lymph node metastasis (pT1bN1, pT2aN1, or pT2bN1) or parametrial involvement (pT2b) proven by pathological examination following surgery, adjuvant postoperative irradiation to the whole pelvis was administered. A daily dose of 2 Gy, five fractions a week, was given using a linear accelerator. The total dose for the whole pelvis was 50 Gy with an opposed anterior and posterior field, or a four-field anterior–posterior and lateral technique. All slides of resected specimens were examined by three to four pathologists independently, and a consensus diagnosis was reached. The categories of lymph–vascular space invasion were defined as follows: after the examination of all slides of tumour tissues, they were categorised as none (no foci of lymph–vascular space invasion), few (1–2 foci), several (3–5 foci), or many (more than 5 foci of lymph–vascular space invasion).

Following the primary treatment, asymptomatic patients underwent pelvic examination, Pap smear, chest radiograph, ultrasonography, and determination of serial tumour markers (SCC, CEA) every 4–6 months. Symptomatic patients underwent the appropriate examination where indicated using computed tomography (CT) and magnetic resonance imaging (MRI).

Statistical methods

Survival and relapse-free survival (RFS) curves were obtained by the Kaplan–Meier method and the survival curves were compared by non-parametric survival analysis (log-rank test). A *P*-value of <0.05 was considered to indicate statistical significance. Variables that showed a significant association with survival were included in multivariate analysis based on the Cox proportional–hazard model with a stepwise method (forward selection). A *P*-value of <0.05 was adopted as inclusion criteria, and a *P*-value of >0.10 was adopted as exclusion criteria for the forward selection. For categorical variables, Fisher's exact test, or χ^2-test was used. Patients who died of other causes were included as deaths in the survival analysis. Follow-up continued through to December 2007. All statistical analyses were carried out with the statistical software package SPSS for Windows (version 11.0J; SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

In all, 123 patients with cervical AC and 455 patients with cervical SCC met the study criteria. The characteristics of the patients are summarised in Table 1. Median age of the patients with AC was 48 years (range: 29–71) and median age of the patients with SCC was 47 years (range: 22–73). Following surgery, 226 patients received adjuvant therapy. Majority of the patients received standard adjuvant therapy, which was irradiation to the whole pelvis, but five patients with AC who refused radiotherapy received chemotherapy. Among the seven patients with positive surgical margin, five patients received radiotherapy to control microscopic residual tumour in the vaginal stump, and the remaining two patients refused postoperative treatment.

Table 1 Patient characteristics

	Adenocarcinoma	Squamous cell carcinoma	
	No. (%)	**No. (%)**	***P*-value**
FIGO stage			
IB	96 (78)	275 (60)	0.021
IIA	5 (4)	51 (11)	
IIB	22 (18)	129 (29)	
Pathological stage			
pT1b	88 (72)	229 (50)	<0.001
pT2a	14 (11)	112 (25)	
pT2b	21 (17)	114 (25)	
Tumour size (mm)			
≦20	37 (30)	92 (20)	0.024
21–40	46 (37)	222 (49)	
>40	40 (33)	141 (31)	
Depth in cervical wall			
<1/3	34 (28)	68 (15)	0.002
1/3–2/3	31 (25)	107 (23)	
>2/3	58 (47)	280 (62)	
Number of positive pelvic lymph nodes			
None	91 (74)	309 (68)	0.329
1–4	25 (20)	104 (23)	
≧5	7 (6)	42 (9)	
Lymph–vascular space invasion			
None	53 (43)	102 (22)	<0.001
Few	32 (26)	149 (33)	
Several	27 (22)	110 (24)	
Many	11 (9)	94 (21)	
Infiltration to vagina			
No	94 (76)	280 (62)	0.003
Yes	29 (24)	175 (38)	
Ovarian metastases			
Negative	116 (94)	448 (98.5)	0.024
Positive	6 (5)	6 (1.3)	
Not resected	1 (1)	1(0.2)	
Surgical margin			
Free	121 (98)	450 (99)	0.644
Close or involved	2 (2)	5 (1)	
Postoperative therapy			
Not carried out	94 (76)	253 (56)	<0.001
Radiotherapy	24 (20)	202 (44)	
Chemotherapy	5 (4)	0	

FIGO = the International Federation of Gynecology and Obstetrics.

All 578 patients were followed for 1–288 months, including until death, and the median follow-up period was 93 months. The details with regard to recurrent sites are not available for one patient, who died of the disease at another hospital.

