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Kushal Naik Date

Chemo-radiation With or Without Surgery for Resectable Esophageal Cancer: An Analysis of Survival among 11,122 Patients in the National Cancer Data Base (NCDB)

By

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Master of Public Health

Epidemiology

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By

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MBBS, Seth GS Medical College and KEM Hospital, Mumbai (MUHS), 2013

Thesis Committee Chair: Michael Goodman MD MPH

An abstract of

a thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

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in Epidemiology

2016

Abstract

Chemo-radiation With or Without Surgery for Resectable Esophageal Cancer: An Analysis of Survival among 11,122 Patients in the National Cancer Data Base (NCDB)

By

Kushal Naik

Background: Locally advanced resectable esophageal cancers (rEC) are managed either with concurrent chemo-radiation followed by surgery (CRSx) or concurrent chemo-radiation alone (cCR). There is insufficient evidence comparing the overall survival (OS) of these two groups in a large population.

Methods: The National Cancer Data Base (NCDB) was queried for rEC cases diagnosed from 2003 to 2011. Patients with previous cancers, cervical rEC, clinical stage T1N0 or metastatic disease were excluded. cCR was defined as chemotherapy and radiotherapy given within 30 days of each other. CRSx was defined as cCR followed by surgical resection within 90 days of initiation of cCR. The overall survival in the two groups was compared using Kaplan-Meier methods and extended Cox-proportional hazard models.

Results: A total of 11,122 eligible patients were identified; of those, 8,091 (72.7%) received cCR and the rest were treated with CRSx. The odds of receiving CRSx was higher among patients with stage II disease, adenocarcinoma, lesions of lower third of esophagus, private insurance, and those living more than 25 miles away or in areas with higher median income or greater proportion of high school-educated residents. Patients over 70 years of age, females, African-Americans, those with (two or more) co-morbidities, or those treated at community programs were most likely to receive cCR alone. After adjusting for confounders the hazard ratio (HR) for CRSx compared to cCR alone was 0.66 (95% confidence interval [CI]: 0.45-0.97, p=0.03). In a propensity-score matched analysis the corresponding HR was 0.50 (95% CI: 0.46-0.54, p<0.001).

Conclusion: Data from the NCDB strongly support the inclusion of surgery after concurrent chemo-radiation for patients with locally advanced, resectable esophageal cancer.

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Background

Esophageal cancer is the 6th most common cause of cancer-related death in the world with a global age-adjusted annual mortality rate of approximately 5 per 100,000 people. In the United States, the 5-year survival rate following an esophageal cancer diagnosis is less than 20% with an age-adjusted mortality rate of 7.6 per 100,000 for males and 1.5 per 100,000 for males. [1-3].

There are two main histological subtypes of esophageal cancer: squamous cell carcinoma (SCC) and adenocarcinoma (AC). The main risk factors for SCC are smoking and alcohol use, while AC is associated with gastroesophageal reflux disease and high body mass index [4, 5]. In addition, divorce, widowhood, living alone, low educational attainment, and low income increase the risk of esophageal cancer [6]. AC comprises the majority of cases in the United States and its incidence has been increasing while incidence of SCC has been on a decline [7-9].

Primary treatment options for esophageal cancer include surgery (esophagectomy with lymph node dissection), chemotherapy, radiation therapy or a combination of these approaches. A choice of treatment modalities may depend on stage, histology, grade and presence of metastases [7]. The optimal management for locally advanced resectable esophageal cancer (rEC) remains a matter of debate and the usual care may include surgery with or without neoadjuvant treatment or a completely non-surgical approach with definitive concurrent radiation and chemotherapy [10-12]. It is also unclear which patients benefit most from the different management approaches. While two European clinical trials failed to show the benefit of combining surgery with chemo-radiation relative to

chemo-radiation alone it remains unclear if the findings from these trials are generalizable to the general population of the US patents [13-15]. In view of this existing uncertainty we sought to compare survival following definitive concurrent chemo-radiation with or without surgery in rEC patients captured by the National Cancer Database (NCDB).

Methods

The NCDB is maintained jointly by the Commission on Cancer of the American College of Surgeons and the American Cancer Society [16]. It includes more than 1,500 commission-accredited cancer programs in the United States and collects detailed clinical and pathology information on more than 70% of cancers that had been diagnosed in the United States since 1989.

Concurrent chemo-radiation alone (cCR) was defined as chemotherapy and radiotherapy initiated within 30 days of each other without previous or subsequent surgery. Concurrent chemo-radiation followed by surgery (CRSx) was defined as concurrent chemotherapy and radiation followed by surgical resection within 90 days of initiation of cCR.

