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Clinical Investigation

Postoperative Chemoradiation Therapy in High-Risk Cervical Cancer: Re-evaluating the Findings of Gynecologic Oncology Group Study 109 in a Large, Population-Based Cohort

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Summary

In this analysis of patients with high-risk cervical cancer treated with hysterectomy within the National Cancer Database, adjuvant chemoradiation therapy was associated with improved overall survival over external beam radiation therapy alone. This benefit was found in patients with pathologic lymph node involvement and not identified in patients with positive margins and/or parametrial invasion.

Purpose: To review the National Cancer Database (NCDB) to evaluate postoperative high-risk cervical cancer patients for factors associated with a benefit from chemoradiation therapy (CRT) over external beam radiation therapy alone (EBRT).

Methods and Materials: The National Cancer Database was queried for women with cervical cancer treated with hysterectomy and adjuvant EBRT from 2002 to 2012. Only patients with pathologic lymph node involvement (LN+), positive surgical margins, and/or parametrial invasion were included in our analysis (on the basis of Peter's criteria). Univariable and multivariable analyses (MVA) were performed, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to investigate for factors associated with of CRT utilization and overall survival (OS).

Results: A total of 3053 patients met inclusion criteria, and 2479 received adjuvant CRT (81%), whereas 574 (19%) received EBRT alone. Factors associated with increased CRT utilization on MVA included age <69 years, year of diagnosis ≥2008, non-adenocarcinoma histology, and LN+. Use of CRT improved OS among the entire cohort on MVA (HR 0.76, CI 0.601-0.962; $P=.022$). On MVA, CRT improved OS in patients with LN+ as their sole Peter's criteria (HR 0.58, CI 0.413-0.814; $P=.002$). Chemoradiation therapy did not improve OS in patients with only positive margins ($P=.73$), only parametrial invasion ($P=.95$), or any combination of these 2 factors without LN+ ($P=.63$).

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Conclusions: The use of adjuvant CRT after hysterectomy improves OS in patients with high-risk cervical cancer compared with EBRT alone, but this benefit seems to be restricted to patients with LN+. The benefits of adjuvant CRT over EBRT alone in patients with parametrial invasion and/or positive margins (without nodal involvement) are unknown.

Introduction

Pathologic risk factors for recurrence after radical hysterectomy for cervical cancer were first identified in the 1980s (1-3). Concurrent but independent phase 3 trials conducted by the Gynecologic Oncology Group (GOG) in the early 1990s aimed to define the role of postoperative external beam radiation therapy alone (EBRT; GOG 92) and postoperative concurrent chemoradiation therapy (CRT; GOG 109) in patients with "intermediate-risk" and "high-risk" cervical cancer, respectively (4, 5). Each trial used mutually exclusive inclusion criteria that had been identified as risk factors for recurrent disease in previous retrospective series (1-3, 6-9). GOG 109 provided prospective evidence that adjuvant CRT improved overall survival (OS) in patients meeting inclusion criteria, which included pathologic lymph node involvement, positive surgical margins, and/or parametrial involvement—commonly referred to as the "Peter's criteria" (5). This landmark trial forms the backbone for current consensus guidelines recommending adjuvant CRT after radical hysterectomy in patients with at least one of Peter's criteria (10).

Although as a whole patients meeting these inclusion criteria had improved survival with CRT, because of this trial's size (243 patients) there was limited statistical power to demonstrate improvement for each of the individual pathologic inclusion criteria (5, 11). For example, only 36 patients included in this trial were without pathologic evidence of nodal disease. As a result, physicians have limited data to support adjuvant CRT over EBRT alone in patients with, as an example, pathologic parametrial invasion but no lymph node or surgical margin involvement.

Our objective was to utilize the National Cancer Database (NCDB) to retrospectively evaluate the results for high-risk cervical cancer patients treated with adjuvant radiation therapy (RT) and CRT. Using a large retrospective cohort, we aim to better understand which disease characteristics demonstrate a survival advantage with adjuvant CRT.

Methods and Materials

Database

The NCDB is a jointly sponsored database that collects clinical outcomes data from more than 1500 accredited facilities (12). The NCDB includes approximately 70% of newly diagnosed cancers in the United States. We queried the NCDB for women with cervical cancer in early 2015 and identified 148,998 evaluable patients. The study was reviewed and determined to have exempt status by our institutional review board.

Cohort selection

The cohort selection diagram for this study is illustrated in the supplemental materials (Fig. E1; available online at www.redjournal.org). The final cohort consists only of patients that were treated with initial surgery and lymph node dissection for nonmetastatic cervical cancer after 2002, to allow for the dissemination of the results of GOG 109 into clinical practice (published in 2000). A total of 41,653 patients were excluded because their surgery was done before the study period, 2002 to 2012. Patients with stated contraindications to or unknown utilization of chemotherapy and/or RT as defined by the NCDB coding key were also excluded (13).

