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Predictors of quality of care and survival in a three-state cohort of locally advanced cervical cancer patients and development of a predictive model to identify women at risk of incomplete treatment

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Abstract

To expand our prior statewide analysis of care distribution for locally advanced cervical cancer in Virginia to include 2 more states and to develop a tool for predicting quality of care. Complete treatment was defined as receiving chemotherapy (CT), brachytherapy (BT), and external beam radiotherapy.

State cancer registry databases yielded a three-state cohort of 3197 women diagnosed with locally advanced cervical cancer from 2000 to 2013. A logistic regression evaluated predictors for receipt of BT, CT, and high (2–3 modalities received) versus low (0–1 modalities received) quality care. A Cox proportional hazards models determined predictors of survival. Finally, a predictive model was developed and preliminarily validated using our cohort.

Only 35.3% of the cohort received complete treatment and only 57.3% received BT. Significant predictors of lower odds of receiving high quality care varied by state but included: 66+ age at diagnosis as compared to 18 to 42, 42 to 53, or 53 to 66; cancer stage IVA as compared to IIIx, IIx, or IB2; public insurance with supplement as compared to private; treatment at a low volume facility; and closer distance quintiles to a high volume treatment center as compared to the furthest quintile. Significant predictors of worse survival varied by state but included: low quality score (0–1 modalities received); 2000 to 2004 or 2005 to 2009 year of diagnosis as compared to 2010 to 2013; 66+ age at diagnosis as compared to 18 to 42, 42 to 53, or 53 to 66; cancer stage IVA as compared to IIIx, IIx, or IB2; treatment at a low volume facility; and unmarried/unknown marital status as compared to married. Our treatment quality prediction tool included age, age^2, treatment at high volume facility, and cancer stage and demonstrated 78.2% sensitivity and a 62.9% specificity.

Only 35.3% of patients received complete guidelines-concordant treatment. Additionally, in 2/3 states it appeared that BT usage may have decreased during the study period. Our predictive model may help identify patients/regions at risk of receiving low quality care to target interventions aimed at improving cervical cancer treatment quality and survival.

Abbreviations: ACS = American Census Survey, BT = brachytherapy, CI = confidence interval, CT = chemotherapy, EBRT = external beam radiotherapy, FIGO = International Federation of Gynecology and Obstetrics, HS = high school, HR = hazard ratio, OR = odds ratio, QP = quality points, TX = treatment.

Keywords: brachytherapy, cervical cancer, disparities, quality

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1. Introduction

With an estimated 12,820 new cases and 4210 deaths in 2017, cervical cancer is the third most common gynecological cancer in the United States.[1] The treatment of locally advanced cervical cancer is complex and requires coordination of several treatment modalities. Both the National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend treatment regimens that include brachytherapy (BT), external beam radiation therapy (EBRT), and concurrent chemotherapy (CT) for cervical cancer patients diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stages IB2 and higher.[2,3]

Unfortunately, many patients presenting with this disease stage do not receive treatment with the full set of recommended therapies. A recent National Cancer Database analysis showed that the percentage of cervical cancer patients with locally advanced disease who received all 3 components of care (BT, EBRT, and CT) was only 44.3%, and that this group had

significantly improved overall survival.[4] Several factors have been associated with decreased probability of receiving all components of care including treatment at a low volume facility,[4–7] lack of insurance[8] or Medicaid status,[6] and African-American race.[4,6] Several publications have also identified a concerning trend toward decreasing BT administration for cervical cancer patients in the United States.[9–11]

The exclusion of core therapies from treatment regimens for locally advanced cervical cancer has been associated with poorer outcomes. Omitting BT may decrease overall survival by almost two-fold[4,9] and omitting CT has similar ramifications depending on disease stage.[3] Therefore the low and potentially decreasing compliance rates, as well as identified disparities, are concerning.

Our prior research examined predictive factors for receipt of high versus low quality care in a cohort of patients with locally advanced cervical cancer in Virginia. We found that only a third of this cohort received all 3 components of standard treatment and that treatment at low volume facilities was predictive of poorer quality care and increased mortality.[7] The present study expands this sample beyond Virginia to evaluate our findings in additional states and to develop a predictive model that will help identify individuals, populations, and geographic areas at higher risk of receiving low quality care for locally advanced cervical cancer. We envision this predictive model being applied to select patients and/or regions in order to identify targets for intervention and ultimately mitigate disparities.

2. Methods

2.1. Cohort selection

Following approval from each cancer registry authority and the University of Virginia Institutional Review Board for the project, we searched the Virginia, Kentucky, and North Carolina state cancer registries to obtain a cohort of cervical cancer patients diagnosed between 2000 and 2013. Since concurrent CT was established as a standard of care in 1999,[12] the year 2000 was chosen as the lower limit to restrict this cohort to patients treated after national guidelines had been updated. For each state-specific cohort, date ranges varied within these limits (Fig. 1) based on availability of data. International Classification of Disease codes C53.0 to C53.9 were included; there were no cases with exclusion histology codes 9590 to 9992, 9050 to 9055, and 9140. Patients with FIGO stage IB2 to IVA were retained and those treated with definitive surgery were excluded. Patients with a previous primary tumor, patients under the age of 18 years old, and patients with out-of-state home locations were excluded.

