# Postoperative Radiation Therapy in the Management of Early Cervical Cancer

Jae-Chul Kim, M.D.

Department of Radiation Oncology, Kyungpook National University School of Medicine, Daegu, Korea

**Purpose**: This study identified the result of postoperative radiation therapy and the prognostic factors to affect survival rates in cervical cancer patients.

**Materials and Methods**: One hundred and thirty three patients with cervical cancer who were treated with postoperative radiation therapy following surgery at our institution between June 1985 and November 2002 were retrospectively analyzed. One hundred and thirteen patients had stage IB disease, and 20 patients had stage IIA disease. Histological examination revealed 118 squamous cell carcinoma patients and 15 adenocarcinoma patients. Sixty seven patients were noted to have stromal invasion greater than 10 mm, and 45 patients were noted to have stromal invasion 10 mm or less. Positive lymphovascular invasion was found in 24 patients, and positive pelvic lymph nodes were noted in 39 patients. Positive vaginal resection margin was documented in 8 patients. All of the patients were treated with external beam radiation therapy to encompass whole pelvis and primary surgical tumor bed. Intracavitary radiation therapy was added to 19 patients who had positive or close surgical margins.

**Results**: Actuarial overall and disease-free survival rates for entire group of the patients were 88% and 84% at 5 years, respectively. Five-year disease-free survival rates for patients with stromal invasion greater than 10 mm and 10 mm or less were 76% and 97%, respectively ($p < 0.05$). Also there was a significantly lower survival in patients with positive pelvic lymph nodes compared with patients with negative pelvic lymph nodes ($p < 0.05$). However, lymphovascular invasion, positive vaginal resection margins were not statistically significant prognostic factors. Addition of neoadjuvant chemotherapy or type of surgery did not affect disease-free survival.

**Conclusion**: Postoperative radiation therapy appears to achieve satisfactory local control with limited morbidity in cervical cancer patients with high pathologic risk factors. Distant metastasis was a dominant failure pattern to affect survival in cervical cancer patients after radical surgery and radiation and more effective systemic treatment should be investigated in these high-risk patients.

**Key Words**: Cervical cancer, Radiation therapy, Hysterectomy

## Introduction

Stage IB and IIA cervical cancer is usually treated by radical hysterectomy and pelvic lymphadenectomy though radiation therapy is as effective as surgery. Five-year disease-free survival rates approach approximately 90% after radical

surgery.[1] However, 10 to 25% of early-stage cervical cancers treated with radical surgery will eventually relapse.[2] Approximately 90% of initial relapsed sites will be the pelvis and pelvic relapse will be often accompanied by distant metastases.[3]

One of the possible advantages of surgical treatment in early-stage cervical cancer is that groups of patients could be identified with more extensive disease than was initially evaluated. Adjuvant radiation therapy could contribute to improve local control in patients who have unfavorable pathologic risk factors found in surgical specimen. Postoperative radiation therapy can improve local control of cervical cancer patients by sterilizing remaining microscopic or

gross residual disease left behind even with radical surgery. Careful histological evaluation of the surgical specimen reveals factors which can differentiate patients at higher risk of failure in surgically treated patients. These factors include positive pelvic lymph nodes, deep stromal invasion, positive surgical margins, lymphovascular space invasion, and large tumor size.[4~9] Adjuvant postoperative radiation therapy has been given to improve local control and survival in those high-risk patients. Our postoperative radiotherapy policy in early-stage cervical cancer is to irradiate the patients with unfavorable pathological findings after radical hysterectomy and patients who have undergone simple hysterectomy.

We retrospectively analyzed the survival rates and the patterns of failure of early cervical cancer patients who were treated with surgery and postoperative radiation therapy to identify the prognostic factors to affect survival rates.

## Materials and Methods

We retrospectively reviewed the clinical records of 133 patients with early cervical cancer who were treated with surgery and postoperative radiation therapy at our institution

Table 1. Characteristics of the Patients

| Characteristics | No. of patients |
|---|---|
| Stage | |
| IB | 113 |
| IIA | 20 |
| Histology | |
| Squamous cell ca | 118 |
| Adenocarcinoma | 15 |
| Stromal invasion | |
| Unknown | 21 |
| 10 mm or less | 45 |
| >10 mm | 67 |
| Resection margin | |
| Negative | 125 |
| Positive | 8 |
| Lymphovascular invasion | |
| Negative | 109 |
| Positive | 24 |
| Pelvic lymph node | |
| Negative | 94 |
| Positive | 39 |
| Total | 133 |

between June 1985 and November 2002. Postoperative radiation therapy was added if one of following factors was found in the surgical specimen; positive surgical margins, positive pelvic lymph nodes, lymphovascular space invasion, deep stromal invasion, and disease discovered incidentally at simple hysterectomy.

