Yonsei Medical Journal
Vol. 31, No. 4, 1990

Postoperative Radiotherapy for Stage IB Carcinoma of the Uterine Cervix

Jinsil Seong, John J.K. Loh, Gwieon Kim, Changok Suh, Jaewook Kim[1], and Tchankyu Park[1]

Sixty patients, treated with postoperative radiation therapy following radical hysterectomy and pelvic lymphadenectomy for stage Ib carcinoma of the uterine cervix between Jan. 1980 and Dec. 1984 at Department of Radiation Oncology, Yonsei University College of Medicine, were retrospectively analysed. The minimum follow-up period was 5 years. The indications for postoperative radiotherapy were positive pelvic lymphnode (34 pts), a large tumor size more than 3cm in longest diameter (18 pts), positive surgical margin (10 pts), deep stromal invasion (10 pts), and lymphatic permeation (9 pts). The overall 5-year survival rate was 81.8%. The univariate analysis of prognostic factors disclosed tumor size (<3cm, ≥3cm) and the status of the surgical margin (positive, negative) as significant factors (tumor size; 88.1% vs 63%, surgical margin; 85.5% vs 60%, p<0.05). Age (≤40, >40 yrs) was marginally significant (90.2% vs 73.1%, p<0.1). Multivariate analysis clarified two independent prognostic factors; tumor size (p=0.010) and surgical margin (p=0.004). Analysis of the tumor factors with the radiation dose disclosed a better survival rate for patients with a positive surgical margin who were given over 50 Gy than for those who were given below 50 Gy in patients (4/4, 100% vs 2/6, 33.4%; p=0.06). Significant complications requiring surgical correction were not observed. In conclusion, it is believed that the status of the surgical margin and tumor size both have important prognostic significance, and that a radiation dose over 50 Gy is advisable for patients with a positive surgical margin.

Key Words: Postoperative radiotherapy, stage Ib cervical carcinoma, survival, prognostic factor

Stage IB (FIGO) carcinoma of the uterine cervix can be effectively treated by either radical surgery or radical radiation therapy. Prospective (Cullhead 1978; Morley *et al.* 1976; Newton 1975; Roddick *et al.* 1971) and retrospective studies (Brady 1979; Delgado 1978; Musubuchi *et al.* 1969; Perez *et al.* 1979; Selim *et al.* 1971) have shown comparable survival rates for both treatments, with a 5 year survival rate of 80-90%. The value of postoperative irradiation in patients with unfavorable pathological findings in the surgical specimen has not been proved in prospective randomized studies.

The policy in our center is to treat the early stage of cervical cancer with radical hysterectomy and pelvic lymph node dissection (RAH/PLD), except for young patients in whom preservation of ovarian and vaginal function is desired. Postoperative pelvic radiation has been systematically added to the primary treatment when the analysis of the surgical specimen has shown pelvic lymph node metastasis, large tumor size, positive surgical margin, deep stromal invasion, or vascular invasion, in the hope of preventing recurrences and improving survival.

This reports our 5 year experience with this combined surgical-radiotherapeutic approach for stage IB cancer of cervix in an attempt to evaluate the treatment outcome, analyze the prognostic factors, and suggest therapeutic implications, if any.

Received June 18, 1990
Accepted August 17, 1990

Departments of Radiation Oncology, Department of Obstetrics and Ginecology[1] Yonsei University College of Medicine, Seoul, Korea

Supported by a grant from Yonsei University College of Medicine (1990)

Address reprint requests to Dr. J J K Loh, Department of Radiation, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul, Korea, 120-752

MATERIALS AND METHODS

The medical records of 202 patients who had stage Ib cancer of the cervix, treated between Jan. 1980 and Dec. 1984 in the Department of Radiation Oncology, Yonsei University College of Medicine, were reviewed.