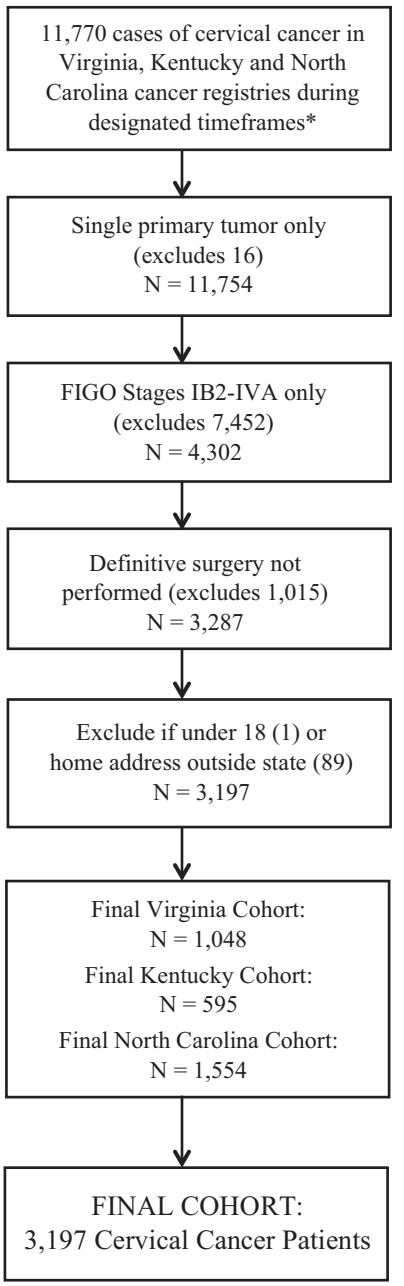

Figure 1. Cohort selection flow diagram. FIGO = International Federation of Gynecology and Obstetrics. *, Virginia: 2000–2012; Kentucky and North Carolina: 2000–2013.

2.2. Predictors and outcomes

For each patient, all known or suspected predictors of high versus low quality care were collected. This included year of diagnosis, age at diagnosis, cancer stage, race, insurance type, marital status, treatment center, and home location. Distance to treatment facility was expressed in terms of proximity to registry-provided treatment facility for North Carolina and highest volume treatment facility for Virginia and Kentucky. For Virginia, distance to treatment facility was calculated as driving distance, and then equally distributed into quintiles. Straight line distance was calculated for Kentucky due to fact that residence location was only given at the county level and then also equally distributed into quintiles. For North Carolina, observations had previously been grouped into quintiles in the state registry and, due to data limitations, the actual distance to treatment facility for each observation could not be calculated. Observations for this state were therefore left in the quintiles to which they originally belonged in the state registry.

The United States Department of Health and Human Services Area Health Resource File was referenced in order to determine several regional factors for each patient. The Rural/Urban Continuum Codes from the United States Department of Agriculture were used to classify home location as either metropolitan (codes 1–3), urban (codes 4–7), or rural (codes 8 and 9), the American Community Survey Summary File was used

to determine median income distribution as well as education level, and the Small Area Income Poverty Estimates files were used to determine whether counties were classified as low poverty or not. Facilities were classified as either high volume or low volume based on the annual volume of cervical cancer cases, with high volume facilities defined as the top quartile of yearly cervical cancer cases. If multiple facilities were associated with a single case then facility size was classified according to the highest volume center where care was received.

Treatment outcomes included the administration of BT, administration of CT, and an overall quality score. Quality was scored on a scale of 0 to 3, as performed previously by Showalter et al,[7] with 1 point awarded for each guideline-concordant treatment modality received: 1 point each for EBRT, CT, and BT. Receipt of BT and CT was the main focus of these analyses as opposed to receipt of EBRT because EBRT is considered the backbone of nonsurgical definitive therapy and the delivery of CT and BT concurrent with EBRT requires complex coordination.

In order to assess the association between the potential predictors previously listed and treatment outcomes, logistic regression models with random intercepts were employed using the "glimmix" procedure in SAS 9.4 (SAS Institute; Cary, NC). Unmeasured effects of the largest volume treatment facility were represented by random intercepts. For purposes of the analysis, quality scores were dichotomized into 0 to 1 (lower quality) and 2 to 3 (higher quality).

