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GYNECOLOGIC ONCOLOGY

Post-treatment follow-up procedures in cervical cancer patients previously treated with radiotherapy

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Abstract
Purpose We investigated the role of physical examination, CT scan, chest X-ray, and Pap smear in the routine follow-up program for cervical cancer patients previously treated with radiotherapy.
Methods The records of women who had developed recurrent cervical cancer after radiotherapy were retrospectively reviewed. The optimal procedure for the detection of recurrence was evaluated according to the disease-free interval (DFI). Survival analysis was performed based on the Kaplan–Meier method and comparisons between groups were made using the log-rank test.
Results A total of 146 recurrent cervical cancer patients were included in our database. The majority of recurrences were diagnosed either by symptoms, physical examination, or CT scan. The patients whose recurrent disease was detected by Pap smear, physical examination, or CT scan had a significantly longer survival than those detected by symptoms. When analyzed according to DFI, physical examination, and CT scan led to the detection of recurrence in patients with a DFI of 1–5 years. In contrast, chest X-ray and Pap smear only had a clinical impact on the diagnosis of recurrence in patients with a DFI of 1–2 years.
Conclusions Chest X-ray and Pap smear can be routinely performed for the first 2 years after radiotherapy, but can be omitted or used sparingly thereafter.

Keywords Follow-up · Cervical cancer · Recurrence · Chest X-ray · Pap smear

Abbreviations

CT	Computed tomography
ISBT	Interstitial brachytherapy
OS	Overall survival
DFI	Disease-free interval
SCLN	Supraclavicular lymph node
EBRT	External beam radiotherapy
RT	Radiation therapy
CCRT	Concurrent chemoradiotherapy
MRI	Magnetic resonance imaging

Introduction

Cervical cancer is still one of the most frequent malignancies in women worldwide. It has been estimated that 12,200 new cases and 4,210 deaths occurred in the USA in 2010 [1]. In Japan, 6–7,000 new cases are reported annually [2]. Patients with early stage cervical cancer treated with surgery or radiotherapy are likely to have a good prognosis [3]. However, substantial treatment failure still occurs, especially in advanced-stage patients. Patients who suffer recurrence have a dismal prognosis with a 1-year survival rate of between 15 and 20% [4].

Traditionally, all patients who have been treated for cervical cancer undergo long-term routine follow-up in secondary care. However, since there are no formal recommendations based on a good level of evidence,

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post-treatment follow-up programs widely differ among institutions and are mainly based on experience [5]. In Western countries, patients are usually followed up every 3 months in the first year, every 4 months in the second year, every 6 months in the third to fifth year, and annually thereafter. On the other hand, in Japan, patients are usually followed up every 1–2 months in the first year, every 2–3 months in the second year, every 3–4 months in the third year, every 6 months in the fourth to fifth year and annually thereafter, which is a more frequent and intensive program than in Western countries. However, because of a lack of prospective randomized controlled studies, the effectiveness of follow-up with regard to survival and the best method of follow-up after the treatment of uterine cervical cancer remain controversial. Moreover, the most appropriate procedure and the optimal timing of follow-up appointments also remain unknown.

The aim of the present study was to evaluate the role of routine physical examination, CT scan, chest X-ray, and Pap smear in the detection of recurrence in cervical cancer patients who had been treated with radiotherapy as part of their initial treatment.

Materials and methods

Patients

Permission to proceed with the data acquisition and analysis was obtained from the Osaka University Hospital's Institutional Review Board. Consecutive Japanese women with recurrent cervical cancer who had undergone radiotherapy as part of their initial treatment at the Osaka University Hospital from 1995 to 2007 were identified through a chart review and their clinical records were retrospectively reviewed.

Primary tumors were treated in accordance with the institutional treatment guidelines. Basically, patients with FIGO stage I–II cervical cancer under the age of 70 years underwent surgery with or without adjuvant radiotherapy. Patients with FIGO stage III–IV disease, patients with FIGO stage I–II disease above the age of 71 years, or patients with FIGO stage I–II disease under the age of 70 years who desired definitive radiotherapy rather than surgery received definitive radiotherapy as described previously [6, 7]. Based on the US National Cancer Institute (NCI) alert [8], we have started a clinical practice of platinum-based concurrent chemoradiotherapy (CCRT) in the setting of both adjuvant treatment after radical surgery [6] and definitive radiotherapy [7] since 1999. CCRT was indicated in all patients below the age of 75 years. However, patients who refused concurrent chemotherapy or patients with cervical cancer before the introduction of CCRT had been treated with radiation therapy (RT) alone.

Recurrence was defined as the presence of disease after a greater than 3-month disease-free interval after the end of primary treatment. The disease-free interval (DFI) was defined as the time from completion of primary treatment until the detection of recurrence.

For all patients, data on the following characteristics of the patient and their primary and recurrent tumors were collected: age, clinical stage, histology, primary therapy, method of recurrence detection, the date of recurrence diagnosis, presence or absence of symptoms, site of the recurrent cancer, primary method of recurrence detection, mode of treatment of the recurrence, and the date of death or the last visit.

Follow-up modalities

The follow-up was conducted by both gynecological oncologists and radiation oncologists in an outpatient clinic every month in the first year, every 2 months in the second year, every 3 months in the third year, every 4 months in the fourth year, every 6 months in the fifth year, and annually thereafter until 10 years after treatment.

The follow-up protocol employed in our institution is shown in Table 1. The standard clinical surveillance conducted at each visit consisted of: clinical history; physical examinations including palpation of enlarged lymph nodes, abdominal or pelvic bimanual, and speculum examinations; a Pap smear from the vaginal vault or

Table 1 Follow-up protocols after primary treatment

Schedule	1st year 2 m	2nd year 3 m	3rd year 4 m	4th year 6 m	5th year 6 m	<6th year 1 y
Modality	History	Phys exam	Pap smear	X-ray	CT scan	
	Every visit	Every visit	Every visit	6 m[a]	6 m[b]	

[a] Every 6 months during the 1st and the 5th year, and annually thereafter until the 10th year

[b] Every 6 months during the 1st and the 5th year

2 m every 2 months, *3 m* every 3 months, *4 m* every 4 months, *6 m* every 6 months, *1 y* every year, *history* history talking, *Phys exam* physical examination, *X-ray* chest X-ray

uterine cervix. When clinically indicated, abdominal or vaginal ultrasounds were performed. Chest X-rays were performed every 6 months from the 1st to 5th year, and annually until the 10th year. CT scans of the pelvis and abdomen were performed every 6 months from the 1st to 5th year.

Diagnosis and treatment of recurrence

In patients with a suspicious history or with signs at the physical examination, further evaluations including chest X-rays, CT scans of the pelvis and abdomen, and magnetic resonance imaging (MRI) were performed. Lesions suspected for recurrence were confirmed by histological or cytological diagnosis, whenever possible. In cases where histology or cytology could not be assessed, the diagnosis of recurrence was made by positive imaging studies.

The patients were grouped by the site of relapse as follows: central pelvis, pelvic sidewall, single distant metastasis, lymph nodes outside of the pelvic area, and multiple locations.

Recurrences were considered symptomatic if the patient reported symptoms prior to the examination. Conversely, recurrences were considered asymptomatic in patients who had no relevant complaints prior to the routine follow-up.

The patients were also grouped according to the first abnormal test leading to the diagnosis of recurrence: symptoms, physical examination, Pap smear, chest X-ray, and CT scan.

