SPANDIDOS PUBLICATIONS

Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma

SHIN NISHIO[1,3], NORIYUKI KATSUMATA[1], KOJI MATSUMOTO[1], HIROSHI TANABE[1], KAN YONEMORI[1], TSUTOMU KOHNO[1], CHIKAKO SHIMIZU[1], MASASHI ANDO[1], TAKAHIRO KASAMATSU[2] and YASUHIRO FUJIWARA[1]

Departments of [1]Medical Oncology and [2]Gynecologic Oncology, National Cancer Center Hospital, Tokyo 104-0045, Japan

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Abstract. The aim of this study was to evaluate the clinicopathological prognostic factors in patients with stage IVb cervical carcinoma (CC). All patients with stage IVb CC included in the study were diagnosed from 1997 to 2006 at the National Cancer Center Hospital. We retrospectively examined clinicopathological parameters in these patients, including the efficacy of chemotherapy. Survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using a Cox's proportional hazard model. Thirty-six patients (median age 54 years) were diagnosed with stage IVb CC. The median progression-free survival and overall survival were 3.8 and 11.1 months, respectively. As initial treatment, 4 patients underwent hysterectomy, 13 received chemotherapy, 17 received radiotherapy, and the remaining 2 patients refused treatment. A total of 21 patients received chemotherapy, of which 13 were initial cases, 7 were persistent/recurrence cases, and 1 was a postoperative adjuvant case; 15 patients were never treated with chemotherapy. On univariate analysis, poor performance status (PS) and non-chemotherapy groups were considered poor prognostic factors, respectively. On multivariate analysis, poor PS (p=0.007; hazard ratio, 2.64) and non-chemotherapy (p=0.016; hazard ratio, 6.03) were independent prognostic factors of survival, respectively. Poor PS and non-chemotherapy groups were found to have poor prognosis in patients with stage IVb CC. Chemotherapy may improve the survival for stage IVb CC.

Correspondence to: Dr Shin Nishio, [3]*Present address*: Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
E-mail: nishio_shin@hotmail.com

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Introduction

Cervical carcinoma is the main cause of death in females throughout the world, despite the fact that a useful screening method has been established (1). In stage I/II patients, conventional treatments such as surgery and radiotherapy have achieved good results. In stage III/IV patients, various treatments such as the combination of surgery and radiotherapy, radiotherapy, and chemoradiation therapy are being examined, though their long-term results are still poor (2,3). The 5-year survival of stage IVb patients ranges from 0 to 44%, and approximately 50% of these patients show a fatal outcome within 1 year (4-6). No standard therapy has been established, and palliative surgery, radiotherapy, and best supportive care (BSC) have been performed as initial treatment. However, since stage IVb cervical carcinoma is a systemic disease, surgery and radiotherapy are useful for local control, but are insufficient. In addition, BSC is not effective for the severe local pain characteristic of this disorder (7). Since 1990, chemotherapy has been employed as a type of BSC in patients with good general condition and organ function (8). However, as this therapy targets the relief of symptoms and improvements in quality of life (QOL), regimens with less toxic low-dose agents were initially administered (9). No randomized comparative study has examined whether chemotherapy for stage IVb cervical carcinoma prolongs survival compared to BSC.

Several studies have investigated single-agent chemotherapy for cervical carcinoma, and reported that the response rates to cisplatin, ifosfamide, paclitaxel, vinorelbine and topotecan of 20-30% (5,8,10-12), 14-40% (13-15), 17% (16), 15% (17,18) and 12-19% (19,20), respectively. Cisplatin has been the most frequently used agent, and has achieved the highest response rate. Therefore, cisplatin has been employed as a key drug for more than 20 years. However, the response to single-agent cisplatin has been limited, and combination chemotherapy with other agents has been administered to achieve improvement in prognosis, exceeding the enhancement of its toxicity. Result of recent phase III studies have indicated that combination regimens with cisplatin/paclitaxel (21) or cisplatin/topotecan (22) are more effective than single-agent cisplatin.

