ONCOLOGY

Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial

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OBJECTIVE: The objective of the study was to confirm that concurrent cisplatin (CT) with radiation therapy (RT) is associated with improved long-term progression-free survival (PFS) and overall survival (OS), compared with RT alone in stage IB bulky carcinoma of the cervix, when both groups' therapy is followed by hysterectomy.

STUDY DESIGN: Three hundred seventy-four patients entered this trial. There were 369 evaluable patients; 186 were randomly allocated to receive RT alone and 183 to receive CT plus RT. Radiation dosage was 45 Gray (Gy) in 20 fractions followed by low dose-rate intracavitary application(s) of 30 Gy to point A. Chemotherapy consisted of intravenous cisplatin 40 mg/m^2 every week for up to 6 weekly cycles. Total extrafascial hysterectomy followed the completion of RT by 6-8 weeks.

RESULTS: Preliminary results have been published, at which time there were 292 censored observations, and median duration of follow-up was only 36 months. Patient and tumor characteristics were well balanced between the regimens. The median patient age was 41.5 years; 81% had squamous tumors; 59% were white. Median follow-up is now 101 months. The relative risk for progression was 0.61 favoring CT plus RT (95% confidence interval [CI] 0.43 to 0.85, $P < .004$). At 72 months, 71% of patients receiving CT plus RT were predicted to be alive and disease free when adjusting for age and tumor size, compared with 60% of those receiving RT alone. The adjusted death hazard ratio was 0.63 (95% CI 0.43 to 0.91, $P < .015$) favoring CT plus RT. At 72 months, 78% of CT plus RT patients were predicted to be alive, compared with 64% of RT patients. An increased rate of early hematologic and gastrointestinal toxicity was seen with CT plus RT. There was no detectable difference in the frequency of late adverse events.

CONCLUSION: Concurrent weekly cisplatin with RT significantly improves long-term PFS and OS when compared with RT alone. Serious late effects were not increased. The inclusion of hysterectomy has been discontinued on the basis of another trial. Pending further trials, weekly cisplatin with radiation is the standard against which other regimens should be compared.

Key words: cervical carcinoma, chemoradiotherapy

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★ EDITORS' CHOICE ★

Five randomized trials, published in 1999,[1-5] showed a significant improvement in outcomes for patients with cervical carcinoma who received concurrent chemoradiation. Each of these trials had slightly different interventions, control groups, and eligibility, but the consistency of the finding was sufficient for the National Cancer Institute to issue a Clinical Alert on the subject. Since

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then, chemoradiation has replaced irradiation alone as the standard of care for those patients with carcinoma of the uterine cervix who are not candidates for radical operation.

One of these trials, the Gynecologic Oncology Group (GOG) #85, was mature at the time of publication,[1] with a median follow-up of 8.7 years and few censored observations. Another 1 of these trials, # 123,[2] was analyzed only 18 months after the study was closed to patient entry. Only 88% of the number of events needed for final analysis had been reported. The purpose of this trial, GOG #123, was to evaluate whether weekly cisplatin, administered concurrent with radiation therapy to patients with bulky stage IB carcinoma of the cervix, would improve local control, progression-free interval, and survival. The other 3 trials also had limited median follow-up of 35, 42, and 43 months,[3-5] but publication of all these trials was expedited because of the impact of the collective results.

At the time of the original publications, it was not known whether the benefits conferred by concurrent chemoradiation would be durable or transient or whether concurrent chemoradiation would potentiate the late adverse effects of radiation. There have been follow-up reports published on 2 of these trials,[6,7] which provide support to continuing concurrent chemoradiation as standard therapy. The purpose of this report is to provide long-term follow–up on the outcomes and toxicities observed on GOG #123.

Materials and Methods

To be eligible for this trial, patients were required to have primary, previously untreated, biopsy-confirmed carcinoma of the uterine cervix, International Federation of Gynecology and Obstetrics (FIGO) stage IB. The primary tumor had to be 4 cm or greater in greatest dimension or be considered to be barrel shaped by the treating physician (consistent with current FIGO stage IB_2). Patients had to have adequate renal, hepatic, and bone marrow function, and a GOG performance status 0-3. Patients had to be entered within 8 weeks of original diagnosis.

Patients were ineligible if they had had any prior malignancy (except for nonmelanoma skin cancer), had received any prior radiation therapy or chemotherapy, or had had a prior supracervical hysterectomy. All patients underwent a chest radiograph; and ureteral status was determined by either an intravenous pyelogram or computed tomography of the abdomen. The paraaortic lymph nodes were required to be negative for metastatic disease by computed tomography or extraperitoneal surgical staging.

