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Oncologic Outcomes of Stage IVB or Persistent or Recurrent Cervical Carcinoma Patients Treated With Chemotherapy at Siriraj Hospital
Thailand's Largest Tertiary Referral Center

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Objectives: To determine response rate and survival outcomes of chemotherapeutic treatment in stage IVB, persistent, or recurrent cervical carcinoma patients.

Methods: Medical records of stage IVB or persistent or recurrent cervical carcinoma patients who received chemotherapy from January 2006 to December 2013 were retrospectively reviewed. Patients with neuroendocrine carcinoma and patients who received only 1 cycle of chemotherapy were excluded. The demographic data, tumor characteristics, chemotherapeutic agents, and response rate were reported. Factors associated with overall response rate from the first-round chemotherapeutic treatment were analyzed using χ^2 test. Kaplan-Meier method and Cox proportional hazards model were used for survival analysis.

Results: Of 286 cervical carcinoma patients, 47 patients had stage IVB and 239 patients had persistent or recurrent disease. One hundred sixty-nine patients (59.1%) had squamous cell carcinoma (SCC). A majority of disease sites (38.8%) had both local and distant metastases. Overall response rate for first-round chemotherapeutic treatment was 37.8%, with 23.1% of patients having a complete response and 14.7% of patients having a partial response. Regarding disease response, 32.2% of patients had stable disease and 30% had disease progression. Median overall survival (OS) and progression-free survival (PFS) for first-round chemotherapeutic treatment were 11.6 (range, 0.7–108.3) months and 5.6 (range, 0.7–102.2) months, respectively. Patients with distant metastasis had a shorter OS duration with an adjusted hazard ratio (HR) of 1.78, 95% confidence interval (CI) of 1.09 to 2.90; $P = 0.02$. Patients with a body mass index of 25 kg/m^2 or more had a longer PFS duration than those with a normal body mass index (adjusted HR, 0.72; 95% CI, 0.55–0.94; $P = 0.018$). Patients with non-SCC had a longer PFS duration than that of patients with SCC (adjusted HR, 0.77; 95% CI, 0.60–0.99; $P = 0.041$).

Conclusions: Response rates, median PFS, and median OS of cervical cancer patients treated by chemotherapy in our center were rather high when compared with those of previous gynecologic oncology group studies.

Key Words: Cervix, Cervical cancer, Chemotherapy, Treatment, Outcomes

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Cervical carcinoma is a common cancer, significantly causing much burden in developing countries.[1] In Thailand, cervical carcinoma is the second most common female malignancy with an age-standardized incidence rate of 16.7 in 100,000 women per year.[2] Systemic chemotherapy is the treatment of choice in a patient with systemic disease, such as the International Federation of Gynecology and Obstetrics (FIGO) stage IVB and in patients with persistent or recurrent disease that develops after primary treatment. Chemotherapy is also useful in inoperable locoregional persistent or recurrent disease; however, palliative therapy is often the objective in such cases.

Various chemotherapeutic regimens are used to treat cervical carcinoma patients. Combination chemotherapy, including cisplatin combined with ifosfamide, paclitaxel, or topotecan, is superior to cisplatin alone with regard to response rate and longer progression-free survival (PFS). Moreover, treatment with cisplatin and topotecan demonstrated an overall survival (OS) benefit.[3–5] Gynecologic Oncology Group (GOG) trial no. 204 compared 4 arms of cisplatin doublets, including paclitaxel, topotecan, vinorelbine, and ifosfamide, and revealed a trend in favor of cisplatin plus paclitaxel in terms of PFS and OS duration and the most favorable side effects.[6] These cisplatin-based combinations resulted in a median PFS of 4 to 5.8 months and a median OS of 10 to 12.9 months. The combination of cisplatin and fluorouracil had a response rate of 21.8% when used in the treatment of advanced squamous cell carcinoma (SCC) of the cervix.[7] Mitomycin-C alone has been reported to have only modest activity on advanced, persistent, or recurrent SCC of the cervix, with a response rate of 12%.[8]

Thailand health care policy is composed of 3 major health insurance schemes, including Universal Coverage Scheme, Social Security Scheme, and Government or State Enterprise Officer Scheme. The Universal Coverage and Social Security Schemes do not cover the cost of cisplatin combined with topotecan or paclitaxel because of the higher cost of these drug combinations. As such, various regimens are prescribed in tertiary and medical school hospitals, such as cisplatin or mitomycin alone or doublets of cisplatin with fluorouracil, ifosfamide, paclitaxel, or topotecan.

