Treatment Result of Postoperative Radiotherapy of Carcinoma of the Uterine Cervix

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The early carcinoma of the uterine cervix may be treated by either radical surgery or radical radiotherapy according to the patient's characteristics, and the survival is high with either treatment. But, because of the size of the lesion, metastasis to lymph nodes, and vascular space invasion by tumor have all been shown to influence recurrence and survival, postoperative radiotherapy may be considered as their histopathologic finding after radical surgery. However, there are still debates on the increasing survival rates with postoperative radiotherapy.

Two hundreds and three patients with carcinoma of the uterine cervix who were treated with postoperative radiotherapy from February 1979 to September 1982 in the Department of Therapeutic Radiology, Seoul National University were analyzed and following results were obtained. 3-year actuarial survival rate and 3-year disease free sruvival rate were 83.4% and 73.4% respectively and 3-year actuarial survival rates by stages were 90.7% for IB, 69.6% for IIA, and 85.2% for IIB. 3-year disease free survival rates by stage IB, IIA, IIB were 79.8%, 67.8%, 68.3% respectively.

The overall failure rate was 25.1% (51/203); local recurrence rate was 8.4%, distant metastasis rate was 14.3% and simultaneous local recurrence and distant metastasis was 2.4%. Failure rates by stages were 19.8% (18/19) for IB, 29.1% (16/55) for IIA and 29.8% (17/57) for IIB.

The overall acute complication rate was 57.6%; tolerable cases was 50.2% and severe cases was 7.4%. Late complication rate was 7.9% and the major late complication were intestinal obstruction, aggravated urinary symptom, radiation cystitis in order of frequency.

Key Words: Carcinoma of the uterine cervix, Postoperative radiotherapy, Actuarial survival, Failure rate, Complication

INTRODUCTION

It is the current fashion to declare that the death from carcinoma of the uterine cervix could entirely be prevented by the application of knowledge and skills that we already now have, so death rate from carcinoma of the uterine cervix has fallen dramatically over the past 30 years, because of the steady trend towards the earlier diagnosis and improvements in the methods of therapy.[1] However, in Korea, the carcinoma of the uterine cervix is the most common cause of death due to malignancy in

women and constitues 12.8% of all reported malignancies annually and 28% of all reported malignancies in female.[2]

Stage IB and IIA cervical carcinoma could be treated by either radical radiotherapy or radical surgery, Since the survival of this cancer is high with either treatment, other factors are needed to be considered when choosing a therapy. Since the size of the lesion, metastasis to lymph nodes, and vascular space invasion by the tumor have all been shown to influence survival,[3-6] the postoperative radiotherapy may be considered on their histopathologic finding after radical surgery. However, there are still debates on the increasing survival rates with postoperative radiotherapy in carcinoma of the uterine cervix.

We preliminarily report the incidence and pattern of the recurrence, survival rate by each stage, and complications of 203 cases of carcinoma of the uterine cervix which were treated by postoperative radiotherapy in Seoul National University Hospital last 4 years.

MATERIALS AND METHODS

This is a retrospective analysis of 203 patients with carcinoma of the uterine cervix who received postoperative radiotherapy between February 1979 and September 1982 in the Department of Therapeutic Radiology, Seoul National University. The minimum follow-up period was 36 months. Seventy-three patients were lost to follow-up and one hundred thirty patient were available for this analysis. Nineteen patients were lost to follow-up after recur. Patients with following conditions were excluded from this analysis

1) referred for postoperative radiotherapy after 6 months following surgery 2) gross residual disease 3) recurrent cases 4) stages over IIIA.

The indications for postoperative radiotherapy were determinated after discussion with radiation oncologist and gynecologist. They are as followings.

1. The primary lesion is over 4cm in diameter.
2. Microscopic tumor infiltration in vaginal resection margin.
3. Lymph node metastasis.
4. Tumor infiltration over middle one-third of cervix stroma.
5. Angio- or lymphangio-invasion.
6. Incomplete surgery, which means that lymph node dissection was not applied since preoperative diagnosis was carcinoma in situ, or microinvasion.