Following study entry and randomization, all patients on both regimens received external irradiation to the whole pelvis in daily fractions of 1.8 to 2.0 Gray (Gy), 5 days a week for 4-5 weeks. The prescribed total midpelvic dose was 45.00 Gy. Following the external therapy, patients received 1 or 2 low-dose rate intracavitary applications using stem and ovoid applicators to a dose of 30.00 Gy to point A. A boost was delivered to the pelvic side walls if necessary. A parametrial boost could be delivered, if necessary, to bring the point B dose to 55 Gy.

Patients were randomly assigned to receive concurrent chemotherapy or no concurrent chemotherapy. Randomization was stratified across institutions. Those patients assigned to the experimental regimen were given cisplatin, 40 mg/m^2 weekly, not to exceed 70 mg total dose per week during external and intracavitary therapy, for a maximum of 6 cycles. Six to 8 weeks following the completion of radiation (and chemotherapy), all patients were to undergo total extrafascial hysterectomy.

All patients gave written informed consent prior to study entry in compliance with all local and federal guidelines. Quality control was provided by study chair review (H.M.K., F.B.S.) of all submitted records. Eligibility was confirmed by the Gynecologic Oncology Committee of the GOG. All patients' biopsy tissue was reviewed by the GOG Pathology Committee. Radiation therapy quality control was provided by the study chair (H.M.K.) the Radiation Oncology Committee of the GOG and the Radiation Physics Center (Houston, TX). GOG Adverse Effects Criteria (1988 version) were used for adverse effects reporting.

Endpoints included complete response rate, time to recurrence, survival, and sites of recurrence. A 40% decrease in recurrence was considered clinically important. To have an alpha of 0.05 and a 1-beta of 0.80, 156 recurrences would be needed (1-sided test). There were 2 interim analyses performed after 160 and 238 patients had been entered to assure that it was appropriate to continue the study. Life tables were calculated according to Kaplan-Meier.[8] Differences in survival and progression free survival (PFS) were calculated using log-rank test.[9] Cox's model was used to adjust for known prognostic factors (tumor size and histologic grade of the tumor)[2] and calculate differences between groups.[10] All *P* values in this report are 2 tailed.

After the completion of therapy, patients were to be followed up every 3 months for 2 years and then twice a year for the next 3 years, and updates were to be submitted to the GOG Statistical and Data Center (SDC) in Buffalo, NY. This report is based on data at the SDC by December 31, 2005. Progression-free interval and survival are presented using intent-to-treat methodology. As of this writing, 136 patients have either recurred or died; the median follow-up for all patients is 101 months.

A more complete description of the study methods can be found in the preliminary report published in 1999.[2]

Results

Between February 1992 and April 1997, there were 374 patients entered on to GOG protocol #123. Five patients were declared ineligible. After randomization, risk factors including cell type, tumor grade, age, performance status, and tumor size were balanced between the 2 randomization arms (Table 1). There were 27 patients who underwent preentry surgical evaluation of the lymph nodes; 13 on the radiation therapy alone arm; and 14 on the radiation therapy plus cisplatin arm. All other patients had radiographic assessment of lymph nodes. Of the patients randomized to ra-

diation therapy alone, 184 of 186 received radiotherapy. Of the patients randomized to radiation therapy plus cisplatin regimen, 181 of 183 received radiotherapy. The median dose to point A in the 2 regimens was 74.4 and 74.5 cGy, respectively. Median doses to point B were 53.0 and 53.1 cGy. The median duration of radiation treatment was 50 days for both arms. Four patients assigned to the concurrent cisplatin received no chemotherapy.

On the radiation therapy regimen, 168 patients had hysterectomy, 18 refused or progressed, or the operation was contraindicated. On the radiation therapy plus cisplatin arm, 174 had hysterectomy, and 9 did not. A somewhat higher percentage of the patients allocated to the radiation therapy plus cisplatin arm had hysterectomy (96% vs 90%), and of those who did undergo hysterectomy, there were more patients whose cervix had no residual cancer on microscopic examination (52% vs. 41%). If paraaortic nodes were sampled at the time of extrafascial hysterectomy, the probability of positive paraaortic nodes was similar in both regimens (4 of 164 vs 6 of 168, n.s.).

In the previous report, there were 69 patients on the radiation therapy–only regimen whose disease had recurred and 49 who had died. On the combined therapy arm, 38 patients had suffered a recurrence and 28 had died. At the time of this report, there are 72 patients on the radiation therapy arm whose disease has recurred, and 41 patients on the radiation therapy plus cisplatin arm whose disease has recurred. There have been 68 and 48 deaths respectively (Table 2).

