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# Impact of human papillomavirus genotype on response to treatment and survival in patients receiving radiotherapy for squamous cell carcinoma of the cervix

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**Abstract.** To determine the clinical implications and prognostic value of the human papillomavirus (HPV) genotype, we evaluated the various HPV types in patients receiving radiotherapy for squamous cell carcinoma of the cervix. The study population included 113 invasive squamous cell carcinoma patients treated with radiation or chemoradiation between 1993 and 2002. The median age of the patients was 61 years. Tumors were classified by the International Federation of Gynecology and Obstetrics staging as stage IB in 11 patients, stage II in 39, stage III in 57 and stage IVA in 6 patients. To investigate HPV infection and its genotypes in the tumor specimens, L1 consensus PCR was performed followed by the direct nucleotide sequencing of the PCR products. Ninety-five samples (84.1%) were positive for HPV DNA. The most prevalent type was HPV-16 (34.7%). Poorer response to radiotherapy was observed in the patients with the HPV-16 genotype, in which 7 of the 33 patients had persistent disease. Only 1 of the 10 patients with HPV-58, 1 of the 5 with HPV-31 and 5 of the 10 patients with HPV-33 had a recurrence. The 5-year survival rate was 90, 80, 69.4 and 39% in the HPV-58, HPV-31, HPV-16 and HPV-33 type groups, respectively. Patients with HPV-31 and HPV-58 types were found to have better survival, whereas patients with the HPV-33 type experienced a higher risk of death. HPV genotyping may serve as a potential biomarker of response to radiation and prognosis in cervical carcinoma patients undergoing radio- or chemoradiotherapy.

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*Key words:* human papillomavirus genotype, cervical cancer, radiotherapy, chemoradiotherapy, radiation response, prognosis

## Introduction

Cervical cancer is the second most common cancer among Japanese women. Studies in several parts of the world have demonstrated a very strong association between the human papillomavirus (HPV) and cervical cancer with odds ratios of over 15 (1). Prospective studies have shown that infection with high-risk HPV precedes the development of cervical neoplasia (2). HPV has now been accepted as a necessary cause of cervical cancer (3).

It has been accepted that the prognosis of cervical carcinoma is related to clinical stage, lymph node metastasis, parametrial invasion, primary tumor size, histological type, depth of cervical stromal invasion and lymph vascular space involvement. (4) However, recurrent cervical carcinoma will develop in approximately 10-15% of stage I-IIA patients and in 30-50% of stage IIB-III patients due to variable responses to surgery or radiotherapy (5). Further stratification based on novel specific molecular markers for cervical carcinoma is crucial to improve the survival rate in this heterogeneous group of patients. This type of classification may help clinicians in developing appropriate therapeutic strategies for molecular subtyping of patients at a high risk of disease recurrence.

Although HPV infection has been established as an important initial event in the tumorigenesis of cervical carcinoma, reports on the clinical impact of different HPV types are conflicting. Previous attempts to determine the prognostic significance of the presence or absence of detectable HPV DNA and HPV types in cervical cancer patients have generated conflicting results (6-13). Some studies have reported that patients infected with HPV-18 had worse prognoses and higher disease recurrence rates than patients with HPV-16 infection (6-8,10). In a recent study, infection with multiple HPV types was also considered an indicator of poor response to radiotherapy (7,11). However, other reports did not demonstrate an association between HPV type and clinical outcome (8,9,12,13). Conversely, Lai *et al* reported that cervical carcinoma patients infected with HPV-58-related types had a favorable outcome (10). These discrepancies have made it difficult to interpret the relevance of the HPV genotype and clinical outcome.

The present study was designed to analyze the relationship between HPV DNA status and clinicopathological parameters in order to further elucidate the role of the HPV type in relation to clinical outcome of cervical carcinoma. Finally, to determine the clinical implications and prognostic value of the HPV genotype in cervical carcinoma, we evaluated whether various HPV types in patients receiving radiotherapy for squamous cell carcinoma of the cervix correlate with survival.

## Materials and methods

*Patients.* The study population included 113 invasive squamous cell carcinoma patients treated with radiation or chemoradiation between 1993 and 2002. These patients were successfully followed-up at the University of the Ryukyus Hospital, Okinawa, Japan. Patient age, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, hemoglobin level before treatment and status of lymph node enlargement were recorded after thorough clinical investigations. Written informed consent was obtained from all patients, and our Institutional Research Board approved the study.

*Radiotherapy and concurrent chemoradiotherapy.* The patients were treated with anterior-posterior and postero-anterior parallel opposed ports of external beam radiotherapy (EBRT). The dose of ERBT was 50 Gy delivered in 25 fractions. The center shield (4-cm width at the midline) was set up after delivering 40 Gy. High-dose rate intracavitary radiotherapy was delivered once a week with a fraction dose of 6 Gy at point A for 3 or 4 times. Forty patients received cisplatin (20 mg/m$^2$) for 5 days every 3 weeks, concomitant with radiotherapy (14).

*Typing of HPV DNA.* Specimens were freshly collected from biopsies. They were snap frozen in liquid nitrogen and stored at -70°C until use. Part of each specimen was examined pathologically for diagnosis. To test for the presence of HPV, the DNA extracted from the specimen was subjected to polymerase chain reaction (PCR), using an L1 consensus primer pair [L1C1 and L1C2; reported by Yoshikawa *et al* (15)], as described elsewhere (16). PCR with a β-globin primer pair was performed in parallel, and β-globin-negative samples were not included in further analyses. The L1 PCR products obtained from HPV-positive samples were stored frozen. To identify the HPV genotypes, direct nucleotide sequencing of PCR products was performed as described previously (27). Similarities of the obtained L1 sequences between those of various HPV DNA sequences in the database were examined with BLAST analysis (http://www.ncbi.nih.gov/BLAST).

*Statistical analysis.* JMP 6.0 software (SAS Institute, Cary, NC) was used for statistical analyses. Survival curves were estimated by the Kaplan-Meier method, and differences were tested by the log-rank test. Furthermore, p-values <0.05 were considered significant.

## Results

Patient characteristics are listed in Table I. The median age of the patients was 61 years (range 30-80 years). Tumors were classified by FIGO staging as stage IB in 11 patients, stage II in 39, stage III in 57 and stage IVA in 6 patients. The tumor size of the cervix, determined by magnetic resonance imaging (MRI) was ≤4 cm in 50 cases and >4 cm in the remaining 53 cases. Pelvic lymph node enlargement, which was defined as an enlargement >10 mm in the shortest dimension by computed tomography or MRI, was observed in 53 cases. Follow-up examinations were conducted every month for the first year, every other month for the second year and then every 3-6 months. During the follow-up period (median 64 months; range 6-164 months), 45 patients died, 44 deaths being directly related to the disease.