Of these, 93 patients were treated with radiation

Table 1. Patients' characteristics

No. of patients (Jan. 1980-Dec. 1984):	60
Age distribution (yrs):	≤ 30: 3
	31 - 40: 19
	41 - 50: 29
	51 - 60: 8
	≥ 61: 1
Histologic type: squamous cell ca.:	56
adenocarcinoma:	4
Pelvic lymph node: negative:	26
positive, ≤3:	30
positive, >3:	4
Tumor size (longest diameter): <3cm:	42
≥3cm:	18
Stromal invasion (over 10mm): absent:	50
present:	10
Surgical margin: negative:	50
positive:	10
Vascular invasion: absent:	51
present:	9
Endometrial extension: absent:	56
present:	4

therapy alone and 109 received postoperative radiotherapy. In 21 patients, postoperative radiotherapy was given for unexpected stage Ib cancer of the cervix following a simple hysterectomy. In another 28 patients, postoperative radiotherapy was given without any knowledge of pelvic lymph node status because RAH was done for those patients without dissection of pelvic lymph nodes. Thus, the number of patients who were treated with postoperative radiotherapy following RAH/PLD was 60. These 60 patients were the subjects of this report.

The ages of the patients ranged from 26 to 65 with an average of 45 years. Fifty-six patients had squamous cell carcinoma and four had adenocarcinoma (Table 1).

Indications for postoperative radiotherapy

The most common indication for radiation therapy after RAH/PLD was positive pelvic lymph nodes. Thirty-four patients had metastases in the pelvic lymph nodes, 26 patients had three or fewer positive lymph nodes and 4 patients over 4 positive lymph nodes. A larger tumor size over 3cm also indicated postoperative radiotherapy in 18 patients. A positive surgical resection margin and deep stromal invasion over 10 mm were found in each of 10 patients. Nine patients had extensive vascular space invasion in the histological specimen. Each patient had one or more pathological findings among those listed above (Table 1).

Radiotherapy

Radiotherapy was done at 4-6 weeks following RAH/PLD. The whole pelvis was irradiated using a 4-field box technique with high energy Linac. The upper border of the field was the promontorium or the intervertebral space L4-L5, except for patients with lymph node metastasis in the common iliac group or up to the bifurcation where the upper border was extended up to the intervertebral space T12-L1. The lateral border of the field was 2cm lateral to the true pelvic brim. The lower border of the field was at the middle of the obturator foramen. Daily tumor dose was 2 Gy. In some patients, a boost of 10-16 Gy was added to the high risk area according to pathological findings after a pelvic dose of 44 Gy. Thus, the total tumor dose ranged from 44 to 60 Gy (mean 50.1 Gy).

Follow-up and statistical analysis

The minimum follow-up period was 5 years. It is our principle is to assess the patients clinically once every 3 months for the first year, every 4 months for the 2nd and 3rd year, every 6 months up to the fifth year and thereafter once every year. Unfortunately, more than half of the patients were not followed in this manner but were contacted by telephone or mail at their home addresses. Fifty-eight patients were followed by the clinical assessment and/or telephone or mail; so, the follow-up rate was 96.7%

Survival rates were estimated by the Kaplan-Meier method and were not corrected for intercurrent death. Univariate analysis was done with log rank test for prognostic analysis. Analysis of tumor factors by radiotherapy dose was done with Fisher's exact test. The program BMDP2L was used for the multivariate analysis (Cox's proportional hazard regression model).

RESULTS

Survival

The 5-year survival rate was 81.1% and the survival curve is presented in Fig. 1.

Prognostic factors

The univariate analysis of prognostic factors is presented in Table 2. The most significant factors were tumor size and the status of the surgical margin ($p<0.05$); a marginally significant factor was the age

of the patients ($p<0.1$). There were 18 patients who presented a large tumor over 3cm in greatest diameter. Among them, the number of patients with tumor size between 3 and 4, 4 and 5, 5 and 6, and more than 6cm in longest diameter were 10, 5, 2, and 1, respectively. Those with a larger tumor over 3cm