Recurrent disease was treated in accordance with the institutional treatment guidelines. Basically, single distant recurrent tumors were treated with salvage external beam radiotherapy (EBRT) or with salvage surgery. Patients who suffered recurrence in the central pelvis were treated with salvage surgery or, whenever possible, with interstitial brachytherapy (ISBT). Patients with pelvic sidewall or multiple recurrences were treated with platinum-based chemotherapy. Patients with a single distant tumor that could not be salvaged by either surgery or radiotherapy were also treated with platinum-based chemotherapy. Patients who refused salvage chemotherapy or radiotherapy were treated with palliative care alone. Survival from recurrence was defined as the time from the diagnosis of recurrence to death or the last observation.

Statistical analysis

The survival analysis was performed based on the Kaplan–Meier method, and comparisons between groups were made with the log-rank test. p values of <0.05 were considered to be statistically significant.

Results

Patients

During the study period, 168 patients were identified to have suffered cervical cancer recurrence. Of these, ten patients were excluded due to persistent disease, which was defined as the presence of disease 3 months or less from the completion of treatment; six patients were excluded due to insufficient data because their primary treatments were performed at a facility other than Osaka University; and six patients were lost to follow-up, and so a total of 146 patients with recurrent cervical cancer were included in this study. The primary disease was treated by definitive radiotherapy in 92 patients, and radical hysterectomy followed by adjuvant radiotherapy in 48 patients.

The clinicopathologic characteristics of the patients are summarized in Table 2. The mean and median ages of the

Table 2 Patient characteristics

		Number of patients (All patients; $n = 146$)	(%)
Age	<35	10	7
	35–70	105	72
	>70	31	21
Stage	I	25	17
	II	58	40
	III	38	26
	IVa	10	7
	IVb	15	10
Histology	SCC	116	79
	Non SCC	30	21
Prior chemoradiotherapy	Yes	25	17
	No	121	83
Disease-free interval	<13 months	80	55
	13–24 months	34	23
	25–36 months	15	10
	37–48 months	5	3
	49–60 months	0	0
	>60 months	12	8
Site of recurrence	Pelvic sidewall	14	10
	Central pelvis	41	28
	Distant	24	16
	Nodes	23	16
	Multiple	44	30
Treatment modality	Palliative care	37	25
	Radiotherapy	55	38
	Chemotherapy	46	32
	Surgery	8	5

patients were 57.2 and 57.5 years, respectively. One hundred and sixteen patients had squamous cell carcinoma and 30 had non-squamous histology. Twenty-five were treated with platinum-based chemoradiotherapy as part of their initial treatment. One hundred and twenty-nine recurrences (88.4%) were diagnosed within 3 years of the primary treatment. The median and mean disease-free intervals were 11 and 17.4 months, respectively.

Recurrent disease was localized centrally in 41 cases, at the pelvic sidewall in 14, at a distant site in 24, in the lymph nodes in 23, and at multiple sites in 44.

The treatment modalities for recurrence were palliative care alone in 37 patients, radiotherapy in 55, chemotherapy in 46, and surgery in 8. Surgery was performed in two patients with isolated pulmonary recurrence, one patient with liver recurrence, three patients with recurrence at the uterine cervix, one patient with isolated pelvic lymph node recurrence, and one patient with rectal recurrence. The overall median survival from recurrence was 15 months.

Method of detection of recurrence

The findings regarding the first abnormal test leading to the detection of recurrence and survival after recurrence according to the method of recurrence detection are summarized in Table 3. As shown, symptoms, physical examination, and CT scans led to the detection of recurrence in most patients. Of the 146 patients, 49 (33.6%) were symptomatic at the time of detection. Their symptoms included pain ($n = 26$), bleeding ($n = 8$), coughing ($n = 5$), bowel obstruction ($n = 2$), swelling of the leg ($n = 2$), fever ($n = 2$), urinary frequency ($n = 1$), fatigue ($n = 1$), bloody sputum ($n = 1$), and self-detection of a supraclavicular lymph node swelling ($n = 1$).

Among the asymptomatic patients, the vast majority of recurrences were diagnosed by physical examination and CT scan. CT scan was the first abnormal test leading to the diagnosis of recurrence in 45 patients. Of the remaining 52 patients, recurrence was first detected by physical examination in 31 patients, Pap smear in 9 patients, and by chest X-ray in 12 patients.

Table 3 Survival in relapsed patients by method of detection

	Number of patients *n* (%)	Survival after recurrence median (months)
Symptoms	49 (33.6)	10
Phys exam	31 (21.2)	21
Pap smear	9 (6.2)	24
X-ray	12 (8.2)	11.5
CT scan	45 (30.8)	20

Phys exam physical examination, *X-ray* chest X-ray

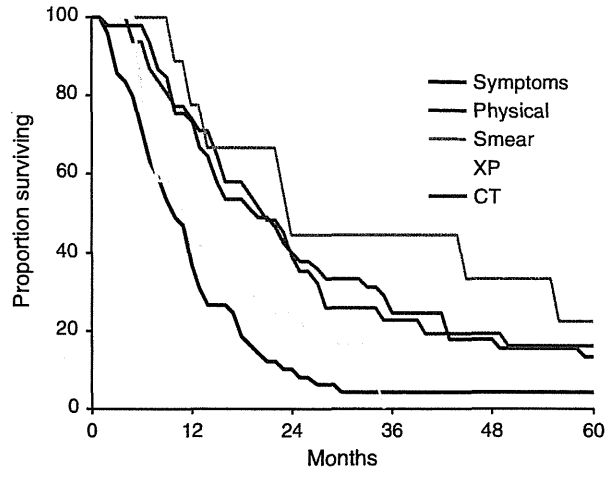

Fig. 1 Survival after detection of recurrence according to modality of diagnosis. The patients who first presented with symptoms and those who first presented on a chest X-ray had similar survival after recurrence ($p = 0.4219$). However, the patients who first presented with abnormal physical findings, an abnormal Pap smear, or abnormal CT scan findings had significantly better survival than those who first presented with symptoms: physical examination versus symptoms; $p = 0.0003$, Pap smear versus symptoms; $p = 0.0054$, CT scan versus symptoms; $p < 0.0001$

The median survival after recurrence for those who first presented with symptoms, physical findings, Pap smear, chest X-ray, and CT scan were 10, 21, 24, 11.5, and 20 months, respectively. As shown in Fig. 1, there were no significant differences in survival between those who first presented with symptoms and those who first presented with abnormal chest X-ray findings. However, the patients who first presented with abnormal physical findings, an abnormal Pap smear, or abnormal CT scan findings had significantly better survival than those who first presented with symptoms.

We next analyzed the methods of recurrence detection according to the time from completion of the initial treatment as illustrated in Fig. 2. As shown, symptoms, physical examination, and CT scans played a significant role as the first abnormal test in patients with a DFI of 1–5 years. In contrast, chest X-ray and Pap smear only had a clinical impact on the diagnosis of recurrence in patients with a DFI of 1–2 years. No recurrence was detected by Pap smear or chest X-ray in patients with a DFI of three or more years. As the number of women with a DFI of 5 years or more was too small ($n = 4$), we could not draw any reliable conclusions about this group.

