Radiotherapy for Locoregional Recurrent Cervix Cancer after Surgery

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=Abstract=

Purpose: The role of radiotherapy in the management of patients with locoregional recurrent cervix cancer after radical surgery were retrospectively analyzed.

Methods and materials: Twenty-eight patients treated with radiotherapy for locoregional recurrence after primary surgery for carcinoma of the cervix between 1989 and 1993 were analyzed. The median follow-up of survivors was 15 months (ranged 7-43 months). Eight patients had their disease confined to the vagina and 19 patients(68%) had pelvic mass as part of their locoregional recurrent disease. Within 24 months after the initial surgery, 82% of recurrences manifested themselves. All patients had whole pelvic irradiation with or without intracavitary radiotherapy(ICR).

Results: Complete response(CR) was achieved in 18 patients(64%). Five of eighteen patients(28%) with initial CR developed second locoregional recurrence. Response to radiotherapy correlated strongly with tumor volume, site of recurrence and total radiation dose. The overall 2 year survival rate was 43% and the disease free survival was 31%. Survival rate was significantly influenced by the factors of interval from operation to recurrence, size and site of recurrent tumor, radiation dose, response of radiotherapy, lymph node status as initial presentation. The principal cause of death was lung metastasis(36%).

Conclusion: Radiotherapy is an excellent modality for control of locoregional recurrent cervix cancer. To improve local control and survival rate, whole pelvic external radiotherapy in addition to ICR with more than 75.0Gy at the depth of 1.0cm from vaginal mucosa is needed and frequent follow up and early detection of recurrence is suggested as well.

Key Words : Radiotherapy, Cervix cancer, Recurrent

INTRODUCTION

It is generally recognized that the initial treatment of cervix cancer offers by far the best chance for cure. Radical hysterectomy with pelvic node dissection is a well accepted mode of therapy for early cervix cancer. But 10-40% of the cases may anticipate treatment failures depending on the prognostic factors[1,2]. The prognosis of recurrent cervix cancer is so poor that 5-year survival rate is ranged 0 to 30%[1,3-7].

To exclude any cases of residual disease left behind at the time of radical surgery, I defined recurrence as tumor regrowth in completely resected cases in 3 months of surgery.

Numerous reports in the literature dealing with recurrent cervix cancer include patients with all stages of cervical malignancies who were treated primarily by radiotherapy. This article attemps to analyze the experience gained from management of 28 cases of recurrent cervix cancer fol-

lowing radical hysterectomy and pelvic node dissection. This paper analyzes in detail the results of radiotherapy with respect to local tumor control and overall survival rate. The importance of aggressive radiotherapy in the management of recurrent cervix cancer will be discussed.

METHODS AND MATERIALS

From August, 1989 to August, 1993, twenty eight patients were accepted by the Department of Therapeutic Radiology, Gil Hospital, for radiotherapy of a locoregional recurrence following radical surgery of the primary cervix cancer. Patients with concomitant distant metastasis were excluded from the study. The median follow up period of survivors was 15 months, ranged 7-43 months. The patient's age ranged from 33 to 72 years old(median 59 years). At the time of initial presentation, there were 2 patients with FIGO stage CIS, 7 with stage I, 12 with stage II, and 5 with stage III, and other two patients had no informations available. Ten patients showed lymph node involvement. Seventeen patients should have been considered candidates for elective postoperative radiotherapy because of positive pelvic node, large tumor size, and/or stromal invasion. Twenty six had primary squamous cell carcinoma and two had adenocarcinoma. Radical hysterectomy was performed in 22 patients and total abdominal hysterectomy in remaining 6 patients. Ten patients received 2 or 3 cycles of preoperative chemotherapy and two patients received postoperative chemotherapy with 5-fluorouracil (5-FU) and Cis-platinum. The recurrence was histologically and clinically confirmed in all patients.

The disease free interval after primary surgery ranged from 4 to 168 months with median of 9 months. Twenty patients(71%) showed detectable locoregional recurrence within a year of surgery and twenty three patients(82%) had recurrent tumor by 2 years(Table 1). The site of recurrences are shown in Table 2. The vagina and pelvic wall was the most common site of recurrence.