Table I. Patient characteristics.

| Variables | No. (n=113) | % |
|---|---|---|
| Age (median 61 years, range 30-80 years) | | |
| ≤50 | 34 | 30.1 |
| >50 | 79 | 69.9 |
| FIGO stage | | |
| I | 11 | 9.7 |
| II | 39 | 34.5 |
| III | 57 | 50.4 |
| IV | 6 | 4.4 |
| Tumor size | | |
| ≤4 cm | 61 | 54.0 |
| >4 cm | 52 | 46.0 |
| Lymph node enlargement | | |
| Positive | 53 | 46.9 |
| Negative | 60 | 53.1 |
| Hemoglobin level | | |
| ≤11.3 | 42 | 37.2 |
| >11.3 | 71 | 62.8 |
| Treatment | | |
| Chemoradiotherapy | 40 | 35.4 |
| Radiotherapy alone | 73 | 64.6 |
| Response to treatment | | |
| Persistence | 16 | 23.0 |
| Complete response | 97 | 77.0 |
| Prognosis | | |
| No evidence of disease | 69 | 61.1 |
| Died of disease | 44 | 38.9 |

Prevalence and the HPV genotypes in cervical carcinoma are summarized in Table II. Of the 113 specimens, 95 (84.1%) were positive for HPV DNA. The most prevalent types were HPV-16 (34.7%), HPV-33 (10.5%), HPV-58 (10.5%) and HPV-52 (7.3%). Multiple HPV infections (HPV-16 and HPV-33) were detected in only 1 sample. The relationship between HPV genotypes and clinicopathological variables are shown in Table III. The HPV genotype was found to be associated with age. HPV-16 type was found more frequently in younger patients (16 of 33 cases) as compared to other HPV

Table II. HPV genotype distribution.

| Genotype | No. | % |
|---|---|---|
| Total | 113 | |
| HPV(+) | 95 | 84.1 |
| HPV-16 | 33 | 34.7 |
| HPV-18 | 3 | 3.2 |
| HPV-31 | 5 | 5.2 |
| HPV-33 | 10 | 10.5 |
| HPV-35 | 3 | 3.2 |
| HPV-51 | 1 | 1.1 |
| HPV-52 | 7 | 7.3 |
| HPV-53 | 3 | 3.2 |
| HPV-54 | 1 | 1.1 |
| HPV-56 | 4 | 4.2 |
| HPV-58 | 10 | 10.5 |
| HPV-59 | 3 | 3.2 |
| HPV-66 | 2 | 2.1 |
| HPV-70 | 1 | 1.1 |
| HPV-73 | 1 | 1.1 |
| HPV-82 | 1 | 1.1 |
| HPV-16 + 33 | 1 | 1.1 |
| Undetermined | 6 | 6.4 |
| HPV(-) | 18 | 15.9 |

types. However, the HPV genotype was not associated with other clinicopathological parameters, namely, FIGO stage, lymph node swelling, tumor size and hemoglobin level.

Poorer response to radiotherapy was observed in the HPV-16 genotype. Although 53 of the 56 patients with other types of HPV achieved complete response to radiotherapy, 7 of the 33 patients with HPV-16 had persistent disease after completion of radiotherapy (p=0.096). In terms of disease recurrence, among patients with HPV-16, 11 had a local recurrence. Only 1 of the 10 patients with HPV-58, 1 of the 5 patients with HPV-31 and 5 of the 10 patients with HPV-33 had a recurrence. Forty-four patients (39.2%) died of cervical carcinoma at the end of the follow-up period. For overall survival, univariate analysis based on the log-rank test is summarized in Table IV. The 5-year survival rate was 90% in the HPV-58 type group (n=10), 80% in the HPV-31 type group (n=5), 69.4% in the HPV-16 type group (n=33) and 39% in the HPV-33 type group (n=10). Patients with HPV-31 and HPV-58 types were found to have better survival than patients with the HPV-16 type (Fig. 1), which was not statistically significant. However, patients with the HPV-33 type experienced a higher risk of death than patients with the HPV-58 (p=0.0508), HPV-31 (p=0.3298) and HPV-16 type (p=0.4726; Fig. 1).

## Discussion

In this study, we report the clinicopathologic factors of 113 squamous cell carcinoma patients treated with radio- or chemoradiotherapy, and the results of our analysis of these factors with regard to HPV genotypes. Previous attempts

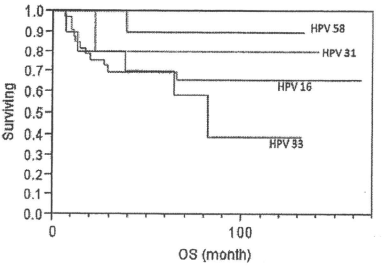


Figure 1. Kaplan-Meier curves for overall survival stratified in accordance with human papillomavirus (HPV)-16, HPV-31, HPV-33 and HPV-58 in cervical carcinoma patients.

to determine the prognostic significance of the presence or absence of detectable HPV DNA and HPV types in cervical cancer patients have generated conflicting results (6-13). These discrepancies have made it difficult to interpret the relevance of the HPV genotype and clinical outcome.

We sought to identify the prognostic significance of the HPV DNA genotype only in squamous cell carcinoma patients treated with radio- or chemoradiotherapy. A poorer response to radiotherapy was observed in the HPV-16 genotype. Although 53 of the 56 patients with other types of HPV achieved complete response to radiotherapy, 7 of the 33 patients with HPV-16 had persistent disease after completion of radiotherapy. We are not aware of such a report in the literature. Some biological difference may exist between HPV-16 and other types of HPV-positive cancer cells; we need to further investigate this using a larger population of patients.

Results of prognostic analysis showed that the HPV-58 and HPV-31 types had a tendency to predict favorable survival, thus suggesting that these 2 types may be predictors of good prognosis. Although this finding has to be substantiated in a larger number of patients, HPV genotyping has the potential to serve as a biomarker of prognosis in combination with established markers in patients with squamous cell carcinoma of the cervix.

Despite the high prevalence of HPV-58 and its related types in East Asia, the clinical behavior and prognostic value of these viral infections are unclear. The present study showed that HPV-31 and HPV-58 were more prevalent in the older age group than in the younger. Increasing prevalence of HPV types other than 16 and 18 was observed in older patients in Japan (16-18), where HPV-58 was also relatively prevalent. Patients infected with HPV-31 and HPV-58 may actually experience an indolent clinical course and develop cancer at an older age, since it was found that they were not older than other patients with squamous cell intraepithelial lesions without such infection (16). Infection by HPV-31 and HPV-58 may be partly responsible for cervical cancer in the older population in these areas. Lai *et al* (10) demonstrated that, in comparison to the HPV-16-related group, the relative risk of death in the HPV-58-related (types 58, 33 and 52) group was 0.32 (95% CI 0.07-1.49); these types were prevalent in the older population and appeared to confer a favorable prognosis. Huang *et al* (11)

Table III. Patient characteristics for each HPV genotype.

