

Concurrent Cisplatin-Based Chemoradiation and Adjuvant Hysterectomy for Bulky Stage IB-IIA Cervical Cancer

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Objectives: To evaluate the outcomes and adverse effects of concurrent cisplatin-based chemoradiation and adjuvant hysterectomy for bulky stage IB-IIA cervical cancer.

Material and Method: All eligible, thirty-four patients with bulky stage IB-IIA cervical cancer were assigned to receive weekly cisplatin 40 mg/m² for 6 cycles concurrently with radiation followed by extrafascial hysterectomy 6 weeks after completion of radiation.

Results: Estimated 5-year progression-free and disease-free survival rates of 80% were observed after a median follow-up of 42 months. The overall recurrent rate was 18%. Grade 3 neutropenia and anemia were noted in only 5.9% and 2.9%, respectively. All acute toxicities were transient and were manageable. There were no treatment-related deaths or late toxicities.

Conclusion: For appropriately selected patients with bulky stage IB-IIA cervical cancer, concurrent cisplatin-based chemoradiation followed by adjuvant hysterectomy offers an effective treatment option with acceptable toxicity.

Keywords: Concurrent chemoradiation, Adjuvant hysterectomy, Stage IB-IIA cervical cancer

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Cervical cancer remains one of the major causes of death from gynecologic cancer worldwide. It is the most common cancer and a major health problem in Thai women⁽¹⁾. The disease affects younger women more than other malignancies. Therefore, improvements in cure rate can profoundly affect longevity⁽²⁾. Patients with stage IB and IIA are appropriately treated by either radical hysterectomy with pelvic lymphadenectomy or radiation therapy, with equivalent results⁽³⁾. A choice between these two modalities is frequently in-

fluenced by the availability of specialists, the age of the patient, and perceived toxicities⁽⁴⁾. Based on analyses of large series of radical hysterectomies, depth of cervical stromal invasion, clinical lesion size, and patient's age are also independent prognostic factors⁽⁵⁻⁸⁾. However, patients with bulky cervical tumor tend to have persistent or residual disease even after completion of radiation therapy⁽⁹⁾. Failure to obtain local-regional control for patients with locally advanced disease usually results in death. Recently, five randomised clinical trials have demonstrated superiority to the concurrent use of cisplatin-based chemotherapy with radiation therapy in a variety of advanced stage or high-risk settings, and reduction of relative risk of relapse or death by 30-50%^(4,10-13). Since the late 1960s, the opti-

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mal treatment for bulky stage IB cervical cancer has been controversial. The recognition, in some centers that patients with bulky stage IB cancers had a higher rate of recurrent disease within the cervical area led to the inclusion of adjuvant extrafascial hysterectomy in the treatment regimen for these women⁽¹⁴⁻¹⁶⁾. The objective of the present study was to evaluate the outcomes of concurrent cisplatin-based chemoradiation and adjuvant hysterectomy for bulky stage IB-IIA cervical cancer in terms of progression-free survival, recurrent rate, and adverse effects.

Material and Method

From August 1999 to September 2001, 34 consecutive and previously untreated FIGO bulky stage IB-IIA (primary tumor 4 cm or more, non-neuroendocrine) cervical cancer patients were collected for this analysis in the Department of Obstetrics and Gynecology, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University. Other eligibility criteria included: age ≤ 70 years, Zubrod performance status score of ≤ 2 , no evidence of pelvic or paraaortic lymphadenopathy on computed tomography (CT) scanning and no evidence of cancer on fine-needle aspiration and histologic evaluation in those with clinically enlarged or suspicious-appearing lymph nodes, adequate bone marrow, renal, and hepatic function (WBC $\geq 3000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, serum creatinine level < 2.0 mg/dL (177mmol/L), serum bilirubin level ≤ 1.5 times the normal upper limit and serum aspartate aminotransferase level ≤ 3 times the upper limit), negative HIV antibody, no history of other cancers and medically suitable for extrafascial hysterectomy. All eligible patients underwent a complete physical and pelvic examination, chest radiography and abdominal/ pelvic CT scanning. All patients were scheduled to undergo external radiation and intracavitary brachytherapy. Pelvic radiation was delivered with the four-field technique with cobalt-60 or linear accelerator of 4-6 MV. The treatment field was set to extend 3 cm beyond the known extent of disease and to encompass iliac and lower common iliac lymph nodes. Fractions of 2.0 Gy were delivered 5 days a week over a period of 4.5 to 5 weeks, for a total dose of 46- 50 Gy. External irradiation was withheld if the WBC $< 3000/\text{mm}^3$ or platelet count $< 100,000/\text{mm}^3$. High-dose brachytherapy was performed in four intracavitary applications after the completion of external pelvic radiotherapy using Henschke's applicators. The dose to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 30 Gy, for a cumulative dose of 75 Gy, and the cumulative dose to point B (the pelvic