All cause survival was analyzed as the main long-term outcome. With respect to data collection, state coroners' data was searched in order to identify mortality events for Virginia with live cases censored to November 1, 2014, and registry provided survival time for North Carolina (up to date for December 2015) and Kentucky. Following data collection, survival was analyzed against all known or potential predictors, including quality score. In order to accomplish this, a Cox Proportional Hazards model was fitted using the SAS procedure "phreg." Patients who did not survive at least 6 months were removed from the analysis in an attempt to minimize the effect of immortal time bias,[13] which would tend to falsely increase survival for patients who had received completed treatment, since these patients cannot die between diagnosis and initiation of treatment.

For both the logistic regression and the all cause survival analysis, incomplete observations were not retained with the only exception being observations with unknown marital status. There were a number of patients for whom marital status could not be obtained. In an attempt to include this variable in the analyses while at the same time refraining from eliminating all patients that had unknown marital status, patients were grouped into married versus unmarried/unknown marital status.

2.3. Predictive model development and evaluation

Model development began with the pooling of the 3 previously collected cohorts from Virginia, Kentucky, and North Carolina state cancer registries. Quality score was determined as before, but was further dichotomized into low (scores 0–1) and high (scores 2–3)-quality treatment. All potential or known predictors of treatment quality were identified including tumor stage, age at diagnosis, year of diagnosis, marital status, insurance type, race, and facility volume, as well as geographic indicators as described previously including rural/urban continuum, median income, county education level, low poverty status, and distance traveled for treatment. Distance traveled was arranged into quintiles as previously described. The age variable was initially grouped into 4 categories selected by approximated quartiles, but was later treated as a continuous variable with a quadratic term to improve fit. Observations with incomplete data were not included in the analysis.

Stepwise and forward regression procedures using SAS PROC HPGENSELECT were performed on the predictors listed with quality of treatment as the dependent variable and all possible interaction terms (2–3–4-max) included as candidates, allowing for the preservation of hierarchy (i.e., main effects prioritized over interaction effects). Candidate models were selected by varying several parameters including search method (stepwise vs. forward) and the *P* value limit for entry into the model (.01, .05, .10, .15, and .20). For continuous variables such as age, a scatter plot with smoothed trend was employed to provide visual information on whether a quadratic or polynomial term should be added to the set of candidate variables. The best model selection among candidate models was chosen using Akaike information criterion values, which help estimate the relative quality of statistical models for a given dataset.[14]

Several procedures were then implemented to evaluate the predictive accuracy of the predicted model. In order to measure discrimination (how well the final model classified the patients) a standard receiver operating curve was created and the concordance statistic (c-index) was determined. The c-index is an indicator of the predictive power of a model; a value of 0.5 indicates the model has no discriminatory ability and a value of 1.0 indicates the model has perfect discrimination.[15] In order to correct for optimism due to fitting the curve on the training sample, a cross-validated receiver operating characteristic curve was created with PROC LOGISTIC using the leave-one-out principle, which drops the data of 1 subject and re-estimates the parameter estimates. Furthermore, a classification table helped correct for bias and a candidate threshold was selected that resulted in an ideal trade-off between sensitivity and specificity. In order to assess calibration (the bias between expected probabilities of the model with the actual observed probabilities) a calibration plot was done as documented in Harrell.[16] This plot shows the relationship trend between predicted probabilities from the model with the observed probabilities given predicted probability. The plot also helps assess shrinkage of the relationship due to overfit in the training sample by bias correcting the trend through the use of bootstrapping.[16]

3. Results

3.1. Cohort characteristics

Data collection and refinement (Fig. 1) yielded a 595 patient Kentucky cohort, a 1554 patient North Carolina cohort, and a 1048 patient Virginia cohort, for a grand total of 3197 qualifying patients. Table 1 shows cohort demographics with mean quality points and BT percentage by state. The overall cohort had mostly stage IIx or IIIx cervical cancer (79.5%) and some form of insurance (75.1%). The majority of patients received care at a high-volume treatment center (74.2%) and did not undergo a surgical procedure (91.6%). The cohort was distributed fairly equally between the 4 age categories (range 23.4–26.5% per category) and between the 3 temporal diagnosis categories (range 30.5–39.0% per category). Most patients were white (69.6%) and lived in a metropolitan location (70.6%). Just under a third (30.3%) of the cohort lived in an area with a median income of less than 38k, three-quarters (75.4%) lived in a low-poverty

Table 1

Cohort demographics with mean quality points and brachytherapy percentage by state.

