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Radiation duration in women with cervical cancer treated with primary chemoradiation: a population-based analysis

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Abstract

This study examines factors associated with prolonged radiation duration and its impact on survival in women with cervical cancer treated with primary chemoradiation. Women in the National Cancer Database with stage IB2-IVA cervical cancer from 2003-2011 who received radiation and chemotherapy were included. Of 7209 women who met inclusion criteria, 3401 (47.1%) and 3808 (52.8%) completed radiation in ≤8 and >8 weeks, respectively. There was no overall survival difference for radiation duration ≤8 vs. >8 weeks. Sensitivity analyses showed that inferior overall survival is only seen with radiation duration of >10 to 12 weeks.

Introduction

Contemporary treatment for locally advanced cervical cancer, commonly defined as stage IB2 to IVA disease, consists of radiotherapy and chemotherapy (chemoradiation). Radiotherapy includes external beam radiation to the whole pelvis, along with brachytherapy delivered locally to the cervix. Concurrent chemoradiation became the standard of care in 1999 with the publication of 5 clinical trials demonstrating that the addition of chemotherapy to the radiation regimen confers a substantial survival benefit [1-5].

Several retrospective, mostly small, single-institution studies have demonstrated that the duration of radiotherapy can negatively affect cervical cancer outcomes; prolonging the radiation course in these studies was associated with a decrease of 0.5% to 1.2% in pelvic control and cause-specific survival per additional day of treatment [6-11]. The adverse effects of prolonged radiation have been demonstrated in head and neck cancers as well

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[11-15]. A possible physiologic mechanism for these adverse outcomes is accelerated tumor cell repopulation during radiotherapy when there is a lag period after initiation of radiation [12].

The National Comprehensive Cancer Network (NCCN) Cervical Cancer Guidelines recommend that chemoradiation be completed within 8 weeks [16], and this is being proposed as a quality measure for cervical cancer treatment. However, this recommendation is based on the aforementioned studies that were published prior to the incorporation of chemotherapy in the treatment of cervical cancer. The literature on the effect of radiation duration in the era of concurrent chemotherapy is limited. Recently, two single-institution retrospective studies demonstrated that prolonged chemoradiation duration did not negatively impact survival [17,18]. We performed a population-based analysis to determine factors associated with prolonged chemoradiation duration and to assess its impact on overall (not cause-specific) survival in women with locally advanced cervical cancer treated with primary chemoradiation.

Materials and Methods

Study Design and Data Source

We utilized data from the National Cancer Database (NCDB). The NCDB, established in 1989, is a joint project of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons (ACS). NCDB collects data from over 1,500 hospitals in the US with Commission-accredited cancer programs, capturing 70% of all newly diagnosed cancers in the US per year. Data pertaining to the initial diagnosis and first course of treatment are collected and submitted to the NCDB using nationally standardized data item and coding definitions [19]. Participating registries report follow-up of vital status to the NCDB on a yearly basis. An annual 90% follow-up rate for all patients diagnosed within the preceding 5 years and an 80% follow-up rate for all other cases is required.

Cohort Selection

All patients diagnosed with stage IB2 to IVA cervical cancer diagnosed from 2003 to 2011 who received combination external beam radiation therapy and brachytherapy with concurrent chemotherapy were included (Figure 1). Women were excluded if they had more than one reported cancer diagnosis. We did not include women who were diagnosed prior to 2003 because the variable describing radiation treatment in the database was reported as an optional item, and comorbidity data were not collected until the year 2003. Women were excluded if they underwent a definitive surgical procedure, such as a trachelectomy, simple or radical hysterectomy, or exenteration. Additionally, since our primary outcome of interest and predictor of survival was prolonged radiation, we focused our analysis on women who completed at least 6 weeks of radiation. We excluded women with radiation treatment duration greater than 26 weeks, since such cases represent extremely rare clinical scenarios and/or spurious data collection.