Ages ranged from 20 years to 60 years and of them, 90 patients (44.3%) are 40 years, 55 patients (27.1%) are 50 years. (Table 1) Patients were clinically staged according to FIGO (International Federation of Gynecology and Obstetrics) staging system as shown in Table 2. Most patients are stage IB.

Most patients received radical hysterectomy and pelvic lymphadenectomy and patients who were diagnosed CIS or microinvasion receiced total abdominal hysterectomy. (Table 3) The distribution of histologic type is presented in Table 4. We analyzed according to Wentz-Reagan subclassification based on neoplastic cell type which was adopted by the WHO, but the patients who referred from other hospital was analyzed according to traditional Broder grading system and slide review was not available. So two classification was shown in this study.

Patients were treated with 10 MV x-ray of linear accelerator (Clinac®18, Varian) or x-ray of Cobalt-60 teletherapy unit (Picker). Most of the boost therapy patients were treated with external irradiation which were delevered five days a week by AP PA parallel opposing field or by Box-technique. The total dose ranged from 4,500 cGy to 5,000 cGy in 5 to 6 weeks

Table 1. Carcinoma in Uterine Cervix: Distribution by Age

Age	No. of Pts
21 — 30	9
31 — 40	37
41 — 50	90
51 — 60	55
61 — 70	12

Table 2. Carcinoma in Uterine Cervix: Distribution by Stage (FIGO)

Stage	No. of Pts	Percent
Ib	91	44.8
IIa	55	27.1
IIb	57	28.1
Total	203	100

Table 3. Carcinoma in Uterine Cervix: Summary of Surgical Procedures

Surgical procedure	No. of Pts
Radical Hysterectomy with Lymph node Dissection	174
Total Abdominal Hysterectomy	29

with daily dose of 180 cGy. Patients who had tumor infiltration in vaginal resection margin received boost therapy with Cesium applications.

Survival rates were calculated by the life-table method of Kaplan-Meier and the statistical comparison of survival rates was performed by the Log-Rank test.

RESULTS

1. Treatment Failure

Local recurrence and distant metastasis were noted in 51 patients out of the 203 patients (25.1%), and 17 patients (8.4%) showed local recurrence (Table 5). Local recurrence and distant metastasis by stages are presented in Table 6.

The time of recurrence is presented Table 7. 84.3% of the failure occurred within 3 years and most of all occurred within 5 years. The distribution of sites in 22 patients with local recurrence is shown in Table 8.

Distant metastasis was noted in 34 patients and the frequent sites are supraclavicular lymph node, lung and bone.(Table 9) As the indication for the postoperative radiotherapy is based on risk factors, the failure rate by combination of risk factors is shown in Table 10. Postoperative radiotherapy without risk factors was done when outside hospital referred patients on supicion of tumor infiltration on operation field inspite of no tumor infiltration in the pathologic finding. It was noted that

Table 4. Carcinoma in Uterine Cervix: Histologic Distribution

Histologic type	No. of Pts	Percent
Squamous cell carcinoma	188	92.6
Large non-keratinizing	68	33.5
Large keratinizing	65	32.0
Small cell	10	4.9
Well differentiated	2	0.9
Moderately differentiated	6	3
Poorly differentiated	6	3
Not specified	31	15.3
Adenocarcinoma	11	5.4
Adenosquamous carcinoma	4	2.0

Table 5. Carcinoma in Uterine Cervix: Pattern of Failure

Failure Site	No. of Pts	Percent
LR*	17	8.4
LR + DM**	5	2.4
DM	29	14.3
Total	51/203	25.1

