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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

Bradley J. Monk[a,*], Jianmin Wang[b], Samuel Im[a], Richard J. Stock[c,d], William A. Peters III[e,1], P.Y. Liu[f], Rolland J. Barrett II[g,2], Jonathan S. Berek[h], Luis Souhami[i], Perry W. Grigsby[j], William Gordon Jr.[k], David S. Alberts[l]

[a]*Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Chao Family Comprehensive Cancer Center, University of California, Irvine Medical Center, 101 The City Drive, Building 23, Room 107, Orange, CA 92868, USA*
[b]*Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Center, Buffalo, NY 14263, USA*
[c]*Pathology, Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA 23501, USA*
[d]*Departments of Pathology and Obstetrics and Gynecology, Naval Medical Center, Portsmouth, VA 23708-2197, USA*
[e]*Obstetrics and Gynecology, University of Washington, Seattle, WA 98104, USA*
[f]*Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA*
[g]*Piedmont Gynecologic Oncology, Winston-Salem, NC 27103, USA*
[h]*Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, David Geffen School of Medicine at UCLA, University of California at Los Angeles, Los Angeles, CA 90095, USA*
[i]*Department of Oncology, Division of Radiation Oncology, McGill University, Montreal, Canada*
[j]*Radiation Oncology/Nuclear Medicine, Mallinckrodt Institute of Radiology, St. Louis, MO 63110, USA*
[k]*Radiotherapy Department, Deke Slayton Cancer Center, Webster, TX 77598, USA*
[l]*Pharmacology and Public Health, University of Arizona, Arizona Cancer Center, Tucson, AZ 85724, USA*

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Abstract

Objective. To retrospectively analyze data from a previously reported randomized trial of either pelvic radiation (RT) or RT + chemotherapy (CT) in patients undergoing radical hysterectomy and pelvic lymphadenectomy with positive pelvic lymph nodes, parametrial involvement, or surgical margins; to explore associations between RT + CT; and to investigate histopathologic and clinical factors which might be predictive of recurrence.

Methods. Histopathologic sections from biopsies and hysterectomies and clinical data were reviewed from patients with stage IA2, IB, or IIA cervical cancer treated with RT or RT + CT (cisplatin 70 mg/m^2 plus fluorouracil 1000 mg/m^2 every 3 weeks for four cycles). A univariate analysis was performed because the relatively small sample size limited the interpretation of a multivariate analysis.

Results. Of the 268 enrolled women, 243 (RT = 116; RT + CT = 127) were evaluable. The beneficial effect of adjuvant CT was not strongly associated with patient age, histological type, or tumor grade. The prognostic significance of histological type, tumor size, number of positive nodes, and parametrial extension in the RT group was less apparent when CT was added. The absolute improvement in 5-year survival for adjuvant CT in patients with tumors ≤2 cm was only 5% (77% versus 82%), while for those with tumors >2 cm it was 19% (58% versus 77%). Similarly, the absolute 5-year survival benefit was less evident among patients with one nodal metastasis (79% versus 83%) than when at least two nodes were positive (55% versus 75%).

* Corresponding author. Fax: +1 214 854 0770.
E-mail addresses: bjmonk@uci.edu, dmackey@gog.org (B.J. Monk).
[1] Present address: Pacific Gynecologic Specialists, P.C., Seattle, WA 98104, USA.
[2] Affiliate of University of Virginia Health Sciences Center, USA.

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Conclusions. In this exploratory, hypothesis-generating analysis, adding CT to RT after radical hysterectomy, appears to provide a smaller absolute benefit when only one node is positive or when the tumor size is < 2 cm. Further study of the role of CT after radical hysterectomy in patients with a low risk of recurrence may be warranted.

Keywords: Cisplatin; Radiation; Radiosensitization; Radical hysterectomy

Introduction

In the United States, the majority of cervical carcinoma patients are diagnosed with early stage disease. Among the 13,458 staged patients with cervical carcinoma registered by the SEER program between 1973 and 1987, 71% were diagnosed with FIGO stages I–IIA tumors [1]. Most of these women with early lesions are cured with surgery or radiation (RT) alone. However, patients with metastatic disease or those more advanced lesions are at significant risk of recurrence and account for the majority of cervical cancer deaths in the United States. These deaths occur despite current surgical and radiotherapy protocols, often as a direct result of local or in-field treatment failure [2].