Variable Definition

Radiation duration is defined as the number of days between the radiation start and end date, categorized into number of weeks. Age was modeled as a continuous variable. Race was categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian/other, and unknown. Insurance status was categorized as private, Medicare, Medicaid, uninsured, and other/unknown. The Charlson/Deyo comorbidity score (CDS), commonly used in health outcomes studies employing administrative databases, provides an indicator of various comorbid conditions based on reported ICD-9-CM codes [19, 20]. In the NCDB, the scores have been classified as 0, 1, or 2. Year of diagnosis was modeled as a categorical variable with each year as a separate category. Clinical and pathologic data, including tumor histology, grade, and AJCC clinical stage were recorded. Vital status and the number of months between the date of diagnosis and date of last contact were also recorded. Patients who were alive at last contact were censored.

Environmental and structural factors, including reporting facility type, reporting facility geographic location, woman's neighborhood level median income, neighborhood level educational attainment, and neighborhood-level measure of rurality/urbanicity were recorded. Reporting facility type is assigned in the NCDB as an Academic Program, Community Cancer Program, Comprehensive Community Cancer Program, and other specified types of cancer programs. Reporting facility location was consolidated into four categories based on US Census Divisions: Northeast, Midwest, South, and West. Neighborhood-level median income and educational attainment are derived in the NCDB by linking the woman's zip code at the time of diagnosis to US Census data files from the year 2000; therefore these data represent the zip-code of the woman's residence and not that of the individual woman. Median household income and educational attainment were categorized as quartiles based on equally proportioned income and educational attainment ranges for all US zip codes. The neighborhood-level measure of rurality/urbanicity was obtained using the typology published by the USDA Economic Research Service.

Statistical analysis

Radiation duration was modeled as a dichotomous variable, with prolonged duration defined as greater than 8 weeks for our primary analysis. Frequency distributions between categorical variables by radiation duration were compared using chi-squared tests. Binomial logistic regression analysis was used to determine factors associated with receipt of prolonged radiation, including age, race, stage, histology, grade, year of diagnosis, CDS, income, education, rurality/urbanicity, facility type and facility location. Outcomes are reported as odds ratios with 95% confidence intervals. In accordance with the NCDB Participant Use File Guide, survival analysis was limited to cases diagnosed from 2003 to 2006 to allow for at least 5 years of follow-up time. Kaplan Meier survival analysis with the log-rank test for statistical significance was performed to assess impact of prolonged therapy on survival. Cause of death is not reported in the NCDB, so cause-specific survival could not be calculated. Cox proportional hazards models were used to examine the impact of prolonged radiation on risk of death, adjusted by age, race, stage, histology, grade, year of diagnosis, CDS, education, rurality/urbanicity, facility type and facility location.

Covariates included in the regression models were selected a priori based on clinical relevance. We found evidence of multi-collinearity between education and income, and therefore did not include both measures in the final models. The Akaike Information Criterion value [21] for the logistic regression model including education was slightly better than the model including income, and since education may be a stronger indicator of socioeconomic status [22], income was not included in the final models. In order to explore effect modification by stage, we performed stage-stratified analyses for early (stages I/II) and late stage (stages III/IV) tumors were performed. We also performed sensitivity analyses using additional cut-offs for prolonged radiation duration: or > 9, 10, and 12 weeks. Statistical significance was set to a p-value of less than 0.05. All statistical tests were two-sided and all analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Of the 51,181 women with stage IB2 – IVA cervical cancer reported in the NCDB from 1998 to 2011, 9905 met initial inclusion criteria of having been treated with external beam radiation, brachytherapy, and chemotherapy. After applying the exclusion criteria, the final cohort included 7209 women (Figure 1). Of these, 3401 (47.1%) and 3808 (52.8%) completed radiation in 8 weeks or less and greater than 8 weeks, respectively. Figure 2 shows the distribution of radiation duration by number of weeks, which demonstrates a sharp decline in the number of women with radiation duration greater than 9 to 10 weeks. Age, race, CDS, clinical stage, tumor histology and size, insurance status, education, facility location, and neighborhood rurality/urbanicity were all associated with prolonged radiation duration on bivariate analysis, as shown in Table 1 ($p < 0.05$ for all). A time trend was seen by diagnosis year, where women diagnosed in years 2003 to 2007 were more likely to have prolonged radiation duration, and those diagnosed after 2007 were more likely to have radiation duration less than 8 weeks ($p = 0.001$).