Discussion

The effectiveness of follow-up programs after the treatment of uterine cervical cancer has been evaluated in

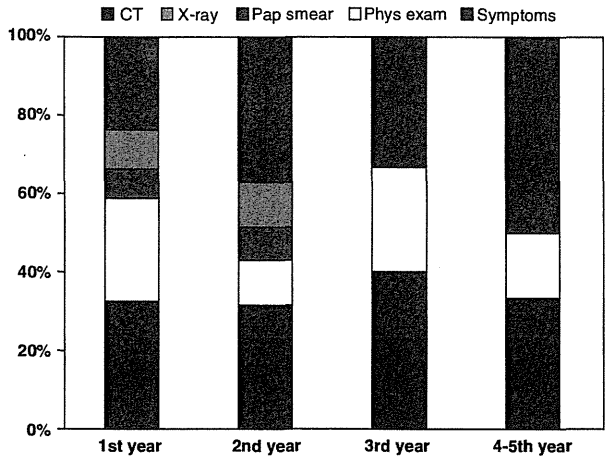

Fig. 2 Distribution of cases according to disease-free interval (DFI) and method of recurrence detection. *Phys exam* physical examination, *X-ray* chest X-ray

several retrospective studies [9–16]. However, the patient backgrounds in these studies were not uniform. Some studies followed up patients treated with radical hysterectomy, whereas other reports followed up patients treated with radiotherapy alone or radical hysterectomy followed by adjuvant radiotherapy. The patients evaluated in the current study were all treated with radiotherapy as part of their initial treatment.

The results of the current study showed that the patients who first presented with abnormal physical findings, an abnormal Pap smear, or abnormal CT scan findings had significantly better survival than those who first presented with symptoms (Table 3; Fig. 1), which indicates that patients may benefit from routine follow-up using these diagnostic procedures for detecting asymptomatic recurrence.

Our results also showed that history taking, physical examination, and CT scans were the most common first abnormal tests leading to the diagnosis of recurrent disease in patients with a DFI of 1–5 years (Fig. 2). These three procedures detected 86% of the recurrences.

Physical examination was shown to be less effective than symptoms and CT scans in detecting recurrence. However, it did detect 21.2% of the recurrences in this study and was demonstrated to be an effective procedure in patients with a DFI of 1–5 years. To confirm the size and the location of the recurrent diseases, all 31 patients who first presented with abnormal physical findings subsequently received CT scans. Of these, recurrent tumors could be confirmed by CT scans only in 12 patients (data not shown). These results indicate that physical examination may be more sensitive than CT scans in a particular group of patients with small recurrent lesions that cannot be confirmed by CT scan. Moreover, patients whose recurrences were detected by routine physical examination showed significantly longer survival than those detected by clinical symptoms (Table 3; Fig. 1). Therefore, we recommend that physical examination be included in the routine follow-up program for cervical cancer patients who had been initially treated with radiotherapy.

In the current study, performing a routine Pap smear from the vaginal vault or uterine cervix benefited only 6.2% of patients with cervical cancer recurrence. However, the patients whose recurrence was detected by routine Pap smear showed significantly longer survival than those whose recurrence was detected by clinical symptoms (Table 3; Fig. 1), which may have been due to the fact that most patients whose recurrence was detected by Pap smear developed pelvic central recurrence that can be salvaged by intracavitary brachytherapy (ICBT) or interstitial brachytherapy (ISBT). When analyzed by DFI, the use of a Pap smear was found to have a clinical impact on the diagnosis of recurrence only in patients with a DFI of 1–2 years. Our data are in accordance with previous studies, which indicated that vaginal cytological evaluation is ineffective for cervical cancer surveillance [9]. Thus, we question the economic justification for performing routine Pap smears in post-treatment years 3–5 in this patient population. However, the ACOG guidelines on the diagnosis and treatment of cervical carcinomas [17] suggest that a Pap smear should be performed once a year, while the NCCN Clinical Practice Guidelines on Cervical Cancer treatment [18] recommend that a Pap smear should be performed at every visit; i.e., every 3 months for the first year, every 4 months for the second year, and every 6 months for another 3 years. However, since performing a routine Pap smear benefited only a small proportion of the patients with a DFI of 1–2 years in the current study, we recommend that it be routinely performed for the first 2 years after radiotherapy, but can be omitted thereafter.

The NCCN Clinical Practice Guidelines on Cervical Cancer treatment [18] and the ACOG guidelines on the diagnosis and treatment of cervical carcinomas [17] recommend a chest X-ray once a year. In the current study, chest X-ray demonstrated a marginal role in the diagnosis of cervical cancer recurrence. As shown in Table 3, routine chest X-ray led to the detection of recurrence in only 8.2% of patients with cervical cancer. When analyzed by DFI, routine chest X-ray only had a clinical impact on the diagnosis of recurrence in patients with a DFI of 1–2 years. This result is consistent with a previous study, which indicated that 96% of pulmonary metastases from cervical cancer occur within 2 years of diagnosis of the primary tumor [19]. Moreover, patients whose recurrence was detected by routine chest X-ray showed similar survival to those whose recurrence was detected by clinical symptoms, which may have been due to the fact that patients whose

recurrence was detected by chest X-ray further developed distant metastasis or systemic disease. This result may indicate the ineffectiveness of routine chest X-ray in detecting asymptomatic recurrence with regard to survival. Our data are in accordance with previous studies, which indicated that solitary lung metastases are uncommon, occurring in 18–25% of cases [19]. Given the limited clinical value of routine chest X-ray demonstrated by the current study, we propose that it be routinely performed for the first 2 years after radiotherapy, but can be omitted thereafter.

CT scans were the second most common initial tests leading to the diagnosis of recurrence (Table 3) and resulting in significantly longer survival than those detected by clinical symptoms (Fig. 1). This may have been due to the fact that 20 of the 45 patients whose recurrence was detected by CT scans developed isolated paraaortic node (PALN) recurrence, which can be salvaged by external beam radiotherapy (EBRT). However, we cannot define the optimal timing of performing CT scans as part of the routine follow-up program from our results. To avoid exposing the patients to unnecessary radiation and excessive cost, the role of routine CT scans in the detection of asymptomatic recurrence should further be investigated.

Due to the lack of a prospective randomized study investigating the impact of routine follow-up on survival and patient's quality of life, we cannot say frequent and extensive follow-up is better than infrequent follow-up. Moreover, we cannot define the optimal or minimum follow-up schedule from retrospective investigations including our results. However, since 88% of recurrences occurred within the first 3 years after primary treatment in the present study, we propose frequent follow-up evaluations during the first 3 years after primary treatment in order to detect recurrence at an asymptomatic stage.

As all patients enrolled in the current study had been treated with radiotherapy as part of their initial treatment, we cannot define the optimal procedure for the detection of recurrence in cervical cancer patients who were initially treated with radical hysterectomy alone. Patients who had not received pelvic radiotherapy may suffer more local or pelvic recurrence than those who had received pelvic radiotherapy, and thus the optimal follow-up procedures may differ between these groups of patients. This issue should be investigated in future studies.

Due to its retrospective nature, we have to recognize the potential sources of biases in our study. First is the "lead time bias", in which earlier diagnosis of asymptomatic recurrence allows patients to live with recurrent disease longer without contributing to any real survival advantage than later diagnosis of symptomatic recurrences. Second is the "length time bias", in which patients with less aggressive tumors are more likely to have recurrence diagnosed by Pap smear, physical examination, or CT scans, leading to earlier detection of recurrence in asymptomatic patients. The only way to exclude these biases is through a prospective randomized study.

