Long-term Outcomes of Concurrent Chemoradiotherapy with Weekly Carboplatin in Locally-Advanced Carcinoma of the Uterine Cervix Patients

Somphob Sangkittipaiboon MD*

** Lopburi Cancer Hospital, Department of Medical Service, Ministry of Public Health, Lopburi, Thailand*

Objective: *To study the treatment outcomes of concurrent chemoradiotherapy with weekly carboplatin in locally-advanced carcinoma of the uterine cervix patients and the complications resulting from the treatment.*

Material and Method: *Between August 2005 and July 2007, the author identified 105 patients with carcinoma of the uterine cervix. The International Federation of Gynecology and Obstetrics Clinical Stages were IIB, III, and IVA in 83, 19, and three cases, respectively. Mean age was 51.5 years old, ranging from 33 to 79 years. Carboplatin was prescribed weekly concurrent with external irradiation.*

Results: *The most acute toxicities were in grade 1-2 (grade 3 hematological toxicities were 3.8%). Complete response was achieved in 95 patients (90.5%). Among the 95 responders, 27 experienced recurrences: local recurrences in eight (8.4%), distant failure in 17 (17.9%), and both local and distant failure in two (2.1%). The follow-up time was ranging from three to 96 months (median 76 months). Significant prognostic factors for disease-free survival in multivariate Cox regression analysis were tumor stage and tumor response. With regard to overall survival, multivariate Cox regression analysis confirmed prognostic significance of patients' age, tumor stage, and tumor response. Five-year disease free survival rate was 52.38% (56.63%, 42.11%, and 0% in stage IIB, III, and IVA, respectively) while five-year overall survival rate was 56.19% (61.45%, 42.11%, and 0% in stage IIB, III, and IVA, respectively). Late grade 3-4 gastrointestinal and genitourinary toxicities were 3.2% and 0%, respectively.*

Conclusion: *Concurrent weekly carboplatin and radiation therapy yields high response rate with modest disease-free and overall survivals in locally advanced carcinoma of the uterine cervix. The regimen is feasible with minimal toxicities. Prognostic factors identified in the present study are consistent with other reports.*

Keywords: *Toxicities, Response, Recurrence, Disease-free survival rate, Overall survival rate*

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Cervical cancer was the third most common malignancy in women worldwide after breast cancer and colorectal cancer with global estimates of 530,000 new cases in 2008[1]. More than 85% lived in developing countries. In Thailand, cervical cancer was the third most common malignancy in women after breast cancer and hepatobiliary cancer with an average age standardized incidence rates (ASR) of 17.7 per 100,000 between 2004 and 2006[2].

Radiotherapy plays an important role in the treatment of patients with cervical cancer. At the present, about 250 new cases per year are treated at Radiation Oncology Section, Lopburi Cancer Hospital by radiotherapy alone, radiotherapy in combination with chemotherapy, and postoperative radiotherapy with or without chemotherapy.

Correspondence to:
Sangkittipaiboon S, Radiation Oncology Section, Lopburi Cancer Hospital, Pahonyotin Road, Talaechoupsorn, Muang, Lopburi 15000, Thailand.
Phone: 081-694-6694
E-mail: somphob87@gmail.com

The role of concurrent chemoradiotherapy in the treatment of patients with cervical cancer had been studied in six prospective randomized trials[3-8]. Five of the six demonstrated a statistically significant difference. That was to reduce the likelihood of recurrence of the disease up to 30 to 50% when cisplatin was used in combination with radiotherapy. Consistent with the meta-analysis of 19 research studies found that progression-free and overall survival rates were increased by 16% and 12%, respectively[9]. Cisplatin was substituted by carboplatin in the treatment of cervical cancer patients at Radiation Oncology Section, Lopburi Cancer Hospital due to the ease of administration, less nausea and vomiting side effects, no nephro-neuro-ototoxicities, and effective control of the disease as well[10-13].