The NCDB was queried for locally advanced rEC cases diagnosed from 2003 to 2011. As shown in Figure 1, after exclusion of non-eligible cases the final dataset was limited to patients 18-90 years of age with locally advanced AC or SCC rEC based on the American Joint Commission on Cancer (AJCC) [17] clinical stages II and III, and those who received cCR or CRSx with known start dates at one of the NCDB reporting facilities.

Further excluded were patients with EC originating in the cervical region of the esophagus, history of previous cancers, and those who received radiation therapy at locations other than esophagus.

Patients who received cCR and those treated with CRSx were compared with respect to the distributions of various demographic, health care provider- and disease-related characteristics including age, sex, race, insurance type, census tract levels of education and income, treatment facility location and type, distance from treatment facility, year of diagnosis, Charlson-Deyo comorbidity index, histologic subtype, histologic grade, clinical stage and tumor location. Multivariable logistic regression models were used to identify factors associated with receipt of surgery. The results of these logistic regression analyses were expressed as adjusted odds ratios (ORs) along with the corresponding 95% confidence intervals (CIs)

Overall survival in the two groups was compared using Kaplan-Meier methods accompanied by a log-rank test. In the multivariable survival analyses the two groups were compared after adjusting for the covariates included in the logistic regression models.

As follow up for surgical patients, includes a time interval between diagnosis and surgery the analyses had to take into consideration the "immortal-time" bias [18]. To address this issue we used an extended Cox model in which surgery is treated as a time-varying variable [19]. Using this approach, the pre-surgery interval among CRSx patients is included with the cCR group, while surgical follow up starts only after the patients had the procedure.

To reduce confounding by indication, a separate set of survival analyses used the propensity score matching method. The propensity score was calculated using a separate

logistic regression model with treatment modalities (CRSx vs cCR) as the dependent variable; and age, sex, race, insurance type, patient census tract education and income levels, treatment facility location and type, distance from treatment facility, year of diagnosis, Charlson-Deyo comorbidity index, histologic subtype, histologic grade, clinical stage and tumor location used as independent variables. Patients from each study cohort were matched at a ratio of 1:1 based on the propensity score using a greedy 5-1 digit match algorithm [20]. After matching, the balance of covariate between two cohorts was evaluated by the standardized differences and a value of < 0.1 was considered as negligible imbalance [21]. As the propensity score matched sample does not consist of independent observations, we fit a Cox proportional hazards with a robust variance estimator [22] that was stratified on the matched pairs to assess overall survival. The results of the Cox models were expressed as hazard ratios (HRs) along with the 95% CI estimates.

To further explore the association between radiation and survival we performed a sub-analysis based on whether patients received high or low radiation dose. The total dose was measured based on both the regional and the boost radiation therapy. High dose radiation was defined as combined (regional plus boost) radiation dose of more than 60Gy and low dose was defined as less than 60Gy.

All statistical analysis was done using SAS® Software Version 9.4 (SAS Institute Inc., Cary, NC) and SAS macros or software developed at the Biostatistics and Bioinformatics at Winship Cancer Institute [23]. The cutoff for statistical significance was set at a two sided type I error of 0.05.

Results

As shown in Table 1 patients who had surgery were significantly younger than those treated with chemo-radiation alone. The cCR group compared to the CRSx group had a greater proportion of non-Hispanic Blacks (13.4% vs 4%), persons with government insurance (66.4% vs 37.8%) those treated at a community hospital (12.5% vs 5.6%) those residing less than 10 miles from the facility (56.5% vs 38.2%). Surgically treated patients were also more likely to have carcinoma in the upper or middle third of the esophagus (31.1% vs 12.6%) and have tumors with squamous cell histology (44.2% vs 17.3%).

Factors significantly associated with receipt of surgery were assessed using a multivariable logistic regression analyses that included all covariates as shown in Table 2. Patients over 50 years of age (especially older than 70), females, African-Americans, and those with two or more co-morbidities and with government insurance or no insurance were most likely to receive cCR. Other factors associated with cCR receipt included squamous histology, lesions of upper or middle third of esophagus, stage III disease and treatment at non-academic programs.

As shown in Figure 2, survival of patients in the CRSx group was better than survival of patients treated with cCR alone. The difference in survival between the two groups was observed for both AC and SCC histologic types (both log rank p-values <0.0001). The median survival in the CRSx group 32.5 months (95% CI: 29.6-34.8) was longer than the median survival in the cCR group (14.2 months; 95% CI: 13.4-15.5). The 5- and 10-year survival estimates in the surgical group were 35.9% (95% CI: 33.3-38.5) and 23.8% (95% CI: 20.0-27.9) respectively. The corresponding 5- and 10-year survival

estimates in the non-surgical group were 15.2% (95% CI: 13.3-17.2) and 6.1% (95% CI: 3.9-9.0).