All patients included in the analysis had at least 1 of Peter's criteria. Lymph node involvement and surgical margin status (positive or negative) were defined by their respective NCDB codes (13), and parametrial invasion was defined as American Joint Committee on Cancer (AJCC) T-stage of at least 2b. Patients with unknown margin or nodal status were excluded. Neuroendocrine and carcinosarcoma histologies were excluded because they were not included in GOG 109, and as such the role of adjuvant CRT is less defined (5). Patients receiving brachytherapy as an external beam boost (with or without chemotherapy) were excluded to better replicate the treatment of patients in GOG 109. Patients who did not receive EBRT (brachytherapy alone, chemotherapy alone, or no adjuvant therapy) were also excluded.

Remaining patients were stratified into two groups: postoperative RT alone and postoperative CRT. Similar to GOG 109, the primary endpoint of our analysis was OS from the date of diagnosis as determined by NCDB vital status. The design of this observational cohort study aimed to recapitulate the GOG 109 comparison of CRT and RT in a real-world, nonrandomized setting.

Prognostic variables

Clinical variables included in statistical analyses included patient age, year of diagnosis, race, Charlson/

Table 1 Clinical and disease characteristics of the postoperative cervical cancer cohort (n = 3053) in the National Cancer Database 2002 to 2012 compared with GOG 109 (n = 243)

	Present analysis				GOG 109			
	Chemoradiation therapy		Radiation therapy alone		Chemoradiation therapy		Radiation therapy alone	
Characteristic	n	%*	n	%*	n	%*	n	%*
No. of patients	2479	81.2	574	18.8	127	52.3	116	47.7
Clinical characteristics								
Age (y)								
18-29	166	6.7	33	5.7				
30-49	1397	56.4	270	47.0				
50-69	785	31.7	196	34.1				
>69	131	5.3	75	13.1				
Year of diagnosis								
2002-2007	1324	53.4	379	66.0				
2008-2012	1155	46.6	195	34.0				
Race								
White	1729	69.7	374	65.2	82	64.6	76	65.5
Black	275	11.1	71	12.4	22	17.3	19	16.4
American Indian	16	0.6	4	0.7	0	0.0	0	0.0
Asian/Pacific Islander	99	4.0	22	3.8	0	0.0	0	0.0
Unknown	52	2.1	12	2.1	4	3.1	7	6.0
Hispanic	308	12.4	91	15.9	18	14.2	11	9.5
Charlson/Deyo score								
0	2701	83.5	452	78.7				
1	213	8.6	38	6.6				
2	22	0.9	7	1.2				
Unknown	173	7.0	77	13.4				
Median income of ZIP code ($)								
<30,000	495	20.0	131	22.8				
30,000-34,999	587	23.7	149	26.0				
35,000-45,999	635	25.6	141	24.6				
≥46,000	688	27.8	131	22.8				
Unknown	74	3.0	22	3.8				
Insurance								
Medicare/commercial	1728	69.7	401	69.8				
Medicaid	477	19.2	103	17.9				
Uninsured	179	7.2	47	8.2				
Government	37	1.5	4	0.7				
Unknown	58	2.3	19	3.3				
Distance to hospital (mi)								
<25	1753	70.7	411	71.6				
25-100	550	22.2	121	21.1				
>100	90	3.6	17	3.0				
Unknown	86	3.5	25	4.4				
Facility volume†								
1-5	665	26.8	133	23.2				
6-12	625	25.2	194	33.8				
13-26	589	23.8	145	25.3				
>26	600	24.2	102	17.8				
Disease characteristics								
Pathologic AJCC T stage‡								
pT1 or less	1493	60.2	336	58.5	119	93.7	110	94.8
pT2	778	31.3	191	33.3	8	6.3	6	5.2
pT3	129	5.2	32	5.6	0	0.0	0	0.0
pT4	66	2.7	9	1.6	0	0.0	0	0.0
Unknown	13	0.5	6	1.0	0	0.0	0	0.0
Histology								
Squamous cell carcinoma	1729	69.7	388	67.6	97	76.4	96	82.8
Adenocarcinoma	381	15.4	122	21.3	18	14.2	13	11.2

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Present analysis				GOG 109			
	Chemoradiation therapy		Radiation therapy alone		Chemoradiation therapy		Radiation therapy alone	
	n	%*	n	%*	n	%*	n	%*
Adenosquamous	180	7.3	31	5.4	12	9.4	7	6.0
Carcinoma NOS	189	7.6	33	5.7	0	0.0	0	0.0
Grade								
Well differentiated	140	5.6	35	6.1	12	9.4	14	12.1
Moderately differentiated	964	38.9	238	41.5	67	52.8	52	44.8
Poorly or undifferentiated	1145	46.2	236	41.1	45	35.4	47	40.5
Unknown	230	9.3	65	11.3	3	2.4	3	2.6
Tumor size >4 cm	721	29.1	164	28.6				
LVSI positive	415	16.7	70	12.2	90	70.9	78	67.2
Peters criteria								
pN+	1996	80.5	361	62.9	110	86.6	97	83.6
Positive margin	543	21.9	164	28.6	5	3.9	7	6.0
Parametrial invasion§	734	29.6	182	31.7	42	33.1	41	35.3

Abbreviations: AJCC = American Joint Committee on Cancer; GOG = Gynecologic Oncology Group; LVSI = lymphovascular space invasion; NOS = not otherwise specified; pN+ = pathologic nodal involvement.