The purposes of this study are

1. To study the treatment outcomes (response rate, disease-free survival rate, and overall survival

rate) of concurrent chemoradiotherapy with weekly carboplatin in locally-advanced carcinoma of the uterine cervix patients.

2. To study the short-term and long-term complications resulting from the treatment.

Material and Method

Patients

After an approval from the Ethics Committee for Human Research of the Department of Medical Service, Ministry of Public Health, the author reviewed the archives of Radiation Oncology Section, Lopburi Cancer Hospital to identify locally-advanced cervical cancer patients treated by concurrent chemoradiotherapy between August 2005 and July 2007. It revealed 105 patients with curative intent into the study. All cases were proven by biopsy for pathological diagnosis. FIGO classification 2001 was used to identify disease stage. Pre-treatment investigations performed were chest X-ray, cystoscopy, proctoscopy, and intravenous pyelogram.

Treatment and evaluation

Radiation treatment composed of external beam irradiation with six MV linear accelerator for the total pelvic dose of 56 to 60 Gy applied in daily fractions of 1.8 to 2.0 Gy, five fractions per week. One to two fractions of medium dose rate[14] or four fractions of high dose rate[14] intracavitary brachytherapy on weekly fractions were applied before and after December 2006, respectively. A total dose at point A was calculated in dose equivalent of 72.1 to 87.3 Gy using LQ model[15,16] depend on tumor volume. Carboplatin was given with radiation with a weekly dosage of AUC 2 (Calvert dose). Complete blood count and serum creatinine were obtained before each cycle of chemotherapy. Any patients with hemoglobin level <10 g/dl received packed red cell transfusion before further treatment. Hematological and non-hematological toxicities were assessed using EORTC Common Toxicity Criteria.

Treatment follow-up

Evaluate the response to treatment at three months after the end of treatment with WHO criteria. Post-treatment surveillance was conducted by complete physical examination every three months during the first year, every four months in the second year, every six months for another three years, and annually thereafter. Imaging study was done only if indicated by abnormal physical findings. Any patients suspected to have local recurrence were confirmed by histology. Late complications of gastrointestinal and genitourinary tracts were recorded using RTOG/EORTC Late Radiation Morbidity Scoring Criteria.

Data analysis

Data were analyzed using SPSS statistical software version 11.5. Descriptive statistic was used to summarize in number, mean, median, and percentage. Disease-free survival and overall survival rates were analyzed by the Kaplan-Meier method and compared between groups with log-rank test. The Cox proportional hazards regression was used to adjust for all prognostic factors in multivariate analysis, p-value <0.05 was considered statistically significance.

Results

During the study period, 105 locally-advanced cervical cancer patients were included. Mean age was 51.5 years old (SD 10.2 years), ranging from 33 to 79 years. Almost all of patients had stage IIB and III with more than 70% were larger than 4 cm in diameter. Majority had squamous cell carcinoma. Ninety-nine patients received carboplatin four times or more (median 5 times). More than 85% had a total point A dose less than 80 Gy (median 78.7 Gy) and about 79% had anemia during the treatment.

The majority of acute toxicities during the treatment were in grade 1-2. Only four patients (3.8 percent) had grade 3 hematological toxicities. Regarding hematological toxicities; 79%, 55%, and 15% of patients experienced anemia, leucopenia, and thrombocytopenia, respectively. For non-hematological toxicities; symptoms of nausea/vomiting and diarrhea were reported in 32% and 25%, respectively. No one experienced grade 3-4 non-hematological toxicities.

Evaluation after completion of treatment showed that 95 from 105 (90.5%) had complete response. Ten patients who were in stage IIB (6 cases), stage IIIB (3 cases), and stage IVA (1 case) had partial response. Unfortunately, all of the partial responders were dead from their diseases within three to 27.9 months (median survival of 10.8 months). From a median follow-up of 76 months (ranging from 3 to 96 months), 27 out of 95 complete responders experienced recurrences: local recurrences in eight (8.4%), distant failure in 17 (17.9%), and both local and distant failure in two (2.1%). The pattern of failure by stage of disease was shown in Table 1.

