Survival Rate of Recurrent Cervical Carcinoma

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Objective: *To determine the survival rate of recurrent cervical carcinoma and clinical variables influencing survival.*
Material and Method: *Eighty eligible patients with recurrent cervical carcinoma were identified from the tumor registry record of gynecologic oncology division, Rajavithi Hospital between January 2004-December 2010. The pathological and clinical data were retrospective reviewed. Numerous clinical variables were analyzed including age, histopathology, primary staging, site of recurrence, complete treatment time to recurrence and initial treatment after recurrence.*
Results: *Among the 80 patients, mean age of the patients were 48.11 years (SD = 9.62). Median time from complete primary treatment to recurrence was 11.7 months. Fifty four cases (67.5%) were squamous cell carcinoma and the others were non-squamous cell carcinoma. Seventy two cases (90.1%) were previously treated with radiation therapy. Sixty six cases (82.5%) had only pelvic recurrence without distant disease. Median follow-up period of the present study was 14.2 months. Two-year survival rate of the group was 33.7%, median survival was 15.4 months. Two years survival rate of the patients received surgery, radiation, chemotherapy and supportive only as initial treatment after recurrence were 43.6%, 53.3%, 18.1% and 25.0%, respectively. Whereas median survival of the patients received surgery, radiation, chemotherapy and supportive only as initial treatment after recurrence were 20.7, 24.5, 11.4 and 10.8 months respectively. Site of recurrent and type of initial treatment modality after recurrence had statistic significance in multivariable analysis (p = 0.001 and p = 0.026, respectively).*
Conclusion: *Survival rate of recurrent cervical carcinoma was poor. Surgery and radiation as initial treatment modality after recurrence may have survival benefit in well selected patients.*

Keywords: *Recurrent cervical cancer, Survival rate*

J Med Assoc Thai 2012; 95 (Suppl. 3): S125-S130
Full text. e-Journal: *http://www.jmat.mat.or.th*

Cervical cancer is the most common malignancy in Thai women. The reported incidence in 1998 was 23.4 per 100,000 populations[1]. In 2003, The International Agency for Research on Cancer (IARC) reported that there were 6,234 new cervical cancer cases in Thailand each year and 2,620 deaths or there were 7 Thai women who died of cervical cancer everyday. Although cervical cancer was good response to primary treatment, recurrence of the disease was a poor prognosis. The two-year survival rate of 18.5% was reported[2]. Clinical aspects of recurrent disease showed 65 % were pelvic side wall recurrence and 35% were central recurrence[3]. Central recurrence is the only situation that the disease can be cured by pelvic exenteration. Generally, median survival rate for recurrent cervical cancer was 5.49-13 months[4-6]. A lot of chemotherapeutic regimens have been trialed for treatment, platinum based chemotherapy seem to have some activity to the disease. Toxicity of chemotherapy has to be concerned for the impact to quality of life in a short median survival disease. Palliative care is an option to be discussed with all patients and their relatives.

Rajavithi Hospital is a referral center among hospitals in the Ministry of Public Health. The context of Rajavithi Hospital and the present patients may be different from others. In 2007 the authors had 2,726 visits of cervical cancer at the out-patient department. Recurrent cervical cancer is a common and difficult problem for both patients and care givers due to its grave prognosis. The treatment modality after recurrence of disease was different from patient to patient due to various clinical factors and patient's desire.

The present study aimed to determine the survival rate of recurrent cervical carcinoma patients in Rajavithi Hospital.

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Material and Method

The present study was conducted after the approval of the ethics committee of Rajavithi Hospital. Data was retrieved from the database of tumor registry record of Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Rajavithi Hospital, during 2004-2010. Variables collected were age, date of primary diagnosis, histological type, International Federation of Gynecology and Obstetrics (FIGO) staging, the type of primary treatment, date of treatment completion, date and site of recurrence, the type of treatment after recurrence and date of death or date of known to be alive. Date of death was collected from the tumor registry record and the population death registry of ministry of The Bureau of Registration Administration, Ministry of Interior. Recurrent cervical cancer was diagnosed if any evidence of a new lesion was detected after completion of primary treatment at least 6 months. Evidence of recurrence was made by physical examination, laboratory findings *e.g.*, cervical or vaginal stump Pap smear, fine needle aspiration cytology, tissue biopsy from any recurrent sites or the unequivocal gross tumor masses from the radiologic imaging studies.