Survival

The overall survival and the RFS of the patients with AC were assessed by log-rank test in two clinical and nine pathological subgroups (Table 2). In these, multivariate analysis testing for differences in survival among statistically significant subgroups of FIGO stage, tumour size, depth in cervical wall, number of positive nodes, degree of lymph–vascular invasion, pathological

Table 2 Overall survival and disease-free survival in 123 patients with adenocarcinoma

	No. (%)	5-year survival (%)	Log-rank *P*-value	RFS at 36 (months)[a] (%)	Log-rank *P*-value
Age					
≦48	67 (54)	84	0.091	85	0.017
>48	56 (46)	77		80	
FIGO stage					
IB	96 (78)	86	0.004	89	0.001
IIA	5 (4)	53		60	
IIB	22 (18)	59		59	
Tumour size (mm)					
≦20	37 (30)	95	<0.001	97	<0.001
21–40	46 (37)	91		91	
>40	40 (33)	55		59	
Depth in cervical wall					
<1/3	34 (28)	97	0.004	100	0.001
1/3–2/3	31 (25)	87		87	
>2/3	58 (47)	67		87	
Number of positive nodes					
None	91 (74)	91	<0.001	93	<0.001
1–4	25 (20)	60		63	
≧5	7 (6)	14		14	
LVS invasion[b]					
None	53 (43)	98	<0.001	98	<0.001
Few	32 (26)	81		84	
Several	27 (22)	56		61	
Many	11 (9)	55		55	
Parametrial invasion					
Negative	102 (83)	89	<0.001	92	<0.001
Positive	21 (17)	38		43	
Infiltration to vagina					
No	94 (76)	87	<0.001	89	<0.001
Yes	29 (24)	61		62	
Ovarian metastases					
Negative	94 (95)	84	<0.001	85	<0.001
Positive	6 (5)	17		20	
Histological subtype					
Mucinous	73 (59)	75	0.543	78	0.180
Endometrioid	50 (41)	88		90	
Histological grade					
Grade 1	86 (70)	85	<0.001	86	<0.001
Grade 2	23 (19)	87		86	
Grade 3	14 (11)	47		56	

FIGO = the International Federation of Gynecology and Obstetrics; LVS = lymph–vascular space; RFS = relapse-free survival. [a]RFS at 36 months. [b]LVS invasion.

parametrial involvement, infiltration to vagina, ovarian metastases, and histological grade was carried out. The Cox model with a forward stepwise method identified that tumour size (over 40 mm) and number of positive nodes were independent prognostic factors for overall survival. Similarly, the RFS was also assessed in the subgroups according to age in addition to the same parameters as overall survival. The Cox model showed that infiltration to vagina and number of positive nodes were independent prognostic factors for relapse (Table 3). Among the patients who recurred, one patient with pT1b-2N1 disease survived after recurrence.

Table 3 Multivariate analysis of prognostic factors for OS and RFS in 123 patients with AC (with a stepwise method, forward selection)[a]

	OS			RFS		
	HR	95% CI[b]	*P*-value	HR	95% CI	*P*-value
Infiltration to vagina						
No	—	—	—	1.00		
Yes	—	—	—	2.58	1.15–5.76	0.020
Tumour size (mm)						
≦20	1.00					
21–40	2.25	0.45–11.29	0.323	—	—	—
>40	6.44	1.35–30.71	0.019	—	—	—
Number of positive nodes						
None	1.00			1.00		
1–4	2.63	1.13–6.10	0.024	3.86	1.58–9.41	0.003
>5	16.50	5.09–53.44	<0.001	19.39	6.39–58.87	<0.001

AC = adenocarcinoma; CI = confidence interval; FIGO = the International Federation of Gynecology and Obstetrics; HR = hazard ratio; LVS = lymph–vascular space; OS = overall survival; RFS = relapse-free survival. [a]The analysis was adjusted for FIGO stage, tumour size, depth in cervical wall, number of positive node, degree of LVS invasion, pathological parametrial involvement, infiltration to vagina, ovarian metastases, and histological grade. [b]95% confidence interval.