Up to patients' characteristics, the author found that patients younger than 40 years experienced

Table 1. Pattern of failure among the complete responders

Stage	Local recurrence	Metastases	Both	Total pelvic failure	Total metastatic failure
IIB (%)	7/77 (9.1)	12/77 (15.6)	2/77 (2.6)	9/77 (11.7)	14/77 (18.2)
III, IVA (%)	1/18 (5.6)	5/18 (27.8)	0/18 (0)	1/18 (5.6)	5/18 (27.8)

60% recurrences compared with about 30% in patients older than 40 years. Patients with more advanced stage and larger tumor size had more proportion of recurrences. Patients with adenocarcinoma and adenosquamous cell carcinoma experienced more proportion of recurrences than patients with squamous cell carcinoma. Patients who received more than five times and less than four times of carboplatin, recurrences were reported in 20.6% and 50%, respectively. Patients who received a total dose at point A less than 80 Gy had local recurrences about 20% while only 6.7% in those who received 80 Gy or more. Patients with nadir hemoglobin <8 g/dl experienced recurrences of 50% compared with 22.7% for those who had nadir hemoglobin not less than 12 g/dl as shown in Table 2.

The author evaluated the following prognostic factors for possibility to affect survival: patients' age, tumor stage, tumor size, histology, tumor grade, cycles of chemotherapy administered, total dose equivalent at point A, nadir hemoglobin, and tumor response. In multivariate Cox regression analysis, significant prognostic factors for disease-free survival were tumor stage and tumor response. With regard to overall survival, multivariate Cox regression analysis confirmed prognostic significance of patients' age, tumor stage, and tumor response as shown in Table 3.

By the time of the present study, 55 patients were still alive without evidence of cancer and three patients were alive with their diseases (1 with local recurrence, 1 with bone metastases, and another 1 with local recurrence and lung metastases). Five-year disease free survival rate was 52.38% with 56.63%, 42.11%, and 0% in stage IIB, III, and IVA, respectively (p-value = 0.0068, Log-rank test) while five-year overall survival rate was 56.19% with 61.45%, 42.11%, and 0% in stage IIB, III, and IVA, respectively (p-value <0.0001, Log-rank test) as shown in Fig. 1, 2.

At the time of the present study, late complications were found in 29 complete responders (30.5%). Most of them were in grade 2. Severe late gastrointestinal and genitourinary tracts complications were found at 3.2% and 0.0%, respectively.

Table 2. Treatment failure and patient characteristics

Patient characteristics	Number	No. of failure
Age (year)		
≤40	15 (14.3%)	9 (60.0%)
>40-60	68 (64.8%)	22 (32.4%)
>60	22 (20.9%)	6 (27.3%)
Stage		
IIB	83 (79.0%)	27 (32.5%)
III	19 (18.1%)	8 (42.1%)
IVA	3 (2.9%)	2 (66.7%)
Tumor size (cm)		
≤4	29 (27.6%)	10 (34.5%)
>4 and <6	51 (48.6%)	15 (29.4%)
≥6	25 (23.8%)	12 (48.0%)
Histology		
SCCA	85 (81.0%)	29 (34.1%)
Adenocarcinoma and adenosquamous cell CA	20 (19.0%)	8 (40.0%)
Histological grade		
Grade 1	22 (21.0%)	7 (31.8%)
Grade 2	54 (51.4%)	23 (42.6%)
Grade 3	12 (11.4%)	3 (25.0%)
Unknown	17 (16.2%)	4 (23.5%)
No. of chemotherapy		
<4	6 (5.7%)	3 (50.0%)
4-5	65 (61.9%)	27 (41.5%)
>5	34 (32.4%)	7 (20.6%)
Dose equivalent at point A (Gy)		
<78	38 (36.2%)	7 (18.4%)*
78-79.9	52 (49.5%)	12 (23.1%)*
≥80	15 (14.3%)	1 (6.7%)*
Nadir hemoglobin (g/dl)		
6.5-7.9	2 (1.9%)	1 (50.0%)
8-9.9	30 (28.6%)	13 (43.3%)
10-<11.9	51 (48.6%)	18 (35.3%)
12-18	22 (20.9%)	5 (22.7%)