See references (5) and (11).

* Percentages listed as a percentage within respective category.

† Facility volume was calculated by the total number of patients treated at a facility that had at least 1 pathologic Peter's criteria during the study period (2002-2012).

‡ GOG 109 is reported as clinical stage.

§ Defined as pT2b, pT3a, pT3b, or pT4a.

Deyo score, median household income of patient ZIP code, patient insurance, distance from patient home to hospital, and facility volume. Facility volume was defined as the total number of patients meeting the inclusion criteria at the identified center during the study period, and grouped in quartiles. Disease-specific variables included pathologic AJCC tumor stage (pT), histology, grade, size ($\leq$ or $>$ 4 cm), lymphovascular space invasion (LVSI) (yes or no), lymph node involvement (yes or no), positive surgical margin (yes or no), and parametrial invasion (yes or no).

Statistical analysis

Data in Table 1 are presented as the number of patients and the percentage of each subgroup. Potential prognostic variables (identified above) were evaluated for an association with CRT utilization using logistic regression models with univariable analysis (UVA) and multivariable analysis (MVA). For survival analyses, patients with unknown Charlson/Deyo score (n=250) and unknown pT stage (n=19) were excluded. Survival data were not available in patients diagnosed in 2012 (n=250), and these patients were excluded from the survival analysis cohort (remaining n=2542). Overall survival was estimated using the Kaplan-Meier method, with differences tested using the log-rank test. Multivariable Cox proportional hazards models were used to investigate potential independent prognostic factors for OS after diagnosis. Variables with $P \leq .10$ on UVA were included in the final multivariable models. All tests were 2-tailed, and $P < .05$ was considered statistically significant. Patients were

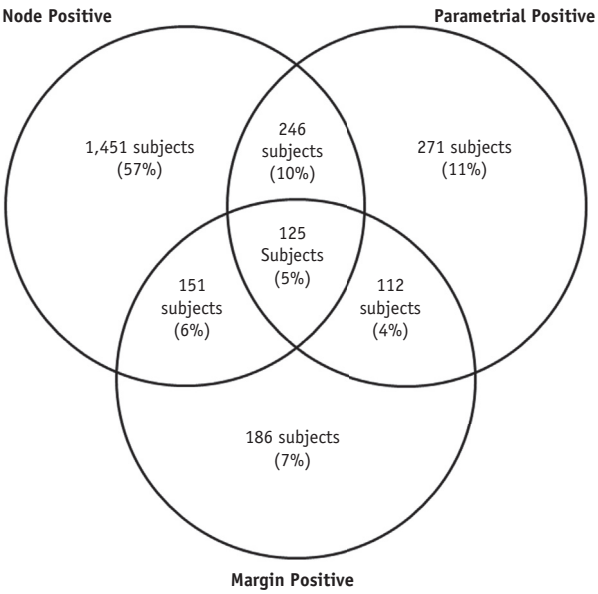

Fig. 1. Diagram of patients in the National Cancer Database with Peter's criteria included in overall survival analysis (n=2542).

Table 2 Analysis of factors that contribute to chemoradiation therapy utilization compared with radiation therapy alone (n = 3053) in the National Cancer Database 2002 to 2012

