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Oncologic outcomes according to the level of disease burden in patients with metachronous distant metastases from uterine cervical cancer: a Korean Radiation Oncology Group study (KROG 18-10)

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ABSTRACT

Objective: This study aimed to evaluate the oncologic outcomes according to disease burden in uterine cervical cancer patients with metachronous distant metastases.

Methods: Between 2005 and 2015, 163 patients with metachronous distant metastases from uterine cervical cancer after receiving a definitive therapy were evaluated at seven institutions in Korea. Low metastatic burden was defined as less than 5 metastatic sites, whereas high metastatic burden was others. Each metastasis site was divided based on the lymph node (LN) and organs affected. The overall survival (OS) and progression-free survival (PFS) were assessed. Cox proportional hazards models, including other clinical variables, were used to evaluate the survival outcomes.

Results: The median follow-up duration was 22.2 months (range: 0.3–174.8 months). Para-aortic LNs (56.4%), lungs (26.4%), supraclavicular LNs (18.4%), and peritoneum (13.5%) were found to be the common metastasis sites. Among 37 patients with a single metastasis, 17 (45.9%) had LN metastases and 20 (54.1%) had organ metastases. The 1- and 2-year OS rates were 73.9% and 55.0%, respectively, whereas the PFS rates were 67.2% and 42.9%, respectively. SCC Ag after recurrence and high metastatic burden were significant factors affecting the OS (p=0.004 and p<0.001, respectively). Distant organ recurrence, short disease-free interval (≤2 years), and high metastatic burden were unfavorable factors for PFS (p=0.003, p=0.011, and p=0.002, respectively).

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No potential conflict of interest relevant to this article was reported.

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Conclusion: A favorable oncologic outcome can be expected by performing salvage treatments in selected patients with a long disease-free interval, low metastatic burden, and/or lymphatic-only metastasis.

Keywords: Uterine Cervical Neoplasm; Recurrence; Metachronous Neoplasm; Neoplasm Metastasis; Lymphatic Metastasis

Synopsis
This multicenter study aimed to evaluate the oncologic outcomes according to disease burden in uterine cervical cancer patients with metachronous distant metastases. Long disease-free interval, low metastatic burden, and/or lymphatic-only metastasis are good prognostic factors for metachronous distant metastatic cervical cancer.

INTRODUCTION

Uterine cervical cancer is the fourth most common type of cancer in women worldwide and the fifth most common type of cancer in Korea [1,2]. The primary treatment for uterine cervical cancer is surgery, radiation therapy, or concurrent chemoradiation therapy (CCRT), depending on the disease stage. Unfortunately, 11%–22% and 28%–64% of patients experience relapse of Federation of International Gynecology and Obstetrics (FIGO) stage IB–IIA cancer and stage IIIB–IVA cancer, respectively, after receiving definitive treatment [3-5], and these patients have a poor prognosis [4].

In general, when distant metastasis occurs in patients with solid malignant cancer, chemotherapy is deemed to be the only viable option. However, successful salvage treatment of metastatic patients with a low disease burden has yielded favorable outcomes [6,7]. Furthermore, recent developments in local modalities, including precision radiotherapy and minimally invasive surgery, have extended the possibility of performing salvage treatment for metastatic disease with disease burden [8]. According to recent literature, salvage local treatment in uterine cervical cancer patients with recurrence or metastasis in a limited site can suppress tumor progression for approximately 1–2 year [9-11]. However, available literature related to this topic is limited, and the difference in prognosis according to disease burden in patients with metachronous distant metastases is not well known.

Therefore, we aimed to evaluate the oncologic outcomes according to disease burden in patients with uterine cervical cancer with metachronous distant metastases, and to identify a group of patients with good prognoses in order to help in making appropriate medical decisions.

MATERIALS AND METHODS

1. Patient recruitment and evaluation

Between January 2005 and December 2015, patients with metachronous distant metastatic uterine cervical cancer who underwent definitive therapy at seven institutions in Korea were evaluated. The patients in our study were selected based on the 2009 FIGO staging. Patients 1) with histologically or clinically proven metachronous metastatic uterine cervical cancer, 2) who completed curative treatment and maintained a disease-free status for more than