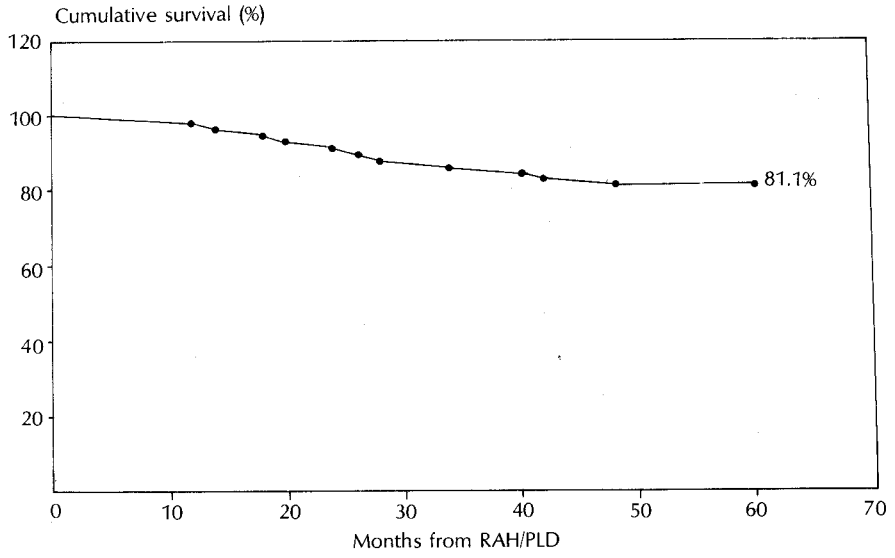

Fig. 1. *Postop RTX for stage IB CA. of the cervix overall 5-YR survival curve*

Table 2. Analysis of prognostic factors (univariate analysis)*

Factors	No. of patients	5-yr survival (%)	
Age (yrs): ≤40	22	95.2	p<0.1*
>40	38	73.1	
Hb level (g/dl): <11	10	70	
≥11	50	83.6	
Size (cm in diameter): <3	42	88.1	p<0.05*
≥3	18	63	
Histology: squamous cell:	56	81.8	
adenocarcinoma	4	66.7	
Margin: negative	50	85.5	p<0.05*
positive	10	60	
Lymph node: negative	26	80.2	
positive	34	81.8	
Stromal invasion: absent	50	79.6	
(>10mm) present	10	90	
Vascular invasion: absent	51	78	
present	9	92	
Endometrial extension: absent	56	81.6	
present	4	75	
Radiation dose: <50Gy	43	79.1	
≥50Gy	17	86.7	