* Loco-regional
** Distant metastasis

Table 6. Carcinoma in Urterine Cervix: Failure Pattern by Stage

	LR	LR+DM	DM	Total (%)
Ib	6	1	11	18/91 (19.8)
IIa	4	2	10	16/55 (29.1)
IIb	7	2	8	17/57 (29.8)

Table 7. Carcinoma in Uterine Cervix: Time to Failure

Time	No. of Pts	Cumulative Percent
6M	11	21.6
1Y	11	43.4
2Y	14	70.6
3Y	7	84.3
4Y	6	96.1
5Y	1	98
7Y	1	100

Table 8. Carcinoma in Uterine Cervix: Sites of Locoregional Failure in 22 Patients

Site	No. of Pts
Stump	14
Parametrium	10
Vagina	1

Table 9. Carcinoma in Uterine Cervix: Sites of Distant Metastasis in 34 Patients

Site	No. of Pts
Supraclavicular LN*	11
Lung	11
Bone	9
Paraaortic LN*	5
Pleura	4
Bladder	2
Kidney	1
Urethra	1
Liver	1
Peritoneum	1

* Lymph node

the more numbers of risk factor are associated with, the higher rate of failure, but the trend was not significant statistically. ($p>0.05$)

2. Complication

The complication occurred during the radiotherapy is considered as acute complication, while the complication occurred after the completion of radiotherapy is considered as the late complication. Acute complication was noted in 117 patients (57.6%). 102 patients (50.2%) had tolerable complication as nausea, vomiting, and mild diarrhea which were easily controlled by conservative methods or drugs. 15 patients (7.4%) had severe complication such as diarrhea which disrupted the treatment, or required fluid therapy. (Table 11) Rec-

Table 10. Carcinoma in Uterine Cervix: Failure Rate by Risk Factors

Risk Factor	N	No. of Pts	Percent
0	47	8	17
1	80	16	20
2	43	16	37.2
3	22	10	45.5
4	1	1	100

Table 11. Carcinoma in Uterine Cervix: Acute Complication

Complication	No. of Pts	Percent
Tolerable	102	50.2
Severe	15	7.4
Wet Desquamation	6	3.0
Rectal Bleeding	4	2.0
Diarrhea	3	1.5
U-V fisutula	1	0.5
Hematuria	1	0.5
Total	117	57.6

Table 12. Carcinoma in Uterine Cervix: Late Complication

Complication	No. of Pts
Intestinal Obstruction	4
Aggravated urinary Sx.	3
Radiation Cystitis	2
Radiation Colitis	1
V-V Fistula	1
Pubic Swelling	2
Cuff Telangiectasis	2
Deep Vein Thrombosis	1
Total	16 (7.9%)