* Pelvic recurrences only
SCCA = squamous cell carcinoma; CA = carcinoma

Discussion

The use of cisplatin combined with radiation in the treatment of locally-advanced cervical cancer patients with good performance status was accepted as a standard treatment. The problem was side effects

Table 3. Multivariate Cox proportional hazards model for predicting disease-free survival and overall survival

Variables	n	Disease-free survival		Overall survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)					
≤40	15	0.374 (0.139-1.006)	0.051	0.267 (0.102-0.699)	0.007
>40	90				
Stage					
IIB	83	2.057 (1.072-3.947)	0.030	3.395 (1.691-6.818)	0.001
III	19				
IVA	3				
Tumor size (cm)					
≤4	29	1.094 (0.687-1.740)	0.706	1.305 (0.792-2.150)	0.297
>4 and <6	51				
≥6	25				
Histology					
SCCA	85	1.373 (0.562-3.355)	0.486	1.964 (0.824-4.680)	0.127
Others	20				
Tumor grade					
Grade 1	22	1.126 (0.663-1.913)	0.661	1.062 (0.602-1.872)	0.836
Grade 2	54				
Grade 3	12				
Unknown	17				
No. of chemotherapy					
<4	6	0.925 (0.523-1.638)	0.790	0.616 (0.314-1.205)	0.157
4-5	65				
>5	34				
Dose equivalent at point A (Gy)					
<80	90	0.900 (0.323-2.507)	0.840	1.153 (0.397-3.350)	0.794
≥80	15				
Nadir hemoglobin					
≥10	73	1.427 (0.708-2.876)	0.320	1.540 (0.771-3.076)	0.221
<10	32				
Tumor response					
CR	95	9.075 (3.456-23.828)	0.000	3.009 (1.275-7.102)	0.012
PR	10				

CR = complete response; PR = partial response

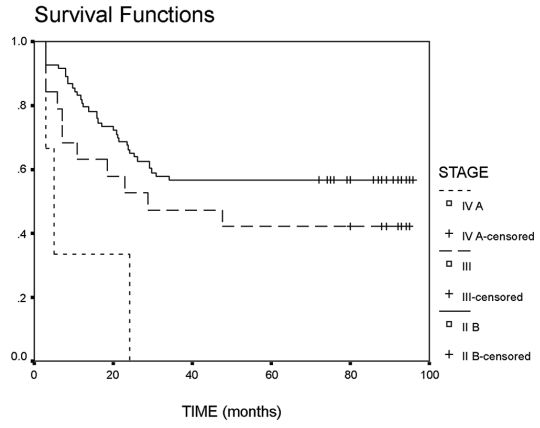

Fig. 1 Disease-free survival rates after definitive concurrent chemo radiotherapy in the study cohort.

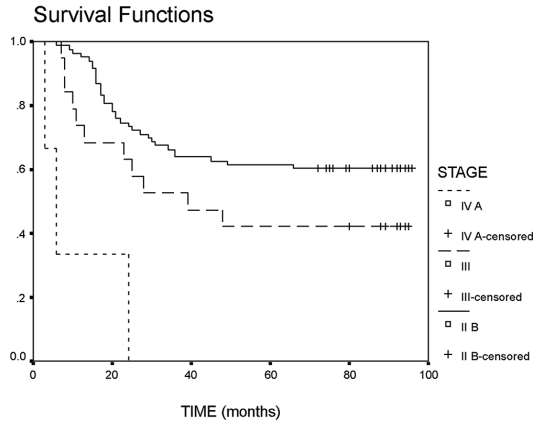

Fig. 2 Overall survival rates after definitive concurrent chemo radiotherapy in the study cohort.