wall) was 55 Gy. Patients received cisplatin 40 mg/m² intravenously once a week (the total dose not to exceed 70 mg per week) for 6 consecutive weeks concomitantly with radiotherapy. Weekly check up of CBC, urinalysis, AST, ALT, BUN, serum creatinine level and keep up hemoglobin level of at least 10 g/dL. Adverse effects were recorded in accordance with the WHO criteria. Treatment with cisplatin was withheld if the total WBC $< 3000/\text{mm}^3$ or the platelet count $< 50,000/\text{mm}^3$ or if creatinine clearance by the Cockcroft-Gault formula was less than 30-50 ml per minute. Extrafascial hysterectomy was performed six weeks after the completion of radiotherapy. All hysterectomy specimens were evaluated for residual tumor. All patients were evaluated during the courses of treatment, before, and after the surgery. Clinical examination was performed every 3 months during the first year, every 4 months the second year, and every 6 months thereafter. Progression-free survival was calculated from the date of study entry to the date of disease recurrence or the last follow-up visit. Disease-free survival was calculated from the date of completion of treatment to the date of recurrence or the last follow-up visit. Recurrences were classified as local if they were detected in the pelvis, or vagina and as distant if they were detected in extrapelvic locations. Statistical calculations were performed using SPSS software version 10.0 for Windows (SPSS Inc., Chicago, IL). Estimated 5-year progression-free survival and disease-free survival were calculated using Kaplan-Meier method. Factors that may be related with recurrence of disease were analyzed using Fisher's exact test or Mann-Whitney U test. All tests were considered significant if p - value was less than 0.05.

Results

From August 1999 to September 2001, a total of 34 cases of bulky stage IB and IIA cervical cancer underwent extrafascial hysterectomy after receiving concurrent cisplatin-based chemoradiation. The mean age of the patients was 44.18 ± 7.32 years (30-66 years). Approximately 50 percent of cases were between 41-50 years of age. All patients in this study had a good performance status (Zubrod performance status score of 0). Twenty-nine patients were FIGO stage IB and 5 patients were stage IIA. Twenty-two tumors were classified as squamous cell carcinoma, 11 as adenocarcinoma, and 1 as adenosquamous cell carcinoma. Nine carcinomas were graded as well differentiated (G1), 16 as moderately differentiated (G2), and 6 as poorly differentiated (G3). The most common gross appearance

of the tumor was exophytic type (73.5%). The tumor size ranged from 4.0 – 8.0 cms, mean 5.35 ± 1.07 cms. The clinicopathological features of the 34 tumors are shown in Table 1. Upon obtaining a surgical specimen and pathologic examination, 18 patients (52.9%) had no residual lesion, 11 patients (32.4%) had a microscopic residual lesion and 5 patients (14.7%) showed some macroscopic residual tumor. There were no treatment-related deaths. The frequencies of adverse effects are shown in Table 2. The most common adverse effect was hematologic toxicity. Grade 3 and 2 neutropenia were observed in 2/34 (5.9%) and 8/34 (23.5%). These reactions consisted almost exclusively of transient hematologic effects. Grade 3 and 2 anemia were also observed in 1/34 (2.9%) and 7/34 (20.6%), respectively. Only 1 patient had grade 1 neurotoxicity with spontaneous recovery after finishing treatment. Other adverse reactions such as nausea and vomiting or diarrhea were also found and were manageable. After completion of therapy, 1 patient was subsequently lost to follow-up. The remaining 33 cases have been followed. The median follow-up time was 42 months (7-58 months). The 5-year progression-free survival rate was 80% (95% confidence interval, 72% to 87%) (Fig. 1). The 5-year disease-free survival rate was 80% (95% confidence interval, 72% to 87%) (Fig. 2). Six patients (18.2%) developed recurrence and 5 of them died. All recurrences occurred within 2 years following the completion of treatment, 1 (3.0%) had distant metastases; another 3 (9.0%) had pelvic recurrences and the remaining 2 (6.0%) had combined distant and pelvic recurrences. The recurrences were analyzed in relation to initial tumor size, histopathologic subtypes, tumor grade and residual tumor. All of these factors were not statistically significant (Table 3).

