

Prognostic Factors and Treatment Outcome for Patients with Stage IVB Cervical Cancer

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Abstract. *Aim: We report a retrospective evaluation for patients with stage IVB cervical cancer in order to identify survival rates and to improve our current practice. Patients and Methods: We analyzed 85 patients with stage IVB cervical cancer. For patients appropriate for radical treatment, a combination of external-beam radiotherapy and intracavitary brachytherapy was delivered with/without chemotherapy. Patients with distant metastasis were treated using systemic chemotherapy or palliative radiotherapy. Results: Forty-two patients were treated using radiotherapy alone, 31 using chemotherapy followed by radiotherapy, eight using chemotherapy alone, and four using best supportive care. The 5-year overall survival rate was 9.9%. Multivariate analysis revealed leukocytosis and a poor performance status were independent prognostic factors. Of the 43 patients without these prognostic factors, patients with only lymph node metastasis had a 5-year overall survival rate of 40.5%. Conclusion: Radical treatment should be considered in patients who have only lymph node metastasis and are without leukocytosis and a poor performance status.*

Cervical cancer remains the second most common cancer among women worldwide (1) and is a significant cause of cancer-related mortality in women. By the International Federation of Obstetrics and Gynecology (FIGO) clarification, stage IVB cervical cancer is defined as a disease in which the tumor metastasizes to distant lymph nodes or organs (2). This is a relatively rare condition, accounting for around 5% of all cervical neoplasms. The 5-

year survival rate of patients with stage IVB disease ranges from 0 to 44%, and approximately 50% of these patients have a fatal outcome within 1 year (3). In Japan, 2.5-8.4% of patients with invasive cervical cancer are diagnosed with stage IVB disease. The 5-year survival rates for patients treated between 2001 and 2008 for this stage of cancer ranged from 17.0% to 24.7% (4, 5).

There is no standard treatment for patients with stage IVB cervical cancer. Such a patient population is heterogeneous in nature, ranging from patients with metastasis confined to the lymph nodes (LNs), such as supraclavicular, inguinal, or para-aortic LNs, to patients with multiple organ metastases. Treatment for patients with stage IVB cervical cancer varies according to the patient's symptoms and performance status, as well as the physician's preference. Without known superiority of a particular treatment method over all methods, radiotherapy, chemotherapy, combination chemoradiotherapy, palliative treatment, and supportive care are considered as practical treatment options (6). Nevertheless, due to the rarity of this condition, only a few studies have reported on the treatment options for patients with stage IVB cervical cancer (7-10).

In the present article, we report a retrospective study that evaluated the results of our treatment for patients with stage IVB cervical cancer in order to identify survival rates and to improve our current practice.

Patients and Methods

Patients. We retrospectively analyzed 85 patients with FIGO stage IVB cervical cancer who were treated between 1994 and 2013 at the University of the Ryukyus Hospital, Japan. Stage IVB cervical cancer was diagnosed at the time of examination using computed tomography and magnetic resonance imaging. Metastasis of para-aortic LNs detected using imaging studies was excluded from the diagnosis of stage IVB cervical cancer. Percutaneous needle aspiration biopsies were performed in patients with palpable lymphadenopathy in the axilla or neck. None of the patients analyzed in this study had received prior treatment, and all patients provided written informed consent. Patient charts were reviewed in order to collate relevant clinicopathological data, and the study was approved by the Institutional Review Board of our University (#928).

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Treatment. An individualized treatment strategy was considered for each patient according to our treatment manual. For patients who were considered as candidates for radical treatment, a combination of external beam radiotherapy (EBRT) of 29-50.4 Gy (median: 50 Gy) and high-dose-rate intracavitary brachytherapy of 6-18 Gy in 1-3 fractions at point A, was delivered with/without chemotherapy (11). In radical radiotherapy, the target volume of the EBRT varied according to the patients' disease status and general condition: extended field involving para-aortic LNs with/without other distant LNs, whole pelvis, and small pelvis involving only gross cervical tumor. For patients who were considered to have benefit from palliative radiotherapy, EBRT alone was indicated. The radiotherapy schedule most frequently utilized was 30 Gy/10 fractions. Targets of the palliative radiotherapy were: gross cervical tumor, cervical tumor and distant metastases, and distant metastases alone. The concurrent chemoradiotherapy (CCRT) regimen comprised 20 mg/m² cisplatin for 5 days every 3 weeks (12) or 40 mg/m² weekly (13), administered concomitantly with radiotherapy.