The concept of routine follow-up after treatment with curative intent is based on the premise that detecting recurrence before symptoms have developed will permit earlier treatment and improve survival as well as the patient's quality of life. Early detection of asymptomatic loco-regional recurrence will allow curative therapy, such as surgery or radiotherapy. However, early detection of recurrence, in which effective treatment is not available, may adversely affect the patient's quality of life. In the current study, the median survival from recurrence in asymptomatic patients was 20 months, which is shorter than the reported survival in patients with platinum-sensitive recurrent ovarian cancer [20]. This may be due to the lack of effective systemic chemotherapy for recurrent cervical cancer [21]. Thus, in addition to the establishment of evidence-based and economic follow-up programs, the development of effective systemic treatment including chemotherapy or biologic therapy for recurrent disease is urgently needed.

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Conflict of interest None.

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ORIGINAL RESEARCH

Significance of lymphovascular space invasion in epithelial ovarian cancer

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Abstract

While the prognostic significance of lymphovascular space invasion (LVSI) is well established in endometrial and cervical cancer, its role in ovarian cancer is not fully understood. First, a training cohort was conducted to explore whether the presence and quantity of LVSI within the ovarian tumor correlated with nodal metastasis and survival (n = 127). Next, the results of the training cohort were applied to a different study population (validation cohort, n = 93). In both cohorts, histopathology slides of epithelial ovarian cancer cases that underwent primary cytoreductive surgery including pelvic and/or aortic lymphadenectomy were examined. In a post hoc analysis, the significance of LVSI was evaluated in apparent stage I cases (n = 53). In the training cohort, the majority of patients had advanced-stage disease (82.7%). LVSI was observed in 79.5% of cases, and nodal metastasis was the strongest variable associated with the presence of LVSI (odds ratio [OR]: 7.99, 95% confidence interval [CI]: 1.98–32.1, P = 0.003) in multivariate analysis. The presence of LVSI correlated with a worsened progression-free survival on multivariate analysis (hazard ratio [HR]: 2.06, 95% CI: 1.01–4.24, P = 0.048). The significance of the presence of LVSI was reproduced in the validation cohort (majority, early stage 61.3%). In apparent stage I cases, the presence of LVSI was associated with a high negative predictive value for nodal metastasis (100%, likelihood ratio, P = 0.034) and with worsened progression-free survival (HR: 5.16, 95% CI: 1.00–26.6, P = 0.028). The presence of LVSI is an independent predictive indicator of nodal metastasis and is associated with worse clinical outcome of patients with epithelial ovarian cancer.

Introduction

Ovarian cancer remains a deadly disease and the most common cause of death among gynecologic malignancies. In 2012, over 22,300 women in the United States are estimated to be diagnosed with ovarian cancer, and over 15,500 will die of this disease [1]. The majority of ovarian cancer patients were present with advanced-stage disease, and cytoreductive surgery remains a mainstay in management [2]. Cytoreductive surgery for ovarian cancer includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy,

and omentectomy. Information obtained from the surgical specimen is useful for determining prognosis including histology, grade, and the extent of disease spread. However, given the imperfect predictive nature of these factors, additional markers are needed.

Lymphovascular space invasion (LVSI) is defined as the presence of tumor cells inside the capillary lumens of either the lymphatic or the microvascular drainage system within the primary tumor. The significance of LVSI has been extensively studied in other types of gynecologic malignancies such as endometrial [3–7], cervical [8–13], and vulvar cancer [14–16]. In each, the presence of LVSI in the tumor is associated with increased risk of disease spread (especially nodal metastases), increased chance of disease recurrence, and decreased survival outcomes. In contrast, there has been little investigation on the impact of LVSI in epithelial ovarian cancer [17, 18], and the role of LVSI in the outcome of women with ovarian cancer remains unclear. The aim of this study is to evaluate the impact of the presence of LVSI within the ovarian malignancy on clinical variables and survival outcomes in women with ovarian cancer.

Methods

Training set cohort

After Institutional Review Board (IRB) approval was obtained in Mercy Medical Center in Baltimore, a previously established ovarian cancer database was utilized for this study [19]. Inclusion criteria included cases with epithelial ovarian cancer that underwent primary cytoreductive surgery including pelvic and/or aortic lymphadenectomy between January 1995 and January 2009. Cases with metastatic disease from sites other than ovarian primary, synchronous cancer types, and tumors of low malignant potential were excluded from the study. Variables abstracted from the medical records were patient demographics and survival outcomes after surgery.

The histopathology slides of the cases that met inclusion criteria were examined. The total number of slides stained with hematoxylin and eosin, the number of slides that contained ovarian tumor, and the number of slides with ovarian tumor that contained foci of LVSI were recorded for each case. The number of foci of LVSI was manually counted and the average number of foci of LVSI per slide was determined per case, and classified into "none" for no LVSI, and "low" (1–33 percentile), "moderate" (34–66 percentile), and "high" ($\geq$67 percentile) among LVSI presenting tumors. For instance, if five slides contained LVSI within the ovarian tumor for a total of 10 foci, the average number of LVSI foci per slide was classified as 2 for that case. The gynecologic pathologist who evaluated the slides in this cohort was completely blinded to the clinical information. The total number of lymph nodes examined and the number of lymph nodes with tumor metastasis were also recorded. The presence and quantity of LVSI were then correlated with clinical variables, nodal metastasis, and survival outcome.

Validation cohort

By utilizing the results of the training set cohort, an additional cohort was conducted and examined using a previously collected database for ovarian cancer in the participating institutions (Gynecologic Oncology Group in Osaka, Japan). IRB approval was obtained at each site. This study group was chosen to demonstrate whether the training set results were reproducible in a different population. Similar to the training set cohort, the histopathology slides of women with epithelial ovarian cancer who underwent primary cytoreductive surgery including pelvic and/or aortic lymphadenectomy were examined by different gynecologic pathologists who were blinded to the results of the training set cohort and to clinical information. Pulled slides were examined manually and the quantity of LVSI was scored as none, low, moderate, and high as defined by the training set cohort.

Definition

Detailed description for the definition of LVSI is shown in Supplemental Methods. Among serous histology, grade 2 and 3 tumors were grouped as high-grade serous carcinoma analyzed as an independent group, whereas grade 1 tumors were grouped as low-grade serous carcinoma based on the recent accumulating data [20, 21]. In this two-tier grading system, it adequately correlates to conventional FIGO (the International Federation of Gynecology and Obstetrics) grading system and further provides valuable clinical outcome for ovarian cancer patients when compared with FIGO grading system demonstrating high-grade serous carcinoma as the distinct ovarian cancer subtype [20]. The significance of the presence of LVSI within the ovarian tumor was evaluated in apparent stage I disease across the two cohorts defined as ovarian tumor grossly confined to the ovary. The date of progression was determined by clinical examination, imaging studies, and/or CA-125 levels. Progression-free survival was defined as the time interval from the date of primary cytoreductive surgery to the date of documented first recurrence or progression of disease. If there was no recurrence, progression-free survival was determined as the date of last follow-up. Overall survival was defined as the interval between the primary cytoreductive surgery and the date of death or last follow-up.