In the multivariable Cox regression models the difference between two treatment groups remained evident after adjustment for possible confounders. As shown in Table 3, patients who received surgery were 34% more likely to survive than patients who received chemo-radiation alone (HR=0.66; 95% CI: 0.45-0.96, p=0.03).

Other patient-related factors associated with poor survival included age above 70 years, having government insurance or being uninsured, receiving treatment at facilities in the Mountain states (Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, Wyoming), and having at least one co-morbidity. Disease-related prognostic factors included lesions in the middle third or in the overlapping areas of the esophagus, higher tumor grade, and AJCC clinical stage III disease. Better survival was observed among women, Hispanics, patients treated at academic or research centers, those living in areas more than 25 miles from facility, and those treated after 2006. Survival did not differ by histologic type (AC vs. SCC), or race (non-Hispanic Whites vs. non-Hispanic Blacks).

The median survival with the CRSx group was longer (32.5 months; 95% CI: 29.6-34.8) as compared to the cCR group (14.2 months; 95% CI: 13.4-15.5). The 5- and 10-year survival in the surgical group was 35.9% (95% CI: 33.3-38.5) and 23.8% (95% CI: 20.0-27.9) respectively. Similarly, the 5- and 10-year survival in the non-surgical group was 15.2% (95% CI: 13.3-17.2) and 6.1% (95% CI: 3.9-9.0) respectively.

Figure 4 presents the survival curves comparing the cCR with CRSx in the propensity score matched sample. There were 1774 matched pairs after matching on the 15 co-variates. The propensity score matched analysis showed that survival following CRSx

was significantly better compared to survival in the cCR group with an HR of 0.50 and a 95% CI from 0.46 to 0.54 ($p<0.001$).

Among those receiving definitive chemo-radiation without surgery, the median combined radiation dose was 50.4 Gy with an inter-quartile range (IQR) from 45.0 to 54.0 Gy, the median regional radiation dose was 45.0 Gy (IQR: 39.6-50.4) and the median boost radiation dose was 12.6 Gy (IQR: 9.0-18.0). In the CRSx group the median combined radiation dose was 50.4 Gy (IQR: 45.0-50.4), the median regional radiation dose was 45.0 Gy (IQR: 45.0-50.4) and the median boost radiation dose was 9.0 Gy (IQR: 5.4-14.4).

In the CRSx group, the majority of patients (97%) received low dose (<60 Gy) radiotherapy. There was no significant difference in survival between surgically treated patients who received high dose compared to those who received low dose ($p=0.61$). In the cCR group, 85% of patients were treated with low dose radiation. Among patients treated with chemo-radiation alone high dose was associated with a modestly elevated mortality (HR=1.12; 95% CI: 1.04-1.20; $p=0.0018$). When the low dose radiation in the cCR was further subdivided into three categories: 43-48Gy, 48-53Gy, and 53-58Gy, there was no apparent difference in survival of patients across these three categories.

Discussion

In the management of locally advanced rEC, preoperative concurrent therapy followed by surgery is the most widely accepted treatment modality. Yet, the data from phase III clinical trials do not appear to support this approach. The lack of any current evidence results from the difficulty in randomizing patients onto such trials.

Two European trials [14, 15] addressed this question by randomly assigning rEC patients to either definitive chemo-radiation or chemo-radiation with surgery. Both of these studies observed no difference in overall survival between the two treatment groups and concluded that there was no benefit of adding surgery to chemo-radiation. It is important to point out, however, that both of these trials were conducted more than a decade ago and their results may not apply to the current practices as both diagnostic and treatment methods have changed. In addition the two earlier studies were conducted in single center settings (one in Germany and another in France) and the standard of care at these institutions may have been different compared to more current treatment practices in the United States.

While clinical trials remain the 'gold standard' for testing efficacy of interventions, the results of trials may not always apply to real-life clinical settings [24]. For this reason it is useful to compare results of clinical trials to the corresponding findings from large observational cohorts such as the one used in the present analysis.

Ours is not the only observational study addressing this issue. Another population-based study from Los Angeles County [25] also found that surgery is an important component of management for rEC.

A distinguishing characteristic of our analysis is the use of a large national study sample. The large sample size ensures greater statistical power whereas the national study population makes study results more generalizable [26]. Internal validity of the current study is enhanced by taking into consideration multiple sociodemographic, clinic-related factors and through the use of alternative modeling approaches including propensity score matching. As the study did not rely on patient recruitment, selection bias is unlikely to play

an important role, whereas correction for the "immortal time bias" was achieved by using the extended Cox models.