* log rank test

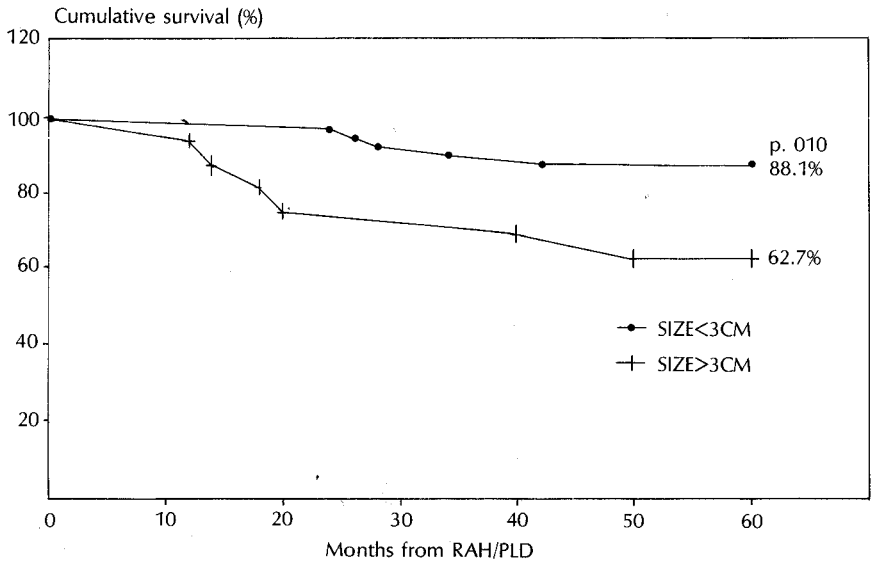

Fig. 2. *Postop RTX for stage IB CA. of the cervix survival curve by tumor size*

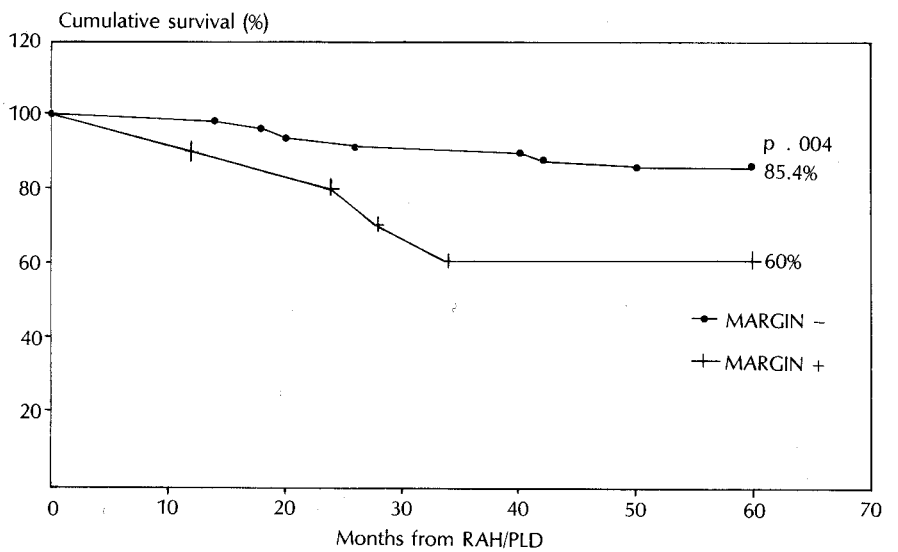

Fig. 3. *Postop RTX for stage IB CA. of the cervix survival curve by status of margin*

had a worse 5-year survival rate than those with a smaller one; 63% vs 88.1%. The surgical resection margin was microscopically positive in 10 patients; their 5-year survival rate (60%) was lower than that of those with a negative surgical margin (85.5%). The patients younger than 40 years did better than those older than 40; the 5-year survival rate was 95.2% vs. 73.1%, which was marginally significant ($p<0.1$). On histology, the 5-year survival rate in squamous cell carcinoma was higher than in adenocarcinoma (66.7%), and the 5-year survival rate in those without deep stromal invasion (90%) was also higher than in those

Table 3. Analysis of prognostic factors (multivariate analysis)*

Factors	P value	Hazard ratio
Age	.084	6.270
Size	.010	9.279
Margin	.004	14.02

* Cox's proportional hazard regression model

Table 5. Complications of radiotherapy

Complication	No. PTS
Cystitis	2
Proctitis	1
Lymphedema	1
Total	4 (6.6%)

with deep stromal invasion (79.6%); but these two factors were not statistically significant. Other factors such as pelvic lymph node status, vascular invasion, endometrial extension, initial Hb level, and radiation dose were not statistically significant as prognostic factors to predict survival.

Multivariate analysis, presented in Table 3, clarified two factors as the most singificant prognostic factors: tumor size (p=.010) and surgical margin (p=.004). Differences in survivals according to tumor size (<3cm vs. ⩾3cm) and surgical margin (positive vs. negative) are shown in Figs. 2 and 3, respectively.

Analysis of the tumor factors in relation to the treatment factors (radiation dose)

Analysis of the tumor factors in cases with a size over 3cm, positive margin, adenocarcinoma, positive pelvic lymph nodes, deep stromal invasion, vascular invasion, or endometrial extension was done in relation to the treatment factors (radiation dose). Although the number was small, the 5-year survival rate was better for patients with a positive margin who received over 50 Gy than those who received below 50 Gy (4/4, 100% vs. 2/6, 33.4%; p=0.06 by Fisher's exact test). (Table 4).