			Multivariable			
Factor	% CRT	Univariable *P*	*P*	OR	Lower 95%	Upper 95%
Clinical characteristics						
Age (y)		<.001*	<.001*			
18-29	83.4			ref		
30-49	83.4			1.008	0.673	1.510
50-69	80.0			0.843	0.555	1.279
>69	63.6			0.427*	0.261	0.698
Year of diagnosis		<.001*	<.001*			
2002-2007	77.7			ref		
2008-2012	85.6			1.645*	1.340	2.018
Race		.277				
White	82.2					
Black	79.5					
American Indian	80.0					
Asian/Pacific Islander	81.8					
Unknown	81.3					
Hispanic	77.2					
Charlson/Deyo score		<.001*	.005*			
0	82.1			ref		
1	84.9			1.408	0.968	2.048
2	75.9			0.891	0.359	2.211
Unknown	69.2			0.632*	0.465	0.860
Median income of ZIP code ($)		.081	.174			
<30,000	79.1			ref		
30,000-34,999	79.8			1.060	0.808	1.391
35,000-45,999	81.8			1.174	0.893	1.543
≥46,000	84.0			1.371*	1.038	1.810
Unknown	77.1			0.941	0.553	1.602
Insurance		.389				
Uninsured	79.2					
Insured	81.5					
Distance to hospital (mi)		.647				
<25	81.0					
25-100	82.0					
>100	84.1					
Unknown	77.5					
Facility volume		.133				
1-5	83.3					
6-12	76.3					
13-26	80.2					
>26	85.5					
Disease characteristics						
Pathologic AJCC T stage		.905				
pT1 or less	81.6					
pT2	80.3					
pT3	80.1					
pT4	88.0					
Histology		.002*	.022*			
Squamous cell carcinoma	81.7			ref		
Adenocarcinoma	75.7			0.723*	0.568*	0.920
Adenosquamous	85.3			1.199	0.799	1.800
Carcinoma NOS	85.1			1.173	0.788	1.747
Grade		.18				
Well differentiated	80.0					
Moderately differentiated	80.2					
Poorly or undifferentiated	82.9					
Unknown	78.0					

(*continued on next page*)

Table 2 (*continued*)

Factor	% CRT	Univariable *P*	Multivariable			
			P	OR	Lower 95%	Upper 95%
Tumor size >4 cm	81.5	.753				
LVSI positive	85.6	.863				
Peters criteria						
pN+	84.7	<.001*	<.001*	2.261*	1.804	2.832
Positive margin	76.8	.001*	.773	1.035	0.819	1.308
Parametrial invasion	80.1	.205				

Abbreviations: % CRT = percentage of subgroup adjuvant chemoradiation therapy utilization; HR = hazard ratio; ref = reference category. Other abbreviations as in Table 1.

* $P<.05$.

grouped according to their specific Peter's criteria (Fig. 1), and then similar analyses were performed to determine the effect of CRT for the different subgroups. All statistical analyses in this study were performed using commercially available statistical software (SPSS version 22.0; SPSS, Chicago, IL).

Results

Patient cohort

A total of 3053 patients were identified meeting the inclusion criteria with at least one Peter's criteria (Fig. 1).

