

compartments in which regional lymph nodes are classified into the three compartments: compartment-I (N1), compartment-II (N2), or compartment-III (N3). Other nodes (N4) were considered to be distant from the EGJ. Based on this concept, the extent of lymph node metastasis (N category) was determined rationally. We consider that the extent of lymph node metastasis should be expressed not only quantitatively by the number of the metastatic lymph nodes, but also qualitatively according to the spread of lymph node metastases. The new N category is also useful to express the extent of lymph node dissection as a D grading. In the Japanese guidelines for esophageal cancer and gastric cancer [4,9], the D grading (the extent of lymph node dissection) is required to be larger than the N grading (the spread of lymph node metastasis) for complete R0 resection of cancers.

The definition of each lymph node compartment and the significance of the multiplicity values are described in Table 3. We consider that the multiplicity value indicates the efficacy of lymph node dissection [11,12]. The multiplicity value varies with the 5-year survival rate and with the observed metastatic rate. Moreover, it should be noted that the criteria for classifying lymph node compartments are changeable according to the disease, institution, and other factors. The multiplicity values described in Table 3 are values derived empirically in our studies in order to illustrate the basis for proposing the N category for cancer in the EGJ using the registration data of those cancers operated during the period from 1990 to 1999 in many Japanese institutions. These multiplicity values are therefore specific only to our study and will need further studies to be confirmed for wider generalization.

There are discrepancies in the N categories of No. 19 and No. 20 lymph nodes, between the new N category shown in Table 6 and the lymph node compartment classification based on the multiplicity values of the metastatic rate and the 5-year survival rate shown in Tables 4 and 5. Our data include those cases that underwent operation during the period from 1990 to 1999. However, the lymph nodes No. 19 and No. 20 were at first defined in the 12th edition of the *General rules for the gastric cancer study* published in 1993 [17]. Before 1993, the No. 19 lymph nodes might be classified

as being in other lymph node groups, for example, the No. 2 nodes, while the No. 20 lymph nodes might be classified as being included in among the No. 110 nodes. The No. 19 and No. 20 nodes have low frequencies of metastasis in the data, and have low multiplicity values from the metastatic rates and the 5-year survival rates. The existence and significance of these nodes should be reevaluated in future studies.

According to the new N category for an esophagus-dominant tumor, the compartment-I (N1) and compartment-II (N2) nodes can be resected by lower esophagectomy with proximal gastrectomy through a left thoracoabdominal approach. Compartment-I (N1) and compartment-II (N2) nodes for a stomach-dominant tumor can be resected by partial esophagectomy with proximal gastrectomy through a mediastinoabdominal approach – extended radical gastrectomy [6,14]. On the other hand, in order to resect compartment-III (N3) nodes for an esophagus-dominant tumor, subtotal esophagectomy with total gastrectomy through a right thoracoabdominal approach is required, and then colon interposition is needed for esophageal reconstruction. In order to resect compartment-III (N3) nodes for a stomach-dominant tumor, total gastrectomy with lower esophagectomy through a left thoracoabdominal approach is required. Complete dissection of those mediastinal lymph nodes including the compartment-III is difficult to achieve through a transhiatal approach – mediastinoabdominal approach. However, compartment-III (N3) lymph nodes need not be resected if a patient is at high risk for mortality and morbidity because of the low incidence of metastasis and poor prognosis in any case after resection of these nodes. In this new N category, we have indicated some of the N3 nodes for which lymphadenectomy can be omitted because of the low value of the metastatic rate multiplied by the 5-year survival rate.

The new N category is compared with the N category in the Japanese guidelines for esophageal cancer [4] and with that in the Japanese guidelines for gastric cancer [9] (Table 6). A majority of the lymph nodes were classified into the same N grading. The new N categories for an esophagus-dominant tumor (EG) and a stomach-dominant tumor (GE) of cancers in the EGJ are respectively similar to the N categories of cancers in the abdominal esophagus (Ae)

**Table 6.** Comparison among N categories for cancer in the esophagogastric junction

| N category            | New N category                                  |  | JSED                             |                                    | JRSGA                                |
|-----------------------|---|--|----------------------------------|------------------------------------|--------------------------------------|
|                       | EG  | GE   | Ae                               | EG/E=G/GE                          | U + E                                |
| Compartment-I<br>N1   | 110,1,2,3,7,20                                  | 1,2,3,7,20   | 1,2,3,20                         | 1,2,3                              | 1,2,3,4sa,4sb,20                     |
| Compartment-II<br>N2  | 108,111,8a,9,11,19                              | 4sa,4sb,8a,9,11,19                                     | 110,111,(4),7,9,<br>(10),(11),19 | (110),(111),(4),7,9,<br>10,11      | 4d,7,8a,9,10,11,19                   |
| Compartment-III<br>N3 | 106rec,107,(109)<br>112,(4sa),(4sb),(4d)(5),(6) | (108),110,(111),(112)<br>4d,5,6,8p,10<br>(16a2),(16b1) | 108,5,8,(112)                    | 108,(112),5,6,8,(12),<br>(13),(14) | 110, 111,112,5,6,<br>8p,12,16a2,16b1 |