Patients with distant organ metastasis who were not candidates for definitive radiotherapy were usually treated using systemic chemotherapy (14). Patients who achieved a good response to chemotherapy were then given definitive radiotherapy; otherwise, the chemotherapy regimen was changed or palliative radiotherapy was added. The chemotherapy regimens used were cisplatin alone, cisplatin combination, weekly paclitaxel, and paclitaxel and carboplatin combination. Patients with a poor performance status or those who refused chemotherapy or radiotherapy were treated with best supportive care (BSC) alone. BSC was defined as treatment targeting the relief of symptoms without surgery, radiotherapy, or chemotherapy, as described above.

Follow-up examinations were conducted every month for the first year, every 2 months for the second year, and subsequently every 3-6 months thereafter.

Statistical analysis. All statistical analyses were performed using JMP software version 10.0 (SAS Institute, Cary, NC, USA). Overall survival (OS) curves were estimated using the Kaplan-Meier method, and differences were tested using the log-rank test. The Cox proportional hazard model was used to perform multivariate analysis; a *p*-value of less than 0.05 was considered significant.

Results

Patients' characteristics are presented in Table I. The median age was 55 years (range=31-90 years), while the median follow-up period was 9 months (range=1-194 months). The majority of patients (81%) had squamous cell carcinoma. The median tumor size was 55 mm (range=15-120 mm). The majority of patients were treated using radiotherapy alone (49%) or chemotherapy followed by radiotherapy (37%).

Sites of distant metastasis are shown in Table II. Thirty-one patients (37%) exhibited only lymph node metastases, while 54 (62%) exhibited distant organ metastases. The most frequently affected organ was the lung followed by bone and liver. Twenty-six patients (31%) exhibited isolated organ metastasis, while the remaining 59 patients (69%) exhibited multiple organ metastases.

Table I. Patients' characteristics (N=85).

Variable	
Median age, (range), years	55 (31-90)
Performance status	
0	51
1≤	34
Median tumor size (range), mm	55 (15-120)
Histological subtype	
Squamous cell carcinoma	69
Adenocarcinoma	14
Small cell carcinoma	2
WBC, n/μl	8,300 (3,700-30,400)
Hb, g/dl	8.2 (3.4-13.9)
SCC, ng/ml	10.6 (0.5-1440)
Primary treatment	
Radiotherapy	42 (49%)
Chemotherapy + radiotherapy	31 (37%)
Chemotherapy	8 (9%)
Best supportive care	4 (5%)
Follow up period, months	9 (1-194)

WBC: White blood cell count; Hb: hemoglobin ; SCC: squamous cell carcinoma.

Within the total cohort of 85 patients, the median OS was 10 months, and the 2-year and 5-year OS rates were 16.3% and 9.9%, respectively (Figure 1). Log-rank tests identified a significant correlation between OS and each of the following clinicopathological variables: age, performance status (PS), white blood cell (WBC) count, site of metastasis, and primary treatment (Table III). Cox proportional regression analysis further revealed a significant correlation between OS and a WBC ≥10,000/μl [hazard ratio (HR)=3.041, 95% confidence interval (CI)=1.517-6.038, *p*=0.0020] and a PS ≥1 (HR=2.836, 95% CI=1.496-5.439, *p*=0.0015) (Table IV). Regarding these two factors, 43 patients had neither of the two, 33 patients had one, and the remaining nine patients exhibited the both factors. The median OS for these three categories of patients was 14, 9, and 4 months, respectively (*p*<0.0001).

When evaluating treatment in terms of the number of prognostic factors, it was found that more patients were treated using chemotherapy followed by radiotherapy and more cycles of chemotherapy were administered in patients without a negative prognostic factor compared to patients with such factors (Table V). Of the 43 patients without a negative prognostic factor, patients with only LN metastasis had a median OS of 14 months and a 5-year OS rate of 40.5%, while patients with distant-organ metastasis had a median OS of 14 months and a 5-year OS rate of 0% (*p*=0.0324) (Figure 2).

Discussion

For our cohort of patients, the median OS was 10 months and the 5-year OS rate was 9.9%. We also demonstrated that

Table II. Patients' characteristics (N=85) regarding metastasis of International Federation of Gynecology and Obstetrics stage IVB cervical cancer.