Comparison of survival rate was made between the patients with AC and those with SCC according to UICC pathological stage. Among the patients with AC, the cumulative 5-year survival rates of the patients with pathological stage pT1b, pT2a, and pT2b diseases were 89, 92, and 38%, respectively. Among the patients with SCC, the 5-year survival rates of the patients with pT1b, pT2a, and pT2b diseases were 89, 89, and 62%, respectively. Univariate analysis revealed no significant difference in survival between patients with AC and SCC (log-rank, $P=0.640$ in the patients with pT1b disease, $P=0.317$ in pT2a disease, and $P=0.074$ in pT2b disease). Similarly, among the patients with AC, the RFS rates at 36 months of the patients with pT1b, pT2a, and pT2b diseases were 91, 100, and 38%, respectively, compared with 91, 91, and 61% of the patients with SCC, respectively. There were no significant differences in relapse between patients with AC and SCC (log-rank, $P=0.860$ in the patients with pT1b disease, $P=0.227$ in pT2a, and $P=0.137$ in pT2b). To adjust for other clinicopathological characteristics, the Cox model was used for survival and RFS analyses among the subgroups according to age, postoperative therapy, tumour size, depth in cervical wall, lymph node status, LVS invasion, ovarian metastasis, and histological types (AC or SCC). The Cox model-adjusted clinicopathological characteristics showed no significant difference in survival or relapse between the AC and SCC groups (Tables 4 and 5). Histological type was not shown to be an independent factor of survival or relapse at any pathological stage.

Spread pattern and failure sites

Among the 123 patients with AC, the positive rate of pelvic lymph node metastasis at the initial surgery was 16% (14 of 88) of the patients with pT1b disease, 14% (2 of 14) of the patients with pT2a disease, and 76% (16 of 21) of the patients with pT2b disease, compared with 17% (38 of 229), 21% (23 of 112), and 75% (85 of 114), respectively, of the patients with SCC. There were no significant differences in the positive node rates between AC and SCC groups (Fisher's exact test, $P=1.000$ in the patients with pT1b disease, $P=0.735$ in the patients with pT2a disease, and $P=1.000$ in the patients with pT2b disease). With regard to the paraaortic lymph node status, in the AC group, no enlarged paraaortic nodes were found during the operation. Further, common iliac node

Table 4 Multivariate analysis of prognostic factors for OS in 123 patients with AC and 455 patients with SCC (with a stepwise method, forward selection)

	pT1b		pT2a		pT2b	
	HR	95% CI	HR	95% CI	HR	95% CI
Age						
≦48	1.00		$P>0.10^a$		$P>0.10$	
>48	2.15	1.61–3.98				
Postoperative therapy						
Carried out	$P>0.10$		$P>0.10$		1.00	
Not carried out					2.44	1.38–4.32
Tumour size (mm)						
≦20	1.00		$P>0.10$		$P>0.10$	
21–40	2.37	0.95–5.90				
>40	4.00	1.48–10.75				
Number of positive nodes						
None	1.00		1.00		1.00	
1–4	1.71	0.80–3.68	1.99	0.54–7.29	1.66	0.88–3.16
>5	7.76	2.70–22.27	46.38	3.26–658.60	5.25	2.65–10.39
Ovarian metastases						
Negative	$P>0.10$		$P>0.10$		1.00	
Positive					2.66	1.00–7.04
Depth in cervical wall						
<1/3	$P>0.10$		$P>0.10$		$P>0.10$	
1/3–2/3						
>2/3						
LVS invasion						
None	$P>0.10$		$P>0.10$		$P>0.10$	
Few						
Several						
Many						
Histological type						
SCC	$P>0.10$		$P>0.10$		$P>0.10$	
AC						

AC = adenocarcinoma; CI = confidence interval; FIGO = the International Federation of Gynecology and Obstetrics; HR = hazard ratio; LVS = lymph–vascular space; OS = overall survival; SCC = squamous cell carcinoma. [a]$P>0.10$ was exclusion criteria for the stepwise, forward selection.

Table 5 Multivariate analysis of prognostic factors for RFS in 123 patients with AC and 455 patients with SCC (with a stepwise method, forward selection)

