Survival Rate of Recurrent Cervical Cancer Patients

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Objectives: *To determine the survival rate of recurrent cervical cancer patients and factors influencing survival*
Material and Method: *The subjects were identified from the Gynecologic Oncology Unit tumor registry record. The pathological, clinical data including the follow-up information of recurrent cervical cancer patients who were treated in the Gynecologic Oncology Unit, Bangkok Metropolitan Administration Medical College and Vajira Hospital between 1992 and 2003 were retrospective reviewed.*
Results: *During the study period, 144 recurrent cervical cancer patients were identified. Mean age of the patients was 52 years. The median time from complete primary treatment to disease recurrence was 14.8 months. Seventy-two patients (50%) had previous stage III disease. The most common histopalogy was squamous cell carcinoma (72.9%). Approximately half of the recurrences were local (73 patients or 50.7%) and distal recurrences were encountered in 71 patients or 49.3%. Overall 109 patients received treatment for their recurrences, i.e. radiation alone (55 patients, 38.2%), chemotherapy (31 patients, 21.5%), chemotherapy and radiation (18 patients, 12.5%), surgery (5 patients, 3.5%), and 35 patients (24.3%) received only supportive treatment. Two-year survival rate of the group was 18.5%. Median survival was 8 months (95%CI, 7-10 months). The patients with only local recurrence had a 2-year survival rate of 22.2% compared to 14.6% in those with distant recurrence. (p = 0.245). Two-year survival rate of those who received any kind of treatment was 22.4% compared to 4.0% in those who received only supportive treatment (p = 0.014 and 0.017 in univariable and multivariable analysis respectively).*
Conclusion: *Survival rate of recurrent cervical cancer was low, especially in those who received only supportive treatment.*

Keywords: *Recurrent cervical cancer, Survival rate*

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Cervical cancer is the most common gynecologic cancer in Thailand. The reported incidence of cervical cancer in 1998 was 23.4/100,000 populations[1], which is relatively high in comparison with other developing countries in Southeast Asia[1].

Varieties of treatments have been employed for invasive cervical cancer patients such as surgery, radiation therapy, chemotherapy, or any combination of those. Despite these various available treatments, many patients experience recurrences after primary treatment. The prognosis of recurrent cervical cancer patients are generally poor, with the median survival ranging from 7-12 months[2-5]. Many factors have a prognostic significance in the recurrent setting, thus affect survival time. These factors are for example disease-free interval (DFI), size of recurrent tumors, site of recurrence, performance status of the patients, and treatment modality [5-8].

Most reports on the clinical course of disease and survival of cervical cancer patients come from the countries where cervical cancer is not as common as in Thailand. The authors do not know whether the

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figures from those reports could theoretically refer to the presented patients. Some factors might play a certain role such as the stage distribution of disease or the modality or technique of treatment used in each institution.

The Bangkok Metropolitan Administration Medical College and Vajira Hospital serves as a referral center for gynecologic cancer treatment among the hospitals in the Bangkok Metropolitan Administration Ministry. The number of new cervical cancer patients is approximately 100-140 patients per year[9-11]. Although the standard treatments are available in our institution, many patients, especially those who are in advanced stage, experience recurrences.

The aim of the present study was to evaluate the survival rate of recurrent cervical cancer patients who were treated in our institution. Factor associated with their survival were also studied.

Material and Method

The present study was conducted after the approval of the Ethics Committee of our institution. Recurrent cervical cancer patients who were treated in the gynecologic oncology unit, Bangkok Metropolitan Administration Medical College and Vajira Hospital were included in the present study. The eligibility criteria were patients who had cervical cancer and developed recurrence between January 1992 and December 2003.

The patients were identified from the tumor registry record of the Gynecologic Oncology Unit. Patient's clinical and pathological data were collected from the in-patient and out-patient charts. Data were collected on age, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor histologic cell type and grade, date of primary diagnosis, the type of primary treatment and date of treatment completion, date and sites of recurrences, treatment for recurrence, death date and date of last follow-up visit. Those patients, who were lost to follow-up, were contacted by telephone or by mail. The death status and date of death were also searched from the computerized data at the National Registry Information with permission of the district registrar.