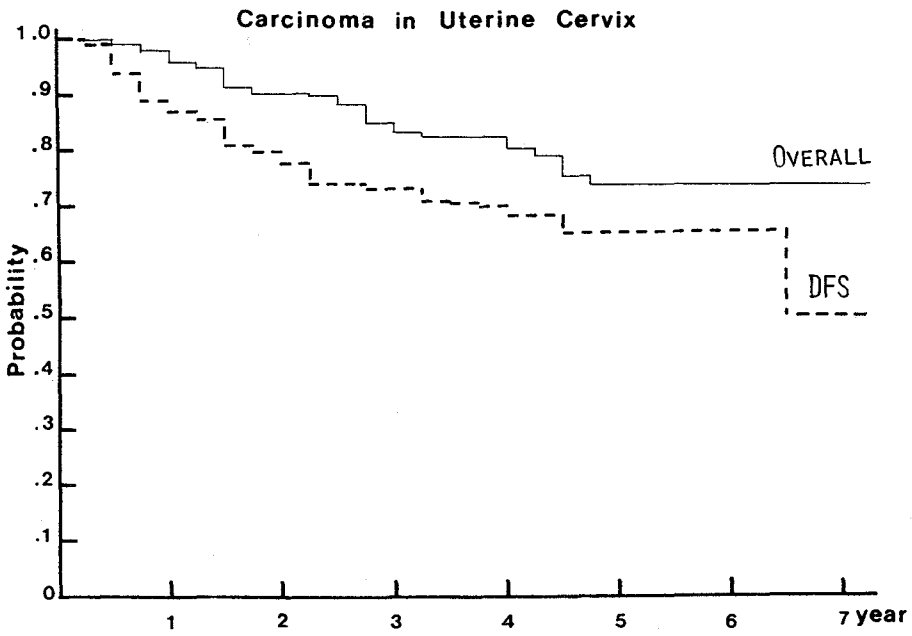

Fig. 1. Actuarial Overall & Disease Free Survival

tal bleeding and U-V fistula during the radiotherapy seemed to be related with a certain condition after radical surgery.

16 patients (7.9%) showed late complications such as intestinal obstruction, aggravation of urinary symptom and radiation cystitis in the order to decreasing frequencies. (Table 12)

