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Research Article

The Effect of Treatment Facility, Race, and Chemoradiation on Survival for Signet Ring Cell Carcinoma of the Esophagus: An Analysis of the National Cancer Database

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ABSTRACT

Background: Signet ring cell carcinoma of the esophagus (SRCCE) is an aggressive tumor that represents approximately 3.5-5.0% of all esophageal cancers. Prior studies have shown a strong correlation between treating facility and survival for different cancers, but this has not been studied in SRCCE. The goal of this study is to assess differences in survival based on the type of treatment facility.

Methods: There were 2,021 patients with SRCCE identified using the histology 8490 and topography codes C15.0-C15.9 in the National Cancer Database (NCDB). Descriptive analysis, Kaplan-Meier curves, and a multivariable Cox hazard regression analysis were all utilized to determine the significance of treatment facility type and other variables.

Results: The cohort mostly received treatment at academic centers (47.7%). As age increased, mortality also increased (HR=1.01; 95% CI:1.01-1.02, $p<0.001$). African Americans (HR=1.44; 95% CI:1.02-2.02, $p=0.036$) had an increased risk of mortality when compared to Non-Hispanic Caucasians. Patients at academic facilities demonstrated a decreased risk of mortality when compared to community programmes (HR=0.73; 95% CI:0.64-0.84, $p<0.001$) and integrated cancer programmes (HR=0.69; 95% CI:0.58-0.83, $p=0.008$). Neoadjuvant chemoradiation resulted decreased mortality when compared to adjuvant chemoradiation (HR=1.41; 95% CI:1.21-1.63, $p<0.001$) and no chemoradiation (HR=1.84; 95% CI:1.58-2.14, $p<0.001$).

Conclusion: For patients diagnosed with SRCCE, receiving treatment at academic centers resulted in better survival probabilities compared to nonacademic facilities. Older patients, African Americans, increasing tumor stage, no and adjuvant chemoradiation, and comorbidities with Charlson-Deyo scores of 1 and 2+ were all associated with an increased risk of mortality from SRCCE.

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Introduction

Squamous cell carcinomas are the most common esophageal carcinomas, however the incidence of adenocarcinoma of the esophagus is steadily increasing in the United States [1]. Signet ring cell carcinoma (SRCC), a subset of adenocarcinoma, originates in mucin producing

glandular cells that resemble signet rings, hence its name. The World Health Organization defines SRCC when greater than 50% of malignant tumor cells contain cytoplasmic mucins [2]. This variant characteristically has cytoplasmic mucin and an eccentric nucleus in the periphery [3]. Signet ring adenocarcinoma presents in a variety of different primary sites in the gastrointestinal and genitourinary systems including the colon, rectum, and the urethra [4-6].

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Signet ring cell carcinoma of the esophagus (SRCCE) is a relatively rare cancer accounting for only 3.5-5% of all esophageal cancers. This cancer has a much poorer prognosis than other forms of esophageal carcinoma, with 1- and 5-year cancer specific survivals estimated at 48.4% and 21.6%, respectively [7]. It has been previously reported that patients with SRCCE present with a higher grade and a higher stage at diagnosis [8]. Predictors of increased disease-specific mortalities for SRCCE include being unmarried, tumor size > 5 cm, higher tumor grade, invasion of adjacent organs, regional lymph node metastasis, distant metastasis, and no chemotherapy [9]. Previous studies have shown a strong correlation between type of treatment facility and survival for different cancers, but the effect of treatment facility on survival has not been studied in SRCCE [10-13]. The goal for this study is to assess any difference in survival based on treatment facility type and race. An additional goal is to further quantify the most accurate prognostic data for patients with SRCCE.

Methods

Data from 2004-2016 was abstracted from the National Cancer Database (NCDB) for this study. The NCDB is a data bank composed of patient information from a total of more than 1,500 Commission on Cancer accredited facilities in the United States. The NCDB was formed as a joint venture between the American Cancer Society and American College of Surgeons encompassing approximately 70% of all new cases of cancer in the United States. Our data was acquired through the NCDB Participant Use Data Files programme.