Presumably, pelvic control in patients with cervical cancer is influenced not only by stage and tumor volume, but also by intrinsic tumor biology that determines radiation sensitivity and/or resistance. The ability of certain chemotherapeutic agents to overcome this intrinsic radiation resistance and improve radiation sensitivity has been addressed in several randomized phase III clinical trials. To date, five such trials conducted by cooperative groups have demonstrated a significant improvement, not only in local control but also in survival, with the addition of cisplatin-based systemic chemotherapy (CT) to pelvic RT in the treatment of cervical carcinoma [3]. This benefit is apparently due, in part, to the "radiosensitizing" effect of cisplatin, which makes otherwise resistant cancer cells sensitive to RT. While this process is more complex than described here, the model allows scientists and clinicians the opportunity to evaluate local RT and CT protocols that may be of clinical importance.

Only one sufficiently powered prospective randomized trial has addressed the role of synchronous adjuvant RT and CT after radical hysterectomy and lymphadenectomy: Gynecologic Oncology Group (GOG) 109/Southwest Oncology Group (SWOG) 8797/Radiation Therapy Oncology Group (RTOG) 91-12 [4]. This study evaluated women, found to have positive pelvic lymph nodes and/or microscopic involvement of the parametrium and/or positive surgical margins, who were randomly allocated to receive either pelvic RT alone or RT in combination with CT (intravenous bolus cisplatin 70 mg/m^2 and a 96-h infusion of fluorouracil 1000 mg/m^2 every 3 weeks for four cycles). The results of this clinical trial demonstrated that progression-free survival (PFS) and overall survival (OS) were significantly improved with the addition of CT (hazard ratio 2.01, $P = 0.003$, and 1.96, $P = 0.007$, respectively). Five-year survival for the adjuvant RT + CT group was projected to be 81% in this "high-risk" group of patients.

Another pivotal GOG trial investigated the role of RT alone after radical hysterectomy. Protocol 92 studied "intermediate risk" women; namely, those with at least two of the following risk factors after radical hysterectomy: >1/3 stromal invasion, lymph vascular space involvement, or large clinical tumor diameter. Of 277 patients, 137 were randomly allocated to receive pelvic RT and 140 to receive no further treatment (NFT). Twenty-one patients (15%) in the RT group and 39 (28%) in the NFT group had a cancer recurrence, of which 18 and 27, respectively, recurred in the vagina and pelvis. This difference translated into a 47% reduction in risk of recurrence (relative risk = 0.53, $P = 0.008$, one-tail) after RT, with a 2-year recurrence-free rate of 88% versus 79% [5].

In determining the eligibility for both of these trials, every attempt was made to enroll a group of patients with an equivalent risk of recurrence. This challenging task was based on multiple previous trials investigating certain clinical and pathologic risk factors for stage I cervical cancer; in particular, a study of 645 women enrolled in a GOG study of clinical and pathologic predictors of recurrence among women with surgically treated stage I carcinoma of the cervix. This analysis confirmed the prognostic significance of tumor size, depth of invasion, lymph vascular space invasion, margin status, parametrial involvement, and nodal status [6,7]. Nevertheless, even following this thorough analysis, both the intergroup trial and GOG 92 still contained very heterogeneous groups of patients. Moreover, it has become clear that many women have very high cure rates after radical surgery alone or after surgery plus radiation without CT [8]. This is particularly important because the morbidity of multimodality therapy is well documented and the clear trend is to treat most women, particularly those with large tumors, with two or even three modalities [9].

