

Role of Postoperative Radiation Therapy in the Management of Cervical Cancer

Ha Chung Chun, M.D. and Myung Za Lee, M.D.

Department of Therapeutic Radiology, Hanyang University Medical College, Seoul, Korea

Purpose: To evaluate the effectiveness of postoperative radiation therapy in cervical cancer patients and define the prognostic factors to affect survival rates.

Materials and Methods: Eighty one patients with cervical cancer who were treated with postoperative radiation therapy following surgery at our institution between May 1992 and April 2000 were retrospectively analyzed. Forty two patients had stage IB disease, 17 had stage IIA disease, and remaining 22 had stage IIB disease, respectively. Histological examination revealed 76 squamous cell carcinoma and 5 adenocarcinoma. Sixty one patients were noted to have stromal invasion greater than 8 mm and 20 patients were noted to have stromal invasion 7 mm or less. Sixteen patients had parametrial invasion and 65 patients did not. Positive vaginal resection margin was documented in only eight patients and positive lymphovascular invasion was in twelve patients. All of the patients were treated with external beam radiation therapy alone. Majority of the patients were treated with 4 field brick technique to encompass whole pelvis. Total of 5,500 cGy was delivered to the primary surgical tumor bed. Minimum follow up period was four years.

Results: Actuarial disease free survival rates for entire group of the patients were 95% and 89% at 2 and 5 years, respectively. Five year disease free survival rates for patients with stage IB, IIA, and IIB disease were 97%, 87% and 70%, respectively. Local recurrences were documented in 5 patients. Cumulative local failure rate at 3 years was 6%. Five year disease free survival rates for patients with stromal invasion greater than 8 mm and 7 mm or less were 88% and 92%, respectively ($p > 0.05$). Five year disease free survival rate for patients with parametrial invasion was significantly lower than those with no invasion (72% vs 92%, $p < 0.05$). Also there was significantly lower survival in patients with positive vaginal resection margin, compared with patients with negative resection margin (64% vs 94%, $p < 0.05$). However, lymphovascular invasion was not a statistically significant prognostic factor. Parametrial invasion and positive surgical resection margins were noted to be significant prognostic factors.

Conclusions: Postoperative radiation therapy appears to be beneficial in controlling local disease in cervical cancer patients with high pathologic risk factors. Parametrial invasion and positive resection margins were noted to be significant prognostic factors to affect survival and more effective treatment should be investigated in these patients.

Key Words: Cervical cancer, Postoperative radiation therapy

Introduction

Early stage cervical cancers are adequately treated either by a radical hysterectomy with bilateral pelvic lymphadenectomy

or by curative radiation therapy. Five-year disease free survival rates approach approximately 90%.¹⁾ However, 10 to 25% of patients treated with surgery will ultimately relapse.^{2,3)} In approximately 90% of relapsed patients, the site of initial failure will be the pelvis and may be accompanied by distant metastases.⁴⁾

Careful histological evaluation of the surgical specimen reveals characteristics which make some patients at high risk for recurrence. These factors include positive lymph nodes, deep invasion, positive surgical margins, lymphovascular space

Submitted December 7, 2004 accepted December 10, 2004
Reprint requests to Ha Chung Chun, Department of Therapeutic Radiology, Hanyang University Hospital, Seoul 133-792, Korea
Tel: 02)2290-8617, Fax: 02)2292-7735
E-mail: rthcchun@hanyang.ac.kr

invasion, and tumor size.^{5~10)} The 5-year survival rate in patients with high risk factors is 40 to 66%, but decreases to less than 10% after recurrence develops.^{11,12)} Adjuvant postoperative radiation therapy has been given in an attempt to improve local control and survival in these high risk patients. There are many studies which suggest that postoperative radiation therapy improve local control rates in patients with cervical cancer. However, it has been controversial that postoperative radiation therapy could improve long term survival.^{13,14)}

We retrospectively analyzed the records of 81 patients with cervical cancer treated with postoperative radiation therapy following hysterectomy and tried to evaluate the effectiveness of radiation therapy and define the prognostic factors.

Materials and Methods

We retrospectively analyzed the records of eighty one patients with cervical cancer who were treated with postoperative radiation therapy following surgery at our institution between May 1992 and April 2000. The characteristics of the patients in study are shown in Table 1. Age of the patients was ranged from 36 to 72 and the median age was 56. All of

the patients were staged according to the FIGO staging system. Forty two patients had Stage IB disease, 17 had Stage IIA disease, and remaining 22 had Stage IIB disease, respectively. Histological examination revealed 76 squamous cell carcinoma and 5 adenocarcinoma. Sixty one patients were noted to have stromal invasion greater than 8 mm and 20 patients were noted to have stromal invasion 7 mm or less. Sixteen patients had parametrial invasion and 65 patients did not. Positive vaginal resection margin was documented in only eight patients and positive lymphovascular invasion was in twelve patients. Status of the pelvic lymph nodes were evaluated in 48 patients. Of those 48 patients, 23 patients were found to have positive pelvic lymph nodes.

