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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[1,2,3]

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Objective. **The objective of this study was to evaluate the benefits and risk of adjuvant pelvic radiotherapy aimed at reducing recurrence in women with Stage IB cervical cancer treated by radical hysterectomy and pelvic lymphadenectomy.**

Methods. **Two hundred seventy-seven eligible patients were entered with at least two of the following risk factors: >1/3 stromal invasion, capillary lymphatic space involvement, and large clinical tumor diameter. Of 277 patients, 137 were randomized to pelvic radiotherapy (RT) and 140 to no further treatment (NFT).**

Results. **Twenty-one (15%) in the RT group and 39 (28%) in the NFT group had a cancer recurrence, 18 of whom were vaginal/pelvic in the RT and 27 in the NFT group. In the RT group, of 18 (13%) who died, 15 died of cancer. In the NFT group, of the 30 (21%) who died, 25 died from cancer. Life table analysis indicated a statistically significant (47%) reduction in risk of recurrence (relative risk = 0.53, $P = 0.008$, one-tail) among the RT group, with recurrence-free rates at 2 years of 88% versus 79% for the RT and NFT groups, respectively. Severe or life-threatening (Gynecologic Oncology Group grade 3 or 4) urologic adverse effects occurred in 4 (3.1%) in the RT group and 2 (1.4%) in the NFT group; 3 (2.3%) and 1 (0.7%) hematologic; 4 (3.1%) and 0 gastrointestinal (GI); and 1 (0.8%) and 0 neurologic, respectively. One patient's death was attributable to grade 4 GI adverse effects.**

Conclusions. **Adjuvant pelvic radiotherapy following radical surgery reduces the number of recurrences in women with Stage IB cervical cancer at the cost of 6% grade 3/4 adverse events versus 2.1% in the NFT group.**

INTRODUCTION

Stage I cervical cancer has a relatively favorable prognosis with an 80% cure rate achieved with radical hysterectomy or radiotherapy. However, the 20% mortality after surgery has remained virtually unchanged during the past three decades [1].

Certain clinical and pathologic risk factors for Stage 1 cervical cancer recurrence have been identified. Pelvic lymph node metastases, for example have been known to decrease the 5-year survival from 82 to 90% in patients with negative nodes to 38 to 61% in patients with positive lymph nodes [2]. Additional risk factors for recurrence, e.g., large tumor diameter (LTD), deep stromal invasion (DSI), and presence of tumor in the capillary lymphatic spaces (CLS) found on microscopic examination have been only recently recognized and less extensively investigated than lymph node metastases. However, sufficient data have been reported in the literature to categorize LTD, DSI, and CLS as independent risk factors because of their frequent association with increased cancer recurrence and mortality [3–7]. An analysis of data on 575 women enrolled in a previous Gynecologic Oncology Group (GOG) study of clinical and pathologic predictors of surgically treated stage carcinoma of the cervix confirmed the roles of LTD, DSI, and CLS as risk factors, increasing the probability of cancer recurrence at 3 years from 2 to 31%. Furthermore, that study estimated that the proportion of women with such risk factors was 25% of all Stage IB cervical cancer patients with negative

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[2] Reprint requests should be addressed to GOG Administrative Office, Suite 1945, 1234 Market Street, Philadelphia, PA 19107.

[3] The Radiological Physics Center (RPC) through its comprehensive quality assurance program ensured that the radiation doses delivered to all patients in this study are clinically comparable. The RPC reviewed all technical aspects of the treatment, verified the reported doses, and participated in the clinical evaluation of all patients. In addition, the RPC monitored the calibration of the therapy units using mailed dosimeters at all participating institutions and on-site evaluations of selected institutions as needed.

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TABLE 1
Eligibility Criteria

CLS[a]	Stromal invasion	Tumor size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2 cm
Positive	Superficial 1/3	≥5 cm
Negative	Deep or middle 1/3	≥4 cm

[a] Capillary lymphatic space tumor involvement.

lymph nodes. The results of that GOG study were subsequently published in 1990 [8].