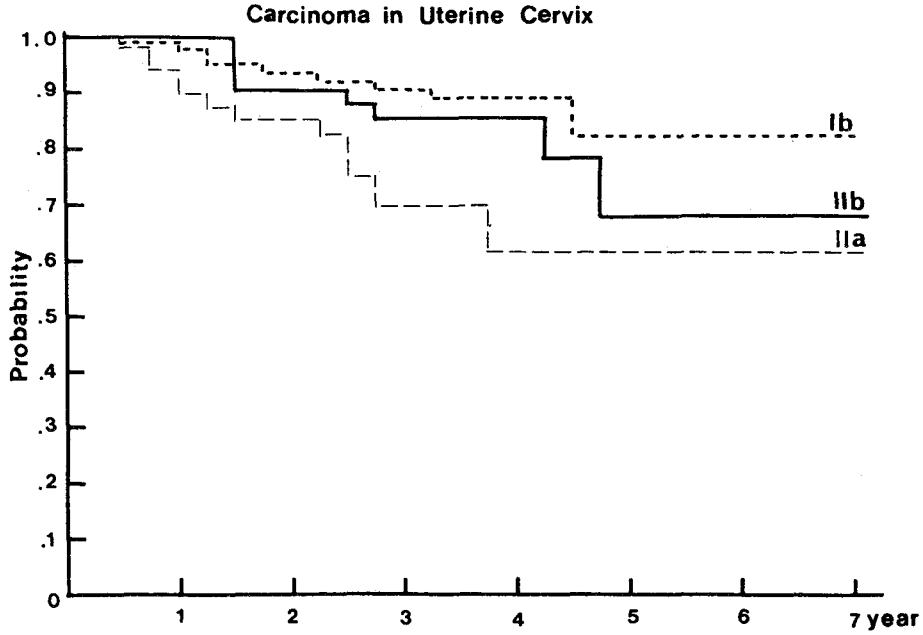

Fig. 2. Actuarial Survial by Stage

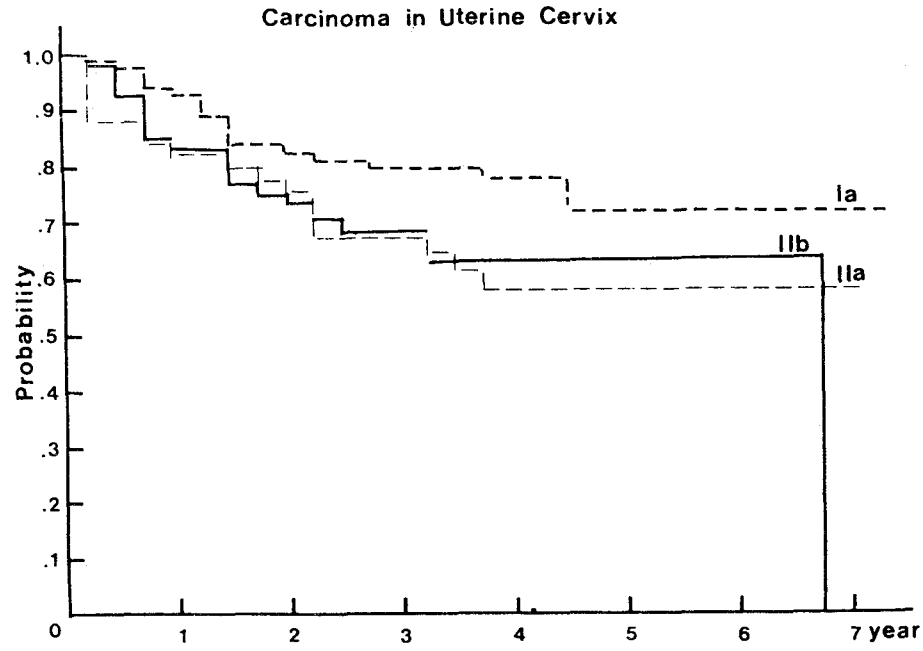

Fig. 3. Disease Free Survival by Stage

Table 13. Carcinoma in Uterine Cervix: Upstaging After Operation

Site	No. of Pts
Corpus	20
Parametrium	4
Ovary	2
Salpinx	2
Bladder	1
Mesoappendix	1

3. Survival

The actuarial survival rate at 3 years was 83.4% and the disease free survival rate was 73.4%. (Fig. 1) Analysis by the stages is shown in Figure 2 and 3. The actuarial survival rate at 3 years was 90.7% for stage IB, 69.6% for stage IIA and 85.2% for stage IIB. ($p<0.001$). Patients with stage IIB survived longer than the patients with stage IIA, but there were more patients in the stage IIb lost to follow-up after recurrence.

Disease free survival rate at 3 years for stage IB, IIA, IIB were 79.8%, 67.8% and 68.3% respectively. (Fig. 3, $p<0.001$)

DISCUSSION

The radical surgery of cervical carcinoma was started by Clark, Reis, and Wertheim in the late 1880's. Operative morbidity and mortality were high, but there were no other treatment available at that time. By the 1920's, radiotherapy had essentially replaced surgery due to its effectiveness and low morbidity. Meigs revised the surgical approach in the invasive cervical carcinoma in mid 1940s.

The choice of definite radiotherapy or radical surgery for stage IB and IIA carcinoma of the cervix remains controversial. And the preference to the one procedure over the other depends on the institution, the gynecologist, or the radiation oncologist involved, besides the general condition of the patient and characteristics of the lesions. An operation has been preferred in young women by some surgeons with desire to preserve the ovarian function.[8,9] Other reasons why choosing the radical surgery over the radiation are concomittent inflammatory disease of the bowel, previous radiation therapy for other diseases, presence of pelvic inflammatory disease or an adnexal neoplasm along with the malignancy, and of course the preference of the patient and physicians. It is generally agreed that either surgery or radiation therapy is equally effective in the treatment of stages IB and IIA carcinoma of the cervix. Numerous noncontrolled studies support the merits of either modality.[10-15]

Newton[16] and Roddick and Greenlaw[17] reported comparable survival and pelvic recurrences in patients with stages IB and IIA carcinoma of the cervix treated with a radical hysterectomy or radiotherapy alone.

In addition to the stage, size of the tumor[3] in some instances the histologic types of the lesion, and vascular invasion,[4,18,19] there are other factors that affect the prognosis of the cervical carcinoma patients.

According to Nahhas and associates, 88 cervical carcinoma patients in the stages IB and IIA showed that the depth of stromal invasion was associated with the greater incidence of metastatic lymph node.

Piver and Chung[3] reported 89% 5-year survival rate in the stage IB for the lesions up to 3 cm in diameter and only 66% survival for the tumor of 4 to 5 cm in diameter in a large series of women treated by radical hysterectomy. They also found the correlation of pelvic node metastasis with the size of the tumors; 18% up to 1 cm, 22% with 2 to 3 cm lesion, and 35% with tumors of 4 to 5 cm.

