Table 5 Results of recent studies

Factors	Reference					Present study
	[9]	[10]	[11]	[4]	[12]	
No. of patients	64	30	101	114	73	42
Age, years (range)	29.5[a] (11–41)	32.5[b] (23–41)	31[b] (19–43)	33[a] (25–40)	31[a] (22–39)	32[a] (22–39)
FIGO stage						
1A1	16	0	3	9	5	1
1A2	7	2	8	12	10	4
1B1	36	25	88	93	58	37
≤2 cm	22	20	–	–	29	34
>2 cm	14	5	–	–	24	3[c]
≥1B2	0	3	2	0	0	0
Histology						
SCC	50	15	40	99	64	42
Non-SCC	12	15	61	15	9	0
Median follow-up, months	22.8	24	–	33	20.6	29.9
Recurrences	0	2	0	–	0	3
Pregnancy	2	3	28	31	0	5
Median operation time, min	148	170	–	–	177[b]	304
Median blood loss, ml	–	813	–	–	322[b]	848
Blood transfusion, %	6.25	20	–	–	–	11.9
Median no. of PLN retrieved	25	24	24	–	26	35

FIGO International Federation of Gynecology and Obstetrics, *SCC* squamous cell carcinoma, *PLN* pelvic lymph node

[a] Median value

[b] Mean value

[c] Postoperative evaluation

cervical stenosis has been reported as a major complication of trachelectomy, the frequency of postoperative cervical problems has been reported to range from 7.8 [9] to 21 % [13]. Moreover, recent results of total laparoscopic radical trachelectomy [14] reported that 52 % of patients also needed assisted reproductive technology, though intra-pelvic inflammation was correlated with fertility problems. Although the detailed mechanisms are still unknown, less-invasive surgical procedures should be performed to prevent surgical complications, including fertility problems. A more recent review reported that less-radical surgical options, such as simple trachelectomy and cervical conization with or without sentinel lymph node biopsy and pelvic lymph node dissection, may be considered for cases of low-risk early-stage cervical cancer, including squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma; tumor size <2 cm; stromal invasion <10 mm [15]. Previously, we have reported the usefulness of sentinel lymph node detection in early-stage cervical cancer [16–18]. As the results of robot-assisted laparoscopic radical trachelectomy have been recently reported [19], radical trachelectomy using a robot-assisted laproscopic approach with sentinel lymph node sampling may be implemented in the near future.

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Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Evaluation of postoperative chemotherapy in patients with uterine carcinosarcoma: a retrospective survey of the Tohoku Gynecologic Cancer Unit

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Abstract
Background The aim of this study was to evaluate prognostic factors including efficacy of postoperative chemotherapy in Japanese patients with uterine carcinosarcoma.
Methods We conducted a retrospective survey of seven medical facilities in the Tohoku Gynecologic Cancer Unit.
Results A total of 45 patients who had undergone hysterectomy and bilateral salpingo-oophorectomy were enrolled. No significant difference was observed in overall survival according to patient age (≤50 years vs >50 years) or retroperitoneal lymphadenectomy (performed vs. not performed). However, the International Federation of Gynecology and Obstetrics stage (stage I/II vs stage III/IV) and postoperative chemotherapy (provided vs not provided) were significant prognostic factors in both univariate and multivariate analyses for the 25-month median follow-up period.
Conclusions Our results revealed that postoperative chemotherapy should be considered for all uterine carcinosarcoma stages in Japanese patients.

Keywords Uterine carcinosarcoma · Prognostic factor · Chemotherapy · Retrospective study

Introduction

Carcinosarcoma is a rare, aggressive tumor with a poor prognosis and consists of both carcinoma and sarcoma components [1–3]. We previously completed a retrospective study on factors affecting the prognosis of carcinosarcoma, endometrial stromal sarcoma, and leiomyosarcoma [4], and reported that chemotherapy did not significantly predict overall survival for endometrial stromal sarcoma ($p = 0.0714$) or leiomyosarcoma ($p = 0.989$). However,

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the effect of postoperative chemotherapy on overall survival in carcinosarcoma remains unknown. Moreover, according to the results of phase III trials conducted by the Gynecologic Oncology Group (GOG), the National Comprehensive Cancer Network (NCCN) guidelines (version 1.2014) recommend postoperative chemotherapy using a combination of ifosfamide and cisplatin [5] or ifosfamide and paclitaxel [6] for all stages of carcinosarcoma.

Nevertheless, ifosfamide-based combination regimens are frequently accompanied by severe hematological toxicities; ifosfamide and cisplatin resulted in grade 3/4 hematological toxicities including leukopenia (87 %), granulocytopenia (60 %), and thrombocytopenia (58 %) [5], and ifosfamide and paclitaxel with granulocyte-colony stimulating factor led to leukopenia (31 %), granulocytopenia(38 %), and thrombocytopenia (3 %) [6]. Furthermore, death following ifosfamide and cisplatin treatment has been reported [7]. Therefore, we conducted a multicenter survey and analyzed treatment outcomes in Japanese uterine carcinosarcoma patients to evaluate different chemotherapy regimens and to determine if postoperative chemotherapy could predict prognosis even in early stage patients.

Materials and methods

The survey, with unlinkable anonymization, was conducted by mail between January 1995 and December 2005 at the following medical facilities—Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine; Department of Obstetrics and Gynecology, Hirosaki University School of Medicine; Department of Obstetrics and Gynecology, Iwate Medical University; Department of Obstetrics and Gynecology, Akita University Graduate School of Medicine; Department of Obstetrics and Gynecology, Yamagata University Faculty of Medicine; Department of Obstetrics and Gynecology, Fukushima Medical University; and Department of Gynecology, Miyagi Cancer Center. The survey collected information on patient age, whether the patient had undergone retroperitoneal lymphadenectomy, surgical staging determined by the International Federation of Gynecology and Obstetrics (FIGO; 1988), chemotherapy regimens, and prognosis following hysterectomy and bilateral salpingo-oophorectomy. The survey was approved by the ethics committee of each of the participating facilities. A standardized computer software package (JMP 9, SAS Institute Japan, Tokyo, Japan) was used for statistical analysis. The log-rank test and Cox hazard test were used to analyze data, and p values of <0.05 were considered significant.

Results

Patients

A total of 45 histopathologically confirmed uterine carcinosarcoma patients were enrolled into this survey. Patient characteristics are shown in Table 1. All patients underwent hysterectomy and bilateral salpingo-oophorectomy, and 27 (60.0 %) received postoperative chemotherapy. The postoperative chemotherapy regimens were ifosfamide, epirubicin, and cisplatin in 13 patients; cyclophosphamide, doxorubicin, and cisplatin in 6 patients; paclitaxel, doxorubicin, and carboplatin in 4 patients; paclitaxel and carboplatin in 3 patients; and doxorubicin and cisplatin in 1 patient. The median follow-up period was 25 months (1–166 months). However, confirmation of the detailed histopathological component of the carcinosarcomas (homologous or heterologous) remained at 25 (55.6 %) patients.

Survival analysis

Figure 1 shows the overall survival of all enrolled patients; the median survival time was 27.8 months. Furthermore,

Table 1 Patient characteristics

Number of patients	45
Median age (range)	60 (30–94)
Stage (FIGO, 1988)	
I	18
II	3
III	1
IV	8
Types of sarcoma component	
Homologous	10
Heterologous	15
Not obtained	20
Retroperitoneal lymphadenectomy	
Performed	30
Not performed	15
Chemotherapy	
Provided	27
IEP	13
CAP	6
PEC	4
TC	3
AP	1
Not provided	18

FIGO International Federation of Gynecology and Obstetrics, *IEP* ifosfamide, epirubicin, and cisplatin, *CAP* cyclophosphamide, doxorubicin, and cisplatin, *PEC* paclitaxel, doxorubicin and carboplatin, *TC* paclitaxel and carboplatin, *AP* doxorubicin and cisplatin