Statistical analysis

Continuous variables were assessed for normality (Kolmogorov–Smirnov test) and expressed as appropriate (mean with SD or median with range). Student's *t*-test or Mann–Whitney *U*-test was performed for continuous variable as appropriate. Categorical variables were evaluated with Fisher's exact test or chi-square test as appropriate, expressed with odds ratio (OR) and 95% confidence interval (CI). Risk factor of LVSI was evaluated with logistic regression test, and multivariate logistic regression test was further performed among significant variables in univariate analysis. Receiver–operator characteristic (ROC) curve analysis was performed to identify the risk factors for nodal metastasis expressed with area under the curve (AUC), and the cutoff analysis was performed to maximize the risk of nodal metastasis. Sensitivity, specificity, positive and negative predictive values, and accuracy of nodal metastasis were determined with the results of LVSI status. For survival data analysis, to determine the significance of variables for the survival outcomes for progression-free survival and overall survival, univariate (log-rank) and multivariate (Cox proportional hazard regression test) analyses were performed as appropriate. Survival curves were constructed with the Kaplan–Meier method. *P*-values of less than 0.05 were considered statistically significant (all, two-tailed). The Statistical Package for Social Science software (SPSS, version 12.0, IL) was used for all analyses.

Results

The clinical characteristics of patients comprising the training set cohort are provided in Table 1. Mean age was 61 (±10.4), and the majority were Caucasian (89.0%), had advanced-stage disease (82.7%), and had high-grade serous tumors (73.2%). LVSI was noted in 101 (79.5%, 95% CI: 72.5–86.5) among 127 cases with the median number of LVSI foci per slide being 2 (range 0–53 foci, Kolmogorov–Smirnov's $P < 0.001$). Median number of slides containing LVSI was 5 (range 1–28) per case. In univariate analysis, nodal metastasis was associated with the presence of any LVSI (95.9% vs. 56.7%, $P < 0.001$), tumor stage (proportion of LVSI presenting tumor, T1 vs. T2 vs. T3: 23.1% vs. 50% vs. 90.2%, $P < 0.001$), and high-grade serous carcinoma (86.0% vs. 61.8%, $P = 0.004$) (Table 2, Fig. 1A–C). The magnitude of the significance of the presence of LVSI for nodal metastasis was similar between pelvic and aortic nodes (OR, 22.6 vs. 22.1). In multivariate analysis, tumor stage and nodal metastasis remained significantly associated with the presence of LVSI, and nodal metastasis was the strongest among significant variables (OR: 7.99, 95% CI: 1.98–32.1, $P = 0.003$, Table 2).

Table 1. Patient demographics in the two cohorts.

	Training set cohort	Validation cohort	*P*
Cases	*n* = 127	*n* = 93	
Age	61 (±10.4)	52 (±8.8)	<0.001
Race			
White	113 (89.0%)	0	<0.001
Black	11 (8.7%)	0	
Asian	2 (1.6%)	93 (100%)	
Hispanic	1 (0.8%)	0	
FIGO stage			
I	11 (8.7%)	37 (39.8%)	<0.001
II	11 (8.7%)	20 (21.5%)	
III	90 (70.9%)	31 (33.3%)	
IV	15 (11.8%)	5 (5.4%)	
FIGO grade			
1	1 (0.8%)	24 (27.0%)	<0.001
2	20 (15.7%)	40 (44.9%)	
3	105 (82.7%)	25 (28.1%)	
Histology type			
Serous	94 (74.0%)	34 (36.6%)	<0.001
Endometrioid	7 (5.5%)	23 (24.7%)	
Clear cell	11 (8.7%)	24 (25.8%)	
Mucinous	2 (1.6%)	7 (7.5%)	
Others	13 (10.2%)	5 (5.4%)	
Two-tier grading system[1]			
High-grade serous	93 (73.2%)	28 (31.5%)	<0.001
Low-grade serous	1 (0.8%)	5 (5.6%)	
Other	33 (26.0%)	56 (62.9%)	
Nodal metastasis			
Pelvic lymph nodes[2]	66 (53.2%)		<0.001
Para-aortic lymph nodes[2]	31 (48.4%)		
Any lymph nodes	74 (58.3%)	17 (18.3%)	
Total slides examined[3]	41 (13–94)	18 (2–42)	<0.001
Slides for ovarian tumor[3]	9 (2–29)	7 (1–20)	0.001
Slides presenting LVSI[3]	5 (1–28)	2 (1-10)	<0.001
LVSI presenting tumor	101 (79.5%)	48 (51.6%)	<0.001

Mean (±SD), median (range), or number (%) is shown. FIGO, the International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion.

[1]Grade 2 and 3 tumors are grouped as high-grade serous carcinoma, whereas grade 1 tumors are grouped as low-grade serous carcinoma among serous carcinoma.

[2]In training set cohort, pelvic and para-aortic lymph nodes were evaluated in 124 and 64 cases, respectively.

[3]Number of slides per each case. Grade: 4 and 1 cases missed in training and validation cohort, respectively.

Next, the correlation between the quantity of LVSI and the risk of nodal metastasis was examined. Among 127 cases, 124 (97.6%) were available for pelvic lymph node evaluation and 64 (50.4%) cases for aortic lymph node evaluation. Median numbers of lymph nodes sampled from the pelvic and aortic areas were 4 (range 1–20) and 2.5 (range 1–11), respectively. In a predictive model with

Table 2. Variables associated with lymphovascular space invasion in ovarian cancer.

		Univariate analysis		Multivariate analysis	
	Case number	OR (95% CI)	*P*	OR (95% CI)	*P*
Training set cohort					
Tumor stage (per stage)	13 vs. 12 vs. 103	6.54 (3.13–13.7)	<0.001	3.90 (1.46–10.4)	0.007
Any nodal metastasis (yes vs. no)	74 vs. 53	18.1 (5.06–65.0)	<0.001	7.99 (1.98–32.1)	0.003
Pelvic lymph nodes (yes vs. no)	66 vs. 58	22.6 (5.03–101)	<0.001		
Para-aortic lymph nodes (yes vs. no)	31 vs. 33	22.1 (2.68–182)	0.004		
High-grade serous carcinoma (yes vs. no)	93 vs. 34	3.81 (1.54–9.43)	0.004		0.78
Validation cohort					
Tumor stage (per stage)	40 vs. 22 vs. 31	2.45 (1.46–4.11)	0.001		0.16
Any nodal metastasis (yes vs. no)	17 vs. 76	9.77 (2.09–45.7)	0.004	5.74 (1.13–29.2)	0.035
High-grade serous carcinoma (yes vs. no)	28 vs. 61	3.37 (1.28–8.83)	0.014		0.16

Logistic regression test for presence of tumoral LVSI (yes vs. no). Examined all the collected variables and only significant variables are listed. OR, odds ratio; 95% CI, 95% confidence interval; LVSI, lymphovascular space invasion.

ROC analysis, the extent of LVSI significantly predicted lymph node metastasis (pelvic nodal metastasis, AUC 0.95, 95% CI: 0.91–0.99, $P < 0.001$; and aortic lymph nodal metastasis, AUC 0.93, 95% CI: 0.86–0.99, $P < 0.001$). To evaluate the significance of quantification of LVSI, a cutoff analysis was performed that showed that the presence of any LVSI ($\geq$1 focus) was the strongest predictor of lymph nodal metastasis (OR for nodal metastasis per cutoff for LVSI foci per slide, 18.1 for 1 focus, 8.91 for 2 foci, and 11.9 for 3 foci, respectively). Among 101 cases containing LVSI, the quantity of LVSI was significantly correlated with the risk of nodal metastasis ($P < 0.001$). Based on the analysis, cases were classified into the following categories: none (LVSI, 0 foci), low (maximum 1 focus per slide per case), moderate (maximum 2 foci per slide per case), and high (3 or more foci per slide per case), respectively. Of cases with no LVSI, the proportion with lymph nodal metastasis was 11.5%, as compared with 48.5% in low cases, 70.6% in moderate cases, and 91.2% in high cases, ($P < 0.001$).