| | HPV-16 | HPV-18 | HPV-31 | HPV-33 | HPV-35 | HPV-52 | HPV-56 | HPV-58 | HPV-59 | Others | HPV-16, -33 | Undetermined | Not detected |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of patients | 33 | 3 | 5 | 10 | 3 | 7 | 4 | 10 | 3 | 10 | 1 | 6 | 18 |
| Age | | | | | | | | | | | | | |
| ≤50 | 16 | 1 | 0 | 1 | 0 | 1 | 3 | 2 | 1 | 2 | 0 | 3 | 4 |
| >50 | 17 | 2 | 5 | 9 | 3 | 6 | 1 | 8 | 2 | 8 | 1 | 3 | 14 |
| FIGO stage | | | | | | | | | | | | | |
| I | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 1 | 2 |
| II | 11 | 1 | 4 | 3 | 1 | 2 | 2 | 3 | 1 | 3 | 0 | 1 | 7 |
| III | 17 | 2 | 0 | 6 | 1 | 5 | 2 | 5 | 2 | 5 | 0 | 4 | 8 |
| IV | 2 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Tumor size | | | | | | | | | | | | | |
| ≤4.0 cm | 19 | 2 | 3 | 7 | 1 | 2 | 1 | 5 | 1 | 6 | 1 | 4 | 9 |
| >4.0 cm | 14 | 1 | 2 | 3 | 2 | 5 | 3 | 5 | 2 | 4 | 0 | 2 | 9 |
| Lymph node enlargement | | | | | | | | | | | | | |
| Positive | 15 | 1 | 3 | 1 | 2 | 4 | 3 | 3 | 2 | 4 | 0 | 4 | 11 |
| Negative | 18 | 2 | 2 | 9 | 1 | 3 | 1 | 7 | 1 | 6 | 1 | 2 | 7 |
| Hb level | | | | | | | | | | | | | |
| ≤11.3 | 13 | 1 | 2 | 3 | 1 | 3 | 3 | 3 | 3 | 1 | 1 | 2 | 5 |
| >11.3 | 20 | 2 | 3 | 7 | 2 | 4 | 1 | 7 | 0 | 9 | 0 | 4 | 13 |
| Radiation | | | | | | | | | | | | | |
| CCRT | 12 | 1 | 2 | 2 | 1 | 4 | 3 | 1 | 1 | 4 | 0 | 3 | 6 |
| RT | 21 | 2 | 3 | 8 | 2 | 3 | 1 | 9 | 2 | 6 | 1 | 3 | 12 |
| Response to RT | | | | | | | | | | | | | |
| Persistence | 7 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 6 |
| CR | 26 | 2 | 5 | 9 | 3 | 7 | 3 | 10 | 3 | 10 | 1 | 6 | 12 |
| Recurrence | 11/33 | 2/3 | 1/5 | 5/10 | 2/3 | 3/7 | 3/4 | 1/10 | 2/3 | 4/10 | 0 | 1/6 | 9/18 |
| Local | 11 | 1 | 1 | 3 | 2 | 1 | 3 | 1 | 2 | 1 | 0 | 1 | 7 |
| Distant | 0 | 1 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 3 | 0 | 0 | 2 |
| Prognosis | | | | | | | | | | | | | |
| DOD | 11 | 2 | 1 | 5 | 2 | 3 | 3 | 1 | 2 | 4 | 0 | 1 | 9 |
| NED | 22 | 1 | 4 | 5 | 1 | 4 | 1 | 9 | 1 | 6 | 1 | 5 | 9 |

CCRT, concurrent chemoradiotherapy; RT, radiotherapy; CR, complete response; DOD, died of disease; NED, no evidence of disease.

Table IV. Life-table analysis of 113 patients with cervical cancer.

| Characteristics | No. of patients | 5-year overall survival (%) | p-value |
|---|---|---|---|
| Age | | | |
| ≤50 | 34 | 57.6 | 0.300 |
| >50 | 79 | 69.1 | |
| FIGO stage | | | |
| I-II | 50 | 79.0 | 0.012 |
| III-IV | 63 | 44.7 | |
| Tumor size | | | |
| ≤4 cm | 61 | 71.0 | 0.140 |
| >4 cm | 52 | 60.0 | |
| Lymph node enlargement | | | |
| Positive | 53 | 41.6 | <0.001 |
| Negative | 60 | 86.5 | |
| Hemoglobin level | | | |
| ≤11.3 | 42 | 44.6 | <0.001 |
| >11.3 | 71 | 77.4 | |
| HPV type[a] | | | |
| 16 | 33 | 69.4 | vs. HPV16 |
| 18 | 3 | 33.0 | 0.23 |
| 31 | 5 | 80.0 | 0.50 |
| 33 | 10 | 39.0 | 0.47 |
| 35 | 3 | 33.0 | 0.42 |
| 52 | 6 | 68.0 | 0.51 |
| 56 | 4 | 25.0 | 0.07 |
| 58 | 10 | 90.0 | 0.14 |
| 59 | 3 | 67.0 | 0.67 |
| Others | 10 | 60.0 | 0.89 |
| Undetermined | 6 | 83.0 | 0.30 |

[a]One case with HPV-16 + 33 was excluded.

showed that the presence of HPV-31-related types was an independent predictor of better survival in patients with cervical carcinoma. However, in their study, HPV-31-related types included types 31, 33, 35 or 67, and hence, the results of these two studies are not exactly consistent with our findings. If the conflicting results are due to misclassification and the number of HPV cases, analyses of a larger number of patients with stratification by distinct type would be useful to clarify the discrepancies. Further investigation of the natural history of HPV-31- and HPV-58-associated cervical neoplasia and their underlying biological mechanisms are obviously warranted.

On the other hand, patients with the HPV-33 type experienced higher risk of death than patients with the HPV-16 type, which had a relatively poor response to radiotherapy and a significantly worse prognosis than patients with HPV-58 or HPV-31. With regard to HPV-33 in particular, the patients had more favorable clinicopathological factors, such as prevalence in older age, smaller tumor size, less frequent lymph node swelling and good response to radiotherapy; however, a higher rate of distant recurrence and poor prognosis were observed. Hagmar *et al* (19) found that patients with HPV-33- or HPV-18-associated tumors had worse prognoses than patients with other types of HPV infections, although the reason for this remains unclear. It is necessary to investigate the underlying biological mechanisms of HPV-33-associated cervical cancer.

Previous studies have reported that patients with HPV-18-containing tumors have an increased risk of death and disease recurrence. On the molecular level, strong evidence suggests that HPV-18 confers increased oncogenic potential, given the fact that its transforming activity was 5 times that of HPV-16 in cell culture systems (20). This finding is consistent with the findings of previous studies (8,9,11,12). Unfortunately, we were unable to confirm this since only 3 patients had HPV-18. Other groups included HPV-52, HPV-53, HPV-54, HPV-66, HPV-70, HPV-73 and HPV-82, which were all classified as intermediate- or low-risk subtypes for carcinogenesis of cervical cancer. Further investigation on the maintenance of malignant phenotypes by these intermediate- or low-risk HPV subtypes is also warranted.

The results of the present study demonstrated the possibility that HPV-58 and HPV-31 are predictors of good prognosis, HPV-33 is a predictor of poor prognosis and the HPV-16 type is a predictor of poor response in squamous cell carcinoma patients treated with radiation or chemoradiation. Although this finding must be substantiated in a larger number of patients, HPV genotyping may serve as a potential biomarker of prognosis in combination with established markers in patients with cervical carcinoma.

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ORIGINAL ARTICLE

# Prolonged long-term survival of low-grade endometrial stromal sarcoma patients with lung metastasis following treatment with medroxyprogesterone acetate

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**Abstract**
*Background* The aim of this study was to investigate the usefulness of medroxyprogesterone acetate (MPA) therapy for patients with metastatic low-grade endometrial stromal sarcoma (LGESS).
*Methods* A retrospective review was performed of five patients with metastatic LGESS lesions in whom MPA therapy prolonged survival.
*Results* The diagnosis was established by hysterectomy in all five patients. Three patients had stage I disease and two patients had stage IV. The median follow-up period was 77 months (range, 15–283 months). All five patients had recurrent disease in the lung. The median disease-free interval was 50 months (range, 7–120 months). Three of the five patients received several types of chemotherapy, and all of these patients received the same MPA (200–600 mg/day) hormonal therapy. One patient died 149 months after disease recurrence. Interestingly, after the recurrence in the lung, three patients were alive with persistent pulmonary metastases for more than 120 months. The median overall survival from the time of recurrence was 41 months (range, 9–163 months).
*Conclusion* The patients in this study demonstrate that MPA treatment may extend the survival of patients with LGESS that is metastatic to the lung.