3 months (radical treatment is defined as R0 or R1 surgical resection or radiation therapy with a radiation dose of >50 Gy delivered to the cervix), and 3) with an Eastern Cooperative Oncology Group performance score of 0–2 at the time of metachronous metastases were included in the study. By contrast, those 1) with lymph node (LN) metastases that exceeded the regional LNs at the time of initial diagnosis based on the American Joint Committee on Cancer Staging, 7th edition; 2) with metastases in distant organs at the time of initial diagnosis; 3) who underwent elective radiotherapy to the para-aortic LNs as a curative treatment (if the upper boundary of the pelvic irradiation is between T12 and L3, it is considered as para-aortic LN radiotherapy); 4) who experienced pelvic recurrence 1 month prior to the occurrence of distant recurrences; and 5) with previous history of other malignancies were excluded. Various treatments were performed in patients who had metachronous recurrence. Based on the first treatment performed after the cancer recurrence occurred, surgery or radiation therapy (including CCRT) was defined as local treatment, whereas chemotherapy was defined as systemic treatment. This study was approved by the Institutional Review Board of each participating institution (principal institution IRB number: 2018AS0110) and the Korean Radiation Oncology Group (KROG 18-10). We retrospectively reviewed the patients' medical records after approval.

Oncologic outcomes, including overall survival (OS) and progression-free survival (PFS), were evaluated. The OS and PFS were estimated from the date of the first metachronous metastases to the date of death, the last follow-up examination, or tumor progression. The OS from the initial diagnosis (OSi) was also described in this study. A low metastatic burden was defined as a limited number of metastatic sites (5 or fewer). If more than 5 metastases were found, it was defined as a high metastatic burden. In this study, recurrence was categorized into LN metastasis and organ metastasis. LN metastasis was subdivided into para-aortic metastasis, mediastinal metastasis, supraclavicular metastasis, cervical metastasis, inguinal metastasis, and metastasis in other LNs. Distant organ metastases were subdivided into lung metastasis, liver metastasis, brain metastasis, bone metastasis, peritoneum metastasis, and metastasis in other areas. In each area, the number of recurrences within the area was not considered.

Local treatment was defined as initial therapy after recurrence, followed by surgery and radiation therapy (including CCRT). Each institution followed their standard guidelines in conducting a follow-up, and follow-up schedules were carried out according to the following protocol. All patients had follow-ups at 3- or 6-month intervals after treatment. At each follow-up, a detailed questionnaire was administered to assess the patients' clinical status and to conduct a physical examination; magnetic resonance imaging, computed tomography (CT), and/or positron emission tomography/CT (PET/CT) were also performed.

The primary goal of this study was to evaluate the OS and PFS of patients with metachronous distant metastases that occurred after curative treatment of uterine cervical cancer according to the clinical information. We analyzed the prognostic factors such as age, squamous cell carcinoma antigen (SCC Ag) level, recurrence sites (LNs or organs), number of metastases, disease-free interval (DFI), and treatment method. We intend to classify a favorable prognostic group that will show an improvement in survival after undergoing curative salvage treatment for uterine cervical cancer. In addition, as a secondary goal, the patterns of distant metastases and the type of treatment were analyzed.

2. Statistical analysis

The Kaplan-Meier method was used to evaluate the probability of cumulative survival. Univariate and multivariate Cox proportional hazards models were used to evaluate the association between variables and survival outcomes. The backward elimination method was used to select the principal factors in the multivariate analyses. A p-value of <0.05 was considered significant. Statistical Package for the Social Sciences (SPSS version 21.0) was used to perform all statistical analyses (IBM Corp., Armonk, NY, USA).

RESULTS

1. Patients' characteristics

Between January 2005 and December 2015, 163 patients with metachronous distant metastases from uterine cervical cancer were enrolled in seven institutions in Korea. The patients' median age was 53 years (range: 27–86 years) at the date of the first metachronous metastases. Approximately 67.5% of the patients had clinically detected metastases by CT, magnetic resonance imaging (MRI), and/or PET/CT, but did not undergo biopsy in the recurrent sites. Among 110 patients who underwent clinical assessment, 105 patients were identified with PET/CT, 1 with MRI, and 4 with CT alone. PET/CT was also performed in 39 of 53 patients who underwent pathologic confirmation. Of the total patients, 114 (69.9%) had non-regional LN metastases, 49 (30.1%) had organ metastases, and 44 had metastases in both sites (**Table 1**). A total of 123 (75.5%) patients had a low metastatic burden, whereas the remaining 24.5% had a high metastatic burden. After recurrence, these patients underwent a variety of treatments, including surgery, radiation therapy (RT), and chemotherapy. Among all patients, 71 (43.6%) underwent local treatment and 26 (40.5%) underwent systemic treatment. Of the 66 patients, 11 received chemotherapy followed by RT, 2 received chemotherapy followed by surgery, and the remaining 53 received chemotherapy alone treatment. Of the 71 patients who received local treatment, a total of 42 patients received RT. Fifteen patients received RT followed by chemotherapy, 16 people received CCRT, and 11 people received RT alone. Of the 26 patients who received other treatment, 21 received the best supportive care, and treatment information for the remaining 5 patients was unknown. The median DFI was 1.56 years (range: 0.38–10.6 years), and the DFI of 63.2% of the patients was less than 2 years. Among all patients, 37