that occurred during treatment. Prior studies reported 21 to 38% grade 3-4 hematological toxicities[4,7]. Grade 3-4 gastrointestinal toxicities were reported ranging from 6 to 14%[3-7]. Carboplatin was used in the treatment of cervical cancer patients with radiation at Radiation Oncology Section, Lopburi Cancer Hospital due to the ease of administration and the reported side effects were minimal[10-13]. Furthermore, Carboplatin as a radiosensitizer was reported to have both lethal effects to the hypoxic cell population and to inhibit reparative process of sublethal damage from radiation[17]. This study provided carboplatin AUC 2[18,19] once a week in combination with radiation therapy. Ninety-nine patients (94.3%) received chemotherapy at least four times. Acute side effects during the treatment period were mostly in grade 1-2 (grade 3 hematological toxicities were 3.8%) and did not experience grade 3-4 gastrointestinal toxicities. Consistent with the study of Veerasarn et al[20], grade 3-4 anemia, leucopenia, and gastrointestinal toxicities were found in 1%, 4%, and 1%, respectively and the study of Katanyoo et al[21], which did not find grade 3-4 acute toxicity.

The present study showed that 95 from 105 (90.5%) had complete response. Twenty-seven out of 95 complete responders experienced recurrences: local recurrences in eight (8.4%), distant failure in 17 (17.9%), and both local and distant failure in two (2.1%). Consistent with the study of Katanyoo et al[21], complete responders were 95.9% who experienced local recurrence in seven (4.7%), distant failure in 25 (16.9%), and both local and distant failure in four (2.7%). Pattern of failure correlated with the stage of disease. Perez et al[22] showed incidence of tumor recurrence by stage of cervical cancer patients treated with concurrent chemoradiotherapy between 1984 and 1992. The collected data showed that 1/24 (4.2%) and 3/24 (12.5%) of patients with stage IB-IIB had total pelvic failure and total metastatic failure, respectively while patients with stage III-IVA were found in 14/34 (41.2%) and 18/34 (52.9%), respectively. This study showed that 9/77 (11.7%) of patients with stage IIB (without stage IB-IIA) had total pelvic failure which was relatively high. One in 18 (5.6%) and 5/18 (27.8%) of patients with stage III-IVA experienced total pelvic and metastatic failure, respectively that was found quite a few. However, metastatic failure was a major site of treatment failure especially in more advanced stage.

To date, a few studies have ever reported long-term survival rate of cervical cancer patients treated by concurrent carboplatin with radiation. This study showed 5-year overall survival rate of 56.19% with 61.45%, 42.11%, and 0% in stage IIB, III, and IVA, respectively, consistent with long-term study of Katanyoo et al[21], which reported 5-year overall survival rate of 63.5%.

The author found from multivariate analysis that advanced stage, patients' age under 40 years, and partial responses were significant poor prognostic factors for survival. The study of cervical cancer from Washington University found no difference in prognosis between younger and older patients[23,24] while some reports found that patients younger than 35 years[25] or 40 years[26] had less chance of survival than older patients because of the type usually found was more poorly differentiated tumor. For the present study, the author found that patients younger than 40 years experienced 60% recurrence compared to about 30% in patients older than 40 years. In multivariate Cox analysis, patients under 40 years had less chance of survival than older patients significantly though the reported data showed that none had poorly differentiated tumor type. It was found that 60% of such patients had hemoglobin level less than 10 g/dl during the treatment.

Evans and Bergsjo[27] Bush[28] Vigario et al[29] found that patients with hemoglobin level less than 10 to 11 g/dl had likely pelvic recurrence and less chance of survival than patients with high level of hemoglobin. Teh J et al[30] found that pre-treatment hemoglobin level less than 10 g/dl and nadir hemoglobin less than 10 g/dl were significantly associated with poor overall survival and disease-free survival, respectively. In the present study, the author found that patients with nadir hemoglobin less than 10 g/dl had more recurrent rates than patients with higher nadir hemoglobin (43.8% and 31.5%, respectively) but did not reach statistical significant difference in multivariate analysis.