**Keywords** LGESS · Hormonal therapy · Medroxyprogesterone acetate (MPA) · Survival

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## Introduction

Endometrial stromal sarcoma (ESS) is a rare uterine malignancy that accounts for less than 1% of all uterine cancers and approximately 7%–15% of all uterine sarcomas [1]. The tumor is classified as either low-grade endometrial stromal sarcoma (LGESS) or high-grade endometrial stromal sarcoma (HGESS) based on the mitotic rate [2]. LGESS has fewer than 10 mitoses per 10 high-power fields (HPFs) and the cell nuclei are not atypical or pleomorphic. HGESS is characterized by more than 10 mitoses per 10 HPFs, is more aggressive, frequently metastasizes, and carries a poor prognosis. LGESS is generally a slow-growing malignancy with an indolent clinical course, but with a tendency for late recurrence.

Although there is no universal staging system for ESS, the International Federation of Obstetricians and Gynecologists (FIGO) surgical staging system for endometrial cancer is used. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the standard treatment for women suffering from ESS. Debulking is recommended when extrauterine tumor is present. The role of adjuvant therapy, in the form of chemotherapy, radiation, or hormonal treatment, has not been established. Several studies have consistently shown the presence of estrogen and progesterone receptors in LGESS [3, 4]. Additionally, LGESS has recently been shown to respond to hormonal therapies including aromatase inhibitors and megestrol acetate [3, 5,

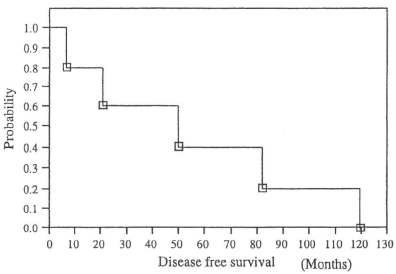


**Fig. 1** Disease-free intervals in the five patients with low-grade endometrial stromal sarcoma (LGESS). *Open squares,* patients who were alive with disease

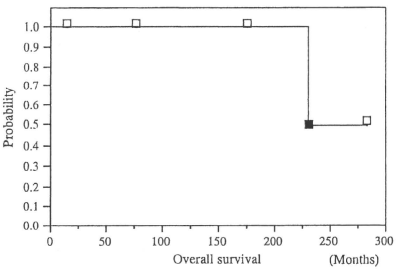


**Fig. 2** Overall survival of the five patients with LGESS. *Open squares,* patients who were still alive. *Closed square,* patient who died

6]. However, the impact of these treatments on the outcome of LGESS requires further investigation. Several reports have revealed that synthesized progestins such as medroxyprogesterone acetate (MPA) are effective as a conservative treatment of endometrial cancer [7, 8]. Recently, we reported two cases in which patients with metastatic LGESS lesions had prolonged survival with MPA therapy [9]. Herein we discuss the cases of five LGESS patients with lung metastasis who were treated with MPA and had an objective response and prolonged survival.

## Patients, methods, and results

A total of five patients with metastatic ESS, treated at the Shimane University Hospital (cases 2, 3), Tohoku University Hospital (case 1), and Ryukyu University Hospital (cases 4, 5) from 1980–2008 were identified. All five patients had LGESS according to the classification of Norris and Taylor [2].

A total abdominal hysterectomy and bilateral salpingo-oophorectomy had been performed in all patients at a median age of 43 years (range, 32–59 years). All developed pulmonary metastases. The median time from first diagnosis or hysterectomy to metastasis was 50 months (range, 7–120 months) (Fig. 1). All of the patients had recurrent disease in the lung. One of the five patients died of her disease. The overall 10 year survival rate was 100% (Fig. 2).

A summary of the patients' characteristics and clinical outcomes is listed in Table 1. Three patients did not receive first-line adjuvant chemotherapy (cases 2, 4, and 5). Case 1 received three courses of GD (gemicitabine + docetaxel) and four courses of IAP (ifosfamide + doxorubicin + cisplatin) for first-line chemotherapy. Case 3 received MPA 600 mg/day as her first-line adjuvant therapy. All patients had lung recurrences and received MPA 200–600 mg/day as hormonal therapy. All patients had a measurable lesion in the lung; four of the five patients showed a partial response (PR), and one patient showed no change (NC) as the initial response (6 months after the initial administration of MPA). All MPA treatment was administered orally. The median duration of MPA treatment for the five patients was 126 months (range, 9–163 months). In case 3, the lung metastasis progressed 67 months after the initial administration of MPA, so the hormonal therapy was changed from MPA to letrozole. Interestingly, three of the patients were alive with persistent lung metastases more than 120 months from when the lung recurrences were first detected (Fig. 3). The overall 10 year survival rate from the time of recurrence (lung metastasis) was 100% (Fig. 3). Case 2 had pulmonary metastases that were significantly attenuated following the initiation of MPA therapy. This extended her survival beyond 120 months (Fig. 4).

## Discussion

Although the behavior of LGESS is relatively indolent, late recurrences and distant metastases may occur [10]. The risk of recurrence is thought to be as high as 50%, although these tumors are usually slow growing and the recurrences occur late. In one large series, the interval between diagnosis or a hysterectomy and recurrence ranged from 3 months to 23 years, with a median interval of 3 years. In the largest clinical study to date on LGESS, the median time between a hysterectomy and relapse was 5.4 years for stage I and 9 months for stages III–IV [11]. In the present study, the median disease-free interval was 50 months, similar to that in the previous study [11].

The usefulness of lymphadenectomy for long-term survival in patients with LGESS is still controversial [12, 13].

**Table 1** Patient characteristics, treatment strategy, and outcomes

| Case | Age at hysterectomy (years) | Stage | Interval from diagnosis to recurrence (months) | Site of lesion or recurrence | 1st line chemotherapy | 2nd line chemotherapy | Current status | Alive since primary diagnosis (months) | Alive since diagnosis of recurrence (months) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | IVb | 7 | Lung | ①GD (3 courses) | ①MPA 400 mg/day | AWD | 15 | 9 |
| | | | | | ②IAP/IP (4 courses) | ②CPT-11 | | | |
| 2 | 43 | Ib | 50 | Lung, pelvic tumor | None | ①ICA (3 courses) | AWD | 175 | 126 |
| | | | | Vagina, bladder | | ②MPA 600 mg/day | | | |
| 3 | 58 | Ic | 21 | Lung, PLN, PAN | ①MPA 600 mg/day | ①MPA 600 mg/day | AWD | 77 | 41 |
| | | | | | | ②ICA (3 courses) | | | |
| | | | | | | ③Radiation (WP 50 Gy) | | | |
| | | | | | | ④Letrozole (2.5 mg/day) | | | |
| 4 | 32 | IVb | 82 | Lung | None | ①MPA 200–600 mg/day | DOD | 231 | 149 |
| 5 | 41 | Ib | 120 | Lung | None | ①MPA 200 mg/day | AWD | 283 | 163 |

