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CLINICAL INVESTIGATION **Cervix**

A PHASE III RANDOMIZED TRIAL OF POSTOPERATIVE PELVIC IRRADIATION IN STAGE IB CERVICAL CARCINOMA WITH POOR PROGNOSTIC FEATURES: FOLLOW-UP OF A GYNECOLOGIC ONCOLOGY GROUP STUDY

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Purpose: To investigate, in a phase III randomized trial, whether postoperative external-beam irradiation to the standard pelvic field improves the recurrence-free interval and overall survival (OS) in women with Stage IB cervical cancers with negative lymph nodes and certain poor prognostic features treated by radical hysterectomy and pelvic lymphadenectomy.

Methods and Materials: Eligible patients had Stage IB cervical cancer with negative lymph nodes but with 2 or more of the following features: more than one third (deep) stromal invasion, capillary lymphatic space involvement, and tumor diameter of 4 cm or more. The study group included 277 patients: 137 randomized to pelvic irradiation (RT) and 140 randomized to observation (OBS). The planned pelvic dose was from 46 Gy in 23 fractions to 50.4 Gy in 28 fractions.

Results: Of the 67 recurrences, 24 were in the RT arm and 43 were in the OBS arm. The RT arm showed a statistically significant (46%) reduction in risk of recurrence (hazard ratio [HR] = 0.54, 90% confidence interval [CI] = 0.35 to 0.81, $p = 0.007$) and a statistically significant reduction in risk of progression or death (HR = 0.58, 90% CI = 0.40 to 0.85, $p = 0.009$). With RT, 8.8% of patients (3 of 34) with adenosquamous or adenocarcinoma tumors recurred vs. 44.0% (11 of 25) in OBS. Fewer recurrences were seen with RT in patients with adenocarcinoma or adenosquamous histologies relative to others (HR for RT by histology interaction = 0.23, 90% CI = 0.07 to 0.74, $p = 0.019$). After an extensive follow-up period, 67 deaths have occurred: 27 RT patients and 40 OBS patients. The improvement in overall survival (HR = 0.70, 90% CI = 0.45 to 1.05, $p = 0.074$) with RT did not reach statistical significance.

Conclusions: Pelvic radiotherapy after radical surgery significantly reduces the risk of recurrence and prolongs progression-free survival in women with Stage IB cervical cancer. RT appears to be particularly beneficial for patients with adenocarcinoma or adenosquamous histologies. Circumstances that may have influenced the overall survival differences are considered.

Stage IB cervical cancers, Postoperative pelvic irradiation, Prognostic factors.

INTRODUCTION

The surgical or radiotherapeutic treatment of Stage IB cancer of the uterine cervix is predicated by the tumor's character to confine itself to the cervix, and then spread in a progressive and predictable manner through regional lymphatics. Thus, in instances where lymph nodes are negative, treatment failures in Stage IB with disease apparently still localized would suggest faulty radiotherapeutic or surgical technique (1, 2).

Metastasis to lymph nodes has long been identified as a major prognostic factor in early stage cervical cancer. However, certain histopathologic features of cervical carcinomas have been shown to be independent risk factors

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for locoregional failures related to disease retained in lymphatic plexi, irrespective of lymph node status. These features include large tumor diameter (LTD), deep stromal invasion (DSI), and presence of tumor in the capillary lymphatic spaces (CLS). A Gynecologic Oncology Group (GOG) study of 575 women estimated that such risk factors existed in 25% of all Stage IB cancers and that these factors increased the risk of recurrence from 2% to 31% at 3 years (3). Earlier, external irradiation (RT) had been proposed to be of benefit in reducing recurrences in this group of patients (4). This prospect led to the development of the current study, GOG Protocol 92 (5). The hypothesis to be tested was that postoperative external-beam RT to the standard pelvic field reduces recurrence and improves the recurrence-free interval in women with Stage IB cervical cancers with negative lymph nodes and certain poor prognostic features treated by radical hysterectomy and pelvic lymphadenectomy.