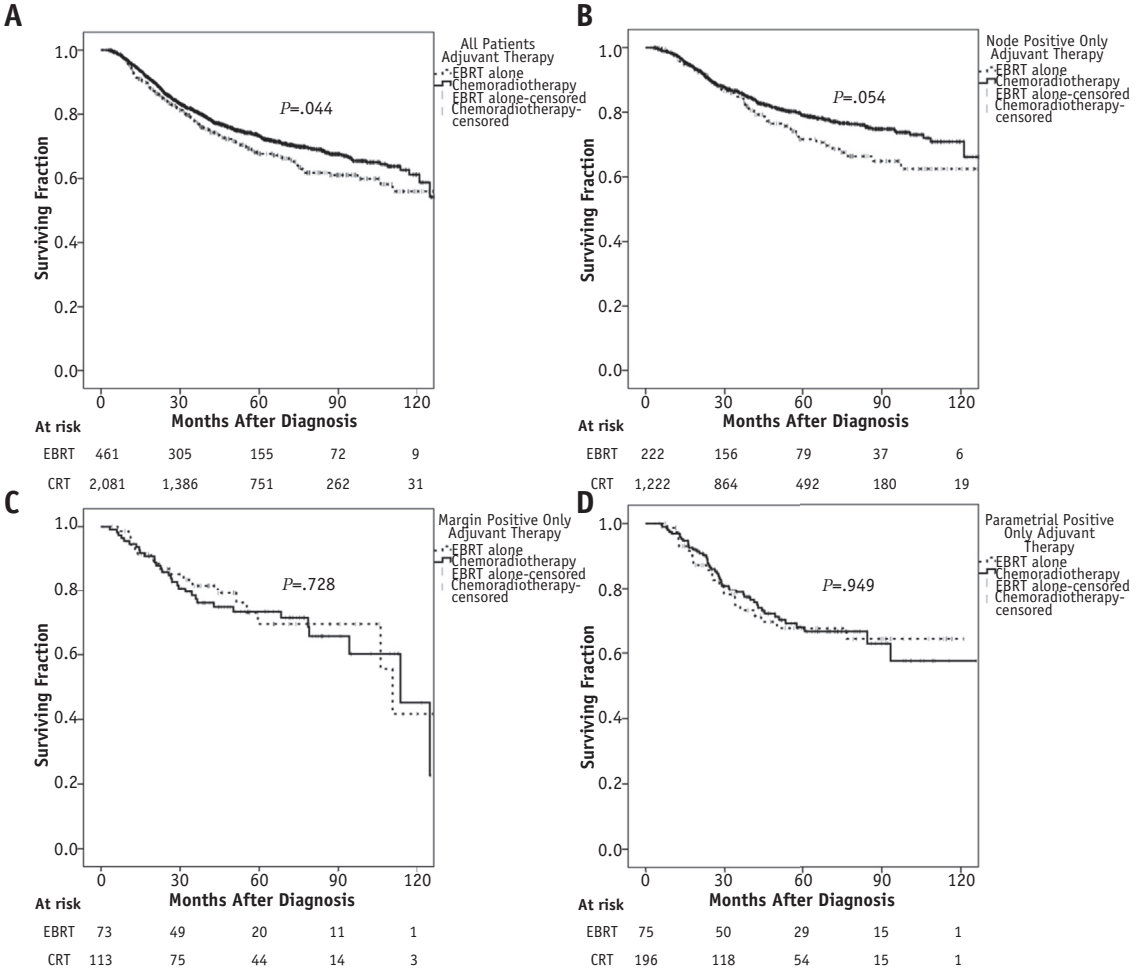

Fig. 2. Kaplan-Meier analysis of overall survival for patients with (A) at least 1 Peter's criteria, (B) only positive nodes, (C) only positive margin, and (D) only parametrial invasion receiving adjuvant external beam radiation therapy with and without chemotherapy in the National Cancer Database 2003 to 2012 (with corresponding log−rank *P* values; n = 2542, 1451, 186, and 271, respectively).

Table 3 Analysis of factors that contribute to overall survival among all patients (n = 2542) in the National Cancer Database 2003 to 2012

Factor	n	Univariable *P*	Multivariable			
			P	HR	Lower 95%	Upper 95%
Clinical characteristics						
Age (y)		<.001*	<.001*			
18-29	168			ref		
30-49	1392			0.690*	0.487	0.979
50-69	816			0.901	0.630	1.288
>69	166			1.431	0.915	2.238
Year of diagnosis		.737				
2002-2007	1443					
2008-2011	1099					
Race		<.001*	.003*			
White	1752			ref		
Black	294			1.276	0.979	1.663
American Indian	16			0.521	0.128	2.115
Asian/Pacific Islander	104			0.688	0.401	1.181
Unknown	55			0.744	0.364	1.523
Hispanic	321			0.573*	0.406	0.811
Charlson/Deyo score		<.001*	.244			
0	2294			ref		
1	220			1.169	0.866	1.577
2	28			1.591	0.832	3.041
Median income of ZIP code ($)		<.001*	.001*			
<30,000	534			ref		
30,000-34,999	614			0.659*	0.502	0.864
35,000-45,999	646			0.738*	0.562	0.970
≥46,000	670			0.757*	0.574	0.996
Unknown	78			1.571	0.976	2.530
Insurance		.908				
Uninsured	2283					
Insured	194					
Distance to hospital (mi)		.281				
<25	1810					
25-100	550					
>100	93					
Unknown	89					
Facility volume		.069*	.578			
1-5	670			ref		
6-12	674			0.874	0.679	1.126
13-26	624			0.899	0.696	1.161
>26	574			0.832	0.632	1.095
Disease characteristics						
Pathologic AJCC T stage		<.001*	†			
pT1 or less	1557					
pT2	777					
pT3	141					
pT4	67					
Histology		<.001*	.003*			
Squamous cell carcinoma	1760			ref		
Adenocarcinoma	416			1.230	0.950	1.592
Adenosquamous	179			1.737*	1.247	2.419
Carcinoma NOS	187			1.420*	1.020	1.977
Grade		<.001*	.344			
Well differentiated	147			ref		
Moderately differentiated	999			1.132	0.744	1.723
Poorly or undifferentiated	1149			1.271	0.837	1.931
Tumor size >4 cm	740	<.001*	<.001*	2.041*	1.690	2.465

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Table 3 (*continued*)

Factor	n	Univariable *P*	Multivariable *P*	Multivariable HR	Multivariable Lower 95%	Multivariable Upper 95%
LVSI positive	324	.284				
Peters criteria						
pN+	1973	.016*	.001*	1.542*	1.192	1.994
Positive margin	574	<.001*	<.001*	2.008*	1.620	2.489
Parametrial invasion	754	<.001*	<.001*	1.606*	1.301	1.983
Treatment modality						
Chemoradiation therapy	2081	.044*	.022*	0.761*	0.601	0.962

Abbreviations as in Tables 1 and 2.
* $P<.05$.
† AJCC T stage not included in multivariable analysis because of a direct dependence on the presence/absence of parametrial invasion (as defined).

Seventy percent of these patients underwent radical hysterectomy, and 27% underwent total abdominal hysterectomy without complete parametrial dissection. The remaining patients (3%) underwent a subtotal hysterectomy. Table 1 demonstrates the clinical and disease characteristics of our cohort compared with the patients enrolled in GOG 109. Notably, many patients in the NCDB group have unknown LVSI status, although all of these patients underwent pathologic nodal dissection. Also note that whereas patients with positive margin are an underrepresented portion of GOG 109 (4% and 6% received CRT and EBRT, respectively) (5), a positive margin was present in 22% and 29% of patients in the NCDB CRT and EBRT groups, respectively.