	Kentucky			North Carolina			Virginia		
	N	BT%	QP	N	BT%	QP	N	BT%	QP
All	595	80	2.61	1554	51	2.01	1048	54	2.08
Year of diagnosis									
2000–2004	59	78	2.52	521	60	2.20	394	60	2.07
2005–2009	305	79	2.57	531	47	1.94	411	50	2.08
2010–2013	231	82	2.68	502	45	1.89	243	51	2.10
Age at diagnosis									
18–42	162	88	2.78	355	62	2.20	265	59	2.26
42–53	152	87	2.74	406	53	2.13	263	63	2.23
53–66	170	76	2.58	419	53	2.06	257	58	2.17
66+	111	66	2.20	374	35	1.65	263	37	1.66
Cancer stage									
IB2	73	94	2.76	221	59	2.10	122	59	2.32
IIx	213	89	2.74	608	58	2.14	412	61	2.12
IIIx	269	75	2.54	604	46	1.95	437	50	2.05
IVA	40	43	2.10	121	23	1.53	77	29	1.67
Surgery									
No surgical procedure	557	80	2.60	1417	50	2.02	955	54	2.08
Biopsy/excision	38	89	2.68	137	58	1.98	93	58	2.08
Race									
(Missing)	–	–	–	18	28	1.78	16	60	2.33
White	539	80	2.61	968	50	2.02	694	56	2.10
Other	56	79	2.54	568	53	2.00	338	50	2.04
Facility volume (75th percentile)									
(Missing)	–	–	–	–	–	–	43	53	1.91
No	20	26	1.83	665	43	1.94	129	32	1.68
Yes	575	82	2.63	889	57	2.07	876	57	2.15
Insurance									
(Missing)	–	–	–	–	–	–	10	40	1.90
Uninsured	99	81	2.60	435	60	2.21	261	59	2.20
Private	185	86	2.79	435	51	2.09	382	60	2.18
Public without supplement	233	77	2.55	512	47	1.88	272	49	1.98
Public with supplement	78	74	2.36	172	37	1.70	123	37	1.74
Distance to TX facility*									
(Missing)	10	20	1.7	132	40	1.88	43	53	1.91
1st quintile (closest)	117	78	2.54	691	49	1.98	201	46	1.95
2nd quintile	117	84	2.63	460	51	2.03	201	46	2.00
3rd quintile	117	74	2.56	212	63	2.13	201	54	2.05
4th quintile	117	83	2.65	48	53	2.21	201	62	2.18
5th quintile (furthest)	117	88	2.72	11	18	1.91	201	64	2.27
Rural/urban continuum									
(Missing)	–	–	–	3	33	1.00	–	–	–
Metro	308	81	2.62	1111	50	2.00	837	54	2.08
Urban	222	79	2.58	397	52	2.05	151	55	2.08
Rural	65	83	2.62	43	50	2.10	60	56	2.03
ACS median income									
(Missing)	–	–	–	3	33	1.00	–	–	–
0–38 k	236	80	2.58	448	52	2.01	284	54	2.04
38–42 k	103	76	2.60	345	52	2.04	106	52	2.05
42–46 k	128	81	2.63	346	50	1.98	74	53	2.14
46 k+	128	82	2.63	412	49	2.02	584	54	2.1
Low poverty county (<19% below poverty line)									
(Missing)	–	–	–	3	33	1.00	–	–	–
No	205	80	2.61	405	50	2.00	176	55	2.11
Yes	390	80	2.61	1146	51	2.02	872	54	2.07
High education county (<24% did not graduate HS)									
(Missing)	–	–	–	3	33	1.00	–	–	–
No	174	80	2.59	238	53	2.06	140	54	2.08
Yes	421	80	2.61	1313	50	2.00	908	54	2.08
Marital status									
(Missing)	22	86	2.64	233	59	2.25	145	52	1.93
Unmarried	333	77	2.53	825	49	1.93	556	53	2.07
Married	240	84	2.71	496	51	2.04	347	57	2.17

ACS = American Census Survey, BT = brachytherapy, HS = high school, QP = quality points, TX = treatment.

* Driving distance for VA, straight line distance for KY, and preexisting registry quintile classifications kept for NC.

county, and most (82.7%) lived in a county classified as high education. Most observations pulled from the North Carolina registry (80.9%) were in the 1st and 2nd state registry quintiles of distance to their treatment facility, whereas the other state cohorts were equally distributed between the quintiles set by this research team. Over a third of patients were married (38.7%).

Mean quality points and BT utilization percentage ranged from 2.01 to 2.61 points and 51% to 80% by state, respectively. Overall, 35.3% of nonmissing patients received all 3 treatment modalities (EBRT, BT, and CT). The remaining most common combinations received were EBRT + CT at 27.9%, CT + BT at 16.2%, and EBRT at 9.1%. The rates of overall administration for each modality were 80.8% CT, 76.0% EBRT, and 57.3% BT.