Complications

Complications relating to radiotherapy are presented in Table 5. There were 4 complications (4/60, 6.6%); two cystitis, one proctitis, and one lymphedema. There were no severe major complications requiring surgical intervention or a long hospital stay.

DISCUSSION

One of the possible advantages advocated by surgical treatment in the early stage of uterine cervix carcinoma is that subgroups of patients with more extensive disease than was clinically suspected could be identified. Piver and Chung (1975) and Freidell and Graham (1959) have confirmed that there is a good correlation between the size of cervical tumor, lymph node metastasis, and survival. In Van Nagell and associates' series (1978) of 100 patients with stage Ib cervical carcinoma who underwent radical hysterectomy, vascular invasion was associated with a significant increase in nodal matastases and tumor recurrences. Boyce and associates (1984) also noticed that there was good correlation between the depth of stromal invasion, vascular invasion, and prognosis in stage Ib cervical carcinoma. And the importance of endometrial extension as a prognostic parameter was refocused by Perez *et al.* (1981) in his retrospective review of 473 patients with cervical carcinoma, which showed a high rate of distant metastasis and resulting low survival rate with endometrial extension.

Table 4. Analysis of tumor factors by treatment factor (RT dose)

Factors	No. of patients	<50 Gy: *5YSR (%)	⩾50 Gy: 5YSR (%)
Size ⩾3cm	18	8/13 (61.5)	3/5 (60)
Margin +	10	2/6 (33.4)	4/4 (100) p=0.06**
Adenocarcinoma	4	1/2 (50)	1/2 (50)
Lymph node +	34	19/23 (82.6)	8/11 (72.7)
Stromal invasion	10	1/2 (50)	7/8 (87.5)
Vascular invasion	9	6/6 (100)	2/3 (66.7)
Endometrial extension	4	1/2 (50)	2/2 (100)

*5-year survival rate **Fisher is exact test

While postoperative radiation treatment has been advocated and widely used for patients with adverse prognostic factors as listed above, the benefits have not been adequately confirmed; some authors (Chung *et al.* 1980; Kjorstad *et al.* 1983; Marziale *et al.* 1981) reported improved relapse-free survival and overall survival while others (Figge and Tamimi 1981; Morrow 1980) did not. However, it is also necessary to have detailed knowledge about the postoperative radiotherapy group. Radiotherapy might still be an important adjuvant treatment, and we need to discern some parameters associated with the prognosis in this group.

In our series, the 5-year survival rate of 81.8% was comparable to or slightly higher than that of others' series (Fuller 1982; Guttman 1970).

Multivariate analysis identified two independent prognostic factors. Tumor size greater than 3cm in longest diameter had a poor prognosis; a 63% 5-year survival rate as compared to 88.1% for those less than 3cm. Chung et al. (1980) reported that the patients with a bulky tumor (>4cm) had a higher incidence of failure and Piver and Chung (1975) also reported 84-90% of 5-year survival rates wih less than 3cm, while survival dropped to 66% with more than 3cm in longest diameter. Rotman *et al.* (1981) even suggested a newer subclassification of stage Ib, adopting tumor size (<2cm or >2cm) and other factors in his modified FIGO staging system. The other independent prognostic factor was the status of the surgical margin. The resection margin was positive in the parametrial side in 10 patients which indicates microscopical infiltration in the parametrium. Fuller *et al.* (1982) reported a 43% 5-year survival rate in 32 patients who had both lymph node metastasis and parametrial spread. In Gonzalez's retrospective analysis (1989) the 5-year survival rate decreased from 76% in patients with lymph node metastasis alone to 39% when, in addition, invasion of the parametrium was found. Kim *et al.* (1988) also reported 5 recurrences among 7 margin positive patients.

There have been some suggestions in radiotherapy of margin positive patients. Kim *et al.* (1988) reported that all 5 patients with paracevical margins treated with vaginal ovoid irradiation alone had pelvic recurrence, and no local failure occurred in the other three patients treated with whole pelvic irradiation. However, all patients with vaginal margin alone treated with vaginal ovoid or whole pelvic irradiation had no recurrence in the pelvis. He suggested that whole pelvis irradiation with or without vaginal ovoid irradiation is necessary with a close paracervical margin. But careful analysis of the radiotherapy method in his study showed that the dose to the paracervical area was less than 30% of the prescribed dose because the vagina was shortened after surgery, and he prescribed 50 Gy at 1cm above and between two ovoids. Therefore, it can be suggested that excellent local control in the pelvis is related more to the total tumor dose than to the treatment method.