Recurrent cervical cancer was defined as any new lesion evidenced after primary treatment by physical examination or any laboratory findings of the followings: cervical or vaginal stump Pap smear, fine needle aspiration cytology or tissue biopsy from any recurrent sites, or the unequivocal gross tumor masses from the radiologic imaging studies. Disease-free interval (DFI) was calculated from the date of completion of primary treatment to the date of recurrences. Overall survival after recurrence was defined as interval from the date of recurrence to the date of death or last follow-up visit. For patients who were alive at the end of the present study, overall survival data were right-censored at the time of the last evaluation or contact.

Data were analyzed using SPSS statistical software version 11.5 (SPSS, Chicago, IL). Descriptive statistics were used for demographic data and summarized as mean with standard deviation or frequency with percentage. The survival rate was analyzed with the Kaplan-Meier method. Survival data between groups were compared with the Log-rank test for univariable analysis and Cox regression analysis for multivariable analysis. The outcomes were significant only if $p < 0.05$.

Results

During the study period, 150 cervical cancer patients developed disease recurrences after primary treatment. Six patients had incomplete data at primary diagnosis such as primary stage, primary treatment modality or loss to follow, after primary treatment. One hundred and forty four patients met the eligible criteria and were included in the present study.

Mean age of the patients at primary diagnosis was 50.2 ± 11.1 years. Most patients who developed recurrences had primary stage at presentation as stage II or stage III diseases, 37.1% and 50.3% respectively. The most common histopathology was squamous cell carcinoma, which was found in 74.5%. The clinical features of the patients at their primary diagnosis and histopathologic characteristic of the tumors are shown in Table 1.

Mean age of the patients at the time of recurrences was 52.5 ± 11.0 years. Median DFI was 14.8 months (range, 3-143 months). Those who were primarily treated with surgery had the median disease free interval of 18.0 months compared to 14.5 months in those primarily treated by radiotherapy and/or chemotherapy.

Diagnosis of recurrence was made by means of pathological tissue biopsy in 56 patients (38.9%) and imaging studies in 63 patients (43.7%). Only 25 patients of recurrences (17.4%) were evidenced by the obvious clinical findings such as gross tumor masses. Regarding the sites of recurrences, approximately half of the recurrences were localized in the pelvis (73 patients or 50.7%). Isolated distant recurrences were encountered in 60 patients (41.7%). The remaining 11

Table 1. Basic characteristics of recurrent cervical cancer patients at primary diagnosis (n = 144)

Characteristic features	n (percent)
Age at primary diagnosis (years) (n = 144)	
≤ 39	27 (18.7)
>39-49	42 (29.2)
>49-59	45 (31.2)
>59-69	22 (15.3)
>69	8 (5.6)
Histopathologic (n = 141)*	
Squamous cell carcinoma	105 (74.5)
Adenocarcinoma	34 (24.1)
Adenosquamous	2 (1.4)
Tumor grade (n = 126)*	
1	29 (23.0)
2	75 (59.5)
3	22 (17.5)
Primary Stage (n = 143)*	
I	14 (9.8)
II	53 (37.1)
III	72 (50.3)
IV	4 (2.8)
Primary Treatment (n = 144)	
Radiation	105 (72.9)
Radiation and Chemotherapy	24 (16.7)
Surgery	15 (10.4)

* Only patients with available data

Table 2. Characteristics of recurrent cervical cancer patients at recurrence diagnosis (n = 144)

Characteristic features	n (percent)
Age at recurrence (years)	
≤39	14 (9.7)
40-49	44 (30.6)
>49-59	49 (34.0)
>59-69	24 (16.7)
≥69	13 (9.0)
Disease free interval (years)	
≤ 1	58 (40.3)
>1-2	41 (28.5)
>2-3	22 (15.3)
>3-5	8 (5.5)
>5	15 (10.4)
Site of recurrence	
Local	73 (50.7)
Distant	60 (41.7)
Local and Distant	11 (7.6)
Treatment after recurrence	
Radiation	55 (38.2)
Chemotherapy	31 (21.5)
Radiation and combined Chemotherapy	18 (12.5)
Surgery	5 (3.5)
Supportive	35(24.3)

patients (7.6%) had both loco-regional and distant metastases. The median interval from the end of primary treatment to recurrence in patients with localized diseases was shorter than those with distant diseases, 13.7 versus 17.8 months (p = 0.178).