*AWD* alive with disease, *DOD* died of disease, *PLN* pelvic lymph node, *PAN* para-aortic lymph node, *GD* gemicitabine + docetaxel, *MPA* medroxyprogesterone acetate, *IAP/IP* ifosfamide + doxorubicin + cisplatin/ifosfamide + cisplatin, *CPT-11* irinotecan, *ICA* ifosfamide + carboplatin + doxorubicin, *WP* whole pelvis

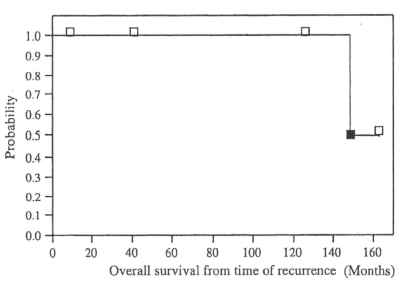


**Fig. 3** Overall survival of the five patients with LGESS from the time of recurrence. *Open squares*, patients who were still alive. *Closed square*, patient who died

In our case series, two patients were found to be at stage IVb before surgery and the other three patients were found to be at stage Ib or Ic, but they were diagnosed with LGESS after surgery. Therefore, in our case series, no patients received lymphadenectomy for either pelvic or paraaortic lesions. Only case 4 had a recurrence to pelvic and paraaortic lymph nodes, but these recurrences were controlled by using MPA.

While systematic studies of the merits of adjuvant chemotherapy in LGESS do not exist, several retrospective analyses have demonstrated a certain level of efficacy for doxorubicin and ifosfamide combination chemotherapy [14–17]. In the present study, three patients who were treated with doxorubicin and ifosfamide-containing chemotherapy achieved a partial response (data not shown).

Several case reports have described the expression of estrogen and progesterone receptors in ESS tumors and have evaluated the efficacy of progestins as a treatment modality [2, 18–21]. Studies have also investigated the effectiveness of the aromatase inhibitors aminoglutethimide, letrozole, and anastrozole (the latter in combination with progestin) in the treatment of metastatic ESS [5, 22–24]. However, no large-scale cohort studies or prospective studies of hormone treatment for ESS have been published to date. In our retrospective analysis, all five patients treated with MPA derived benefit from the hormonal therapy and had extended survivals. Our findings contrast with a recent report showing only two of the four treated patients deriving benefit from MPA [6]. This difference in the sensitivity to MPA between the patients in the present study and the previously reported cases, while intriguing, is probably the result of the small sample sizes of both studies.

The present study had the limitation that the number of patients studied was small. Larger studies with more cases are needed to clarify the significance of MPA treatment for the survival of patients with LGESS metastatic to the lung.

Due to the rarity of LGESS, relatively few publications have addressed this issue, with most data published being case reports. As shown by studies of tissue samples from recurrent LGESS, these malignancies retain their steroid receptor-positive status for an extended period; therefore, responsiveness to hormonal therapy may often cause regression or stabilization of recurrent disease [25, 26].

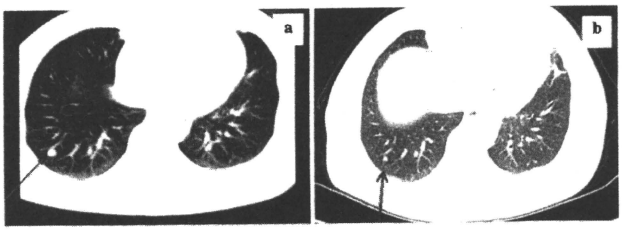


**Fig. 4** **a** Before medroxyprogesterone acetate (MPA) was started in case 2: focus on a right basal lung metastasis (*red arrow*) in a thoracic computed tomography (CT) scan performed during the survey. **b** 2 Years after the initiation of MPA treatment in case 2: control of the metastatic nodule (*red arrow*) shown in **a**, evidenced on a new thoracic CT scan. The partial response still continued 2 years after the initiation of MPA treatment

Unfortunately, the patients in the present study underwent surgery in the 1970s, so the steroid receptor status of the patients in this series was not available due to the age of the samples. In conclusion, we found that recurrent LGESS in the lung may be controlled by hormonal therapy using MPA. However, this study evaluated only a small number of patients; therefore, a larger multicenter series is needed to confirm the usefulness of MPA in patients with recurrent LGESS in the lung.

**Conflict of interest statement** The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

# Concomitant postoperative radiation and chemotherapy following surgery was associated with improved overall survival in patients with FIGO stages III and IV endometrial cancer

**Kentaro Nakayama · Yutaka Nagai · Masako Ishikawa · Yoichi Aoki · Khoji Miyazaki**

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**Abstract**
*Objective* The aim of this study was to investigate the usefulness of concomitant postoperative radiation and chemotherapy in patients with the International Federation of Gynecology and Obstetrics (FIGO) stages III and IV endometrial cancer.
*Methods* A retrospective review at Shimane University and Ryukyu University, Japan, was performed of 76 patients with FIGO stages III and IV endometrial cancer. All patients had received a comprehensive staging procedure including hysterectomy, bilateral salpingo-oophorectomy, ± selective pelvic/aortic lymphadenectomy, surgical debulking, and treatment with adjuvant chemotherapy and/or radiotherapy.
*Results* Seventy-six patients with FIGO stages III and IV endometrial cancer were identified who received postoperative adjuvant therapies; 26% ($N = 20$) received radiotherapy alone, 40% ($N = 30$) chemotherapy alone, and 34% ($N = 26$) chemotherapy and radiotherapy. The median age was 55 years; 92% had the endometrioid type and 97% were optimally debulked. The median follow-up period was 54 (range 6–188) months. Combination therapy with chemotherapy and radiation correlated with longer overall survival compared with either chemotherapy alone ($P = 0.0298$) or chemotherapy alone + radiation alone ($P = 0.0345$). Combination therapy correlated with longer overall survival compared with radiation alone with marginal significance ($P = 0.0521$). No significant differences in the disease-free interval were seen among the combination therapy and chemotherapy alone or radiation alone groups.
*Conclusion* Combined treatment with radiation and chemotherapy may improve overall survival in patients with FIGO stages III and IV endometrial cancer.

**Keywords** Endometrial cancer · Radiation therapy · Chemotherapy · Multimodality therapy · Survival

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## Introduction

Endometrial cancer is the most common gynecological malignancy and the fifth leading cancer in women worldwide [1]. The number of patients with endometrial cancer is increasing in Japan as well as in the United States and other countries [2]. The optimal management for these patients is yet to be defined, particularly for patients at the highest risk for recurrence. Postoperative therapy increases long-term survival and cure rates in patients with extrauterine disease [3, 4]. Whereas whole-pelvic (WP) irradiation therapy with or without fields extended (EXT) to include the para-aortic nodes can control local/regional disease, there is a risk of recurrence outside of the radiation field [5–7]. Radiotherapy alone following surgery has long been the standard of care for advanced-stage endometrial cancer in the United States. In Japan, however, the standard approach for patients with advanced endometrial cancer is postoperative chemotherapy. This strategy seems justifiable in light of a recent randomized study that showed a survival advantage favoring adjuvant chemotherapy compared with adjuvant radiotherapy in advanced endometrial

cancer [8]. Nevertheless, >50% of patients in that study recurred or progressed. Combined chemotherapy and radiation holds promise as a means of eradicating local/regional minimal residual disease and treating distant metastasis in patients at a high risk for recurrence [9–11]. Given the uncertainty regarding optimal adjuvant treatment for patients with advanced-stage endometrial cancer following cytoreductive surgery, we examined the outcomes of patients with advanced-stage endometrial cancer treated with postoperative adjuvant chemotherapy alone, radiation alone, or both.