The study was designed with a primary endpoint of disease recurrence, defined as the length of time from study entry until disease recurrence. In the initial report of this study (5), 60 patients had recurred and 48 patients had died, including 4 who died of non–cancer-related causes. At that time, only preliminary results of survival were presented. Since that report, 7 additional recurrences have been observed and 19 additional deaths have occurred (including 4 additional non–cancer-related deaths). The purpose of this report is to provide final results of analysis of overall survival and to update the results on recurrence-free interval, on the basis of an extended follow-up period, for the patients enrolled in GOG Protocol 92. This report also discusses the possible reasons for differences between recurrence and survival results.

METHODS AND MATERIALS

Detailed information on patient eligibility, randomization, treatment details, and methods for this study have been published previously (5) and are summarized briefly here as necessary. Patients with International Federation of Gynecology and Obstetrics (FIGO) Stage IB primary cervical carcinoma and 2 or more risk factors, defined as DSI, CLS tumor involvement, and tumor diameter of 4 cm or more (large tumor diameter = LTD), were eligible for this study.

The eligibility criteria arose from a previous multiple-regression analysis of a large surgicopathologic study that identified a group of cervical Stage IB cancers of substantial size and with certain risk factors to justify adjuvant therapy (6). In that report, 2 of every 10 patients with these risk-factor combinations would relapse within 2 years, and another would fail during the third year (3, 6).

Before randomization, all patients provided written informed consent, which fulfilled all institutional, state, and federal regulations. Eligible patients had Stage IB squamous, adenosquamous, or adenocarcinoma of the cervix, initially treated with a standard radical hysterectomy and pelvic lymphadenectomy, had negative lymph nodes, and had at least 2 of the previously described risk factors (Table 1). There were no stratification factors, but randomization was balanced within each institution.

Radical hysterectomy required removal of the uterus, parametrial and paravaginal tissues, and the 25% of the vagina along the uterosacral ligaments. The ureter was dissected from its entry into the broad ligament to its portion in the bladder wall and dissected laterally from its attachment to the cardinal ligament. Pelvic lymphadenectomy included removal of all nodal tissue and dis-

Table 1. Patient and tumor characteristics

Characteristic	Radiation therapy (n = 137) No.	%	Observation (n = 140) No.	%
Patient				
Cell type				
Squamous cell	103	75.2	115	82.1
Adenocarcinoma	16	11.7	11	7.9
Adenosquamous	18	13.1	14	10.0
Maximum tumor dimension				
≤3 cm	39	29.3	58	42.6
>3 cm	94	70.7	78	57.4
Unknown size*	4	—	4	—
Tumor				
CLS/stromal invasion/tumor size				
+CLS, deep third, any	60	43.8	69[†]	49.3
+CLS, middle third, ≥2 cm	28	20.4	37	26.4
−CLS, middle third, ≥4 cm	23	16.8	13	9.3
−CLS, deep third, ≥4 cm	25	18.3	21	15.0
+CLS, superficial third, ≥5 cm	1	0.7	0	0.0

Abbreviation: CLS = capillary lymphatic space.

* Not included in percentage computation.

[†] One patient originally classified as +CLS, superficial third, ≥5 cm was, upon a second review by our central pathology laboratory, discovered to have deep invasion. This finding occurred after publication of the preliminary results in 1999 (5).

section and cleaning of all vessels from the middle of the common iliac artery to the circumflex iliac vein, from the middle portion of the psoas muscle to the ureter medially, including the hypogastric artery and vein, and from the obturator fossa anteriorly to the obturator nerve. Tumor diameter was estimated by earlier palpations. The depth of stromal invasion and the presence of CLS were determined by institutional pathologic examination and confirmed by a central GOG Pathology Committee review.