3.2. Predictors of BT, CT, and quality score

Following logistic regression and calculation of odds ratios (ORs), several factors were found to be significant predictors of BT and CT receipt, as well as quality score (see Table, Supplemental Table, http://links.lww.com/MD/D179, which contains the results of the logistic regression). The 2005 to 2009 year of diagnosis category predicted worse odds of receiving CT in 1 of the 3 states (OR = 0.55, $P = .044$) as compared to the 2010 to 2013 diagnosis category. In another state, the 2000 to 2004 year of diagnosis category predicted superior odds of receiving BT (OR = 1.69, $P = .010$). Younger age at diagnosis, as compared to the 66+ years of age category, was a significant predictor for improved odds of receiving CT and BT and for high quality care in every age bracket for every state. The size of this impact by outcome and age bracket varied as follows. For CT the ORs ranged from 2.97 ($P = .003$) to 10.83 ($P < .001$), for BT they ranged from 2.14 ($P = .049$) to 5.33 ($P < .001$), and for high quality care the ORs ranged from 3.43 ($P < .001$) to 8.56 ($P < .001$). Cancer stage was often a significant predictor, with earlier stage at diagnosis always associated with higher odds of receiving BT, CT, and a high quality care. For categories found to be statistically significant, the size of this impact varied as follows. For CT the ORs ranged from 2.09 ($P = .008$) to 4.61 ($P < .001$), for BT they ranged from 2.44 ($P < .001$) to 20.18 ($P < .001$), and for high quality care ORs ranged from 2.36 ($P = .005$) to 24.07 ($P = .007$). White race was a significant predictor of improved odds of receiving CT in 1 of the 3 states (OR = 1.41, $P = .043$). In another state, treatment at a low volume facility was associated with reduced odds of receiving BT (OR = 0.49, $P = .020$) and high quality care (OR = 0.53, $P = .016$). As compared to public insurance with supplement, private insurance in 1 state was associated with a higher likelihood of receiving high quality care (OR = 11.67, $P = .031$) and public without supplement was associated with a lower likelihood of receiving CT in another state (OR = 0.54, $P = .012$). Surprisingly, closer distance to treatment facility was associated with lower odds of receiving high quality care for each quintile as compared to the furthest quintile in 1 state. This effect ranged from an OR of 0.12 ($P = .004$) for the 1st quintile to an OR of 0.24 ($P = .039$) for the 4th quintile. In another state, residing in the 3rd quintile was associated with higher odds of receiving BT (OR = 8.20, $P = .017$) as compared to the 5th and furthest quintile.

3.3. Survival

Hazard ratios (HRs) calculated for all-cause mortality are displayed in Table 2. In 1 state, earlier year of diagnosis categories were associated with a higher risk of mortality as compared to the 2010 to 2013 category (2000–2004 HR = 1.42, 95% confidence interval [CI] 1.04, 1.93; 2005–2009 HR = 1.47, 95% CI 1.09, 1.98). Earlier age category at diagnosis, as compared to the 66+ age category, was associated with a reduced risk of mortality for all age categories in 1 state (age 18–42, HR 0.38, 95% CI 0.23, 0.63; age 42–53, HR 0.44, 95% CI 0.27, 0.71; age 53–66, HR 0.42, 95% CI 0.26, 0.67) and in another state the 18 to 42 age category was predictive of reduced mortality as opposed to the 66+ category (HR = 0.66, 95% CI 0.51, 0.86). In all 3 states, earlier cancer stage at diagnosis was significantly associated with a reduced risk of mortality for the IB2 (HR range = 0.34–0.36) and IIx (HR range = 0.35–0.49) categories. Additionally, in 1 of the 3 states, stage IIIx was found to also be predictive of improved survival (HR = 0.72, 95% CI 0.55, 0.96). Receiving treatment at a low volume facility was found to be a significant predictor of increased mortality in 2 states (HR range = 1.71–3.55). In 2 states, married patients showed improved survival as compared to unmarried patients or patients without a known marital status (HR = 0.58, 95% CI 0.44, 0.78; HR = 0.72, 95% CI 0.60, 0.86). High quality care (2–3 vs. 0–1 points) was found to be predictive of lower mortality in every state (HR range = 0.40–0.59).

3.4. Predictive model

Elimination of observations with incomplete data reduced observations utilized for model development from 3197 to 3102. Following forward and stepwise regression, we selected a parsimonious model with cancer stage, age, age squared, and being in the 75th volume percentile. Quadratic terms for age were added to improve fit (see Figure, Supplemental Figure 1, http://links.lww.com/MD/D179, which shows the LOESS fit plot). This resulted in a final model (Table 3) with a bias corrected c-index of 0.755 (see Figures, Supplemental Figures 2 and 3, http://links.lww.com/MD/D179, which show ROC curves). Further analysis showed model sensitivity (rate of persons with high quality scores that will be correctly classified) of 78.2% and specificity (rate of persons with low quality scores that will be correctly classified) of 62.9%. The calibration plot (see Figures, Supplemental Figure 4, http://links.lww.com/MD/D179, which shows the calibration plot) shows predicted and observed probabilities match excellently as the smoother is close to the 45° ideal line. The bias-corrected smoother was almost indistinguishable to the uncorrected smoother, suggesting shrinkage is minimal.