A proper interpretation of our findings requires understanding the limitations of the NCDB. The NCDB does not provide information on the agents, toxicity of chemo-radiation, number of doses of chemotherapy administered, and does not capture disease recurrence. While we do have information regarding the anatomic target and dose for radiotherapy, there is no information on the specific type of adjuvant radiation administered.

These limitations notwithstanding, our analysis supports the inclusion of surgery after concurrent chemo-radiation for patients with locally advanced, rEC. In the absence of randomized controlled trials that are representative of the general population of EC patients in the US, these observational data may justify surgical resection. Future studies are needed to determine the optimal chemo-radiation regimen that would prevent systemic recurrence and decrease EC mortality.

Footnote

The data used in the study were derived from a de-identified National Cancer Data Base file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or for the conclusions drawn from these data by the investigator.

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Figure 1: CONSORT Flow Diagram Demonstrating Selection of the Study Sample Based on Inclusion and Exclusion Criteria

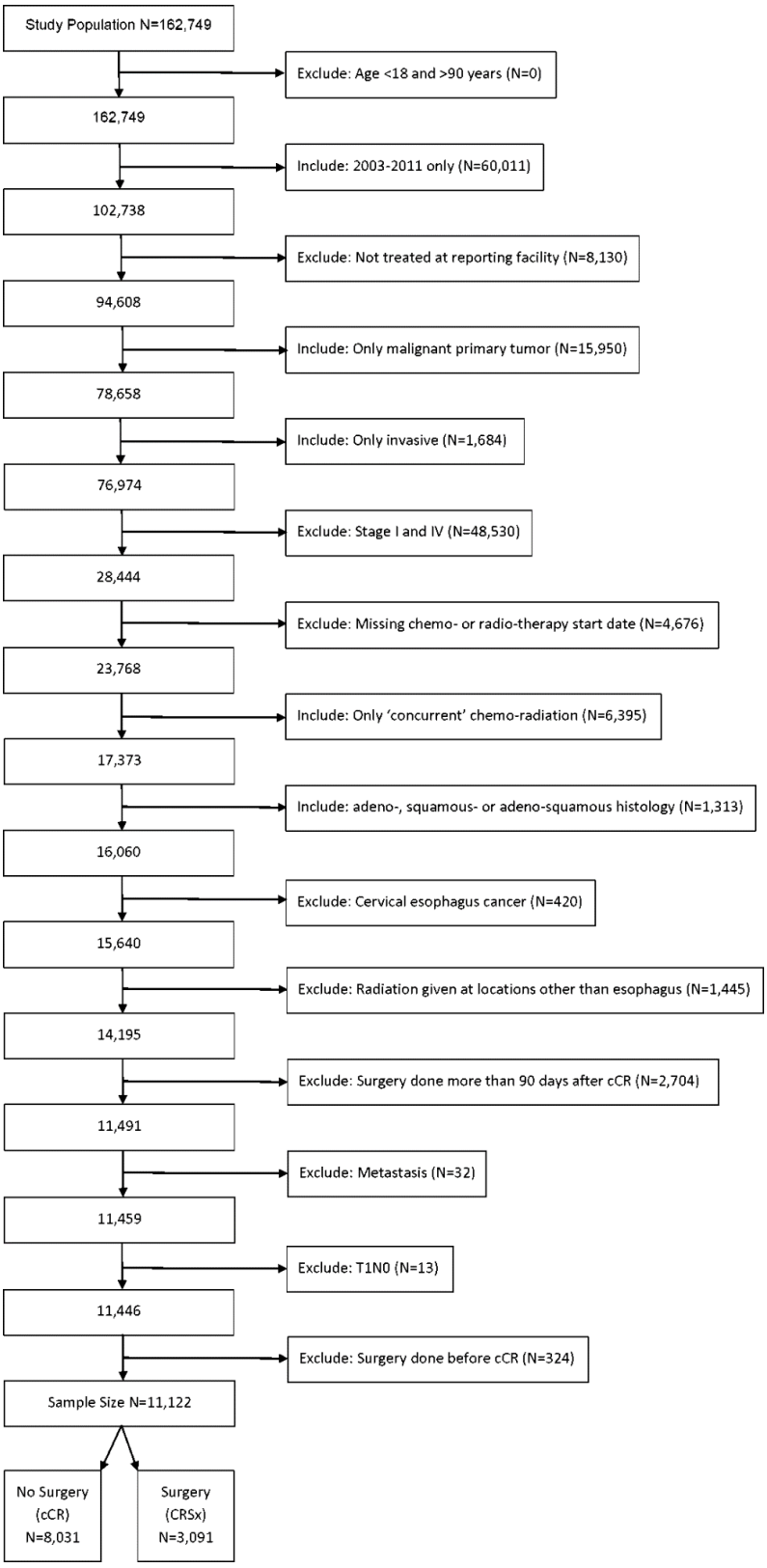


Table 1: Demographic, Provider-related and Clinical Characteristics of Patients Treated with Chemo-radiation Followed by Surgery (CRSx) and Those Managed with Concurrent Chemo-radiation Alone (cCR)