Variable	n
Site of distant metastasis	
PAN only	1
DLN only	11
PAN + DLN	19
Distant organ only	31
Distant organ + DLN	11
Distant organ + PAN	3
Distant organ + DLN + PAN	9
Distant organ of metastasis	
Lung	26
Bone	23
Liver	8
Vulva	2
Vagina	2
Ovary	2
Cranium	1
No. of distant metastasis	
1	26
2	36
3	16
4	5
5	2

PAN: Para-aortic lymph node, DLN: distant lymph node.

PS and pretreatment WBC count were significant negative prognostic factors for OS in patients with stage IVB cervical cancer. Prognostic factors for stage IVB cervical cancer include PS, age, histological subtype, main organ metastases, and distant metastases (6-10). PS is a global assessment of the actual level of function and ability for self-care of a patient with cancer. From the clinical point of view, this represents a simple but important clinical tool that predicts comorbidities and outcomes, such as response to treatment, and duration of response or survival (15, 16). In particular, it is very important to assess the PS of patients with advanced-stage cancer because it is difficult to convince patients with poor PS to continue treatment; furthermore these patients are expected to have poor compliance with treatment, which therefore cannot meet the level required to control cancer.

Reports show that the frequency of leukocytosis is high, ranging from 16% to 30% in non-hematological malignancies (17, 18). Leukocytosis is most commonly associated with the lung, head and neck, gastric, pancreatic, brain, as well as malignant melanoma. Indeed, previous studies have suggested that tumor-related leukocytosis occurs in around 10% of patients with cervical cancer (18, 19). Cancer-associated myeloproliferation was previously considered to merely represent a paraneoplastic phenomenon of questionable importance. However, it subsequently

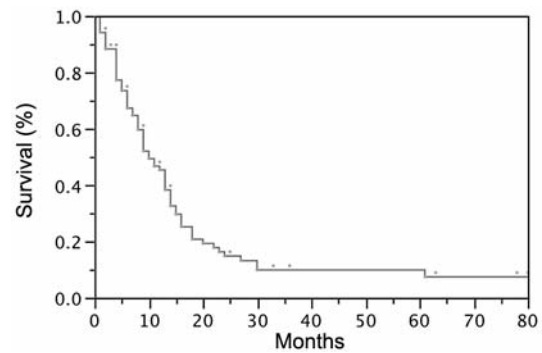


Figure 1. Kaplan-Meier curve for overall survival (OS) in the total cohort of 85 patients with International Federation of Gynecology and Obstetrics stage IVB cervical cancer. The median overall survival was 10 months, and the 2-year and 5-year OS rates were 16.3% and 9.9%, respectively.

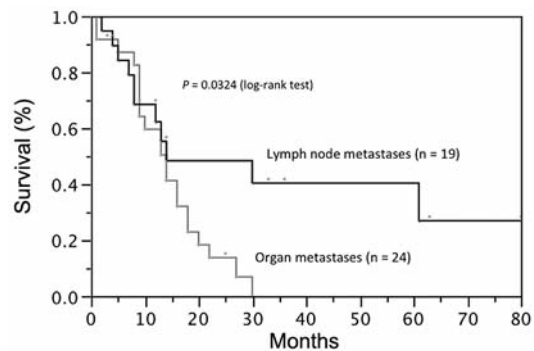


Figure 2. Kaplan-Meier curve for overall survival (OS) in 43 patients with International Federation of Gynecology and Obstetrics stage IVB cervical cancer without negative prognostic factors. The median OS and the 5-year OS rate were 14 months and 40.5%, respectively, in patients who had only lymph node metastasis, while they were 14 months and 0%, respectively, in patients who had distant organ metastasis.

transpired that this mechanism leads to suppression of host immunity and promotion of tumor angiogenesis, both of which play an important role in tumorigenesis and metastasis and are associated with rapid tumor progression and poor prognosis (17). Furthermore, a recent study suggested that leukocytosis caused by tumor-derived granulocyte colony-stimulating factor stimulates tumor angiogenesis, inducing immune suppression and tumor progression in cervical cancer (20). Indeed, univariate and multivariate analyses carried out in our present study showed that an elevated WBC count is a significant predictor of poorer OS, which is in strong agreement with a recent publication (9).

Our analysis also showed that patients with stage IVB cervical cancer exhibiting metastases confined to LNs achieved superior survival rates compared to those exhibiting

Table III. Univariate analysis for overall survival (N=85) of patients with International Federation of Gynecology and Obstetrics stage IVB cervical cancer.