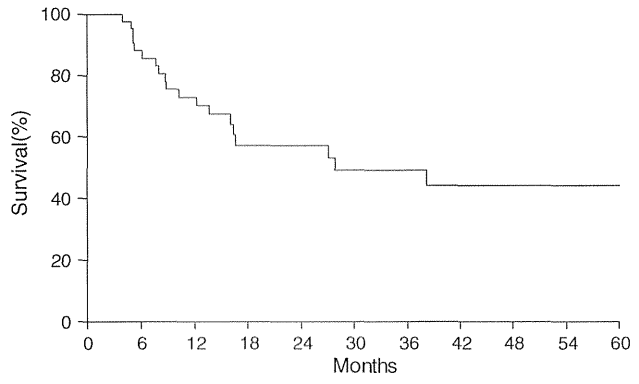

Fig. 1 Overall survival in patients with uterine carcinosarcoma. The median survival time was 27.8 months

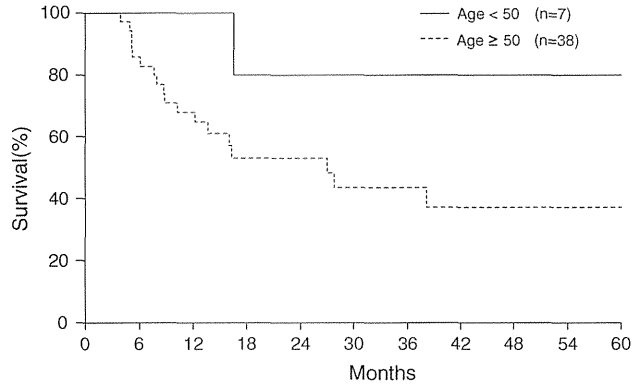

Fig. 2 Overall survival in patients with uterine carcinosarcoma subdivided by patient age. No significant survival difference was observed between <50 years and ≥50 years ($p = 0.091$)

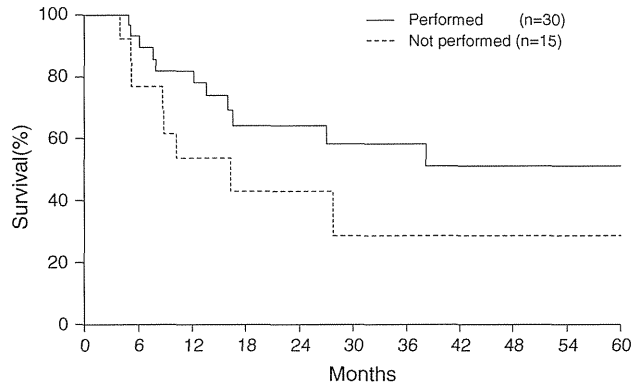

Fig. 3 Overall survival in all patients with uterine carcinosarcoma subdivided by retroperitoneal lymphadenectomy. No significant survival difference was observed with regard to retroperitoneal lymphadenectomy ($p = 0.123$)

no significant survival difference was observed with regard to patient age (<50 years vs ≥50 years, $p = 0.091$; Fig. 2) or retroperitoneal lymphadenectomy (performed vs not performed, $p = 0.123$; Fig. 3). Moreover, while the

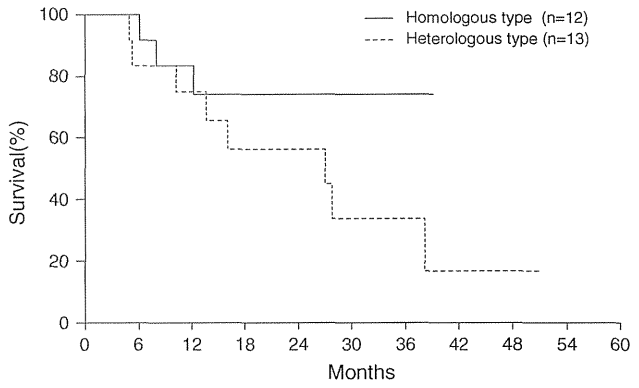

Fig. 4 Overall survival in patients with uterine carcinosarcoma subdivided by sarcoma component. No significant survival difference was observed between the homologous and heterologous types ($p = 0.248$)

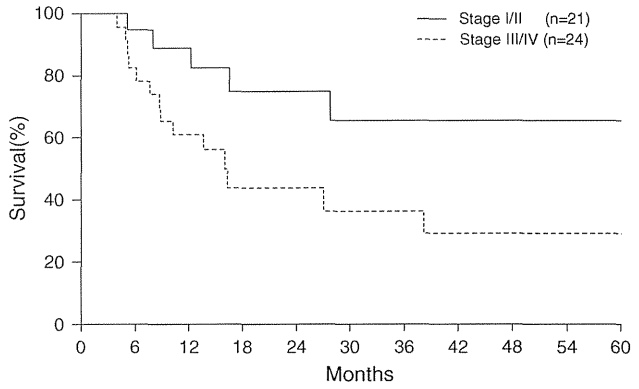

Fig. 5 Overall survival in patients with uterine carcinosarcoma subdivided by postoperative chemotherapy. Postoperative chemotherapy significantly predicted the survival of patients ($p = 0.049$)

number of patients with complete information was insufficient, no significant survival difference was observed according to the histological subtype of the sarcoma component (homologous vs heterologous, $p = 0.248$; Fig 4). However, the FIGO stage (I/II vs III/IV, $p = 0.034$; Fig. 5) and postoperative chemotherapy (provided vs not provided, $p = 0.049$; Fig. 6) significantly predicted survival. Moreover, multivariate analysis showed that both the FIGO stage ($p = 0.017$) and postoperative chemotherapy ($p = 0.018$) were significant prognostic factors for uterine carcinosarcoma patients who underwent hysterectomy and bilateral salpingo-oophorectomy (Table 2).

Discussion

Uterine carcinosarcoma has been classified as a type of endometrial carcinoma, and FIGO staging and recommendation for the primary treatment of uterine carcinosarcoma in the NCCN guidelines are also similar to those

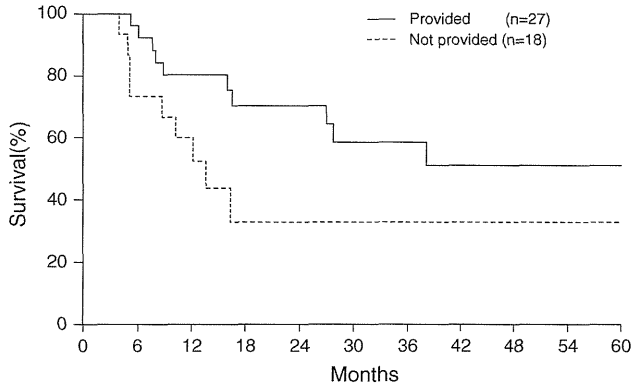

Fig. 6 Overall survival in patients with uterine carcinosarcoma subdivided by stage. The FIGO stage significantly predicted the survival of patients ($p = 0.034$)

Table 2 Prognostic significance

Factor	Hazard ratio	95 % CI	p value
Chemotherapy (performed vs not performed)	3.208	1.219–8.441	0.018
Stage (I/II vs III/IV)	3.620	1.254–10.451	0.017

CI confidential interval

for endometrial carcinoma. Although several studies have reported that patient age [8] and retroperitoneal lymphadenectomy including para-aortic lymph nodes for patients with intermediate and high risk of recurrence [9] were significant prognostic factors in endometrial carcinoma, these factors showed no significant effect on uterine carcinosarcoma. These results suggest a more aggressive biological behavior of uterine carcinosarcoma than of endometrial endometrioid adenocarcinoma. Several studies [10, 11] have also reported that although stage I/II was more frequently observed in uterine carcinosarcoma cases, the clinical outcome of this disease was significantly worse than grade 3 endometrioid endometrial carcinoma and non-endometrioid endometrial carcinoma. The most significant prognostic factor for predicting poor survival is the extension of the tumor beyond the uterus [12–15]. However, even in stage I/II disease, 32 % of patients exhibited extra-uterine disease spread [16] and 20–31 % [17, 18] had retroperitoneal lymph node metastasis in uterine carcinosarcoma. These results suggest that, in addition to optimal surgery, postoperative adjuvant therapy is key to improving the prognosis for carcinosarcoma patients. Although several chemotherapy regimens were included, the present results clearly demonstrated that postoperative chemotherapy is a significant independent prognostic factor for all FIGO stage patients who underwent hysterectomy and bilateral salpingo-oophorectomy.