## Materials and methods

A retrospective analysis of patients with surgical stages III and IV endometrial cancer, treated between 1985 and 2007, was conducted at Shimane University Hospital and Ryukyu University Hospital, Japan. The study was approved by the Institutional Review Board in each institution. Tumor registries were reviewed to identify all patients with stages III or IV endometrial cancer who received primary surgical treatment followed by adjuvant therapy with chemotherapy, radiation therapy, or both at the two university hospitals between 1985 and 2007. Inclusion criteria were surgical stages III or IV disease and a surgical procedure that included comprehensive staging with hysterectomy, lymphadenectomy (pelvic or pelvic and aortic), and cytoreduction followed by adjuvant therapy. Exclusion criteria included stage IIIa disease based on positive peritoneal cytology alone without extrauterine invasion. Operative reports were reviewed for procedures performed and surgical findings. Pathology reports were reviewed for tumor grade, depth of invasion, number of lymph nodes removed, number of positive nodes, and the presence of positive cytology and disease spread to the adnexa and uterine serosa. In this study, we considered debulking optimum if the residual was $\leq 2$ cm. Kaplan–Meier survival curves were constructed, and differences in survival were compared with the log-rank test. Chi-square and Fisher's exact test were used to identify differences between groups for categorical variables.

## Results

### Patient characteristics and adjuvant therapy

Seventy-six patients with the International Federation of Gynecology and Obstetrics (FIGO) stages III and IV endometrial cancer who received postoperative adjuvant treatment between 1985 and 2007 were identified. The median age was 55 (range 24–74) years. The dominant histologic subtype was endometrioid (70/76; 92%). Adenosquamous carcinoma and clear-cell carcinoma accounted for 7 and 1%, respectively (Table 1). Ninety-seven percent (74/76) were optimally debulked, whereas 3% (2/76) were suboptimally cytoreduced. Eighty-nine percent (68/76) and 11% (8/76) had stages III and IV disease, respectively.

Adjuvant therapy was administered to all patients and included the following: 26% received (20/76) radiation alone, 40% (30/76) chemotherapy alone, and 34% (26/76) chemotherapy and radiation (Table 1). There were no statistically significant differences between treatment groups in terms of histological subtype, grade, peritoneal cytology, and cytoreductive status (Table 1). Patients who received adjuvant chemotherapy were of a significantly higher stage (stage IV; 23%, 7/30) than patients who received combined therapy with chemotherapy and radiation (stage IV; 0%, 0/26) ($P = 0.016$). Patients who received adjuvant radiation were of a significantly lower positive peritoneal cytology (positive peritoneal cytology; 5%, 1/20) than patients who received chemotherapy (positive peritoneal cytology; 56%, 10/18) ($P = 0.009$) or combined therapy with chemotherapy and radiation (stage IV; 42%, 11/26) ($P = 0.006$). Patients receiving adjuvant radiotherapy alone ($N = 20$) received WP radiotherapy (14/20; 70%), extended-field radiotherapy (EFRT) (WP and para-aortic radiation) (5/20; 25%), and para-aortic radiation (1/20; 5%) (Table 2).

Patients receiving adjuvant chemotherapy alone ($n = 30$) received cisplatin, Adriamycin, cyclophosphamide (CAP) (22/30; 73%), paclitaxel, carboplatin (TC) (4/30; 13%), docetaxel, carboplatin (DC) (3/30; 10%), and carboplatin alone (1/30; 3%) (Table 2). Patients receiving combined chemotherapy and radiation ($n = 26$) received radiation followed by chemotherapy (6/26; 23%) and chemotherapy followed by radiation (20/26; 77%). The patients receiving multimodality therapy were treated with CAP (19/26; 73%), TC (5/26; 19%), DC (1/26; 4%), and Adriamycin, cisplatin (AP) (1/30; 3%) (Table 2). The radiotherapy regimens were as follows: WP (13/26; 50%), EFRT (12/26; 46%), and para-aortic radiation (1/26; 4%) (Table 2).

### Patient outcome

Follow-up data were available on all 76 patients. The median follow-up time among the censored patients was 54 (range 6–188) months overall; 31 (range 6–160) months for patients treated with chemotherapy alone, 61 (range 6–169) months for patients treated with radiation alone, and 66 (range 17–188) months for patients treated with combined chemotherapy and radiation. Fifty-four patients (71%) were alive, whereas 22 (29%) patients were deceased at the time of last follow-up. All patients died from cancer progression. A total of 26 patients were

**Table 1** Clinical characteristics of the International Federation of Gynecology and Obstetrics (FIGO) stages III and IV endometrial cancer

| | Radiation ($N = 20$) | Chemotherapy ($N = 30$) | Chemotherapy + radiation ($N = 26$) |
|---|---|---|---|
| Age | | | |
| Mean (SD) | 56 (11.8) | 53 (9.7) | 54 (9.3) |
| Median (range) | 58 (24–72) | 53 (32–70) | 55 (31–70) |
| Histology | | | |
| Endometrioid | 18 | 28 | 24 |
| Adenosquamous | 2 | 2 | 1 |
| Clear cell | 0 | 0 | 1 |
| Grade | | | |
| 1 | 12 | 9 | 13 |
| 2 | 2 | 10 | 6 |
| 3 | 4 | 8 | 6 |
| Unknown | 2 | 3 | 1 |
| FIGO stage | | | |
| IIIa | 4 | 8 | 4 |
| IIIb | 0 | 1 | 1 |
| IIIc | 19 | 14 | 21 |
| IVb | 1 | 7 | 0* |
| Peritoneal cytology | | | |
| Positive | 1 | 10** | 11*** |
| Negative | 19 | 8 | 15 |
| Unknown | 0 | 2 | 0 |
| Debulking status | | | |
| Optimal | 20 | 28 | 20 |
| Suboptimal | 0 | 2 | 0 |

*$P = 0.016$ (chemotherapy vs. chemotherapy + radiation)
**$P = 0.0009$ (radiation vs. chemotherapy)
***$P = 0.006$ (radiation vs. chemotherapy + radiation)

**Table 2** Summary of interventions in radiation, chemotherapy, and combined chemotherapy and radiation

| Modality | Radiation ($N = 20$) | Chemotherapy ($N = 30$) | Chemotherapy + radiation ($N = 26$) |
|---|---|---|---|
| Surgery | | | |
| TAH + BSO ± omentectomy | 2 | 3 | 2 |
| TAH + BSO ± PLND ± PALND ± omentectomy | 12 | 22 | 14 |
| mRH + PLND ± PALND ± omentectomy | 1 | 4 | 8 |
| RH + PLND ± PALND ± omentectomy | 5 | 1 | 2 |
| Chemotherapy | | | |
| CAP (6–12 courses) | | 22 | 19 |
| TC (6 courses) | | 4 | 5 |
| DC (6 courses) | | 3 | 1 |
| AP (4 courses) | | | 1 |
| CBDCA | | 1 | |
| Radiation | | | |
| WP (45–50.4 Gy) | 14 | | 13 |
| EFRT (36–50.4 Gy) | 5 | | 12 |
| WA 45.6 Gy | | | |
| PAN 45 Gy | 1 | | 1 |