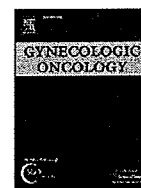
Figures in parentheses indicate lymph nodes for which dissection can be omitted under certain circumstances  
JSED, Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus (Japanese Society for Esophageal Diseases); JRSGA, Japanese Classification of Gastric Carcinoma (Japanese Research Society for Gastric Cancer); EG, esophagus-dominant tumor; GE, stomach-dominant tumor; Ae, abdominal esophagus; EG/E=G/GE, tumor located at the esophagogastric junction; U+E, upper gastric cancer with esophageal invasion

and those located in the EGJ with respect to the Japanese guidelines for esophageal cancer [4]. On the other hand, the N category of an upper gastric cancer with esophageal invasion (U + E) in the Japanese guidelines for gastric cancer [9] regards the perigastric and abdominal paraaortic nodes as more important. When it is verified that this new N category for a cancer in the EGJ is more rational than that for a cancer located in the EGJ with the Japanese guidelines of esophageal cancer [4], the new N category may replace the N-grading of a cancer in the EGJ in the guidelines.

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## Prognostic significance of positive peritoneal cytology in adenocarcinoma of the uterine cervix

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### ABSTRACT

**Objective.** A retrospective analysis was carried out to evaluate the prognostic significance of peritoneal cytology in cervical adenocarcinoma.

**Methods.** The records of 107 patients with FIGO stage IB to IIB cervical adenocarcinoma who underwent hysterectomy were reviewed.

**Results.** Sixteen patients (15%) had positive peritoneal cytology. The 5-year survival rate among patients with positive or negative cytology was 50% or 87%, respectively, showing a significant difference (log-rank,  $P < 0.001$ ). The recurrence-free survival (RFS) rate at 36 months in the cytology-positive or -negative group was 53% or 87%, respectively, the difference being significant (log-rank,  $P = < 0.001$ ). Cox model analysis revealed positive cytology [hazards ratio (HR) 6.27, 95% confidence interval (CI) 2.13–18.41], positive lymph node (HR 6.20, 95% CI 1.87–20.57), ovarian metastasis (HR 5.20, 95% CI 1.18–22.82), and histological grade (HR 5.97, 95% CI 2.00–17.78) to be independent adverse risk factors for survival among the factors analyzed (lymph node status, lymph-vascular space invasion, tumor size, depth in cervical wall, pathological parametrial involvement, infiltration to vagina, ovarian metastasis, and histological grade). Cox model analysis showed that positive cytology (HR 4.58, 95% CI 1.48–14.16), positive lymph node (HR 7.61, 95% CI 2.69–21.54), and histological grade (HR 6.13, 95% CI 2.14–17.77) were independent adverse risk factors for RFS. The incidence of peritoneal spread at the first recurrence among the cytology-positive group (62.5%) was significantly higher than that among the cytology-negative group (12.5%) (Fisher's exact test,  $P = 0.021$ ).

**Conclusion.** The presence of positive peritoneal cytology appears to be an independent prognostic risk factor in patients with cervical adenocarcinoma.

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### Introduction

The prognostic value of peritoneal cytology in ovarian carcinoma among gynecological malignancies is widely accepted, and it is included in the International Federation of Gynecology and Obstetrics (FIGO) nomenclature (1994) [1]. Although positive peritoneal cytology is included in the FIGO staging system for endometrial carcinoma (1988) [1], there is controversy regarding the significance of positive peritoneal cytology and there are conflicting reports in the literature [2]. As for cervical carcinoma, several reports on the significance of peritoneal cytology have been published [3–14]. Among patients with squamous cell carcinoma, the incidence of positive peritoneal cytology in FIGO stage I or II disease is low (0.3–1.8%), and it is considered that peritoneal cytology is of little value in

treatment planning [3,4,10]. On the other hand, most of the remaining 10% of cervical carcinoma cases have adenocarcinoma lesions [1], and few reports on the prognostic value of peritoneal cytology in patients with cervical adenocarcinoma have been published, because of the potential limitation of small cohorts of patients. The question of the prognostic value of peritoneal cytology in cervical adenocarcinoma remains unanswered. The present retrospective study was undertaken to clarify the prognostic significance of peritoneal cytology in surgically treated patients with FIGO stage IB to IIB cervical adenocarcinoma.