The European Organization for Research and Treatment of Cancer evaluated the role of adjuvant pelvic radiotherapy for patients with stage I/II uterine sarcomas [19] and reported that although patients with carcinosarcoma displayed a trend for better local disease control, no significant overall survival improvement was observed. Furthermore, results from a phase III trial [7] showed no significant advantage of adjuvant chemotherapy over adjuvant radiotherapy for the recurrence rate or survival after adjusting for stage and age. These findings therefore suggest that postoperative chemotherapy in patients with early stage disease was not effective. However, a multi-institutional cohort study [20] has shown that adjuvant chemotherapy is associated with an improved progression-free survival compared with adjuvant radiation therapy and observation. Moreover, the Cochrane Review [21] analyzed three randomized trials of 579 women and reported that although abdominal radiotherapy was not associated with improved survival, combination chemotherapy had a lower risk of death and disease progression in the advanced stage for metastatic and recurrent disease. However, it remains unknown if postoperative adjuvant chemotherapy could also improve prognosis for FIGO stage I/II patients. Furthermore, a recent study has shown that adjuvant chemotherapy with doxorubicin and ifosfamide was not associated with a significant survival benefit for patients with stage I/II uterine leiomyosarcoma [22]. While several chemotherapy regimens were included in this survey, our results clearly show that postoperative chemotherapy is a significant independent prognostic factor for all FIGO stage patients who underwent hysterectomy and bilateral salpingo-oophorectomy. Although it is unknown why postoperative adjuvant chemotherapy contributed to a survival benefit for carcinosarcoma but not leiomyosarcoma, the presence of an epithelial component may be an important predictive factor. Moreover, even though both leiomyosarcomas and carcinosarcomas occur in the uterus and include a sarcomatous component, they are distinct tumor entities with different clinical features.

A current clinical problem is the improvement of treatment feasibility for uterine carcinosarcoma, especially for ifosfamide-based combination therapy. GOG has recently conducted a new phase III trial to compare paclitaxel plus carboplatin and paclitaxel plus ifosfamide in chemotherapy-naive patients with newly diagnosed stage I–IV persistent or recurrent carcinosarcoma (GOG 261). We have determined from our clinical experience with 6 Japanese patients with advanced or recurrent uterine carcinosarcoma that paclitaxel and carboplatin is a feasible and effective chemotherapy combination [23]. Moreover, although the number of enrolled patients did not reach the designed sample size, we recently reported results of a phase II study to evaluate the effects of paclitaxel and

carboplatin therapy for advanced or recurrent uterine carcinosarcoma [24]. The study found that the overall response rate was 66.7 % and the progression-free survival was 9.1 months with acceptable toxicities. Our present survey has evaluated important information for the improvement of the long-term prognosis of patients with uterine carcinosarcoma. An additional well-designed clinical trial to evaluate paclitaxel and carboplatin as an adjuvant therapy for Japanese uterine carcinosarcoma patients is needed.

Conflict of Interest The authors declare that they have no conflict of interest.

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Potential impact of combined high- and low-risk human papillomavirus infection on the progression of cervical intraepithelial neoplasia 2

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Abstract

Aim: Few studies have examined the effect of combined low-risk human papillomavirus (LR-HPV) and high-risk human papillomavirus (HR-HPV) infection on the progression of cervical intraepithelial neoplasia (CIN)2 to CIN3. This multi-institutional prospective cohort study investigated the risk of progression of CIN2 with various combinations of HR-HPV and LR-HPV infection.

Methods: Between January 2007 and May 2008, 122 women with CIN2 (aged 20–50 years) from 24 hospitals throughout Japan were enrolled in the study. Ninety-three women were analyzed after a 2-year follow-up with cytology, colposcopy, HR-HPV testing and HPV genotyping. Colposcopy-directed biopsy was performed at entry and the end of this study, or when disease progression was suspected.

Results: Among 93 women with CIN2, 87 (93.5%) had HR-HPV infection. Among these 87 cases, 24 (27.6%) progressed to CIN3 and 49 (56.3%) regressed. None of the six women with CIN2 without HR-HPV infection progressed. The progression rate was significantly lower in women with combined HR-HPV and LR-HPV infection (3/28, 10.7%) than in those with HR-HPV infection only (21/59, 35.6%; $P = 0.016$). Multivariate analyses showed that CIN2 progression in women with HR-HPV infection was negatively associated with LR-HPV co-infection (hazard ratio = 0.152; 95% confidence interval [CI] = 0.042–0.553). CIN2 regression was positively associated with LR-HPV co-infection (odds ratio = 4.553; 95% CI = 1.378–15.039).

Conclusion: The risk of CIN2 progression is low in women with combined infection of HR-HPV and LR-HPV. The finding may be useful for management of women diagnosed with CIN2.

Key words: cervical intraepithelial neoplasia, human papillomavirus, infection screening, management of precancer, virus genotyping.

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Introduction

Almost all cases of cervical cancer and precancer are caused by persistent high-risk (HR) human papillomavirus (HPV) infection.[1,2] Although HR-HPV infection is necessary for the development of precancer, other factors play a role, because the majority of precancerous lesions regress spontaneously.[3–8] The specific factors that contribute to progression of HPV are not well understood. Approximately 13 HPV genotypes are considered to be oncogenic, but they do not all have the same oncogenic potential.[3,9–13] A recent prospective study found that persistent HPV16 infection in women with normal Papanicolaou smears was associated with the highest absolute risk of progression to high-grade cervical lesions.[9]

Only a few studies have examined the effect of combined low-risk (LR)-HPV and HR-HPV infection on the progression of cervical intraepithelial neoplasia (CIN). One study found that women with HPV16 infection tended to have different risks of progression depending on whether they had co-infection with none, one or multiple non-carcinogenic HPV types.[13] This multi-institutional prospective cohort study examined the 2-year risk of progression of CIN2 to CIN3 in women with various combinations of HR-HPV and LR-HPV infection, because CIN3 progresses to invasive cervical cancer three-times more frequently than CIN2.[6]

Methods

Study design

Two hundred Japanese women diagnosed with CIN2 were recruited from January 2007 to May 2008 from 24 regional cancer center hospitals throughout Japan. The women were aged 20–50 years and had no prior history of abnormal cytology and/or biopsy-confirmed cervical abnormalities. Biopsy specimens from lesions found under abnormal colposcopy findings of these women diagnosed with CIN2 by the attending hospital pathologists were submitted for central pathological review (CPR) (Fig. 1). CPR was performed blindly by two pathologists at the Cancer Institute of the Japanese Foundation for Cancer Research, Department of Pathology, using hematoxylin–eosin-stained sections according to the World Health Organization classification. When the results differed between pathologists, a final diagnosis was determined after discussion between them. Thirty-eight women with CIN1, 28 women with CIN3

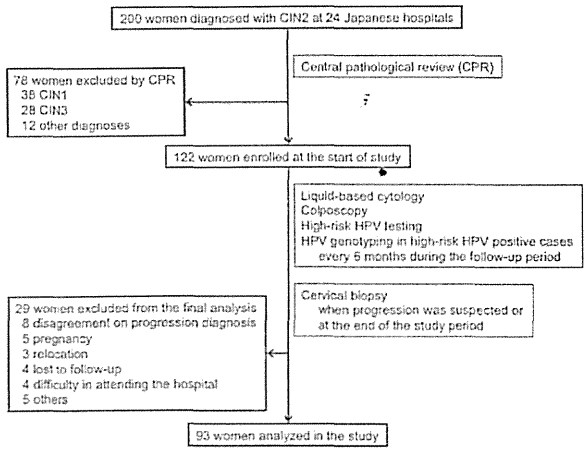

Figure 1 Trial profile. CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

and 12 women with other diagnoses were excluded, and the remaining 122 women with CIN2 were enrolled in the study (Fig. 1). At the time of enrolment and every 6 months during the 24-month follow-up period, all participants underwent liquid-based cytology testing, HR-HPV testing, HPV genotype analysis if HR-HPV testing was positive, and colposcopy (Fig. 1). All liquid-based cytology diagnoses were accompanied by comments on CIN grade for attending physicians. At the end of the follow-up period, or earlier if progression was suspected by cytology or colposcopy results, a cervical biopsy was taken from lesions found under abnormal colposcopy findings, and a pathological diagnosis was determined (Fig. 1). Progression to CIN3 was considered as the study endpoint for analyses. Women diagnosed with CIN3 on CPR exited the study and received appropriate treatment. Twenty-nine cases were excluded from the final analysis for the following reasons: they were diagnosed with CIN3 by the hospital pathologist but not confirmed by CPR ($n = 8$), pregnancy ($n = 5$), relocation ($n = 3$), lost to follow-up ($n = 4$), difficulty in reaching the hospital for personal reasons ($n = 4$) and others ($n = 5$) (Fig. 1). At the end of the follow-up period, all biopsy samples were submitted for CPR and final diagnosis. A total of 93 women were included in the present analysis (Fig. 1).