Postoperative radiation therapy was initiated 4 to 6 weeks after surgery. All of the patients were treated with external beam radiation therapy alone and brachytherapy was performed in none of the patients. Radiation therapy was delivered through linear accelerator producing 10 MV Photons and treatment was given once a day, five times a week. Daily fractionation was 180 cGy. Majority of the patients were treated with 4 field brick technique to encompass whole pelvis. Upper margin of the whole pelvic field was top of the fifth lumbar vertebra and lower margin was ischial tuberosity. Lateral margins were located at 1.5 cm lateral to pelvic brim. Total of 4,500 cGy was delivered to whole pelvis and coned down field was employed to treat boost radiation after that. Usually anterior posterior parallel opposed field with size of 10×10 cm was used for boost field. Most of the patients received 1,000 cGy as a boost. Thus, total of 5,500 cGy was delivered to the primary surgical tumor bed. Total treatment time was 6 weeks.

Patients were followed by us or their referring physicians once a month in first three months. After that, patients were followed every 3 month in next 2 years. Minimum follow up period was four years. Survival period was counted from day one of the radiation therapy. Kaplan Meier method was used to calculate survival and evaluation of the prognostic factors was made with log rank test.

Results

As shown in Fig. 1, actuarial disease free survival rates for entire group of the patients were 95% and 89% at 2 and 5

Table 1. Characteristics of the Patients

	No. of Patients
Stage	
IB	42
IIA	17
IIB	22
Histology	
Squamous cell ca	76
Adenocarcinoma	5
Stromal invasion	
7 mm or less	20
>8 mm	61
Parametrial invasion	
Negative	65
Positive	16
Resection margin	
Negative	73
Positive	8
Lymphovascular invasion	
Negative	69
Positive	12
Total	81

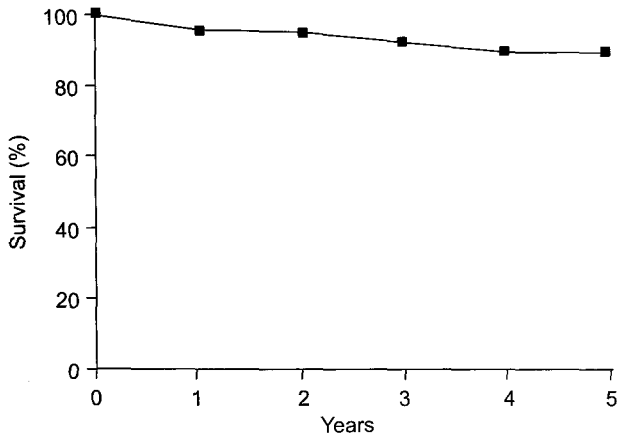


Fig. 1. Actuarial disease free survival rate for entire group of patients.

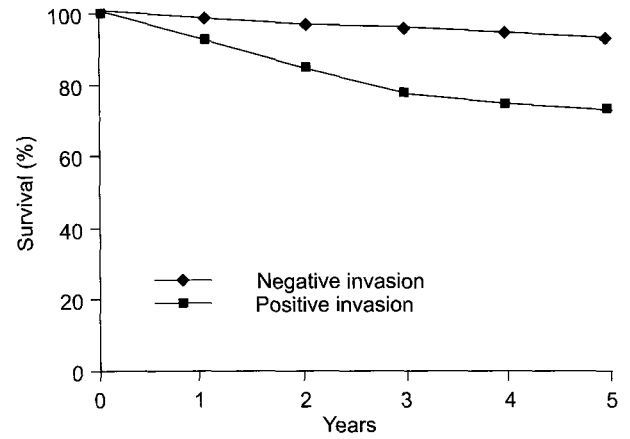


Fig. 3. Disease free survival rates according to parametrial invasion.