		N (%) = 11122	
Variables	**Categories**	**cCR**	**CRSx**
Age Group	Less than 50 years	585 (7.2)	466 (15.4)
	50-60 years	1816 (22.4)	1069 (35.3)
	60-70 years	2463 (30.4)	1073 (35.4)
	More than 70 years	3227 (39.9)	423 (14.0)
Sex	Male	6160 (76.1)	2610 (86.1)
	Female	1931 (23.9)	421 (13.9)
Race	Non-Hispanic White	5903 (80.3)	2545 (91.6)
	Non-Hispanic Black	988 (13.4)	110 (4.0)
	Hispanic	254 (3.5)	72 (2.6)
	Others	204 (2.8)	50 (1.8)
	Missing	742	254
Insurance	Not Insured	325 (4.1)	71 (2.4)
	Private Insurance	2347 (29.5)	1784 (59.8)
	Government	5292 (66.4)	1126 (37.8)
	Missing	127	50
Urban/Rural	Rural	185 (2.4)	84 (2.9)
	Urban	1462 (19.0)	615 (21.3)
	Metro	6057 (78.6)	2187 (75.8)
	Missing	387	145
Median Income Quartiles 2008-2012	<$38,000	1694 (21.7)	452 (15.4)
	$38,000-$47,999	2072 (26.5)	728 (24.8)
	$48,000-$62,999	2035 (26.0)	784 (26.7)
	$63,000 +	2017 (25.8)	977 (33.2)
	Missing	273	90
Percent No High School Degree 2008-2012	<7%	1556 (19.9)	791 (26.9)
	7.0-12.9%	2621 (33.5)	1091 (37.1)
	13-20%	2224 (28.4)	707 (24.0)
	>=21%	1424 (18.2)	352 (12.0)
	Missing	266	90
Facility Type	Community Program	1008 (12.5)	170 (5.6)

	Comprehensive Community Program	4336 (53.6)	1293 (42.8)
	Academic Program	2743 (33.9)	1561 (51.6)
	Missing	4	7
Facility Location	New England	599 (7.4)	241 (8.0)
	Middle Atlantic	1062 (13.1)	385 (12.7)
	South Atlantic	1975 (24.4)	690 (22.8)
	East North Central	1685 (20.8)	646 (21.3)
	East South Central	459 (5.7)	190 (6.3)
	West North Central	713 (8.8)	400 (13.2)
	West South Central	445 (5.5)	100 (3.3)
	Mountain	353 (4.4)	124 (4.1)
	Pacific	800 (9.9)	255 (8.4)
Great Circle Distance	0) Live <5 Miles	2700 (33.4)	586 (19.3)
	1) 5-10 Miles	1870 (23.1)	573 (18.9)
	2) 10-25 Miles	1853 (22.9)	746 (24.6)
	3) 25+ Miles	1668 (20.6)	1126 (37.1)
Charlson-Deyo Comorbidity Score	0	6039 (74.6)	2387 (78.8)
	1	1551 (19.2)	548 (18.1)
	2+	501 (6.2)	96 (3.2)
Year of Diagnosis	0) 2003-2005	2317 (28.6)	800 (26.4)
	1) 2006-2008	2597 (32.1)	1039 (34.3)
	2) 2009-2011	3177 (39.3)	1192 (39.3)
Primary Site	Lower third	4503 (55.7)	2401 (79.2)
	Middle third	1914 (23.7)	341 (11.3)
	Upper third	596 (7.4)	38 (1.3)
	Overlapping lesion of esophagus	394 (4.9)	102 (3.4)
	Esophagus, NOS	684 (8.5)	149 (4.9)
Grade / Differentiation	Well differentiated	380 (5.9)	129 (5.1)
	Intermediate, Moderate	2948 (45.9)	1071 (42.0)
	Poor / Undifferentiated / anaplastic	3094 (48.2)	1350 (52.9)
	Missing	1669	481
Histology	Adenocarcinoma	4447 (55.0)	2485 (82.0)
	Squamous Cell	3580 (44.2)	524 (17.3)

	Mixed adeno/squamous	64 (0.8)	22 (0.7)
AJCC Clinical Stage Group	Clinical Stage 2	3661 (45.2)	1419 (46.8)
	Clinical Stage 3	4430 (54.8)	1612 (53.2)