Variable	n	No. of deaths	Median survival (months)	p-Value*
Age (years)				
≥55	47	42	9	0.044
<55	38	27	12	
Histological subtype				
SCC	69	54	11	0.126
Non SCC	16	15	9	
Tumor size (mm)				
≥55	55	46	14	0.369
<55	30	23	9	
Performance status				
0	51	39	14	0.0004
1-4	32	29	6	
Hb (g/dl)				
>10	56	48	10	0.423
≤10	22	17	9	
WBC (/μl)				
≥10,000	19	17	6	0.0040
<10,000	56	44	13	
SCC (ng/ml)				
≥10	41	32	12	0.160
<10	37	31	9	
Site of metastasis				
Lymph node only	31	21	13	0.0143
Distant organ	54	48	9	
Primary treatment				
Radiotherapy	42	36	7	0.0004
Chemotherapy+radiotherapy	31	24	14	
Chemotherapy	8	5	16	
Best supportive care	4	4	2.5	

Hb: Hemoglobin; WBC: white blood cell count; SCC: squamous cell carcinoma. *By log-rank test.

distant organ metastases. This relationship was consistent with the findings of previous studies (9-10), although our statistical approach showed significance with the log-rank test but not with multivariate analysis. Of the 43 patients without negative prognostic factors (such as poor PS and leukocytosis), the survival rate of 19 patients with only LN metastasis was superior to that of 24 patients with distant organ metastasis. Of the 19 patients with only LN metastasis, 10 were treated using chemotherapy followed by radiotherapy and seven were treated using radiotherapy alone, six of whom were treated by CCRT. This approach led to a median OS of 14 months and a 5-year OS rate of 40.5%. For this group of patients, it is important to consider more appropriate types of treatment, such as extended-field radiotherapy/CCRT and systemic chemotherapy followed by radiotherapy/CCRT. Such an approach should improve the survival rates.

Table IV. Cox proportional hazard model for overall survival of patients with International Federation of Gynecology and Obstetrics stage IVB cervical cancer.

Factor	Overall survival		
	HR	95% CI	p-Value
Age ≥55 years	1.043	0.575-1.932	0.892
Histological subtype non SCC	1.261	0.501-2.957	0.609
Tumor size ≥55 mm	0.759	0.372-1.612	0.463
Performance status ≥1	2.836	1.496-5.439	0.0015
Hb <10 g/dl	1.807	0.921-3.729	0.0863
WBC ≥10,000/μl	3.041	1.517-6.038	0.0020
SCC ≥10 ng/ml	0.997	0.553-1.839	0.993
Site of metastasis, distant organ	1.248	0.661-2.467	0.503

Hb: Hemoglobin; WBC: white blood cell count; SCC: squamous cell carcinoma.

Table V. Treatment of patients with International Federation of Gynecology and Obstetrics stage IVB cervical cancer by the number of prognostic factors (N=85).

Treatment	No. of prognostic factors	
	0 (n=43)	1 or 2 (n=42)
Radiotherapy	14 (33%)	28 (67%)
Radiotherapy	10	25
CCRT	4	3
Chemotherapy + radiotherapy	21 (49%)	10 (23%)
Chemotherapy + radiotherapy	16	9
Chemotherapy+CCRT	5	1
Chemotherapy alone	6 (14%)	2 (5%)
Paclitaxel+carboplatin	1 (4 cycle)	1 (1 cycle)
Carboplatin	1 (8 cycles)	0
Cisplatin	2 (2, 3 cycles)	0
Cisplatin combination	2 (5, 17 cycles)	1 (1 cycle)
Best supportive care	2 (4%)	2 (5%)

CCRT: Concurrent chemoradiotherapy.

The strength of the present study is that we were able to enroll a relatively large number of patients with stage IVB cancer from a single institution. The major limitation of the study is that it was a retrospective analysis performed over a relatively long period of time. Furthermore, during the study period, the chemotherapy regimen and mode of radiotherapy were changed. We focused only on OS; however, relief and supportive care in terms of quality of life is a very important consideration for this group of patients.

In conclusion, PS and leukocytosis are significant prognostic factors for patients with stage IVB cancer of the cervix. Radical treatment should be considered in patients

who have only LN metastasis and are without these two risk factors, as this approach will lead to improvement in the survival rate.

Conflicts of Interest

The Authors state they have no conflicts of interest with regard to this article.

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