Traditionally, women with lymph node metastases have been treated with postoperative adjuvant radiotherapy. Several authors proposed that patients with certain primary tumor-related factors such as LTD, DSI, and CLS might also benefit from postoperative radiotherapy [3, 6, 7, 9]. One of them reported favorable results from an uncontrolled trial of adjuvant radiotherapy [3].

In 1988 the GOG initiated a prospective randomized study (GOG #92), reported here, to investigate the benefits and risks of adjuvant radiotherapy for Stage I cervical cancer patients treated by conventional radical hysterectomy and pelvic lymphadenectomy and who were at high risk for recurrence, because of LTD, DSI, CLS, but excluding patients with lymph node metastases.

PATIENTS AND METHODS

Study Design

The GOG #92 multicenter prospective randomized study was designed to determine whether postoperative pelvic radiotherapy following radical hysterectomy and pelvic node dissection would reduce the rate of recurrence and decrease the mortality in Stage IB cervical cancer patients with large tumor diameter, deep stromal invasion by tumor, and presence of tumor in the capillary lymphatic spaces found on microscopic examination. A previous GOG study estimated that women with one of the following combinations of risk factors had, on average, a 31% chance of recurring in 3 years [2]. Women with one of the combinations of risk factors as defined in Table 1 were eligible to enter this study.

The study's target sample size was set at 169 eligible patients based on a desire to detect a 55% decrease in recurrence rate (exponential model with $\lambda = 0.01$ recurrences/month) with the use of radiation therapy [10]. In 1993, the sample size goal was increased because of the lower than expected recurrence rate, a better estimate of the change in the recurrence rate over time, and a small, but significant, frequency of noncompliance in the radiation therapy (RT) regimen. The revised sample size goal was 260 patients and the final analysis of recurrence-free interval would occur once 60 recurrences were observed. This goal would allow the detection of a 47% reduction in the risk of recurrence with complete compliance or 50% reduction with 8% noncompliance among those registered to the RT regimen [11, 12]. All designs allowed for 80% statistical power when performing a one-tail test at the 0.05 level.

Eligibility

Written informed consent was obtained from all patients prior to entry on study fulfilling all institutional, state, and federal regulations. Patients were eligible for the study if they had primary Stage IB squamous, adenosquamous carcinoma, or adenocarcinoma of cervix initially treated with a standard radical hysterectomy and who had negative lymph nodes but one of the previously described combination of risk factors. Radical hysterectomy required removal of the uterus and contiguous parametrial tissue to its most lateral extent along with paravaginal tissue and upper quarter of the vagina along the proximal uterosacral ligaments. The ureter had to be unroofed from its entry into the broad ligament to its intramural portion in the bladder and dissected laterally from its attachments to the cardinal ligament. Pelvic lymphadenectomy required bilateral removal of all nodal tissue and skeletonization of all vessels from the mid portion of the psoas muscle to uterer medially including the hypogastric artery and vein and from the obturator fossa anterior to the obturator nerve. Tumor diameter was estimated by palpation. Institutional pathologists measured the depth of stromal tumor invasion with a millimeter ruler and made a determination of a presence or absence of CLS. Other eligibility criteria for enrollment into the study included normal blood counts, normal liver and kidney function, absence of genitourinary tract abnormality as determined by intravenous pyelogram, renal sonogram, or computerized tomography, and absence of intercurrent diseases or other conditions that might not permit completion of the study or the required follow-up. After the eligibility criteria were verified, patients were randomly assigned to one of the two regimens: pelvic radiation or no further therapy.

Radiation Therapy

Radiation therapy was started within 4 to 6 weeks postoperatively. Patients received external beam irradiation and no brachytherapy. The pelvic irradiation was given with a four-field technique with a megavoltage beam, although cobalt-60 was allowed if the SSD was greater than 80 cm. Radiation dose was from 46 Gy in 23 fractions to 50.4 Gy in 28 fractions, 5 fractions per week. Each patient was to be given daily fractions of 1.80–2.00 Gy over 41/2 to 6 weeks. Treatment breaks for clinical problems (vomiting or diarrhea) were allowed to total no more than 1 week.