### Materials and methods

#### Patients

We reviewed the medical records and pathological materials that had been obtained from 1182 patients with FIGO stage IB–IVA invasive carcinoma of the uterine cervix, who were treated at the Gynecology

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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 primary invasive adenocarcinoma that originated from the uterine cervix; the patient had FIGO stage IB, IIA, or IIB disease; the patient underwent abdominal hysterectomy; the peritoneal cytology was determined in a peritoneal washing obtained by laparotomy immediately upon entering the peritoneal cavity during primary surgery; and the patient had no macroscopic extrauterine disease disseminating over the surface of the peritoneum or organs in the abdominal cavity at the primary surgery. Patients with microscopic peritoneal dissemination in the abdominal cavity that was proven by pathological analysis of the resected samples were also excluded. Patients with a tumor that directly extended to the abdominal cavity through the myometrium, or a tumor that disseminated over the surface of the adnexa were excluded. Patients who received adjuvant therapy before primary surgery were excluded. Patients with squamous cell carcinoma or other epithelial tumors including adenosquamous carcinoma were excluded. Those who had other simultaneous primary malignancy including endometrial cancer, ovarian cancer, or tubal cancer were also excluded.

All of the patients were staged according to the FIGO (1994) staging system [1]. Patients treated before 1994 were restaged retrospectively on the basis of their clinical records and pathological materials. Postoperative pathological classification was performed according to the International Union Against Cancer (UICC) TNM classification of malignant tumors [15]. Histological typing was evaluated according to the criteria of the World Health Organization International Histological Classification of Tumors [16].

#### Cytopathology

Cytopathological diagnosis was performed according to the following procedure [2]. Cytological specimens were obtained by laparotomy immediately upon entering the peritoneal cavity. Approximately 30 ml of sterile saline was instilled into the pelvis over the uterus, and then aspirated in the cul-de-sac. When a sufficient amount of ascites was present, the fluid was removed with a 20- to 30-ml syringe. The samples were subjected to cytocentrifugation onto slide glasses at 1400 rpm at room temperature for 60 s. The slides were then fixed in 95% ethanol, followed by Papanicolaou stain and Alcian blue stain. Additional slides were stained immunocytochemically for CEA (Mochida, CEA010, Tokyo, Japan), and also for epithelial antigen using an antibody against BerEP4 (DAKOPATTS, Glostrup, Denmark). Two to three cytotechnologists and cytopathologists independently examined all of the slides to make a consensus diagnosis. A patient was considered to have positive peritoneal cytology if adenocarcinoma cells were detected regardless of the number of cancer cells. In cases where atypical cells were present but they could not be definitively identified as cancer cells, the peritoneal cytology was considered to be negative in this study.

#### Treatment

Our standard surgical procedure for FIGO stage IB–IIB adenocarcinoma of the uterine cervix was abdominal radical hysterectomy with bilateral salpingoophorectomy and pelvic lymphadenectomy. If a paraaortic node was found to be enlarged at the surgery, sampling for pathological examination was performed. 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, 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-field anterior–posterior and lateral technique. Following the primary treatment, asymptomatic patients underwent pelvic examination, Pap smear, chest

radiograph, and determination of serial tumor markers every 4–6 months. Symptomatic patients underwent appropriate examinations where indicated by ultrasonography, computed tomography and/or magnetic resonance imaging.

#### Statistical methods

Survival and recurrence-free survival (RFS) curves were obtained by the Kaplan–Meier method and the survival curves were compared by nonparametric survival analysis (log-rank test). Patients were followed up through December 2007 for survival and RFS analyses. 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. Fisher's exact test or Chi-square test was used to examine the differences in distribution for categorical variables, and independent sample *t*-test was used for statistical analysis of continuous variables. A *P*-value of <0.05 was considered to indicate statistical significance. Patients who died of other causes were included as deaths in the survival analysis. All statistical analyses were performed with the statistical software package SPSS for Windows (version 11.0J; SPSS Inc., Chicago, IL, USA).

#### Results

##### *Patient and tumor characteristics*

A total of 161 patients with adenocarcinoma lesion in the uterine cervix of FIGO stage IB to IIB disease were treated during the study period. Of these 161 patients, 54 patients were excluded from the present study for the following reasons: 8 patients received primary radiotherapy, 1 patient had a lesion that involved the surface of the rectum at laparotomy, and 45 patients had no sample of peritoneal cytology. Of these 45 patients with no cytological samples, 1 patient had a tumor that disseminated to the mesosalpinx. The remaining 107 patients met the study criteria. The 107 patients were followed for 1 to 281 months, including until death, and the median follow-up period was 72 months. No patient was lost to follow-up.