CRT utilization and survival

Of the 3053 patients included, 2479 (81.2%) received adjuvant CRT after surgery. Of patients receiving adjuvant CRT, 1765 (71.2%) received single-agent chemotherapy, and 444 (17.9%) received multi-agent therapy (270 unknown). Table 2 provides a univariable and multivariable analysis of factors predictive for CRT utilization (over EBRT alone). Whereas CRT was utilized in 84.7% of patients with pathologically involved lymph nodes, it was utilized in 80.1% and 76.8% of patients with parametrial invasion and positive margins, respectively. As illustrated, other factors predictive for receipt of CRT include age <70 years and diagnosis after 2007.

Overall survival after diagnosis was strongly associated with the total number of Peter's criteria (log−rank $P<.001$; Supplemental Table 7; available online at www.redjournal.org). Figure 2A is an unadjusted Kaplan-Meier survival analysis illustrating the 5.6% improvement in OS at 5 years after adjuvant CRT over EBRT alone (73.3% vs 67.6%, respectively, $P=.044$). Table 3 provides the results of our univariable and multivariable analysis of factors associated with OS. As demonstrated, age, race, median income of ZIP code, histology, tumor size, and each of Peter's criteria were all predictive of survival. Additionally, among all patients the utilization of adjuvant CRT was associated with improved survival on MVA (hazard ratio 0.76, 95% confidence interval 0.601-0.962; $P=.022$).

Survival with CRT according to lymph node status

Table 4 provides a univariable and multivariable analysis of patients with regional lymph node metastases but no parametrial invasion or involved surgical margin (n=1451). As demonstrated, for this subgroup of patients adjuvant CRT use was associated with improved survival on MVA (hazard ratio 0.58, 95% confidence interval 0.413-0.814; $P=.002$). Among patients with involved lymph nodes, the magnitude of benefit of adjuvant CRT utilization varied according to the number of positive lymph nodes (1, 2-3, or >3, $P=.010$).

In contrast, CRT use did not improve survival for node-negative patients with positive surgical margins alone ($P=.728$; Table 5), parametrial invasion alone ($P=.949$; Table 6), or any combination of positive surgical margins with parametrial invasion but with no nodal involvement ($P=.627$; Supplemental Table 8; available online at www.redjournal.org).

Discussion

The results of the present analysis provide several meaningful results. First, they confirm the results of GOG 109. As demonstrated, for patients meeting at least 1 of Peter's criteria (any combination of positive lymph nodes, parametrial invasion, and/or positive margins), adjuvant CRT use is associated with improved OS compared with EBRT alone. Second, these results demonstrate that there is an underutilization of CRT among all subsets of patients, but particularly those with positive surgical margins and/or parametrial invasion but negative lymph nodes. In this group of patients for whom there exists phase 3 evidence in support of adjuvant CRT, only 81% of patients received standard therapy. Third, the present analysis identifies improved OS with CRT for patients with pathologic nodal

Table 4 Analysis of factors that contribute to overall survival among patients whose sole Peter's criteria was regional lymph node metastases (n = 1451) in the National Cancer Database 2003 to 2012

			Multivariable			
Factor	n	Univariable *P*	*P*	HR	Lower 95%	Upper 95%
Clinical characteristics						
Age (y)		<.001*	.007*			
18-29	116			ref		
30-49	913			0.710	0.435	1.161
50-69	366			0.948	0.563	1.594
>69	56			1.703	0.872	3.323
Year of diagnosis		.766				
2002-2007	855					
2008-2011	596					
Race		.044*	.057			
White	1017			ref		
Black	153			1.247	0.846	1.837
American Indian	9			0.001	0.0	†
Asian/Pacific Islander	56			0.358*	0.131	0.978
Unknown	35			1.682	0.775	3.648
Hispanic	181			0.656	0.398	1.079
Charlson/Deyo score		.003*	.269			
0	1328			ref		
1	115			1.319	0.846	2.058
2	8			1.824	0.647	5.142
Median income of ZIP code ($)		.187				
<30,000	313					
30,000-34,999	330					
35,000-45,999	360					
≥46,000	403					
Unknown	45					
Insurance		.764				
Uninsured	113					
Insured	1302					
Distance to hospital (mi)		.696				
<25	1022					
25-100	325					
>100	55					
Unknown	49					
Facility volume		.034*	.186			
1-5	366			ref		
6-12	396			0.688*	0.476	0.992
13-26	353			0.740	0.509	1.074
>26	336			0.739	0.500	1.093
Disease characteristics						
Pathologic AJCC T stage		<.001*	<.001*			
pT1 or less	1307			ref		
pT2a	144			2.004*	1.377	2.915
Histology		<.001*	<.001*			
Squamous cell carcinoma	994			ref		
Adenocarcinoma	231			1.303	0.892	1.906
Adenosquamous	116			2.402	1.560	3.698
Carcinoma NOS	110			1.570	0.996	2.474
Grade		.008*	.278			
Well differentiated	81			ref		
Moderately differentiated	593			1.042	0.570	1.903
Poorly or undifferentiated	644			1.295	0.713	2.352
Tumor zize >4 cm	394	<.001*	<.001*	2.148*	1.626	2.836
LVSI positive	185	.185				