Follow-up Observation

Patients were to be evaluated by physical examination, blood counts, blood chemistries, and chest x-rays, every 3

TABLE 2
Patient Characteristics

Characteristic	Radiation therapy	No further therapy
Cell type		
Squamous cell	103 (75.2%)	115 (82.1%)
Adenocarcinoma	16 (11.7%)	11 (7.9%)
Adenosquamous	18 (13.1%)	14 (10.0%)
Age		
≤30	16 (11.7%)	16 (11.4%)
31–60	108 (78.8%)	111 (79.3%)
61–80	13 (9.5%)	14 (9.3%)
GOG performance grade		
0	92 (67.2%)	93 (66.4%)
1	41 (29.9%)	45 (32.1%)
2	4 (2.9%)	2 (0.7%)
Race		
White	72 (52.6%)	79 (56.4%)
Black	30 (21.9%)	26 (18.6%)
Hispanic	14 (10.2%)	13 (9.3%)
Asian	10 (7.3%)	11 (7.9%)
Other	11 (8.0%)	11 (7.9%)
Maximum tumor parameter		
≤2 cm	10 (7.5%)	28 (20.6%)
2.1–3.0 cm	29 (21.8%)	30 (22.1%)
3.1–4.0 cm	60 (45.1%)	38 (27.9%)
5.1–6.0 cm	29 (21.8%)	31 (22.8%)
≥6.0 cm	5 (3.8%)	9 (6.6%)
Unknown size[a]	4 —	4 —

[a] Not included in percentage computation.

months during the first 2 years of follow-up, and every 6 months during the subsequent years. Intravenous pyelogram, renal sonogram, or computed tomography (CT) scan with contrast was to be done at 6 months and then yearly. Results of these tests as well as changes of therapy, adverse effects, progression, or death were reported.

Quality Control

All histology slides were reviewed by two pathologists of the GOG Pathology Committee who measured the depth of stromal invasion expressed in thirds of cervical thickness and ascertained the presence or absence of the capillary lymphatic space tumor involvement and the tumor cell type. Any disagreement among the reviewing pathologists was resolved by a GOG referee pathologist. The Radiotherapy Committee examined therapy forms, diagrams of irradiated fields, dosimetry curves, and portal fields for each external field. Review of operative reports was conducted to evaluate the completeness of surgical procedures.

Statistical Methods

The primary outcome variable was recurrence-free interval (RFI). RFI was defined as the time from study entry to physical or radiographic evidence of disease recurrence, or date the patient was last seen. Similarly, survival is defined from date of study entry to death, or date last seen. Sites of recurrence were classified as local if detected in the pelvis or vagina, and distant if detected in extrapelvic locations. Life tables were computed using the method of Kaplan and Meier [13]. The difference in RFI and survival by treatment regimen was evaluated using the log-rank test [14] applying the intent-to-treat principle. The difference between treatment regimens, while adjusting for prognostic factors, was accomplished using the Cox Model [15]. Imbalances between patient and disease characteristics and treatment regimens was accomplished using the Pearson's χ^2 test [16]. When the characteristic was continuous (e.g., age) the Kruskal–Wallis test [17] was used.

RESULTS

Between March 1988 and September 1995, 299 women were accessioned into the study. Twenty-two patients were excluded: 14 because of lack of documentation of high risk criteria, 4 for wrong stage, 1 for inadequate surgery, 2 for inadequate pathology material for review, and 1 for not having an intravenous pyelogram or CT scan. Of the remaining 277 eligible patients, 137 were randomly assigned to radiotherapy and 140 to no further treatment. One hundred and fifty-one patients (55%) were white, 56 (20%) were black, 27 (10%) were Hispanic, and 21 (8%) were Asian. The median age at study entry was 41 (range: 20–80) and the 25th and 75th percentiles were 34 and 50, respectively. The tumor cell type was squamous in 218 (79%) women, adenosquamous in 32 (12%), and adenocarcinoma in 27 (10%). The distribution of these factors as well as the GOG performance scale were well balanced between the two treatment regimens (Table 2). There were 128 (46%) patients with the risk factors of positive CLS and deep one-third stromal invasion, 65 (23%) had positive CLS, middle third stromal invasion and tumor size ≥2 cm, 82 (30%) had negative CLS, middle or deep third stromal invasion and a ≥4-cm tumor, and 2 (0.7%) had positive CLS, superficial stromal invasion, and tumor size ≥5 cm (Table 3). The distribution of individual risk factors between the treatment regimen was somewhat imbalanced. There was a disproportionately