The purpose of this report is to describe the results of an exploratory analysis of patients treated on GOG 109/SWOG 8797/RTOG 91-12. This study was undertaken to assess the benefit from RT + CT after radical hysterectomy in subgroups of patients, and to investigate common histopathologic and clinical factors that might be predictive of recurrence. Although unplanned when the study was initially developed, it is hoped that this exploratory investigation might be useful in the planning of future prospective trials. Importantly, the inferences drawn from the current analysis are weaker than the conclusions drawn in the original study because they were developed retrospectively and are primarily data driven.

Methods

Eligibility criteria

To be eligible for this randomized clinical trial, patients must have been treated with a radical hysterectomy and pelvic lymphadenectomy for clinical stage IA2, IB, or IIA cervical carcinoma. Patients were eligible if they had squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma and had histologically confirmed positive pelvic lymph nodes, positive parametrial involvement, or a positive surgical margin and had a SWOG performance status of 0–2 as well as normal bone marrow, kidney, and liver function, the details of which have been previously described [4]. All institutions participating in this study obtained approval of their Institutional Review Board (IRB), and all patients provided signed informed consent consistent with federal, state, and local requirements prior to receiving protocol therapy. This retrospective review of data was also approved by the IRB for the University of California, Irvine.

Treatment plan

Patients were randomly allocated to receive either pelvic RT or pelvic RT plus CT as previously described and outlined above [4]. No prospective stratification factors were employed. Pelvic RT was given in 1.7 Gy fractions Monday through Friday using a four-field box technique for a total of 29 fractions, delivering a total dose of 49.3 Gy. Patients with common iliac nodal metastases were given 45 Gy of extended field RT covering the aortic lymph nodes. The radiation source was required to be 4 MeV or more. Brachytherapy was not permitted.

Patients in the RT + CT group received intravenous bolus cisplatin 70 mg/m^2 and a 96-h infusion of fluorouracil 1000 mg/m^2 every 3 weeks for four cycles. The third and fourth cycles of CT were given after completion of RT [4]. Toxicity was monitored according to standard SWOG criteria with treatment modifications made according to the protocol [4].

Statistical analysis

This study was open to three cooperative groups: GOG, SWOG, and RTOG. Pertinent histopathologic sections from biopsies and radical hysterectomies were submitted from member institutions for independent review. The histologic type of each tumor was confirmed, and the tumor grade and depth of invasion, as well as the margin, parametrial, nodal, and lymph vascular space status, were recorded. Tumor measurements were performed on formalin fixed stained sections.

This analysis includes all eligible patients regardless of the amount of study treatment received. The number of women not receiving treatment was small (five or fewer in each arm). Survival data since the time of the original report were updated. Survival was estimated using the Kaplan–Meier method with differences analyzed using a log-rank test. A univariate statistical analysis is reported because the relatively small sample size limits the interpretation of a multivariate analysis. The P values cited in this exploratory analysis serve as an index of the strength of association rather than a probability of rejecting prespecified null hypotheses.

Results

Between 1991 and 1996, 268 women were entered into this study, with 25 deemed ineligible and 243 considered eligible and evaluable (RT = 116; RT + CT = 127). The reasons for ineligibility, as well as the details of RT and CT administration, are presented in the original publication of the trial [4]. Ninety-four percent of women in the RT alone group and 89% in the RT + CT group received more than 45 Gy of pelvic RT; and 71% in the combined modality group received at least three doses of CT. Clinical and pathologic data for the evaluable patients are presented in Table 1. Patients were well matched between the two groups with respect to commonly defined clinical and histologic risk factors.

After a median follow-up of 5.2 years, the estimated 5-year survival for the RT + CT group was 80% compared to 66% for the RT alone group. As demonstrated in Table 2, age, histologic type, and tumor grade were not prognostic within either treatment group and the benefit of CT was evident among women regardless of these clinical and pathologic characteristics. However, there was a trend for tumors larger than 2 cm to do worse in the RT alone group (P = 0.09) (Fig. 1). Interestingly, when examining tumor size in a univariate fashion, the benefit from the addition of CT was most evident among women with tumors larger than 2 cm (P = 0.17 for size ≤2 cm; P = 0.009 for size >2 cm). Similarly, women with two or more pelvic nodal metastases did worse in the RT alone group (P = 0.01) while this was less evident in the RT + CT group (P = 0.37). Also, the absolute benefit of adjuvant CT was less apparent among patients with only one nodal metastasis because 5-year survival was 79% for women in the RT alone group compared to 83% in the RT + CT group (Fig. 2). The benefit of CT in the group of women with ≥2 positive nodes is demonstrated by the estimated 20% improvement in 5-year survival for this group (P = 0.006) (Fig. 3). Because of the small number of recurrences, it was not possible to perform statistical analysis on local and distant sites, although these data (presented in Tables 3 and 4) may be important because RT was only administered to the pelvis and brachytherapy was not permitted.