The characteristics of the patients in the present study are shown in Table 1. Age of the patients ranged from 27 to 74 and the median age was 48. All patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification revised in 1994. Prior to surgery, clinical staging was done by using pelvic examination, routine blood chemistry, chest x-ray, intravenous pyelogram, cystoscopy, sigmoidoscopy, and pelvic CT scan. One hundred and thirteen patients had stage IB disease, and 20 had stage IIA disease. Pathologic examination revealed 118 cases of squamous cell carcinoma and 5 of adenocarcinoma. Sixty seven patients were noted to have stromal invasion more than 10 mm, 45 patients were noted to have stromal invasion 10 mm or less, and 21 showed unknown depth of invasion. Positive vaginal resection margin was documented in 8 patients and positive lymphovascular invasion was noted in 24 patients. Pelvic lymph node was positive in 39 patients.

Postoperative radiation therapy was started 4 to 6 weeks after surgery. All of the patients were treated with 4 field box technique to encompass whole pelvis by linear accelerators producing 6 or 10 MV photons and treatment was given once a day, five times a week. Daily fractionation was 1.8 Gy. Total of 45 to 50.4 Gy was delivered to whole pelvis during 5 to 6 weeks. Nineteen patients with positive or close (<5 mm) vaginal surgical margins received intracavitary vaginal ovoids loaded with Cs-137 (approximately 25 cGy/min) by remote afterloading (Buchler, Germany). The dose to the vaginal surface was 15 Gy in 5 fractions for close margins and 39 Gy in 13 fractions for positive margins. Brachytherapy was delivered at the conclusion of the external beam irradiation. Cisplatin-based neoadjuvant chemotherapy was done in 58 patients who had tumors of 4 cm or more. Neoadjuvant chemotherapy regimens were as follows: cisplatin and mitomycin in 32 patients, bleomycin, vincristine, mitomycin, and cisplatin in 15 patients, cisplatin and 5-fluorouracil in 3 patients, paclitaxel and cisplatin in 8 patients. The range of chemotherapy cycles was 1~4 (median 2).

Major treatment-related toxicities were defined as those requiring surgical correction and/or major medical intervention. These included blood loss requiring 4 units or more of blood transfusion, intra-abdominal infection, fistulae, pulmonary embolism, deep venous thrombosis, small bowel obstruction, severe proctitis or cystitis delaying treatment more than 2 weeks. Patients were followed regularly and median follow up period was 48 months (range 4 to 219 months). Survival time was counted from the end of radiation therapy. Kaplan-Meier method was used to calculate survival and evaluation of the prognostic factors was performed with log rank test. Multivariate analysis was performed using a Cox regression analysis in a forward stepwise manner.

## Results

As shown in Fig. 1, actuarial overall and disease-free survival rates for entire group of the patients were 88% and 84% at 5 years, respectively. Five-year disease-free survival rates for patients with stromal invasion 10 mm or less and greater than 10 mm were 97% and 76%, respectively (Fig. 2, $p < 0.05$). Five-year disease-free survival rates for patients with negative and positive pelvic lymph nodes were 88% and 74%, respectively (Fig. 3, $p < 0.05$). Five-year disease-free survival rates for patients with 2 or fewer pelvic nodes and those with more than 2 pelvic nodes were 88% and 66%, respectively (Fig. 4, $p < 0.05$). There was no significant difference in 5-year disease-free survival between ages younger than 45 and
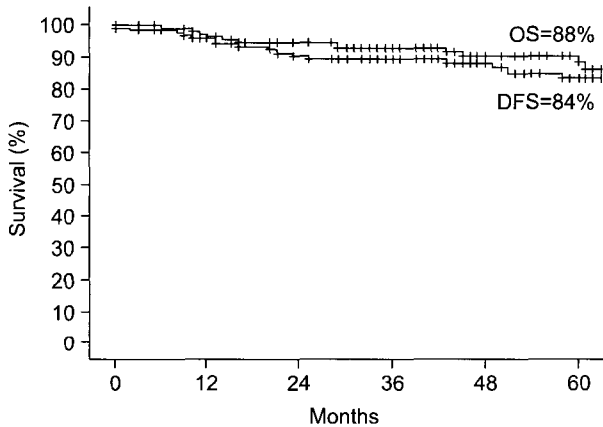