TABLE 3
Combination of the Three Risk Factors: CLS, Stromal Invasion, and Tumor Size by Treatment Regimen

CLS	Stromal invasion	Tumor size	Radiation therapy	No further therapy
+CLS	Deep 1/3	Any	60 (43.0%)	68 (48.6%)
+CLS	Middle 1/3	≥2 cm	28 (20.4%)	37 (26.4%)
−CLS	Deep or middle 1/3	≥4 cm	48 (35.0%)	34 (29.3%)
+CLS	Superficial 1/3	≥5 cm	1 (0.7%)	1 (0.7%)
			137 (100.0%)	140 (100.0%)

Note. CLS, capillary lymphatic space.

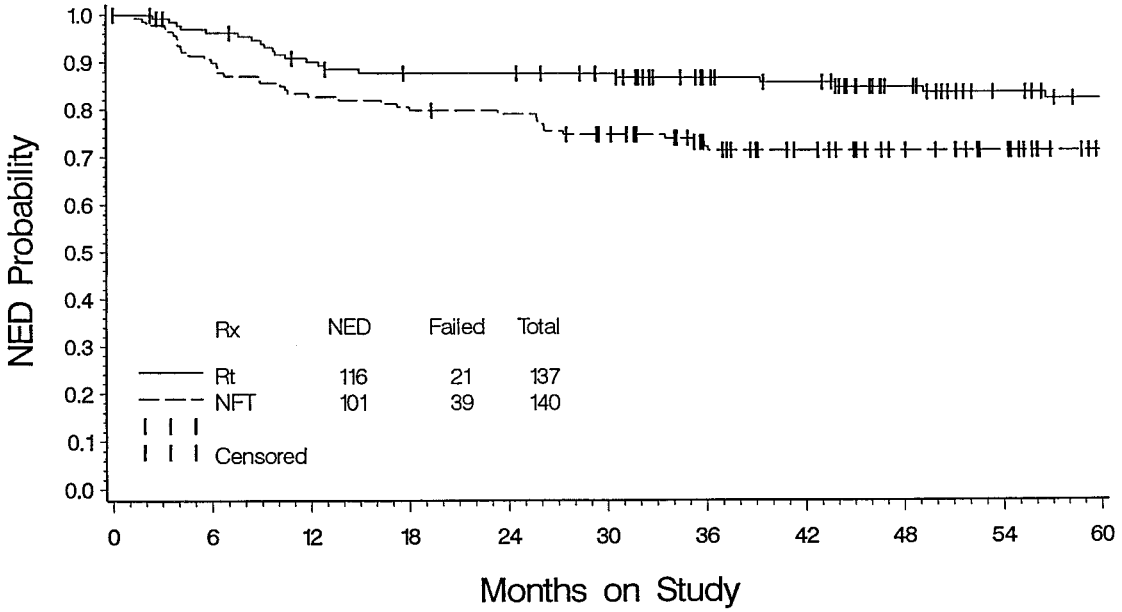

FIG. 1. Recurrence-free interval by treatment.

larger number of patients with positive CLS among the NFT regimen (24% versus 35%) and more patients with >4 cm diameter tumors in the RT regimen (62% versus 54%). However, the overall risk for recurrence was very similar in each regimen when all three risk factors were considered as a group (See Cox Model analyses).