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Table 4 (*continued*)

Factor	n	Univariable *P*	Multivariable			
			P	HR	Lower 95%	Upper 95%
Treatment modality						
Chemoradiation therapy	1229	.054*	.002*	0.580*	0.413	0.814

Abbreviations as in Tables 1 and 2.
* $P<.05$.
† Greater than 1000.

involvement as their only high-risk criteria. Although not the goal of GOG 109, given the distribution of patients in GOG 109 (85% node-positive), we suspect that most of the statistical improvement in OS found in GOG 109 was found in these patients.

Fourth, and perhaps most interestingly, although the total number of Peter's criteria was associated with OS, our results failed to demonstrate an improvement in OS in patients without pathologic nodal involvement (parametrial invasion alone, positive surgical margin, and a combination of the two). These results are in contrast to the commonly held interpretation of GOG 109—that any patient with at least 1 of Peter's criteria demonstrates improved OS with adjuvant CRT over EBRT alone (5, 10).

In 2000, Peters et al (5) reported the results of GOG 109, a phase 3 trial evaluating 243 patients with high-risk cervical cancer randomized after radical hysterectomy to adjuvant EBRT alone or CRT with concurrent and adjuvant cisplatin and 5-flurouracil (2 cycles with EBRT and 2 cycles after EBRT). Their results demonstrated improved OS with CRT over EBRT alone, but most patients (85%) had pathologic lymph node involvement found at the time of surgery, and only 15% did not. Since then the results of this trial have been extrapolated to all patients meeting the trial's inclusion criteria (ie, having at least 1 of Peter's criteria [10]), despite limited evidence to support adjuvant CRT in patients with node-negative disease. Our results suggest that providers may be considering this level of evidence to some extent, in that patients with node-negative disease were less likely to receive adjuvant CRT than their node-positive counterparts.

Monk et al (11) attempted an unplanned subgroup analysis of GOG 109 but were again limited by the study's sample size. Their results demonstrate that on UVA, CRT improved OS in patients with nodal disease and/or parametrial invasion. Other small, retrospective series have demonstrated similar outcomes and failed to confirm an OS benefit of CRT in patients with high-risk, node-negative disease (14, 15).

The present study is limited given this is a retrospective analysis of NCDB. Specifically, patients treated with incomplete surgery and with sequential rather than concurrent CRT could have been included in the analysis unknowingly. Additionally, details regarding specific systemic therapy agents, number of cycles, and delays in systemic therapy are unknown. The detailed therapy tolerance, dosimetric details, and toxicity results collected in a prospective trial would be critical in further comparing CRT with EBRT alone in this patient population.

Because this study is nonrandomized, there is potential for various measured and unmeasured confounders. Our analysis adjusted for measured cofounders through MVA. Perhaps the most noteworthy limitation to this study is that whereas the NCDB contains information on survival, it does not contain information on local or regional disease control. Although patients without involved lymph nodes did not demonstrate improved OS with CRT in the present series, it is possible that adjuvant CRT is associated with improved locoregional control in these patients, and this did not translate to an OS advantage.

Despite these results, we do not support the omission of adjuvant CRT for node-negative patients at this time in routine practice. Although CRT seems to provide limited benefit over EBRT in terms of OS in node-negative patients, these data do not report on locoregional control, toxicity, or patient-reported outcomes. This analysis can, however, serve to identify patients that could be evaluated as part of a prospective trial omitting chemotherapy in high-risk, node-negative patients to provide evidence that better informs an individualized approach to adjuvant therapy. Conversely, these data demonstrate that patients meeting Peter's criteria are indeed high risk, and strategies to improve OS in this cohort, such as chemotherapy or radiation therapy dose escalation, targeted therapies, and/or immunotherapies, should be further evaluated with prospective trials.

A current international prospective trial (GOG 263) is evaluating the roles of adjuvant CRT in patients with "intermediate-risk" disease as defined by GOG 92 (based on LVSI, cervical stromal depth of invasion, and tumor size) (16). An additional open trial (GOG 0724) is evaluating the role of consolidation carboplatin and paclitaxel after CRT in patients with high-risk disease after trimodality therapy (high-risk defined by lymph node involvement and/or parametrial invasion) (17). The results of this trial could help to prospectively identify patients who benefit from adjuvant CRT over EBRT alone in the future.