The adjusted relative risk for progression is 0.61 (95% confidence interval [CI] 0.43 to 0.85, $P < .004$) favoring radiation therapy plus cisplatin. At 72 months, 71% of patients receiving radiation plus cisplatin were predicted to be alive and disease free when adjusting for age and tumor size, compared with 60% of those who received radiation therapy alone (Figure 1).

The adjusted relative risk of death was 0.63 (95% CI 0.43 to 0.91, $P < .015$) favoring irradiation plus cisplatin. At 72 months, 78% of the combined modality patients were predicted to be alive, compared with 64% of the radiation therapy–alone patients. (Figure 2). There were 4 deaths from other causes on the irradiation-only regimen: 1 from treatment and 3 patients from unknown causes, although they had been disease free at last contact. There were 10 deaths from other causes on the combination regimen: 1 due to a motor vehicle accident, 5 due to known intercurrent disease (cardiac, hepatic, diabetes, renal, and breast cancer), and 4 patients from unknown causes, who had been disease free at last contact.

In our previous report, a higher rate of early hematologic and gastrointestinal toxicity was noted in patients randomized to radiotherapy plus cisplatin.[2] At last follow-up, there were 118 patients alive on the irradiation-only regimen and 135 patients alive on the combination regimen who could be assessed for long-term adverse effects. Long-term adverse effects on the gastrointestinal tract, genitourinary tract, and skin were

TABLE 1
Characteristics of the patients*

Characteristic	RT only (n = 186)	RT plus CIS (n = 183)
Cell type		
Squamous cell carcinoma	151 (81)	147 (80)
Adenocarcinoma or adenosquamous	24 (13)	26 (14)
Other	11 (6)	10 (6)
Tumor grade		
1 (well differentiated)	9 (5)	15 (8)
2 (moderately differentiated)	118 (63)	98 (54)
3 (poorly differentiated)	56 (30)	69 (38)
Not graded	3 (2)	1 (1)
Age (years)		
Mean ±SD	43.0 ± 11.0	43.0 ± 11.0
First, second, and third quartiles	36.0, 42.0, 48.0	36.0, 41.0, 47.0
Range	23-78	21-81
GOG performance status		
0 (normal activity, asymptomatic)	157 (84)	156 (85)
1 (symptomatic, fully ambulatory)	26 (14)	26 (14)
2 (symptomatic, in bed less than 50% of time)	3 (2)	1 (1)
Race		
White	108 (58)	110 (60)
Black	46 (25)	40 (22)
Hispanic	23 (12)	24 (13)
Other	9 (5)	9 (5)
Tumor size (cm)		
4 or greater	15 (8)	14 (8)
(4-5)	36 (19)	55 (30)
(5-6)	68 (37)	53 (29)
(6-7)	40 (22)	30 (16)
Greater than 7	27 (15)	31 (17)

CIS, cisplatin; *RT*, radiation therapy.

* Percentages are in parentheses. Because of rounding error, not all percentages total 100.

TABLE 2
Rates of disease progression and death*

Outcome	RT only (n = 186)	RT+CIS (n = 183)
Progression status (recurrence**)		
Local	39 (21)	16 (9)
Distant	28 (15)	21 (11)
Combined	5 (3)	4 (2)
NED	114 (61)	142 (79)
Vital status		
Died of disease	64 (34)	38 (21)
Died of other causes	4 (2)	10 (5)
Alive	118 (63)	135 (74)

CIS, cisplatin; *RT*, radiation therapy.

* Percentages are in parentheses. Because of rounding, not all percentages total 100.

** Recurrences were classified as local if they were first detected in the pelvis, cervix, or vagina; as distant if they were first detected outside the pelvis; and as combined if they were first detected at sites within and outside the pelvis.

uncommon in both regimens. There were 4 patients who experienced 6 major adverse events on the irradiation regimen. There was 1 patient who experienced an intestinal obstruction, 1 a rectovaginal fistula, and 1 a vesicovaginal fistula. A fourth patient suffered a vesicovaginal fistula, an enterovaginal fistula, and a rectovaginal fistula. There were 7 patients with 7 events on the irradiation plus chemotherapy regimen. There were 3 patients with vesicovaginal fistula, 2 with rectovaginal fistula, and 1 each with intestinal perforation and colonic perforation. This difference was not significant.