	pT1b		pT2a		pT2b	
	HR	95% CI	HR	95% CI	HR	95% CI
Age						
≦48	$P>0.10^a$		$P>0.10$		$P>0.10$	
>48						
Postoperative therapy						
Done	$P>0.10$		$P>0.10$		1.00	
Not done					3.14	1.75–5.64
Tumour size (mm)						
≦20	1.00		$P>0.10$		$P>0.10$	
21–40	2.63	0.87–7.94				
>40	7.25	2.34–22.48				
Number of positive nodes						
None	1.00		1.00		1.00	
1–4	1.75	0.79–3.86	3.63	1.15–11.47	2.04	0.93–4.93
>5	8.30	2.83–24.33	13.85	2.83–67.68	6.62	3.00–14.64
Ovarian metastases						
Negative	$P>0.10$		$P>0.10$		$P>0.10$	
Positive						
Depth in cervical wall						
<1/3	$P>0.10$		$P>0.10$		$P>0.10$	
1/3–2/3						
>2/3						
LVS invasion						
None	$P>0.10$		$P>0.10$		$P>0.10$	
Few						
Several						
Many						
Histological type						
SCC	$P>0.10$		$P>0.10$		$P>0.10$	
AC						

AC = adenocarcinoma; CI = confidence interval; FIGO = the International Federation of Gynecology and Obstetrics; HR = hazard ratio; LVS = lymph–vascular space; OS = overall survival; RFS = relapse-free survival; SCC = squamous cell carcinoma. [a]$P>0.10$ was exclusion criteria for the stepwise, forward selection.

metastasis was proven in 10 (31.3%, 10 of 32) patients with positive pelvic lymph nodes. In the SCC group, 41 (28.1%, 41/146) patients with positive pelvic lymph nodes had common iliac node metastasis. Of these, eight patients had paraaortic lymph node metastasis, which was proven histopathologically, and enlarged paraaortic lymph nodes were not found during the operation in the remaining patients.

Among the patients with AC, ovarian metastasis was found in one patient (1.1%, 1 of 87) with pT1b disease, no patient with pT2a disease, and five patients (23.8%, 5 of 21) with pT2b disease. Among the patients with SCC, ovarian metastasis was found in one patient (0.4%, 1 of 228) with pT1b disease, two patients (1.7%, 2 of 112) with pT2a disease, and three patients (2.6%, 3 of 114) with pT2b disease. Significant difference was found in ovarian metastatic rate between AC and SCC groups with pT2b disease (Fisher's exact test, $P=0.477$ in the patients with pT1b disease, $P=1.000$ in the patients with pT2a disease, and $P=0.002$ in the patients with pT2b disease). From the viewpoint of clinical FIGO stage, the ovarian metastatic rates in the AC group were 3.2% (3 of 95) of patients with FIGO stage IB, 0% (0 of 5) with FIGO stage IIA, and 13.6% (3 of 22) with FIGO stage IIB. Similarly, in the SCC group, the ovarian metastatic rates were 0.4% (1 of 274) of patients with FIGO stage IB, 1.9% (1 of 51) with FIGO stage IIA, and 3.1% (4 of 129) with FIGO stage IIB.

Among the 123 patients with AC, 27 patients (22%) suffered tumour recurrence. Of these, the initial failure sites were located inside the pelvis in 10 (38%) patients, outside the pelvis in 15 (58%) patients, and both inside and outside the pelvis in 1 (4%) patient. Unknown site was in one patient. Among the 455 patients with SCC, 89 (20%) patients suffered recurrence. The initial failure sites were located inside the pelvis in 28 (32%) patients, outside the pelvis in 57 (64%) patients, and both inside and outside the pelvis in 4 (4%) patients. No significant difference was found in location of initial failure sites between AC and SCC groups (χ^2-test, $P=0.288$).

Of all initial failure sites located outside the pelvis in the 15 patients with AC who recurred, the most frequent sites were distant nodes (48%) and peritoneal spread (48%), followed by the lung (8%) and bone (8%). In the 57 patients with SCC, the most frequent sites located outside the pelvis were distant nodes (48%), followed by the lung (25%), bone (16%), the liver (9%), and peritoneal spread (2%).