*TAH* total abdominal hysterectomy, *BSO* bilateral salpingo-oophorectomy, *PLND* pelvic lymphadenectomy, *PALND* para-aortic lymphadenectomy, *mRH* modified radical hysterectomy, *RH* radical hysterectomy, *CAP* cisplatin + adriamycin + cyclophosphamide, *TC* paclitaxel + carboplatin, *DC* docetaxel + carboplatin, *AP* adriamycin + cisplatin, *CBDCA* carboplatin, *WP* whole pelvic irradiation, *EFRT* extended-field irradiation, *WA* whole abdominal irradiation, *PAN* para-aortic irradiation

**Table 3** Recurrence site stratified by type of adjuvant administered

| Recurrence site | Radiation ($N = 20$) | Chemotherapy ($N = 30$) | Chemotherapy + radiation ($N = 26$) |
|---|---|---|---|
| Vaginal | 0 (0%) | 2 (18.2%) | 1 (14.3%) |
| Pelvic (without vagina) | 1 (12.5%) | 5 (45.4%) | 0 (0%) |
| Extrapelvis | 7 (87.5%) | 4 (36.4%) | 6 (85.7%) |

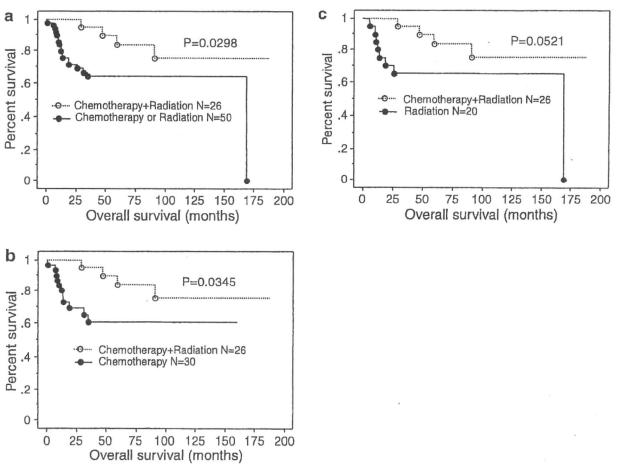


**Fig. 1** Kaplan–Meier overall survival analysis for women with advanced endometrial cancer by adjuvant treatment group. **a** Combination radiation and chemotherapy correlated with longer overall survival compared with the chemotherapy alone or radiation alone group ($P = 0.028$). **b** Combination radiation and chemotherapy correlated with longer overall survival compared with chemotherapy alone ($P = 0.0345$). **c** Combination therapy correlated with longer overall survival compared with radiation alone with marginal significance ($P = 0.0521$)

identified as having either recurrence or disease progression. Forty percent (8/20), 37% (11/30), and 27% (7/26) of patients treated with radiation alone, chemotherapy alone, and combined chemotherapy and radiation, respectively, had either a documented tumor recurrence or disease progression (Table 3). Of the 26 patients who had a documented site of recurrence or progression, nine (35%) were in the pelvis or vagina and 17 (65%) in a distant site. The percentage of documented distant recurrences was higher in the radiation alone (35%) (7/20) and combined radiation and chemotherapy (23%) (6/26) groups than in the chemotherapy alone (13%) (4/30) group; however, these findings were not statistically significant (Table 3).

Kaplan–Meier estimates of disease-free/overall survival are plotted in Figs. 1 and 2. Kaplan–Meier 5-year overall survival rates associated with radiation, chemotherapy, and combined therapy with chemotherapy and radiation were 62, 60, and 82%, respectively (Fig. 1).

Combination therapy with chemotherapy and radiation correlated with longer overall survival compared with either chemotherapy alone ($P = 0.028$) or chemotherapy alone + radiation alone ($P = 0.0345$) (Fig. 1). Combination therapy correlated with longer overall survival compared with radiation alone with marginal significance ($P = 0.0521$) (Fig. 1). No significant differences in the disease-free interval were seen following treatment with combination therapy and chemotherapy alone or radiation alone in patients with stages III and IV endometrial cancer (Fig. 2). Treatment completion rate of radiation alone, chemotherapy alone, and combined chemotherapy and radiation were 100% (20/20), 100% (30/30), and 80% (20/25), respectively. Combined chemotherapy and radiation was well tolerated in the majority of patients (Table 4). Two of 26 (7.7%) patients had grade 4 chronic small-bowel complication, and one of 26 (3.8%) patients had grade 3 chronic renal dysfunction in the combined chemotherapy and radiation group (Table 4). Radiation alone and chemotherapy alone had no grade 3 or 4 chronic toxicity.

## Discussion

Advanced endometrial cancer patients generally have a poor long-term prognosis if treated with surgery only.

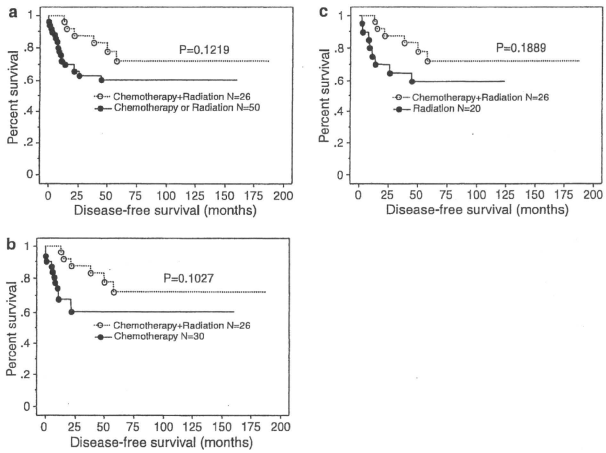


**Fig. 2** Kaplan–Meier progression-free survival analysis for women with advanced endometrial cancer by adjuvant treatment group. **a–c** No significant disease-free differences between combination therapy and chemotherapy alone and/or radiation alone were found in patients with stages III, IV endometrial cancer

**Table 4** Late chemotherapy + radiotherapy toxicity ($n = 26$)

| Toxicity | Grade 3, 4 |
|---|---|
| Skin | 0 |
| Vaginal mucosa | 0 |
| Small bowel | 2 (7.7%) |
| Large bowel | 0 |
| Bladder | 0 |
| Bone | 0 |
| Renal | 1 (3.8%) |
| Hematologic | 0 |
| Nausea/vomiting | 0 |
| Other | 0 |
| Total | 3 (11.5%) |

Various postoperative adjuvant treatment regimens, including radiotherapy, chemotherapy, and hormonal therapy, have been used in the attempt to reduce the risk of pelvic and distant recurrences. A standard regimen, however, has not been established. There is much debate about the optimal adjuvant therapy after surgery. Historically, endometrial cancer patients receive adjuvant radiation therapy to reduce the risk of pelvic relapse; [12, 13] but this does not seem to improve overall survival because it does not reduce the risk of distant recurrence. The efficacy of adjuvant chemotherapy alone, however, has also not been established [14].