Table 1. Interval from Operation to Recurrence

Interval(year)	No. of pts	Cumulative %
≤0.5	11	39
0.5-1	9	71
1-2	3	82
2-3	3	93
>3	2	

Table 2. Site of Recurrence Vs Response to RT

Site of recur.	No. pts	CR	Second recur.
Vagina	8	8	1*
Vagina+Pelvis	12	6	3
Pelvis	7	3	1
Suburethra	1	1	-

* She achieved CR after reirradiation.

All patients had external radiotherapy with 6 MV X-ray using two or four portals given in 5 fractions per week with 1.8Gy per fraction. After external radiotherapy fifteen patients received high dose rate intracavitary radiotherapy with Co^{60} using vaginal colpostat or vaginal cylinder in 2 fractions per week with 3.0 to 3.75Gy per fraction. The total dose at the depth of 1.0cm from vaginal mucosa ranged from 40.0 to 88.4Gy. Five patients also received three cycles of chemotherapy with 5-FU and Cis-platinum after radiotherapy for recurrence.

The response to treatment was evaluated by pelvic examination and imaging studies. The response recorded here was the best response achieved by the patients during the follow-up period.

Survival was counted from the date of starting radiotherapy and estimated by the Kaplan-Meier method, and statistical survival differences were tested with a long-rank test and Wilcoxon rank test.

RESULLTS

1. Response

Complete response was achieved in 64%, 18 or 28 patients. All 8 patients with recurrence limited to vagina achieved CR and remained disease free until last follow up(Table 2). Six out of twelve patients with recurrence extending from vagina to pelvic wall, and three out of seven patients with a recurrence limited to the pelvic wall showed a complete response after radiotherapy, and among nine cases who achieved CR, only five(56%) patients showed persistent tumor control.

Thirteen out of fourteen(93%) patients who received radiotherapy more than 75.0Gy at the depth of 1.0cm from vaginal mucosa using external and intracavitary radiotherapy had complete response in contrast to 38% CR in cases who received less than 75.0Gy. Those who received radiotherapy between 60.0Gy and 75.0Gy achieved 46% CR rate, and 33% only in whom received less than 60.0Gy. Among 15 patients treated with ICR, thirteen(87%) showed complete response and comparing to 31% CR in those who did not receive ICR.

2. Survival

The 2 year survival after treatment for locoregional recurrence was 43%, and 2 year disease free survival was 31%(Fig. 1). Survival was not influenced by primary tumor size, stage and type of initial treatment but it was affected by the status of lymph node involvement(Table 3). In the patients who had more than 4 lymph nodes involvement, all died within 14 months. Two patients with adenocarcinoma died of disease and all four squamous cell carcinoma, large cell non-keratinizing survived with no evidence of disease(NED).

Among 7 patients who had angioinvasion or lymphatic emboli, four of them expired. But the survival difference was not so statistically significant whether lymphatic emboli or angioinvasion was present or not.

The interval from initial treatment to recurrence affected survival(Fig. 2). Recurrence within the first 6 months was associated with 100% mortality within two years of treatment for recurrence and recurrences after 6 months was

Table 3. Survival by Initial Parameter

	No. pts	2 YRS(%)	P value
Stage			
CIS	2	100	
I	7	42	
II	12	56	
III	5	40	
unknown	2		0.34
Primary size			
5cm >	9	88	
5cm <	14	40	0.16
unknown	5		
Lymph node involvement			
0	10	80	
1-3	6	67	
>4	4	0	0.001
unknown	8		
Chemotherapy			
yes	12	44	
No	16	45	0.71

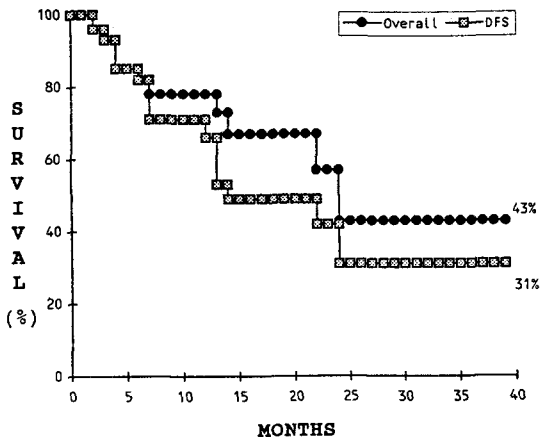

Fig. 1. The 2 year survival after treatment for locoregional recurrence was 43%, and 2 year disease free survival was 31%.