The objectives of this study were to evaluate (i) response rate; (ii) PFS and OS in patients with stage IVB, persistent, or recurrent cervical carcinoma treated with chemotherapy; and (iii) independent factors that affect oncologic outcomes in cervical carcinoma patients.

MATERIALS AND METHODS

This study was conducted as a retrospective design for reviewing medical records of women with stage IVB or persistent or recurrent cervical carcinoma and received chemotherapy at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, from January 1, 2006, to December 31, 2013. Patients with only 1 cycle of chemotherapy or who had neuroendocrine carcinoma were excluded. Follow-up data included patient data collected until September 30, 2014. This study was approved by the Siriraj Institutional Review Board (COA no. Si105/2013).

Cervical carcinoma patients were clinically staged according to the FIGO guidelines. In patients with locally advanced or distant metastasis, primary treatment may have been changed from concurrent chemoradiation therapy (CCRT) to systemic chemotherapy with palliative radiation therapy (RT) depending on patients' symptoms and computed tomography scan findings. Chemotherapeutic regimens were determined according to international guidelines and Thailand health care policy. Carboplatin was given as an alternative to cisplatin in patients with impaired renal function. Second- or third-line chemotherapy was prescribed when a complete response (CR) could not be achieved with first-line chemotherapy. Response rate after each line of regimen and overall response to chemotherapy were determined. Clinical assessment was performed every 1 to 3 months according to response outcomes, symptoms, and residual disease. *Second-round chemotherapy* was defined as palliative chemotherapy used to treat recurrent cases after a complete course of systemic chemotherapy. Most of the regimens of second-round chemotherapy were the same as the chemotherapy regimens used previously that resulted in a response outcome.

Patients' demographic and tumor characteristics, chemotherapeutic agents, response rate, and follow-up data were collected from the medical records. Histopathology was classified as SCC, mucinous adenocarcinoma, adenosquamous carcinoma, undifferentiated carcinoma, and mixed-type carcinoma. Response to chemotherapy was assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) guidelines.[9] *Overall response rate* was defined as the summation of CR and partial response (PR) rates. Progression-free survival duration was calculated from the first date of chemotherapeutic treatment to the date of recurrence or progression or the most recently contact date in those with CR and without disease recurrence. Overall survival duration was calculated from the first date of chemotherapeutic treatment to the date of death or the most recent contact date. Adverse effects from chemotherapy were defined according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0).[10]

The accumulated data were analyzed using SPSS version 18.0 (SPSS, Inc, Chicago, Ill). We used descriptive statistics to describe patients' and tumor's characteristics, chemotherapeutic agents, and response rates. The association between predictors and response rate of first-round chemotherapeutic treatment was compared using χ^2 test. Kaplan-Meier method was used for created survival curves. Univariate Cox proportional hazard model was used to

identify factors associated with OS or PFS. Multivariate Cox analysis with forward selection procedure was used taking into consideration all factors having $P \leq 0.1$ in the univariate analysis. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Three hundred thirty-eight cervical carcinoma patients received chemotherapy treatment during the study period.