Of the 137 patients randomized to radiotherapy, 9 (6.6%) refused all radiotherapy and 6 (4.4%) refused to continue therapy after receiving less than 85% of the prescribed dose of 50.4 Gy (3.6, 3.6, 10.4, 14.4, 16.2, and 36.0 Gy). One patient discontinued radiotherapy due to an adverse reaction after receiving 21.6 Gy. In addition, 9 (6.6%) noncompliant patients had acceptable radiation doses (≥85% of 50.4 Gy) but in excess of 20% protraction of overall treatment time. Two other patients exceeded 20% protraction of treatment time due to an adverse reaction to the radiation requiring interruption of therapy.

Thirty-nine (27.9%) of the 140 women in the NFT group developed cancer recurrence, 27 (19.3%) local (vagina or pelvis), and 10 (7.1%) distant. By contrast, there were only 21 (15.3%) cancer recurrences, 18 (13.1%) local and 3 (2.2%) distant among the 137 patients treated with postoperative radiation. The site of recurrence was unknown for 2 patients. Notably, there were only 2 isolated vaginal vault recurrences in the irradiated group versus 8 among the NFT patients. The log–rank test was statistically significant ($P = 0.008$, one-tail). The crude estimate in the reduction in risk in patients receiving adjuvant radiotherapy was 47% (i.e., relative risk = 0.53) with the recurrence-free rate of 88% in the radiotherapy group and 79% in the no-further-therapy group at 2 years (Fig. 1). Forty-five (78%) of 58 recurrences were local only (vagina or pelvis) (Table 4). Eighty-six percent of patients have either died or have been followed at least 3 years. The median follow-up is 5 years for those who are alive with no evidence of disease.

The Cox model analysis indicated that when adjusting for all combinations of the three risk factors—tumor size, CLS, and the depth of invasion—the risk of recurrence was significantly reduced by 44% in the radiation group ($P = 0.019$, one-tail).

Forty-eight patients have died as of this report (final analysis of survival awaits further follow-up until 60 deaths have occurred). Thirty (21%) patients among those in the NFT group died, 25 (18%) from cancer, compared to 18 (13%) deaths in the RT group, 15 (11%) of whom died from cancer with one attributable to treatment (Table 5). The relative mortality rate is

TABLE 4
Recurrences by Treatment Regimen

Site of recurrence	Radiation therapy ($N = 137$)	No further therapy ($N = 140$)
No evidence of disease	116 (84.7%)	101 (72.1%)
Recurrences	21 (15.3%)	39 (27.9%)
Local	18 (13.1%)	27 (19.3%)
Vagina	2	8
Pelvis	15	17
Vagina and pelvis	1	2
Distal	3 (2.2%)	10 (7.1%)
Abdomen	0	3
Abdomen and pelvis	0	1
Lung	2	2
Lung and pelvis	0	2
Lung and brain	0	1
Bone and supraclavicular lymph node	1	1
Unknown	0 (0.0%)	2 (1.4%)

TABLE 5
Deaths by Treatment Regimen

Status	Radiation therapy ($N = 137$)	No further therapy ($N = 140$)
Alive	119 (86.9%)	110 (78.6%)
Dead	18 (13.1%)	30 (21.4%)
Treatment	1	0
Disease	15	25
Other	2	2
Unknown	0	3

estimated at 0.64 which indicates 36% less mortality in the radiation group; a significance level is not provided because the survival data are not mature.

There is a small but noteworthy imbalance in the follow-up between the two treatment regimens. Of those who are alive, six patients are lost-to-follow-up within the first year in the RT group while one is lost in the NFT group. Within 2 years on study, there are eight and three patients in the RT group and NFT group, respectively. In an attempt to evaluate the impact of this imbalance, the log–rank test was recalculated assuming the first five patients lost (the excess number) in the RT group recurred at the time of their last clinical evaluation. The difference between treatment groups remained statistically significant.

The adverse effects by organ system and treatment group are displayed in Table 6. Nine (7.0%) of the 128 patients who received radiotherapy had 11 episodes of grade 3 (severe) or 4 (life-threatening) adverse effects compared to 3 (2.1%) from the NFT group. Of the 3 patients with grade 4 toxicities, 1 patient had a complication involving the urogenital tract, 1 gastrointestinal, and 1 both hematologic and urogenital toxicity. The patient who developed an enteric fistula managed by enterocoelic bypass died from cancer. Another patient with a vesico-vaginal fistula died from complications of bacteremia, including renal and liver failure and disseminated intravascular coagulation. One patient with severely decreased bladder volume required a permanent Indiana pouch urinary conduit for relief of urinary incontinence. Other serious adverse effects regressed either spontaneously (transient paraplegia in one patient), or after treatment (percutaneous nephrostomies for bilateral ureteral obstruction and transfusion of packed cells for severe anemia with a drop of hematocrit to 20%).