Table 1. Patient characteristics

Variables	No. of patients (%) (n=163)
At first metachronous metastases	
Age (yr)	
Median (range)	53 (27–86)
<50 yr	66 (40.5)
≥50 yr	97 (59.5)
ECOG performance	
0	47 (28.8)
1	49 (30.1)
2	10 (6.1)
Unknown	57 (35.0)
Confirmation of recurrence	
Clinical assessment	110 (67.5)
Pathological assessment	
Squamous cell carcinoma	35 (21.5)
Adenocarcinoma	18 (11.0)
Non-regional LN recurrences	114 (69.9)
Organ recurrences	73 (57.1)
Both LNs and distant organ recur	44 (27.0)

(continued to the next page)

Table 1. (Continued) Patient characteristics

Variables			No. of patients (%) (n=163)
Recurrence site			
	Non-regional LNs recurrences		114 (69.9)
		Para-aortic LNs	102 (62.6)
		Inguinal LNs	8 (4.9)
		Supraclavicular LNs	30 (18.4)
		Cervical LNs	12 (7.4)
		Mediastinal LNs	20 (12.7)
		Other LNs*	17 (10.4)
	Organ recurrences		73 (57.1)
		Peritoneal space	22 (13.5)
		Lung	47 (28.8)
		Liver	11 (6.7)
		Brain	2 (2.1)
		Bone	12 (7.4)
		Other sites	18 (11.0)
No. of metastases site			
	Single		37 (22.7)
	2–5		86 (52.8)
	>5		40 (24.5)
SCC Ag level			Mean 1.9 (0.0–251.2)
Disease free interval (yr)			
	Median (range)		1.56 (0.38–10.6)
	≤2		103 (63.2)
	>2		60 (36.8)
Initial therapy after recurrence			
	Local treatment		71 (43.6)
	Systemic treatment		66 (40.5)
	Others		26 (16.0)
At initial Diagnosis			
	FIGO stage		
		IA	2 (1.2)
		IB	40 (24.5)
		IIA	25 (15.3)
		IIB	76 (46.6)
		IIIA/B	13 (7.9)
		IVA	7 (4.3)
	Pathology		
		Squamous cell carcinoma	116 (71.2)
		Adenocarcinoma	36 (22.1)
		Adenosquamous cell carcinoma	5 (3.1)
		Others	6 (3.7)
	Treatments		
		Surgery alone	7 (4.3)
		Op → RT (or CCRT)	52 (31.9)
		CTx → Op → RT	3 (1.8)
		RT alone	9 (5.5)
		CCRT	86 (52.8)
		CCRT → CTx	1 (0.6)
		Unknown	5 (3.1)

CCRT, concurrent chemoradiotherapy; CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; FIGO, Federation of International Gynecology and Obstetrics; LN, lymph node; Op, operation; RT, radiation therapy; SCC Ag, squamous cell carcinoma antigen.
*Other LNs: axilla, mesenteric, perirectal, internal mammary, paravertebral, etc.; †Other sites: abdominal wall, spleen, colorectum, ovary, etc.

(22.7%) had single metastasis, 86 had 2–5 metastases (52.8%), and 40 had >5 lesions (24.5%). Among the non-regional LN metastases, para-aortic LN metastasis was the most common (62.6%), followed by supraclavicular LN metastases (18.4%). The lung was the most common site of metastasis in other distant organs (28.8%), followed by the peritoneum (13.5%).

The initial characteristics before recurrence are described in **Table 1**. At the time of initial diagnosis, 71.2% of the patients had squamous cell carcinomas and 22.1% of the patients had adenocarcinomas. Histology (SCC/non-SCC) did not significantly affect the prognosis of OS, OSi, and PFS (p=0.558, p=0.441, and p=0.267, respectively). In initial FIGO stage, 25.8% of the patients had stage I disease, whereas 62.0% of the patients had stage II disease. For initial treatment, 53.4% of the patients underwent definitive CCRT, whereas 36.2% of the patients underwent surgery.