In our study, analysis of tumor factors in relation to radiation dose disclosed that all four margin positive patients who were given over 50 Gy survived more than 5 years (100%), while only 2 among 6 margin positive patients who were given less than 50 Gy survived 5 years (33.4%); this difference was marginally significant ($p=0.06$). It is not easy to increase the radiation dose to the pelvic area, which has already been surgically dissected, since there is a high risk of complications. Although 50 Gy has become a widely accepted regimen for eradication of clinically occult, microscopic cancer cell (Fletcher 1973), the dose required to eradicate subclinical disease in 90% of patients who received radical surgery may be substantially higher. Hogan *et al.* (1982) noted that 6 of 6 high risk patients achieved local control when a minimum dose of 60 Gy was prescribed, whereas only 9 of 14 attained local control when a lesser dose was given. Russell *et al.* (1984) reported a similar result with 60 Gy. Data supporting this hypothesis exist in published dose-response relationships for postoperative treatment for carcinomas of the rectum (Allee *et al.* 1981) and carcinomas of the aerodigestive tract (Marcus *et al.* 1979) following surgery.

The other possible prognostic factors which were analysed included age, histology, lymph node status, stromal invasion, vascular invasion, endometrial extension, as well as initial Hb level. However, these were not found to be independent prognostic factors in our series, although some of them showed a distinct difference in survival rate in some reports. Lymph node status, in particular, has been a matter of debate for a long time; some (Kjorstad *et al.* 1983; Marziale *et al.* 1981) reported a benefit from postoperative radiotherapy in the lymph node positive group, but others (Morrow 1980) did not. Our data might suggest that the addition of radiotherapy to operation dose not affect the prognostic significance of lymph node status; however, it is too early to conclude this.

Severe complications requiring surgical correction were not observed. Complications, as listed in Table 6, were not detrimental to the patients. The reason why our complication rate is lower than reported by other authors (Chung *et al.* 1980; Gonzalez *et al.* 1989; Patanaphan *et al.* 1986) seems due to the treatment

technique; whole pelvic irradiation did not exceed 50 Gy while additional radiation was boosted to the local risk area by the shrinking field technique.

In conclusion, the role of postoperative radiation following radical surgery in stage Ib carcinoma of the uterine cervix is not yet definitively established. Until the results of a randomized clinical trial are available, postoperative pelvic irradiation may benefit a small subset of patients. It is believed that the status of the surgical resection margin and tumor size have an important prognostic significance. On the basis of our data, an increment of radiation dose over 50 Gy is advisable for those with positive margins.

REFERENCES

Allee PE, Gunderson LL, Munzenrider JE: Postoperative radiation therapy for residual colorectal carcinoma(Abstr). *Int J Radiat Oncol Biol Phys 7:1208, 1981*

Boyce J, Fruchter RG, Nicastri A: Prognostic factors in stage I carcinoma of the cervix. *Gynecol Oncol 12:154-165, 1981*

Brady LW: Surgery or radiation therapy for stage I and IIA carcinoma of the cervix. *Int J Radiat Oncol Biol Phys 5:1877-1879, 1979*

Chung CK, Nahhas WA, Stryker JA: Analysis of factors contributing to treatment failures in stages Ib and IIA carcinoma of the cervix. *Am J Obstet Gynecol 138: 550-556, 1980*

Cullhead S: Carcinoma cervix uteri stages I and IIA-treatment, histopathology, prognosis. *Acta Obstet Gynecol Scand(Suppl) 75:1-49, 1978*

Delgado G: Stage IB squamous cancer of the cervix: The choice of treatment. *Obstet Gynecol 138:550-556, 1978*