From 144 patients, 109 patients received the following treatments for their recurrent diseases: radiation therapy (55 patients or 38.2%), chemotherapy (31 patients or 21.5%), combination of chemotherapy and radiation therapy (18 patients or 12.5%), surgery (5 patients or 3.5%). Thirty-five patients (24.3%) who had either poor performance status or denied further definite treatment hence received only palliative and supportive care. The clinical characteristics of the patients at the time of recurrences and their treatments are shown in Table 2.

At the time of analysis, 115 patients (79.9%) had died, with the median time from recurrence to death of 6.7 months (1-60 months). Twenty-nine patients (21.1%) were alive with median follow up time of 18.3 months (1-83 months). The median survival after recurrence for all patients was 8 months (95%CI, 7-10 months). The 2-year survival rate was 18.5% (95% confidence interval [CI], 11.7%-25.3%), while 1-year, 3-year and 5-year survival rate were 38.1% (95%CI, 29.8%-46.4%), 14.9% (95%CI, 8.6%-21.2%), and 9.0% (95%CI, 3.10%-15.0%) respectively.

The authors studied some clinical and pathological factors that might associate with the survival of the recurrent cervical cancer patients (Table 3). Only "the treatment" or "no treatment" had significant impact on survival of these recurrent patients in both univariable and multivariable analysis. As expected, the patients who had treatment for their recurrent diseases had significantly higher 2-year survival rate than those who received only supportive treatment, 22.4% versus 4.0% (p = 0.014) (Fig. 1a). The other favorable factors that tended to prolong survival outcome but did not reach statistical significance were early stage at primary diagnoses, squamous cell type, longer DFI, and site of recurrence (Fig. 1b-1e).

Table 3. Association between clinicopathologic factors and survival after recurrence

	Two-year survival [% (95%CI)]	Median survival [months (95%CI)]	p value
Age (years)			
≤50 (n = 64)	14.7 (5.4-24.1)	8 (5-11)	0.277[a]
>50 (n = 80)	21.3 (11.7-31.0)	9 (6-12)	0.374[b]
Histopathology			
Squamous cell carcinoma (n = 105)	23.3 (14.6-32.0)	8 (6-11)	0.129[a]
Non squamous cell carcinoma(n = 36)	3.4 (0-9.8)	9 (7-11)	0.451[b]
Tumor grade (p value compared between grade 1 vs grade 2-3)			
1 (n = 29)	7.5 (0-17.5)	6 (0-17)	0.286[a]
2 (n = 75)	19.4 (9.7-29.1)	8 (5-10)	
3 (n = 22)	22.3 (5.4-39.1)	10 (7-12)	0.823[b]
Primary Stage			
I-II (n = 67)	21.6 (11.2-32.1)	10 (7-13)	0.177[a]
III-IV (n = 76)	15.8 (6.9-24.8)	7 (5-10)	0.503[b]
Primary Treatment (p value compared between surgery vs non-surgery group)			
Surgery (n = 15)	26.7 (4.3-49.1)	9 (2-16)	0.603[a]
Radiation (n = 105)	18.1 (10.0-26.1)	10 (7-12)	
Chemo and Radiation (n = 24)	13.7 (0-28.2)	6 (3-9)	0.374[b]
Disease free interval			
≤2 years (n = 99)	16.5 (8.6-24.5)	8 (6-10)	0.143[a]
>2 years (n = 45)	22.6 (9.7-35.5)	11 (5-18)	0.422[b]
Site of recurrence			
Without distant recurrence (n = 73)	22.2 (12.0-32.3)	10 (6-13)	0.245[a]
With distant recurrence (n = 71)	14.6 (5.6-23.5)	8 (5-10)	0.279[b]
Treatment after recurrence			
No Treatment (n = 35)	4.0 (0-11.6)	5 (2-9)	0.014[a]
Treatment (n = 109)	22.4 (14.1-30.6)	10 (7-12)	0.017[b]

[a] p value from univariable analysis by log rank test
[b] p value from multivariable analysis by Cox regression analysis

Discussion

Cervical cancer is still one of the major health problems in Thailand. Aside from being the most common gynecologic cancer, it is an important cause of gynecologic cancer death in Thai women. Most patients present in the advanced stage of the disease. These patients frequently have unsatisfactory outcomes despite treatment. Treatment failure may present with either persistent disease at the primary treatment or as a recurrent disease afterward. The prognosis of the persistent or recurrent cervical cancer is generally poor.