On multivariable analysis (Table 2), black race remained a significant factor associated with prolonged radiation, with black women being 20% more likely to receive prolonged radiation compared to white women (OR 1.20, 95% CI 1.04 – 1.37). Other racial/ethnic groups had similar odds of receiving prolonged radiation as white women. Women with CDS of 1 and 2 were also more likely to have prolonged radiation duration relative to those with CDS of 0, although this was only statistically significant for women with a score of 1 (CDS 1: OR 1.19, 95% CI 1.01 – 1.40; CDS 2: OR 1.33, 95% CI 0.96 – 1.89). Clinical stage greater than IIA2 was found to be significantly associated with prolonged radiation. Medicaid recipients were 19% more likely to receive prolonged radiation compared to women with private insurance (OR 1.19, 95% CI 1.06 – 1.34), whereas women with other/unknown insurance status were less likely (OR 0.73, 95% CI 0.55 – 0.98) to have a prolonged course of radiotherapy. Women living in the Northeast and the South were 36% (OR 1.36, 95% CI 1.18 – 1.56) and 17% (OR 1.17, 95% CI 1.04 – 1.33) more likely to get prolonged radiation therapy, respectively, than those living in the Midwest. Residents of rural neighborhoods were 78% more likely to have prolonged radiation therapy than those in urban neighborhoods (OR 1.78, 95% CI 1.20 – 2.64).

There was no difference in survival seen between women with radiation duration of greater than 8 weeks vs. 8 or fewer weeks ($p=0.209$) (Figure 2). In the series of sensitivity analyses in which varying cut points for duration of radiation were examined, inferior survival was seen with radiotherapy duration greater than 9 weeks ($p=0.001$), 10 weeks ($p<0.001$), and 12 weeks ($p<0.001$).

Our primary Cox proportional hazards model included radiation duration dichotomized using an 8-week cut-point (Table 3) and showed no association between radiation duration of >8 weeks and survival. Effect modification by stage was explored by stratifying the Cox model. There was no difference in risk of death with prolonged radiation duration in either stage group (stages I/II: HR 0.88, 95% CI 0.74 – 1.04; stages III/IV: HR 1.10, 95% CI 0.93 – 1.28).

In additional exploratory Cox models, there was no evidence that the risk of death increased per additional day of radiation duration (HR 1.01, 95% CI 0.99 – 1.03), and no difference in risk of death with a 9-week cut-point (HR 1.12, 95% CI 1.00 – 1.26). However, women with duration of greater than 10 weeks had a 15% higher risk of death compared to those who completed radiation in less than 10 weeks (HR 1.15, 95% CI 1.01 – 1.30). Women with duration of greater than 12 weeks had a 23% higher risk of death compared to those who completed radiation in less than 12 weeks (HR 1.23, 95% CI 1.04 – 1.47). Since there was a difference in survival seen with a 10-week cut-off, we explored factors associated with radiation duration of greater than 10 weeks using logistic regression. The results were similar for the logistic regression analysis using an 8-week cut-off. Black race, Medicaid insurance, living in the Northeast and the South, and living in rural neighborhoods remained significant factors associated with prolonged radiation duration. In addition, Hispanic women and those who were treated in Community and Comprehensive Community Cancer Programs were also found to be more likely to receive radiation duration (see supplemental table).

Discussion

Our findings demonstrate that prolonging the course of radiation up to 10 weeks has no effect on survival when chemotherapy is given concurrently. Sociodemographic factors are important predictors of radiotherapy duration for cervical cancer. This study provides strong evidence against the use of radiation duration of less than 8 weeks as a quality metric for cervical cancer in the era of chemoradiation.

There is an overall paucity of data on the impact of radiation duration on survival in women treated with concurrent chemoradiation for cervical cancer. Concurrent chemotherapy has been shown to increase the biologic effective dose of radiation and reduce the accelerated repopulation of tumor cells that occurs with prolonged radiation duration [23, 24, 25]. In a study on the effect of prolonged treatment with high-dose-rate intracavitary radiation in women with cervical cancer published in 2003, the authors found that the pelvic control rate and 5-year cause-specific survival were significantly worse for those whose treatment duration exceeded 63 days. However, only 45 of 257 subjects (17.5%) received chemotherapy, and the regimen was not the current standard of weekly cisplatin [26]. Two