After a median follow-up time of 10.7 months, 85 (66.9%) women developed recurrence or progression of disease. On univariate analysis, significant predictors of progression-free survival were high-grade serous carcinoma (5-year rate, 5.0% vs. 41.3%, $P = 0.004$), FIGO stage (I, II, III, and IV: 76.2%, 67.5%, 6.4%, and 0%, $P < 0.001$), and presence of LVSI (8.3% vs. 47.1%, hazard ratio [HR]: 3.36, 95% CI: 1.67–6.74, $P < 0.001$) (Table 3 and Fig. 1D). For overall survival, FIGO stage (5-year rate, I, II, III, and IV: 100%, 79.0%, 28.7%, and 0%, $P = 0.013$) and presence of LVSI (26.5% vs. 67.7%, HR: 3.29, 95% CI: 1.32–8.24, $P = 0.007$) were significant predictors on univariate analysis (Fig. 1E). On multivariate analysis controlling for FIGO stage and high-grade serous carcinoma, the presence of LVSI remained a statistically significant variable for progression-free survival (HR: 2.06, 95% CI: 1.01–4.24, $P = 0.048$, Table 3). After controlling for FIGO stage, the presence of LVSI showed a trend toward worse overall survival although it did not reach statistical significance (HR: 2.16, 95% CI: 0.85–5.45, $P = 0.10$). Further analyses were performed on women whose ovarian tumors contained LVSI to determine whether the quantity of LVSI (low, moderate, or high) added further prognostic information. While the presence of tumoral LVSI was significantly associated with survival outcome (Fig. 1D and E), the quantity of LVSI present did not further impact progression-free survival (5-year rate, low, moderate, and high: 20.3%, 8.9%, and 0%, respectively, $P = 0.84$, Fig. 1F) or overall survival ($P = 0.70$, Fig. 1G).

Validation cohort

To determine whether our findings would be consistent in an independent cohort, we utilized a validation set of 93 cases from an entirely different study population. Patients in the validation cohort were younger, more likely to be of Japanese heritage, more likely to have early-stage disease, and less likely to have high-grade serous tumors (all, $P < 0.001$, Table 1). The presence of LVSI was noted in 48 (51.6%, 95% CI: 41.5–61.8) cases (low, moderate, and high LVSI: 56.3%, 35.4%, and 8.3%, respectively) and was less common than the frequency noted in the training set cohort ($P < 0.001$). In univariate analysis, the presence of LVSI was significantly correlated with nodal metastasis (AUC 0.77, 95% CI: 0.65–0.89, $P < 0.001$, Fig. 2A), tumor stage (T1, T2, and T3: 37.5%, 36.4%, 80.6%, $P = 0.001$, Fig. 2B), and high-grade serous carcinoma (71.4% vs. 42.6%, $P = 0.013$, Fig. 2C). Low-grade serous carcinoma showed significantly lower frequency of LVSI when compared with high-grade serous carcinoma (high-grade serous vs. low-grade serous vs.

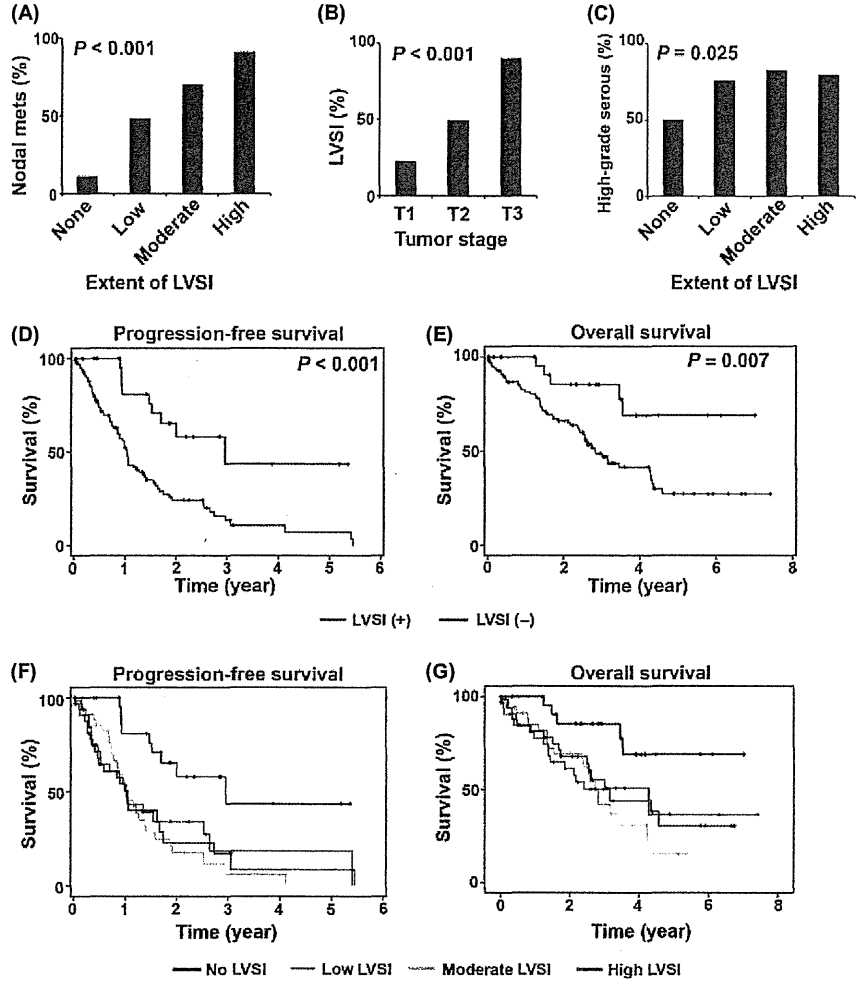

Figure 1. Lymphovascular space invasion and ovarian cancer in training set cohort. (A) Risk of lymph node metastasis based on the extent of LVSI is shown. (B) Correlation between tumor stage and LVSI. (C) Proportion of high-grade serous carcinoma is shown based on the extent of LVSI. (D) and (E) Survival curves based on LVSI status are shown. (F) and (G) Survival curves based on the extent of LVSI are shown. No LVSI, tumor expresses no LVSI, and low LVSI (1–33 percentile), moderate LVSI (34–66 percentile), and high (≥67 percentile) among LVSI presenting tumors in training set cohort. LVSI, lymphovascular space invasion; nodal mets, nodal metastasis.

nonserous histology: 71.4% vs. 40% vs. 42.9%, $P = 0.041$). In multivariate analysis, the presence of LVSI remained a statistically significant predictive factor for nodal metastasis (OR: 5.74, 95% CI: 1.13–29.2, $P = 0.035$) after controlling for tumor stage and high-grade serous carcinoma (Table 2).

On univariate analysis, the presence of LVSI was associated with a worsened progression-free survival (5-year rate, 40.8% vs. 78.6%, HR: 3.65, 95% CI: 1.72–7.78, $P = 0.0003$) and overall survival (5-year rate, 59.6% vs. 85.0%, HR: 2.54, 95% CI: 1.64–3.92, $P = 0.006$) (Table 3, Fig. 2D and E). Similar to the training set cohort, the quantity of LVSI among ovarian tumors containing LVSI did not add further prognostic information: 5-year progression-free survival rate in low versus moderate/high, 45.7% versus 35.0%, respectively ($P = 0.30$, Fig. 2F); and 5-year overall survival rate, 68.9% versus 46.6%, respectively ($P = 0.071$, Fig. 2G). On multivariate analysis, the presence of LVSI remained as a marginally significant predictive factor associated with a worsened progression-free survival (HR: 1.99, 95% CI: 0.90–4.20, $P = 0.09$) after controlling for high-grade serous carcinoma ($P = 0.26$) and stage ($P < 0.001$). The presence of LVSI was not associated with overall survival in this study population (HR: 1.87, 95% CI: 0.74–4.85, $P = 0.18$) after controlling for high-grade serous carcinoma and stage.