A few studies have reported that factors affecting the prognosis of stage IVb cervical carcinoma include main organ

metastases, multiple lymph node metastases, poor performance status (PS), and non-squamous cell carcinoma (23-29). According to some studies, the results of surgery combined with radiotherapy or radiotherapy alone are relatively good in stage IVb cervical carcinoma patients with para-aortic lymph node metastases alone (30-33). However, chemotherapy for stage IVb patients with cervical/mediastinal lymph node or main organ metastases, without surgery and radiotherapy, has been reported to have only slight effect.

In this study, we retrospectively investigated the clinicopathological features of stage IVb cervical carcinoma, and evaluated the efficacy of chemotherapy for this stage of cancer.

Patients and methods

Patients with stage IVb cervical carcinoma were diagnosed and treated in the National Cancer Center Hospital between April 1997 and March 2006. Stage was evaluated according to the FIGO staging. We rectrospectively reviewed the medical chart of these patients.

Treatment. Therapeutic strategies were selected for individual patients. For surgery, total hysterectomy (radical hysterectomy in some patients) and bilateral salpingo-oophorectomy were performed. Pelvic and/or para-aortic lymphadenctomy were performed in some patients. For radiotherapy, the area of external irradiation was established as the entire pelvic region from the closed pore to the L4/5 lumbar vertebrae, with a radiation dose of 2 Gy per treatment (total dose, 50-60 Gy). When the cumulative dose reached 20-30 Gy, external irradiation was combined with high-dose intra-cavity irradiation, with a central shield, at a radiation dose of 5 Gy (total dose, 20-25 Gy). When imaging findings suggested para-aortic lymph node metastases, biopsy was performed. After a definitive diagnosis of metastases was made, the irradiation field was extended to include the para-aortic node. For chemotherapy, eligible patients participated in a phase II clinical study with an in-house protocol that we previously reported, including paclitaxel (PTX)/carboplatin (CBDCA) therapy (Kitagawa R, *et al*, Proc ASCO 22: abs. 5048, 2004) (PTX, 175 mg/m^2, CBDCA AUC5, day 1, every 3 weeks for 6 cycles), and carboplatin (CBDCA)/irinotecan (CPT) therapy (Hori S, *et al*, Proc ASCO 21: abs. 835, 2002) (CBDCA AUC5, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles). For patients with PS of 3, weekly PTX/CBDCA therapy (PTX 80 mg/m^2, CBDCA AUC2, continuous administration for 20 weeks) was administered. In 1 patient with small cell carcinoma, cisplatin (CDDP)/CPT therapy (CDDP, 60 mg/m^2, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles) was administered as postoperative adjuvant therapy.

Best supportive care (BSC) was defined as treatment targeting the relief of symptoms without surgery, radiotherapy or chemotherapy, as described above.

Evaluation. Pretreatment clinical evaluation was repeated before each treatment cycle with the exception of radiography or CT/MRI imaging, which was repeated at least every other treatment cycle. Treatment was continued until disease progression or adverse effects precluded further administration. The response to treatment, in terms of the best response achieved in a given patient, was assessed using standard clinical criteria. A complete response (CR) was defined as the disappearance of all gross evidence of disease for at least 4 weeks. A partial response (PR) was defined as a >50% reduction in the product of perpendicular diameters obtained from the measurement of each lesion, sustained for at least 4 weeks. Progressive disease (PD) was defined as a >50% increase in the product of perpendicular diameters of any lesion documented within 2 months of study entry or the appearance of any new lesion within 8 weeks of study entry. Stable disease (SD) was any condition not meeting any of the above three criteria. Overall survival was measured as the observed length of life from protocol entry to death or (for living patients) date of last contact. Progression-free survival was measured from the date of initiation of protocol to the first progression or death, or to the date of last contact for patients who were alive and progression-free.

Persistent disease was defined as carcinoma at a pelvic site known to be previously involved within 6 months of staging. Recurrent disease was classified as a new tumor in the extrapelvic area or pelvic disease >6 months after staging in a location previously tumor-free. Persistent or recurrent disease was documented by surgical exploration, biopsy or progression on imaging studies. The time of recurrence or death was calculated from the date of original staging. The end of the follow-up period was March 2006.

Statistical analysis. Statistical analysis was performed using SPSS. The impact of clinical and pathologic risk factors on survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using Cox's proportional hazard model. P-values <0.05 were considered significant.