TABLE 1. Clinical characteristics of 286 patients with stage IVB, persistent, or recurrent cervical carcinoma

Characteristics	n (%)
Histopathology	
SCC	169 (59.1)
Adenocarcinoma	91 (31.8)
Mucinous cell carcinoma	6 (2.1)
Adenosquamous cell carcinoma	10 (3.5)
Clear cell carcinoma	3 (1.0)
Mixed SCC and adenocarcinoma	1 (0.3)
Undifferentiated carcinoma	6 (2.0)
Initial clinical FIGO stage	
IA1	2 (0.7)
IA2	1 (0.3)
IB1	31 (10.8)
IB2	13 (4.5)
IIA1	12 (4.2)
IIA2	1 (0.3)
IIB	83 (29.0)
IIIA	1 (0.3)
IIIB	91 (31.8)
IVA	7 (2.4)
IVB	39 (13.6)
Inadvertent hysterectomy	4 (1.4)
Unavailable data	1 (0.3)
Primary treatment	
RT	38 (13.3)
CCRT	167 (58.4)
Surgery	34 (11.9)
CT	47 (16.4)
Reason for chemotherapy	
Primary treatment	47 (16.4)
Persistent disease	85 (29.7)
Recurrent disease	154 (53.8)
Disease sites	
Locoregional	91 (31.8)
Distant	92 (32.2)
Both	103 (36.0)

CCRT, concurrent chemo-radiation; CT, chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; RT, radiation therapy; SCC, squamous cell carcinoma.

After exclusion of 23 patients with neuroendocrine carcinoma and 29 patients receiving only 1 cycle of chemotherapy, a total of 286 cervical carcinoma patients were used for data analysis. Median age was 50.7 years (interquartile range [IQR], 44.2–58.6 years), median body mass index (BMI) was 22.7 kg/m² (IQR, 19.9–26.2 kg/m²), median parity was 2 (IQR, 1–3), and 128 patients (44.8%) were in postmenopausal period. Tumor characteristics and primary treatment modalities were presented in Table 1.

Of 286 patients, 47 patients (16.4%) received chemotherapy for primary treatment and 239 patients (83.6%) received chemotherapy for persistent or recurrent diseases. First-line chemotherapeutic agents used in these patients included platinum-based combined with paclitaxel (188 [65.7%] of 286 patients), platinum-based combined with fluorouracil (28 [9.8%] of 286 patients), cisplatin plus mitomycin (13 [4.5%] of 286 patients), cisplatin plus ifosfamide (12 [4.2%] of 286 patients), platinum-based combined with topotecan (10 [3.5%] of 286 patients), and other combinations (5 [1.7%] of 286 patients) and single drug, such as cisplatin, mitomycin, or paclitaxel (30 [10.5%] of 286 patients). Median number of first-line drug treatment was 6 cycles (range, 2–12). Eighty-one patients received second-line chemotherapy because of nonresponsiveness or intolerance to side effects of the first-line chemotherapy, with a median number of 4 treatment cycles (range, 2–11). Overall response rate by first-round chemotherapy was 37.8% (108 of 286 patients), with a CR rate of 23.1% (66 of 286 patients) and a PR rate of 14.7% (42 of 286 patients). Ninety-two patients (32.2%) had stable disease (SD), and 86 patients (30.0%) had disease progression. The remaining 21 patients were treated with second-round chemotherapy, and all of them were in the persistence/ recurrence group.

Response of treatment was classified as either primary treatment in advanced-stage cervical carcinoma or treatment for persistent/recurrent disease after primary surgery or CCRT. Response rate of 47 patients who received first-round chemotherapy for primary treatment are shown in Table 2. The overall response rate was 38.3%; CR rate of 17% and PR rate of 21.3%. Seven patients had a CR, of which 4 of 7 patients had no recurrence, and 1 of 7 patients developed local recurrence with a CR after RT. For the remaining non-CR, 7 patients received second-line chemotherapy, including (i) 3 patients from initial PR resulted in CR in 1 patient, continued PR in 1 patient, and SD in 1 patient; (ii) 3 patients from initial SD resulted in PR in 2 patients and progressive disease (PD) in 1 patient; and (iii) 1 patient from initial PD still had PD.