In order to classify patients into high and low quality, Table 3 can be used to create a composite score based on the regression weights and the patient variables. For example, if the patient has Stage IIx, is 32 years old, and is treated at a high-volume facility, the composite score from Table 3 would be:

$$-2.1493 + 1.5399 + (0.1436 * 32) + (-0.00164 * 32^2) + 0.3906 = 2.70$$

To get the probability of complete treatment, take the exp*it* of the score, which in the above example is:

$$exp\,it(2.70) = .\mathbf{94}$$

In order to obtain a classifier with 78.2% sensitivity, the threshold with which to compare this value is .84. In the above

Table 2

Cox proportional hazards model for all-cause mortality by state.

	Kentucky N = 530*		North Carolina N = 1258*		Virginia N = 887*	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Year of diagnosis						
2000–2004	0.68	(0.41, 1.12)	1.21	(0.97, 1.52)	1.42	(1.04, 1.93)
2005–2009	0.91	(0.66, 1.25)	1.06	(0.86, 1.31)	1.47	(1.09, 1.98)
2010–2013	1.00	Ref	1.00	Ref	1.00	Ref
Age at diagnosis						
18–42	0.38	(0.23, 0.63)	0.66	(0.51, 0.86)	0.74	(0.53, 1.05)
42–53	0.44	(0.27, 0.71)	0.87	(0.69, 1.11)	0.81	(0.58, 1.13)
53–66	0.42	(0.26, 0.67)	0.91	(0.72, 1.16)	0.96	(0.70, 1.31)
66+	1.00	ref	1.00	ref	1.00	ref
Cancer stage						
IB2	0.34	(0.17, 0.66)	0.35	(0.25, 0.50)	0.36	(0.22, 0.60)
IIx	0.35	(0.20, 0.61)	0.45	(0.34, 0.60)	0.49	(0.33, 0.72)
IIIx	0.69	(0.41, 1.18)	0.72	(0.55, 0.96)	0.81	(0.55, 1.19)
IVA	1.00	Ref	1.00	Ref	1.00	Ref
No surgical procedure (vs. biopsy)	2.15	(0.94, 4.91)	1.08	(0.81, 1.43)	1.14	(0.80, 1.62)
White race (vs. other)	1.36	(0.82, 2.26)	0.88	(0.74, 1.03)	1.01	(0.81, 1.25)
TX at low volume facility (vs. $\geq 75^{th}$ percentile)	3.05	(1.29, 7.19)	1.12	(0.94, 1.34)	1.63	(1.18, 2.24)
Insurance						
Uninsured	1.46	(0.79, 2.69)	0.76	(0.56, 1.04)	0.73	(0.49, 1.09)
Private	1.72	(0.97, 3.04)	0.76	(0.55, 1.05)	0.70	(0.47, 1.03)
Public without supplement	1.62	(0.97, 2.69)	1.02	(0.77, 1.34)	0.87	(0.61, 1.22)
Public with supplement	1.00	Ref	1.00	Ref	1.00	Ref
Distance to TX facility†						
1st quintile (closest)	1.14	(0.70, 1.86)	0.74	(0.32, 1.73)	0.83	(0.57, 1.19)
2nd quintile	0.84	(0.49, 1.44)	0.75	(0.32, 1.73)	0.86	(0.60, 1.24)
3rd quintile	0.86	(0.53, 1.38)	0.57	(0.24, 1.34)	1.01	(0.71, 1.30)
4th quintile	1.07	(0.71, 1.61)	0.94	(0.37, 2.38)	1.28	(0.93, 1.76)
5th quintile (furthest)	1.00	Ref	Ref	Ref	1.00	Ref
Rural/urban continuum						
Metro	1.04	(0.55, 1.97)	1.14	(0.63, 2.08)	1.16	(0.68, 2.00)
Urban	0.99	(0.64, 1.53)	1.29	(0.72, 2.31)	1.16	(0.69, 1.94)
Rural	1.00	Ref	1.00	Ref	1.00	Ref
ACS median income						
0–38k	1.49	(0.79, 2.79)	0.92	(0.67,1.26)	1.06	(0.75, 1.50)
38–42k	1.27	(0.79, 2.04)	1.19	(0.94, 1.51)	1.10	(0.78, 1.54)
42–46k	1.00	(0.64, 1.55)	0.87	(0.69, 1.09)	0.97	(0.65, 1.46)
46k+	1.00	Ref	1.00	Ref	1.00	Ref
Low poverty county (yes vs. no)	1.51	(0.93, 2.44)	0.86	(0.66, 1.12)	0.90	(0.65, 1.27)
High education county (yes vs. no)	0.82	(0.51, 1.32)	0.97	(0.75, 1.26)	1.14	(0.74, 1.74)
Married (yes vs. no/unknown)	0.58	(0.44, 0.78)	0.72	(0.60, 0.86)	0.85	(0.68, 1.06)
Treatment quality score (high 2–3 vs. low 0–1)	0.40	(0.25, 0.63)	0.56	(0.45, 0.68)	0.59	(0.46, 0.75)

Hazard ratio >1 implies greater mortality risk, while hazard ratio <1 implies lower mortality risk.