2. Survival analysis

The median follow-up duration was 22.2 months (range: 0.3–174.8 months) from the date of the first metachronous metastases for all patients, and 71 of the 163 patients survived during the follow-up period. The 1- and 2-year OS rates were 73.9% and 55.0%, respectively. The 1- and 2-year PFS rates were 67.2% and 42.9%, respectively. The median follow-up duration was 45.9 months (range: 6.4–196.8 months) from the date of the initial diagnosis for all patients. The 5-year OSi rate was 50.2%.

The number of metastases, which was expressed using continuous and categorical variables (single/2–5/>5, and low/high metastatic burden), appeared as a factor related to the survival outcomes (p<0.05). For OS, SCC antigen levels after a recurrence and high metastatic burden were significant factors in both univariate and multivariate analyses (p=0.004 and p<0.001, respectively; **Table 2**). LN-only recurrence, DFI, and metastatic burden were significant prognostic factors (p=0.003, p=0.011, and p=0.002, respectively, in the multivariate analysis) for PFS in both univariate and multivariate analyses (**Table 3**). SCC Ag level after recurrence, DFI, and a high metastatic burden were significant factors for OSi (p=0.004, p<0.001, and p<0.001, respectively; **Table S1**).

Table 2. Predictive factors influencing overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Factors after recurrence				
Age (<50/≥50 yr)	1.863 (1.193–2.909)	0.005		
SCC Ag level*	1.012 (1.007–1.017)	<0.001	1.048 (1.015–1.081)	0.004
LN (only/others)	2.110 (1.371–3.248)	0.001		
No. of metastases*	1.115 (1.056–1.178)	<0.001		
No. of metastases		<0.001		
Single	1			
2–5	2.70 (1.373–5.309)	0.004		
>5	5.104 (2.472–10.539)	<0.001		
Disease-free interval (>2/≤2 yr)	1.810 (1.153–2.841)	0.010		
Low/high metastatic burden (≤5/>5)	2.296 (1.462–3.606)	<0.001	6.079 (2.770–13.342)	<0.001
Local/systemic treatment	1.794 (1.121–2.872)	0.015		
Factors for initial diagnosis				
Initial FIGO stage		0.028		
Stage I	1			
Stage II	1.236 (0.752–2.031)	0.403		
Stage III	2.805 (1.323–5.948)	0.005		
Stage IV	2.313 (0.875–6.118)	0.091		
Initial pathology (SCC/non-SCC)	1.141 (0.734–1.772)	0.558		
Initial LN metastases (−/+)	1.050 (0.696–1.584)	0.817		
Initial SCC Ag level*	1.001 (0.991–1.010)	0.897		

CCRT, concurrent chemoradiotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, Federation of International Gynecology and Obstetrics; HR, hazard ratio; LN, lymph node; SCC Ag, squamous cell carcinoma antigen.
*Continuous variables.

Table 3. Predictive factors influencing progression-free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Factors after recurrence				
Age (<50/≥50 yr)	1.315 (0.857–2.019)	0.210		
SCC Ag level*	1.007 (1.002–1.013)	0.011		
LN (only/others)	1.660 (1.089–2.532)	0.019	2.514 (1.374–4.598)	0.003
No. of metastases*	1.072 (1.015–1.131)	0.012		
No. of metastases		0.003		
Single	1			
2–5	2.005 (1.108–3.627)	0.021		
>5	3.157 (1.631–6.109)	0.001		
Disease-free interval (>2/≤2 yr)	1.918 (1.216–3.025)	0.005	2.346 (1.220–4.511)	0.011
Low/high metastatic burden (≤5/>5)	1.938 (1.216–3.086)	0.005	3.007 (1.498–6.035)	0.002
Local/systemic treatment	2.056 (1.327–3.184)	0.001		
Factors for initial diagnosis				
Initial FIGO stage		0.156		
Stage I	1			
Stage II	1.268 (0.774–2.079)	0.346		
Stage III	2.534 (1.124–5.714)	0.025		
Stage IV	1.661 (0.496–5.562)	0.411		
Initial pathology (SCC/non-SCC)	1.268 (0.825–2.004)	0.267		
Initial LN metastases (−/+)	1.062 (0.701–1.608)	0.778		
SCC Ag level*	0.993 (0.981–1.004)	0.223		

CCRT, concurrent chemoradiotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, Federation of International Gynecology and Obstetrics; HR, hazard ratio; LN, lymph node; SCC Ag, squamous cell carcinoma antigen.
*Continuous variables.