Table 5 Analysis of factors that contribute to overall survival among patients whose sole Peter's criteria was positive surgical margins (n = 186) in the National Cancer Database 2003 to 2012

			Multivariable			
Factor	n	Univariable *P*	*P*	HR	Lower 95%	Upper 95%
Clinical characteristics						
Age (y)		.025*	.015*			
18-29	6			ref		
30-49	75			0.653	0.074	5.761
50-69	74			0.585	0.066	5.208
>69	31			2.900	0.300	28.029
Year of diagnosis		.591				
2002-2007	93					
2008-2011	93					
Race		.004*	.552			
White	108			ref		
Black	29			1.227	0.486	3.098
Asian/Pacific Islander	11			2.29	0.49	10.712
Unknown	6			0.0	0.0	†
Hispanic	32			0.477	0.139	1.633
Charlson/Deyo score		.042*	.0679			
0	166			ref		
1	16			1.539	0.496	4.779
2	4			0.745	0.127	4.354
Median income of ZIP code ($)		.153				
<30,000	40					
30,000-34,999	58					
35,000-45,999	49					
≥46,000	37					
Unknown	2					
Insurance		.478				
Uninsured	12					
Insured	171					
Distance to hospital (mi)		.032*	.493			
<25	135			ref		
25-100	43			1.056	0.475	2.346
>100	5			2.985	0.491	18.125
Facility volume		.868				
1-5	50					
6-12	56					
13-26	45					
>26	35					
Disease characteristics						
Pathologic AJCC T stage		.985				
pT1 or less	138					
pT2a	48					
Histology		.094	.659			
Squamous cell carcinoma	122			ref		
Adenocarcinoma	36			1.753	0.713	4.308
Adenosquamous	11			1.435	0.265	7.775
Carcinoma NOS	17			1.105	0.381	3.207
Grade		.939				
Well differentiated	16					
Moderately differentiated	73					
Poorly or undifferentiated	80					
Tumor size >4 cm	51	<.001*	.005*	3.028*	1.407	6.517
LVSI positive	20	.269				
Treatment modality						
Chemoradiation therapy	113	.728				

Abbreviations as in Tables 1 and 2.

* $P<.05$.

† Greater than 1000.

Table 6 Analysis of factors that contribute to overall survival among patients whose sole Peter's criteria was parametrial invasion (n=271) in the National Cancer Database 2003 to 2012

			Multivariable			
Factor	n	Univariable *P*	*P*	HR	Lower 95%	Upper 95%
Clinical characteristics						
Age (y)		.172				
18-29	10					
30-49	93					
50-69	132					
>69	36					
Year of diagnosis		.202				
2002-2007	147					
2008-2011	124					
Race		.429				
White	193					
Black	32					
American Indian	3					
Asian/Pacific Islander	14					
Unknown	4					
Hispanic	25					
Charlson/Deyo score		.935				
0	231					
1	36					
2	4					
Median income of ZIP code ($)		.081	.258			
<30,000	58			ref		
30,000-34,999	65			0.432	0.178	1.049
35,000-45,999	64			0.639	0.271	1.506
≥46,000	74			0.545	0.227	1.308
Unknown	10			1.262	0.390	4.086
Insurance		.239				
Uninsured	19					
Insured	247					
Distance to hospital (mi)		.108				
<25	193					
25-100	54					
>100	14					
Unknown	10					
Facility volume		.951				
1-5	73					
6-12	68					
13-26	73					
>26	57					
Disease characteristics						
Pathologic AJCC T stage		<.001*	.088			
pT2b	211			ref		
pT3	39			1.609	0.694	3.728
pT4	21			2.714*	1.041	7.077
Histology		.612				
Squamous cell carcinoma	193					
Adenocarcinoma	53					
Adenosquamous	11					
Carcinoma NOS	14					
Grade		.007*	.405			
Well differentiated	20			ref		
Moderately differentiated	93			1.093	0.306	3.904
Poorly or undifferentiated	127			1.666	0.484	5.733
Tumor size >4 cm	91	.013*	.047*	1.926*	1.009	3.678
LVSI positive	28	.461				

(*continued on next page*)

Table 6 (*continued*)

Factor	n	Univariable *P*	Multivariable *P*	HR	Lower 95%	Upper 95%
Treatment modality						
Chemoradiation therapy	196	.949				

Abbreviations as in Tables 1 and 2.
* $P<.05$.

Conclusion

The use of adjuvant CRT after hysterectomy improves OS in patients with high-risk cervical cancer compared with EBRT alone, but this benefit seems to be restricted to patients with pathologic lymph node involvement. The merit of adjuvant CRT over EBRT alone in patients with parametrial invasion and/or positive margins (without nodal involvement) should be prospectively evaluated.

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