Patients were identified using the ICD-O-3 histology code 8490 corresponding to patients with SRCCE. Patients with any missing data, secondary tumors, and primary anatomical sites outside the esophagus (sites other than ICD-O-3 topography codes C15.0, C15.1, C15.2, C15.3, C15.4, C15.5, C15.8, C15.9) were excluded from this study. Descriptive analysis was performed for multiple variables including sex, age, race, type of treatment facility, Charlson-Deyo score, tumor stage, treatment received, and use of neoadjuvant and adjuvant chemoradiation. Age was separated into 4 categories: 0-50, 51-70, 71-90, and 90+ years. Race was stratified into Non-Hispanic Caucasian, African American, Hispanic Caucasian and other. Treatment facility was divided into community, academic and integrated cancer programmes. Community cancer programmes are defined as less than 500 newly diagnosed cancer cases every year, while Academic facilities have more than 500 diagnosed cancer cases and participate in postgraduate medical education. Integrated cancer programmes contain at least one hospital, sometimes more, and are characterized by having a unified cancer committee, a uniform data repository and coordinated practitioners. Tumor stage was determined utilizing the NCDB analytical stage variables. This accounts for the pathologic stage and if the pathologic stage was not available, the clinical stage was utilized.

This study utilized Kaplan-Meier curves and life tables to estimate both the 1- and 5-year survival for the variables listed above. To determine the significance of 1- and 5-year survival probabilities, log-rank analysis was performed for each Kaplan-Meier curve. Further, a Cox proportional hazards regression model was used to examine survival associated with the variables listed above after adjusting for potential confounders. We investigated the functional form of continuous variables with plots of Martingale residuals, and a check for proportionality of hazards was

conducted with log-negative-log survival plots as well as the creation of time dependent coefficients to determine if there was an interaction with time for each variable of interest. We accommodated the clustering of patients within a facility with the computation of the robust sandwich covariance estimate. All of these analyses were conducted utilizing SPSS version 26 (IBM Corporation, Armonk, NY) and SAS 9.4 (SAS Institute Inc., Cary, NC) with a statistical threshold of $p < 0.05$.

Results

Epidemiology data for 2,021 patients with SRCCE is presented in (Table 1). The vast majority were male (86.3%). Approximately 61% of the patients were between the age of 51-70 years, with a median age of 64 years. The cohort was overwhelmingly Non-Hispanic Caucasian at 95.7%, followed by African Americans at 2.3%, other races at 1.6% and Hispanic Caucasian at 0.3%. They were most commonly treated at academic facilities (47.7%) followed by community programmes (39.9%) and integrated cancer programmes (12.5%). The majority of the cohort (72.3%) had no comorbid conditions signified by a Charlson-Deyo Score of 0, followed by 19.5% with a score of 1 and 8.1% with a score of 2+.

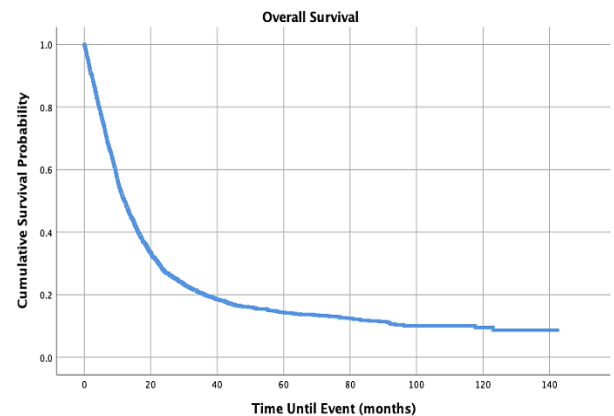
Table 1: Data on epidemiology for 2,021 SRCCE patients.