The 2-year OS rates were 61.5% in patients with low metastatic burden, which was significantly higher than the 34.6% in those with a high metastatic burden (p<0.001, **Fig. 1A**). A significant difference was also observed according to the number of metastases. The 2-year OS rates in patients with single, 2–5, and >5 metastases were 76.1%, 55.3%, and 34.6%, respectively (p<0.001, **Fig. 1B**). The 2-year PFS rates were 48.3% in patients with low metastatic burden,
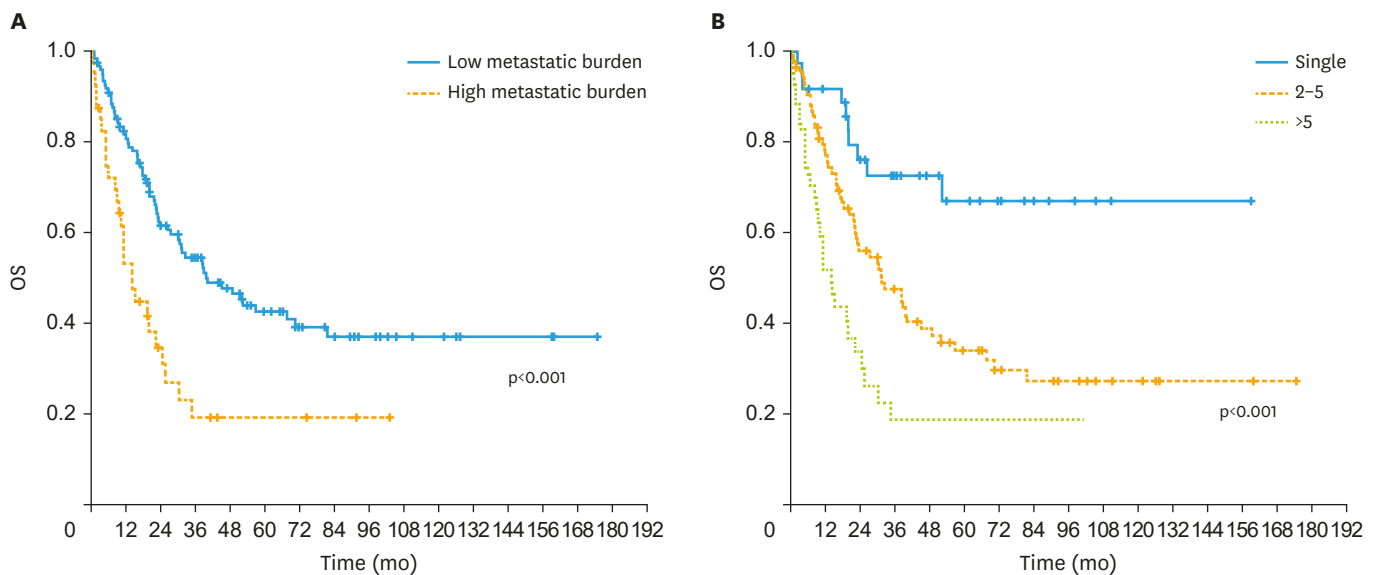