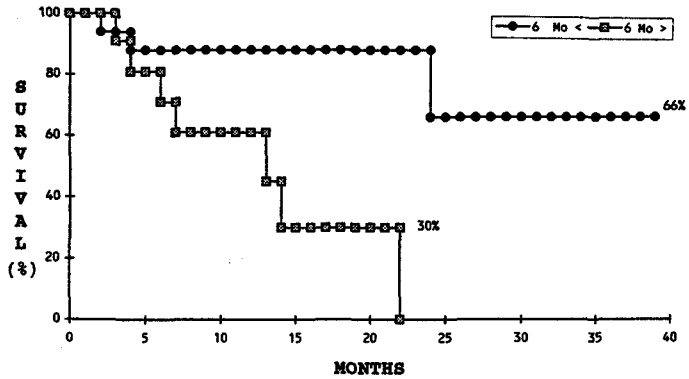

Fig. 2. Recurrence within the first 6 months was associated with 100% mortality within two years of treatment and recurrences after 6 months was with 66% of 2 year survival rate(p=0.002)

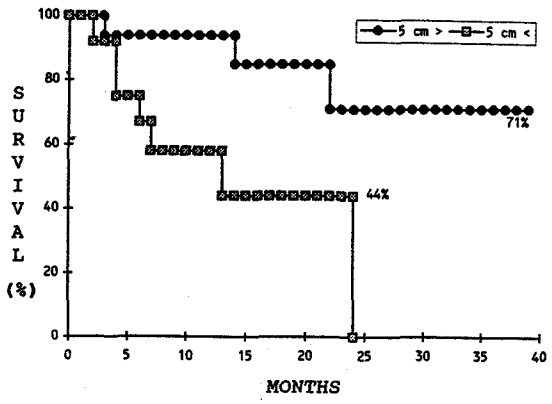

Fig. 3. By pelvic examination and imaging studies, we could evaluate the size of recurrent tumors. Sixteen who had tumors of 5cm or less showed 71% of 2 year survival rate and all of twelve patients who had tumors more than 5cm expired within 2 years(p=0.008)

Table 4. Cause of Death

Cause	No. pts
Renal failure	3
Tumor cachexia	1
Lung metastasis	4*
Liver metastasis	1*
unknown	2

* one patient suffered from both of them.

Table 5. Complication

Complication	No. pts	Months*
Leg edema	2	5, 13**
Hematuria	1	13**
Suprapubic edema	1	8
Total	3(11%)	

* ; time of appearing complication
**; one patient suffered from both of them.
All of them received more than 80Gy.

with 66% of 2 year survival rate.

Sixteen who had tumors of 5cm or less showed 71% of 2 year survival rate and all twelve patients who had tumors of more than 5cm expired within 2 years(Fig. 3).

According to the site of recurrence, better result was obtained in those cases where the recurrent tumor appeared to be confined to the vagina-100% of 2 year survival rate, and worse result was obtained in those patients with recurrence in the vagina and pelvis-20% of it(Fig. 4). Hence, all 8 patients who had hydronephrosis at the time of recurrence could not survive 2 years.

The patients who received more than 75.0Gy showed better results with 66% of 2 year survival rate than the patients who received less than 75.0Gy with 32% of it(Fig. 5). Among 9 patients who received less than 60.0Gy, six(67%) patients died within 7 months of treatment. Fifteen patients who received ICR did well with 67% of

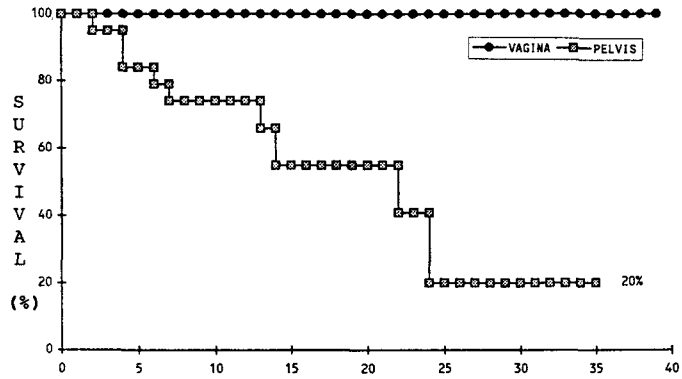

Fig. 4. According to the site of recurrence, better result was obtained in those cases where the recurrent tumor appeared to be confined to the vagina-100% of 2 year survival rate, and worse result was obtained in those patients with recurrence in the vagina and pelvis-20%of it(p=0.02)

