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RADIATION THERAPY WITH OR WITHOUT WEEKLY CISPLATIN FOR BULKY STAGE IB CERVICAL CARCINOMA; FOLLOW-UP OF A GYNECOLOGIC ONCOLOGY GROUP TRIAL

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Abstract

Purpose—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 to RT alone in stage IB bulky carcinoma of the cervix, when both groups' therapy is followed by hysterectomy.

Methods—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+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/M² every week for up to six weekly cycles. Total extrafascial hysterectomy followed the completion of RT by six to eight 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

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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+RT (95% confidence interval [CI]: 0.43–0.85, $p<0.004$). At 72 months, 71% of patients receiving CT+RT were predicted to be alive and disease-free when adjusting age and for tumor size compared to 60% of those receiving RT alone. The adjusted death hazard ratio was 0.63 (95% CI: 0.43–0.91, $p<0.015$) favoring CT+RT. At 72 months, 78% of CT+RT patients were predicted to be alive, compared to 64% of RT patients. An increased rate of early hematologic and gastrointestinal toxicity was seen with CT+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 to 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.

Keywords

Cervical carcinoma; chemoradiotherapy

INTRODUCTION

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 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, Gynecologic Oncology Group #85, was mature at the time of publication¹ with a median follow-up of 8.7 years and few censored observations. Another one of these trials, # 123², 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 if 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 three 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 two 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

In order to be eligible for this trial, patients were required to have primary, previously untreated, biopsy-confirmed carcinoma of the uterine cervix, FIGO stage IB. The primary tumor had to be greater than or equal to 4 cm in greatest dimension or be considered to barrel-shaped by the treating physician (consistent with current FIGO Stage IB₂). Patients had adequate renal, hepatic and bone marrow function, and a GOG performance status 0–3. Patients had to be entered within eight weeks of original diagnosis.

Patients were ineligible if they had had any prior malignancy (except for non-melanoma skin cancer), if they had received any prior radiation therapy or chemotherapy, or if they 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 para-aortic lymph nodes were required to be negative for metastatic disease by computed tomography or by extra-peritoneal surgical staging.

Following study entry and randomization, all patients on both regimens received external irradiation to the whole pelvis in daily fractions of 1.8–2.0 Gy, five days a week for four to five weeks. The prescribed total mid-pelvic dose was 45.00 Gy. Following the external therapy, patients received one or two 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/M² weekly, not to exceed 70 mg total dose per week during external and intracavitary therapy for a maximum of six cycles. Six to eight 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 (HMK, FBS) 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 (HMK) 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. End-points included complete response rate, time to recurrence, survival, and sites of recurrence. A 40% decrease in recurrence was considered clinically important. In order to have an alpha of 0.05 and a 1-beta of .80, 156 recurrences would be needed (one-sided test). There were two 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 PFI 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 two-tailed.

After the completion of therapy, patients were to be followed every three months for two years and then twice a year for the next three years and updates were to be submitted to the GOG Statistical and Data Center in Buffalo, NY (SDC). 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 two randomization arms (Table I). There were 27 patients who underwent pre-entry surgical

evaluation of the lymph nodes; thirteen on the radiation therapy alone arm and fourteen on the radiation therapy plus cisplatin arm. All other patients had radiographic assessment of lymph nodes. Of the patients randomized to radiation therapy alone, 184/186 received radiotherapy. Of the patients randomized to radiation therapy plus cisplatin regimen, 181/183 received radiotherapy. The median dose to point A in the two 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, nine 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 para-aortic nodes were sampled at the time of extrafascial hysterectomy, the probability of positive para-aortic nodes was similar in both regimens (4/164 vs 6/168, 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 II).