Results

Thirty-six patients were treated between April 1997 and March 2006. Table I shows the patient characteristics. The median age was 54 years. In 34 patients, PS was almost 0, 1 or 2. In the remaining 2 patients, PS was 3. As initial treatment, surgery was performed in 4 patients, radiotherapy in 17, and chemotherapy in 13. BSC was performed in two patients who did not wish to receive aggressive treatment. Histopathologically, 18 patients had squamous cell carcinomas, 16 had adenocarcinomas and 2 had small cell carcinomas. The median primary tumor diameter was 4.1 cm, with a maximum of 7.7 cm. In addition, a bulky mass was detected in 28 patients. In 13 patients, hydronephrosis was noted, with 8 of these having bilateral hydronephrosis. The number of distant metastases was 1 in most patients, but 3 or 4 in some patients. The metastatic lesion sites included the para-aortic node in 7 patients and the main organs in 8 patients. Table II shows the sites of distant metastases (including duplicating patients). In the abdominal cavity, para-aortic lymph node metastases were detected in 18 patients (50%), comprising the highest percentage. In the extraperitoneal region, supraclavian lymph node metastases were detected in 13 patients (36%). Among main organ metastases, liver metastases were detected in 7

atient characteristics.

Age (year), median (range)	54 (28-77)
PS 0/1/2/3	5/18/11/2
No. of patients	36
Initial treatment	
Surgery	4
Radiotherapy	17
Chemotherapy	13
Best supportive care	2
Pathology	
Squamous cell carcinoma	18
Adenocarcinoma	16
Small cell carcinoma	2
Primary tumor size (cm), median (range)	4.1 (2.1-7.7)
Bulky mass >4 cm	
Negative	8
Positive	28
Hydronephrosis	
Negative	23
Unilateral	5
Bilateral	8
No. of distant metastases	
1	20
2	13
3	2
4	1
Site of distant metastases	
Para-aortic lymph node only	7
Distant lymph node only	7
Organ metastases only	1
Para-aortic lymph node + Distant lymph node	10
Para-aortic lymph node + Organ metastases	1

Table II. Distant metastases in patients.

Metastatic sites	n (%)
Intra-abdominal metastases	
Para-aortic lymph node	18 (50)
Liver	7 (19)
Spleen	2 (5.5)
Small intestine	1 (2.7)
Extra-abdominal metastases	
Lung	4 (11)
Bone	2 (5.5)
Supraclavicular lymph node	13 (36)
Mediastinal lymph node	2 (5.5)
Inguinal lymph node	2 (5.5)

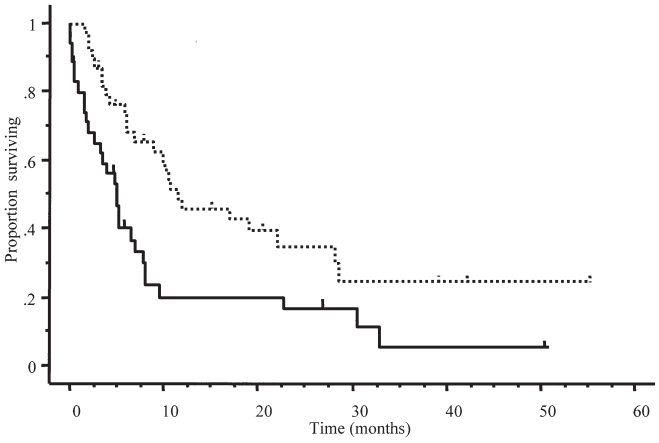

Figure 1. Kaplan-Meier analysis of progression-free survival (solid line) and overall survival (dotted line). Vertical bars indicate censored cases.

Table III. Characteristics of 21 patients with chemotherapy.

	n=21
Indication for therapy	
Initial case	13
Persistent/recurrence case	7
Postoperative case	1
Regimens	
Paclitaxel/carboplatin	9
Irinotecan/carboplatin	9
Weekly paclitaxel/carboplatin	2
Irinotecan/cisplatin	1

patients, comprising the highest percentage, followed by lung metastases in 4 patients. The median progression-free survival and overall survival were 3.8 months and 11.1 months, respectively (Fig. 1).