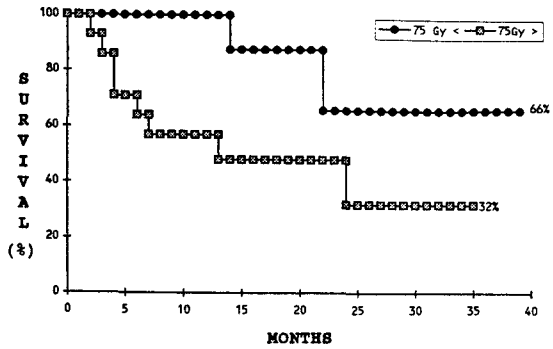

Fig. 5. The patients who received more than 75.0Gy showed better results with 66% of 2 year survival rate than the patients who received less than 75.0Gy with 32 % of it(p=0.01). Among 9 patients who received less than 60.0Gy, six(67%) patients died within 7 months of treatment.

2 year survival rate and thirteen patients who didn't receive ICR showed 29% of it(Fig. 6).

The patients with complete response had 2 year survival of 83% and patients who had less than CR did very poorly with 15% of 1 year survival rate and no survivor at 2 years(Fig. 7).

Five patients were treated with adjuvant chemotherapy for recurrence before radiotherapy. Two patients showed partial response (PR) and others, no response. Those who showed PR to chemotherapy did not so well because they expired within 6 months.

Five of eighteen patients(28%) who showed complete response(CR) developed a second locoregional recurrence(Table 2). Excluding 2 patients whose cause of death we could not know, 4 patients(16%) suffered from distant metastasis of lung and liver within 7 months after treatment. The principal cause of death was lung metastasis(Table 4).

The complication rate was 11%, 3 out of 28 patients(Table 5). All of them received more than 80Gy.

DISCUSSION

Approximately 12-42% of women with invasive cervical cancer will develop recurrent disease after primary surgery or radiation therapy[8-12]. Gary reported the prognosis of 272 patients with untreated recurrent cancer of the cervix; only one patient survived 5 years or more(0.4%)[13]. Treatment options for these patients will depend on the mode of initial therapy and the site of recurrence. Pelvic recurrence after radical hysterectomy should initially be treated with radiation therapy. Five year survival rates of 20-25 % can be achieved with individualized combina-

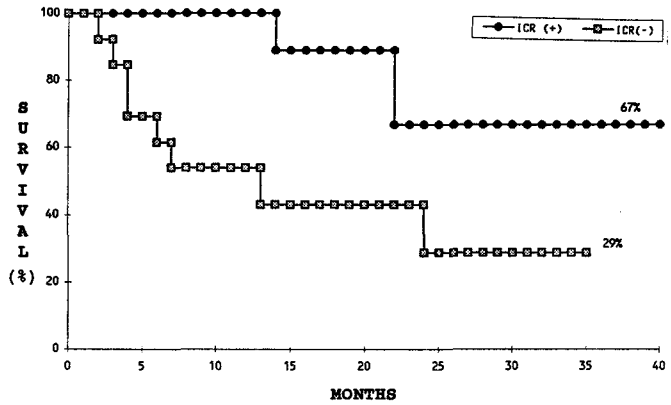

Fig. 6. Fifteen patients who received ICR did well with 67% of 2 year survival rate and thirteen patients who didn't receive ICR showed 29% of it(p=0.004).

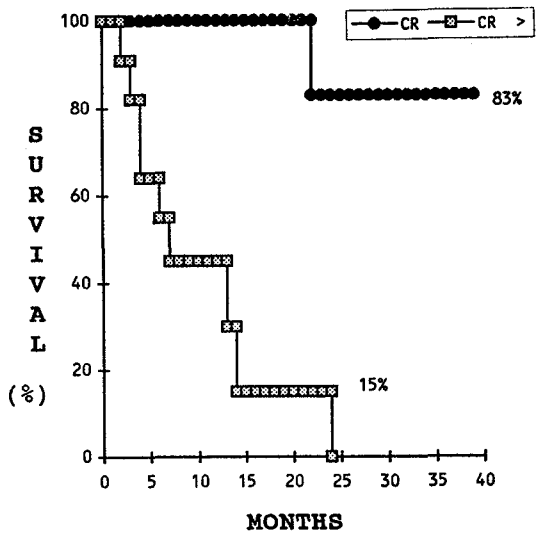

Fig. 7. The patients with complete response had 2 year survival of 83% and patients who had less than CR did very poorly with 15 % of 1 year survival rate and no survivor at 2 years(p=0.0001).