Variable	N = 2,021	% of total
Sex		
Female	276	13.7
Male	1745	86.3
Age (years)		
0-50	198	9.8
51-70	1227	60.7
71-90	565	28.0
90+	31	1.5
Race		
Non-Hispanic Caucasian	1935	95.7
African American	47	2.3
Hispanic Caucasian	6	0.3
Other	33	1.6
Treatment Facility		
Community	806	39.9
Academic	963	47.7
Integrated Cancer Programme	252	12.5
Charlson-Deyo Score		
0	1462	72.3
1	395	19.5
2+	164	8.1

Clinical factors including tumor and treatment characteristics are presented in (Table 2). These factors included advanced lesions at presentation, with 33.8% at stage III followed closely by stage IV (33.5%), stage II (22.5%), and stage I (10.1%). Chemotherapy was utilized in 78.8% of cases, while radiation was utilized in 44.2%. Furthermore, 776 patients were treated with adjuvant chemoradiation, while 479 received neoadjuvant chemoradiation.

Table 2: Tumor and treatment characteristics for 2,021 SRCCE patients.

Variable	N = 2,021	% of Total
Stage		
Stage I	205	10.1
Stage II	455	22.5
Stage III	684	33.8
Stage IV	677	33.5
Chemoradiation Therapy		
No Chemoradiation	766	37.9
Adjuvant Chemoradiation	776	38.4
Neoadjuvant Chemoradiation	479	23.7
Treatment		
Surgery	714	35.3
Radiation	1371	67.8
Chemotherapy	1592	78.8

**Figure 1:** Overall survival for 2,021 SRCCE patients.**Table 3:** 1- and 5-year survival probabilities and median survival for 2,021 SRCCE patients.

Variable	Probability of 1-Year Survival (%)	Probability of 5-Year Survival (%)	Median Survival (months)
Overall Survival	50.3	14.4	12.1±0.4
Sex			
Male	51.0	14.5	12.3±0.5
Female	46.0	13.6	10.7±0.8
Age (years)			
0-50	55.3	15.5	13.6±1.3
51-70	51.7	16.0	12.8±0.6
71-90	46.6	11.5	10.7±0.7
90+	19.4	0.0	4.2±0.5
Race			
Non-Hispanic Caucasian	50.5	19.1	12.2±0.4
African American	32.3	3.5	7.5±1.1
Hispanic Caucasian	50.0	0.0	12.3±7.4
Other	48.5	15.6	11.1±5.1
Treatment Facility			
Community	44.6	10.2	10.2±0.5
Academic	56.6	18.8	15.2±0.8
Integrated Cancer Programme	44.4	11.0	10.2±0.6
Charlson-Deyo Score			
0	51.3	15.7	12.5±0.5
1	49.1	12.2	11.8±0.9
2+	44.1	7.9	10.6±1.0
Stage			
Stage I	75.1	39.2	35.6±6.7
Stage II	70.5	23.4	20.2±1.6
Stage III	57.9	13.1	14.8±0.7
Stage IV	21.4	2.5	5.9±0.3
Chemoradiation Therapy			
No Chemoradiation Therapy	34.8	7.3	7.0±0.5
Adjuvant Chemoradiation	48.6	7.1	11.5±0.5
Neoadjuvant Chemoradiation	77.4	17.0	24.0±1.8

Both 1- and 5-year survival probabilities and median survival are presented in (Table 3). Kaplan-Meier curves for overall survival, race, facility type and chemoradiation therapy are displayed in (Figures 1-4). The overall 1- and 5- year survivals were 50.3% and 14.4%, respectively. Male patients showed slightly better survival probabilities compared to females (51.0% to 46.0% and 14.5% to 13.6% for 1- and 5-year

survivals). As age increased, overall survival markedly decreased. Hispanic Caucasian patients demonstrated the best survival probability with a 12.3 ± 7.4 -month median survival followed by Non-Hispanic Caucasians at 12.2 ± 0.4 months, other races at 11.1 ± 5.1 months, and African Americans at 7.5 ± 1.1 months. Patients receiving treatment at academic facilities demonstrated the best 1- and 5-year survival

probabilities (56.6% and 18.8%), compared to integrated cancer programmes (44.4% and 11.0%) and community programmes (44.6% and 10.2%). As tumor stage increased, overall survival markedly worsened, with stage IV disease culminating in 1- and 5-year survival probabilities of 21.4% and 2.5%. No chemoradiation therapy resulted in a median survival of 7.0 ± 0.5 months, which was a full year less compared to 11.5 ± 0.5 and 24.0 ± 1.8 months for adjuvant and neoadjuvant chemoradiation, respectively.