Of the 107 patients, 16 patients (15%) had positive peritoneal cytology and 91 (85%) had negative cytology. The characteristics of the patients and tumors are shown in Table 1. The positive cytology rate was 15% (13/89) among those with FIGO stage IB disease, 50% (1/2) among those with stage IIA disease, and 13% (2/16) among those with stage IIB disease. The positive cytology rate among those with pT1b1 disease, pT1b2 disease, pT2a disease or pT2b disease was 7% (5/68), 31% (5/16), 22% (2/9), or 29% (4/14), respectively. In the positive cytology group, no enlarged paraaortic lymph node was found at laparotomy in any patient, and common iliac node metastasis was found in 3 patients (18.8%, 3/16). In the negative cytology group, paraaortic lymph node metastasis was proven pathologically in 1 patient, and common iliac node metastasis was found in 5 patients (5.5%, 5/91). One patient in the positive cytology group had clear cell carcinoma and one patient in the negative cytology group had mesonephritic adenocarcinoma; however, we did not determine the histological grade of clear cell carcinoma and mesonephritic adenocarcinoma in the present study because the role of the histological grade of these tumors has not been confirmed and is still controversial. Of these 2 patients, the patient with clear cell carcinoma suffered recurrence in the lung and died of the disease. The patient with mesonephritic tumor suffered recurrence in the vagina, and she was alive with disease after receiving salvage chemotherapy at 62 months. Eight patients (7%, 8/107) with pT1b1 disease in the negative cytology group underwent extrafascial simple hysterectomy without

**Table 1**  
Characteristics of the patients with cervical adenocarcinoma.

|                                       |                           | Positive peritoneal cytology<br>n = 16 | Negative peritoneal cytology<br>n = 91 | P-value |
|---------------------------------------|---------------------------|--|--|---------|
| Median age (years)                    |                           | 48 (range, 30–66)                      | 48 (range, 29–70)                      | 0.811   |
| FIGO stage                            |                           |  |  |         |
|                                       | IB                        | 13 (81%)                               | 76 (84%)                               | 0.365   |
|                                       | IIA                       | 1 (6%)                                 | 1 (1%)                                 |         |
|                                       | IIB                       | 2 (13%)                                | 14 (15%)                               |         |
| Pathological stage                    |                           |  |  |         |
|                                       | pT1b                      | 10 (62%)                               | 74 (81%)                               | 0.031   |
|                                       | pT1b1                     | 5 (31%)                                | 63 (69%)                               |         |
|                                       | pT1b2                     | 5 (31%)                                | 11 (12%)                               |         |
|                                       | pT2a                      | 2 (13%)                                | 7 (8%)                                 |         |
|                                       | pT2b                      | 4 (25%)                                | 10 (11%)                               |         |
| Number of positive pelvic lymph nodes |                           |  |  | 0.072   |
|                                       | None                      | 11 (69%)                               | 68 (75%)                               |         |
|                                       | 1–4                       | 2 (12%)                                | 14 (15%)                               |         |
|                                       | ≥5                        | 3 (19%)                                | 3 (3%)                                 |         |
|                                       | Not resected              | 0                                      | 6 (7%)                                 |         |
| Lymph-vascular space invasion         |                           |  |  | 0.171   |
|                                       | Negative                  | 4 (25%)                                | 42 (46%)                               |         |
|                                       | Positive                  | 12 (75%)                               | 49 (54%)                               |         |
| Tumor size (mm)                       |                           |  |  | 0.008   |
|                                       | ≤40                       | 6 (38%)                                | 67 (74%)                               |         |
|                                       | >40                       | 10 (62%)                               | 24 (26%)                               |         |
| Depth in cervical wall                |                           |  |  | 0.541   |
|                                       | <1/3                      | 3 (19%)                                | 29 (32%)                               |         |
|                                       | 1/3–2/3                   | 5 (31%)                                | 21 (23%)                               |         |
|                                       | >2/3                      | 8 (50%)                                | 41 (45%)                               |         |
| Pathological parametrial involvement  |                           |  |  | 0.174   |
|                                       | Negative                  | 12 (75%)                               | 73 (80%)                               |         |
|                                       | Positive                  | 4 (25%)                                | 10 (11%)                               |         |
|                                       | Not resected              | 0                                      | 8 (9%)                                 |         |
| Infiltration to vagina                |                           |  |  | 0.155   |
|                                       | No                        | 11 (69%)                               | 77 (85%)                               |         |
|                                       | Yes                       | 5 (31%)                                | 14 (15%)                               |         |
| Ovarian metastasis                    |                           |  |  | 0.105   |
|                                       | Negative                  | 14 (88%)                               | 89 (98%)                               |         |
|                                       | Positive                  | 2 (12%)                                | 2 (2%)                                 |         |
| Histological subtype                  |                           |  |  | 0.026   |
|                                       | Mucinous                  | 8 (50%)                                | 57 (63%)                               |         |
|                                       | Endometrioid              | 5 (31%)                                | 31 (34%)                               |         |
|                                       | Serous                    | 2 (13%)                                | 1 (1%)                                 |         |
|                                       | Clear cell                | 1 (6%)                                 | 0                                      |         |
|                                       | Mesonephritic             | 0                                      | 1 (1%)                                 |         |
|                                       | Undifferentiated          | 0                                      | 1 (1%)                                 |         |
| Histological grade                    |                           |  |  | 0.511   |
|                                       | Well differentiated       | 10 (63%)                               | 66 (73%)                               |         |
|                                       | Moderately differentiated | 3 (19%)                                | 13 (14%)                               |         |
|                                       | Poorly differentiated     | 2 (12%)                                | 11 (12%)                               |         |
|                                       | Unclassified              | 1 (6%)                                 | 1 (1%)                                 |         |
| Surgery                               |                           |  |  | 0.603   |
|                                       | Radical hysterectomy      | 16 (100%)                              | 83 (91%)                               |         |
|                                       | Simple hysterectomy       | 0                                      | 8 (9%)                                 |         |
| Surgical margin                       |                           |  |  | 0.150   |
|                                       | Free                      | 15 (94%)                               | 91 (100%)                              |         |
|                                       | Close                     | 1 (6%)                                 | 0                                      |         |
| Postoperative therapy                 |                           |  |  | 0.044   |
|                                       | Not done                  | 11 (69%)                               | 71 (78%)                               |         |
|                                       | Radiotherapy              | 2 (12%)                                | 17 (19%)                               |         |
|                                       | Chemotherapy              | 3 (19%)                                | 3 (3%)                                 |         |