Most studies of recurrent cervical cancer reported the treatment outcome in patients according to the sites of relapse or the specific type of salvage treatments. A few reports have provided a general overview or a large-scale result of the recurrent cervical cancer. The authors studied the clinical and some pathological characteristics of recurrent cervical cancer patients who were treated in our institution by any type of treatments.

The DFI of recurrent cancer was 14.8 months in this study while other studies reported it at 18 months[6,13]. This difference may lie on the different population group. More than half of the presented recurrent patients were in advanced stage at primary

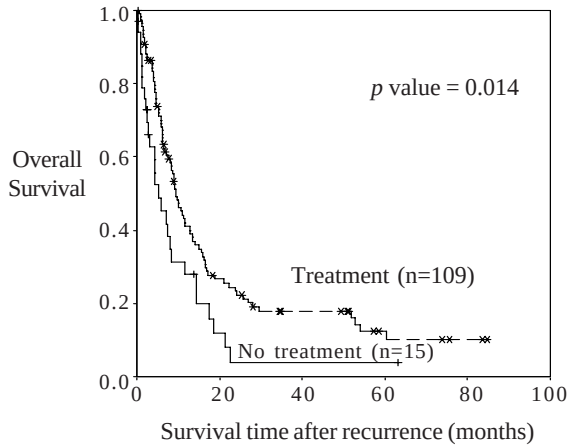

Fig. 1a Comparison between treatment and no treatment group

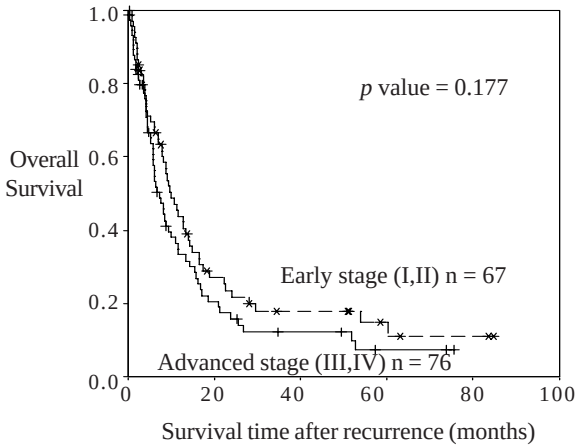

Fig. 1b Comparison between early stage (I,II) and advanced (III,IV)

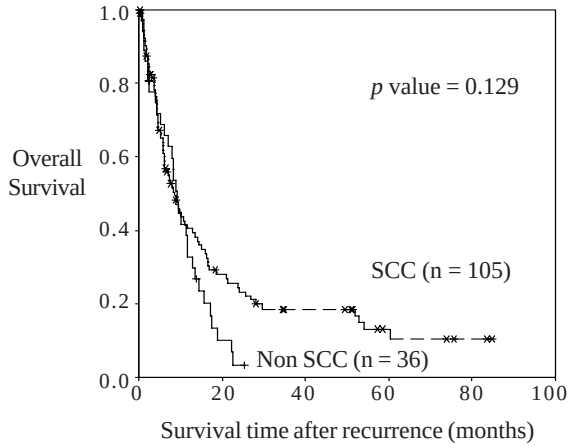

Fig. 1c Comparison between squamous cell Carcinoma (SCC) and non squamous cell carcinoma

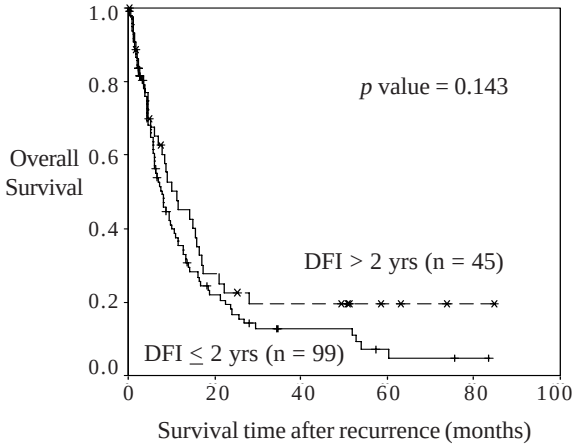

Fig. 1d Comparison between patients with disease free interval ≤ 2 years and > 2 years