ACS = American Census Survey, CI = confidence interval, TX = treatment.

* Only complete cases with >6 months survival included in analysis. Number of observations initially read: KY = 548; NC = 1406; VA = 958.

† Driving distance for VA, straight line distance for KY, and preexisting registry quintile classifications kept for NC.

Table 3

Final predictive model.

Variable	Estimate (β)	Standard error	*P*
Intercept	–2.1493	0.7037	.0023
Stage IB2	1.5258	0.2356	<.0001
Stage IIx	1.5399	0.1777	<.0001
Stage IIIx	0.9921	0.1685	<.0001
Stage IVa	0		
Age	0.1436	0.0233	<.0001
Age^2	–0.00164	0.000193	<.0001
High volume*	0.3906	0.1147	.0007

* Defined as volume ≥75th percentile.

example, since the probability is above the threshold, the patient would be classified into the high-quality category.

4. Discussion

The current three-state analysis expands upon prior work on delivery of guidelines-concordant multimodality care for locally advanced cervical cancer and includes the development of a risk classifier tool to help predict quality of care distributions across populations and geographic areas. The predictors of care and survival identified in this study are largely reflective of predictors identified in national database analyses and therefore serve to reaffirm these findings at the state level for the regions in this study. We found that a low proportion of patients received all 3

core therapies recommended by national guidelines, with an especially low rate of compliance for BT administration. There was, however, 1 positive outlier state that treats the vast majority of its patients at high-volume centers and may provide insights into quality care delivery at the statewide level that can be applied in future health system interventions aimed at improving care in locales. The predictive tool presented in this publication may aid in future research that seeks to delve deeper into the patterns of care for this disease.

Just over a third of patients received guideline-concordant treatment with all 3 core therapies (BT, CT, and EBRT). This rate is lower than a recent National Cancer Database analysis by Robin et al[4] which found that of 15,194 patients diagnosed with stage IB2 through IVA cervical cancer and treated between 2004 and 2012 only 44.3% received all 3 core modalities, though this was not broken down to the level of individual states. Our analysis suggests that the risks associated with receiving low quality care (0 to 1 quality points) versus high (2 to 3 quality points) were potentially severe and supports the current literature demonstrating that the administration of more comprehensive and guideline-concordant treatment regimens is associated with substantially improved survival outcomes.[3,4,9] The least frequently utilized modality was BT at a 57.3% overall rate of administration in the cohort. Additionally, there was a statistically significant trend of decreased BT utilization in 1 state and a decrease in BT utilization in another from 60% to 45% over the collection period, though this second state did not meet statistical significance. These trends are concerning and may support the findings from other publications showing decreasing BT rates in the United States.[9–11] As previously mentioned, the omission of BT may decrease overall survival by almost two-fold,[4,9] therefore there exists substantial opportunity for improvement in care through increasing the application of this treatment modality.

One state, however, appeared to be a positive outlier in this analysis, relative to prior national-level reports,[9–11] featuring a higher rate of BT administration (80%) and overall quality score (2.61). It may be noteworthy that 96.6% of the patients in this state received care at a high volume facility, which is substantially higher than the other 2 states (87.2% and 57.2%). But how did so many patients receive care at a high volume treatment center in this state, despite some residing a long distance from these centers? According to a recent study by a high-volume academic center in this state regarding cervical cancer survival for patients referred to a tertiary care center, patients receiving primary care at local community hospitals are typically referred to their high-volume center for initial treatment planning and care coordination following a diagnosis of locally advanced cervical cancer. Local community radiation and medical oncologists generally do not perform BT in this state, but do consistently refer patients to this high-volume academic center with BT capabilities to ensure access to guideline-concordant care. Additionally, this center stated that it makes extensive efforts to provide quality treatment regardless of ability to pay. Therefore many patients in rural areas receive the entirety of their cervical cancer care at this high-volume center due to lack of insurance.[17] This may partially explain our findings that further distance from a high-volume center was not predictive of worse care in this state (and in fact, the opposite was true for the furthest category). Theoretically, this model of consistent referral to a high-volume center for planning, coordination, and BT could have been a driving factor in the high rate of BT utilization in this state and higher overall quality score.