Discussion

Among women with the earliest stages of (stage IA1 or microinvasive) cervical cancer, a simple hysterectomy is

Table 1
Patient characteristics

	RT alone		RT + CT	
Age (years) [median (range)]	38 [20–64]		40 [19–74]	
Characteristic	No.[a]	%	No.[a]	%
Race				
White	62	53	70	55
Black	18	16	18	14
Hispanic	18	16	18	14
Other	6	5	2	2
Histology				
Squamous	95	82	98	77
Nonsquamous	21	18	29	23
Grade				
1	14	12	12	9
2	52	45	67	53
3	47	41	45	35
Size (cm)[b]				
Median (range)	2.1	[0.2–4.0]	2.2	[0.6–5.2]
Depth of invasion				
Inner 1/3	3	3	4	3
Middle 1/3	10	19	14	11
Outer 1/3	71	61	79	62
Margin status				
Negative	108	93	119	94
Positive	8	7	8	6
Parametrial extension				
Negative	69	60	77	61
Positive	47	40	50	39
Node status[c]				
Negative	19	16	17	13
1 Positive node	44	38	55	43
≥2 Positive nodes	53	46	56	44
Lymph vascular space				
Negative	32	28	35	28
Positive	78	67	90	71

[a] Data not available for all patients in all categories.
[b] Tumor dimensions, based on measurements provided on H & E sections, were taken along the greatest dimension of the gross tumor (per protocol).
[c] Lymphatic metastases were identified using light microscopy of H & E slides. Immunochemistry techniques were not used to identify positive nodes.

generally recommended. Conventional treatment of patients with stages IA2, IB, and IIA cervical carcinoma consists of either radical hysterectomy with bilateral pelvic lymph node dissection or RT combining whole pelvic teletherapy with local brachytherapy [10]. These treatment modalities are considered equally efficacious with respect to local control and survival if lesions are small and nodal metastasis absent. Surgery is often preferred to radiotherapy in younger women because ovarian function is eliminated and sexual function may be compromised following RT. In addition, the late complications of RT can be avoided when patients are treated with surgery alone [11].

At the time of radical hysterectomy, operative and pathologic data can identify those patients at highest risk of recurrence. Adjuvant therapy, either RT alone or in combination with CT, may then be administered to reduce the risk of recurrence and death among these high-risk women. Importantly, adjuvant therapy should only be given to those who would otherwise not survive to avoid unnecessary, costly, and morbid treatment for those likely not to benefit. Two recently published cooperative group studies, GOG Protocol 92 and the intergroup study GOG 109/SWOG 8797/RTOG 91-12, addressed the activity of RT alone or in combination with CT after radical hysterectomy [4,5]. The objective of the current report is to reanalyze the latter study in an exploratory fashion to determine which patients benefited most from the addition of CT. Not surprisingly, the women at highest risk experienced the greatest absolute reduction in risk of recurrence, as well as improved survival.

It is possible, when reanalyzing data from a well-controlled randomized trial, to draw spurious conclusions because factors analyzed individually do not necessarily function independently. However, our results suggest that the addition of adjuvant CT to RT after radical hysterectomy in women with positive surgical margins, parametrial extension, and/or positive pelvic nodes is beneficial regardless of patient age, histologic type, or tumor grade.

In addition, we report that the prognostic significance of cell type, tumor size, number of positive nodes, and parametrial extension among women treated with radical hysterectomy and RT alone is less apparent when CT is added.