Among 239 patients who received chemotherapy for persistent/recurrent disease, 167 patients were treated primarily by CCRT, 38 patients by RT alone, and 34 patients by surgery. Response rates of this group were presented in Table 3. Overall response rate of first-round chemotherapy was 37.7%, with a CR rate of 24.3%, and a PR rate of 13.4%. From 47 patients with CR by first-line drug of first-round chemotherapy, 23 patients had long-term response until the last follow-up date. Of 75 patients from 192 non-CR patients by first-line drug who received second-line drug in first-round chemotherapy: (i) from 14 initial PR patients, 4 were found to have a CR, 4 had a PR, 3 had SD, and 3 had PD; (ii) from

TABLE 2. Response evaluation in 47 patients who received primary treatment with chemotherapy

Treatment	No. Patients	Response Evaluation, n (%)			
		Complete Response	Partial Response	Stable Disease	Progressive Disease
First drug	47	7 (14.9)	10 (21.3)	16 (34.0)	14 (29.8)
Second drug	7	1 (14.3)	3 (42.9)	1 (14.3)	2 (28.5)
Final treatment outcomes	47	8 (17.0)	10 (21.3)	13 (27.7)	16 (34.0)

54 SD patients, 7 achieved a CR, 7 had a PR, 27 had SD, and 13 had PD; and (iii) 7 initial PD patients still had PD. During the follow-up period, 21 patients had disease recurrence and were counseled for second-round chemotherapy, with 6 patients receiving a second drug. Of 4 SD patients receiving a second drug of second-round chemotherapy, one had PR, one had PD, and the other 2 patients with PD still had PD. The final response rate of second-round chemotherapy for persistence/recurrence disease was 33.4%, with a CR rate of 19.1% and a PR rate of 14.3%.

Table 4 presents the response of treatment with various first-line chemotherapeutic regimens of first-round treatment. Various factors associated with response rate and survival outcomes of 286 study patients treated by first-round chemotherapy were presented in Table 5. Median OS was 11.6 months (range, 0.7–108.3), and median PFS was 5.6 months (range, 0.7–102.2). Figure 1 presented the OS curves of 286 studied patients, which was separated by BMI and disease sites. Curves describing PFS relative to cumulative survival in 286 studied patients specific to BMI and histopathology subtype were presented in Figure 2.

Observed side effects included nausea/vomiting grade 3 in 9 patients (3.1%) and grade 1 to 2 in 26 patients (9.1%), neuropathy grade 3 in 4 patients (1.4%) and grade 1 to 2 in 69 patients (24.1%), and myelosuppression grade 3 to 4 in 26 patients (9.1%) and grade 1 to 2 in 25 patients (8.7%). Renal function impairment was detected in 6 patients (2.1%). Two patients had febrile neutropenia, and 2 patients had abnormal liver function test results. Palmar plantar erythrodysesthesia was found in 4 patients, one of which had grade 3 toxicity.

DISCUSSION

Doublets of cisplatin-based chemotherapy regimens provide longer PFS than single cisplatin.[3–5] Various agents are used to achieve better OS. Only the combination of cisplatin and topotecan has better OS than cisplatin alone.[3] According to GOG protocols 169 and 179, cisplatin was the most cost-effective drug in the treatment of cervical carcinoma.[11] In this study, overall response rate of each round of chemotherapy was 33.4% to 38.3%, slightly higher than the result from other GOG studies (22.3%–35%)[3–6,12] but lower than that from a Japanese Gynecologic Oncology Group study (58.8%–62.6%).[13] To achieve the level of overall response rate described in the present study, the following protocol should be followed: (i) prescribe only first-line agent for primary treatment of metastatic disease; (ii) in cases of persistent/recurrent disease, use first-line and second-line agents of first round of treatment until first regimen of second round of treatment; and (iii) in cases where PD response status, palliative therapies without chemotherapy should be given. Continued use of chemotherapeutic agents may be ineffective, with side effects potentially worsening the patient's condition.