External-beam RT without additional vaginal brachytherapy was to start 4 to 6 weeks after surgery. The median interval between randomization and beginning of pelvic RT was 14 days (range, 0–59 days, excluding 9 RT patients who received no RT). Pelvic fields consisted of a 4-field technique with beam energies of at least 4 MeV, although ^{60}Co could be used if the source-to-skin distance was 80 cm or greater. Total dose to be delivered was 46 Gy (in 23 fractions of 2.0 Gy) to 50.4 Gy (in 28 fractions of 1.8 Gy), 5 fractions per week. Treatment interruptions were to be no more than 1 week. The median duration of RT treatment was 5.7 weeks (range, 0.1–13.3 weeks) (excluding 9 patients who received no RT).

Treatment portals included the obturator, hypogastric, and external iliac lymphatics. The anteroposterior-posteroanterior (AP-PA) portals extended superiorly to the upper border of L5, inferiorly to the upper third of the obturator foramen, and laterally at least 1 cm beyond the margins of the bony pelvis at the widest plane through the pelvis. The lateral portal boundaries were superior and inferior (the same as the AP-PA boundaries), anterior (transverse line drawn through the pubic symphysis), and posterior (at least 4 cm beyond the cervical marker). The minimum anterior–posterior dimension of the lateral field was 9 cm, including the S2/S3 junction.

A moderate imbalance existed between the 2 treatment groups (Table 1), with regard to histology and size. Among the two groups were 34 patients (24.8%) with adenocarcinoma (n = 16) or adenosquamous (n = 18) histology in the RT arm, compared with 25 patients (17.9%) in the observation (OBS) arm (adenocarcinoma = 11, adenosquamous = 14). Regarding tumor size, 94 patients (70.7%) had tumors greater than 3 cm in the RT arm vs. 78 patients (57.4%) in the OBS arm.

he primary outcome was recurrence-free interval, defined as the time from study entry to physical or radiographic evidence of disease recurrence, or to the date the patient was last seen. Overall survival (OS) was defined as date of entry to date of death or, for living patients, the last date of contact, and progression-free survival (PFS) was defined as the time from study entry to either disease recurrence or death. The sample size was chosen to detect a 47% decrease in the hazard rate for recurrence in RT relative to OBS, with a one-sided

Table 2. Site of first recurrence and treatment regimen

Site	Radiation therapy (n = 137) No.	%	Observation (n = 140) No.	%
No evidence of disease	113	82.5	97	69.3
Recurrences	24	17.5	43	30.7
Local	19	13.9	29	20.7
Vagina	2		8	
Pelvis	16		19	
Vagina and pelvis	1		2	
Distal	4	2.9	12	8.6
Unknown	1	0.7	2	1.4

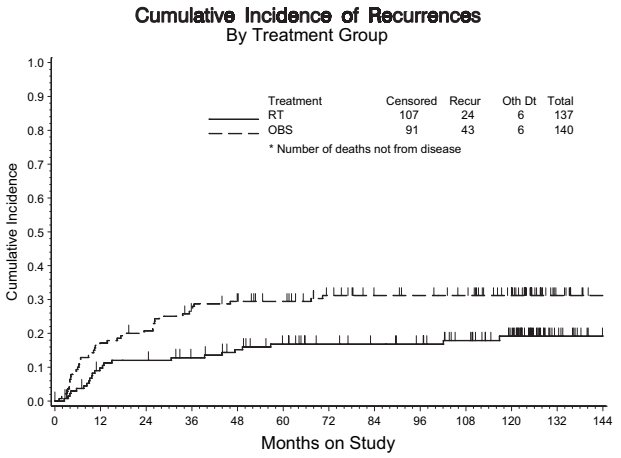

Fig. 1. Cumulative risk of recurrences by treatment group: 24 RT patients and 43 OBS patients recurred, and 3 non–disease-related deaths in each group were treated as censored observations. RT significantly reduced recurrence risk (p = 0.007). OBS = observation; RT = irradiation.