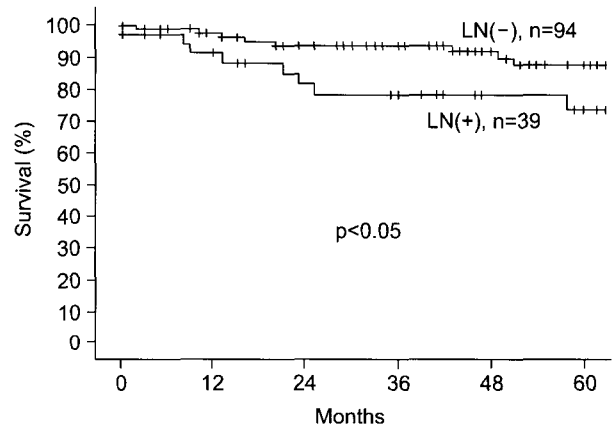**Fig. 1.** Overall survival (OS) and disease-free survival (DFS) rate for entire group of patients.



**Fig. 3.** Disease-free survival rates for patients with positive vs. negative pelvic lymph nodes.
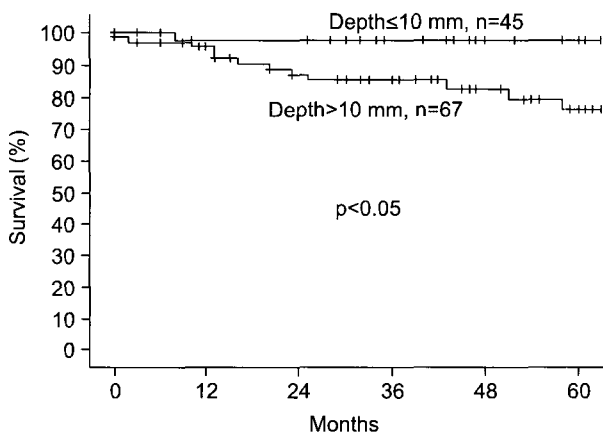


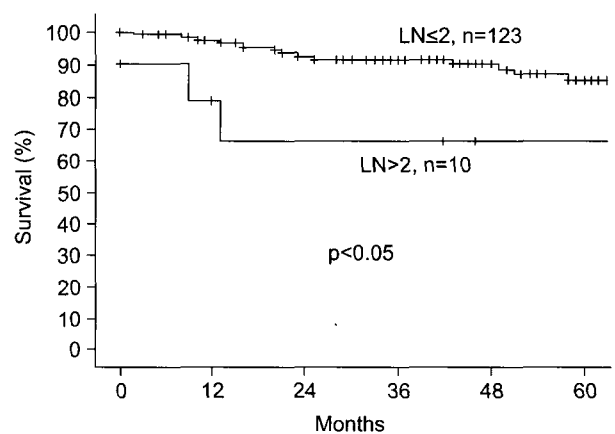**Fig. 2.** Disease-free survival rates according to depth of stromal invasion.



**Fig. 4.** Disease-free survival rates according to number of pelvic lymph nodes.

Table 2. Five-year Disease-free Survival Rates according to Prognostic Factors

| Prognostic variable | 5YDFS* (n) | p value[†] | p value[†] |
|---|---|---|---|
| Stage | | | |
| IB | 88% (113) | | |
| IIA | 83% (20) | N.S. | N.S. |
| Histology | | | |
| Squamous cell ca | 85% (118) | | |
| Adenocarcinoma | 71% (15) | N.S. | N.S. |
| Stromal invasion (mm) | | | |
| Unknown | 78% (21) | | |
| 10 mm or less | 97% (45) | | |
| >10 mm | 76% (67) | <0.05 | <0.05 |
| Resection margin | | | |
| Negative | 86% (125) | | |
| Positive | 84% (8) | N.S. | N.S. |
| Lymphovascular invasion | | | |
| Negative | 86% (109) | | |
| Positive | 84% (24) | N.S. | N.S. |
| Pelvic lymph node | | | |
| Negative | 88% (94) | | |
| Positive | 74% (39) | <0.05 | N.S. |
| Number of pelvic lymph nodes | | | |
| 0~2 | 88% (123) | | |
| >2 | 66% (10) | <0.05 | <0.05 |