recent studies that specifically addressed this question have been published. Song, et al. performed a single-institution retrospective study on 113 women who were treated with chemoradiation from 1997 to 2009 [17]. They found that radiation duration of greater than 8 weeks was associated with increased pelvic tumor recurrence, but not distant site recurrence or cause-specific survival. A similar single-institution retrospective study on 166 women treated with chemoradiation from 1989 to 2009 found that radiation duration of greater than 60 days was not associated with increased pelvic tumor recurrence or cause-specific survival [18]. These findings are consistent with those of our study that a cut-point of 8 weeks is not associated with inferior survival when women are treated with both chemotherapy and radiation. However, the results of these prior studies should be cautiously interpreted given their small sample size.

Several factors were found to be associated with prolonged radiation duration for cervical cancer. Later stage at diagnosis increased the odds of receiving prolonged care. Perhaps this could be explained by a higher risk of complications for those with more advanced stages. Regarding demographic factors, black women and Medicaid recipients were more likely to receive prolonged radiation. This represents a socioeconomic disparity and raises the possibility of unequal access to treatment for racial minorities and the underserved. Women who live in the Northeast or in the South, or in rural areas of the country were also more likely to have radiation duration of greater than 8 weeks. In fact, rural residence had the strongest association with receipt of prolonged radiation. This finding reflects the fact that chemoradiation entails daily travel to a treatment facility, which can be logistically burdensome to patients and their families. If distance to the treatment facility plays a role, increasing the number of facilities that offer chemoradiation may mitigate the number of women who receive prolonged radiation duration.

We comprehensively explored factors associated with prolonged radiation duration and its impact on overall survival in the era of chemoradiation. Since other national cancer databases lack information on radiation duration, a population-based analysis was not possible prior to the availability of the NCDB to outcomes researchers. Another strength conferred by the use of the NCDB includes the large sample size that provides sufficient power to examine our primary outcomes. The database also provides detailed clinical and treatment information, which allowed the analysis to be adjusted for important clinical and demographic parameters.

Our study has several limitations. First, our study is susceptible to selection bias. While the NCDB collects the majority of incident cancer cases in the US, a hospital selection bias may exist since only ACS CoC-approved hospitals contribute data. We also excluded a large number of patients due to the coding of the radiation therapy variable. However, these exclusions are likely non-differential with regards to bias since the coding of radiation duration is not likely to vary across cut-points of radiation duration. Furthermore, we believe that the sensitivity of the radiation duration coding provides confidence that these cases were actually treated with combination external beam radiation and brachytherapy. The study is also limited by the lack of information on cause-specific survival and radiation or chemotherapy toxicity. We used radiation duration as a proxy for completion of the prescribed radiotherapy dose and cycles of chemotherapy. Another limitation is that the

NCDB does not capture cancer recurrence information; therefore we cannot comment on the impact of radiation duration on tumor control. We also don't have information on reasons for prolonged radiation, which is important for informing policy. Lastly, it is not possible to determine individual patient and physician preferences that may have influenced treatment allocation.

Substantial evidence demonstrates inconsistent clinical practice patterns. For example, in a large study of trends in cervical cancer treatment quality in the US, the radiation treatment duration was as follows: greater than 56 days, 63 days, and 70 days for 50%, 36%, and 15% of the 3275 patients included in the study, respectively [27]. Another large population-based study demonstrated that patients who receive their cervical cancer at facilities with a high annual volume of cervical cancer patients are more likely to receive the standard of care [28]. These treatment inconsistencies, in addition to mounting healthcare costs and waning resources, has led to regulatory agencies and other stakeholders developing quality metrics for a gamut of clinical diagnoses and specialties [29, 30]. The National Quality Forum (NQF), in conjunction with the ACS, the NCCN, and the American Society of Clinical Oncology, convened a steering committee in 2002 to address quality measures in cancer care [31]. Currently, there are 19 NQF-endorsed quality measures in breast cancer, colorectal cancer, and palliative care. Hospitals with CoC-approved cancer programs that report to the NCDB are benchmarked according to their performance on these measures [19, 31]. Given the important role that these measures will play in our healthcare system, ideally performance on these measures would result in improved patient outcomes [32, 33].