systemic pelvic lymphadenectomy for the following reasons: 3 patients were elderly patients over 69 years of age, and 5 patients had a lesion of small volume and well-differentiated histological grade. Of these 8 patients, 1 elderly patient with moderately differentiated endocervical-type adenocarcinoma developed recurrence in the lung and died of the disease. While the tumors were completely removed in all cases, the vaginal surgical cut margin of one patient with positive cytology was close microscopically (<5 mm). This patient developed recurrence in the bone and died of the disease. Six patients (6%, 6/107) received postoperative adjuvant chemotherapy, while our standard adjuvant therapy was radiotherapy. The reasons for administration of chemotherapy were vesicovaginal fistula following surgery in 1 patient, and personal agreement between the patient and her physician at that time in the remaining 5 patients.

### Survival

The cumulative survival was assessed in subgroups according to peritoneal cytology (negative or positive), number of positive nodes

(none, 1–4, ≥5, or not resected), lymph-vascular space invasion (negative or positive), tumor size (≤40 mm or >40 mm), depth in cervical wall (<1/3, 1/3–2/3, or >2/3), pathological parametrial involvement (negative, positive or not resected), infiltration to vagina (no or yes), ovarian metastasis (negative or positive), histological subtype (mucinous, endometrioid, or other rare types), and histological grade (well, moderately, poorly differentiated, or unclassified). The 5-year survival rate was 50% [95% confidence interval (95% CI), 38–63%] among the positive cytology group and 87% (95% CI, 83–90%) among the negative cytology group, showing a significant difference (log-rank,  $P < 0.001$ ). Significant differences in survival were also found among the patients in subgroups according to the number of positive nodes, lymph-vascular space invasion, tumor size, depth in cervical wall, pathological parametrial involvement, infiltration to vagina, ovarian metastasis and histological grade (Table 2). Multivariate analysis of testing for differences in survival among these 9 significant variables was performed. The Cox model revealed that positive cytology, lymph node status, histological grade, and ovarian metastasis were independent adverse risk factors for survival (Table 3).

Similarly, the RFS was assessed in the same subgroups. The RFS at 36 months was 53% (95% CI, 40–66%) among the positive cytology group and 87% (95% CI, 83–90%) among the negative cytology group, the difference being significant (log-rank,  $P = 0.0005$ ). Univariate analysis also revealed significant differences in the RFS of patients in subgroups according to the number of positive nodes (log-rank,  $P < 0.001$ ), lymph-vascular space invasion, tumor size, depth in cervical wall, pathological parametrial involvement, infiltration to vagina, ovarian metastasis, and histological grade (Table 2). Among these 9 significant variables, the Cox model showed that positive cytology, lymph node status, and histological grade were independent adverse risk factors (Table 4).