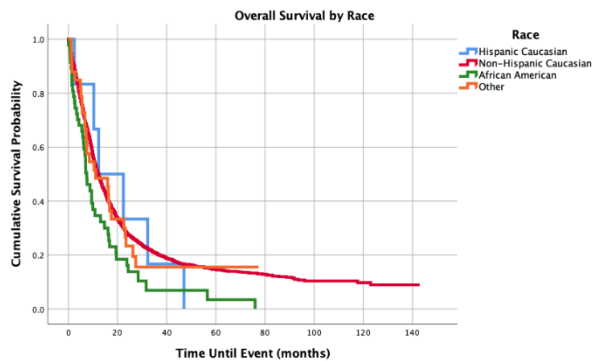


Figure 2: Overall survival by race for 2,021 SRCCE patients, $p=0.021$.

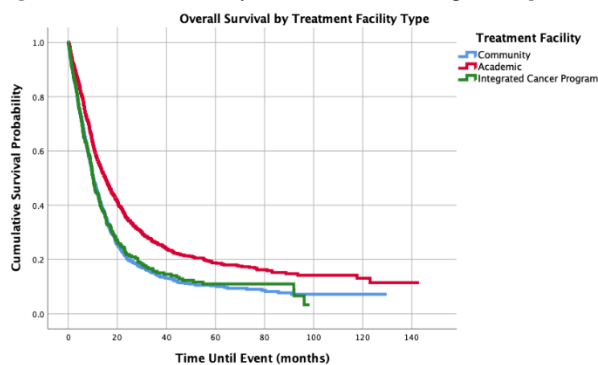


Figure 3: Overall survival by facility type for 2,021 SRCCE patients, $p<0.0005$.

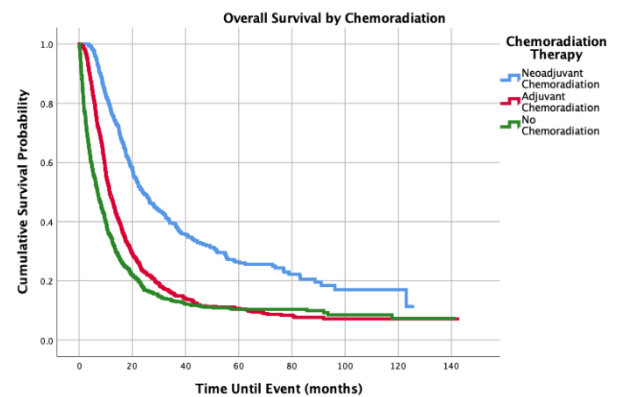


Figure 4: Overall survival by chemoradiation therapy for 2,021 SRCCE patients, $p<0.0005$.

The results of the multivariable analysis are displayed in (Table 4). For each year that age increased, there was an increased risk of mortality (HR = 1.01; 95% CI: 1.01-1.02, $p < 0.001$). When compared to non-Hispanic Caucasians, Africans Americans (HR = 1.44; 95% CI: 1.02-2.02, $p = 0.036$) had a higher risk of death. Patients receiving treatment at academic facilities had a decreased risk of death when compared to community (HR = 0.73; 95% CI: 0.64-0.84, $p < 0.001$) and integrated cancer programmes (HR = 0.69; 95% CI: 0.58-0.83, $p = 0.008$). In a comparison to stage I, stage II disease (HR = 1.76; 95% CI: 1.40-2.20, $p < 0.001$), stage III disease (HR = 2.48; 95% CI: 2.01-3.05, $p < 0.001$), and stage IV disease (HR = 5.33; 95% CI: 4.25-6.69, $p < 0.001$) all were associated with increased risk of death. When compared to a Charlson-Deyo Score of 0, scores of both 1 (HR = 1.27; 95% CI: 1.11-1.46, $p = 0.001$) and 2+ (HR = 1.46; 95% CI: 1.23-1.74, $p < 0.001$) had an increased risk of death. When compared to neoadjuvant chemoradiation, both no chemoradiation (HR = 1.84; 95% CI: 1.58-2.14, $p < 0.001$) and adjuvant chemoradiation (HR = 1.41; 95% CI: 1.21-1.63, $p < 0.001$) were associated with increased risk of death.