The NCCN recommends that chemoradiation be completed within 8 weeks, and chemoradiation duration of less than 60 days may be considered as a national quality measure by professional organizations. However, based on these results and those of other studies, this may not be a valid quality measure for cervical cancer. A cut-point of 10 or 12 weeks appears to be more appropriate based on our findings. Although treatment should be given in a timely manner, if there is an unavoidable delay in radiation duration, patients can be counseled that it should not negatively affect survival if completed within 10 to 12 weeks. Prospective observational studies to evaluate the relationship of sociodemographic disparities to radiation duration, the association of radiation duration on recurrence in the era of chemoradiation, and reasons for prolonged radiation are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
CONSORT diagram detailing cohort selection for analysis.

Figure 2.
Distribution of Radiation Duration in the Study Cohort by Number of Weeks, NCDB 2003 – 2011.

Figure 3. Kaplan-Meier survival analysis by dichotomous radiation duration (A) 8 vs. > 8 weeks; log rank test chi-square statistic = 1.56, $P = 0.209$; (B) 9 vs. > 9 weeks; log rank test chi-square statistic = 10.62, $P = 0.001$; (C) 10 vs. > 10 weeks; log rank chi-square statistic = 12.60, $P < 0.001$; (D) 12 vs. > 12 weeks; log rank test chi-square statistic = 16.11, $P < 0.001$.

Table 1

Association between radiotherapy duration and characteristics of women with stage IB2-IVA cervical cancer treated with primary chemoradiation, NCDB, 2003 – 2011.

Characteristic	All women N = 7209		RT 8 weeks N = 3401		RT > 8 weeks N = 3808		P*
	No.	%	No.	%	No.	%	
Age in years (mean, standard deviation)	51.0 (12.9)	-	50.8 (12.9)	-	51.3 (13.0)	-	0.101
Race							0.002
White, non-Hispanic	4551	63.1	2204	64.8	2347	61.6	
Black, non-Hispanic	1242	17.2	528	15.5	714	18.8	
Hispanic	941	13.1	434	12.8	507	13.3	
Asian/Other	403	5.6	205	6.0	198	5.2	
Unknown	72	1.0	30	0.9	42	1.1	
Charlson/Deyo Comorbidity Index							0.006
0	6362	88.3	3044	89.5	3318	87.1	
1	708	9.8	302	8.9	406	10.7	
2	139	1.9	55	1.6	84	2.2	
Year of Diagnosis							0.001
2003	596	8.3	279	8.2	317	8.3	
2004	699	9.7	314	9.2	385	10.1	
2005	724	10.0	295	8.7	429	11.3	
2006	765	10.6	346	10.2	419	11.0	
2007	835	11.6	387	11.4	448	11.8	
2008	906	12.6	435	12.8	471	12.4	
2009	896	12.4	439	12.9	457	12.0	
2010	836	11.6	412	12.1	424	11.1	
2011	952	13.2	494	14.5	458	12.0	
Clinical Stage							<0.001
IB2	609	8.5	362	10.6	247	6.5	
IINOS	109	1.5	61	1.8	48	1.3	

Characteristic	All women N = 7209		RT 8 weeks N = 3401		RT > 8 weeks N = 3808		<i>P</i> *
	No.	%	No.	%	No.	%	
IIA	484	6.7	263	7.7	221	5.8	
IIA1	23	0.3	11	0.3	12	0.3	
IIA2	47	0.6	23	0.7	24	0.6	
IIB	2547	35.3	1240	36.5	1307	34.3	
IIINOS	86	1.2	36	1.1	50	1.3	
IIIA	173	2.4	76	2.2	97	2.6	
IIIB	2840	39.4	1219	35.8	1621	42.6	
IVNOS	67	0.9	32	0.9	35	0.9	
IVA	224	3.1	78	2.3	146	3.8	
Tumor Size							<0.001
<20 mm	116	1.6	67	2.0	49	1.3	
20-40 mm	824	11.4	402	11.8	422	11.1	
41-60 mm	1941	26.9	992	29.2	949	24.9	
61-80 mm	1222	16.9	563	16.6	659	17.3	
>80 mm	340	4.7	156	4.6	184	4.8	
Unknown	2766	38.4	1221	35.9	1545	40.6	
Tumor Histology							0.010
Squamous	5876	81.5	2738	80.5	3138	82.4	
Adenocarcinoma	628	8.7	320	9.4	308	8.1	
Adenosquamous	223	3.1	124	3.7	99	2.6	
Other	482	6.7	219	6.4	263	6.9	
Tumor Grade							0.953
I	304	4.2	145	4.3	159	4.2	
II	2293	31.8	1077	31.7	1216	31.9	
III	2416	33.5	1150	33.8	1266	33.3	
Unknown	2196	30.5	1029	30.3	1167	30.6	
Insurance							0.003
Private	3055	42.4	1497	44.0	1558	40.9	