Fuller and colleagues[6] reported decreasing survival in stage IB and IIA cervical carcinoma treated with radical hysterectoimy as the number of metastatic lymph node increased.

Perez et al.[20] reported that the incidences of positive pelvic node were 11 to 18% for stage I and 27 to 45% for stage II and preoperative radiotherapy decreased positive pelvic node by 0 to 9% for stage 1 and 0 to 21% for stage II. But the preoperative radiotherapy lengthened the duration of treatment and was unnecessary to the patient without risk factors.

Chung and associates[18] reported 98 patients with stage IB and IIA who were treated with radical surgery alone or postoperative raiotherapy following surgery. They concluded that postoperative radiotherapy prevent local recurrences (40% vs 6%) and improve 2 year tumor free survival (94% vs 55%).

On the other hand, Kielbinska and associates[21] in a long term follow-up of 792 women treated by radiotherapy and 789 women treated with hysterectomy and radiotherapy for stage I, found no difference in survival, general health, incidence of recurrent carcinoma, or appearance of second malignancies. Fuller and associates[25] reported similar result with Keilbinska. They concluded that postoperative ratiotherapy had no improvement in

survival.

Morrow[22] reported that pelvic recurrence in patients with positive pelvic node who were treated with radiotherapy was 50% compared to 84% without radiotherapy.

In our study, the rate of local recurrence and distant metastasis by stages were 19.8% for IB, 29.1% for IIA and 29.8% for IIB. Perez and associates[23] reported the rate of local recurrence and distant metastasis by stages were 14.2% for IB, 28.4% for IIA and 32.5% for IIB, which was similar to ours.

There are no controlled studies showing improved survival with pelvic irradiation following radical surgery, although postoperative radiotherapy has recommended the presence of pelvic node metastasis[24]

Morrow[22] reported that postoperative radio therapy in patients with pelvic node metastasis showed no significant difference in overall survival, but the trend toward better survival in patients with four or more positive nodes (75% vs 41%) and some improvement in pelvic control (50% with radiotherapy vs 84% without radiotherapy) were observed. Our study shows that the failure rates with and without lymph node metastasis were 42.2% and 13.3% respectively, and failure rate with 4 or more lymph node metastasis was 57.1%. This result shows the trend toward higher failure rate as the pelvic node metastasis increases, which was similar to other studies.

3 year actuarial survival rate and 3 year disease free survival rate in our study were 83.4% and 73.4% respectively, and it is hard to compare directly with the results of other studies in which 5 year survival rates was 76%.[24]

3 year actuarial survival rate by stages were 90.7% for IB, 69.6% for IIA, and 85.2% for IIB. The disease free survival rates by stage IB, IIA, IIB were 79.8%, 67.8% and 68.3% respectively. It is difficult to compare directly with the results of other studies in survival rates by stages since ours is the preliminary report of 3-year survival rates, but we expect that it would not make much difference.

Postoperative radiotherapy was performed 3-4 weeks after curative resection of primary tumor. The dose of 5,000 cGy/5-6 weeks is sufficient for the control of microscopic or subclinical disease, which was proven in Morrow's report[22] and Guttman's.[24]

We had 30 patients who could be upstaged after operation, its precise finding is presented in Table 13. Considering Fuller's report[25] which involvement of tumor in lower uterine segment and myometrium and parametrium were another prognostic factors, it is necessary to find its invasiveness. FIGO staging system is based on clinical finding, it does not well correlated with the prognosis. In the cases of lymph node metastasis, vascular space invasion, and large tumor volume the survival rate decreased to half.[3-6,18,19] So these factors should be considered in staging the carcinoma of cervix.