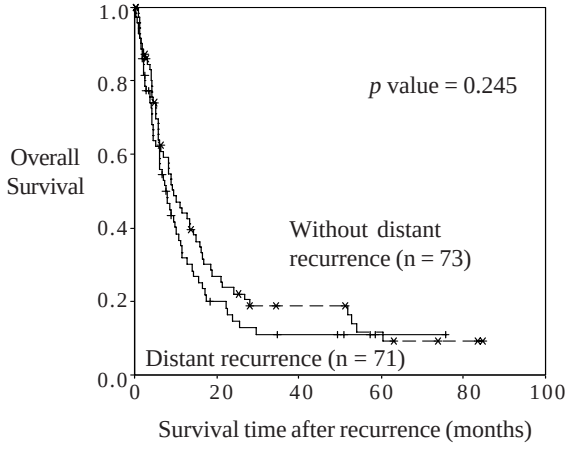

Fig. 1e Comparison between patients with and without distant recurrence

Fig. 1 Survival of recurrent cervical cancer patients factored according to treatment (Fig. 1a), stage group (Fig. 1b), histopathology (Fig. 1c), disease-free interval (Fig. 1d), and site of recurrence (Fig. 1e)

diagnosis, while other studies had fewer patients in this stage group[5,12].

In the present study, approximately half of recurrences localized in the pelvis while the other half were found in association with distant lesions outside the pelvis. These figures were similar to the findings of Duyn et al[5] who found their recurrent diseases to be local in 49% and distant in 51% and may lie in a similar proportion of patients who were treated with radiation therapy or surgery. Radiation treatment would expectedly reduce the number of local recurrences; as seen in the study of Hong et al[13] who focused on the recurrent cervical cancer after radiation, 39.5% had only local recurrence while 60.5% had distant lesions. The other reports of recurrent cervical cancer after radical hysterectomy show the local recurrent diseases could be as high as 52-74%[14-16].

The survival outcomes of recurrent cervical cancer patients in the present study were quite low with the median survival of 8 months, the 2-year and 5-year survival rate of 18.5% and 9% respectively. These figures were comparable with those from other studies, which reported the median survival from 7-12 months[2-5], and the 5-year survival of approximately 10%[13,17-19].

Many prognostic factors were found to be associated with the survival of recurrent cervical cancer patients. The favorable factors are the early stage of the primary disease[8,20], long DFI[5,20,21], small tumor size[7,8,22,23], localized disease in the pelvis[8,18,20,24] and histology of squamous cell carcinoma[12,24]. However, the significance of these prognostic factors was not harmonious in all studies. For example, Duyn et al[5] found that only DFI and treatment modalities were the significant prognostic factors for survival after recurrence while site of recurrence, tumor size and histologic cell type were not. Their median disease-free survival of 18 months (range, 3-50 months), which was longer than that of 14.8 months in the present study might contribute to the better median survival, 12 months (95%CI;10-14 months) in Duyn's study versus 8 months (95%CI; 7-10 months) in the present study.

The present study showed that treatment modality for recurrence was significantly associated with survival. Those who received any kind of treatments had better survival than those who received only palliative care. However, decision on "to treat" or "not to treat" was influenced by many factors such as clinical characteristics of the tumors, previous treatment, and especially the performance status of the patients. Generally, the performance status had significant association with survival in recurrent cancer patients[20]. The patients who would undergo treatment such as chemotherapy or surgery or definite radiation therapy should be in a favorable condition to tolerate the treatment. It was therefore impossible to draw conclusions in this aspect either to treat or not, despite the fact that statistically significant difference in survival was found.

Although, the authors found that some factors such as early stage at primary treatment, squamous cell type, longer DFI, and tumor confined in the pelvis tended to have a more favorable outcome, the authors could not demonstrate any significant impact on survival of the patients in this recurrent setting. The small sample size in the present study might have limited the statistical power to detect any significant impact on survival of each factor.

In conclusion, the prognosis of the recurrent cervical cancer is poor. Future studies with more patients should be carried out to find the independent prognostic factors in these recurrent cancer patients.