The adjusted relative risk for progression is 0.61 (95% C.I. = 0.43–0.85, $p < 0.004$) 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 to 60% of those who received radiation therapy alone. (Figure I)

The adjusted relative risk of death was 0.63 (95% C.I. = 0.43–0.91, $p < 0.015$) favoring irradiation plus cisplatin. At 72 months, 78% of the combined modality patients were predicted to be alive compared to 64% of the radiation therapy alone patients. (Figure II) There were four deaths from other causes on the irradiation-only regimen; one from treatment and three patients from unknown causes, though they had been disease free at last contact. There were ten deaths from other causes on the combination regimen; one due to a motor vehicle accident, five due to known intercurrent disease (cardiac, hepatic, diabetes, renal and breast cancer), and four 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 uncommon in both regimens. There were four patients who experienced six major adverse events on the irradiation regimen. There was one patient who experienced an intestinal obstruction, one a recto-vaginal fistula, and one a vesico-vaginal fistula. A fourth patient suffered a vesico-vaginal fistula, an entero-vaginal fistula and a recto-vaginal fistula. There were seven patients with seven events on the irradiation plus chemotherapy regimen. There were three patients with vesico-vaginal fistula, two with recto-vaginal fistula, and one each with intestinal perforation and with colonic perforation. This difference was not significant.

COMMENT

This report confirms that the preliminary results which 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 to patients treated with irradiation alone. The report from Whitney et al¹ was mature at first publication with few censored observations and a median followup of 104 months. At that time, the median survival for that study had not been reached. Recently, both the RTOG study # 90-01⁴ and the SWOG/GOG intergroup trial⁵ have been updated.^{6,7} When the RTOG trial was first reported the median followup was 43 months.⁴ Eifel et al report a median followup of 6.6 years for the 228 surviving patients and 6.6 years for all patients.⁶ At this point in followup 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 followup was 42 months. With a median followup of 62 months, the estimated five year survival was 80% versus 66% favoring concurrent chemoradiation.⁷ It can be seen from these results and with the other four trials, that most events (progression, death) occur within the first two years after treatment and the hazard drops to close to zero after that interval. When considered collectively, these four 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, 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 five 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 five of these trials share the problems associated with large cooperative trials. Institutions may leave the cooperative group or patients may be lost to followup. 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 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 (RR = 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. While weekly cisplatin was used in this trial and in GOG #120³, other regimens have also been shown to be effective. In a meta-analysis of 19 trials involving 4580 patients, Green et al observed an independent effect for cisplatin.¹³ Lanciano et al were unable to show an advantage for continuous infusion fluorouracil over weekly cisplatin.¹⁴ Another unanswered question is why the National Cancer Institute of Canada report was unable to corroborate the findings of these five trials.¹⁵ The NCIC investigators studied 253 patients with stage IB-IVA squamous cell carcinoma. With a median followup of 82 months, there was no measurable advantage for the addition of weekly

cisplatin in either the three year or the five 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.” (ref 15, p. 971)

We did not observe an excess incidence of late-adverse events associated with concurrent chemoradiation. Since the original publication², 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 post-radiation hysterectomy is not standard. It's 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 was insufficient data to determine whether late toxicity was increased in the chemoradiation group.¹³ In the RTOG trial, Eifel et al⁶ reported 12% of patients on CT+RT had grade 3–4 late complications compared to 13% on the pelvic plus para-aortic 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 observed time adjusted major complications in 9–13% of patients.¹⁶ Pedersen and co-investigators pointed out that disease recurrence and late toxicity are competing risks.¹⁷ 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.

While 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 point out that for early stage patients the relative risk reduction may be constant but the absolute risk of recurrence is much smaller.⁷ 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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University Hospital; Case Western Reserve University; Tampa Bay Cancer Consortium; and The New York Hospital/Cornell Medical Center.

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Figure 1.

Progression-Free survival by treatment group. The adjusted relative risk for progression is 0.61 (95% C.I. = 0.43–0.85, $p < 0.004$) favoring radiation therapy plus cisplatin.

Figure 2.

Overall survival by treatment group. The adjusted relative risk of death was 0.63 (95% C.I. = 0.43–0.91, $p < 0.015$) favoring irradiation plus cisplatin

Table I**Characteristics of the patients ***

Characteristic		RT Only (N=186)	RT+CIS (N=183)
Cell Type:	Squamous Cell Carcinoma	151 (81)	147(80)
	Adenocarcinoma, or Adeno-squamous	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 $\pm$ Standard Deviation	43.0 $\pm$ 11.0	43.0 $\pm$ 11.0
	1 st , 2 nd & 3 rd 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 < 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	15 (8)	14 (8)
	(4–5]	36 (19)	55 (30)
	(5–6]	68 (37)	53 (29)
	(6–7]	40 (22)	30 (16)
	> 7	27 (15)	31 (17)

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

Table II**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)

* 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.