tion of external beam and brachytherapy[5-7]. This paper demonstrates that radiotherapy for locoregional recurrent carcinoma of the cervix achieved 61% CR and 2 year survival rate and 2 year disease fredd survival was 43% and 31%, respectively.

Survival was affected by the status of lymph node involvement and cell type at initial presentation and it was not affected by the stage and type of previous treatment. As other series, a poorer prognosis in patients with pelvic node metastasis or adenocarcinoma was also observed[14-18]. All the patients who had more than 4 lymph nodes involvement or who had adenocarcinoma died of disease. In the presence of angioinvasion and lymphatic emboli, the 2 year survival rate was 24% and in the absence of those factors, it was 40%(p=0.28). But we didn't have enough cases to conclude whether adenocarcinoma or presence of angioinvasion and lymphatic emboli affected survival significantly or not.

Early recurrence probably reflects extreme aggressiveness of the tumor or poor host response, or both. In this study, the patients who had recurrences within the first 6 months did poorly with 2 year survival of 0% compared with 66% of those after 6 months. Krebs and associates noted that 80% of their patients who had disease recurrence within 6 months of surgery died within the first year and patients with recurrences after 6 months had a 50% 1 year survival rate[19,20].

The site of recurrence appeared to be an important prognostic indicator. Recurrences limited to the vaina generally allow for early detection and therefore smaller than those at other sites[3].

So the best results were obtained in patients with recurrence limited to vagina and all of them achieved persistent local control. The presence of recurrent tumor fixed to the pelvic wall carries a much worse prognosis[21-23]. We observed persistent local control in only 5 out of 19 patients with pelvic wall mass recurrence. Pelvic recurrence may reflect incomplete tumor resection in a series of surgically treated patients. Viable tumor cells might stay behind in which cases the individual prognosis is a function of specific tumor aggressivity and host response[1]. From the experience of pelvic exenterative surgery, despite of careful patients selection, approximately 50% of patients explored for exenteration will be found to have extrapelvic disease or unresectable pelvic mass[24]. The frequent association of recurrent tumor in the vagina with the recurrent tumor in the pelvis in this study warrants the use of whole pelvic irradiation even in those cases where tumor is apparantly limited to the vagina. In the case of whole pelvic irradiation is not suitable, an examination under anestesia(EUA) provides an opportunity to confirm the presence of disease recurrence and to establish the extent of recurrence. If pelvic side wall involve is questioned at EUA, CT or MRI may help in prediction adequate radiation field[2].

Tumor volume is considered to be an important factors in response to radiotherapy and survival. Radiotherapy is likely to control small sized tumors and subclinical disease better than bulky tumor masses. So, it must be emphasized that frequent and adequate follow-up is necessary because early detection of tumor recurrence allows better chance of tumor control and survival[25-27].

In all cases in which radiation therapy could not be given in a curative doses, the prognosis was poor(Fig. 5, 6). Which means high dose radiotherapy is necessary to control tumors and to achieve better survival. It may be argued that the incidence of complication could be higher in higher radiation dose, but 11% of complication rate might be acceptable(Table 5) considering the poor survival rate in the case of avoiding adequate treatment[28]. I recommend more than 75.0Gy radiotherapy at the depth of 1.0cm from vaginal mucosa using ICR to control recurrent cervix cancer because higher CR rate was closely associated with higher radiation dose group and it was linked to persistent tumor control and longer survival. It might be the result of the difficulties in delivering high dose radiotherapy to pelvic side wall that patients who had pelvic disease showed poor results in response and survival.

Much effort should be done in the development of technique of delivering high dose to pelvic side wall with reducing complication.

The response of tumor had an impact on persistent local control and survival(Fig. 7). As size and site of recurrent tumor affected survival rate, early diagnosis with adequate follow up be emphasized. And tumor response was closely related to delivered dose, acceptable high dose is recommended during radiotherapy. So, aggressive treatment of locoregionally recurrent cervix cancer is needed for CR in hopes of achieving at least long term locoregional control and survival.