*5-year disease-free survival, [†]univariate analysis, [†]multivariate analysis

45 or older. Also no significant survival difference was noted according to histological classification. Positive vaginal resection margin and lymphovascular invasion were not statistically significant prognostic factors (Table 2). There was also no significant disease-free survival difference between the groups treated with radical and simple hysterectomy. Addition of neoadjuvant chemotherapy did not affect disease-free or metastasis-free survival. According to a multivariate analysis, more than 2 positive pelvic nodes and stromal invasion greater than 10 mm proved to be independent factors (Table 2, p<0.05).

Analysis of the sites of failure disclosed 4 pelvic relapses, 11 distant metastases, and 1 combined pelvic failure with distant metastasis (Table 3). Pelvic recurrences occurred 2 to 51 months after radiation therapy (median 15 months). Distant metastases occurred 4 to 60 months after radiation therapy (median 20 months). Of 16 failures, 12 had stromal invasion more than 10 mm and 8 had positive pelvic nodes in the initial surgical specimen. None of the 16 patients with pelvic

Table 3. Sites of Relapse

| Site of relapse | Number | % |
|---|---|---|
| Pelvic only | 4 | 3 |
| Distant only | 11 | 8 |
| Pelvic + distant | 1 | 1 |
| Total | 16 | 12 |

and/or metastatic failures was successfully treated.

Few treatment-related major toxicities were reported. Two patients suffered small bowel obstruction and underwent surgical resections. These 2 patients received external radiation therapy only. Two patients suffered minor hematuria which was successfully controlled by appropriate medication.

## Discussion

Overall 5-year survival of the entire group of 133 patients treated for stage IB and IIA cervical cancer at our institution was 88% which was in accordance with the literature.[10-12]

Early-stage cervical cancer represents a wide spectrum of disease with considerable variation in prognosis. A disease as small as microinvasive and as large as 6 cm are all included in stage IB group as defined by FIGO. Groups of patients with high risk factors therefore need to be defined so that appropriate adjuvant therapies are applied after surgery. These factors include positive pelvic lymph nodes, deep stromal invasion, positive surgical margins, lymphovascular space invasion, and large tumor size.[4~9]

Pelvic lymph node metastases is probably the most important prognostic factor following radical surgery, with most series showing a 40 to 50% reduction in 5-year survival rates for these patients.[12~15] Number and location of the pelvic metastases are also important. When 3 or fewer lymph nodes were involved, the survival was 79% compared with 33% when 4 or more lymph nodes were involved.[16] Fuller showed that 32% of patients with 1~2 pelvic nodal groups involved by tumor recurred, while 71% of patients with more than 2 nodal groups involved recurred.[17] Patients with metastases below the common iliac nodes do better than patients with metastases involving common iliacs.[18,19] In the present study, patients with 2 or fewer pelvic nodes had a higher disease-free survival than those with more than 2 pelvic nodes.

Unfortunately the importance of lymph node metastases location could not be precisely analyzed in the present study because the surgeons omitted specific lymph node group information. Gynecologic Oncology Group 92 study compared radiation therapy after surgery with surgery alone in high-risk cervical cancer patients without pelvic lymph node metastasis. There was a reduction in the recurrence rate from 28% to 15% with the addition of radiation.[20] Our study included both node-positive and node-negative patients and distant metastases were frequent (Table 1) which might suggest pelvic node metastases indicate dissemination. Whether adjuvant radiation therapy could improve disease-free and overall survival in node-positive cervical cancer needs to be elucidated by a randomized study.

In the present study, depth of invasion in absolute terms showed a strong significance (p<0.05), while depth of invasion in fractional thirds showed only a marginal significance (p=0.06. data not shown). Depth of stromal invasion by cervical cancer strongly correlated with disease-free survival, both in absolute terms (mm) and in fractional thirds.[10] Increasing depth of invasion of the cervical lesion might be associated with greater lateral extension and increasing vascular invasion in the cervix. Patients with disease confined to the cervix had poor outcome if the tumor invaded more than 10 mm and was present in vascular spaces. A possible explanation for these findings is that as a tumor involves a greater fraction of the cervical stroma, the risk for metastatic spread increases because the tumor gains more access to larger lymphatic trunks and blood vessels that insert at the periphery of the cervix. The fractional ratio of invasion is higher in an atrophic cervix than in a large, premenopausal, multiparous cervix, given an equal absolute depth of tumor invasion.[16]

We found no significant difference between the groups treated with radical and simple hysterectomy. This finding supports that adjuvant radiation therapy could successfully compensate the suboptimal surgery for local control.