Type I error rate of 0.05 and power of 0.80. This sample size also provided 80% power to detect a 46% decrease in the hazard rate for OS in RT relative to OBS. Six patients lost to follow-up on the RT arm during the first 2 years were censored and are not considered to be dead of disease. Only 1 patient was lost to follow-up in the first 2 years in the OBS arm. The median follow-up time for patients still alive at last contact was 10.0 years (range, 0.003–16 years), and for the 12 patients still alive with disease recurrence, the median follow-up time was 8.4 years (range, 3.3–13.4 years). The median follow-up time from recurrence for the 12 patients who recurred and are still alive is 6.2 years (range, 0.05–13.2 years). Recurrences were considered local if to the pelvis or vagina and distant if to extrapelvic locations. According to study design, the unadjusted differences in recurrence and survival by treatment arm were evaluated by use of the log-rank test (7) and application of the intent-to-treat principle. Differences between treatment arms, although adjusting for prognostic factors, were assessed by use of Cox proportional-hazards regression models (8). Unless otherwise noted, all statistical tests reported here are one-sided tests with significance level of α = 0.05 and are based on the intent-to-treat population of 277 eligible patients.

The results presented here reflect information received in the GOG Statistical and Data Center as of March, 2005. Patient accrual began on March 9, 1988 and closed on September 18, 1995. Of the 299 women randomized, 22 were excluded from analysis for the following reasons: lack of documentation of high-risk criteria [14], wrong stage [4], inadequate surgery [1], inadequate pathology for review [2], and lack of an i.v. pyelogram or CT scan [1].

Of the 277 patients that formed the intent-to-treat population, 137 were randomly assigned to RT and 140 to OBS. Of the 137 patients on the RT arm, 27 patients did not receive their planned radiotherapy: 9 received no treatment, 5 received less than 33% of the prescribed dose, 2 more received less than 72% of the prescribed dose, and 11 had treatment delays longer than 1 week.

RESULTS

Recurrence

Table 2 shows first recurrences by site of recurrence and treatment regimen. Since the time of the initial report

Table 3. Recurrence by cell type and treatment regimen

	Radiation therapy (n = 137)			Observation (n = 140)		
Cell type	NED	Recurred (%)	Total	NED	Recurred (%)	Total
Adenocarcinoma	16	0 (0)	16	7	4 (36.4)	11
Adenosquamous	15	3 (16.7)	18	7	7 (50.0)	14
Squamous	82	21 (20.4)	103	83	32 (27.8)	115

Abbreviation: NED = No evidence of disease.

(5), 7 additional disease recurrences (3 in RT arm and 4 in OBS arm) were observed, and the initial results have not changed substantially. A significant reduction in risk of recurrence with RT vs. OBS (HR = 0.54; 90% CI = 0.35 to 0.81; p = 0.007) was seen. Both local (13.9% vs. 20.7%) and distal (2.9% vs. 8.6%) recurrence rates were lower in RT vs. OBS.

Figure 1 shows the cumulative incidence of recurrence over a 12-year period by treatment group. Eighty-two percent of all recurrences were seen within the first 3 years after enrollment, and 94% were seen within the first 5 years. In fact, only 2 patients recurred later than 6 years after enrollment; both of these patients were in the RT group. This result explains the small changes to the curve toward the end of the lengthy follow-up period.

Table 3 shows the recurrences by cell type and treatment regimen. Those with adenocarcinoma or adenosquamous histologies from the OBS group had higher failure rates than those in the RT group with the same histology (44.0% [11 of 25 patients] recurrence in OBS arm vs. 8.8% [3 of 34 patients] in RT arm). In fact, a marked decrease was seen in risk of recurrence with RT in patients with adenocarcinoma or adenosquamous histologies relative to others (HR for RT by histology interaction = 0.23; 90% CI = 0.07 to 0.74; p = 0.019). The previously described eligibility criteria resulted in definition of 5 prognostic subgroups by combination of CLS status, DSI, and LTD (5). After controls were applied for prognostic subgroup, RT patients were 44% less likely to recur than were OBS patients (HR = 0.56; 90% CI = 0.37 to 0.86; p = 0.012) (Table 4).