Chemotherapy has been used and numerous studies of single agents and of combination chemotherapy have been reported, however mostly with disappointing results[29-32]. Cis-platinum is presently the most effective single agent in advanced and recurrent cervix carcinoma, producing a response rate of about 30% and median duration of response of 6 months[29,30,33-35]. In this current study, we used 3 cycles of 5-fluorouracil and Cis-platinum for 5 patients, but no additional benefit was obtained by adding chemotherapy. But we couldn't make any conclusion for chemotherapy due to the small cases.

Pelvic exenterative surgery is another modality in the treatment of locoregional recurrence of the cervix. Because of the difficultise often encountered in assesing tumor volume and substantially reducing morbidity and mortality rate achieved in recent years, many gynecologic

oncologists recommed exenteration even patients who appear to have small lesions. But patients suitable for this surgery are highly selected only when recurrence is centrally located and limited to the vagina[2,36].

In summary, radiation therapy is the treatment of choice for patients with recurrence who did not have prior radiation therapy. The complete response rate was 64% and 2 year survival rate was 43%. The site and size of recurrent tumor, interval to recurrence from operation, size, radiation dose, response of radiotherapy and lymph node status as initial presentation were statistically significant prognostic factors. So, early detection with adequate follow up is most important of all, and from my experience, I recommend whole pelvic radiotherapy with sufficient high dose combined with ICR even in the case that recurrence seems to be limited within the vagina. The importance of achieving CR by radiation cannot be overemphasized, not only because it improves the quality of life, but also because patients with CR displayed significantly better survival rates.

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=국문초록=

수술후 국소 재발된 자궁경부암의 방사선 치료

중앙 길 병원 치료방사선과

양 미 경

1989년에서 1993년까지 중앙 길 병원에서, 자궁경부암으로 수술후 국소재발하여 방사선치료를 시행한 28명의 환자를 대상으로, 치료성적, 예후인자 및 치료후 실패양상 등을 분석하였다. 8명은 질부에 국한된 재발을 보였으며, 나머지 19명은 골반부위를 침윤하는 양상을 보였다. 수술후 24개월 이내에 82%가 재발을 보였으며, 완전관해율은 64%였고, 그 중 28%가 후속적 재발을 보였다. 모든 환자가 전 골반부위에 방사선 치료를 받았으며, 그 중 15명이 강내치료를 겸하였다. 치료에 대한 관해율은 재발된 암의 크기와 재발부위 그리고, 방사선 조사양과 관계있었다. 2년 생존율은 43%였고, 무병생존율은 31%였다. 원발병소의 크기, 초기치료등은 생존율에 영향을 끼치지 못하였으나, 임파선 전이 여부와 세포형 등은 유의한 영향을 미쳤다. 6개월 이내에 재발한 경우, 모두 2년 이내에 사망하였으며, 그 후 재발을 보인 경우는, 2년 생존율 66%였다. 재발된 암의 크기가 5cm미만이었던 16명의 환자가가 71%의 2년 생존율을 보인 반면, 5cm이상이었던 12명의 경우는 모두 2년이내 사망하였다. 질부에만 재발한 환자의 2년 생존율은 100%였고, 골반부까지 침윤한 경우는 20%였다. 질점막으로부터 1.0cm 깊이에 75Gy이상의 방사선 치료를 시행받은 경우가, 그 이하를 시행받은 경우보다 좋은 성적을 보였다. 강내치료를 시행받은 15명의 경우, 2년 생존율이 67%였고, 그렇지 않은 경우는 29%였다. 한편, 60.0Gy이하를 시행받은 9명 중 6명이 7개월 이내에 사망하였다. 완전관해를 보인 환자의 2년 생존율을 83%였고, 그렇지 않은 경우는 1년 생존율이 15%였다. 주 사망 원인은 폐전이었다. 좋은 관해율과 높은 생존율은 직접 관계가 있으며, 이를 위하여, 강내치료를 겸한 외부방사선치료가 충분한 조사양으로 시행되어야 하며, 근치적 수술후 국소 재발된 자궁경부암의 경우, 생존율을 높이며 삶의 질을 높인다는 점에서 조기발견과 적극적인 방사선 치료가 절대적으로 필요함을 시사하였다.