COMMENT

This report confirms that the preliminary results that were reported in 1999 are durable. The concurrent administration of weekly cisplatin during irradiation therapy reduces the relative risk of both recurrence and death by approximately 40%, compared with patients treated with irradiation alone. The report from Whitney et al[1] was mature at first publication with few censored observations and a median follow-up of 104 months. At that time, the median survival for that study had not been reached.

Recently both the Radiation Therapy Oncology Group Trial (RTOG) study #90-01[4] and the Southwest Oncology Group (SWOG)/GOG intergroup trial[5] have been updated.[6,7] When the RTOG trial was first reported the median follow-up was 43 months.[4] Eifel et al[6] report a median follow-up of 6.6 years for the 228 surviving patients and 6.6 years for all patients. At this point in follow-up, the risk ratio for recurrence was 0.51 and for death 0.52. In the first report of SWOG 87-97 (GOG #109), the median follow-up was 42 months. With a median follow-up of 62 months, the estimated 5 year survival rate was 80% vs 66% favoring concurrent chemoradiation.[7]

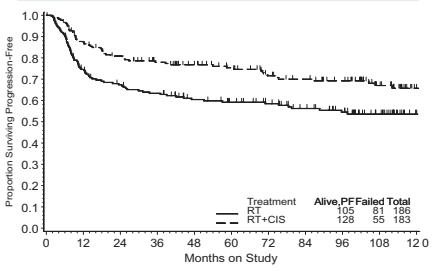
It can be seen from these results and with the other 4 trials that most events (progression, death) occur within the first 2 years after treatment, and the hazard drops to close to zero after that interval. When considered collectively, these 4 mature trials provide evidence of a durable advantage for concurrent chemoradiation for patients with carcinoma of the cervix who require radiation therapy.

The strengths of the current report include the diversity of the patient population studied in terms of race, age, and cell type. These data are broadly generalized. The radiation treatment administered was compliant within the prescribed dose and duration. All patients were to receive hysterectomy in lieu of an additional implant, so the duration (50 days) was expected to be shorter than prescriptions requiring a higher brachytherapy dose, such as the RTOG trial, which had a median duration of 58 days.

This population was expected to have the lowest risk of recurrence or death of these 5 trials. Three of the trials included predominantly patients with stage IIB and IIIB disease.[1,3,4] The patients on the SWOG/GOG study had clinical stage IB disease, but all were required to have high-risk factors such as positive lymph nodes or positive margins. These patients on GOG #123 had the lowest risk of recurrence and the highest rate of long-term survivors among whom late adverse effects could be observed.

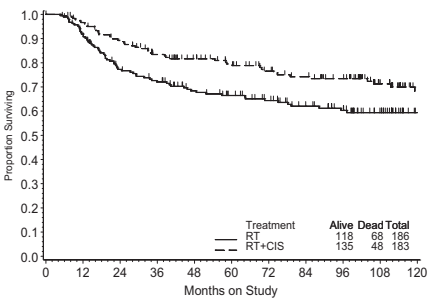
All 5 of these trials share the problems associated with large cooperative trials. Institutions may leave the cooperative group or patients may be lost to follow-up. This trial was designed and opened based on the preliminary findings in GOG #71.[11] The preliminary findings from that trial showed a risk ratio of 0.77

FIGURE 1
Progressive free survival by treatment regimen



Stehman. Radiation therapy with or without weekly cisplatin for bulky Stage 1B cervical carcinoma. AJOG 2007.

FIGURE 2
Overall survival by treatment regimen



Stehman. Radiation therapy with or without weekly cisplatin for bulky Stage 1B cervical carcinoma. AJOG 2007.

for progression-free interval when extrafascial hysterectomy was substituted for additional brachytherapy in this population. There were fewer local failures as well (27% vs 14%). However, when mature, there was no significant difference in survival (risk ratio 0.89). The inclusion of hysterectomy in both arms of this study may be considered by some to cloud these results. Lastly, this trial did not include formal quality of life (QoL) assessment with validated instruments. The Gynecologic Oncology Group has incorporated structured QoL in more recent cervical cancer studies.[12]

There remain unanswered questions about concurrent chemoradiation. Whereas weekly cisplatin was used in this trial and in GOG #120,[3] other regimens have also been shown to be effective. In a metaanalysis of 19 trials involving 4580 patients, Green et al[13] observed an independent effect for cisplatin. Lanciano et al[14] were unable to show an advantage for continuous infusion fluorouracil over weekly cisplatin. Another unanswered question is why the National Cancer Institute of Canada (NCIC) report was unable to corroborate the findings of these 5 trials.[15] The NCIC investigators studied 253 patients with stage IB-IVA squamous cell carcinoma. With a median follow-up of 82 months, there was no measurable advantage for the addition of weekly cisplatin in either the 3 year or 5 year survival. These authors concluded, however, that "despite the negative result of this trial, we think that the balance of evidence favors the use of combined-modality treatment for the types of patients studied in this trial" (p 971).[15]