For patients with stage IVB or persistent or recurrent cervical carcinoma, PFS and OS duration in this study were comparable to targeted therapy trial GOG no. 240 (5.6 vs

TABLE 3. Response evaluation in 239 patients with persistent or recurrent cervical carcinoma who were treated with chemotherapy

Treatment	No. Patients	Response Evaluation, n (%)			
		Complete Response	Partial Response	Stable Disease	Progressive Disease
First-round chemotherapy					
First drug	239	47 (19.7)	35 (14.6)	103 (43.1)	54 (22.6)
Second drug	75	11 (14.7)	11 (14.7)	31 (41.3)	22 (29.3)
Final treatment outcomes	239	58 (24.3)	32 (13.4)	79 (33.0)	70 (29.3)
Second-round chemotherapy					
First drug	21	4 (19.1)	2 (9.5)	10 (47.6)	5 (23.8)
Second drug	6	0	1 (16.7)	1 (16.7)	4 (66.6)
Final treatment outcomes	21	4 (19.1)	3 (14.3)	7 (33.3)	7 (33.3)

TABLE 4. Response outcomes by first-line regimens in 286 patients treated with chemotherapy

Regimens	Complete Response, n (%)	Partial Response, n (%)	Stable of Disease, n (%)	Progressive Disease, n (%)
CDDP + paclitaxel (n = 135)	27 (20.0)	22 (16.3)	52 (38.5)	34 (25.2)
CBP + paclitaxel (n = 50)	8 (16.0)	10 (20.0)	19 (38.0)	13 (26.0)
CDDP/CBP + topotecan (n = 10)	0	0	6 (60.0)	4 (40.0)
CDDP + ifosfamide (n = 12)	5 (41.7)	1 (8.3)	6 (50.0)	0
CDDP/CBP + 5-FU (n = 16)	5 (31.2)	0	7 (43.8)	4 (25.0)
CDDP + capecitabine (n = 12)	2 (16.7)	4 (33.3)	5 (41.7)	1 (8.3)
CDDP + mitomycin (n = 13)	0	4 (30.8)	7 (53.8)	2 (15.4)
CDDP (n = 12)	3 (25.0)	1 (8.3)	6 (50.0)	2 (16.7)
CBP (n = 6)	0	2 (33.3)	2 (33.3)	2 (33.3)
Mitomycin (n = 6)	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)
Other chemotherapy (n = 14)	4 (28.6)	0	7 (50.0)	3 (21.4)

CBP, carboplatin; CDDP, cisplatin; 5-FU, fluorouracil.

TABLE 5. Factors associated with overall response rate, overall survival, and progression-free survival

Variables	Overall Response Rate		Overall Survival		Progression-Free Survival	
	n (%)	P	HR (95% CI)	P	HR (95% CI)	P
Age, y						
<50 (n = 136)	59 (43.4)	0.062	Reference		Reference	
≥50 (n = 150)	49 (32.7)		1.16 (0.78–1.71)	0.471	1.09 (0.86–1.40)	0.477
Menopausal status						
Premenopause (n = 158)	63 (39.9)	0.413	Reference		Reference	
Postmenopause (n = 128)	45 (35.2		1.12 (0.76–1.66)	0.575	1.03 (0.80–1.31)	0.844
Body mass index, kg/m^2						
<18.5 (n = 37)	12 (32.4)	0.032	1.70 (0.994–2.898)	0.053	1.09 (0.75–1.58)	0.662
18.5–24.9 (n = 154)	50 (32.5)		Reference		Reference	
≥25 (n = 95)	46 (48.4)		0.62 (0.40–0.99)	0.043*	0.72 [0.55–0.95)	0.019†
Patient groups						
Primary (n = 47)	18 (38.3)	0.934	Reference		Reference	
Persistence/recurrence (n = 239)	90 (37.7)		0.65 (0.38–1.09)	0.101	0.80 (0.58–1.11)	0.180
Initial clinical FIGO stages						
I–II (n = 143)	56 (39.2)	0.626	Reference		Reference	
III–IV (n = 143)	52 (36.4)		0.96 (0.65–1.42)	0.846	1.16 (0.91–1.48)	0.229
Histopathology						
SCC (n = 169)	62 (36.7)	0.652	Reference		Reference	
Non-SCC (n = 117)	46 (39.3)		0.70 (0.47–1.06)	0.091	0.77 (0.60–0.98)	0.037§
Disease sites						
Locoregional (n = 91)	36 (39.6)	0.668	Reference		Reference	
Distant metastasis (n = 195)	72 (36.9)		1.97 (1.22–3.19)	0.006‡	1.31 (1.00–1.71)	0.050

FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.