### Spread pattern and failure sites

Eight patients (50%, 8/16) in the positive cytology group and 16 patients (22%, 16/91) in the negative cytology group suffered tumor recurrence. As to the distribution of the first recurrent site, among the 8 patients with positive cytology who recurred, the most frequent first recurrent site was peritoneal spread (62.5%, 5/8), followed by the lung (12.5%, 1/8), bone (12.5%, 1/8), and pelvis (12.5%, 1/8). Among the 16 patients with negative cytology who recurred, the most frequent first recurrent sites were the pelvis (27.8%, 5/18), lung (27.8%, 5/18), and distant node (27.8%, 5/18) followed by peritoneal spread (11.1%, 2/18) and liver (5.5%, 1/18). The incidence of peritoneal spread in the recurrent patients with positive cytology (62.5%, 5/8) was significantly higher than that in the recurrent patients with negative cytology (12.5%, 2/16) (Fisher's exact test,  $P = 0.021$ ).

### Discussion

In the present study, we found 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 who had no apparent peritoneal spread at the initial surgery, and that it seems to reflect the potential of developing to peritoneal spread. Since 1980, there have been several reports concerning the peritoneal cytology of patients with cervical adenocarcinoma [4,5,8,9,11,12,14]. In these previous reports, the incidence of positive peritoneal cytology was 0% to 20%. Most of these studies included various stages (stage I to IV), treatment modalities, or clinical status (primary or recurrent disease). Also, the number of enrolled patients was small (range, 6–69, median, 18). As for prognostic evaluation, patients with adenocarcinoma were analyzed together with patients with squamous cell carcinoma,

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

|                                       |              | No. (%)  | 5-year Survival (%) | Log-rank P-value | RFS <sup>a</sup> 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                                 |                  |

<sup>a</sup> 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).<sup>a</sup>

|                             | 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   |

<sup>a</sup> 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).<sup>a</sup>

|                             | 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  |

<sup>a</sup> 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.

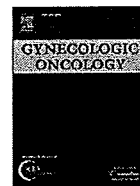
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## Radical hysterectomy for FIGO stage IIB cervical cancer: Clinicopathological characteristics and prognostic evaluation

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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.

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### 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<sup>2</sup> 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%)     |
|   | Negative                     | n = 17 (12%)      |
| 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 |
|--------------------------------------|----------|----------------------|------------------|
| <b>Parametrial involvement</b>       |          |                      |                  |
| Negative                             | 69 (50)  | 85%                  | <0.001           |
| Positive                             | 70 (50)  | 53%                  |                  |
| <b>Pelvic lymph node status</b>      |          |                      |                  |
| Negative                             | 67 (48)  | 82%                  | <0.001           |
| Positive                             | 72 (52)  | 58%                  |                  |
| n = 1–4                              | 49       | 82%                  |                  |
| n = 5–9                              | 12       | 40%                  |                  |
| n ≥ 10                               | 11       | 27%                  |                  |
| <b>Tumor size</b>                    |          |                      |                  |
| ≤ 40 mm                              | 58 (42)  | 81%                  | 0.017            |
| > 40 mm                              | 81 (58)  | 61%                  |                  |
| <b>Lymph–vascular space invasion</b> |          |                      |                  |
| Absent or a few                      | 52 (37)  | 81%                  | 0.007            |
| Several or many                      | 87 (63)  | 63%                  |                  |
| <b>Myometrial invasion</b>           |          |                      |                  |
| <1/3                                 | 5 (4)    | 100%                 | <0.001           |
| <2/3                                 | 16 (11)  | 88%                  |                  |
| <3/3                                 | 58 (42)  | 75%                  |                  |
| ≥ 3/3 <sup>a</sup>                   | 60 (43)  | 56%                  |                  |
| <b>Age</b>                           |          |                      |                  |
| <40 years                            | 29 (21)  | 66%                  | 0.4542           |
| ≥ 40 years                           | 110 (79) | 71%                  |                  |

<sup>a</sup> 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 <sup>a</sup> |
|---------------------------------|---------|--------------|---------------------|
| <b>Parametrial involvement</b>  |         |              |                     |
| Negative                        |         | 1.000        |                     |
| Positive                        | 0.001   | 3.542        | 1.992–6.297         |
| <b>Pelvic lymph node status</b> |         |              |                     |
| Negative                        | 1.00    |              |                     |
| Positive                        | 0.042   | 1.873        | 1.023–3.298         |

<sup>a</sup> 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 <sup>a</sup> | P-value               | Hazard ratio | 95% CI <sup>a</sup> |
| 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         |

<sup>a</sup> 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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# 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. *British Journal of Cancer* (2009) **100**, 1400–1405. doi:10.1038/sj.bjc.6605048 www.bjcancer.com  
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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.