A post hoc analysis of women with apparent stage I ovarian cancer across the two cohorts was performed to

Table 3. Lymphovascular space invasion and survival of women with ovarian cancer.

		Univariate analysis		Multivariate analysis	
	Case number	HR (95% CI)	*P*	HR (95% CI)	*P*
Training set cohort					
Progression-free survival					
High-grade serous carcinoma (yes vs. no)	93 vs. 34	2.20 (1.27–3.83)	0.004		0.19
FIGO stage (per stage)	11 vs. 11 vs. 90 vs. 15	2.30 (1.60–3.30)	<0.001	1.95 (1.26–3.01)	0.003
LVSI (yes vs. no)	101 vs. 26	3.36 (1.67–6.74)	<0.001	2.06 (1.01–4.24)	0.048
Overall survival					
FIGO stage (per stage)	11 vs. 11 vs. 90 vs. 15	2.29 (1.45–3.60)	0.013	2.17 (1.31–3.60)	0.003
LVSI (yes vs. no)	101 vs. 26	3.29 (1.32–8.24)	0.007		0.1
Validation cohort					
Progression-free survival					
High-grade serous carcinoma (yes vs. no)	28 vs. 61	3.77 (1.90–7.46)	<0.001		0.26
FIGO stage (per stage)	37 vs. 20 vs. 31 vs. 5	3.05 (2.09–4.44)	<0.001	2.57 (1.59–4.00)	<0.001
LVSI (yes vs. no)	48 vs. 45	3.65 (1.72–7.78)	0.003	1.99 (0.90–4.20)	0.09
Overall survival					
High-grade serous carcinoma (yes vs. no)	28 vs. 61	2.84 (1.27–6.34)	0.008		0.75
FIGO stage (per stage)	37 vs. 20 vs. 31 vs. 5	2.54 (1.64–3.92)	<0.001	2.60 (1.48–4.57)	0.001
LVSI (yes vs. no)	48 vs. 45	3.35 (1.34–8.40)	0.006		0.18

Cox proportional hazard regression test. Examined all the collected variables and only significant variables are listed. HR, hazard ratio; 95% CI, 95% confidence interval; FIGO, the International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion.

assess the potential impact of the presence of LVSI on nodal metastases and survival. There were 53 women with apparent stage I disease, of whom 18 (34.0%, 95% CI: 21.2–46.7) had tumors containing LVSI. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the presence of LVSI as a predictor of nodal metastases were 100%, 66.3%, 11.1%, 100%, and 68.5%, respectively (likelihood ratio, $P = 0.034$). The presence of LVSI was statistically significantly associated with decreased progression-free survival (5-year rate, 66.5% vs. 93.9%, HR: 5.16, 95% CI: 1.00–26.6, $P = 0.028$, Fig. 3A), but not overall survival (5-year rate, 72.6% vs. 94.0%, HR: 3.77, 95% CI: 0.69–20.6, $P = 0.10$, Fig. 3B). After controlling for high-grade serous carcinoma, the presence of LVSI showed a trend toward increased risk of poor progression-free survival (HR: 4.09, 95% CI: 0.75–22.4, $P = 0.10$).

Discussion

The key findings of our study are that the presence of LVSI within the ovarian tumor is an independent predictive factor of both nodal metastasis and survival in women with ovarian cancer. If LVSI was present, the quantity of LVSI did not add further prognostic information, but it did impact the likelihood of nodal metastases. Our results add new information to the management of ovarian cancer exhibiting LVSI. Several key areas in the study deserve special mention.

In a view of systematic literature review using public searching engine PubMed and MEDLINE between 1955 and March 2012 with entry keywords of "ovarian cancer" and "lymphovascular space invasion," there is little data evaluating the prognostic significance of the presence of LVSI in ovarian cancer [17, 18, 22–24]. These limited numbers of prior studies showed mixed results and were hampered by either small sample, lack of quantification of LVSI, or lack of a validation set. The summary of literature review is provided in Table S1. Collectively, the size, number, and quality of prior studies investigating the prognostic significance of LVSI in ovarian cancer were limited, and the impact of the presence of LVSI in ovarian cancer had not been clearly delineated.

Our study is the first to have a formal review of LVSI by a pathologist of all samples, presenting quantitative data, defining the role of LVSI, and validation in a separate independent cohort in epithelial ovarian cancer. The results demonstrated the strong link between the presence of LVSI and the likelihood of nodal metastases in women with ovarian cancer in two disparate study groups. In each, the quantity of LVSI present, as defined by maximum number of foci per slide, further correlated with likelihood of nodal metastases. When apparent stage I cases were combined in a post hoc analysis, the absence of LVSI within the ovarian tumor was an excellent predictor of negative nodal status. There are two possible clinical implications to these results. The first is that if surgical staging was incomplete in that lymphadenectomy was not performed, the lack of LVSI within the ovarian tumor gives reassurance that the nodes are uninvolved. Second, women with