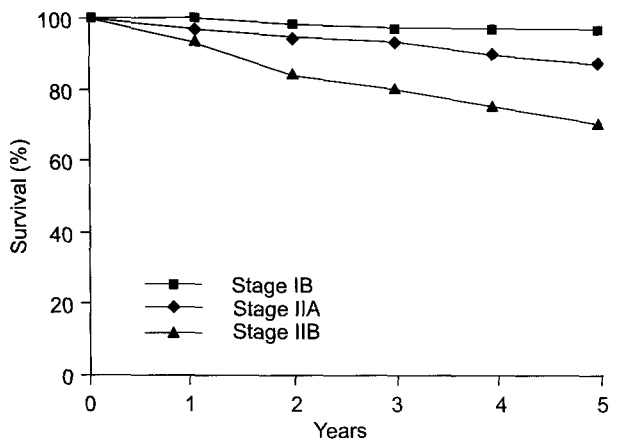


Fig. 2. Disease free survival rates according to stage.

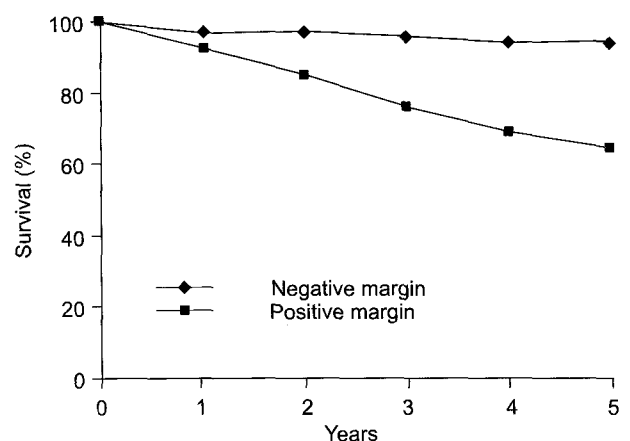


Fig. 4. Disease free survival rates for patients with positive vs. negative resection margin.

years, respectively. Five year disease free survival rates for patients with stage IB, IIA, and IIB disease were 97%, 87% and 70%, respectively. Disease free survival rates according to stage is shown in Fig. 2. Local recurrences were documented in 5 patients. Cumulative local failure rate at 3 years was 6%. Three patients failed with parametrial invasion and two patients failed with vaginal recurrences. Of failed 5 patients, 2 had simultaneous lymphatic failure in the pelvic cavity. With one exception, all recurrences occurred within 2 years.

There was no significant difference in 5 year disease free survival between ages younger than 45 and 45 or older (90% vs 88%, $p > 0.05$). Also no significant survival difference was noted according to histologic classification (squamous 92% vs adeno 80%). Five year disease free survival rates for patients with stromal invasion greater than 8 mm and 7 mm or less

were 88% and 92%, respectively ($p > 0.05$). As shown in Fig. 3, five year disease free survival rate for patients with parametrial invasion was significantly lower than those with no invasion (72% vs 92%, $p < 0.05$). Also there was significantly lower survival in patients with positive vaginal resection margin, compared with patients with negative resection margin (64% vs 94%, $p < 0.05$ Fig. 4) However, lymphovascular invasion was not a statistically significant prognostic factor. Because all of the patients in this study were not evaluated for pelvic lymph node, status of the pelvic nodes was not examined for comparison of the survival. Therefore, parametrial invasion and positive surgical resection margins were noted to be significant prognostic factors in this analysis.

Discussion

Radical hysterectomy has been a well established therapy for early stage cervical cancer. Survival data from several large series of patients with stage IB and IIA disease suggests that approximately 25% of patients eventually have a relapse.³⁾ Pelvic lymph node involvement is probably the most important prognostic factor following radical surgery. Most of the series report 40 to 50% reduction in five year survival rates for these patients.^{11,15,16)} Other factors implicated as risk factors for recurrence include lymphovascular space invasion, depth of invasion, tumor size, positive surgical margins and age. Boyce cited depth of invasion greater than 5 mm and lateral parametrial invasion as risk factors.¹⁷⁾ Delgado found both depth of invasion and tumor size to be predictive factors for length of disease free survival.⁹⁾ Gauthier also considered positive margins to be prognostically significant in addition to lymphovascular invasion, positive lymph nodes and parametrial involvement.¹⁸⁾ Dattoli found a difference in 5-year survival based on age. Five year survival for patients <40 was 54% vs. 90% for those patients >40 years old.¹⁹⁾

Those patients with high risk factors were recommended to be treated with postoperative radiation therapy. There are many studies suggesting postoperative radiation therapy can improve local control rate in cervical cancer patients with high risk factors.^{14,20)} However, it is controversial whether postoperative radiation therapy can improve long term survival or not. Stock et al. reported improved five year survival rate for postoperative radiation group, compared with non irradiated group in retrospective study (58% vs 46%).²¹⁾ Recent prospective study performed by Gynecological Oncology Group reported 44% reduction of recurrence rate and 36% increase of survival rate in irradiated stage IB and IIA patients with high risk factors.²²⁾ Also Lai et al. suggested postoperative radiation therapy can improve disease free survival in patients with high risk factors other than positive lymph nodes.²³⁾ In our institution, patients with positive nodes, positive surgical margins, stromal invasion more than 1/2 and parametrial involvement were treated with postoperative irradiation. Five year disease free survival rate in our study was 89% and this was slightly better or similar to other series.