Overall survival rate after recurrence was defined as interval from the date of recurrence to the date of death or date of last known to be alive. Demographic data was reported using descriptive statistics. The survival data was analyzed using the Kaplan-Meier method. Log-rank test was employed to compare survival curves between groups. p-value of less than 0.05 was considered statistical significance. All statistical data analyses were performed using SPSS 17.0 (SPSS, Chicago, IL).

Results

During 2004-2010, eighty-one recurrent cervical carcinoma patients were diagnosed and registered to the tumor registry. One patient was excluded because of incomplete data at primary diagnosis. Eighty patients met the eligible criteria and were included in the present study. Squamous cell carcinoma was the most common histopathologic type (67.5%) (Table 1). As high as 53% of recurrent patients had primary stage II disease. Seventy-two cases (90.1%) had previous radiation for primary treatment of cervical carcinoma. Median complete treatment time to recurrence was 11.7 months. The most common site of recurrence was 82.5% for the loco-regional recurrence without distant recurrence. The type of initial treatment after recurrence was mainly surgery (48.8%). Regarding surgery, pelvic exenteration was the first choice. Nevertheless ten out of thirty-nine cases were aborted intra-operatively due to pelvic side wall metastasis or proved nodal metastasis.

Table 1. Baseline characteristics of 80 patients with recurrent cervical carcinoma

Characteristics (n=80)	n	%
Age at recurrence diagnosis (years)		
Mean ± SD	48.11 ± 9.62	
< 40	12	15.0
40-49	34	42.5
50-59	23	28.8
≥ 60	11	13.8
Histopathology at primary diagnosis		
Squamous carcinoma	54	67.5
Non-squamous carcinoma	26	32.5
Primary stage		
I	21	26.3
II	42	52.5
III	17	21.3
Previous treatment		
Surgery	8	10.0
Radiation	65	81.3
Surgery+Radiation	7	8.8
Complete treatment time to recurrence		
≤ 1 year	41	51.3
1-2 year	15	18.8
2-5 year	18	22.5
> 5 year	6	7.5
Site of recurrence		
Without distant recurrence	66	82.5
With distant recurrence	14	17.5
Initial treatment after recurrence		
Chemotherapy	30	37.5
Surgery	39	48.8

The median follow-up period of the present study was 14.2 months. Sixty three patients (78.8%) died. The median survival rate was 15.4 months (95%CI: 10.4, 20.4). The overall 2-year, 3-year and 5-year survival rate were 37.7%, 23.9% and 17.3%, respectively. Only site of recurrence and type of initial treatment after recurrence had statistically significant effect on survival ($p = 0.001$ and 0.026, respectively, Table 2). Regarding type of initial treatment, radiation, surgery, supportive treatment and chemotherapy had two-year survival rate of 53.3%, 43.6%, 25.0% and 18.1% respectively. Among patients receiving chemotherapy, the chemo-responsed patients had a higher two-year survival than chemo-resisted patients (80.0% vs. 14.3%, $p < 0.001$). The other clinical variables such as age, histopathologic type,