Figge DC, Tamimi HK: Patterns of recurrence of carcinoma following radical hysterectomy. *Am J Obstet Gynecol 140:213-220, 1981*

Fletcher GH: Clinical dose-response curves of human malignant epithelial tumours. *Br J Radiol 46:1-12, 1973*

Friedell GH, Graham JB: Regional lymph node involvement in small carcinoma of the cervix. *Surg Gynecol Obstet 108:513-517, 1959*

Fuller AF, Elliott N, Kosloff C: Lymph node metastases from carcinoma of the cervix, stage IB and IIA: Implications for prognosis and treatment. *Gynecol Oncol 13:165-174, 1982*

Gonzalez DG, Ketting BW, Bunningen BV, Dijk JDD: 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 16:389-395, 1989*

Guttman R,:Significance of postoperative irradiation in carcinoma of the cervix: A ten year survey. *Am J Roentgenol 108:102-108, 1970*

Hogan WM, Littman P, Grinner L, Miller CL, Mikuta JJ: Results of radiation therapy given after radical hysterectomy. *Cancer 49:1278-1285, 1982*

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 14:445-449, 1988*

Kjorstad KE, Martinbeau PW:Stage IB carcinoma of the cervix. The Norweigian Radium Hospital: Results and complications III-urinary and gastrointestinal complications. *Gynecol Oncol 15:42-47, 1983*

Marcus RB, Million RR, Cassissi NJ: Postoperative irradiation for squamous cell carcinomas of the head and neck: Analysis of time-dose factors related to control above the clavicles. *Int J Radiat Oncol Biol Phys 5:1943-1949, 1979*

Marziale P, Atlante G: Combined radiation and surgical treatment of stages IB and IIA and B carcinoma of the cervix. *Gyncol Oncol 11:175-183, 1981*

Masubuchi K, Tenjin Y: Five year cure rate for carcinoma of the cervix uteri with special reference to the comparison of surgical and radiation therapy. *Am J Obstet Gynecol 103:566-573, 1969*

Morley GW, Seski JC: Radical pelvic surgery versus radiation therapy for stage I carcinoma of the cervix(exclusive of microinvasion). *Am J Obstet Gynecol 126:785-798, 1976*

Morrow CP: Is pelvic radiation beneficial in the postoperative management of stage IB squamous cell carcinoma of the cervix with pelvic node metastasis treated by radical hysterectomy and pelvic lymphadenectomy? Panel report SGO, 1979. *Gynecol Oncol 10:105-110, 1980*

Newton M: Radical hysterectomy or radiotherapy for stage I cervical cancer. A prospective comparison with 5-and 10-year follow-up. *Am J Obstet Gynecol 123:535-542, 1975*

Patanaphan V, Poussin-Rossilo H, Santa UV, Salazar OM: Cancer of uterine cervix stage IB: Treatment results and prognostic factors. *Cancer 57:866-870, 1986*

Perez CA, Breaux S, Madoc-Jones H: Irradiation alone or in combination with surgery in stage IB and IIA carcinoma of the uterine cervix. A nonrandomized comparison. *Cancer 43:1062-1072, 1979*

Perez CA, Camel HM, Kao MS: Endometrial extension of carcinoma of the uterine cervix: A prognostic factor that may modify staging. *Cancer 48:170-180, 1981*

Piver MS, Chung WS: Prognostic significance of cervical lesion size and pelvic node metastases in cervical carcinoma. *Obstet Gynecol 46:507-510, 1975*

Roddick JW, Greenlaw RH: Treatment of cervical cancer. A randomized study of operation and radiation. *Am J Obstet Gynecol 109:754-759, 1971*

Rotman M, John M, Boyce J: Prognostic factors in cervical carcinoma: Implications in staging and management. *Cencer 48:560-567, 1981*

Russell AH, Tong DY, Figge DC, Tamimi H, 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 10:211-214, 1984*

Selim MA, Kurohara SS: Surgical or radiation therapy for cancer of the cervix stage I. *Obstet Gynecol 38:251-255, 1971*

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