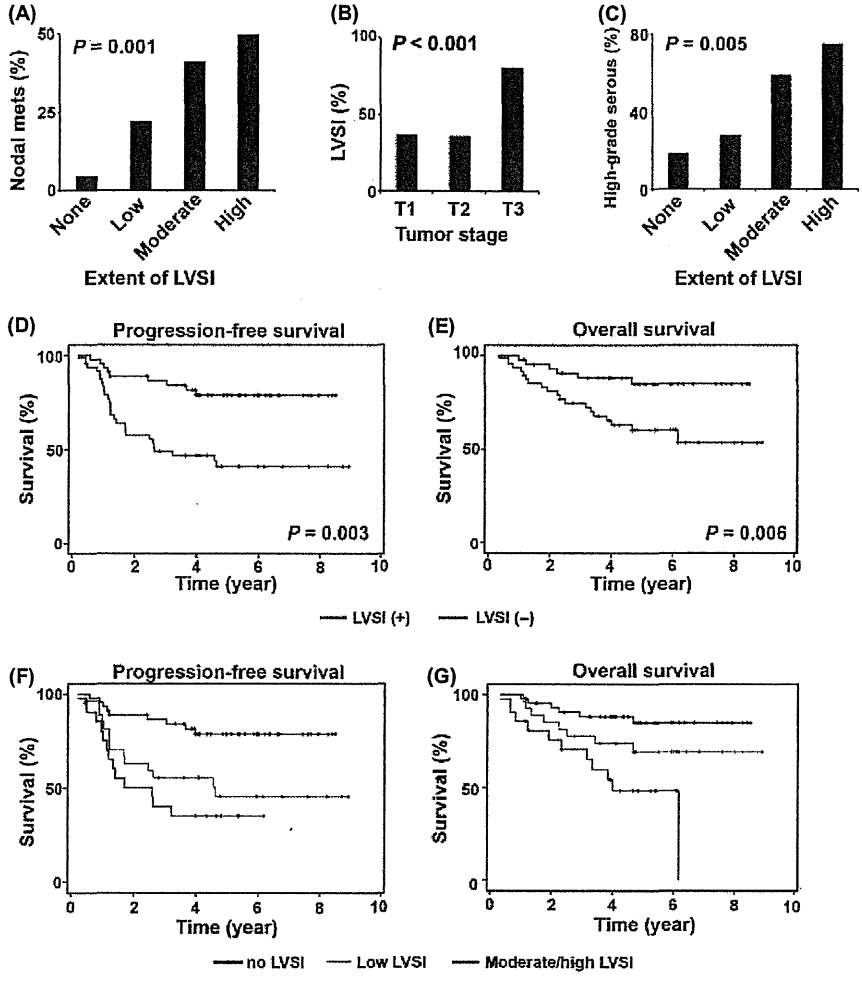

Figure 2. Significance of lymphovascular space invasion in validation cohort. (A) Risk of lymph node metastasis based on the extent of LVSI is shown. (B) Correlation between tumor stage and LVSI. (C) Proportion of high-grade serous carcinoma is shown based on the extent of LVSI. (D) and (E) Survival curves based on LVSI status are shown. (F) and (G) Survival curves based on the extent of LVSI are shown. No LVSI, tumor expresses no LVSI, and low LVSI (1 focus), moderate LVSI (2 foci), and high (≥3 foci) among LVSI presenting tumors in validation cohort. Cases with moderate and high LVSI were grouped due to small number in high (n = 4). LVSI, lymphovascular space invasion; nodal mets, nodal metastasis.

advanced-stage ovarian cancer whose tumors contain LVSI have a worsened progression-free survival and may benefit from consolidation therapy after completion of front-line chemotherapy. As vascular endothelial growth factor (VEGF) pathway is strongly associated with increased LVSI, targeting the VEGF axis

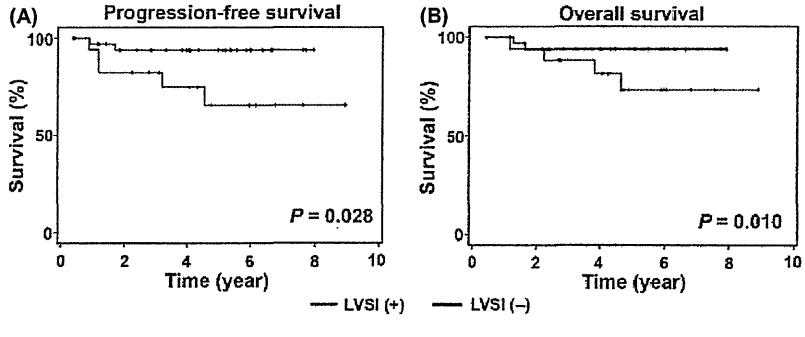

Figure 3. Significance of lymphovascular space invasion in apparent stage I ovarian cancer. (A) and (B) Survival curves for apparent stage I ovarian cancer based on tumor LVSI status. LVSI, lymphovascular space invasion.

with anti-VEGF inhibitor may be an attractive approach in ovarian tumor expressing LVSI [25–27].

A strength of our study is that the sample population is homogeneous in which only primary epithelial ovarian cancer cases who underwent primary surgery were included. Also, this is one of the largest studies evaluating the significance of the presence of LVSI in ovarian cancer. Furthermore, we demonstrated the durability of the impact of LVSI in two disparate cohorts. Potential weaknesses of the study are that it is retrospective in nature and thus confounding factors might have been missed, and that the sample size of women with apparent stage I disease is relatively small. In addition, only 50.4% cases of training set cohort have the information of aortic lymph nodes, and the number of lymph nodes sampled in our study was fewer than the reported literature. Therefore, nodal number may not be enough to evaluate the status of lymph node metastasis in apparent stage I ovarian cancer. Another limitation is that evaluation of the presence of LVSI in our study is based on hematoxylin and eosin staining but not on immunohistochemical analysis; however, it is the former that is widely used to determine the presence of LVSI. Prospective studies will be useful to help to confirm our findings, particularly in terms of the lack of nodal metastases seen in apparent stage I disease when LVSI is absent.

In conclusion, the presence of LVSI is an independent predictive indicator of nodal metastasis and is associated with a worse progression-free survival in ovarian cancer. Standardization of evaluation and scoring of LVSI would potentially yield important information that might help guide management. Further prospective investigation on the impact of the presence and quantity of LVSI in women with epithelial ovarian cancer is warranted.

Acknowledgment

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Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Results of systemic literature review for lymphovascular space invasion and ovarian cancer.

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Impact of histological subtype on survival of patients with surgically-treated stage IA2–IIB cervical cancer: Adenocarcinoma versus squamous cell carcinoma☆

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ABSTRACT

Objectives. To evaluate the significance of adenocarcinoma (AC) compared with squamous cell carcinoma (SCC) with regard to the survival of surgically-treated early stage cervical cancer patients.

Methods. We retrospectively reviewed the medical records of 520 patients with FIGO stage IA2–IIB cervical cancer who were treated with radical hysterectomy with or without adjuvant radiotherapy between January 1998 and December 2008. The patients were classified according to (*i*) pathological risk factors (low-, intermediate-, or high-risk group) and (*ii*) adjuvant radiotherapy (concurrent chemoradiotherapy [CCRT group] or radiotherapy alone [RT group]). Survival outcomes were examined by Kaplan–Meier method and compared with Log-rank test. Multivariate analysis for disease-specific survival (DSS) was performed using Cox proportional hazards regression model to investigate the prognostic significance of histological subtype.

Results. AC histology was associated with significantly decreased DSS compared with SCC histology in the intermediate- and high-risk groups (hazard ratio: 3.06 and 2.88, respectively, both $P<0.05$) while there was no survival difference in the low-risk group ($P=0.1$). Among patients who received any types of adjuvant radiotherapy, DSS of AC histology patients were significantly poorer than SCC histology. Multivariate analysis demonstrated AC histology to be an independent predictor of decreased DSS in both CCRT and RT groups. Moreover, pelvic nodal metastasis significantly predicted the poor survival of patients with AC histology who received CCRT in multivariate analysis.

Conclusions. Adenocarcinoma is an independent prognostic indicator of poor survival in early stage cervical cancer patients with intermediate- and high-risk factors, regardless of the type of adjuvant radiotherapy after radical hysterectomy.

Introduction

The incidence of cervical cancer has decreased by more than 40% during the past 40 years due to the increased implementation of cytological screening. In contrast to the marked decrease in the incidence of squamous cell carcinoma (SCC), the absolute incidence of adenocarcinoma (AC) and its relative proportion compared with SCC have increased significantly [1]. As a result, AC of the cervix currently accounts for approximately 20% of all cervical cancers, which is significantly higher than the incidence of 5–10% observed in the 1970s [1,2].

Currently, cervical cancer patients with AC histology receive the same front-line treatment as those with SCC histology [3]. In a view of literature, however, the prognosis of patients with AC treated either with radical hysterectomy or with definitive radiotherapy is yet to be determined, mainly because of the lack of prospective studies focusing on the prognostic differences between AC and SCC [4–18]. In patients with locally advanced cervical cancer treated with definitive radiotherapy, adenocarcinoma showed lower response rate to the therapy, and associated higher recurrence rate than SCC histology [4]. In early stage cervical cancer patients treated with radical surgery, some previous retrospective studies showed that patients with AC have a poorer prognosis than patients with SCC [5–12], whereas others found no survival differences between the two subtypes [13–18]. As most of these past studies were conducted before concurrent chemoradiotherapy (CCRT) took a role in the treatment of cervical cancer, the prognostic significance of AC in early stage cervical

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