Table 1. Characteristics of the Patients

Characteristic	No. of patients (%) (N = 34)
Age (yr)	
≤ 30	1 (2.9)
31-40	9 (26.5)
41-50	18 (53.0)
51-60	5 (14.7)
61-70	1 (2.9)
FIGO stage	
IB	29 (85.3)
IB1 (lesion = 4 cm)	4 (11.8)
IB2 (lesion > 4 cm)	25 (73.5)
IIA	5 (14.7)
Gross appearance	
Exophytic	25 (73.5)
Endophytic	7 (20.6)
Ulcerative	2 (5.9)
Tumor size (cm)	
4.0-5.0	22 (64.7)
5.1-6.0	7 (20.6)
6.1-7.0	3 (8.8)
7.1-8.0	2 (5.9)
Histologic diagnosis	
Squamous cell carcinoma	22 (64.7)
Adenocarcinoma	11 (32.4)
Adenosquamous cell carcinoma	1 (2.9)
Tumor grade	
1 (well differentiated)	9 (26.5)
2 (moderate differentiated)	16 (47.1)
3 (poorly differentiated)	6 (17.6)
Unknown	3 (8.8)

Table 2. Adverse Effects

Adverse Effects	N = 34				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	percentage of patients				
Neutropenia	44.1	26.5	23.5	5.9	0.0
Thrombocytopenia	100.0	0.0	0.0	0.0	0.0
Anemia	35.3	41.2	20.6	2.9	0.0
Nausea or vomiting	50.0	29.4	17.6	3.0	0.0
Diarrhea	73.5	26.5	0.0	0.0	0.0
Neurologic effects	97.1	2.9	0.0	0.0	0.0
Cutaneous effects	100.0	0.0	0.0	0.0	0.0
Pulmonary effects	100.0	0.0	0.0	0.0	0.0
Cardiovascular effects	100.0	0.0	0.0	0.0	0.0

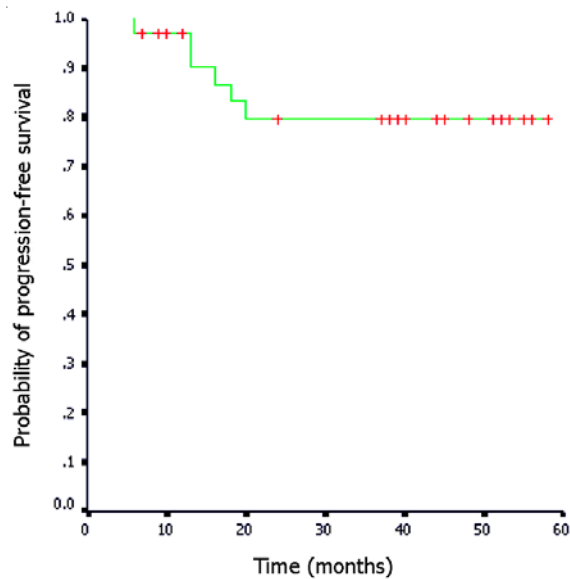


Fig. 1 Kaplan-Meier estimates of progression-free survival in patients with bulky stage IB-IIA given concurrent chemoradiation followed by adjuvant hysterectomy

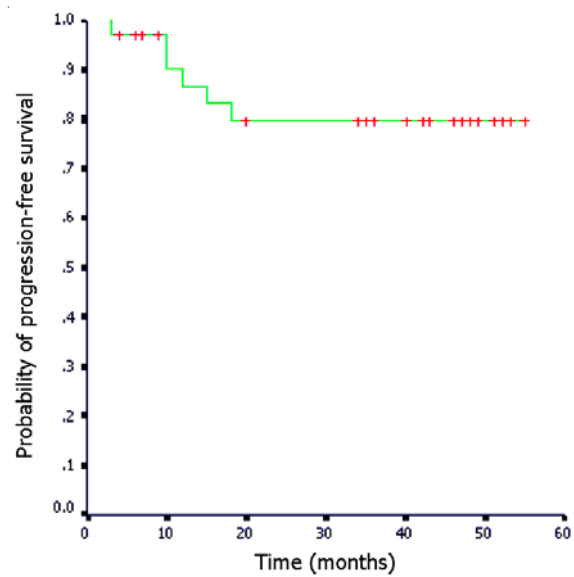


Fig. 2 Kaplan-Meier estimates of disease-free survival in patients with bulky stage IB-IIA given concurrent chemoradiation followed by adjuvant hysterectomy