## 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.

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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  $\chi^2$ -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 11.0); 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 |        | <i>P</i> -value |
|--|----------------|------|-------------------------|--------|-----------------|
|  | No.            | (%)  | No.                     | (%)    |                 |
| <i>FIGO stage</i>                            |                |      |                         |        |                 |
| IB   | 96             | (78) | 275                     | (60)   | 0.021           |
| IIA  | 5              | (4)  | 51                      | (11)   |                 |
| IIB  | 22             | (18) | 129                     | (29)   |                 |
| <i>Pathological stage</i>                    |                |      |                         |        |                 |
| pT1b   | 88             | (72) | 229                     | (50)   | <0.001          |
| pT2a   | 14             | (11) | 112                     | (25)   |                 |
| pT2b   | 21             | (17) | 114                     | (25)   |                 |
| <i>Tumour size (mm)</i>                      |                |      |                         |        |                 |
| ≤20  | 37             | (30) | 92                      | (20)   | 0.024           |
| 21–40  | 46             | (37) | 222                     | (49)   |                 |
| >40  | 40             | (33) | 141                     | (31)   |                 |
| <i>Depth in cervical wall</i>                |                |      |                         |        |                 |
| <1/3   | 34             | (28) | 68                      | (15)   | 0.002           |
| 1/3–2/3                                      | 31             | (25) | 107                     | (23)   |                 |
| >2/3   | 58             | (47) | 280                     | (62)   |                 |
| <i>Number of positive pelvic lymph nodes</i> |                |      |                         |        |                 |
| None   | 91             | (74) | 309                     | (68)   | 0.329           |
| 1–4  | 25             | (20) | 104                     | (23)   |                 |
| ≥5   | 7              | (6)  | 42                      | (9)    |                 |
| <i>Lymph–vascular space invasion</i>         |                |      |                         |        |                 |
| None   | 53             | (43) | 102                     | (22)   | <0.001          |
| Few  | 32             | (26) | 149                     | (33)   |                 |
| Several                                      | 27             | (22) | 110                     | (24)   |                 |
| Many   | 11             | (9)  | 94                      | (21)   |                 |
| <i>Infiltration to vagina</i>                |                |      |                         |        |                 |
| No   | 94             | (76) | 280                     | (62)   | 0.003           |
| Yes  | 29             | (24) | 175                     | (38)   |                 |
| <i>Ovarian metastases</i>                    |                |      |                         |        |                 |
| Negative                                     | 116            | (94) | 448                     | (98.5) | 0.024           |
| Positive                                     | 6              | (5)  | 6                       | (1.3)  |                 |
| Not resected                                 | 1              | (1)  | 1                       | (0.2)  |                 |
| <i>Surgical margin</i>                       |                |      |                         |        |                 |
| Free   | 121            | (98) | 450                     | (99)   | 0.644           |
| Close or involved                            | 2              | (2)  | 5                       | (1)    |                 |
| <i>Postoperative therapy</i>                 |                |      |                         |        |                 |
| 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) <sup>a</sup> (%) | Log-rank P-value |
|---------------------------------|----------|---------------------|------------------|-------------------------------------|------------------|
| <b>Age</b>                      |          |                     |                  |                                     |                  |
| ≤48                             | 67 (54)  | 84                  | 0.091            | 85                                  | 0.017            |
| >48                             | 56 (46)  | 77                  |                  | 80                                  |                  |
| <b>FIGO stage</b>               |          |                     |                  |                                     |                  |
| IB                              | 96 (78)  | 86                  | 0.004            | 89                                  | 0.001            |
| IIA                             | 5 (4)    | 53                  |                  | 60                                  |                  |
| IIB                             | 22 (18)  | 59                  |                  | 59                                  |                  |
| <b>Tumour size (mm)</b>         |          |                     |                  |                                     |                  |
| ≤20                             | 37 (30)  | 95                  | <0.001           | 97                                  | <0.001           |
| 21–40                           | 46 (37)  | 91                  |                  | 91                                  |                  |
| >40                             | 40 (33)  | 55                  |                  | 59                                  |                  |
| <b>Depth in cervical wall</b>   |          |                     |                  |                                     |                  |
| <1/3                            | 34 (28)  | 97                  | 0.004            | 100                                 | 0.001            |
| 1/3–2/3                         | 31 (25)  | 87                  |                  | 87                                  |                  |
| >2/3                            | 58 (47)  | 67                  |                  | 87                                  |                  |
| <b>Number of positive nodes</b> |          |                     |                  |                                     |                  |
| None                            | 91 (74)  | 91                  | <0.001           | 93                                  | <0.001           |
| 1–4                             | 25 (20)  | 60                  |                  | 63                                  |                  |
| ≥5                              | 7 (6)    | 14                  |                  | 14                                  |                  |
| <b>LVS invasion<sup>b</sup></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                                  |                  |
| <b>Parametrial invasion</b>     |          |                     |                  |                                     |                  |
| Negative                        | 102 (83) | 89                  | <0.001           | 92                                  | <0.001           |
| Positive                        | 21 (17)  | 38                  |                  | 43                                  |                  |
| <b>Infiltration to vagina</b>   |          |                     |                  |                                     |                  |
| No                              | 94 (76)  | 87                  | <0.001           | 89                                  | <0.001           |
| Yes                             | 29 (24)  | 61                  |                  | 62                                  |                  |
| <b>Ovarian metastases</b>       |          |                     |                  |                                     |                  |
| Negative                        | 94 (95)  | 84                  | <0.001           | 85                                  | <0.001           |
| Positive                        | 6 (5)    | 17                  |                  | 20                                  |                  |
| <b>Histological subtype</b>     |          |                     |                  |                                     |                  |
| Mucinous                        | 73 (59)  | 75                  | 0.543            | 78                                  | 0.180            |
| Endometrioid                    | 50 (41)  | 88                  |                  | 90                                  |                  |
| <b>Histological grade</b>       |          |                     |                  |                                     |                  |
| 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. <sup>a</sup>RFS at 36 months. <sup>b</sup>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 40mm) 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)<sup>a</sup>