DISCUSSION

The risk factors used to select patients for this study have been investigated and reported in the literature. Both large tumor diameter and deep stromal invasion are indices of large tumor volume, conceivably affecting cancer progression and its metastatic spread. Chung *et al*. reported that cervical cancer larger than 4 cm in diameter determined by preoperative palpation was associated with a 5-fold increase in pelvic lymph node metastases, a 10-fold increase in recurrences, and a 50% decrease in survival [3]. Deep tumor invasion into cervical stroma (measured either in millimeters or in thirds of the total cervical thickness) has been also shown in association with lymph node metastases, recurrence, and poorer survival [4].

The invasion of lymphvascular spaces by tumor has been found to be an unfavorable prognostic factor by many investigators [3–7] but its significance was denied by others [20]. Boyce reported that vascular invasion contributed prognostic information beyond the cervical size. Sedlis *et al.,* in a GOG study of microinvasive cervical carcinoma, reported two deaths among the 23% patients with vascular spread [21]. However, Roche and Norris questioned the validity of the CLS finding because, as they state, if enough sections are made, most cases might show vascular invasion [20]. Boyce *et al.* emphasized that a combination of risk factors correlated better with the survival than one factor alone [7].

Of the three risk factors, depth of invasion seems the most objective and accurate method—a direct measurement on the histological slide. Furthermore, repeat measurements from the same slide can be taken by the reviewers for the quality control procedures.

Estimating tumor diameter by palpation is more subjective and imprecise than the direct measurement of the depth of invasion. In addition, preoperative tumor size cannot be verified for quality control. Nevertheless, we found tumor diameter to be the most significant risk factors in the Cox model analysis of our study results, confirming multiple data sets which demonstrate that the size of the primary cancer is critical for local control despite the imprecision of measurement [22].

The evaluation of capillary lymphatic space involvement is also subjective. Significant interobserver variability was reported by Zaino *et al.* in a recent study on reproducibility of pathologists assessment of vascular invasion and other histological predictors [23]. The formula combining the three risk factors that we used to determine patient eligibility may appear

TABLE 6
Severe or Life-Threatening (GOG Grade 3–4) Adverse Effects by Treatment Regimen

	Radiation therapy $N = 128$[a]	No further therapy $N = 140$
Adverse effect	Grades 3–4	Grades 3–4
Hematologic	3 (2.3)	1 (0.7)
Gastrointestinal	3 (2.3)	0 (0.0)
Genitourinary	4 (3.1)	2 (1.4)
CV	0 (0.0)	0 (0.0)
Neurologic	1 (0.8)	0 (0.0)
Cutaneous	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)

[a] Not included are nine patients who refused all radiotherapy.

complicated. Nevertheless, the use of this formula by the participating institutions has been successful in achieving a high acceptance rate with only 22 patients (7%) found ineligible for the study.

We reanalyzed our results using the Cox model trying to simplify the formula or to use only a single risk factor as a predictor. However, the combination of factors proved more accurate than any of the factors alone.

A detailed GOG clinical pathologic study had established that certain patients with poor prognostic factors related to the primary tumor (i.e., large tumor size, deep stromal invasion, and capillary lymphatic space tumor involvement) but without lymph node involvement had a risk of recurrence of 31% after radical hysterectomy and pelvic lymphadenectomy [8]. The present prospective randomized study showed that adjunctive radiotherapy significantly reduced the number of cancer recurrences in women with the above risk factors by 44% and that the difference in recurrences between irradiated and nonirradiated patients was statistically significant at the $P = 0.019$ level. However, caution must be observed due to the disproportionately higher number of patients that are "lost to follow-up" among those receiving radiation therapy and the need for further follow-up to determine what impact radiation therapy has on survival. It is conceivable that higher pelvic radiation doses could further reduce the pelvic local failure rate. However, addition of vault brachytherapy is unlikely to improve the results since there were only two isolated vault failures.