Multivariate Cox analysis with adjusted HR for overall survival of BMI of 25 kg/m^2 or more*, 0.66 (95% CI, 0.42–1.04), P = 0.073; distant metastasis‡, 1.78 (95% CI, 1.09–2.90), P = 0.020.

Multivariate Cox analysis with adjusted HR for progression-free survival of BMI of 25 kg/m^2 or more†, 0.72 (95% CI, 0.55–0.94), P = 0.018; non-SCC§, 0.77 (95% CI, 0.60–0.99), P = 0.041.
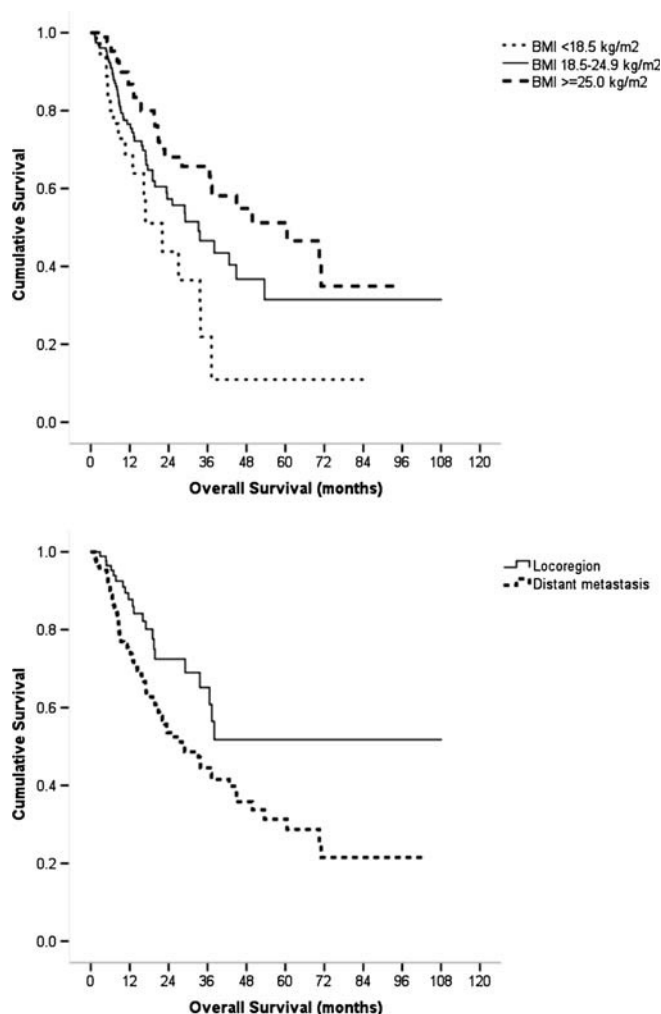
FIGURE 1. Overall survival relative to cumulative survival by body mass index classification (*P* = 0.003) or disease site (*P* = 0.005).

patients; this study did not demonstrate any statistically significant difference in PFS or OS between stages IVB and persistent/recurrent cervical carcinoma patients receiving chemotherapy. Accordingly, the patients in this study should be included in the same study population as the previous phase III trials.[3–6,12–14]