Characteristic	All women N = 7209		RT 8 weeks N = 3401		RT > 8 weeks N = 3808		<i>P</i> *
	No.	%	No.	%	No.	%	
Medicare	1177	16.3	539	15.9	638	16.7	
Medicaid	1915	26.6	855	25.1	1060	27.8	
Not insured	856	11.9	395	11.6	461	12.1	
Other/Unknown	206	2.9	115	3.4	91	2.4	
Median Neighborhood Education							0.012
29% without high school diploma	1791	24.8	789	23.2	1002	26.3	
20 – 28.9%	1939	27.0	923	27.1	1016	26.7	
14 – 19.9%	1530	21.2	740	21.8	790	20.7	
< 14%	1601	22.2	765	22.5	836	22.0	
Unknown	348	4.8	184	5.4	164	4.3	
Median Neighborhood Income							0.095
< \$30,000	1366	19.0	613	18.0	753	19.8	
\$30,000 - \$34,999	1510	20.9	717	21.1	793	20.8	
\$35,000 - \$45,999	2031	28.2	952	28.0	1079	28.3	
\$46,000	1954	27.1	935	27.5	1019	26.7	
Unknown	348	4.8	184	5.4	164	4.3	
Facility Type							0.712
Academic	3555	49.3	1692	49.7	1863	48.9	
Comprehensive Community Cancer	3172	44.0	1474	43.3	1698	44.6	
Community Cancer	459	6.4	224	6.6	235	6.2	
Other	23	0.3	11	0.3	12	0.3	
Facility Location							<0.001
Northeast	1497	20.8	638	18.7	859	22.6	
South	2526	35.0	1156	34.0	1370	36.0	
West	1262	17.5	646	19.0	616	16.2	
Midwest	1924	26.7	961	28.3	963	25.3	
Neighborhood Rurality/Urbanicity							0.019
Metro	5538	76.8	2608	76.7	2930	76.9	

Characteristic	All women N = 7209		RT 8 weeks N = 3401		RT > 8 weeks N = 3808		P*
	No.	%	No.	%	No.	%	
Urban	1164	16.2	567	16.7	597	15.7	
Rural	119	1.6	40	1.2	79	2.1	
Unknown	388	5.4	186	5.5	202	5.3	

Abbreviations: RT = radiation

*P value given for ANOVA for continuous variables and chi-square tests for categorical variables.

Table 2

Multivariable analysis of factors associated with receipt of prolonged radiation ($\leq$ and >8 weeks) for women with stage IB2-IVA cervical cancer treated with primary chemoradiation, NCDB, 2003 – 2011.

	Adjusted* Odds Ratio	95% CI	P value
Age	1.00	1.00 – 1.01	0.566
Race			
White, non-Hispanic	Referent	-	-
Black, non-Hispanic	1.20	1.04 – 1.37	0.010
Hispanic	1.11	0.95 – 1.30	0.182
Asian/Other	0.97	0.78 – 1.20	0.774
Unknown	1.41	0.87 – 2.28	0.159
Charlson/Deyo Comorbidity Index			
0	Referent	-	-
1	1.19	1.01 – 1.40	0.034
2	1.33	0.94 – 1.89	0.111
Year of Diagnosis			
2003	Referent	-	-
2004	1.10	0.88 – 1.38	0.393
2005	1.30	1.04 – 1.62	0.021
2006	1.09	0.87 – 1.35	0.450
2007	1.02	0.82 – 1.26	0.889
2008	0.96	0.78 – 1.18	0.710
2009	0.92	0.74 – 1.13	0.412
2010	0.90	0.72 – 1.11	0.321
2011	0.81	0.66 – 1.00	0.048
Clinical Stage			
IB2	Referent	-	-
IINOS	1.15	0.76 – 1.75	0.498
IIA	1.19	0.91 – 1.49	0.220
IIA1	1.82	0.78 – 4.24	0.166
IIA2	1.84	1.01 – 3.38	0.048
IIB	1.47	1.22 – 1.77	<0.001
IIINOS	1.90	1.20 – 3.03	0.007
IIIA	1.79	1.27 – 2.54	0.001
IIIB	1.88	1.57 – 2.26	<0.001
IVNOS	1.58	0.94 – 2.63	0.081
IVA	2.70	1.95 – 3.73	<0.001
Tumor Histology			
Squamous	Referent	-	-