Table 2. Analysis of prognostic factors

Factors	n	Two years survival (%)	Median survival Months (95%CI)	p-value
Overall survival	80	33.7	15.4 (10.4, 20.4)	-
Age (years)				0.209
< 40	12	25.0	13.2 (3.8, 22.7)	
40-49	34	41.0	13.5 (1.9, 25.1)	
50-59	23	26.1	16.3 (8.8, 23.8)	
≥ 60	11	43.6	15.4 (12.1, 18.7)	
Histopathology				0.874
Squamous carcinoma	54	34.1	14.2 (8.7, 19.7)	
Non-squamous carcinoma	26	33.1	16.3 (6.2, 26.4)	
Primary stage				0.482
I	21	34.8	13.2 (5.8, 20.6)	
II	42	35.8	20.4 (11.7, 29.1)	
III	17	29.4	13.2 (6.2, 20.2)	
Site of recurrence				0.001*
Without distant recurrence	66	38.6	18.3 (12.2, 24.5)	
With distant recurrence	14	0.00	10.0 (5.3, 14.7)	
Primary initial treatment				0.809
Surgery / surgery+radiation	15	42.3	18.3 (8.2, 28.5)	
Radiation	65	32.3	13.5 (8.0, 19.1)	
Complete treatment time to recurrence				0.748
≤ 1 year	41	28.5	13.2 (10.3, 16.1)	
1-2 year	15	30.5	16.3 (10.0, 22.6)	
2-5 year	18	50.5	24.5 (3.9, 45.2)	
> 5 year	6	33.3	15.4 (8.2, 22.6)	
Initial treatment after recurrence				0.026*
Chemotherapy	30	18.1	11.4 (9.8, 12.9)	
Surgery	39	43.6	20.7 (15.6, 25.8)	
Radiation	5	53.3	24.5 (8.5, 40.6)	
Supportive only	6	25.0	10.9 (2.7, 19.0)	
Regimens				0.076
Cisplatin	16	18.8	11.7 (8.0, 15.4)	
Cisplatin+5FU	15	26.7	11.1 (9.3, 12.9)	
Carboplatin + paclitaxel + others	9	36.5	20.7 (18.2, 23.3)	
Response of chemo therapy				<0.001*
CR + PR	8	80.0	-	
Non response	29	14.3	10.8 (9.0, 12.7)	
Type of surgery				0.023*
Complete surgery	29	48.3	22.5 (6.2, 38.8)	
Abort	10	30.0	12.6 (0.0, 25.8)	

* Significant at $p < 0.05$, CR = complete response, PR = partial response

primary stage, primary initial treatment, complete treatment time to recurrence and regimen of chemotherapy had no statistically significant effect on survival.

Discussion

The standard treatment for early stage cervical cancer is either surgery or radiation. The treatment for advanced stage disease is primarily radiation therapy with or without radiosensitizers. Outcome of primary treatment is generally fair with the actuarial 5-year disease-free survival rate being 79.5%, 70.0%, 59.4%, 46.1%, 32.3%, 7.8% and 23.1% for Stage IB, IIA, IIB, IIIA, IIIB, IVA and IVB respectively. The actuarial 5-year overall survival rate was 86.3%, 81.1%, 73.0%, 50.3%, 47.8%, 7.8% and 30.8% for Stage IB, IIA, IIB,

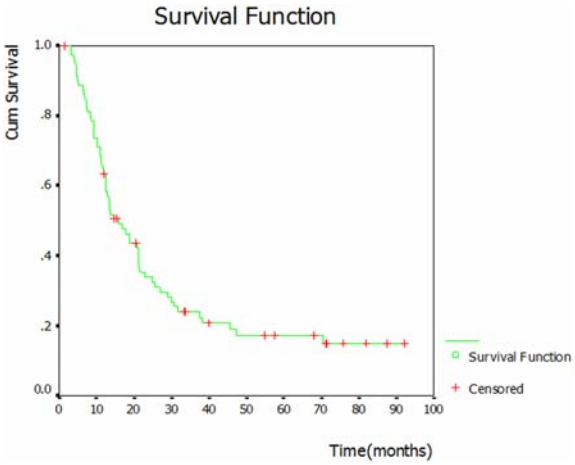

Fig. 1 Survival of recurrent cervical cancer patients

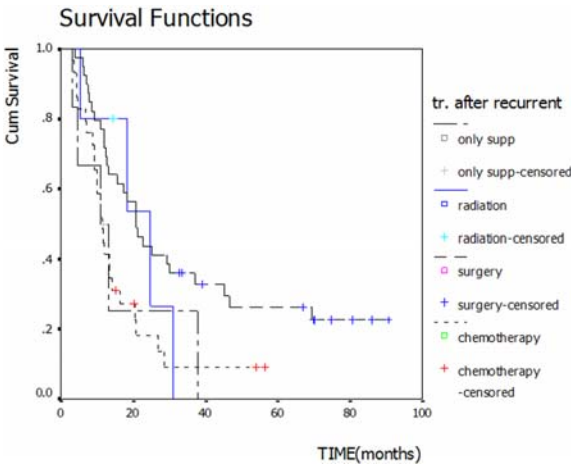

Fig. 2 Survival of recurrent cervical cancer patients fractured according to treatment