Platinum combined with paclitaxel are the most common agents for first-line treatment. The overall response rate of paclitaxel combined with carboplatin versus paclitaxel combined with cisplatin was comparable (36%). Our finding was similar to that of the Japanese Gynecologic Oncology Group 0505 study in advanced or persistent/recurrent cervical carcinoma patients that compared oncologic outcomes between cisplatin combined with paclitaxel and carboplatin combined with paclitaxel. Response rate, PFS, and OS of these 2 regimens were reported to be 62.6% versus 58.8%, 6.9 versus 6.2 months, and 17.5 versus 18.3 months, respectively.[13] A systematic review found similar response rates between cisplatin plus paclitaxel and carboplatin plus paclitaxel (48%–49%), but the former achieved 2 months longer PFS and OS.[15] In
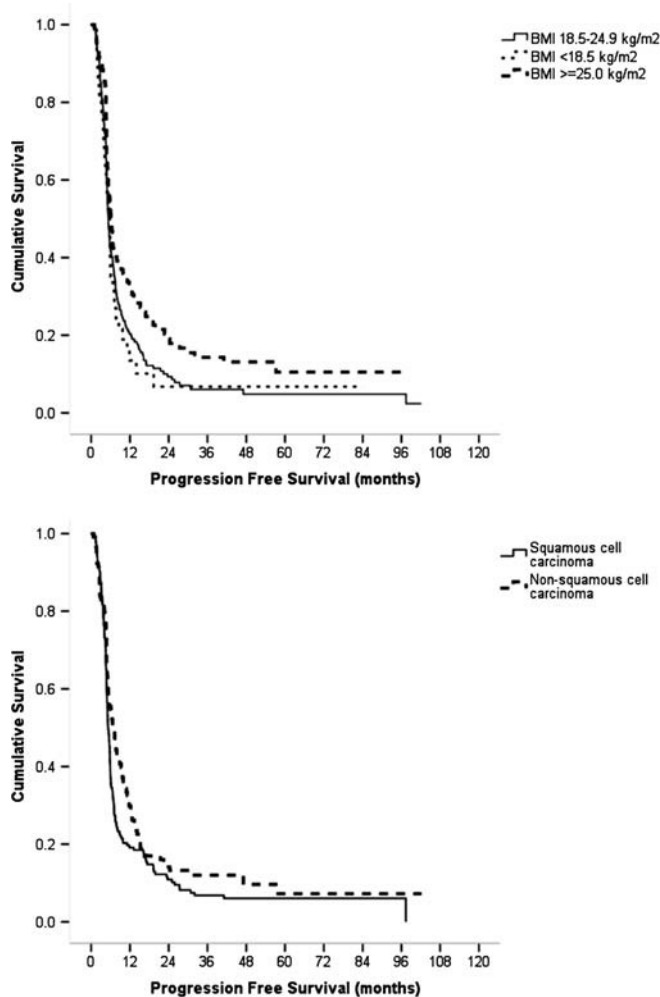
5.7 months and 11.6 vs 12.5 months, respectively) but shorter than those in a Japanese trial (6.2–6.9 months and 17.5–18.3 months, respectively).[13,14] Interestingly, even with previous treatment, such as pelvic radiation or radical surgery for primary treatment, persistence/recurrence patients still had a higher proportion of CR rate than stage IVB patients. Similarly, 70% of patients in GOG trial no. 204 had prior cisplatin-based CCRT, although the radiated field recurrence had a hazard ratio (HR) of 1.4 (95% confidence interval [CI], 1.1–1.8).[6] Furthermore, a systematic review of 14 studies suggested that the response rate would decrease in cases with prior platinum use including both combination of cisplatin or carboplatin with paclitaxel.[15] This may be the result of the nature of the disease. A higher stage of disease has poorer prognosis, resulting in poorer response to treatment. The nature of disease, as characterized by human papillomavirus (HPV) oncogenic genotype and other epigenetic change from HPV infection, tumor biomarkers, individual immunity, race, and geographic area, likely plays an important role in treatment outcomes. Even the CR rate was higher in persistence/recurrence

FIGURE 2. Progression-free survival relative to cumulative survival by body mass index classification (*P* = 0.035) or histopathology subtype (*P* = 0.036).