Although intracavitary radiation therapy did not significantly add to morbidity, there was no survival advantage with the addition of intracavitary radiation therapy in the present study. It is obvious that patients who have positive or close surgical margins after hysterectomy are at increased risk for local recurrence and whole pelvic irradiation plus vaginal ovoid irradiation is necessary in those patients.[21] Although some results supported that additional vaginal cuff irradiation was necessary, others did not with a longer term data.[22]

The dominant pattern of failure in this study was distant metastasis. The prognosis for patients with recurrent cervical cancer was poor, with no patients surviving free of disease after relapse. More effective adjuvant systemic treatments have to be developed to control distant metastases.

Cisplatin-based neoadjuvant chemotherapy in the present study did not improve disease-free or metastasis-free survival. Cisplatin and fluorouracil are radiation sensitizers and their concurrent use seems to be synergistic.[23] The concurrent use of cisplatin (with or without fluorouracil) and pelvic irradiation in patients with advanced disease seemed to improve local control and overall survival in clinical trials.[24~28]

Based on our data, the morbidity of postoperative pelvic radiotherapy was acceptable with only 2 cases of major toxicities though Barter[29] reported that 30% of the patients treated with combined radical hysterectomy and radiation therapy had serious complications.

In conclusion, present analysis indicates that postoperative pelvic radiotherapy can achieve satisfactory local control with limited morbidity. Because of the high incidence of distant metastasis, effective adjuvant systemic chemotherapy should be developed to improve the present therapeutic results.

## References

1. Russell AH, Tong DY, Figge DC, Tamimi HK, Greer BE, Elder SJ. Adjuvant postoperative pelvic radiation 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, Helmkamp BF, Sevin BU, Poliakoff SR, Nadji M, Averette HE. Recurrent cancer of the cervix following radical hysterectomy and pelvic node dissection. Obstet Gynecol 1982;59:422-427

3. Morgan LS, Nelson JH Jr. Surgical treatment of early cervical cancer. Semin Oncol 1982;9:312-330

4. Delgado G. Stage IB squamous cancer of the cervix: the choice of treatment. Obstet Gynecol Surv 1978;33:174-183

5. Stitt JA. Use of postoperative irradiation for carcinoma of the cervix. Semin Radiat Oncol 1994;4:41-45

6. van Nagell JR Jr, Donaldson ES, Wood EG, Parker JC Jr. The significance of vascular invasion and lymphocytic infiltration in invasive cervical cancer. Cancer 1978;41:228-234

7. Pilleron JP, Durand JC, Hamelin JP. Prognostic value of node metastasis in cancer of the uterine cervix. Am J Obstet Gynecol 1974;119:458-462

8. Lee KJ, Moon HS, Kim SC, Kim CI, Ahn JJ. Adjuvant postoperative radiation therapy for carcinoma of the uterine cervix. J Korean Soc Ther Radiol Oncol 2003;21:199-206

9. Chun HC, Lee MZ. Role of postoperative radiation therapy in the management of cervical cancer. J Korean Soc Ther Radiol Oncol 2004;22:265-270

10. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1990;38:352-357

11. Fiorica JV, Roberts WS, Greenberg H, Hoffman MS, LaPolla JP, Cavanagh D. Morbidity and survival patterns in patients after radical hysterectomy and postoperative adjuvant pelvic radiotherapy. Gynecol Oncol 1990;36:343-347

12. Soisson AP, Soper JT, Clarke-Pearson DL, Berchuck A, Montana G, Creasman WT. Adjuvant radiotherapy following radical hysterectomy for patients with stage IB and IIA cervical cancer. Gynecol Oncol 1990;37:390-395

13. Lai CH, Hong JH, Hsueh S, et al. Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of Stage IB or II cervical carcinoma patients with or without pelvic lymph node metastases: an analysis of 891 cases. Cancer 1999;85:1537-1546