DISCUSSION

Since 1980, three studies using multivariate analysis have reported prognostic factors in patients with cervical AC who underwent radical hysterectomy followed by adjuvant radiotherapy. Matthews *et al* (1993) showed that only nodal positivity was the major prognostic factor for survival in 79 patients with clinical stage I disease. Irie *et al* (2000) also reported the same result in 57 patients with FIGO stage I–IIB disease (Irie *et al*, 2000). Ishikawa *et al* (1999) reported that the clinical stage, the presence of nodal metastasis, lymph-vascular space invasion, and tumour size were independent risk factors in 193 patients with FIGO stage I–IV disease, and number of positive nodes and tumour size were independent risk factors in survival and relapse among patients with FIGO stage I disease. These results were dependent on characteristics of the enrolled patients because of their small cohorts. These three reports included several pathological subtypes of adenosquamous cell carcinoma, clear cell carcinoma, or subtypes of which details were not mentioned. As for the prognostic significance of pathological subtype, conflicting results have appeared in the literature (Korhonen, 1984; Alfsen *et al*, 2001; Lea *et al*, 2003). In this study, we employed only ordinary subtypes of AC of the uterine cervix to simplify the analysis. Nonetheless, based on the literature and our data, it is reasonably certain that nodal positivity is recognised as a common independent adverse prognostic factor for survival and relapse of the patient with FIGO stage I–IIB disease who underwent radical hysterectomy. Tumour size was an independent adverse factor only for survival, and vaginal infiltration was an independent risk factor only for relapse. The following is our explanation regarding these issues. In contrast to SCC, cervical AC arises from the endocervix. The lesion expands into the endocervix and characteristically creates a bulky tumour in the cervical canal, after which it invades the vagina directly. In this study, 66% (19 of 29) of the patients in the AC group with vaginal infiltration had large-sized tumours (>40 mm), compared with 42% (74 of 175) in the SCC group. There may be multicollinearity between tumour size and vaginal invasion as assessed by the Cox model.

In this study, there was no significant difference in survival or relapse, after adjusting for other clinicopathological characteristics, between the AC and SCC groups at any pathological stage. One limitation of this study was that it was a retrospective study with a limited number of statistical events, thus, it was difficult to evaluate power calculation statistically. Grisaru *et al* (2001) reported that 799 surgically treated patients with FIGO stage IA–IB disease of AC or SCC had a similar prognosis. Look *et al* (1996) and Lee *et al* (2006) reported same results in 749 and 60 patients with FIGO stage IB disease, respectively. A similar finding was noted in a study from Fregnani *et al* (2008), in which 238 FIGO stage IB–IIA patients with AC or SCC were assessed. In these reports, radical hysterectomy followed by adjuvant radiotherapy was employed as a treatment modality. Nakanishi *et al* (2000) showed that histology of AC was an independent significant risk factor for survival and relapse in pathologic stage IB (pT1b) patients who underwent radical hysterectomy. They also reported that the prognosis of patients with AC was poorer than that of patients with SCC in the presence of lymph node metastasis, whereas the prognosis was equivalent when there was no metastasis. Although further investigation is still needed, considering our data and the present literature, radical hysterectomy followed by adjuvant radiotherapy is still considered the standard treatment option for early stage cervical AC with equivalent results for cervical SCC. However, there is still controversy regarding the advanced stage disease, that is, FIGO stage IIB. Radiotherapy has been employed as the standard treatment option for FIGO stage IIB disease in many countries, and radical hysterectomy has been adopted for stage IB–IIA disease (Suprasert *et al*, 2005). The 25th FIGO annual report from 93 centres throughout the world reported that 72% (2320 of 3233) of the patients with stage IIB disease were treated with radiotherapy (Benedet *et al*, 2003). Accordingly, few reports discuss the radical hysterectomy for patients with FIGO stage IIB cervical AC. On the other hand, it was noted that although primary radiotherapy is effective for patients with small volume stage IB AC lesions with equivalent results for SCC lesions, it does not appear to be sufficient for patients with advanced stage II or large tumour size AC lesions (Eifel *et al*, 1990, 1995; Berek, 1995). This study included the patients with stage IIB disease who also underwent radical hysterectomy. In our institute, 88% of the patients with stage IIB AC underwent radical hysterectomy of classes III and IV, and the remaining 12% were treated by primary radiotherapy during the study period. Consequently, no significant difference was found in survival or relapse between the surgically treated patients with pT2b AC and SCC lesions in this study. Considering the above facts, radical hysterectomy may be a treatment of choice for stage IIB disease in cases of AC in contrast to SCC.

The incidence of ovarian metastasis of AC lesion was significantly higher than that of SCC of pT2b lesion in this study. Similarly, Nakanishi *et al* (2001) reported that the incidences of metastasis of FIGO stages IB and IIB AC lesions were 4.0 (7 of 178) and 14.8% (4 of 27), respectively, whereas the incidences of FIGO stages IB and IIB SCC lesions were 0.5 (3 of 614) and 4.0% (7 of 175), respectively. When pathological parametrial invasion was present, the incidence increased from 3 to 25.6%. In their report, using a logistic analysis with clinicopathological variables revealed that the presence of pathological endometrial invasion, lymph node metastasis, and pathological parametrial invasion were the significant variables associated with ovarian metastasis of AC lesion. Ovarian preservation should not be recommended in cases of AC except for very early lesions.