In our study, the rate of acute severe complication was 7.4% and late complication was 7.9%. Among the patients who developed late complications, only 6 patients (3.0%) were significant and the rests lived well with some discomfort. It is difficult to compare complication rates with the different report and between different therapeutic modalities. The operative morbidity was reported from 4.2% to 44.6% in radical surgery[7] and complication rate of radiotherapy in early cervical carcinoma was reported as 3-5%.[26] But there was no report on complication of postoperative radiotherapy. We expect that the complication rate is not so high because radiotherapy of 5,000 cGy in 5 to 6 week is not so high dose and patients who had severe disadvantage were excluded in postoperative radiotherapy before being referred to the radiotherapy service Further prospective randomized studies are needed to find out the role of radiotherapy in postoperative cases, survival rate and complication.

CONCLUSION

203 cases of carcinoma of the uterine cervix treated with postoperative radiotherapy in the period of February 1979 to September 1982, were analyzed and the following results were obtained.

1. 3-year actuarial survival rate and 3-year disease free survival rate were 83.4%, and 73.4% respectively. 3-year actuarial survival rates by stages were 90.7% for IB, 69.6% for IIA, and 85.2% for IIB. 3-year disease free survival rates by stages were 79.8% for IB, 67.8% for IIA and 68.3% for IIB.
2. The overall failure rate was 25.1% (51/203 patients); local recurrence rate was 8.4%, distant metastasis rate was 14.3%, and simultaneous local recurrence and distant metastasis was 2.4%.
   Failure rates by stages were 19.8% (18/19 patients) for IB, 29.1% (16/55 patients) for IIA, and 29.8% (17/57 patients) for IIB.
3. Overall acute complication rate was 57.6%; tolerable cases was 50.2% and severe cases was 7.4%.

Late complications rates were as 7.9% and they were intestinal obstruction, aggravated urinary symptom, radiation cystitis in order of frequency.

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=국문초록=

자궁경부암의 수술후 방사선 치료성적

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이 효 표 · 신 면 우

조기자궁경부암의 치료에는 환자 개개의 특성에 따라 근치적수술 또는 근치적방사선치료가 행해지고 있으며, 그 치료성적은 비슷한 것으로 보고되고 있다.

그러나 근치적 수술후 병리조직 소견에 따라 원발병소가 크거나, 임파절전이, 혈관 또는 임파관의 종양 침윤이 있으면 이들 소견이 없던 경우에 비해 재발이 현저히 높고, 생존율이 반으로 줄게 되므로, 이를 극복하기 위해 수술후 방사선 치료가 시행되고 있으나 생존율에 대한 기여에는 아직 논란이 많다.

이에 1979년 2월부터 1982년 9월까지 서울대학교병원 치료방사선과에서 자궁경부암으로 수술후 방사선 치료를 받았던 203예에 대한 치료성적을 분석하여 얻은 결과는 다음과 같다.

모든 환자에 있어 actuarial 3년 생존율은 83.4%이었으며 3년 무병 생존율은 73.4%이었다.

병기에 따른 actuarial 3년 생존율은 I_B, II_A, II_B, 각각 90.7%, 69.6%, 85.2%이었다.

병기별 3년 무병 생존율은 I_B, II_A, II_B 각각 79.8%, 67.8%, 68.3%이었다.

재발은 총 203예중 51예(25.1%)에서 관찰되었으며 이중 국소재발이 8.4%, 원격전이가 14.3%이었고, 국소재발과 원격전이가 함께 있던 경우가 2.4%이었다.

병기별 재발율은 I_B, II_A, II_B에서 각각 19.8%(18/91예), 29.1%(16/55예), 29.8%(17/57예)이었다.

합병증중 급성으로 나타난 것이 57.6%이었으나 7.4%만이 심한 증상을 보였고, 만성 합병증은 7.9%에서 관찰되었으며, 장폐색, 비뇨기계증상의 악화, 방사선 방광염등의 순이었다.

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