We did not observe an excess incidence of late adverse events associated with concurrent chemoradiation. Since the original publication,[2] the GOG has published mature results of another randomized trial which demonstrated that planned extrafascial hysterectomy improves local control but does not enhance survival. Therefore, inclusion of postradiation hysterectomy is not standard. Its deletion from the treatment plan may decrease the frequency of severe adverse events. However, late events such as bowel obstruction, fistula, and skin ulceration are rare, and the accrual goal of this trial was based on testing progression-free and survival hypotheses, not the toxicity question. Many more patients would have been required to conclude that there is no potentiation of the late effects of irradiation when concurrent cisplatin is added.

The systematic review of 19 trials concluded that there were insufficient data to determine whether late toxicity was increased in the chemoradiation group.[13] In the RTOG trial, Eifel et al[6] reported 12% of patients on cisplatin plus radiation therapy had grade 3-4 late complications, compared with 13% on the pelvic plus paraaortic radiation arm. The actuarial risk (Kaplan Meier) of adverse effects was not reported. In a long-term Patterns of Care Study report, Komaki et al[16] observed time-adjusted major complications in 9-13% of patients.

Pedersen et al[17] pointed out that disease recurrence and late toxicity are competing risks. A patient has to have long-term survival without recurrence to be reported as having experienced late adverse effects. Late adverse effects increase with advancing stage; there will be more disease deaths among patients with advanced stage disease. The observed frequency of late effects will tend to underestimate the true risk by about 2.5 times. Time-to-event methodology should be applied.

Although patients with lower-stage disease have somewhat lower risk of late adverse effects, these patients have a much lower risk of recurrence. Monk et al[7] point out that for early-stage patients, the relative risk reduction may be constant, but the absolute risk of recurrence is much smaller. This smaller absolute benefit may be negated by the nearly constant risk of adverse effects. There have been no trials confirming the magnitude of benefit of concurrent chemoradiation for patients with stage IB carcinoma of the cervix with negative lymph nodes after radical hysterectomy.

The GOG continues to pursue clinical trials to better define the optimal regimen of irradiation and concurrent chemotherapy. At this time, the GOG has adopted weekly cisplatin, as described in this trial, as our standard control regimen against which other regimens will be tested. ■

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REFERENCES

1. Whitney CW, Sause W, Bundy BN, et al. A randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages 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; 17:1339-48.

2. 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;340:1154-61.

3. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144-53.

4. 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; 340:1137-43.
5. 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;18:1606-13.
6. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of Radiation Therapy Oncology Group Trial (RTOG) 90-01. J Clin Oncol 2004;22:872-80.
7. Monk BJ, Wang J, Im S, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy; a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. Gynecol Oncol 2005;96:721-8.
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
9. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50: 163-70.
10. Cox DR. Regression models and life tables. J R Stat Soc (B) 1972;34:187-220.
11. Keys HM, Bundy BN, Stehman FB, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. Gynecol Oncol 2003;89: 343-53.
12. McQuellon RP, Thaler H, Cella D, Moore DH. Quality of life (QOL) outcomes from a randomized trial of cisplatin versus cisplatin plus paclitaxel for women with metastatic cervix cancer: results from the Gynecologic Oncology Group Study #169. Gynecol Oncol 2006; 101:296-304.
13. Green JA, Kirwan JM, Tierney JF, Symonds L, Collingwood M, Williams CJ. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet 2001;358:781-6.
14. Lanciano R, Calkins A, Bundy BN, et al. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer; a Gynecologic Oncology Group study. J Clin Oncol 2005;23:8289-95.
15. Pearcey R, Brundage M, Drouin P, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 2002;20:966-72.
16. Komaki R, Brickner TJ, Hanlon AL, Owen JB, Hanks GE. Long term results of treatment of cervical carcinoma in the United States in 1973, 1978, and 1983: patterns of care Study (PCS). Int J Radiat Oncol Biol Phys 1995;31:973-83.
17. Pedersen D, Bentzen SM, Overgaard J. Early and late radiotherapeutic morbidity in 442 consecutive patients with locally advanced carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1994;29:941-52.