The association between treatment group and recurrence was also assessed within each prognostic subgroup; these results are shown in the third column of Table 4. In these subgroup analyses, RT showed a statistically significant reduction in risk of recurrence for patients with negative CLS, DSI, and TS of 4 cm or more (HR = 0.16; 90% CI = 0.04 to 0.58; p = 0.010) and for patients with positive CLS and DSI (HR = 0.53; 90% CI = 0.30 to 0.93; p = 0.031).

Results for subgroup analyses of negative CLS, middle third SI, and TS of 4 cm or more, and for positive CLS, middle third SI, and TS of 2 cm or more were inconclusive.

Progression-free survival

Figure 2 shows progression-free survival (PFS) by treatment group. A significant reduction in risk of progression or death occurred with RT compared with OBS (HR = 0.58; 90% CI = 0.40–0.85; p = 0.009). Thus, PFS was significantly improved with adjuvant RT.

Overall survival

Table 5 shows treatment regimen, cause of death, and disease-recurrence status. Both the overall number of deaths (27 [19.7%] RT compared with 40 [28.6%] OBS) and the number of deaths after recurrence (21 [15.3%] RT compared with 34 [24.3%] OBS) are lower for the RT group, compared with the OBS group. In both groups, the vast majority of survivors (97.3% RT, 91% OBS) had no recur-

Table 4. Estimated relative hazard for recurrence by prognostic subgroup, treatment effect, and proportion recurring by subgroup

CLS status, depth of invasion, and tumor size	Hazard ratio (90% CI) of prognostic subgroup*	Hazard ratio (RT/OBS) (90% CI) within prognostic category	Radiation group rec/total	Observation group rec/total
−CLS, middle third, ≥4 cm[†]	1.0	0.29 (0.04–2.14)	1/23	2/13
−CLS, deep third, ≥4 cm	3.07 (1.05–8.96)	0.16 (0.04–0.58)	2/25	9/21
+CLS, superficial third, ≥5 cm	2.45[‡] (0.86–7.00)	1.73[‡] (0.71–4.20)	1/1	0/0
+CLS, middle third, ≥2 cm			7/28	6/37
+CLS, deep third, any size	3.74 (1.39–10.04)	0.53 (0.30–0.93)	13/60	26/69
Overall treatment effect	0.56 (0.37–0.86)[§]	0.54 (0.35–0.81)[¶]	24/137	43/140

Abbreviations: CLS = capillary lymphatic space; rec = recurrences.

* Relative hazard of event for a patient in each prognostic subgroup relative to a patient in reference category, controlled for treatment group.

[†] Reference category.

[‡] Groups were combined to estimate hazard ratio.

[§] Treatment effect, controlled for prognostic subgroup.

[¶] Overall treatment effect.

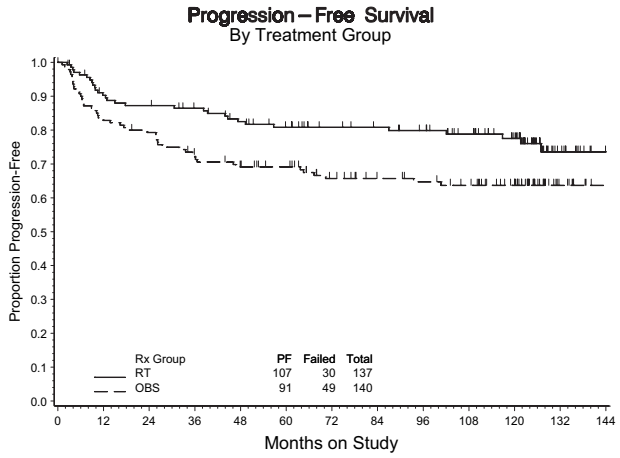

Fig. 2. Progression-free survival by treatment group: 30 RT patients and 49 OBS patients recurred or died. RT significantly increased progression-free survival ($p = 0.009$). OBS = observation; RT = irradiation.

rence, whereas most of those who died did so with recurrent disease (77.8% RT, 85% OBS).