IIIA, IIIB, IVA, and IVB respectively[7]. However, the patients who did not respond to radiation (*i.e.*, having persistent or progression of disease during treatment) and the patients who had a recurrence disease after treatment completion had a poor prognosis, with 18.5% two-year survival rate[2]. Most studies reported the median survival time among recurrent cervical cancer of 5.49-13 months[4-6]. However, the present study showed a little higher survival rate. This may be due to the inclusion criteria of the present study that was limited to the recurrence cases with at least 6 months disease free interval whereas most studies included the persistent cases. Another possible reason is a small number of patients were referred to Rajavithi Hospital for pelvic exenteration, early pelvic recurrence and good performance status.

Site of recurrence is a significant clinical variable affecting survival. Patients with distant recurrence often had pelvic recurrence as well and might have lesions at several organs *e.g.*, liver, bone and lungs resulting in poor survival[3]. Among patients without distant recurrence (*i.e.*, with only pelvic recurrence), those who were radiation naive can further receive radiation which resulted in a good outcome. For patients with previous radiation but could go for pelvic exenteration, outcome after surgery was also good. In general, patients without distant recurrence have a higher two-year survival rate than those with distant recurrence.

Choice of initial treatment after recurrence depends on several factors: site of lesion, previous treatment, performance status and patient desire. Recurrent patients that are suitable for radiation were those with previous surgery (*i.e.*, early stage) and had pelvic recurrence without distant recurrence. After surgery, recurrent cervical carcinoma patients including pelvic recurrence and distant recurrence had a five-year survival rate of 35%[8]. Therefore, patients who had radiation therapy as initial treatment after recurrence had a favorable survival. Before receiving surgery as further treatment, patients usually had extensive preoperative evaluation to exclude extra-pelvic disease. That is, patients had early pelvic recurrence or central recurrence which normally had good prognosis. Furthermore, these patients must have good enough performance status for major surgery. Therefore, survival outcome among patients receiving surgery is better than those receiving chemotherapy. Even though patients receiving surgery had a higher two-year survival (43.6%) compared to chemotherapy and supportive group (18.1% and 25.0%), the two-year survival rate of 43.6% was rather low. The five-year survival was 54-65.8% for pelvic exenteration in recurrent cervical cancer[9,10]. Moreover the median survival of the surgery group was 12.6 months (0.0-25.8) reflecting that some cases had peri-operative mortality. In general the peri-operative mortality rate was 4.8%[10]. Thus, the patients' selection criteria and also adequate patients and relatives counseling is extremely crucial for a good treatment result.

Among patients receiving chemotherapy, the chemo-responsed patients had a higher two-year survival rate than chemo-resisted patients (80.0% vs. 14.3%, $p < 0.001$). There was no difference among chemotherapeutic regimens. All regimens were platinum based. Single agent seemed reasonable for recurrence cervical carcinoma with less toxicity. Based on the

authors data, patients receiving chemotherapy for recurrence cervical carcinoma should be closely observed for efficacy and toxicity. To avoid toxicity, chemotherapy that is not efficacious and decrease the patient's quality of life will be withdrawn promptly.

In conclusion, the prognosis of the recurrence cervical carcinoma is poor. Surgery is a treatment with a better survival only for well selected candidates (*i.e.*, central recurrence). Radiation therapy is a reasonable treatment option for pelvic recurrence and radiation naive patients. Chemotherapy has limited survival outcome and should be administered cautiously to avoid the toxicity. Palliative care should be seriously offered to the patients and relatives regardless of the intervention applied to the patients.