Table 2
Estimated 5-year survival (%) by treatment and characteristic

Characteristic	RT alone	RT + CT	*P* value[a]
Age (years)			
<40	0.61	0.76	0.031
≥40	0.74	0.83	0.029
P value[a]	0.387	0.420	
Tumor size[b]			
≤2 cm	0.77	0.82	0.170
>2 cm	0.58	0.77	0.009
P value[a]	0.090	0.529	
Histology			
Squamous	0.69	0.80	0.019
Nonsquamous	0.55	0.82	0.014
P value[a]	0.170	0.764	
Grade			
Grades 1 and 2	0.66	0.80	0.007
Grade 3	0.67	0.80	0.091
P value[a]	0.703	0.794	
Parametrial extension			
Negative	0.78	0.84	0.052
Positive	0.49	0.73	0.009
P value[a]	0.007	0.196	
Nodes[c]			
1 Positive node	0.79	0.83	0.438
≥2 Positive nodes	0.55	0.75	0.006
P value[a]	0.01	0.37	

[a] *P* values represent log-rank testing of the equivalence of two survival curves.
[b] Tumor dimensions, based on measurements provided on H & E sections, were taken along the greatest dimension of the gross tumor (per protocol).
[c] Lymphatic metastases were identified using light microscopy of H & E slides. Immunochemistry techniques were not used to identify positive nodes.

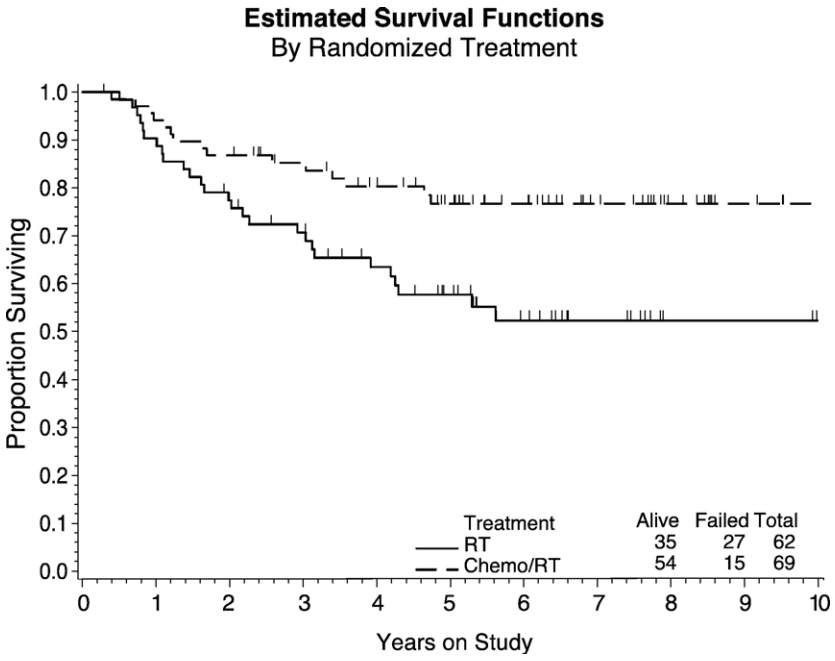

Fig. 1. Survival of women with tumors >2 cm by treatment arm.

Interestingly, women with tumors ≤2 cm or those with only one positive node appeared to have similar outcomes whether they received CT or not. For example, the estimated 5-year cure rate for women in the study group whose tumors were 2 cm or less was 77% in the RT alone group and 82% in the RT + CT group. When the size of the primary lesion is larger than this, the addition of chemotherapy results in a 19% improvement in 5-year survival. Common practice would not dictate the addition of CT to pelvic RT if radical hysterectomy yielded a tumor ≤2 cm, unless other high-risk factors predictive of recurrence such as positive margins or parametrial extension of positive nodes were present [10]. Indeed, it is unlikely that either of the first two risk factors would occur with such a small tumor; thus, the primary indicator for the addition of CT to RT after radical hysterectomy when small tumors are encountered is nodal metastases, which was confirmed in the current study. In fact, size may be simply a surrogate for predicting risk of nodal metastases and may not be itself independently predictive when RT is given after radical hysterectomy. Finan et al. [12] have shown this through multivariate stepwise logistical regression analysis, in which tumor size did not have an independent impact on survival and demonstrated that the impact of tumor size on survival is