The majority of patients with advanced-stage endometrial cancer who recur does so in a distant location [3–5, 8]. Several active chemotherapy agents have been identified in endometrial cancer [15]. The Gynecologic Oncology Group (GOG) 122 is the first randomized multi-institutional study to compare whole abdominal radiation therapy (WAI) versus chemotherapy in patients with optimal residual advanced-stage disease. This study has revealed improved hazard ratios for progression and death of 0.71 and 0.68, respectively, in favor of AP compared with WAI. Patterns of recurrence differed between the two treatment modalities, as chemotherapy was more effective than WAI in preventing distant recurrence (10 vs. 19%), albeit at the cost of a higher pelvic failure rate compared with the WAI arm (18 vs. 13%). This may be addressed by the addition of radiation [8]. Others have reported high pelvic recurrence rates when chemotherapy is used as the sole adjuvant therapy for patients with advanced endometrial cancer [16]. Combination of radiotherapy and chemotherapy is a potential strategy that may be used to improve both local and distant disease control.

In this study, we report that combined multimodality therapy with adjuvant chemotherapy and radiation may improve survival in patients with advanced-stage disease compared with either modality alone. Our findings in patients who were treated with multimodality adjuvant therapy are consistent with other studies reported in the literature [9, 10, 15, 17, 18]. Alvarez Secord et al. reported on 356 patients with advanced endometrial cancer who were treated with multimodal therapy with adjuvant chemotherapy and radiation. This regimen achieved 3-year progression-free (PFS) and overall (OS) survival of 62 and

79%, respectively [10]. Our 5-year PFS and OS for patients treated with both chemotherapy and radiation were 75 and 82%, respectively. Onda et al. reported that radiation combined with chemotherapy for FIGO stage IIIc endometrial cancer resulted in a 5-year OS rate of 84%, and Bruzzone et al. showed that combined therapy enhanced PFS to 30% at 9 years and OS to 53% at 9 years in FIGO stages III–IV endometrial cancer patients [17, 18]. In contrast to previous studies, in this study, we found no significant difference in PFS and extrapelvic recurrence rate between multimodality therapy and radiation alone or chemotherapy alone. This may be due to the small sample size in this study. Further larger, prospective, randomized studies are required to clarify our findings. Our results and those of prior reports suggest that multimodality therapy may improve survival in patients with advanced-stage endometrial cancer.

There is no general consensus among gynecologic or radiation oncologists regarding radiation strategies. At different centers, patients might undergo WAI, or WP radiation, or WP plus para-aortic radiation (EFRT) [19, 20]. Mundt et al. [21] reviewed failure patterns among their patients and found that the optimal adjuvant radiation volume was EFRT, even in women with negative para-aortic lymph node sampling. In our study patients, a multitude of radiation regimens was used, and given the limited sample size, we were unable to detect survival differences between the various radiotherapy treatment algorithms.

In the early 1990s, the CAP regimen was used as the standard chemotherapy for endometrial and ovarian cancer in Japan [22]. Most Japanese gynecologic oncologists have adopted CAP as the standard adjuvant chemotherapy over AP. Therefore, in this study, the dominant chemotherapy regimen was CAP. In Japan, the type of hysterectomy chosen for endometrial cancers (type II modified radical hysterectomy vs. type III radical hysterectomy) differs among institutions [22]. However, in most institutions, radical hysterectomy is generally selected only for patients with macroscopically apparent cervical involvement. Due to the small sample size of this study, we were unable to detect survival differences among the various chemotherapy regimens and various surgical procedures. Although the sample size was small and this was a retrospective analysis, the findings suggest that advanced endometrial cancer may respond to an adjuvant regimen combining chemotherapy and radiotherapy.

Patients identified as FIGO stage IIIa due to positive peritoneal cytology alone often have an excellent prognosis [23, 24]. Positive peritoneal cytology alone will no longer be considered stage IIIa disease in the FIGO surgical staging system of endometrial cancer [25]. Therefore, patients with stage IIIa due to positive peritoneal cytology alone were excluded from this study.

In conclusion, patients with advanced-stage endometrial cancer who are treated with combined modality adjuvant therapy with chemotherapy and radiation may have improved survival compared with those treated with either chemotherapy alone or radiation alone. Larger, prospective studies are now needed to further evaluate outcomes in patients with advanced-stage endometrial cancer treated with multimodal therapy.

**Conflict of interest statement** No author has any conflict of interest.

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ワークショップ(3) 子宮体癌治療の厳しさ

# 3. 子宮体部類内膜腺癌G3，漿液性腺癌，明細胞腺癌の臨床背景と治療予後

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長井 裕 青木 陽一

## はじめに

子宮体癌には臨床病理学的に異なる2つのタイプが存在し，ひとつはエストロゲン依存性の子宮体癌でTypeIと呼ばれ，閉経期もしくはその前の比較的若年の女性に発症する．これに対して，エストロゲンには依存せず，主に閉経後の高齢者に発症するのがType2であり，類内膜腺癌Grade3（ECG3），漿液性腺癌（Uterine papillary serous carcinoma；UPSC），明細胞腺癌（Uterine clear cell carcinoma；UCCC）をその組織型とし，子宮体癌全体としての頻度は低いがTypeIと比較して低分化型であり，体部筋層浸潤が深く，リンパ節転移も高率であり，その結果5年生存率は30%以下ときわめて予後不良といわれている．今回我々は予後不良とされるECG3, UPSC, UCCCの臨床背景，治療法，予後について報告し，その中でもUPSCとUCCCについて文献的考察を若干加えて報告する．

## 対象および方法

### 対象

1985年から2007年に当科にて診断，治療を行った子宮体癌450例中ECG3, UPSC, UCCCと診断された66例を対象とし，診療録を後方視的に調査・検討した．①全66例の患者背景，初診時主訴とECG3症例の治療前子宮鏡所見のまとめ②各組織型の治療方法と予後にわけて検討した．生存曲線はKaplan-Meier法を使用しLog-rank testにて有意差検定を行った．

### 方法

当科での子宮体癌に対する治療方針を記す．当科では類内膜腺癌と特殊型で治療方針の変更を行わないこととしている．但し2006年を境に治療方針の変更があり，2006年以前はI～II期のintermediate risk症例には放射線治療を施行していたが，GOG99, PORTEC-1などの結果と当科の治療成績を再検討し，それ以降は化学療法をIc期のG3と脈管侵襲陽性例にのみ施行する方針としている．III～IV期の治療方針は手術療法に加えて術後化学療法を主体としているが，III期症例には放射線療法を適応としていた症例も認められる．また傍大動脈リンパ節陽性例には化学療法と放射線療法の併用療法を施行していたが2006年以降はIII, IV期に関しては術後療法として化学療法を施行する方針としている．化学療法のレジメンは現在ドセタキセルとカルボプラチンの併用療法を院内の臨床試験として施行中である．

## 結 果

①全例の患者背景，初診時主訴，ECG3症例の治療前子宮鏡所見

患者背景を表1に示す．観察期間の中央値は37カ月，治療年齢の中央値は60歳で，分娩歴は19例が未産婦であり，44例が経産婦であった．組織型はECG3が49例，UPSC11例，UCCC6例であっ