Table 3. Analysis of factors affecting recurrence after concurrent cisplatin-based chemoradiation and adjuvant hysterectomy for bulky stage IB-IIA cervical cancer

	Patients with recurrence (%) (n = 6)	Patients without recurrence (%) (n = 27)	p value
Tumor size (cm)			0.21
4.0-5.0 (n = 21)	2 (9.5)	19 (90.5)	
5.1-6.0 (n = 7)	2 (28.6)	5 (71.4)	
6.1-7.0 (n = 3)	2 (66.7)	1 (33.3)	
7.1-8.0 (n = 2)	0 (0.0)	2 (100.0)	
Histopathologic subtypes			0.83
Squamous cell carcinoma (n = 21)	4 (19.0)	17 (81.0)	
Adenocarcinoma (n = 11)	2 (18.2)	9 (81.8)	
Adenosquamous cell carcinoma (n = 1)	0 (0.0)	1 (100.0)	
Tumor grade ^a			0.80
1 (well differentiated) (n = 9)	2 (22.2)	7 (77.8)	
2 (moderate differentiated) (n = 15)	3 (20.0)	12 (80.0)	
3 (poorly differentiated) (n = 6)	1 (16.7)	5 (83.3)	
Residual tumor			0.09
No (n = 18)	1 (5.6)	17 (94.4)	
Microscopic (n = 10)	4 (40.0)	6 (60.0)	
Macroscopic (n = 5)	1 (20.0)	4 (80.0)	

^a Samples where grading was not known were not included in the analysis

Discussion

Recently, five large cooperative randomized clinical trials comparing cisplatin-based chemoradiation with radiation alone or radiation with hydroxyurea have been performed in advanced stage or high-risk cervical cancer patients^(4,10-13). Based on the results of these five trials, the National Cancer Institute (USA) released a clinical alert declaring the use of chemotherapy concurrently with radiation in women who require radiotherapy as a new standard of treatment for patients with cervical cancer⁽¹⁷⁾. The optimal treatment for patients with bulky stage IB or IIA lesions is controversial. Because of the increased risk of nodal metastasis and recurrent disease, many treatments and combinations of therapy have been evaluated. Primary radiotherapy is advocated by some authorities owing to the increased need for adjuvant therapy because of poor prognostic factors after radical surgery in these patients⁽¹⁸⁾. There were also evidences that patients who had planned adjuvant extrafascial hysterectomy after radiation therapy had few central failures, although overall survival rates were only slightly affected⁽¹⁹⁾. Gallion and associates reported on 75 patients with stage I disease greater than 5 cm in size or barrel-shaped treated with either radiation therapy alone or in combination with extrafascial hysterectomy. Recurrent cancer was noted in 47% of patients treated with irradiation alone compared to 16% of those treated with combined therapy ($p < 0.01$). The incidence of pelvic recurrence was reduced from 19% to 2% and of extrapelvic recurrence from 16% to 7%⁽¹⁶⁾. From the GOG study, Keys and colleagues reported that adding weekly infusions of cisplatin to pelvic radiotherapy followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancer⁽¹³⁾. Green and colleagues performed a systematic review of all known randomized controlled trials carried out between 1981 and 2000 of chemoradiation for cervical cancer that included 4580 randomized patients. Cisplatin was the most common agent used. The findings suggest that chemoradiation improves overall survival (hazard ratio 0.71, $p < 0.0001$), whether platinum was used (0.70, $p < 0.0001$) or not (0.81, $p = 0.20$), especially in stage I and II patients. An improvement in progression-free survival was also seen⁽²⁰⁾.

In this institution, concurrent cisplatin-based chemoradiation and adjuvant extrafascial hysterectomy has been used for the treatment of bulky stage IB-IIA cervical cancer since 1999. With a median follow-up of 42 months, 18% of the presented patients developed