Fig. 1. Overall survival curves. (A) The 2-year OS rates according to metastatic burden. The 2-year OS rates were 61.5% in patients with a low metastatic burden and 34.6% in patients with a high metastatic burden. (B) The 2-year OS rates according to the number of metastases. The 2-year OS rates in patients with single, 2–5, and >5 metastases were 76.1%, 55.3%, and 34.6%, respectively.
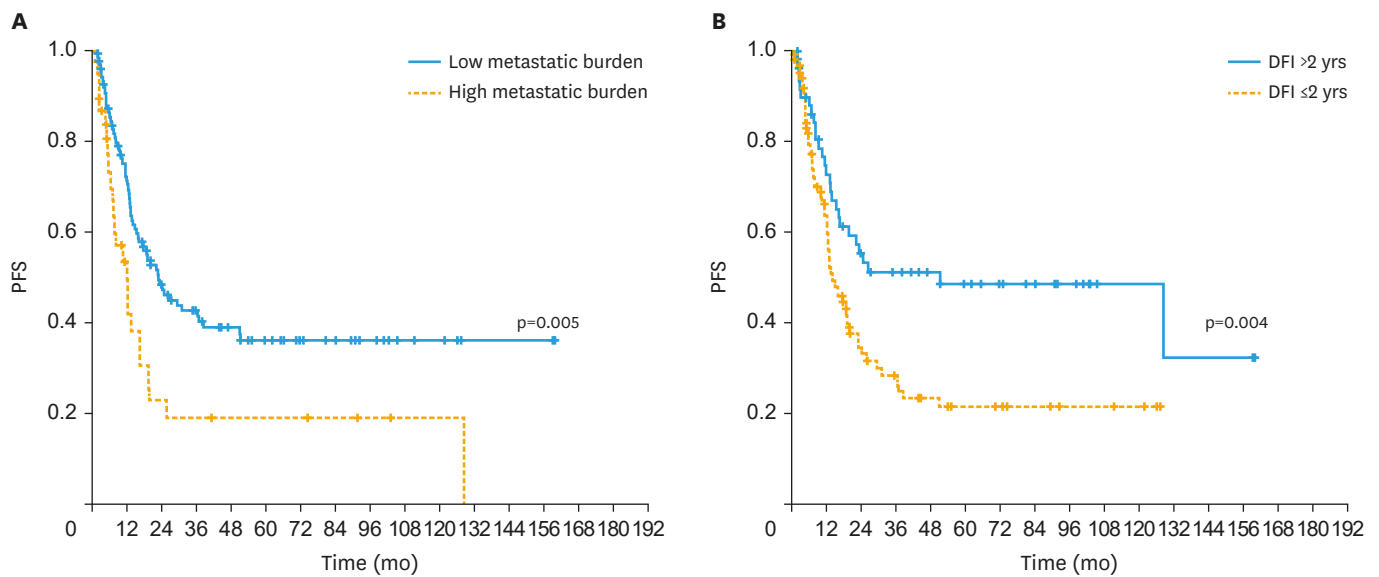OS, overall survival.

Fig. 2. Progression free survival curves. (A) The 2-year PFS rates according to metastatic burden. The 2-year PFS rates were 48.3% in patients with a low metastatic burden and 22.9% in patients with a high metastatic burden. (B) The 2-year PFS rates according to DFI. The 2-year PFS in patients with a DFI of >2 years was 55.2%, whereas that in patients with a DFI of ≤2 years was 34.6%.
DFI, disease-free interval; PFS, progression-free survival.

which was significantly higher than the 22.9% in those with a high metastatic burden (p=0.005, **Fig. 2A**). A significant difference was also found according to the number of metastases. The 2-year PFS rates in patients with single, 2–5, and >5 metastases were 59.3%, 42.7%, and 22.9%, respectively (p=0.002). The 2-year PFS rate of patients with LN-only metastasis was 49.9%, whereas that in patients with metastasis in other sites was 36.8% (p=0.019). The 2-year PFS in patients with a DFI of >2 years was 55.2%, whereas that in patients with a DFI of ≤2 years was 34.6% (p=0.004; **Fig. 2B**).

3. Patterns of failure and therapeutic decision making

Seventy patients (42.9%) had lymphatic-only recurrence and 49 patients (30.1%) had organ recurrence only. **Fig. 3** shows the LNs or organs that were metachronous metastases spread the most; metachronous metastases were divided into 3 groups (single, 2–5, and >5). Among the 37 patients with single metastasis, 17 (45.9%) had LN metastasis and 20 (54.1%) had organ metastases (**Table S2**). Among patients with single LN recurrence, 27.0% had para-aortic LN recurrence. Among 4 other LN-positive patients, 3 had axillary metastasis and one had internal mammary LN metastasis. For organ metastases, 45.0% of the patients had lung metastasis, whereas 10.0% of the patients had peritoneal metastasis.

Among 86 patients with 2–5 metastases, 60 (69.8%) had LN recurrence and 46 (53.5%) had organ recurrence. Among the nodal sites, para-aortic LNs (68.8%) were the main site of recurrence, followed by the supraclavicular lymph nodal area (18.2%). Organ metastases commonly occurred in the lungs and peritoneal spaces (32.6% and 26.1%, respectively).