We examined the effects of chemotherapy on stage IVb cancer (Table III). Chemotherapy was administered to 21 patients, 13 of whom were undergoing initial treatment, 7 of whom had persistent/recurrence, and 1 of whom was undergoing postoperative therapy. The regimens consisted of paclitaxel/carboplatin in 9 patients, irinotecan/carboplatin in 9, weekly paclitaxel/carboplatin in 2, and cisplatin/irinotecan in 1. In 2 patients, including 1 undergoing postoperative adjuvant therapy, chemotherapy was discontinued due to adverse effects. For lesions that could be measured, the response rate was 61.9% (95% CI, 41.1-82.6) including 4 patients with CR and 9 patients with PR (Table IV).

We compared survival in the chemotherapy and non-chemotherapy groups. The median survivals of the chemotherapy and non-chemotherapy groups were 11.1 and 5.1 months, respectively, with a significant difference (p=0.0055) (Fig. 2).

We also compared survival between initial chemotherapy and initial other treatment groups. The median survivals in the initial chemotherapy and initial other treatment groups

Table IV. Response rate of chemotherapy (n=21).

Response (%)					
CR	PR	SD	PD	NE	RR
4	9	4	1	3	61.9% (95% CI, 41.1-82.6%)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; RR, response rate.

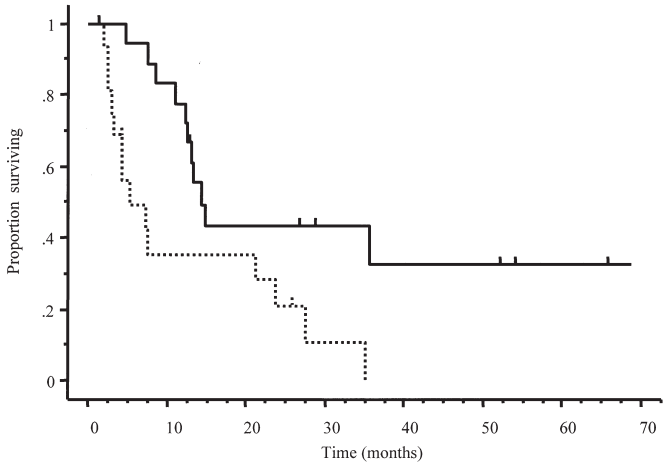

Figure 2. Kaplan-Meier analysis of overall survival according to with/without chemotherapy in stage IVb cervical carcinoma. Chemotherapy group (solid line) is significantly better prognosis (p=0.0055) than non-chemotherapy group (dotted line). Vertical bars indicate censored cases.

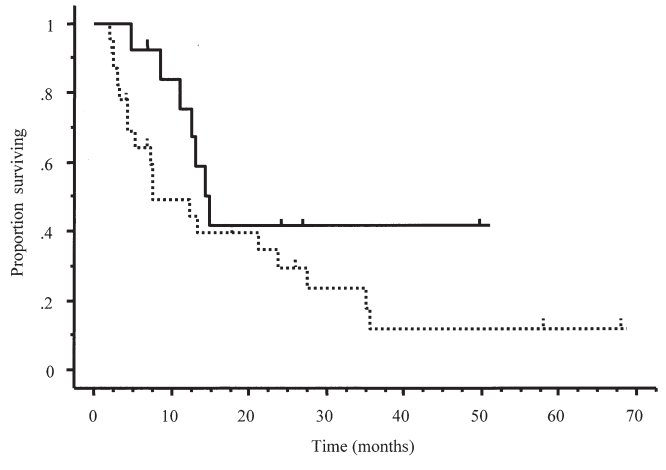

Figure 3. Kaplan-Meier analysis of overall survival according to with/without initial chemotherapy in stage IVb cervical carcinoma. There are no statistical differences (p=0.09) between initial chemotherapy group (solid line) and other initial treatment group (dotted line). Vertical bars indicate censored cases.

were 13.2 and 7.5 months, respectively, but it did not reach statistical significant (p=0.09) (Fig. 3). Two patients treated by chemotherapy alone as an initial treatment have survived disease-free for 51.8 and 68.6 months, respectively. One patient had stage IVb CC with para-aortic lymph node metastases while the other had stage IVb CC with subclavian lymph node metastases and mediastinal lymph node metastases. Both patients were administered paclitaxel/carboplatin for 6 cycles. After 6 cycles, the primary lesion and metastatic site exhibited complete response.