Figure 3 shows survival by treatment group. Seventy percent of all disease-related deaths occurred within the first 3 years after enrollment, and 88% occurred within the first 5 years. In fact, only 4 disease-related deaths occurred later than 6 years after enrollment: 2 RT and 2 OBS. RT patients were 30% less likely to die than were OBS patients (HR = 0.70; 90% CI = 0.46 to 1.05; $p = 0.074$).

Table 6 shows the results of analyses of OS by prognostic category. Risk of death was significantly lower in patients with negative CLS, DSI, and TS greater than 4 cm, but the results were inconclusive for the remaining subgroups. Because of enrollment criteria, these patients also had the largest tumors (≥4 cm). More of these patients were assigned to the RT arm (see Table 1). After adjustment for the prognostic categories, RT patients still had a 26% reduction in risk of death (HR = 0.74; 90% CI = 0.49 to 1.12; $p = 0.111$).

Time, site, and consequences of recurrences in RT patients

In the RT arm 16 of 24 recurrences (66.7%) appeared within 15 months, an additional 4 recurred within 4 years, and the remaining recurrences occurred later than 4 years after enrollment. Three patients with recurrent disease remained alive. Only 4 of 24 reported recurrences were outside the pelvis or distant, whereas 19 of 24 were locoregional failures. This locoregional failure rate differs from RT-alone studies in which pelvic irradiation produced higher locoregional control and higher extrapelvic recurrence rates and suggests the necessity for increased RT doses (or actual delivery of the prescribed doses), either by external beam or in conjunction with brachytherapy.

Complications

Gynecologic Oncology Group Grade 3 or 4 adverse effects (AEs) during the initial treatment period were reported in the previous publication (5). Among the patients were 9 (6.6%) with a total of 11 Grade 3 or 4 AEs (4 genitourinary (GU), 3 hematologic, 3 gastrointestinal (GI), and 1 neurologic) reported out of 137 patients in the RT arm and only 3 patients (2.1%) with Grade 3 or 4 AEs (2 GU, 1 hematologic) reported out of 140 patients in the OBS arm ($p = 0.083$ by Fisher's two-sided exact test). However, even this difference may have been subject to some reporting bias, because the RT patients were seen daily over the course of 5 to 7 weeks (during RT treatment), whereas the OBS patients were seen, at most, once during that same period.

DISCUSSION

The results from retrospective studies have disagreed as to the value of postoperative irradiation in node-negative Stage IB cervix cancer. As discussed in the previous publication (5), complications were a major concern. Although the difference in Grade 3 or 4 AEs in the current report was

Table 5. Cause of death and recurrence status by treatment regimen

	RT			OBS		
Cause of death	No recurrences*	Recurred	Total	No recurrences*	Recurred	Total
Treatment related	0	1	1	0	0	0
Disease	0	19	19	0	31	31
Other	4	0	4	3	1	4
Undetermined	1	1	2	2	2	4
Unknown	1	0	1	1	0	1
Total deaths	6 (22.2)†	21 (77.8)†	27 (19.7)§	6 (15.0)	34 (85.0)†	40 (28.6)§
Alive	107 (97.3)‡	3 (2.7)‡	110 (80.3)§	91 (91.0)	9 (9.0)‡	100 (71.4)§
Total	113 (82.5)§	24 (17.5)§	137	97 (69.3)§	43 (30.7)§	140

* No documented recurrence.
† Percent of group deaths.
‡ Percent of group survivors.
§ Percent of group totals.