Table 2: Multivariable Logistic Regression Analysis of Factors Associated with Receipt of Surgery among Esophageal Cancer patients

Variables	Categories	Odds Ratio (95% CI)	P-value
Age Group	Less than 50 years	-	-
	50-60 years	0.57 (0.44-0.74)	<.001
	60-70 years	0.48 (0.37-0.62)	<.001
	More than 70 years	0.18 (0.14-0.24)	<.001
Sex	Male	-	-
	Female	0.82 (0.67-0.99)	0.042
Race	Non-Hispanic White	-	-
	Non-Hispanic Black	0.55 (0.39-0.76)	<.001
	Hispanic	1.07 (0.68-1.69)	0.762
	Others	1.11 (0.66-1.87)	0.689
	Missing		
Insurance	Private Insurance	-	-
	Government	0.47 (0.40-0.56)	<.001
	Not Insured	0.43 (0.28-0.65)	<.001
	Missing		
Median Income Quartiles 2008-2012	<$38,000	-	-
	$38,000-$47,999	1.04 (0.81-1.33)	0.775
	$48,000-$62,999	1.16 (0.89-1.51)	0.28
	$63,000 +	1.46 (1.08-1.97)	0.014
	Missing		
Percent No High School Degree 2008-2012	<7%	-	-
	7.0-12.9%	0.92 (0.75-1.14)	0.456
	13-20%	0.78 (0.60-1.00)	0.053
	>=21%	0.82 (0.59-1.13)	0.226
	Missing		
Facility Type	Comprehensive Community Program	-	-
	Community Program	0.59 (0.45-0.77)	<.001
	Academic Program	1.70 (1.44-1.99)	<.001
	Missing		
Facility Location	New England	-	-
	Middle Atlantic	0.92 (0.66-1.28)	0.622
	South Atlantic	1.01 (0.74-1.38)	0.929

	East North Central	0.93 (0.68-1.26)	0.63
	East South Central	1.21 (0.81-1.79)	0.355
	West North Central	0.96 (0.69-1.35)	0.822
	West South Central	0.45 (0.29-0.72)	<.001
	Mountain	0.68 (0.45-1.03)	0.068
	Pacific	0.74 (0.52-1.03)	0.077
Great Circle Distance	0) Live <5 Miles	-	-
	1) 5-10 Miles	1.11 (0.89-1.39)	0.364
	2) 10-25 Miles	1.22 (0.99-1.49)	0.062
	3) 25+ Miles	2.41 (1.95-2.97)	<.001
Charlson-Deyo Comorbidity Score	0	-	-
	1	1.03 (0.85-1.24)	0.764
	2+	0.59 (0.42-0.83)	0.002
Year of Diagnosis	0) 2003-2005	-	-
	1) 2006-2008	1.21 (0.99-1.48)	0.069
	2) 2009-2011	1.14 (0.94-1.37)	0.193
Primary Site	Lower third	-	-
	Middle third	0.63 (0.50-0.79)	<.001
	Upper third	0.23 (0.14-0.39)	<.001
	Overlapping lesion of esophagus	0.78 (0.53-1.14)	0.205
	Esophagus, NOS	0.75 (0.53-1.07)	0.112
Grade / Differentiation	Well differentiated	-	-
	Intermediate, Moderate	1.04 (0.75-1.43)	0.82
	Poor / Undifferentiated / anaplastic	1.04 (0.75-1.43)	0.825
	Missing		
Histology	Adenocarcinoma	-	-
	Squamous Cell	0.50 (0.40-0.61)	<.001
	Mixed adeno/squamous	0.81 (0.38-1.73)	0.582
AJCC Clinical Stage Group	Clinical Stage 2	-	-
	Clinical Stage 3	0.82 (0.71-0.95)	0.009