Acknowledgment

The author wish to thank Kanya Boonthongtho for data analysis and interpretation and Assist. Prof. Dr. Chulaluk Kolmontri who reviewed this manuscript before submission.

Potential conflicts of interest

None.

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อัตราการอยู่รอดของผู้ป่วยมะเร็งปากมดลูกระยะกลับเป็นซ้ำในโรงพยาบาลราชวิถี

คเณศร์ ธนกำธร

***วัตถุประสงค์**: เพื่อหาอัตราการอยู่รอด ที่ 2 ปี ของผู้ป่วยมะเร็งปากมดลูกระยะกลับเป็นซ้ำในโรงพยาบาลราชวิถี*

***วัสดุและวิธีการ**: การศึกษาแบบย้อนหลัง โดยเก็บรวบรวมเวชระเบียนของผู้ป่วยมะเร็งปากมดลูกระยะกลับเป็นซ้ำในโรงพยาบาลราชวิถี ตั้งแต่เดือนมกราคม พ.ศ. 2547 ถึง เดือน ธันวาคม พ.ศ. 2553 และข้อมูลการตายจากทะเบียนการแจ้งตาย กระทรวงมหาดไทย แปลผลข้อมูลด้วยสถิติเชิงพรรณนา ทำการเปรียบเทียบปัจจัยที่มีผลต่อการรอดชีพโดยใช้สถิติ Log-rank test*

***ผลการศึกษา**: ในช่วงเวลาที่ทำการศึกษามีผู้ป่วยมะเร็งปากมดลูกระยะกลับเป็นซ้ำทั้งหมด 80 ราย อายุเฉลี่ย 48 ปี ระยะเวลามัธยฐานนับจากสิ้นสุดการรักษามะเร็งปากมดลูกจนถึงวันที่ได้รับการวินิจฉัยการกลับเป็นซ้ำเท่ากับ 11.7 เดือน ผู้ป่วย 54 ราย (67.5%) เป็นมะเร็งปากมดลูกชนิดเซลล์สเควมัส และผู้ป่วยที่เหลือเป็นชนิดที่ไม่ใช่เซลล์สเควมัส ผู้ป่วย 72 ราย (90.1%) เคยได้รับการฉายรังสีก่อนมีการกลับเป็นซ้ำ ผู้ป่วย 66 ราย (82.5%) เป็นการกลับเป็นซ้ำเฉพาะที่ เชิงกรานโดยไม่มีการแพร่กระจายออกนอกเชิงกราน ระยะเวลามัธยฐานของการติดตามผู้ป่วยเท่ากับ 14.2 เดือน อัตราการอยู่รอดที่ 2 ปี เท่ากับ 37.7% ระยะเวลามัธยฐานของการรอดชีพเท่ากับ 15.4 เดือน อัตราการอยู่รอดที่ 2 ปี ของผู้ป่วยมะเร็งปากมดลูกระยะกลับเป็นซ้ำที่ได้รับการรักษาต่อโดยการผ่าตัด รังสีรักษา ยาเคมีบำบัดและการดูแลแบบประคับประคองเท่ากับ 43.6%, 53.3%, 16.1% และ 25.0% ตามลำดับ โดยมีระยะเวลามัธยฐานของการรอดชีพเท่ากับ 20.7, 24.5, 11.4 และ 10.8 เดือนตามลำดับ ตำแหน่งที่กลับเป็นซ้ำ และวิธีการรักษาหลังจากการกลับเป็นซ้ำเป็นปัจจัยที่มีผลต่ออัตราการรอดชีพที่ 2 ปีอย่างมีนัยสำคัญทางสถิติ $p = 0.001$ และ $p = 0.026$ ตามลำดับ*

***สรุป**: ผู้ป่วยมะเร็งปากมดลูกระยะกลับเป็นซ้ำมีพยากรณ์โรคที่ไม่ดี มีอัตราการอยู่รอดที่ 2 ปีเท่ากับ 37.7%*