Reig A et al[31] found that completed response after concurrent chemoradiotherapy was significantly associated with good outcome. The present study, the author found that all of 10 partial responders were dead from their diseases within three to 27.9 months (median survival of 10.8 months) and partial response was significantly associated with poor disease-free survival and overall survival in multivariate Cox analysis.

Long-term side effects of radiotherapy depending on the amount of radiation that patients received, radiation techniques, combined treatment modality, and patients' co-morbidity. Perez et al[22] showed major late complications of cervical cancer patients treated with concurrent chemoradiotherapy between 1984 and 1992. The collected data showed

that 2/58 (3.4%) and 1/58 (1.7%) of patients had late grade 2 gastrointestinal and genitourinary toxicities, respectively while 5/58 (8.6%) and 1/58 (1.7%) had late grade 3-4 gastrointestinal and genitourinary toxicities, respectively. The present study showed that 25/95 (26.3%) and 4/95 (4.2%) of patients experienced late grade 2 gastrointestinal and genitourinary toxicities, respectively, which were relatively high especially intestinal side effects. Three in 95 (3.2%) of patients experienced late grade 3-4 gastrointestinal toxicities and none had late grade 3-4 genitourinary toxicity, which were important to the quality of life of the patients.

Conclusion

1. Concurrent weekly carboplatin and radiation therapy yields high response rate with modest disease-free and overall survivals in locally advanced carcinoma of the uterine cervix. The regimen is feasible with minimal toxicities. Further study to compare the efficacy of carboplatin and cisplatin for treatment of cervical cancer patients is warranted.

2. Metastatic failure is a major site of treatment failure especially in more advanced stage. Further study to compare concurrent chemoradiotherapy and adjuvant chemotherapy after concurrent chemoradiotherapy in advanced stage cervical cancer patients should be done.

3. Significant prognostic factors for disease-free survival in multivariate Cox analysis are tumor stage and tumor response, for overall survival are patients' age, tumor stage, and tumor response consistent with other reports. In the present study, it had not been aware of tumor spreading to the pelvic and para-aortic lymph nodes because the whole abdominal CT scan was not done at that time. At present, it has been done in all patients with stage IB2 and above who have normal creatinine clearance to evaluate intra-abdominal diseases.

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What is already known on this topic?

Concurrent chemoradiotherapy is a standard treatment for locally advanced cervical cancer patients. Cisplatin is the most common drug used in this setting but the limitation is renal toxicity and gastrointestinal toxicity when compared with radiation therapy alone. Carboplatin, a platinum compound, was reported to have some activities that might be useful for the treatment of locally advanced cervical cancer patients with radiation therapy. Because of the easy administration, few side effects, and its activities, this drug has been included in the treatment protocol for cervical cancer of Thai Universal Coverage since January 2013.

What this study adds?

This retrospective study with sufficient number of patients and long-term follow-up for survival or late complications evaluation will support the appropriate use of carboplatin in the treatment of patients with cervical cancer when combined with radiation therapy in Thai Universal Coverage Protocol 2013 for cervical cancer.

Potential conflicts of interest

None.

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การศึกษาผลการรักษาผู้ป่วยมะเร็งปากมดลูกระยะลุกลามด้วยรังสีรักษาร่วมกับยาเคมีบำบัด carboplatin สัปดาห์ละครั้ง

สมภพ แสงกิตติไพบูลย์

วัตถุประสงค์: *เพื่อศึกษาผลของการรักษาผู้ป่วยมะเร็งปากมดลูกระยะลุกลามด้วยรังสีรักษาร่วมกับยาเคมีบำบัด carboplatin สัปดาห์ละครั้ง และภาวะแทรกซ้อนที่เกิดขึ้นจากการรักษา*