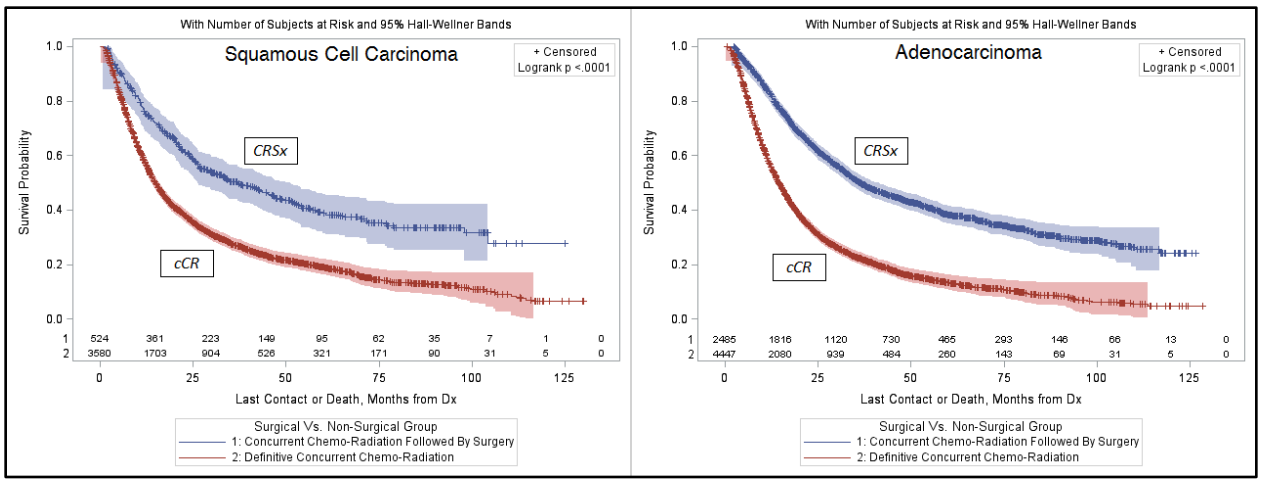
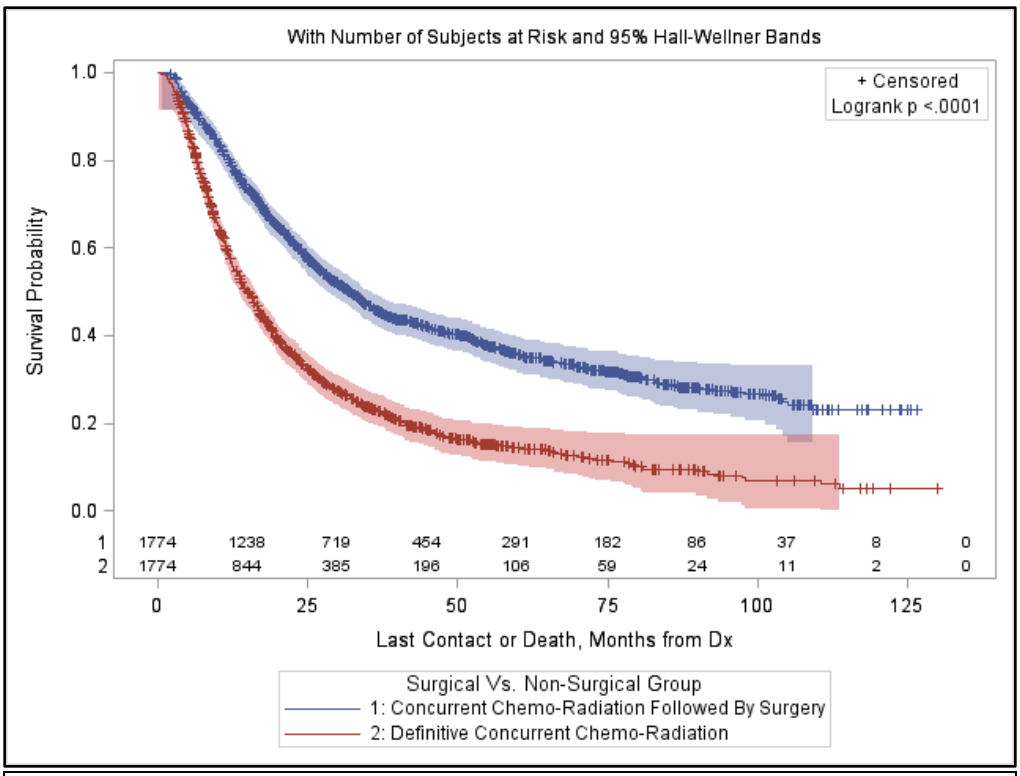

With Number of Subjects at Risk and 95% Hall-Wellner Bands
Squamous Cell Carcinoma
+ Censored
Logrank p <.0001
CRSx
cCR
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1 524 361 223 149 95 62 35 7 1 0
2 3580 1703 904 526 321 171 90 31 5 0
0 25 50 75 100 125
Last Contact or Death, Months from Dx
Surgical Vs. Non-Surgical Group
1: Concurrent Chemo-Radiation Followed By Surgery
2: Definitive Concurrent Chemo-Radiation
With Number of Subjects at Risk and 95% Hall-Wellner Bands
Adenocarcinoma
+ Censored
Logrank p <.0001
CRSx
cCR
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1 2485 1816 1120 730 465 293 146 66 13 0
2 4447 2080 939 484 260 143 69 31 5 0
0 25 50 75 100 125
Last Contact or Death, Months from Dx
Surgical Vs. Non-Surgical Group
1: Concurrent Chemo-Radiation Followed By Surgery
2: Definitive Concurrent Chemo-Radiation