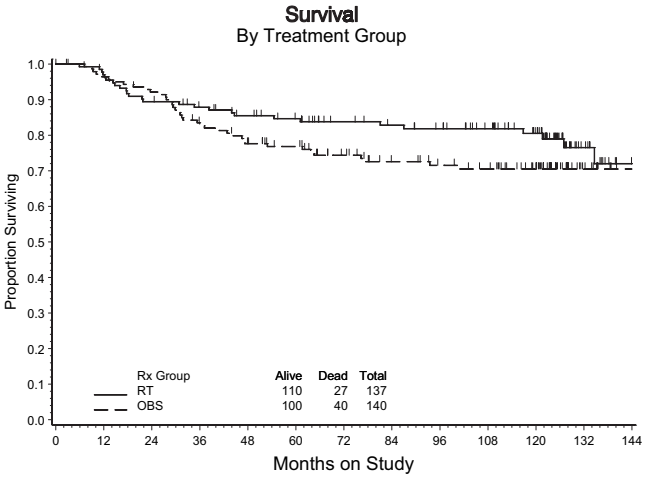

Fig. 3. Survival by treatment group ($p = 0.074$): 27 RT patients and 40 OBS patients died. Beyond 6 years, only 4 disease-related deaths (2 RT, 2 OBS) occurred, and, hence, the convergence of the curves is the result of other causes. OBS = observation; RT = irradiation.

not statistically significant at the traditional 0.05 level (6.6% vs. 2.1%, $p = 0.083$), it was notable enough to warrant that the clinician will need to weigh whether the postoperative RT complications presented an acceptable cost-benefit ratio, despite the significantly higher recurrence rate (30.7% vs. 17.5%) and progression/death rate (35.0% vs. 21.9%) in the OBS arm. If a definite survival benefit had also been shown in this study (HR = 0.70, $p = 0.074$), the decision to use RT would be much easier.

The disparity between recurrence results and survival results in this study is surprising, given that survival comparison usually parallels recurrence comparisons in locally advanced cervix cancer trials (1, 9). However, the sample size may have been too low. The study had 80% power to detect only risk reductions of 46% or greater in OS and did not find significant the 26% to 30% hazard reductions reported above.

Salvage

Of the 12 patients alive with recurrent disease, only 1 of 3 RT patients received salvage therapy, whereas 7 of 9 OBS patients received salvage therapy. Salvage therapy and associated toxicities were not recorded or analyzed as part of this study, but must also be a factor in the clinician's decision.

RT patients who received a less-than-curative dose after randomization

As noted in the Results section, 9 RT-arm patients were not irradiated. Exclusion of these 9 patients did not alter the survival findings (HR = 0.69; 90% CI = 0.46 to 1.05; $p = 0.0732$). An additional 7 patients were irradiated with a dose less than that required by the protocol, and another 11 had treatment protractions (breaks) of more than 20%. Although the merit of excluding all 27 of these patients is debatable, the results are not substantially altered by their exclusion (HR = 0.72; 90% CI = 0.47 to 1.10; $p = 0.1030$). Thus, despite these protocol violations, the results from the intent-to-treat analysis are upheld. The percentage of patients who received no RT in the RT arm was more that twice as high in this study (9 of 137) as in the intergroup (SWOG, GOG, and RTOG) study (4 of 116 in the RT arm and 5 of 127 in the RT + chemo arm), and those who received less than the planned protocol RT dose in this study was more than 3 times higher than in the intergroup study (27 of 137 vs. 7 of 116) (10).

Prognostic factors

Whereas many studies have pointed out the prognostic significance of CLS involvement (11–15), stromal invasion (11), and tumor size (6, 11, 16), either alone or combined (4, 11, 16), others have shown them to have little influence on recurrence rate (17) or survival (18). A prior GOG study (of squamous cervical tumors) confirmed the prognostic significance of CLS involvement, stromal penetration, and tumor size (3).