The status of lesions was defined as progression when CIN2 progressed to CIN3 or worse, and it was defined as regression when CIN2 regressed to CIN1 or no lesion was detected.

All women voluntarily signed informed consent before enrolment. The study was approved by the institutional review boards of all participating institutions.

Cervical sample collection

Cervical cell samples were taken using a Cervex-Brush (Rovers Medical Devices, Oss, the Netherlands), collected in SurePath Preservative Fluid (TriPath Imaging, Burlington, NC, USA) and stored at 2–8°C. The resulting sample solution was used for HPV testing, as well as for cytological diagnosis within 2 weeks.

HPV detection

DNA was extracted from 250 μL of the sample solution and tested for HR-HPV using the Amplicor HPV test (Roche Molecular Systems, Pleasanton, CA, USA) according to the manufacturer's instructions. Amplicor HPV testing involved polymerase chain reaction amplification of target DNA followed by hybridization using microwell plates to detect 13 HR-HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68).

All samples that tested positive on Amplicor HR-HPV testing underwent subsequent HPV genotype analysis using the HPV Linear Array Genotyping Kit (Roche Molecular Systems) according to the manufacturer's instructions. The HPV Linear Array Genotyping Kit involved polymerase chain reaction amplification of target DNA followed by hybridization using a reverse line blot system to simultaneously detect up to 37 HPV genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51–56, 58, 59, 61, 62, 64, 66–73, 81–84, IS39 and CP6018).

Infection was defined as persistent when a specific HPV genotype was continuously positive from baseline until a diagnosis of CIN3 or at the end of the follow-up period.

Statistical analyses

Fisher's exact test was used for univariate analyses of categorical variables and Student's *t*-test was used for comparing continuous variables. The cumulative probability of CIN2 progression was estimated using the Kaplan–Meier method and compared using the log–rank test. The Cox proportional hazards model was used for multivariate analyses on CIN2 progression. The probability of CIN2 regression was estimated using multiple logistic regression for multivariate analyses, because the exact regression times were unknown, with only information on whether regression occurred between baseline and the end of the follow-up period. A *P*-value was considered to be significant at less than 0.05. Analyses were performed using SPSS software ver. 11 (IBM Corporation, Armonk, NY, USA).

Results

Study population

The age distribution of women with HR-HPV infection among the study population is shown in Table 1. Of 93 women (aged 37.1 ± [SD] 6.4 years) with CIN2, 87 (93.5%; aged 37.2 ± 6.4 years) had single or multiple HR-HPV infection at baseline. With regard to the six women without HR-HPV infection, one was aged 20–29 years, three were aged 30–39 years and two were aged 40–50 years. The rate of multiple HR-HPV infections appeared to be higher among the younger groups. There was a significant association between the age groups and the rate of multiple HR-HPV infections ($P = 0.013$, Table 1). Although rates of progression from CIN2 to CIN3 were higher in younger patients by decade, this progression was not statistically significant ($P = 0.683$, Table 1).

Thirteen of the 87 women smoked. The progression rate of CIN2 in the smoking group was 15.4% (2/13) and that of the non-smoking group was 29.7% (22/74). There was no significant association between smoking and CIN2 progression ($P = 0.50$).

Table 1 Age distribution of women with HR-HPV infection

Age (years)	Women with HR-HPV	Single HR-HPV†	Multiple HR-HPV		CIN2 progression	
	n	*n*	*n*	%‡	*n*	%‡
20–29	13	4	9	69.2*	5	38.5
30–39	42	31	11	26.2*	11	26.2
40–50	32	24	8	25.0*	8	25.0
Total	87	59	28		24	

*$P = 0.013$. †Includes women with single HR-HPV infection with/without LR-HPV infection. ‡The denominators of the percentages are the number of women with HR-HPV infection. CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR, high-risk; LR, low-risk.

HPV genotypes at baseline

The HPV genotypes detected at baseline are shown in Table 2. Of the 87 women infected with 129 HR-HPV genotypes in total, 28 also had LR-HPV infection, with 33 LR-HPV genotypes detected in total. The most frequently detected HR-HPV genotypes were HPV16, 52, 58, 51 and 31. HPV18 was detected in only one case (Table 2). The mean age of women with HR-HPV infection but without LR-HPV infection was significantly older (38.2 ± 6.2 years) than that of women with LR-HPV co-infection (35.1 ± 6.4 years, $P = 0.036$).

Table 2 Number of HR-HPV and LR-HPV genotypes at baseline in women with HR-HPV infection

HR-HPV genotype	*n*	Single infection†	Multiple infection‡
Type 16	33	16	17
Type 18	1	0	1
Type 31	11	1	10
Type 33	7	2	5
Type 35	2	0	2
Type 39	5	0	5
Type 45	1	0	1
Type 51	14	7	7
Type 52	23	11	12
Type 56	5	0	5
Type 58	18	6	12
Type 59	2	0	2
Type 68	7	3	4
Total	129	46	83

†Single infection indicates single HR-HPV infection without LR-HPV.
‡Multiple infection indicates single HR-HPV infection with LR-HPV infection, or multiple HR-HPV infection with/without LR-HPV.
LR-HPV genotype (*n*): type 6 = 1, 40 = 2, 42 = 2, 53 = 3, 55 = 1, 61 = 1, 62 = 4, 66 = 5, 70 = 3, 71 = 1, 72 = 1, 8 = 2, 82 = 2, 83 = 1, 84 = 1, CP6108 = 3, and total = 33. HPV, human papillomavirus; HR, high-risk; LR, low-risk.

Prognosis of women with CIN2 and HPV infection

Of the 87 women with CIN2 and HR-HPV infection, 24 (27.6%) progressed to CIN3 and 49 (56.3%) regressed to CIN1 or less within 2 years (Table 3). No cases progressed to invasive cancer, but one woman progressed to adenocarcinoma *in situ* (HPV45 persistent infection). Forty-eight women regressed to CIN1 and one woman regressed to no detectable lesion. Of the six women with CIN2 without HR-HPV infection, none progressed to CIN3. Women with multiple HR-HPV infections tended to progress, and women with combined HR-HPV and LR-HPV infection did not tend to progress (Table 3). Progression at 6 and 12 months was only observed among women without LR-HPV co-infection (Table 3).

In addition, CIN2 progressed to CIN3 among 15 of the 33 (45.5%) women with HPV16 infection (Table 3), among seven of the 39 (17.9%) women infected with HPV18, 31, 33, 35, 45, 52 and 58 without HPV16 co-infection, and among two of the 15 (13.3%) women with other types of HR-HPV infection.

Cervical intraepithelial neoplasia 2 progressed among eight of the 14 (57.1%) women with both HPV16 and other types of HR-HPV infections. Three of the seven (42.9%) women with combined infection of HPV16, other types of HR-HPV infections and LR-HPV infection progressed to CIN3, and five of the seven (71.4%) women progressed when they were infected with both HPV16 infection and other types of HR-HPV infections, but they did not have LR-HPV infection. CIN2 progressed among seven of the 19 (36.8%) women with HPV16 infection but without other types of HR-HPV infection. None of the three (0%) women with HPV16 but without other types of HR-HPV progressed when they were

Table 3 CIN2 prognosis according to the HPV infection pattern

Infection pattern	Cases at baseline	Regressed cases, n (%)	Persistent cases, n (%)	Cases that progressed to CIN3				
				6 M	12 M	18 M	24 M	Total, *n* (%)
Single HR-HPV without LR-HPV	46	24 (52.2)	8 (17.4)	1	3	1	9	14 (30.4)
Multiple HR-HPV without LR-HPV	13	4 (30.8)	2 (15.4)	2	2	2	1	7 (53.8)
Single HR-HPV with LR-HPV	13	11(84.6)	2 (15.4)	0	0	0	0	0 (0)
Multiple HR-HPV with LR-HPV	15	10 (66.7)	2 (13.3)	0	0	1	2	3 (20)
Total	87	49 (56.3)	14 (16.1)	3	5	4	12	24 (27.6)
HPV16 without LR-HPV	23	7 (30.4)	4 (17.4)	3	3	2	4	12 (52.2)
HPV16 with LR-HPV	10	5 (50.0)	2 (20.0)	0	0	1	2	3 (30)
HPV16 total	33	12 (36.4)	6 (18.2)	3	3	3	6	15 (45.5)

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR, high-risk; LR, low-risk; M, months.

infected with LR-HPV. Seven of the 16 (43.8%) women with HPV16 but without other types of HR-HPV progressed when they were not infected with LR-HPV.