Among patients with high metastatic burden, 78.4% had para-aortic recurrence, 40.5% had supraclavicular LN recurrence, and 27.0% had mediastinal recurrence. In terms of organ recurrence, lung (70.4%), peritoneum (29.6%), and liver recurrence (25.9%) accounted for the highest proportion.
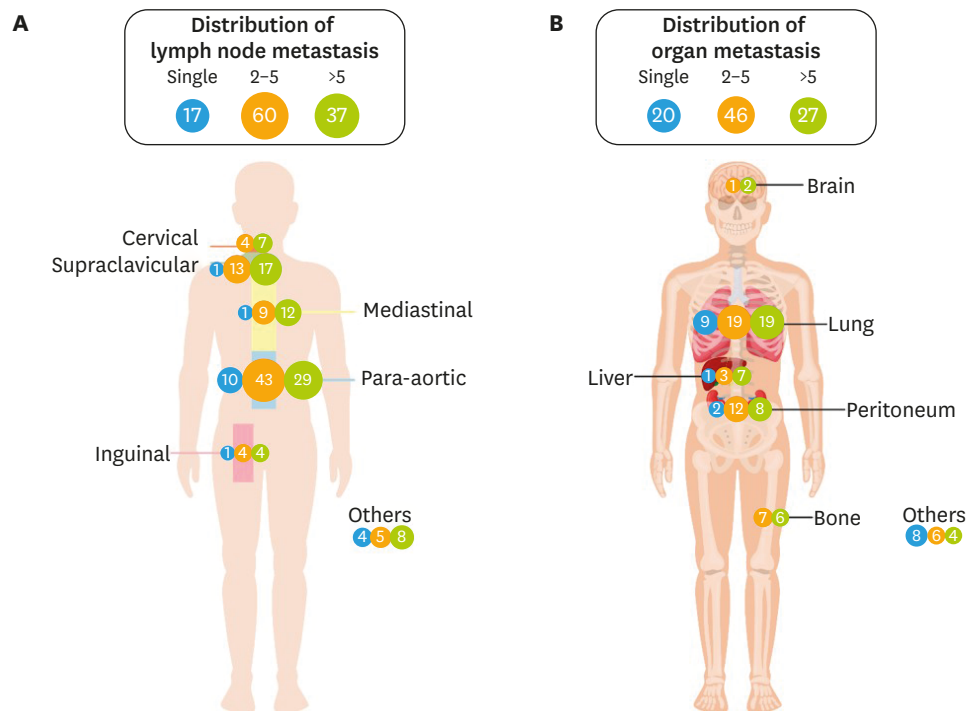
Fig. 3. Patterns of failure. (A) Seventy patients with lymphatic-only recurrence were divided into 3 groups (those with single, 2–5, and >5 recurrences). (B) Forty-nine patients with organ recurrence only were also divided into 3 groups (single, 2–5, and >5 recurrences), and each group was analyzed. The location and number of recurrences are shown in the figure, and the size of a circle is expressed in ratio.

Of the patients with single metastasis, 27 (73.0%) received local treatment, whereas 8 (21.6%) received systemic treatment. Of the 27 patients who received local treatment, 14 underwent RT (or CCRT), whereas 13 underwent surgery. Of the patients with 2–5 metastatic lesions, 31 (36.0%) received local treatment and 41 (47.7%) received systemic treatment. Of the 31 patients who received local treatment, 19 underwent RT (or CCRT), whereas 12 underwent surgery. Of the patients with high metastatic burden, 13 (32.5%) received local treatment and 17 (42.5%) received systemic treatment. Of the 13 patients who received local treatment, 9 underwent RT (or CCRT) and 4 underwent surgery. A significant difference was observed in the treatment pattern among the three groups (patients with single metastasis, 2–5 metastases, and >5 metastases; p=0.004); moreover, marginal significance was also observed between patients with a low metastatic burden and those with a high metastatic burden (p=0.090).

DISCUSSION

In this study, we successfully demonstrated the differences in the survival outcomes between patients with a low metastatic burden and those with high metastatic burden. The 2-year OS rates were 61.5% in the low metastatic burden group and 34.6% in the high metastatic burden group. The PFS rate also showed a similar trend; DFI and LN-only metastases significantly affected the PFS.

In general, distant metastases are the leading cause of cancer-related death and are often considered incurable, thereby limiting the expected survival. Previously, systemic treatment

was regarded as the sole viable option; cytotoxic chemotherapy has been commonly used in patients with metastatic uterine cervical cancer. However, in the late 20th century, salvage local treatment was attempted in patients with relatively low metastatic burden; a significant proportion of patients showed long-term survival [6,7,12-14]. Therefore, whether an intermediate stage may exist, even among metastatic patients for whom the disease burden is relatively low and prognosis is better, remains debatable. Weichselbaum et al. defined "oligometastases" as a stage with a limited number of metastases with a possible difference in prognosis from disseminated metastasis [15].