In this study, there were no significant differences in positive rates of pelvic lymph node between AC and SCC groups at any pathological stage. In the reported literature, no differences were found in positive lymph node rates of FIGO stage IB disease, and positive rates were approximately 5–15% (Look *et al*, 1996; Irie *et al*, 2000; Lee *et al*, 2006). Few reported literature have discussed lymph node status of advanced stage, that is, FIGO stage IIB. Irie *et al* (2000) reported a higher positive rate of lymph node in patients with AC than in those with SCC of FIGO stage II disease (57.1 *vs* 26.9%). This discrepancy is probably because of the number of patients, the difference in histological subtypes of AC, and/or the difference between clinical and pathological stages.

No differences were noted in initial failure sites among the patients in the two histological groups, which were classified into inside and outside the pelvis in this study. A similar finding was reported in a study by Grisaru *et al* (2001), in which 100 patients with FIGO stage IA–IB disease were treated in the same manner. Of the distribution of the distant metastatic sites, peritoneal spread was more frequent in AC (48 *vs* 2%) in our study. Drescher *et al* (1989) reported that disseminated peritoneal involvement was twice as frequent in patients with AC from 21 autopsy findings. Although the data are not yet sufficient, disseminated peritoneal spread might be a characteristic of AC of the uterine cervix.

In conclusion, number of positive nodes is a common independent prognostic factor for survival and relapse among the FIGO stage I–IIB patients with ordinary types of AC who underwent radical hysterectomy followed by adjuvant radiotherapy. Surgically treated patients with AC or SCC have a similar prognosis and spread pattern, but not the ovarian metastasis rate.

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ORIGINAL ARTICLE

Clinicopathological significance of cervical adenocarcinoma associated with lobular endocervical glandular hyperplasia

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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

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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

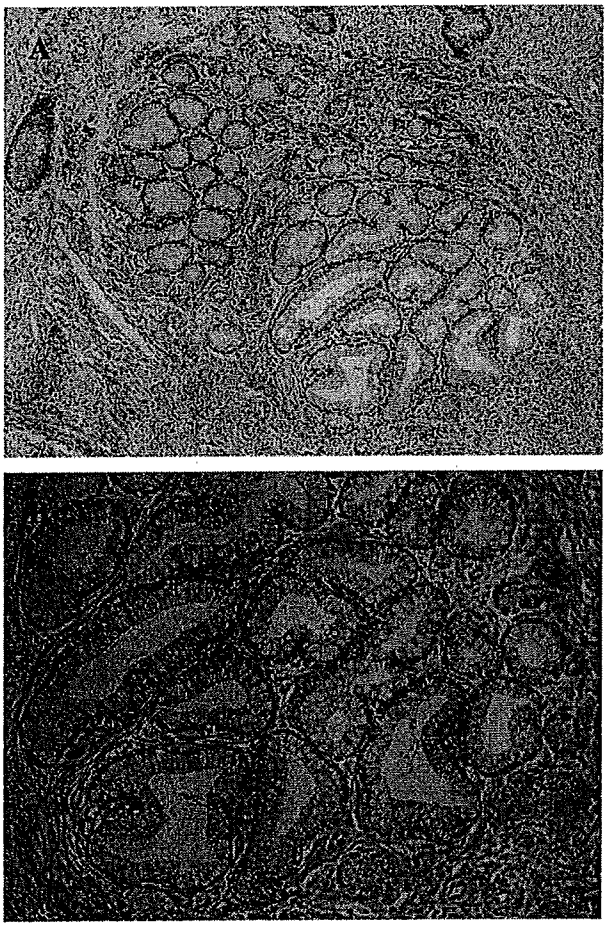

Fig. 1. Histological findings of the lobular endocervical glandular hyperplasia (LEGH) component in obvious cervical adenocarcinoma. (A) Lobular proliferation of small-to-medium-sized rounded glands surrounding larger glands. (B) Hyperplastic glandular lesions are arranged in a lobular fashion, without 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