High-risk HPV infection disappeared in 24 of the 87 women during the study period and there was no case of progression among women whose HR-HPV infection disappeared. HR-HPV infection remained in 40 of the 59 (67.8%) women with HR-HPV infection only, while HR-HPV infection remained in 23 of the 28 (82.1%) women with LR-HPV co-infection. HPV16 infection disappeared in eight of the 33 women. HPV16 infection remained in 19 of 23 (82.6%) women with HR-HPV infection only, while it remained in six of the 10 (60.0%) women with LR-HPV co-infection. The rate of persistent HR-HPV infection between women without LR-HPV co-infection and women with LR-HPV co-infection was not significantly different ($P = 0.204$). The rate of persistent HPV16 infection between the two groups also was not significantly different ($P = 0.205$).

Low-risk HPV genotypes disappeared in 13 of the 28 women with combined HR-HPV and LR-HPV infection, and they remained in 10 of the 28 women. We could not find persistent LR-HPV infection in five women, because HR-HPV infection disappeared in these women and we did not perform genotyping among negative HR-HPV test cases.

Univariate analyses examining the effect of HPV infections according to the infection pattern

When only women without LR-HPV infection were compared, the cumulative 2-year rate of CIN2 progression was significantly higher in women with multiple HR-HPV infections (7/13, 53.8%) than in women with a single HR-HPV infection (14/46, 30.4%, $P = 0.041$, Fig. 2a).

The effect of combined HR-HPV and LR-HPV infection on disease progression is shown in Figure 2(b). Twenty-one of the 59 (35.6%) women with HR-HPV infection, but no LR-HPV infection, progressed to CIN3, while only three of the 28 (10.7%) women with combined HR-HPV and LR-HPV infection progressed to CIN3. The progression rate was significantly lower in women with combined HR-HPV and LR-HPV infection than in women with HR-HPV infection only ($P = 0.016$, Fig. 2b).

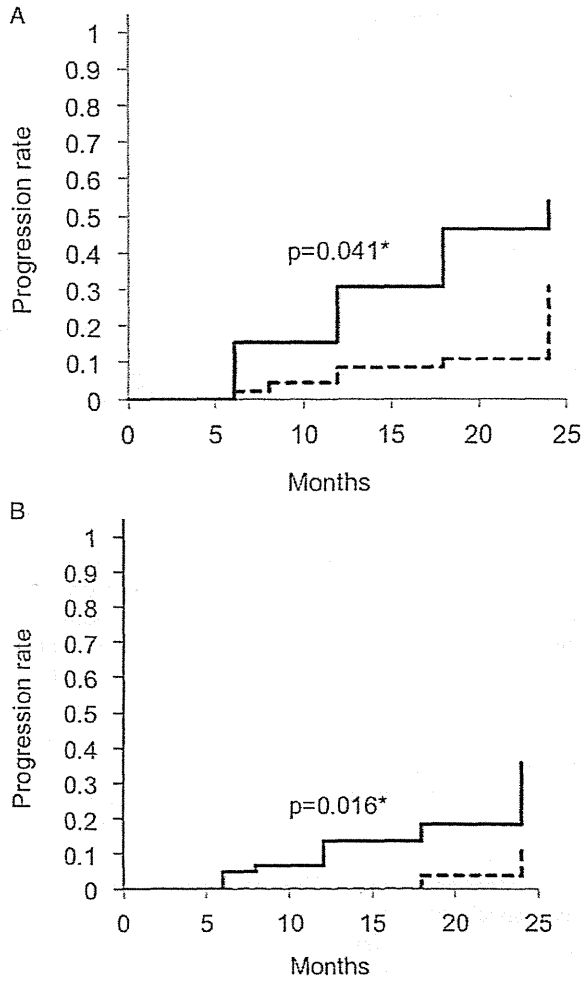

Figure 2 Cumulative rate of progression of CIN2 to CIN3 in (a) women with single or multiple HR-HPV infections who did not have LR-HPV infection and (b) in women with HR-HPV infection who had or did not have LR-HPV co-infection. —, HR-HPV without LR-HPV; ----, HR-HPV with LR-HPV. CIN, cervical intraepithelial neoplasia; HR, high-risk; LR, low-risk; HPV, human papillomavirus.

Multivariate analyses examining the effect of age, multiple HR-HPV infections, HPV16 infection and LR-HPV co-infection on CIN2 progression and regression

The two variables, multiple HR-HPV infection and LR-HPV co-infection, were evaluated using multivariate analysis of CIN2 progression. Age was also included in the multivariate analysis because the age

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Table 4 Multivariate analyses of the effect of variables on CIN2 progression and regression

	Variables			Reference	Risk	95% confidence interval	*P*-value
On progression					Hazard ratio		
	Age				0.960	0.900–1.025	0.222
	HPV16	+	vs	−	3.029	1.312–6.993	0.009*
	HR-HPV	Multiple	vs	Single	2.240	0.945–5.312	0.067
	LR-HPV	+	vs	−	0.152	0.042–0.553	0.004*
On regression					Odds ratio		
	Age				0.977	0.903–1.056	0.554
	HPV16	+	vs	−	0.258	0.096–0.692	0.007*
	HR-HPV	Multiple	vs	Single	0.456	0.146–1.425	0.177
	LR-HPV	+	vs	−	4.553	1.378–15.039	0.013*

*$P < 0.05$. The cumulative probability of CIN2 progression was estimated using the Cox proportional hazards model and the probability of regression was estimated using multiple logistic regression for multivariate analyses. CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR, high-risk; LR, low-risk.

of women with LR-HPV co-infection was significantly lower than that of women with HR-HPV infection only in univariate analysis. HPV16 infection was also included because HPV16 was the most frequently found HR genotype in this study (Table 2) and it is the most important cause of CIN and invasive cervical cancer.[2,9] All four variables also were evaluated using multivariate analysis of CIN2 regression.

Cervical intraepithelial neoplasia 2 progression was positively associated with HPV16 infection and CIN2 regression was negatively associated with HPV16 infection (Table 4). CIN2 progression was negatively associated with LR-HPV co-infection (hazard ratio = 0.152; 95% confidence interval [CI] = 0.042–0.553), and CIN2 regression was positively associated with LR-HPV co-infection (odds ratio = 4.553; 95% CI = 1.378–15.039) with adjustment for the presence of HPV16 infection (Table 4). CIN2 progression was not associated with multiple HR-HPV infections when the analysis was adjusted for the presence of HPV16 infection (Table 4).

Comparison of women with LR-HPV co-infection and those without LR-HPV co-infection with regard to the infection rate of hazardous HR-HPV genotypes

Ten of the 28 (35.7%) women with LR-HPV co-infection also were infected with HPV16, and 23 of the 59 (39.0%) women without LR-HPV co-infection were infected with HPV16. The HPV16 infection rate between the two groups of women was not significantly different ($P = 0.817$).

Fifteen of the 28 (53.6%) women with LR-HPV co-infection also were infected with HPV18, 31, 33, 35, 45, 52 and 58 without HPV16 co-infection, and 23 of the 59 (39.0%) women without LR-HPV co-infection were infected with such genotypes. The infection rate of such genotypes between the two groups of women was not significantly different ($P = 0.250$).