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อัตราการรอดชีวิตของผู้ป่วยมะเร็งปากมดลูกที่กลับเป็นซ้ำ

สุขเกษม พูลเกิด, สุรวุฒิ ลีฬหะกร, สุมนมาลย์ มนัสศิริวิทยา, ศิริวรรณ ตั้งจิตรกมล, เถาวลัย ถาวรามร, พาชื่น ศึกวัฒนา, กมล ภัทราดูลย์

วัตถุประสงค์: *ศึกษาอัตราการรอดชีวิตและปัจจัยที่มีผลต่อการอยู่รอดของผู้ป่วยมะเร็งปากมดลูกที่มีการกลับเป็นซ้ำ*

วัสดุและวิธีการ: *ทำการศึกษาข้อมูลย้อนหลังทางพยาธิวิทยา ทางคลินิก และการติดตามการรักษาของผู้ป่วยมะเร็งปากมดลูกที่กลับเป็นซ้ำที่เข้ารับการรักษาที่หน่วยมะเร็งนรีเวช วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ตั้งแต่ปี พ.ศ. 2536 ถึง พ.ศ. 2547*

ผลการศึกษา: *ในช่วงเวลาที่ศึกษาผู้ป่วยมะเร็งปากมดลูกที่กลับเป็นซ้ำทั้งสิ้น 144 คน ผู้ป่วยมีอายุเฉลี่ย 52 ปี มัธยฐานของระยะเวลาตั้งแต่รักษาครั้งแรกสมบูรณ์จนถึงมีการกลับเป็นซ้ำเป็น 14.8 เดือน ผู้ป่วยส่วนใหญ่เป็นมะเร็งปากมดลูกระยะ III, 72 ราย (ร้อยละ 50.0) ผลทางพยาธิวิทยาส่วนใหญ่เป็น squamous cell carcinoma (ร้อยละ 72.9) ประมาณครึ่งหนึ่งของการกลับเป็นซ้ำเป็นแบบเฉพาะบริเวณอุ้งเชิงกราน (73 ราย หรือร้อยละ 50.7) ขณะที่อีกครึ่งหนึ่งเป็นแบบที่มีการกลับเป็นซ้ำแบบที่มีการกระจายร่วมด้วย 71 ราย หรือ ร้อยละ 49.3 ผู้ป่วย 109 ราย ได้รับการรักษาหลังมีการกลับเป็นซ้ำ แบ่งเป็น รังสีรักษา 55 ราย (ร้อยละ 38.2), เคมีบำบัด 31 ราย (ร้อยละ 21.5), เคมีบำบัด ร่วมกับ รังสีรักษา 18 ราย (ร้อยละ 12.5), ผ่าตัดรักษา 5 ราย (ร้อยละ 3.5), ขณะที่อีก 35 ราย (ร้อยละ 24.3) มีเพียงการดูแลแบบประคับประคอง อัตราการรอดชีวิต 2 ปี ของผู้ป่วยทั้งหมดเป็น ร้อยละ 18.5 โดยมีมัธยฐานของการอยู่รอด 8 เดือน (95%CI, 7-10 เดือน) ผู้ป่วยที่มีการกลับเป็นซ้ำเฉพาะบริเวณอุ้งเชิงกรานมีอัตราการรอดชีวิตที่ 2 ปี เป็นร้อยละ 22.2 เปรียบเทียบกับ ร้อยละ14.6 ในผู้ป่วยที่มีการกลับเป็นซ้ำแบบกระจาย (p = 0.245) อัตราการรอดชีวิตที่ 2 ปี ของผู้ป่วยที่ได้รับการรักษาเป็นร้อยละ 22.4 เปรียบเทียบกับร้อยละ 4.0 ในผู้ป่วยที่ได้รับการรักษาแบบประคับประคอง (p = 0.014 และ 0.017 การวิเคราะห์แบบตัวแปรเดียวและหลายตัวแปรตามลำดับ)*

สรุป: *อัตราการรอดชีวิตของผู้ป่วยมะเร็งปากมดลูกที่กลับเป็นซ้ำนั้นต่ำ โดยเฉพาะในผู้ป่วยที่ได้รับการรักษาแบบประคับประคอง*