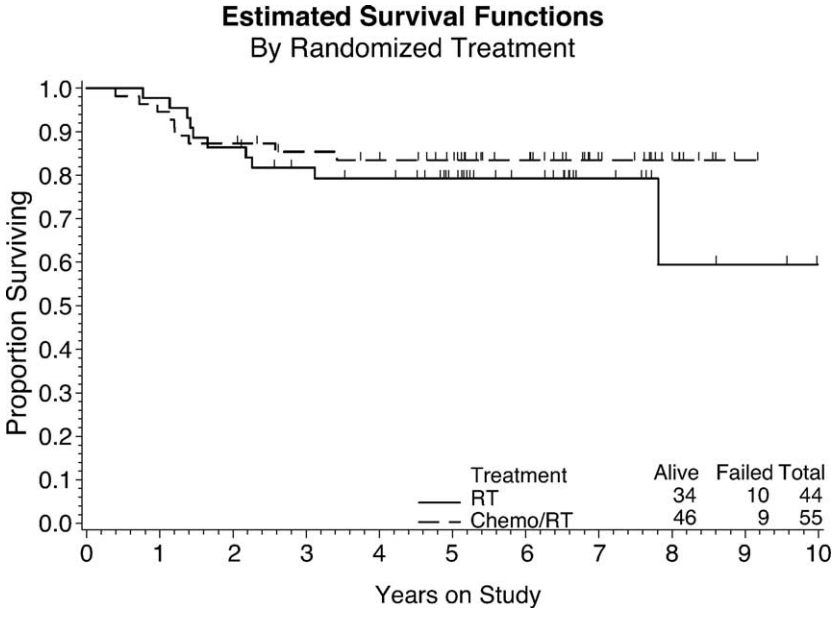

Fig. 2. Survival of women with one nodal metastasis by treatment arm.

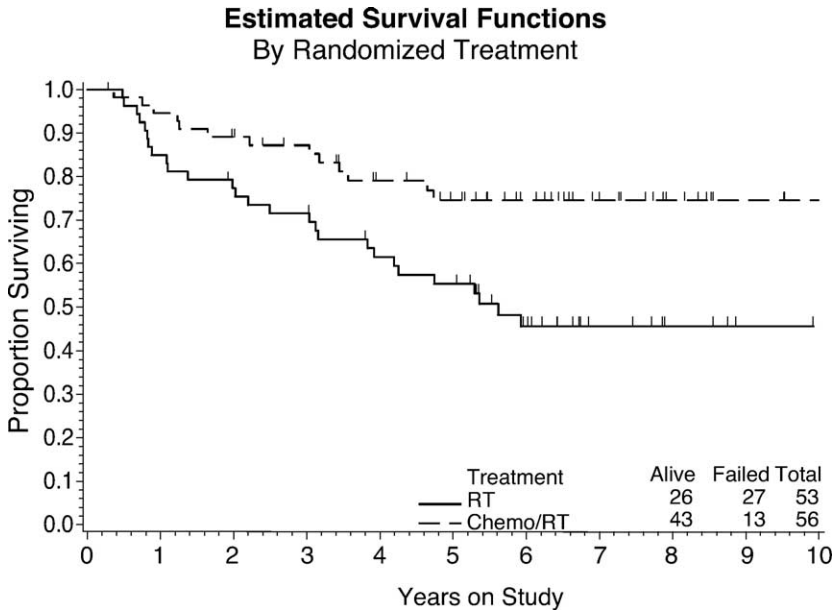

Fig. 3. Survival of women with ≥2 nodal metastases by treatment arm.

through nodal status. This has also been shown by others [13].