It has been well demonstrated that treatment at a low volume facility leads to increased probability of receiving incomplete treatment.[4–6] In the current analysis, 1 state showed treatment at a low-volume facility to be a statistically significant predictor of reduced odds of receiving BT and higher quality care. Additionally, the general trend across states showed reduced odds of comprehensive treatment at a low-volume facility. We did not find that treatment at a low-volume facility was a statistically significant predictor of BT receipt or higher quality treatment in our positive outlier state; however, this may have been due to low observational volume in the low-volume facility category (20 patients) in combination with reduced discriminative power through collinearity with other demographic categories. Cervical cancer treatment regimens are complex and require coordination of several different specialists and treatment schedules. BT is especially resource-intensive and requires specific technologies and personnel that may not be present at low-volume treatment facilities. But if these facilities do not have BT capabilities, then why not refer externally to a center that does? In a study examining trends in the utilization of BT for cervical cancer in the United States, Han et al[10] found that while BT rates decreased from 83% in 1988 to 58% in 2009 rates of intensity modulated radiation therapy increased from 15% in 2002 to 35% in 2004. They postulated that some radiation oncologists who do not feel comfortable performing BT may administer an intensity-modulated radiation therapy or stereotactic body radiation therapy boost in lieu of referring externally for BT, resulting in a lower survival rate.[10] Additionally, some publications have speculated that changes in reimbursement for these therapies may motivate some centers to treat with advanced external beam as opposed to BT.[9,10] BT remains the most effective modality for dose escalation to the tumor while reducing toxicity to surrounding tissues and organs for cervical cancer boost, even as compared to intensity modulated radiation therapy and proton therapy[18] and should not be replaced with advanced external beam therapies.[19] As previously mentioned, the omission of BT substantially reduces survival for cervical cancer patients. Physicians at locations without BT capabilities can therefore maximize their compliance with national guidelines by consistently referring patients with locally advanced cervical cancer to centers with BT capabilities instead of administering boosts with advanced external beam techniques.

In order to aid in examining distributions of care, we developed a risk classifier tool that predicts for high (2–3 quality points) versus low (0–1 quality points) quality care using disease stage, age, and whether treatment was obtained at a high-volume center. These predictive factors are in line with our logistic regression analysis as well as National Cancer Database analyses which have identified older age, later disease stage, and treatment at a low-volume center as being predictive of incomplete treatment.[4,9] This classifier was successfully applied to our cohort and is promising for evaluation in a larger dataset. Ideally this classifier may be used as a tool with which to examine distributions of care. This may include identifying targets at risk of low quality care for intervention as well as serving as a method to identify anomalies that defy the classifier's predictions. Subsequent investigation of these anomalies may provide insights into why some regions experience low quality care despite being predicted as high quality and vice versa. The main limitation of this classifier, however, is a less-than-ideal specificity resulting in a number of patients being classified as low quality who actually

received high quality care. It would be beneficial to evaluate this tool further using a larger dataset.

This analysis has limitations. This is a retrospective analysis and therefore the patients in our cohort may not represent the broader population of locally advanced cervical cancer patients. Due to the fact that comorbidity data were not available, this factor could not be taken into account in the all-cause mortality analysis. However, all statistically significant trends in survival identified in this analysis are in line with national database analyses that did control for comorbidities. Because of data limitations, distance to highest volume treatment facility was calculated using a different method for each state. However, because statistical analyses were run for each state separately as opposed to between states, the driving distance quintiles are thought to serve as reasonable intervals for these separate analyses. Data regarding technical treatment details, such as radiation dose and treatment schedule, were not available. Treatment delays are associated with worse disease control for women with cervical cancer treated with chemoradiation,[20,21] and certain dosimetric factors such as D90 and D100 affect local tumor control.[22,23] National database analyses have not taken these factors into account either, so the effect size of these uncontrolled factors is unknown. There is also the possibility that certain modalities may have been underreported, specifically in the case where patients received some treatment in another state. Underreporting is a limitation of most database analyses, but the fact that our results showing a low rate of compliance with guideline-concordant care, and, specifically, a low and potentially decreasing rate of BT in certain regions, are largely in line with the findings of other analyses using different datasets tends to strengthen these findings.

5. Conclusion

In a 3197 patients cohort from 3 states, we identified a low rate of compliance with guideline-concordant care, with only 35.3% of patients receiving complete treatment using all 3 core modalities. Additionally, in 2 of the 3 states it appeared that BT usage may actually be decreasing. One state, however, served as positive outlier, where we postulated that consistent referral to high-volume treatment centers may have influenced the higher rate of BT and high quality care. We also featured the development of a classifier tool that may help identify patients and regions at risk of receiving low quality care, though this tool will need to be validated using a larger dataset.

National guidelines for cervical cancer treatment have not changed significantly since they were updated in 1999 to reflect the survival advantages associated with concurrent CT, yet the compliance with these guidelines identified through database analyses remains low. It is unclear why so many patients appear to be receiving incomplete treatment for their locally advanced cervical cancer, especially with respect to BT administration. The medical literature viewed as a whole illuminates a landscape of care that is suboptimal for women diagnosed with locally advanced cervical cancer in the United States. It is imperative that future research focus on further elucidating and ultimately eliminating disparities in care for this disease.

Author contributions

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