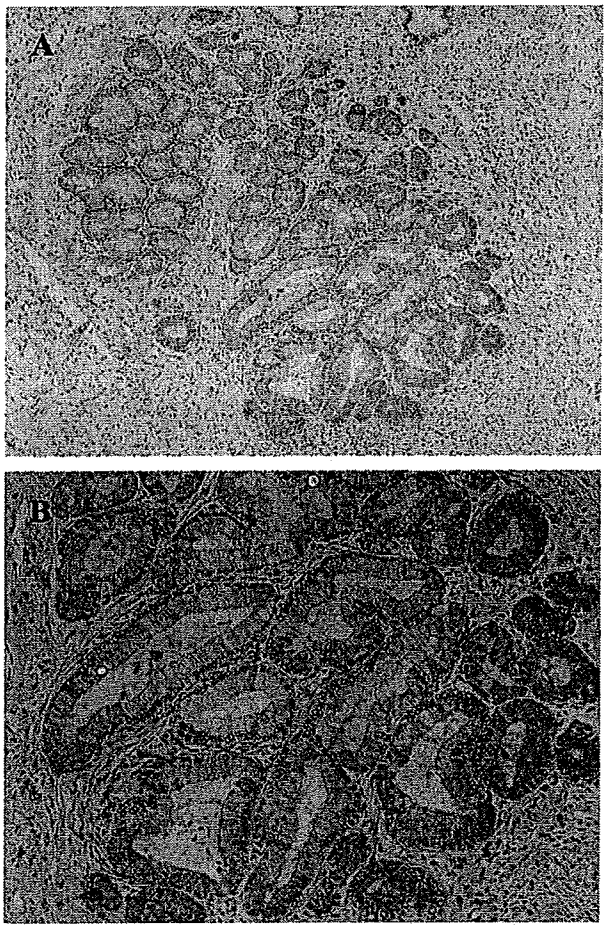

Fig. 2. Gastric mucin expression in lobular endocervical glandular hyperplasia (LEGH) components, detected on immunostaining with HIK1083. (A, B) Gastric mucin is diffusely positive in the cytoplasm of the LEGH component. Immunoperoxidase stain. Original magnification: (A) × 100; (B) × 200.

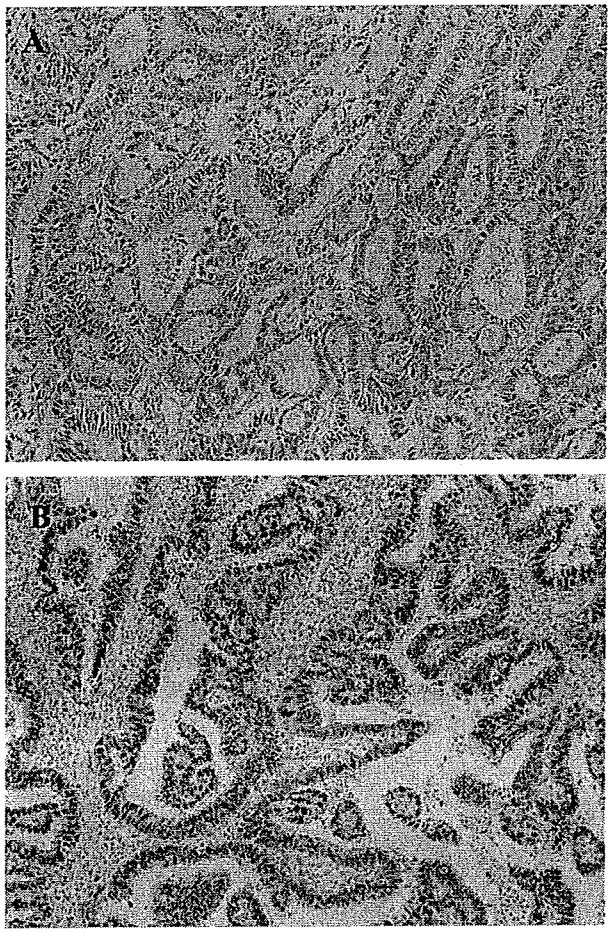

Fig. 3. $p16^{INK4a}$ expression in obvious cervical adenocarcinoma. (A) More than 10% of carcinoma cells show weak nuclear immunoreactivity, scored as 1+. (B) More than 10% of carcinoma cells show strong nuclear immunoreactivity, scored as 3+. Immunoperoxidase stain. Original magnification: (A) × 100;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

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

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 ($\geq$4 cm vs. <4 cm)	0.0002	1.91	0.55–6.57	0.30
Cervical stromal invasion ($\geq$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

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