When CT is not added to RT after radical hysterectomy and two or more nodal metastases are present, the estimated 5-year survival is only 55%. In our study, the addition of CT resulted in fewer local and distant relapses. The improvement in distant control is very interesting because this has not been a consistent finding among all randomized trials investigating the role of cisplatin-based CT with RT in the management of cervical carcinoma [3]. The decrease in extrapelvic recurrences in the current study may be due to the disease stages studied, the use of fluorouracil, or the addition of two doses of CT after the completion of RT. This has particular relevance because many clinicians now use (after radical hysterectomy) the cisplatin schedule studied in GOG Protocol 120, which is weekly for 6

Table 3
Local recurrence according to pathologic variables

Characteristic	RT alone		RT + CT	
	No.[a]	%	No.[a]	%
Histology				
Squamous	19/95	20	9/98	9
Nonsquamous	6/21	29	2/29	7
Grade				
Grades 1 and 2	11/66	17	7/79	9
Grade 3	14/47	30	4/45	9
Depth of invasion				
Inner and middle 1/3	0/13	0	1/18	6
Outer 1/3	20/71	28	7/79	9
Margin status				
Negative	23/108	21	10/119	8
Positive	2/8	25	1/8	13
Parametrial extension				
Negative	9/69	13	7/77	9
Positive	16/47	34	4/50	8
Node status[b]				
Negative	5/19	26	0/16	0
Positive	20/97	21	11/111	10
Number of positive nodes				
1 Positive node	6/44	14	5/55	9
≥2 Positive nodes	14/53	26	6/56	11

[a] Data not available for all patients in all categories.
[b] Lymphatic metastases were identified using light microscopy of H & E slides. Immunochemistry techniques were not used to identify positive nodes.

Table 4
Distant recurrence according to pathologic variables

Characteristic	RT alone		RT + CT	
	No.[a]	%	No.[a]	%
Histology				
Squamous	13/95	14	10/98	10
Nonsquamous	5/21	24	3/29	10
Grade				
Grades 1 and 2	13/66	20	5/79	6
Grade 3	4/47	9	7/45	16
Depth of invasion				
Inner and middle 1/3	1/13	8	1/18	6
Outer 1/3	14/71	20	9/79	11
Margin status				
Negative	15/108	14	12/119	10
Positive	3/8	38	1/8	13
Parametrial extension				
Negative	10/69	15	7/77	9
Positive	8/47	17	6/50	12
Node status[b]				
Negative	2/19	11	1/16	6
Positive	16/97	17	12/111	11
Number of positive nodes				
1 Positive node	5/44	11	6/55	11
≥2 Positive nodes	11/53	21	6/56	11

[a] Data not available for all patients in all categories.
[b] Lymphatic metastases were identified using light microscopy of H & E slides. Immunochemistry techniques were not used to identify positive nodes.

weeks, compared to 12 weeks in the current study [14]. Finally, another possible explanation for the reduction in distant failure may have been related to the antecedent reduction in local failure. Indeed, chemotherapy appeared to be nearly twice as effective in reducing failure within the irradiated volume as reducing failures distant from the irradiated volume.

The role of RT after radical hysterectomy when only one positive node is present has been the subject of much debate [15,16]. This question had apparently been resolved with the results of GOG Protocol 92, which showed adjuvant RT to be beneficial after radical hysterectomy (although that trial was not designed to directly answer this question). The current report seems to add to the controversy by suggesting that the addition of CT to RT may not be needed after radical hysterectomy if only one nodal metastasis is found. However, an alternative conclusion might be that RT is of little benefit as adjuvant therapy when nodal spread is present, and that CT alone accounts for the improved outcome, with the most dramatic effect taking place when $\geq$2 nodes are involved. This conclusion cannot be reached from this study because of its retrospective nature, but there is rationale for a randomized study investigating the expanded role of CT after radical hysterectomy, especially among women with $\geq$2 positive nodes. Perhaps a comparison of therapeutic doses of chemotherapy alone (six cycles every 3 weeks) versus 6 weeks of combination radiation and chemotherapy should be considered. In addition, the value of CT after radical hysterectomy with only one positive node, especially if tumor size is less than 2 cm, warrants further study.

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