recurrence compared to that of 21% reported by Keys et al⁽¹³⁾. Many investigators have shown that tumor size is an important prognostic factor, in particular, for stage Ib cervical carcinoma⁽²¹⁻²⁴⁾. This relation was not found in the present study. A larger number of cases may be required to demonstrate this relationship. Rate of tumor regression or persistence found at the time of intracavitary insertion might be useful as an indication to substitute operation for a second implant⁽¹⁹⁾. Perez and colleagues found that tumors that do not regress promptly are more likely to recur⁽²⁵⁾. Morphologically persistent cancer in the surgical specimen at adjunctive hysterectomy was found to be a prognostically ominous sign by Russell and coworkers⁽²⁶⁾. Maruyama and associates found a small but not significant difference in tumor-free survival between patients with and without persistence at the time of hysterectomy⁽²⁷⁾. There was no statistically significant difference between residual tumor, tumor grade or tumor pathology and recurrence of disease at the time of this analysis in the present study. In a systematic review and meta-analysis on concomitant chemotherapy and radiotherapy for cervical cancer, grade 3 or 4 hematological and gastrointestinal toxicities were significantly greater in the concomitant chemoradiation group⁽²⁰⁾. In the present study, severe adverse effects were infrequent. The most common adverse effect was hematologic toxicity with grade 3 neutropenia and grade 3 anemia accounting for 5.9% and 2.9%, respectively. No grade 4 hematologic toxicity was found in this study. Other toxicities (i.e., gastrointestinal and neurological) were transient, minimal, and manageable. No treatment-related toxicity of late complication has been found. Estimated 5-year progression-free and disease-free survival rates were 80%. In conclusion, concurrent cisplatin-based chemoradiation and adjuvant hysterectomy could be one of the potentially effective treatment options for appropriately selected patients with bulky stage IB-IIA cervical cancer, with minimal and manageable toxicity.

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การรักษามะเร็งปากมดลูกขนาดใหญ่ ระยะ IB-IIA ด้วยการให้รังสีรักษาร่วมกับยาเคมีบำบัดกลุ่ม Cisplatin ก่อนการผ่าตัดมดลูกแบบธรรมดา

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วัตถุประสงค์: เพื่อประเมินผลการรักษาในแง่ของระยะปลอดโรค การคืบหน้า การกลับเป็นซ้ำของโรค และผลข้างเคียงจากการรักษา มะเร็งปากมดลูกขนาดใหญ่ ระยะ IB-IIA ด้วยการให้รังสีรักษาร่วมกับยาเคมีบำบัดกลุ่ม Cisplatin ก่อนการผ่าตัดมดลูกแบบธรรมดา

วัสดุและวิธีการ: ทำการศึกษาในผู้ป่วยมะเร็งปากมดลูกขนาดใหญ่ ระยะ IB-IIA ที่มารับการรักษาที่โรงพยาบาลมหาสารคามศรีเชียงใหม่ จำนวน 34 ราย ซึ่งได้รับรังสีรักษาร่วมกับยาเคมีบำบัด Cisplatin ขนาด 40 มก./ม² ทุกสัปดาห์ จำนวน 6 ครั้ง แล้วตามด้วยการผ่าตัดมดลูกแบบธรรมดา ภายหลังสิ้นสุดรังสีรักษา 6 สัปดาห์

ผลการศึกษา: จากการติดตามผลการรักษาที่มีพื้นฐานของเวลา 42 เดือน พบว่าทั้งอัตราการรอดชีวิตที่ระยะ 5 ปีของผู้ป่วยที่ปลอดโรคภายหลังสิ้นสุดการรักษาและปราศจากการคืบหน้าของโรค มีค่าเท่ากับร้อยละ 80 อัตราการกลับเป็นซ้ำของโรค มีค่าเท่ากับร้อยละ 18 ผู้ป่วยที่มีปริมาณเม็ดเลือดขาวนิวโทรฟิลต่ำและภาวะโลหิตจางเกรด 3 พบร้อยละ 5.9 และ 2.9 ตามลำดับ ผลข้างเคียงแบบเฉียบพลันพบเพียงชั่วคราวและแก้ไขได้ ไม่พบผลข้างเคียงแบบระยะยาวหรือการเสียชีวิตที่เกิดขึ้นจากการรักษา

สรุป: เมื่อใช้เกณฑ์การคัดเลือกผู้ป่วยที่เหมาะสมสำหรับผู้ป่วยมะเร็งปากมดลูกขนาดใหญ่ระยะ IB-IIA พบว่าวิธีการรักษาด้วยรังสีรักษาร่วมกับยาเคมีบำบัดกลุ่ม Cisplatin ตามด้วยการผ่าตัดมดลูกแบบธรรมดา จัดเป็นอีกทางเลือกหนึ่งที่มีประสิทธิภาพและมีผลข้างเคียงที่ยอมรับได้