Discussion

Multiple-type HPV infections are associated with an increased risk of high-grade squamous intraepithelial lesion cytology,[14] all grades of CIN, and cancer.[15] In our study, multiple HR-HPV infection was not associated with an increased risk of CIN2 progression when the hazard ratio was adjusted for HPV16 infection. A previous study found that women with persistent HR-HPV infections had a greater risk of developing CIN than those in whom HPV had disappeared or were sequentially infected with different HPV types.[16] Multiple HR-HPV infection did not have a higher risk than a single HR-HPV infection in this previous study.[16]

Some studies have suggested a reduced risk of CIN and invasive cancer in women with combined (HR) HPV16 and (LR) HPV6 or HPV11 infection.[17,18] A prospective study of women with low-grade squamous intraepithelial lesion cytology found a decreasing trend in the risk of progression to CIN3 or worse when HPV16 infection was combined with single or multiple LR-HPV infections,[13] which is consistent with our study. The study on multiple-type HPV infections cited

above also reported that the risk of CIN3 or worse among the population with multiple-type infection with HPV-16 and LR-HPV is much lower (~25%) than the risk among the population with a single-type infection with HPV16.[15] This finding suggests a protective effect of LR-HPV infection against HR-HPV infection on CIN2 progression to CIN3.

We propose three possible explanations for our observation that the rate of progression from CIN2 to CIN3 was lower in women with combined HR-HPV and LR-HPV infection than in women with HR-HPV infection only. First, HPV infection may have been present for longer in women with HR-HPV infection only than in those who had co-infection with LR-HPV. Therefore, women with HR-HPV infection only may have had a higher risk of progression to CIN3 than those who had co-infection with LR-HPV. LR-HPV infection might have disappeared after a while among women with HR-HPV infection only. Unfortunately, we do not have data on the status of previous HPV infections of participants and could not estimate the period of HPV infection. However, the rate of progression from CIN2 to CIN3 was higher in patients in the young age group (20–29 years) compared with the older age groups (30–39 and 40–50 years), but this progression was not statistically significant, and the first explanation does not appear convincing.

A second explanation is that CIN2 might have been generated by LR-HPV among women who did not progress and had combined infection of HR-HPV and LR-HPV. The risk of CIN2 has been reported to increase with multiple LR-HPV infection, as well as HR-HPV infection.[15]

Finally, co-infection with LR-HPV may have an inhibitory effect on progression by promoting an antagonistic effect among HPV genotypes.[17,18] Antagonism between HPV genotypes in cervical cancer may be at the level of the antibody response.[18] LR-HPV infection is resolved in a shorter time than HR-HPV infection,[19] and may result in production of serum neutralizing antibodies more often than HR-HPV infection. Progression of CIN in women with HR-HPV infection may be inhibited by cross-reactivity of antibodies, which are induced by LR-HPV. A homologous structure in HR-HPV and LR-HPV genotypes, the L2 capsid protein, contains a common neutralization epitope.[20,21] However, in our study, the rates of persistent HR-HPV infection were 82.1% for patients with both HR- and LR-HPV infection versus 67.8% for those only with HR-HPV infection. The cross-reactivity of antibodies does not appear to be associated with this observation in the present study. A cross-protective cell-mediated immune response to HPV infections was also suggested in a study on the antagonistic effect of LR-HPV co-infection.[17] An inhibitory effect of LR-HPV co-infection on CIN2 progression among women with HR-HPV infection is a likely explanation for our observation, but further investigation is required to confirm this.

A previous Japanese prospective cohort study reported that the risk of progression to CIN3 in the next 5 years was significantly higher in women with CIN1/2 and infection of HPV16, 18, 31, 33, 35, 52 and 58 compared with those with CIN1/2 and infection of other HR-HPV.[3] Another study also reported that high-grade squamous intraepithelial lesion infected with HPV16, 18 and 45 preferentially progressed.[22] However, the progression rate of CIN2 among women with infection of HR-HPV, except for HPV16, was low in the present study. This may reflect a potential for early progression of HPV16. There was only one woman with HPV18 infection. The long-term risk of progression of HPV18, 31, 33, 35, 45, 52 and 58 requires further study.

Strengths and limitations

The strengths of this study on the progression of CIN2 to CIN3 include its multi-institutional prospective cohort design, and the detailed HPV genotyping of both HR- and LR-HPV in women with HR-HPV infection. Our study also has some limitations. First, this study enrolled a relatively small number of women with HPV infection, of which approximately 25% were lost to follow-up. However, the CIN2 population size was almost equivalent to population sizes in previous larger studies.[3,14,15] Second, we did not know the lesion sizes of abnormal colposcopy findings because of the nature of the multi-institutional study and could not determine the association between lesion sizes and disease prognosis. We also did not know the number of women in whom the squamocolumnar junction in the uterine cervix was not visible, and the interval between cytology testing at study enrollment and former testing was unknown for the same reason as that for lesion size. Third, it has been reported that CIN2 is not a reproducible diagnosis.[23] However, the CPR pathologists in our study were experienced in the diagnosis of cervical lesions, and were involved in previous studies.[3,24] The CPR pathologists were careful with their diagnoses, which meant that more than one-third of the women who were initially diagnosed with CIN2

by the pathologist at their referring hospital were excluded. Therefore, the CIN2 diagnoses are likely to have been accurate. Fourth, some lesions with LR-HPV infection might not have been 'true' CIN2. However, CIN2 cases without HR-HPV infection were not included in the statistical analyses, and these cases did not progress. All cases with LR-HPV infection statistically analyzed for progression and regression also were infected with HR-HPV. Finally, the 2-year follow-up period was relatively short, and differences in the rate of progression to CIN3 may become insignificant with a longer follow-up period. However, both progression and regression were affected by co-infection with LR-HPV, indicating that differences may continue in the long term.

This study shows, for the first time, that CIN2 tends to regress when women have combined infection of HR-HPV and LR-HPV compared with women with HR-HPV infection only, and the risk of progression of CIN2 is low in women with combined infection of HR-HPV and LR-HPV. These findings may be useful for clinical management of women diagnosed with CIN2.

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Maximum Standardized Uptake Value of Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Is a Prognostic Factor in Ovarian Clear Cell Adenocarcinoma

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Background: Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is useful for diagnosing malignant tumors. Intracellular FDG uptake is measured as the standardized uptake value (SUV), which differs depending on tumor characteristics. This study investigated differences in maximum SUV (SUV_{max}) according to histologic type in ovarian epithelial cancer and the relationship of SUV_{max} with prognosis.

Methods: This study included 80 patients with ovarian epithelial cancer based on histopathologic findings at surgery and who had undergone PET/CT before treatment. Maximum SUV on PET/CT of primary lesions and histopathology were compared based on histologic type, and the prognosis associated with different SUV_{max} was evaluated.

Results: Clinical tumor stage was I in 35 patients, II in 8, III in 25, and IV in 12. Histologic type was serous adenocarcinoma (AC) in 33 patients, clear cell AC in 27, endometrioid AC in 15, and mucinous AC in 5. Median SUV_{max} was lower in mucinous AC (2.76) and clear cell AC (4.9) than in serous AC (11.4) or endometrioid AC (11.4). Overall, median SUV_{max} was lower in clinical stage I (5.37) than in clinical stage ≥II (10.3). However, in both clear cell AC and endometrioid AC, when histologic evaluation was possible, no difference was seen between stage I and stage ≥II. Moreover, in clear cell AC, the 5-year survival rate was significantly higher in the low-SUV_{max} group (100%) than in the high-SUV_{max} group (43.0%, $P = 0.009$).

Conclusions: Maximum SUV on preoperative FDG-PET/CT in ovarian epithelial cancer differs according to histologic type. In clear cell AC, SUV_{max} may represent a prognostic factor.

Key Words: Ovarian epithelial cancer, FDG-PET/CT, SUV_{max}, Histologic type, Clear cell adenocarcinoma, Prognosis

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Malignant tumors have higher cellular proliferative potential and increased glucose metabolism compared with normal tissue. Fluorodeoxyglucose (FDG) is a glucose-like substance that accumulates in tissues with active glucose metabolism. Fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) utilizes these properties to provide both anatomic and glucose metabolic/functional information that is useful for diagnosing malignant tumors.[1–4]

The degree of FDG accumulation is expressed as the standardized uptake value (SUV), a quantitative value in which the radioactive concentration measured on imaging

is corrected for injected dose and body weight. Peak SUV in 1 pixel in the region of interest is used to evaluate maximum (SUV_{max}). Studies have recently started to evaluate therapeutic effects and factors associated with prognosis using SUV_{max} on FDG-PET/CT.[5–7] In the field of gynecology, physiologic uptake of FDG is seen in the endometrium and ovaries, and FDG uptake may occur even in benign tumors. On the other hand, FDG uptake in malignant tumors is influenced by tumor differentiation, cellular division rate, and proliferative potential, but care must be taken because sometimes FDG uptake is not high.