Tasi et al. showed that important prognostic factors

affecting survival rates in stage IB-IIA patients treated with postoperative radiation therapy were lymph node involvement, tumor size and parametrial invasion.⁹⁾ Boyce suggested stromal invasion more than 5 mm and lateral parametrial invasion as high risk factors.²⁴⁾ Gonzalez et al. reported 39% five year survival rate in patients with positive parametrial invasion vs. 76% in those with negative parametrial invasion.¹⁷⁾ In our study, five year disease free survival rate for patients with parametrial invasion was significantly lower than those with no invasion (72% vs 92%, $p < 0.05$).

Positive surgical margin is also considered to be important prognostic factors. Many authors suggested positive resection margin influence the survival. Atkovar et al. reported 78.1% and 34.8% five year disease survival rates in patients with negative resection margin and positive resection margin, respectively.²⁵⁾ There was a significantly lower survival in patients with positive vaginal resection margin, compared with patients with negative resection margin in our study (64% vs 94%, $p < 0.05$).

In conclusion, postoperative radiation therapy appears to be beneficial in controlling local disease in cervical cancer patients with high pathologic risk factors. Parametrial invasion and positive resection margins were noted to be significant prognostic factors to affect survival and more effective treatment should be investigated in these patients.

References

1. Russell A, Tong DY, Figge DC, Tamimi HK, Greer BE, Elder SJ. Adjuvant postoperative radiation therapy for carcinoma of the uterine cervix: Pattern of cancer recurrence in patients undergoing elective radiation following radical hysterectomy and pelvic lymphadenectomy. *Int J Radiat Oncol Biol Phys* 1984;10:211-214
2. Krebs HB, Helmke BF, Sevin BU. Recurrent cancer of the cervix following radical hysterectomy and pelvic lymph node dissection. *Obstet Gynecol* 1982;59:422-427
3. Perez CA, Bedwinek JM, Breaux SR. Pattern of failure after treatment for gynecologic tumors. *Cancer Treat Symp* 1983;2:217-231
4. Morgan S, Nelson JH. Surgical treatment of early cervical cancer. *Semin Oncol* 1982;9:312-332
5. Tsai CS, Lai CH, Wang CC, et al. The prognostic factors for patients with early cervical cancer treated by radical hysterectomy and postoperative radiotherapy. *Gynecol Oncol* 1999;75:328-333
6. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman

- WT, Major F. Prospective surgical pathologic study of the disease free interval in patients with Stage IB squamous cell cancer of the cervix. *Gynecol Oncol* 1990;38:352-357
7. Nelson JH, Macaset MA, Lu T, et al. The incidence and significance of para-aortic lymph node metastases in late invasive carcinoma of the cervix. *Am J Obstet Gynecol* 1974; 118:749-756
 8. Piver MS, Chung WS. Prognostic significance of cervical lesion size and pelvic lymph node metastasis in cervical cancer. *Obstet Gynecol* 1975;46:507-510
 9. Stitt JA. Use of postoperative irradiation for carcinoma of the cervix. *Semin Radiat Oncol* 1994;4:41-45
 10. van Nagell JR, Donaldson ES, Wood EG, Parker JC. The significance of lymphocytic infiltration in invasive cervical cancer. *Cancer* 1978;41:228-234
 11. Fuller AF, Elliot N, Kosloff C. Lymph node metastases from carcinoma of the cervix: Stages IB and IIA: Implications for prognosis and treatment. *Gynecol Oncol* 1982;13:165-170
 12. Morrow PC. Is pelvic irradiation beneficial in postoperative management of Stage IB squamous cell carcinoma of the cervix with pelvic lymph node metastases treated with radical hysterectomy and pelvic lymphadenectomy? *Gynecol Oncol* 1980; 10:105-110
 13. Wang CJ, Lai CH, Huang HJ, et al. Recurrent cervical carcinoma after primary radical surgery. *Am J Obstet Gynecol* 1999;18:518-524
 14. Reny JC, Dimaio T, Fruchter RG, et al. Adjuvant radiation after radical hysterectomy in stage IB squamous cell carcinoma of the cervix. *Gynecol Oncol* 1990;38:161-165
 15. Furke TW, Hoskins WJ, Heller PB, Bibro MC, Weiser EB, Park RC. Prognostic factors associated with radical hysterectomy failure. *Gynecol Oncol* 1987;26:153-159
 16. Himmelmann A, Holmberg G, Jansson I, Oden A, Skogsberg K. The effect of postoperative external radiotherapy on cervical carcinoma Stage IB and IIA. *Gynecol Oncol* 1985;22:73-84
 17. Boyce JG, Fruchter RG, Nicastrri AD. Prognostic factors in Stage I carcinoma of the cervix. *Cancer* 1984;53:1175-1180
 18. Gauthier P, Gore I, Shingleton HM, Soong SJ, Orr JW, Hatch KD. Identification of histopathologic risk groups in Stage IB cervical cancer. *Am J Obstet Gynecol* 1985;66:569-574
 19. Dattoli MJ, Gretz HF, Beller U, et al. Analysis of multiple prognostic factors in patients with Stage IB cervical cancer: Age as a major determinant. *Int J Radiat Oncol Biol Phys* 1989;17: 41-44
 20. Monk BJ, Cha DS, Walker JL, et al. Extent of disease as an indication for pelvic radiation following radical hysterectomy and bilateral lymph node dissection in the treatment of stage IB and IIA cervical carcinoma. *Gynecol Oncol* 1994;54:4-9
 21. Stock RG, Chen AS, Flickinger JC, Kalnicki S, Seski J. Node positive cervical cancer: Impact of pelvic irradiation and patterns of failure. *Int J Radiat Oncol Biol Phys* 1995;31:31-36
 22. Sedlis A, Bundy BN, Rotman AZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncologic Group study. *Gynecol Oncol* 1999;73:177-183
 23. Lai CH, Hong JH, Hsueh S, et al. Preoperative prognostic variables and the impact of postoperative adjuvant radiotherapy on the outcomes of Stage IB or II cervical carcinoma patients: An analysis of 891 cases. *Cancer* 1999;85:1537-1546
 24. Gonzalez DG, Ketting BW, van Bunningen B, van Dijk JDP. Carcinoma of the uterine cervix Stage IB and IIA: Results of postoperative irradiation in patients with microscopic infiltration in the parametrium and/or lymph node metastasis. *Int J Radiat Oncol Biol Phys* 1989;16:389-395
 25. Atkovar G, Uzel O, Ozsahin M, et al. Postoperative radiotherapy in carcinoma of the cervix: treatment results and prognostic factors. *Radiother Oncol* 1995;35:198-205

자궁경부암에서 수술 후 방사선치료의 역할

한양대학교 의과대학 치료방사선과학교실

전 하 정 · 이 명 자

목적: 자궁경부암 환자에서 수술 후 방사선치료의 효과를 평가하고 생존율에 영향을 미치는 예후인자를 알아보고자 함이 본 연구의 목적이다.

대상 및 방법: 1992년 5월부터 2000년 4월까지 본원에서 수술 후 방사선치료를 받은 81명의 자궁경부암 환자를 후향적으로 분석하였다. 42명은 IB 병기였고 IIA 병기는 17명, IIB 병기는 22명이었다. 조직학적 분류는 상피세포암이 76명, 선암이 5명이었다. 자궁기질내 침범은 7 mm 이하가 20명 8 mm 이상이 61명이었고, 자궁주위조직의 침범은 16명에서 발견되었다. 8명은 수술 절제연에 양성이었고 12명에서는 림프혈관강이 침범되었다. 모든 환자에서 외부 방사선만으로 치료하였으며 대부분의 환자에서 총 5,500 cGy를 원발부위에 조사하였다. 최소 추적기간은 4년이었다.

결과: 모든 대상 환자의 2년 및 5년 생존율은 95% 및 89%였으며, IB 병기, IIA 병기 및 IIB 병기의 5년 무병생존율은 각각 97%, 87% 및 70%였다. 5명에서 국소재발을 보였으며 국소재발률은 3년에 6%였다. 자궁기질내 침범에 따른 생존율은 의미있는 차이를 나타내지 않았다. 자궁주위 조직을 침범한 환자(72% vs 92%)와 수술 절제연에서 양성인 환자(64% vs 94%)에서는 5년 무병생존율이 감소하는 양상을 보였다. 그러나 림프혈관강의 침범은 생존율에서 의미있는 차이를 관찰할 수 없었다.

결론: 고위험인자를 가진 자궁경부암 환자에서 수술 후 방사선치료가 효과적인 것으로 생각되며 자궁주위조직의 침범 및 수술절제연의 침범이 의미있는 예후인자임을 알 수 있었다.

핵심용어: 자궁경부암, 수술 후 방사선치료