addition, both studies confirmed that cisplatin was the most effective choice in chemotherapy-naive patients.[13,15]

From the small number of patients who received a combination of cisplatin and ifosfamide in the current study, the outcome was favorable, with a response rate of 50%, which was higher than the outcome from previous GOG studies (31%–32%).[5,12] Platinums combined with fluorouracil-based regimens in the current study resulted in a response rate of 39.3%, higher than that in a report from a phase II study in advanced-stage cervical carcinoma (21.8%).[7] As the incidence of side effects of various chemotherapeutic regimens in this study may be less than the actual rate with a small number of patients in some regimen groups, it could not be compared with other landmark articles.

Surprisingly, patients with BMIs of 25 kg/m^2 or more had a significantly higher response rate than normal-weight or underweight patients. In addition, multivariate Cox analysis found a significant association between BMI and PFS, with an adjusted HR of 0.72 (95% CI, 0.55–0.95; $P = 0.018$). This is consistent with a retrospective study of 404 patients with cervical cancer who underwent chemoradiation therapy. That study found that underweight patients have a lower 5-year OS than normal-weight or obese patients, with 5-year OS rates of 33%, 60%, 68%, respectively. Multivariate analysis of OS revealed that underweight patients had an HR of 2.37 (95% CI, 1.28–4.38; $P < 0.01$ when compared with normal-weight patients.[16] Furthermore, a meta-analysis stated that overweight status does not put a female at an increased risk of cervical cancer.[17] High BMI normally indicates noncachectic status of patients, which may be interpreted as an indirect sign of better health, resulting in a higher rate of treatment response. A recent study in 3086 patients with stage IB1 to IVA cervical carcinoma found that a BMI of 35 kg/m^2 or more (morbid obesity) was an independent poor prognostic factor for all causes of death and disease-specific death, with an HR of 1.26 (95% CI, 1.10–1.45) and 1.24 (95% CI, 1.06–1.47), respectively.[18] Morbid obesity might be related to possible mechanisms such as obesity-related inflammatory cytokines that enhance proliferation and migration or inhibit apoptosis.[19] Another explanation is a potential recovering inadequate chemotherapy dose resulting from uncalculated dose by actual body weight.[18] Based on the current study and previous literature, diet and weight modification may also benefit patients who are underweight or have morbid obesity.

Conflicting results have been reported for treatment response in patients with SCC and non-SCC of the cervix. Most clinicians believed that SCC subtype had poorer response to chemotherapy but better response to radiation when compared with non-SCC histology. A review of short-term efficacy of neoadjuvant chemotherapy for cervical carcinoma demonstrated a nonsignificant difference between SCC and non-SCC subtypes.[20] Histopathology subtype seems to have no impact on treatment outcomes in patients with locally advanced cervical carcinoma treated with CCRT.[21] Moreover, combined data from GOG 85, 120, 123, 165, and 191 trials stated that adenocarcinoma and adenosquamous cell carcinoma had PFS and OS similar to those of SCC when treated with CCRT.[22] Based on data from the current study, non-SCC patients had favorable PFS duration when

compared with that of the SCC type, with an adjusted HR of 0.77 (95% CI, 0.60–0.99; $P = 0.041$). However, these results remain inconclusive and should be interpreted cautiously because of limited data collection and potential confounding factors for treatment outcomes, including disease sites, stage, tumor size, and individual immunity.

This study was settled in a high-incidence developing country with a large sample size and a long follow-up period, supporting the strength of this study. The information from this study can be generalized to clinical practice in other developing countries. Nevertheless, the nature of a retrospective study with some incomplete data records is still a drawback of this study. Additional studies in individual regimen specificity relating to epigenetic change or HPV type, quality of life, and cost-effectiveness are recommended.

In summary, various chemotherapeutic regimens according to Thailand medical insurance coverage generate a good response and favorable survival, similar to results reported in landmark studies from western countries. In developing countries or in patients with medical diseases unable to use cisplatin combined with paclitaxel as in the GOG 204 study, the regimens reported in this study should be considered.

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