The various types of ovarian tumors show differences in growth and progression depending on origin and histologic type. Differences in tumor characteristics based on studies of cellular proliferative potential and genetic analysis have also been found. In addition, characteristic FDG uptake patterns may exist based on histologic type.

The present study investigated characteristic FDG uptake patterns on FDG-PET/CT for different histologic types of ovarian epithelial cancer and the association between prognosis and SUV_{max}.

PATIENTS AND METHODS

Patient Selection and Staging Assessment

This study included 80 patients with ovarian epithelial cancer based on confirmed histopathology of the primary lesions who underwent FDG-PET/CT before treatment at our hospital between January 2008 and December 2012. Because SUV_{max} was being evaluated for different histologic types, mixed epithelial cancers showing a mixture of histologic types were excluded from the study. Eighty patients were clinically diagnosed with stage I-IV based on International Federation of Gynecology and Obstetrics staging. Patients who was provided neoadjuvant chemotherapy were clinically diagnosed stage III or IV by imaging modalities (including CT or magnetic resonance imaging [MRI], FDG-PET/CT) and cytological assessment of ascites or pleural effusion (including ascites cell-block specimens).

Surgical Procedure

The standard surgery included total hysterectomy, bilateral adnexectomy, greater omentectomy, pelvic lymphadenectomy, para-aortic lymphadenectomy with the ascites cytology, and a careful intra-abdominal and evaluation. When the pelvic and para-aortic lymphadenoctomy was not performed to stage I-II patients for various reasons including patient hope, we confirmed that there were no swelling lymph nodes more than minor axis 1 cm in CT imaging and by intraoperative palpation, and we performed lymph node biopsies as needed.

FDG-PET/CT Imaging

Patients fasted for 4 hours before the intravenous injection of approximately 3.0 MBq/kg body weight of FDG. The serum glucose level immediately before the injection was measured to ensure a value less than 120 mg/dL. Dual-modality PET/CT imaging was performed using Aquiduo (Toshiba Medical Systems Corporation, Otawara, Japan). The system provides separate CT and PET datasets, which can be accurately fused on a computer workstation (Voxbase; J-MAC System, Inc, Japan). Whole-body CT (Auto-mA [SDN], 120 kV, 2.0 mm × 16, 0.5 second, 512 × 512 matrix size, 30 mm/rotation [HP15], 2- and 4-mm incremental reconstruction) covered the region between the head and the upper thighs. Whole-body PET images with attenuation correction were acquired approximately 90 minutes later. The acquisition time of PET was adapted according to the patients' body weights. The time was set to 120 seconds per field of view, 500 mm, for patients up to 50 kg body weight; 150 seconds for 50 to 75 kg body weight; and 180 seconds for 75 to 100 kg body weight. Positron emission tomography images were scatter corrected and iteratively reconstructed into a 128 × 128 matrix size with 1.34 zooming, using interactive algorithms (ordered-subset expectation maximization, 2 iterations, 14 subsets) and the CT-based attenuation map; noise was reduced by smoothing the images with a 7-mm, full-width-at-half-maximum Gaussian filter.

Research Methods

This retrospective comparative study was based on medical records for SUV_{max} of the primary lesion before treatment was started, histopathologic diagnosis, and treatment course. Patients were divided into 2 groups based on median SUV_{max} to compare prognosis. Statistical analysis was performed using the Mann-Whitney U test and log-rank test, and the level of statistical significance was $P < 0.05$.

RESULTS

Median patient age was 57 years (range, 33–76 years), and histologic type was serous adenocarcinoma (AC) in 33 patients, clear cell AC in 27, endometrioid AC in 15, and mucinous AC in 5. Clinical tumor stage was I in 35 patients, II in 8, III in 25, and IV in 12 (Tables 1 and 2).

Initial treatment was surgery alone in 8 patients, postoperative adjuvant chemotherapy after surgery in 57 patients, and chemotherapy followed by surgery in 15 patients (exploratory laparotomy was done in 6 of 15 patients; cytologic or cell-block assessment of ascites or pleural effusion was done in 9 patients).The lesion was completely resected

TABLE 1. Patient characteristics

		Patients (n = 80), Mean or n	Range or %
Age (mean), y		57	33–76
Histologic type	Serous	33	41%
	Clear	27	34%
	Endometrioid	15	19%
	Mucinous	5	6%
Stage	I	35	44%
	II	8	10%
	III	25	31%
	IV	12	15%

TABLE 2. Distribution of histologic types by clinical stage[4]

Clinical Stage	Serous	Clear	Endometrioid	Mucinous
I (n = 35)	0	22	9	4
II (n = 8)	2	2	3	1
III (n = 25)	23	1	1	0
IV (n = 12)	8	2	2	0

at initial treatment, including interval debulking surgery, in 54 patients. Histologic types in these 54 patients were serous AC in 13 patients, clear cell AC in 24, endometrioid AC in 12, and mucinous AC in 5.

Median SUV_{max} for primary lesions in the 80 patients overall was 8.17 (range, 1.53–40.45). Median SUV_{max} by histologic type was 11.4 (range, 4.24–20.38) for serous AC, 4.9 (range, 1.53–12.17) for clear cell AC, 11.4 (range, 3.93–40.45) for endometrioid AC, and 2.76 (range, 2.15–13.36) for mucinous AC. Maximum SUV was significantly lower for mucinous AC and clear cell AC than for serous AC or endometrioid AC ($P < 0.01$) (Fig. 1).

Median SUV_{max} by clinical stage was 5.37 (range, 1.53–40.45) for stage I (localized) and 10.3 (range, 2.6–20.38) for stage ≥II (advanced). Maximum SUV was significantly lower in stage I than in stage ≥II ($P < 0.01$). However, in both clear cell AC and endometrioid AC, when evaluation by histologic type was possible, no difference was evident between stage I and stage ≥II (Fig. 2).

Five-year survival rates were compared between the low-SUV_{max} group and high-SUV_{max} group, based on median SUV_{max}. Overall, for the 80 patients, 5-year survival rate did not differ significantly between the high SUV_{max} (77%) and low SUV_{max} (78%) groups. By histologic type, 5-year survival rates were serous AC: high 84%, low 73%; clear cell AC: high 43%, low 100%; and endometrioid AC: high 50%, low 75%. In clear cell AC, the 5-year survival rate was significantly higher in the high-SUV_{max} group than in the low-SUV_{max} group ($P < 0.01$) (Fig. 3).

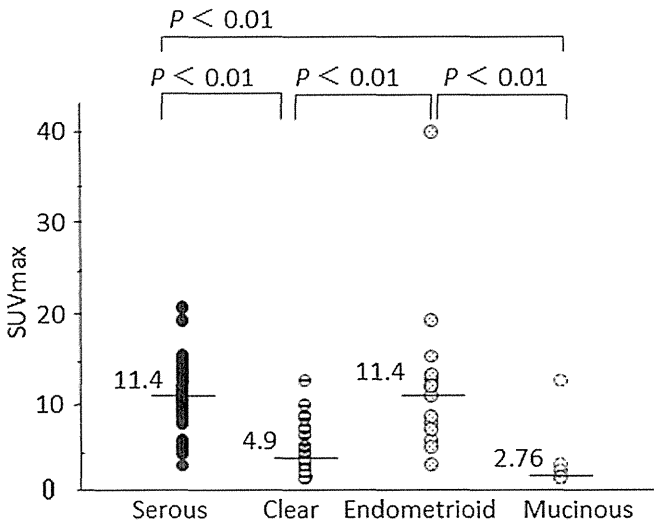

FIGURE 1. Comparison of SUVmax by histologic type (values are median values). The SUVmax in mucinous adenocarcinoma (AC) and clear call AC was significantly lower than in serous AC and endometrioid AC ($P<0.01$).