Table V. Prognostic factors of overall survival.

	Univariate	Multivariate		
Factor	P-value	P-value	HR	95% CI
Age ≥50	0.171	0.506	1.36	0.54-3.43
PS (0 and 1 vs. 2 and 3)	0.005	0.007	2.64	1.42-4.91
Pathology (SCC vs. non-SCC)	0.638	-	-	-
Organ metastases (0 vs. ≥1)	0.792	-	-	-
No. of distant metastases (1 vs. ≥2)	0.109	0.546	1.22	0.63-2.35
Bulky mass	0.478	-	-	-
Chemotherapy	0.011	0.016	6.03	1.97-18.37

We analyzed chemotherapy, age, PS, histological type, main organ metastases, number of distant metastases, and bulky masses as prognostic factors. On univariate analysis, poor PS and non-chemotherapy groups were prognostic factors. On multivariate analysis, a poor PS (p=0.007; hazard ratio, 2.64; 95% CI, 1.42-4.91) and non-chemotherapy groups (p=0.016; hazard ratio, 6.03; 95% CI, 1.94-18.37) also affected overall survival (Table V).

Discussion

The prognosis of stage IVb cervical carcinoma is poor in patients with systemic metastases. No treatment has been established. In the NCI-PDQ, it is described that therapeutic strategies for this stage of cancer include palliative radiotherapy, chemotherapy as a regimen designed by a clinical study, and chemotherapy with cisplatin, which has previously been reported (34).

In stage IVb patients with para-aortic lymph node metastasis alone, surgery with postoperative radiotherapy and extended radiotherapy achieved a 5-year survival rate of 50% (30-33), and radical surgery may also be an option. However, since most metastases involve the main organs, it is difficult to control them by local treatment, and chemotherapy is indicated for most patients (4).

Various regimens of chemotherapy for this stage of cancer, including single-agent, have been investigated. In particular, cisplatin has most frequently been employed, and yields the highest response rate as a single-agent. It has therefore been

a key drug for more than 20 years (5,8,10-12). However, since the efficacy of cisplatin as a single-agent persists for only 6 months, combination regimens have been administered to improve in the prognosis to an extent exceeding the enhancement of its toxicity. In the 1990s, many phase II clinical studies investigated combination regimens with 2-4 agents including cisplatin. Cisplatin with ifosfamide (IFM) yielded the second highest response rate, and bleomycin (BLM), which has commonly been employed to treat other cancers due to its similar high response rate and low toxicity. The usefulness of IP (IFM + CDDP) (35) and BIP (BLM + IFM + CDDP) (36) regimens has also been examined. Some regimens have achieved a response rate of 60% or higher; however, these regimens for the non-advanced and locally advanced stages are quite toxic and shorten the survival of some patients. In addition, no comparative study has been conducted, and the evaluation of each regimen has been insufficient. In the latter half of the 1990s, combination regimens with new agents were designed, and the need for a standard therapy was emphasized.

Recently, carboplatin (37-39), topotecan (19,20) and paclitaxel (40-42) have also been reported to be tolerable and efficacious. Complete responses have also been observed with topotecan and paclitaxel. However, topotecan has greater toxicity than carboplatin or paclitaxel. Therefore, palliation with single-agent cisplatin, carboplatin, paclitaxel or topotecan is a reasonable approach in patients with recurrent disease. A phase II study evaluating the effectiveness of docetaxel in patients who have persistent or recurrent cervical cancer is ongoing (GOG-0127S).

Cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel (21) and cisplatin/topotecan (22) have been extensively investigated in clinical studies. A randomized phase III study comparing paclitaxel and cisplatin versus cisplatin alone showed that the two-drug combination yielded a higher response rate (36 versus 19%) and improved progression-free survival (4.8 versus 2.8 months; $p<0.001$), although no improvement has been seen in median survival (21). Another randomized phase III GOG study investigated the combination of cisplatin and topotecan versus cisplatin alone for persistent/recurrent cervical cancer. In this study of 294 eligible patients, the topotecan combination regimen was superior to single-agent cisplatin with respect to overall response rate (27 versus 13%; $p=0.004$), progression-free survival (4.6 versus 2.9 months; $p=0.014$), and median survival (9.4 versus 6.5 months; $p=0.017$) (22). A phase II study assessed cisplatin and gemcitabine in patients with advanced, persistent/recurrent cervical cancer; 17 patients were evaluated (43). The response rate was 57% in patients who had not previously received radiotherapy, and there was 1 complete response of 14 months. Paclitaxel and carboplatin have recently been assessed for recurrent or persistent cancer of the cervix; 4 of 15 patients had a complete response and 5 showed a partial response for an overall response rate of 60% (39). The median survival of all 15 patients treated was 17 months (range, 4-39 months). The combination of vinorelbine and cisplatin has also been assessed in 42 patients with recurrent or metastatic cervical cancer; the overall response rate was 48% (44). The GOG is currently conducting a phase III trial (GOG204) to assess 4 cisplatin-doublet regimens in patients with advanced metastatic or recurrent cancer (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisiplatin/vinorelbine).

In our hospital, we conducted an in-house clinical study. For eligible patients, paclitaxel/carboplatin or irinitecan/carboplatin therapy was administered. Adverse effects were within the permissible ranges, and there were no treatment-related deaths, as reported in other studies. Response rate as an end-point was also similar to or exceeded that previously reported, suggesting the usefulness of these treatment options in chemotherapy for cervical carcinoma. In patients with poor PS, weekly paclitaxel/carboplatin therapy was safe. Several reports have indicated that the hematological toxicity of this therapy is lower than that of tri-weekly therapy, and that the therapeutic effects of these two regimens are similar (45,46). Weekly paclitaxel/carboplatin therapy may be useful for treating stage IVb cancer patients with poor PS.

In patient with this stage of cancer, nephropathy is frequent, making cisplatin administration difficult in many cases. Carboplatin can be administered to patients with nephropathy, without hydration. Considering the adverse effects, less toxic agents should be reviewed.

In this study, two patients treated by chemotherapy alone as an initial treatment have survived disease-free for 51.8 and 68.6 months, respectively. For patients with recurrence who desired sequential treatment, chemotherapy was administered when we considered them eligible. Considering that the prognosis was significantly better than that in the non-chemotherapy group, chemotherapeutic intervention may be useful in stage IVb patients who have undergone initial treatment and in those with persistent/recurrent metastases.

Eligible, consenting patients should be enrolled in clinical trials employing new drugs and/or strategies. Since there is as yet no evidence for the curative potential of chemotherapy in cervical cancer and no established survival benefit, and uncertainty exists as to how often response translates into symptom relief ('palliation'), non-protocol therapy should not be encouraged. Nevertheless, for a patient who is ineligible or unwilling to participate in a study but who wants treatment, there may still be an indication for chemotherapy giving 'psychological support' or hope. When such a patient insists on treatment and seeks untested remedies rather than a hospice if orthodox chemotherapy is not offered, single-agent cisplatin or carboplatin may be justified, with due attention being paid to contraindications and the toxic side effects. An interval response assessment and finite period of treatment are indicated. Objective benefit is possible, but not likely.

Prognostic factors for stage IVb cervical carcinoma include PS, age, histological type, main organ metastases, and distant metastases (23-29). In this study, univariate and multivariate analysis revealed that non-chemotherapy and poor PS influenced prognosis. In patients with poor PS, it is difficult to continue treatment, and chemotherapy may exceed cancer control due to systemic disease. However, we can not conclude the efficacy of chemotherapeutic intervention, as this study was a retrospective study and involved only a small number of patients. Previously, surgery and radiotherapy have been selected for this stage of cancer. The results of chemotherapy for initial treatment were similar to those for conventional treatment, suggesting the efficacy of chemotherapy as initial

treatment. However, a randomized comparative study should be conducted to demonstrate its efficacy.

In conclusion, the prognosis of stage IVb cervical carcinoma remains poor. Chemotherapy may improve the survival of patients with stage IVb CC.

Acknowledgments

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