Figure 2: Kaplan Meier Survival Curves Comparing Patients Treated with Chemo-radiation Followed by Surgery (CRSx) and Those Managed with Concurrent Chemo-radiation Alone (cCR), Stratified on Carcinoma Histologic Type (Left: Squamous Cell Carcinoma; Right: Adenocarcinoma

Table 3: Multivariable Extended Cox Proportional Hazards Analysis Assessing Factors Associated with Overall Survival

Variables	Categories	Hazard Ratio (95% CI)	P-value
Non-Surgical vs. Surgical Group	cCR	-	-
	CRSx	0.66 (0.45-0.97)	0.034
Age Group	Less than 50 years	-	-
	50-60 years	1.03 (0.93-1.15)	0.53
	60-70 years	1.02 (0.92-1.13)	0.726
	More than 70 years	1.24 (1.11-1.38)	<.001
Sex	Male	-	-
	Female	0.89 (0.83-0.95)	<.001
Race	Non-Hispanic White	-	-
	Non-Hispanic Black	1.06 (0.96-1.17)	0.249
	Hispanic	0.84 (0.71-0.99)	0.037
	Others	0.84 (0.70-1.02)	0.076
	Missing		
Insurance	Private Insurance	-	-
	Government	1.27 (1.19-1.36)	<.001
	Not Insured	1.34 (1.16-1.56)	<.001
	Missing		
Median Income Quartiles 2008-2012	<$38,000	-	-
	$38,000-$47,999	0.99 (0.91-1.07)	0.75
	$48,000-$62,999	0.98 (0.89-1.07)	0.654
	$63,000 +	0.94 (0.85-1.05)	0.286
	Missing		
Percent No High School Degree 2008-2012	<7%	-	-
	7.0-12.9%	1.06 (0.98-1.15)	0.128
	13-20%	1.07 (0.97-1.18)	0.16
	>=21%	1.11 (0.99-1.25)	0.068
	Missing		
Facility Type	Comprehensive Community Program	-	-
	Community Program	1.01 (0.93-1.10)	0.792
	Academic Program	0.87 (0.82-0.93)	<.001
	Missing		

Facility Location	New England	-	-
	Middle Atlantic	0.98 (0.87-1.10)	0.732
	South Atlantic	1.00 (0.90-1.12)	0.975
	East North Central	1.08 (0.97-1.21)	0.144
	East South Central	1.17 (1.02-1.35)	0.027
	West North Central	1.01 (0.89-1.15)	0.825
	West South Central	1.06 (0.91-1.22)	0.475
	Mountain	1.18 (1.01-1.37)	0.038
	Pacific	0.92 (0.82-1.05)	0.218
Great Circle Distance	0) Live <5 Miles	-	-
	1) 5-10 Miles	0.95 (0.88-1.02)	0.15
	2) 10-25 Miles	0.93 (0.87-1.00)	0.067
	3) 25+ Miles	0.90 (0.83-0.97)	0.007
Charlson-Deyo Comorbidity Score	0	-	-
	1	1.12 (1.05-1.20)	0.001
	2+	1.31 (1.17-1.47)	<.001
Year of Diagnosis	0) 2003-2005	-	-
	1) 2006-2008	0.91 (0.85-0.97)	0.003
	2) 2009-2011	0.89 (0.83-0.95)	<.001
Primary Site	Lower third	-	-
	Middle third	1.12 (1.03-1.21)	0.006
	Upper third	0.93 (0.81-1.05)	0.234
	Overlapping lesion of esophagus	1.15 (1.01-1.30)	0.032
	Esophagus, NOS	1.13 (1.02-1.26)	0.022
Grade / Differentiation	Well differentiated	-	-
	Intermediate, Moderate	1.18 (1.04-1.33)	0.008
	Poor / Undifferentiated / anaplastic	1.35 (1.20-1.52)	<.001
	Missing		
Histology	Adenocarcinoma	-	-
	Squamous Cell	1.04 (0.96-1.12)	0.315
	Mixed adeno/squamous	1.18 (0.89-1.56)	0.251
AJCC Clinical Stage Group	Clinical Stage 2	-	-
	Clinical Stage 3	1.32 (1.25-1.39)	<.001



Variables	Categories	N	HR (95% CI)	P-value
Non-Surgical Vs. Surgical Group	cCR	1774	-	-
	CRSx	1774	0.50 (0.46-0.54)	<.001

Figure 4: Adjusted Kaplan Meier Survival Curves Comparing Patients Treated with Chemo-radiation Followed by Surgery (CRSx) and Those Managed with Concurrent Chemo-radiation Alone (cCR) After Propensity Score Matching