|                                 | OS    |                     |         | RFS   |            |         |
|---------------------------------|-------|---------------------|---------|-------|------------|---------|
|                                 | HR    | 95% CI <sup>b</sup> | P-value | HR    | 95% CI     | P-value |
| <b>Infiltration to vagina</b>   |       |                     |         |       |            |         |
| No                              | —     | —                   | —       | 1.00  |            |         |
| Yes                             | —     | —                   | —       | 2.58  | 1.15–5.76  | 0.020   |
| <b>Tumour size (mm)</b>         |       |                     |         |       |            |         |
| ≤20                             | 1.00  |                     |         |       |            |         |
| 21–40                           | 2.25  | 0.45–11.29          | 0.323   | —     | —          | —       |
| >40                             | 6.44  | 1.35–30.71          | 0.019   | —     | —          | —       |
| <b>Number of positive nodes</b> |       |                     |         |       |            |         |
| 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. <sup>a</sup>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. <sup>b</sup>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 <sup>a</sup> |             | 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. <sup>a</sup>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 <sup>a</sup> |            | 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. <sup>a</sup>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 ( $\chi^2$ -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 adenocarcinoma, 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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## Usefulness of third-line chemotherapy for women with recurrent ovarian, fallopian tube, and primary peritoneal cancer who receive platinum/taxane regimens as first-line therapy

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### Abstract

**Background** Limited information is available regarding the usefulness of third-line chemotherapy for recurrent ovarian, fallopian tube, and primary peritoneal cancer treated with platinum-taxane regimens as first-line therapy.

**Patients and methods** We retrospectively reviewed the medical records of women with ovarian, fallopian tube, and primary peritoneal cancer who were treated at the National Cancer Center Hospital between 1999 and 2005 to investigate the relations of clinicopathological factors to important clinical endpoints such as the response rate (RR), time to progression (TTP) and overall survival (OS) after third-line chemotherapy.

**Results** A total of 172 patients received first-line platinum/taxane regimens during the study period, among whom 111 had disease progression after first-line chemotherapy. Eighty-one of these 111 patients received second-line chemotherapy, and 73 had disease progression. Fifty-four of the 73 patients with disease progression received third-line chemotherapy. The RR to third-line chemotherapy

was 40.7% (95% CI, 27.6–53.8%). The median TTP was 4.4 months (range 0–19.5 months), and the median OS was 10.4 months (range 1.5–44.3 months). Performance status (PS) and primary drug-free interval (DFI) were independent predictive factors for the RR to third-line chemotherapy ( $P = 0.04$  and  $P = 0.009$ ). PS and primary DFI were also independent predictive factors for TTP and OS on multivariate analysis ( $P = 0.006$ ,  $P = 0.005$  and  $P = 0.01$ ,  $P = 0.004$ , respectively).

**Conclusions** PS and primary DFI are useful predictors of the response to third-line chemotherapy in women with recurrent ovarian, fallopian tube, and primary peritoneal cancer. In this setting, however, both of these variables are subject to several well-established potential biases and limitations; further prospective studies are thus needed.

**Keywords** Third-line chemotherapy · Recurrent ovarian · Fallopian tube · Primary peritoneal cancer

### Introduction

Ovarian cancer remains the leading cause of death from gynecological neoplasms in the Western world (Greenlee et al. 2001). Most cases are diagnosed when the disease is advanced, resulting in poor survival (Heintz et al. 2001; Engel et al. 2002; Jemal et al. 2003). Despite high rates of objective responses to surgery and primary chemotherapy, relapse rates remain high. Recurrent disease is treated either with the same regimen as that used for first-line chemotherapy (i.e., reinduction therapy) or with second- or third-line regimens. The aim of treatment after relapse is mainly palliative, designed to control disease symptoms, maintain patients' quality of life, and prolong survival. New chemotherapeutic drugs have yielded objective response rates

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