There were significantly fewer recurrences in the irradiated group; the numbers of both pelvic and distal recurrences were less. How local therapy affects distal spread is not clearly understood; hypothetical mechanisms include eliminating the risk of subsequent spread from an uncontrolled primary [18].

The use of adjuvant radiotherapy to improve the outcome in the Stage I cervical cancer patients with large tumor diameter, deep invasion, and CLS has been previously proposed [3, 4]. One report showed that postoperative radiation "prevented local recurrences and improved ten year tumor-free-survival" in a small number of women with CLS, DSI, and microscopically involved lymph nodes [3]. More recently, Thomas and Dembo postulated that women with negative nodes but primary tumor-related poor prognostic factors were more likely to recur in the pelvis than in distant sites and, therefore, may benefit from pelvic irradiation. By contrast, in women with positive nodes local failure is more frequently associated with metastases in distant sites that are not affected by pelvic irradiation [19]. Interestingly, our prospective study did provide conclusive evidence of pelvic radiotherapy being effective in women with primary tumor-related risk factors but negative nodes. However, no such evidence from randomized trials is available about effective treatment of positive lymph nodes. The GOG attempted to conduct a randomized radiotherapy trial for women with positive nodes, but could not complete the study because of failure to enroll a sufficient number of patients (unpublished GOG data). Our present study confirms both predicted and reported benefits from postoperative radiation.

It should be noted that the 27% recurrence rate at 3 years in our study population is lower than the anticipated one-third. This difference can be explained by an overestimation of risk by the regression model which commonly occurs; this phenomena is sometimes referred to as regression to the mean. Partly due to this lower risk, the sample size was increased in August 1993 in order that the statistical power of the trial would be maintained.

A significant number of women with Stage IB cervical cancer should benefit from adjuvant pelvic irradiation because 25% of the lymph-node negative patients have high risk factors according to the 1990 GOG data [8]. Moreover, Thomas and Dembo have demonstrated that, in absolute terms, an equal number of deaths occur among the estimated 85% of Stage IB cervical cancer patients with negative nodes as among the 15% with positive nodes. Since the node-negative group accounts for one-half of all Stage IB cervical cancer deaths adjuvant radiotherapy for women with risk factors should substantially reduce the overall Stage IB mortality [19].

Increased morbidity in patients receiving full course radiotherapy following radical surgery for cervical cancer has been reported [24]. Especially vulnerable to adverse radiation effects are the bladder and the ureters due to compromised circulation from surgical dissection and the intestines because of adhesions and reduced motility. In our study, major life-threatening adverse effects were encountered in 5 (4%) women among the 128 who received radiotherapy. One of these women died from complications of enteric fistula and another died from cancer after successful management of intestinal injury. Three of 5 women with major adverse effects recovered either spontaneously or after appropriate treatment. The rate of postradiation complications in our study was similar to those reported in the literature [24].

Thus, adjunctive radiotherapy is beneficial for Stage I cervical cancer patients with clinical–pathological risk factors for recurrence other than positive nodes. This conclusion is based on a significant reduction of cancer recurrences in patients in our study and acceptably low morbidity with a single treatment-related fatality.

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Hospitals and Clinics, Southwestern Medical Center of Texas, Indiana University Medical Center, Bowman Gray School of Medicine, Albany Medical College, University of California Medical Center at Irvine, Tufts-New England Medical Center, Rush-Presbyterian-St. Lukes Medical Center, Stanford University Medical Center, State University of New York at Brooklyn, University of Kentucky, Eastern Virginia Medical School, Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Pennsylvania Hospital, Washington University School of Medicine, Cooper Hospital/University Medical Center, Columbus Cancer Council/Ohio State, M. D. Anderson Cancer Center, University of Massachusetts Medical Center, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, University of Chicago, University of Arizona.

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