14. Waggoner SE. Cervical cancer. Lancet 2003;361:2217-2225

15. Landoni F, Maneo A, Colombo A, et al. Randomized study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997;350:535-540

16. Hopkins MP, Morley GW. Stage IB squamous cell cancer of the cervix: clinicopathologic features related to survival. Am J Obstet Gynecol 1991;164:1520-1527

17. Fuller AF Jr, Elliott N, Kosloff C, Lewis JL Jr. Lymph node metastases from carcinoma of the cervix, stages IB and IIA: implications for prognosis and treatment. Gynecol Oncol 1982;13:165-174

18. Keys H, Park RC. Treatment and survival of patients with cancer of the cervix and nodal metastases. Int J Radiat Oncol Biol Phys 1976;1:1091-1097

19. Martimbeau PW, Kjorstad KE, Iversen T. Stage IB carcinoma of the cervix, the Norwegian Radium hospital. II. Results when pelvic nodes are involved. Obstet Gynecol 1982;60: 215-218

20. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. 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 Oncology Group study. Gynecol Oncol 1999;73:177-183

21. Kim RY, Salter MM, Shingleton HM. Adjuvant postoperative radiation therapy following radical hysterectomy in stage IB CA of the cervix-analysis of treatment failure. Int J Radiat Oncol Biol Phys 1988;14:445-449

22. Ampil F, Datta R, Datta S. Elective postoperative external radiotherapy after hysterectomy in early-stage carcinoma of the cervix. Is additional vaginal cuff irradiation necessary? Cancer 1987;60:280-288

23. Vokes EE, Weichselbaum RR. Concomitant chemoradiotherapy: rationale and clinical experience in patients with solid tumors. J Clin Oncol 1990;8:911-934

24. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144-1153

25. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154-1161

26. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340: 1137-1143

27. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999;17:1339-1348

28. Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-1613

29. Barter JF, Soong SJ, Shingleton HM, Hatch KD, Orr JW Jr. Complications of combined radical hysterectomy-postoperative radiation therapy in women with early stage cervical cancer. Gynecol Oncol 1989;32:292-296

# 초기 자궁경부암의 수술 후 방사선치료의 효과

경북대학교 의과대학 방사선종양학교실

김 재 철

**목 적**: 초기 자궁경부암 환자에서 수술 후 방사선치료의 결과 및 생존율에 영향을 미치는 예후인자를 알아보고자 하였다.

**대상 및 방법**: 1985년 6월부터 2002년 11월까지 본원에서 수술 후 방사선치료를 받은 133예의 자궁경부암 환자를 후향적으로 분석하였다. 병기는 IB 113예, IIA 20예였고, 조직학적 분류는 상피세포암 118예, 선암 15예였다. 자궁경부 기질 내 침범 10 mm 초과 67예, 10 mm 이하 45예였다. 골반 림프절 양성 39예, 림프혈관강 침범 24예, 수술 절제연 양성 8예가 관찰되었다. 모든 환자를 45~50.4 Gy의 외부방사선으로 치료하였으며, 수술 절제연이 양성이거나 불충분한 경우에는 15~39 Gy의 강내치료를 추가하였다. 추적기간의 중간값은 48개월이었다.

**결 과**: 대상 환자 전체의 5년 생존율 및 무병생존율은 88% 및 84%였다. 자궁경부 기질 내 침범 10 mm 초과한 환자에서는 5년 무병생존율이 감소하는 양상을 보였다($p<0.05$). 골반 림프절 양성인 환자에서도 5년 무병생존율이 감소하는 양상을 보였다($p<0.05$). 조직학적 분류, 림프혈관강 침범, 수술 절제연 양성은 5년 무병생존율의 감소와 무관하였다. 수술의 방법, 항암제 추가 또한 5년 무병생존율의 감소와 무관하였다. 재발의 양상은 골반 내 재발 4예, 원격전이 11예, 골반 및 원격전이 1예 등으로 관찰되었다. 치료에 따른 부작용은 수술을 요한 소장폐색 2예, 내과적 치료를 요한 혈뇨 2예가 관찰되었다.

**결 론**: 고위험인자를 가진 자궁경부암 환자에서 수술 후 방사선치료가 국소제어에 도움이 되지만, 원격전이를 막을 수 있는 보다 효과적인 치료가 필요하다고 생각된다.

**핵심용어**: 자궁경부암, 방사선치료, 자궁절제술