วัสดุและวิธีการ: *ตั้งแต่เดือนสิงหาคม พ.ศ. 2548 ถึง เดือนกรกฎาคม พ.ศ. 2550 ผู้ป่วยมะเร็งปากมดลูกจำนวนทั้งสิ้น 105 ราย เป็นผู้ป่วยระยะ IIB, III, และ IVA จำนวน 83, 19, และ 3 ราย ตามลำดับ มีช่วงอายุระหว่าง 33 ถึง 79 ปี (อายุเฉลี่ย 51.5 ปี) ให้ยาเคมีบำบัด carboplatin ในขณะที่ฉายรังสีสัปดาห์ละครั้ง*

ผลการศึกษา: *ผู้ป่วยมีผลข้างเคียงระยะเฉียบพลันระหว่างทำการรักษาอยู่ในระดับ 1-2 เป็นส่วนใหญ่ (ผลข้างเคียงระดับ 3 ต่อระบบเม็ดเลือด ร้อยละ 3.8) ภายหลังจบการรักษาแล้วประมาณ 3 เดือน ผู้ป่วย 95 ราย คิดเป็นร้อยละ 90.5 ตรวจไม่พบรอยโรคจากการตรวจภายใน ระยะเวลาที่ผู้ป่วยมาตรวจหลังจากสิ้นสุดการรักษาน้อยที่สุด 3 เดือน นานที่สุด 96 เดือน (เฉลี่ย 76 เดือน) เฉพาะผู้ป่วยที่ตรวจไม่พบรอยโรคภายหลังสิ้นสุดการรักษา พบการกลับเป็นใหม่ทั้งสิ้น 27 ราย โดยพบเฉพาะในช่องเชิงกราน 8 ราย คิดเป็นร้อยละ 8.4 พบการแพร่กระจายของมะเร็งนอกช่องเชิงกราน 17 ราย คิดเป็นร้อยละ 17.9 และการกลับเป็นใหม่ภายในช่องเชิงกรานร่วมกับการแพร่กระจายออกนอกช่องเชิงกราน 2 ราย คิดเป็นร้อยละ 2.1 จากการวิเคราะห์หลายตัวแปรพบว่า ระยะของโรคและการตอบสนองต่อการรักษา มีความสัมพันธ์ต่อการอยู่รอดโดยปราศจากโรคอย่างมีนัยสำคัญทางสถิติ อายุของผู้ป่วย ระยะของโรคและการตอบสนองต่อการรักษา มีความสัมพันธ์ต่อการรอดชีวิตอย่างมีนัยสำคัญทางสถิติ อัตราอยู่รอดโดยปราศจากโรคที่ระยะเวลา 5 ปี ภายหลังเริ่มการรักษาเท่ากับร้อยละ 52.38 (ระยะ IIB ร้อยละ 56.63, ระยะ III ร้อยละ 42.11, และระยะ IVA ร้อยละ 0) และอัตรารอดชีวิตที่ 5 ปี ภายหลังเริ่มรักษาเท่ากับ ร้อยละ 56.19 (ระยะ IIB ร้อยละ 61.45, ระยะ III ร้อยละ 42.11, และระยะ IVA ร้อยละ 0) พบภาวะแทรกซ้อนระยะยาวที่รุนแรงระดับ 3-4 เพียงร้อยละ 3.2 ในระบบทางเดินอาหาร และไม่พบในระบบทางเดินปัสสาวะ*

สรุป: *การให้ยา carboplatin สัปดาห์ละครั้งร่วมกับรังสีรักษาในมะเร็งปากมดลูกระยะลุกลามจากการศึกษานี้มีผลการตอบสนองที่ดีมาก และทำให้มีอัตราการหายจากโรครวมถึงอัตรารอดชีวิตที่ดี ผลข้างเคียงขณะให้การรักษาไม่รุนแรงและภาวะแทรกซ้อนระยะยาวน้อยมาก ส่วนปัจจัยที่มีผลกระทบต่อการพยากรณ์โรคที่ไม่ดี ไม่แตกต่างจากการศึกษาอื่น ๆ*