In a randomized controlled trial of patients with prostate cancer, Lan et al. [16] reported that patients with a low metastatic burden had a better prognosis. According to a meta-analysis conducted by Rim et al. [8], pooled analyses of 31 studies investigating the effectiveness of local therapy on OS revealed the odds ratios of 3.04, 2.56, and 1.41 for all studies, balanced studies, and randomized clinical trials, respectively (all $p<0.05$). To date, no study has compared the prognosis of patients with uterine cervical cancer according to the level of metastatic burden.

Previous studies on a low metastatic burden or oligometastatic uterine cervical cancer had certain limitations: the number of studies conducted was relatively few, and the patient groups were heterogeneous. KROG 14-11, a retrospective multicenter study in Korea, reported the results of stereotactic body radiation therapy as treatment for oligometastatic or recurrent uterine cervical cancer. Most of the patients were treated for pelvic or para-aortic LN metastasis, with a median disease-free survival rate of 14.3 months and a 2-year OS rate of 34.4% [9]. MD Anderson Cancer Center [11] reported the results of radiotherapy performed in 38 patients with synchronous or metachronous metastatic uterine cervical cancer and showed favorable outcomes with a 2-year OS rate of 74% and a PFS rate of 48%. Kim et al. [10] reported the treatment results of 205 patients with metachronous uterine cervical cancer, and the 5-year OS rate was 25.1%. Additionally, patients with LN and lung metastases showed favorable outcomes after undergoing salvage treatment, such as surgical resection or radiotherapy. Compared with previous studies, our study reported comparable oncologic outcomes: 2-year OS of 55%, PFS of 42.9%, and OSi of 82.6%. The 2-year OS, PFS, and OSi rates in patients with a low metastatic burden were 61.5%, 48.3%, and 87.5%, respectively; these patients showed significantly better survival outcomes than those with high metastatic burden ($p<0.001$). The rate of local therapy was also higher in patients with a low metastatic burden ($p=0.004$, **Table S2**). This finding shows the treatment pattern in single metastatic patients and at the same time suggests that salvage treatment can produce favorable oncologic outcomes. Moreover, the results of our study will help physicians in making accurate treatment decisions. Future studies must investigate the specific salvage treatment that will be effective in patients with a low disease burden.

In our results, the DFI was a significant prognostic factor for PFS, which is a well-known prognostic factor mentioned in several other studies [17,18]. Duyn et al. [17] reported that the relative risk of death was 0.70 per year in patients with recurrent uterine cervical cancer. In terms of PFS, both univariate and multivariate analyses showed that the prognosis in patients who developed recurrence within 2 years was significantly poor ($p=0.011$ on multivariate analysis). Mabuchi et al. [19] also showed the differences in survival outcomes according to the site of relapse, and a better prognosis was reported in patients who had LN site recurrence. The results of these studies correlate well with those of our study and confirm these results [19].

Our study has some limitations. It was retrospective in nature, and the role of local treatment in metachronous metastasis was not clear because the treatment scheme was not standardized. In future studies, a prospective study must be conducted to examine the benefits of local treatment. In addition, although SCC Ag after recurrence was found to be a significant factor influencing OS and OSi in this study, 22.1% of adenocarcinoma patients were included. Therefore, 116 patients with SCC were analyzed separately, and SCC Ag was found to be a significant factor in OS and OSi. Hazard ratios for OS and OSi were 1.007 (1.002–1.013) and 1.007 (1.002–1.012) (p=0.009 and p=0.003, respectively). There were limitations that we could not develop into a nomogram because the number of patients was small and external validation could not be performed.

In conclusion, this study reported the difference in oncological prognosis according to the level of disease burden in patients with metachronous metastatic uterine cervical cancer. Therefore, we propose that future studies should implement active salvage local treatment for patients with a low metastatic burden. Moreover, a favorable oncologic outcome can be expected through aggressive salvage treatment in selected patients with a long DFI, low metastatic burden, and/or lymphatic-only metastatic patients.

SUPPLEMENTARY MATERIALS

Table S1
Predictive factors influencing overall survival (from initial diagnosis)

Click here to view

Table S2
Patient characteristics by number of metastases

Click here to view

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