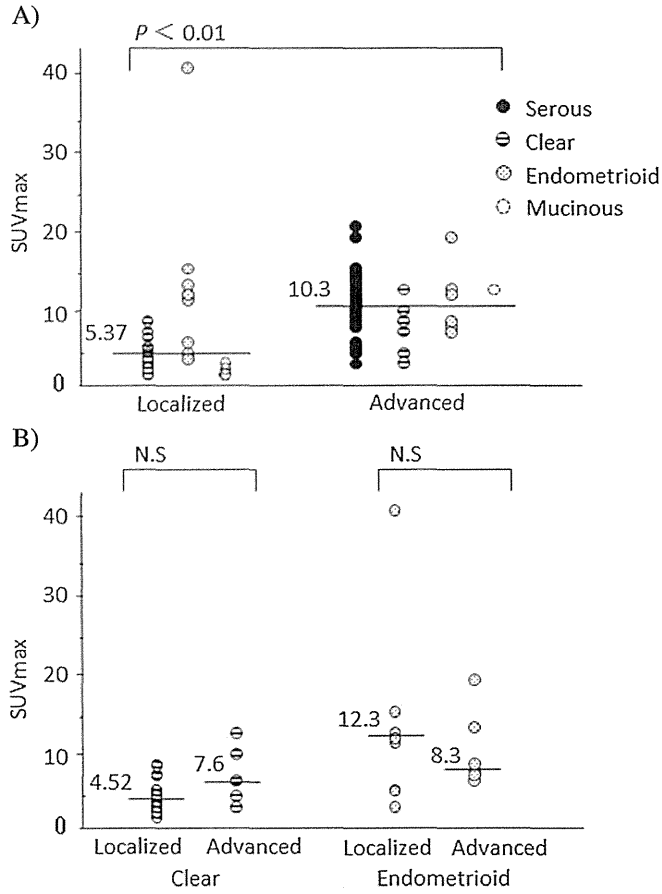

FIGURE 2. Comparison of SUVmax by histologic type (values are median values). A) Overall (n=80) B) Clear cell AC (n=27) and endometrioid AC (n=15) Overall, the SUVmax was significantly lower in stage I (localized) compared to stage≥II (advanced) ($P<0.01$). However, in clear cell AC and endometrioid CA, there were no significant differences.

The 5-year survival rate in the 54 patients with stage I-III in whom complete resection was possible as initial treatment (including interval debulking surgery) was compared. Although no significant differences were seen overall or for any group by histologic type, the 5-year survival rate for clear cell AC tended to be higher in the low-SUV_{max} group (100%) than in the high-SUV_{max} group (63%; $P = 0.061$). Furthermore, when analysis was limited to the 22 patients with stage I clear cell AC, the 5-year survival rate also tended to be higher in the low-SUV_{max} group (100%) than in the high-SUV_{max} group (63%; $P = 0.065$).

DISCUSSION

Fluorodeoxyglucose is a compound in which the hydroxyl group at the C_2 position of glucose is replaced by

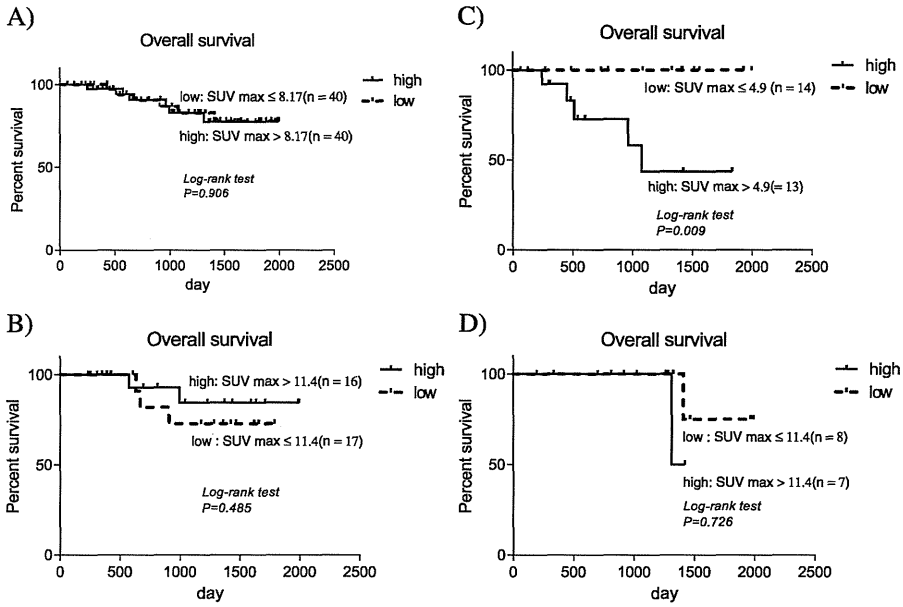

FIGURE 3. Comparison of survival rates according to SUVmax. A) Overall (n=80) high: SUVmax ≥8.17; low: SUVmax ≤8.17 B) Serous adenocarcinoma (n=33) high: SUVmax >11.4; low: SUVmax ≤4.9 C) Clear cell adenocarcinoma (n=27) high: SUVmax >4.9; low SUVmax ≤4.9 D) Endometrioid adenocarcinoma (n=15) high: SUVmax >11.4; low: SUVmax ≤11.4 In clear cell AC, the 5-year survival rate was significantly higher in the low SUVmax group compared to the high SUVmax group (P <0.01).

^{18}F. Fluorodeoxyglucose uptake into cells occurs via glucose transporters (GLUTs). Fluorodeoxyglucose is phosphorylated by hexokinase but, unlike glucose, accumulates in cells without further metabolism after phosphorylation. In other words, FDG uptake in tissue reflects cellular glucose metabolism, and imaging can reflect these differences in glucose metabolism. GLUTs are often overexpressed in malignant tumors, and glucose metabolism is increased. Fluorodeoxyglucose PET/CT utilizes these properties and is thus useful for diagnosing malignant tumors. Fluorodeoxyglucose uptake is organ-specific, and FDG-PET/CT offers high sensitivity (87%–100%) and specificity (74%–100%) for diagnosing the benign or malignant status of ovarian tumors.[1–3] In addition, compared with ultrasonography, CT, and MRI, FDG-PET/CT is useful not only for differentiating benign and malignant lesions, but also for preoperative staging.[2–4] Fluorodeoxyglucose PET/CT is also used clinically to determine treatment strategy.

Biologic characteristics of ovarian epithelial cancer, including tumor growth and prognosis, are known to differ depending on histologic type. This suggests that FDG uptake also differs based on histologic type, but few studies have investigated this issue. Karantanis et al[8] reported no differences based on histologic type, but their histologic types included 32 serous ACs, 2 clear cell ACs, 3 endometrioid ACs, and other mixed tumors; thus, the cases were biased toward serous AC. Clear cell AC accounts for 24.2% of ovarian tumors in Japan, with a higher incidence than in other countries, and many reports about ovarian clear cell AC have been published.

The present study examined differences in SUV_{max} of 80 patients with ovarian epithelial cancer in whom histologic type had been confirmed by postoperative histopathologic diagnosis, and mixed tumors were excluded from the study. We found that SUV_{max} was lower in clear cell AC and mucinous AC than in serous AC or endometrioid AC. Kitajima et al[9] reported that SUV_{max} correlated positively with stage of tumor progression, but SUV_{max} according to histologic type was not evaluated. Clear cell AC and mucinous AC are often localized stage I ovarian tumors at the time of diagnosis, whereas serous AC has often advanced to stage ≥II with progression beyond the ovary. Differences may thus arise due to clinical stage because of a bias in histologic types. However, in our study, in both clear cell AC and endometrioid AC, when evaluation by histologic type was possible, no difference was seen between SUV_{max} values according to clinical stage. Taking into account the fact that SUV_{max} differs according to histologic type, the differences in SUV_{max} based on clinical stage that have been reported to date may reflect a selection bias for histologic types.

Maximum SUV is influenced not only by glucose metabolism, but also by tumor differentiation, proliferative potential, mucinous and fibrous components, and cell density. Mucinous AC is characterized by a lower cell density with fewer cellular components, so FDG uptake is be expected to be low, but the reason for low SUV_{max} in clear cell AC has not been clarified. Among the glucose transporters GLUT-1 to GLUT-12, expression of GLUT-1, which is thought to be involved in the blood-brain barrier and tumors, and expression of GLUT-4, which predominates in striated muscle and adipose tissue, are lower in clear cell AC than in serous AC, and a correlation has been reported between GLUT and VEGF expression.[10] In addition, Ki-67 labeling