Table 4: Multivariable cox hazard regression for the SRCCE patients.

Variables	Hazard Ratio (Confidence Interval)	P-value
Age		
One Year Increments	1.01 (1.01-1.02)	< 0.001
Biological Sex		
Males vs. Females	1.04 (0.89-1.23)	0.771
Race and Ethnicity		
Hispanic Caucasian vs. Non-Hispanic Caucasian	1.24 (0.91-1.67)	0.169
African American vs. Non-Hispanic Caucasian	1.44 (1.02-2.02)	0.036
Other vs. Non-Hispanic Caucasian	0.97 (0.65-1.43)	0.870
Hispanic Caucasian vs. African American	0.86 (0.55-1.35)	0.509
Hispanic Caucasian vs. Other	1.28 (0.80-2.05)	0.311
African America vs. Other	1.49 (0.90-2.46)	0.123
Facility Type		
Community vs Integrated Cancer Programme	0.95 (0.81-1.11)	0.506
Academic vs Integrated Cancer Programme	0.69 (0.58-0.83)	< 0.001
Community vs Academic	0.73 (0.64-0.84)	< 0.001
Charlson-Deyo Score		
1 vs. 0 Charlson/Deyo Score	1.27 (1.11-1.46)	0.001

2+ vs. 0 Charlson/Deyo Score	1.46 (1.23-1.74)	<0.001
2+ vs. 1 Charlson/Deyo Score	1.15 (0.95-1.39)	0.162
Analytical Stage		
Stage II vs. Stage I	1.76 (1.40-2.20)	< 0.001
Stage III vs. Stage I	2.48 (2.01-3.05)	< 0.001
Stage IV vs. Stage I	5.33 (4.25-6.69)	< 0.001
Stage III vs. Stage II	1.41 (1.24-1.60)	< 0.001
Stage IV vs. Stage II	3.03 (2.59-3.56)	< 0.001
Stage IV vs. Stage III	2.15 (1.87-2.47)	< 0.001
Treatment		
Adjuvant Chemoradiation vs Neoadjuvant Chemoradiation	1.41 (1.21-1.63)	< 0.001
No Chemoradiation vs. Neoadjuvant Chemoradiation	1.84 (1.58-2.14)	< 0.001
Adjuvant Chemoradiation vs No Chemoradiation	0.76 (0.67-0.87)	< 0.001

Discussion

This is the largest study to date analysing prognostic factors for signet ring esophageal adenocarcinoma. For cancer patients, prognosis is important in both decision making and patient management, determining how to best treat each patient [14]. This study provides clinicians and patients with important information to guide treatment and other decisions, including palliative care and hospice [15]. There was a very large male predominance of 86.3% of patients diagnosed with SRCCE, although multivariable analysis demonstrated sex was not a significant variable regarding survival. These findings were similar to a Surveillance, Epidemiology, and End Results (SEER) database study, which had a cohort composed of 85.8% male patients and determined that despite the male predominance, sex was not a significant prognostic variable [9]. Two other previous studies showed a male predominance of 85.3% and 93.7% [2, 16]. In Wan's large study, the mean age at diagnosis was 67.2 years, slightly older than our mean age of 64.9 [9]. The previous SEER study determined that age was not a significant variable (HR = 0.994; 95% CI: 0.988-1.001, $p = 0.121$), however, our much larger study confirms age as an important prognostic variable, with a 1% increased risk of death for every additional year of age (HR = 1.01; 95% CI: 1.01-1.02, $p < 0.001$) [9].