	Adjusted* Odds Ratio	95% CI	P value
Adenocarcinoma	0.93	0.79 – 1.11	0.425
Adenosquamous	0.71	0.54 – 0.93	0.013
Other	1.07	0.88 – 1.29	0.511
Tumor Grade			
I	Referent	-	-
II	1.02	0.80 – 1.31	0.860
III	1.00	0.78 – 1.28	0.999
Unknown	1.05	0.82 – 1.35	0.688
Insurance			
Private	Referent	-	-
Medicare	1.06	0.91 – 1.25	0.456
Medicaid	1.19	1.05 – 1.34	0.005
Not insured	1.11	0.94 – 1.30	0.209
Other/Unknown	0.73	0.55 – 0.98	0.035
Median Education Attainment			
29% without high school diploma	Referent	-	-
20 – 28.9%	0.89	0.78 – 1.02	0.095
14 – 19.9%	0.92	0.79 – 1.06	0.248
< 14%	0.95	0.82 – 1.10	0.478
Unknown	0.63	0.45 – 0.87	0.005
Facility Type			
Academic	Referent	-	-
Comprehensive Community Cancer	1.08	0.98 – 1.20	0.118
Community Cancer	0.96	0.79 – 1.17	0.711
Other	0.98	0.42 – 2.26	0.953
Facility Location			
Midwest	Referent	-	-
Northeast	1.35	1.18 – 1.56	<0.001
South	1.17	1.04 – 1.33	0.012
West	0.94	0.81 – 1.10	0.446
Neighborhood Rurality/Urbanicity			
Metro	Referent	-	-
Urban	0.98	0.86 – 1.12	0.761
Rural	1.78	1.20 – 2.64	0.004
Unknown	1.26	0.93 – 1.70	0.130

Abbreviations: CI = confidence interval; UL = upper limit; LL = lower limit

*Adjusted for age, race, stage, histology, grade, year of diagnosis, Charlson/Deyo score, education, rurality/urbanicity, and facility type and location.

Table 3

Adjusted Cox Proportional Hazards Model analysis of survival for women with stage IB2-IVA cervical cancer treated with primary chemoradiation, NCDB, 2003 – 2006.

	No per Group	Adjusted* Hazards Ratio	95% CI	P value
Radiation duration, all stages				
8 weeks	1234	Referent	Referent	Referent
> 8 weeks	1550	0.98	0.87 – 1.10	0.719
Radiation duration, stages I and II				
8 weeks	751	Referent	Referent	Referent
> 8 weeks	794	0.88	0.74 – 1.04	0.132
Radiation duration, stages III and IV				
8 weeks	483	Referent	Referent	Referent
> 8 weeks	756	1.10	0.93 – 1.28	0.265
Radiation duration, all stages				
Continuous, # of days	-	1.01	0.99 – 1.03	1.011
Radiation duration, all stages				
9 weeks	1751	Referent	Referent	Referent
> 9 weeks	1033	1.12	1.00 – 1.26	0.055
Radiation duration, all stages				
10 weeks	2166	Referent	Referent	Referent
> 10 weeks	668	1.15	1.01 – 1.30	0.037
Radiation duration, all stages				
12 weeks	2503	Referent	Referent	Referent
> 12 weeks	281	1.23	1.04 – 1.47	0.018

Abbreviations: CI = confidence interval; UL = upper limit; LL = lower limit

*Results shown are from seven separate models. All models adjusted for age, race, stage, histology, grade, year of diagnosis, Charlson/Deyo score, education, rurality/urbanicity, and facility type and location.