Two prognostic factors that seem to have become increasingly important in recent years have been cell type (adenocarcinomatous and adenosquamous tumors) (19), and size (tumors ≥4 cm in diameter) (18, 19). In this study, the

Table 6. Estimated relative hazard for death by prognostic subgroup, treatment effect, and proportion dying

CLS status, depth of invasion, and tumor size	Hazard ratio (90% CI) of prognostic subgroup*	Hazard ratio (RT/OBS) (90% CI) within prognostic category	Radiation group deaths/total	Observation group deaths/total
−CLS, middle third, ≥4 cm[†]	1.0	0.59 (0.11–3.06)	2/23	2/13
−CLS, deep third, ≥4 cm	2.15 (0.81–5.68)	0.20 (0.05–0.73)	2/25	8/21
+CLS, superficial third, ≥5 cm	2.02[‡] (0.79–5.16)	1.26[‡] (0.52–3.04)	1/1	0/0
+CLS, middle third, ≥2 cm			6/28	7/37
+CLS, deep third, any size	2.99 (1.26–7.11)	0.83 (0.48–1.42)	16/60	23/69
Overall treatment effect	0.74 (0.49–1.12)[§]	0.70 (0.46–1.05)[¶]	27/137	40/140

Abbreviation: CLS = capillary lymphatic space.

* Relative hazard of event for a patient in each prognostic subgroup relative to a patient in reference category, controlled for treatment group.

† Reference category.

‡ Groups were combined to estimate hazard ratio.

§ Treatment effect, controlled for prognostic subgroup.

¶ Overall treatment effect.

prevalence of both of these factors was higher in the RT arm, but these imbalances did not reduce the effectiveness of the RT arm (HR adjusted for cell type and tumor size = 0.60; 90% CI = 0.41 to 0.89; $p = 0.016$). Although tumor size contributes to risk of recurrence and mortality, in this study analysis of the effect of tumor size is precluded because of the confounding influence of the other eligibility criteria (small tumors required both of the other high-risk factors to be included, whereas large tumors required only 1 other factor). Lai *et al*. (19) reported that after control for confounding factors, histologic type (adenocarcinomatous and adenosquamous vs. squamous) was confirmed as an independent prognostic factor for reduced recurrence-free survival (RR = 1.28; $p = 0.009$) and OS (RR = 1.26; $p = 0.0146$) for Stage IB and II cervical cancer patients after primary radical surgery. When only Stage IB patients were considered ($n = 521$), histologic type was no longer a significant factor, although the relative risks for PFS and OS were 1.36 and 1.53, respectively (Lai, personal communication). In the current study, only 8.8% (3 of 34) of the patients with adenocarcinoma or adenosquamous tumors in the RT arm recurred vs. 44.0% (11 of 25) in the OBS arm. This outcome suggests that RT may be very valuable for such patients.

GI/GU complications

The reported incidence of GI/GU complications from use of postoperative irradiation has varied in the literature from 3% to 30% (20–22). The reasons for such a disparity are multiple and include differences in the reporting (all grades or just Grades 3 and 4) of complications. GI toxicity appears to be the most common and of greater concern, although bladder and ureteral toxicity cannot be ignored. The increase in Grade 3 to 4 complications reported in this study (6.6% RT and 2.1% OBS) may have been magnified by reporting bias. Lymphedema of the lower extremity (foot) was not considered in this study, although it has been reported by others as a significant complication of combined radical hysterectomy, lymphadenectomy, and irradiation (23).

Landoni *et al*. (1) reported in the *Lancet* that, in a study of 337 patients, the incidence of severe complications for surgery alone was not significantly different from those for combined surgery plus RT for Stage IB/IIA cervical cancer patients; and both were significantly more frequent than those seen in patients given RT alone (28% vs. 12%; $p = 0.0004$).

CONCLUSION

The continued demonstration of long-term significantly reduced recurrence risk ($p = 0.007$) and progression/death risk ($p = 0.009$) should be of help to clinicians and patients in deciding the initial management of node-negative Stage IB cervical cancer. Several possible attributes of the trial might partially explain the apparent disparity in significance levels (OS, $p = 0.074$), including several which have been described here. The particular effectiveness of adjunctive RT in reducing the recurrence rate of adenocarcinomatous/adenosquamous vs. squamous cervical tumors indicates that tumors with these histologies need further study.

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