Approximately 95.7% of patients were Non-Hispanic Caucasian, similar to the prior SEER studies at 94.1%. A previous SEER study of both adenocarcinoma (11,229 patients) and with a much smaller proportion of signet ring carcinoma of the esophagus (596 patients), reported that African American patients had significantly worse outcomes (HR = 1.17; 95% CI: 1.02-1.35) when compared to Caucasian patients [8]. When African Americans and patients of other races were compared in a cohort of only signet ring carcinoma, no statistically significant difference in survival was reported [9]. Our larger study demonstrated that African American patients had a 44% increased risk of mortality when compared to Caucasian patients. This is particularly striking given the overwhelming prevalence in the Caucasian population (95.7%) which demonstrates the best survival probabilities. This is the first study to determine that race is an important independent variable for SRCCE.

Prior large studies on signet ring carcinoma did not evaluate or control for comorbidities. This study utilized the Charlson-Deyo Comorbidity index and found that it was an accurate and independent prognostic variable in survival. When comparing scores of both 2+ and 1 to 0, there was a 46% and 27% increased risk of mortality, respectively. The

Charlson-Deyo Comorbidity index was originally created in 1992 as a way to quantify and control for comorbidities. Since then, it has demonstrated comorbidities are important prognostic variables in multiple different cancers [17-20]. It has been shown in previous studies that the treatment facility affects survival outcomes for many different cancers [10-13]. This topic has never been studied in SRCCE or in any subtype of esophageal carcinoma. The majority of patients were treated at academic centers (47.7%), followed by community (39.9%) and integrated cancer programmes (12.5%). Treatment received at academic programmes had a 27% and 31% decreased risk of mortality when compared to integrated and community cancer programmes, respectively. This is the first study to conclusively demonstrate that treatment facility type affects survival in patients with SRCCE.

A prior SEER study reported 1- and 5-year disease specific survivals of 48.4% and 21.6%, respectively [9]. This study found similar 1- and 5-year survivals of 50.3% and 14.4%, respectively. As seen in other previous studies, as the tumor stage increased, overall mortality also increased [9, 16]. Since these are usually advanced lesions at presentation (67.4% at stage III or IV in this study), the decreased survival statistics with increased stage explain the poor prognosis of this tumor. Neoadjuvant chemoradiation is typically utilized in aggressive gastric and gastroesophageal junction adenocarcinomas. Patients with signet ring adenocarcinoma have been found to be less responsive to chemoradiation when compared to adenocarcinoma without signet rings [21-23]. Neoadjuvant chemoradiation has not been compared to adjuvant chemoradiation in any prior studies. This study confirmed the advantages of neoadjuvant chemoradiation showing a 41% and 84% decreased risk of mortality when compared to both adjuvant chemoradiation and no chemoradiation.

The most significant limitation to this study is the retrospective design. This inherent limitation prevents controlling and characterizing the variables further. The NCDB reports all-cause mortality and not cancer specific mortality, so this study may not accurately estimate the true survival estimates. This risk is potentially minimized by the large cohort size and the high lethality of SRCCE. The database relies on entries from patient charts and there is a risk that information can be inaccurately entered into the database. Selection bias is unavoidable with this study due to the NCDB only pulling patients from CoC-accredited cancer programmes. This bias is minimized, however, since CoC-accredited facilities encompass around 70% of all newly diagnosed cancers in the United States.

Conclusion

In the largest study to date on signet ring cell carcinoma of the esophagus, treatment facility was determined to be an important variable for prognosis. Patients receiving treatment at academic centers had significantly better rates of survival when compared to both community and integrated cancer programmes. Older patients, African Americans, patients with comorbidities demonstrated by Charlson-Deyo scores of 1 and 2+, increasing tumor stage, and no or adjuvant chemoradiation were all associated with an increased risk of mortality from SRCCE.

Conflicts of Interest

None.

Funding

None.

Ethical Approval

Creighton University Biomedical IRB (project number: 2000552) waived the need for ethical approval. As the data file contained de identified data, formal consent was not necessary.

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