Esophageal Cancer Presentation, Treatment, and Outcomes Vary With Hospital Safety-Net Burden

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Background. Social determinants of health affect diagnosis and delivery of care to patients with esophageal cancer. This study hypothesized that hospital safety-net burden affects presentation, treatment, and outcomes in patients with esophageal cancer.

Methods. The National Cancer Database was queried for patients with esophageal cancer (2004 to 2013). Treating facilities were categorized according to their relative burden of uninsured or Medicaid-insured patients. Hospitals with low (LBH), medium (MBH), and high (HBH) safety-net burden were compared with respect to patient demographics, disease and treatment characteristics, and survival using χ² analysis, Kaplan-Meier survival analysis, and multivariable modeling.

Results. There were 56,115 patients from 1,215 facilities. HBH treated a greater proportion of racial and ethnic minorities and patients with lower socioeconomic status. Patients at HBH presented at later stages and received primary surgical therapy less often than at MBH and LBH. Survival for patients with esophageal adenocarcinoma did not differ significantly between HBH and LBH after adjusting for age, sex, race, ethnicity, income, comorbidity, stage, histologic type, tumor location, facility type, insurance status, and treatment modality (hazard ratio, 1.06; 95% confidence interval, 0.99 to 1.14; p = 0.093). HBH were associated with a higher mortality risk than LBH for patients with squamous cell carcinoma (hazard ratio, 1.11; 95% confidence interval, 1.02 to 1.20; p = 0.014).

Conclusions. There is a mortality risk for patients with squamous cell carcinoma, but not for adenocarcinoma at HBH compared with LBH. Further analysis of unadjusted variables such as performance status, completion of therapy, and continuity of care, and others should be undertaken among safety-net hospitals with the goal of creating appropriate clinical pathways for care of esophageal cancer in vulnerable populations.


Despite advances in cancer therapy, esophageal cancer continues to carry a poor prognosis. The 5-year estimated survival is less than 20%, and it is estimated that there were approximately 17,000 new cases of esophageal cancer in the United States in 2018. Up to 40% of these patients will have presented with metastatic disease [1, 2], whereas patients with stages I to III of esophageal cancer may have been treated with curative intent with surgical resection or multimodality therapy [3, 4].

The need for multidisciplinary care for esophageal cancer opens avenues for disparity in stage of presentation, delivery of care, and outcomes among vulnerable patient populations. Consequently, there have been several studies examining the roles of race, ethnicity, and socioeconomic status on the use of surgery, perioperative therapy, and survival of patients with esophageal cancer [5–17]. These studies have shown that black race, Hispanic ethnicity, and low socioeconomic standing are associated with decreased curative therapy and increased mortality compared with their counterparts [5–17].

Safety-net hospitals are categorized by the relative burden of uninsured and Medicaid patients. Although the impact of safety-net status on the use of multimodality therapy and survival has been studied in patients with pancreatic, rectal, and head and neck cancers, the extent to which relationships have been explored in esophageal cancer has been limited [18–23]. Given the existing disparities in presentation, treatment, and

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outcomes evinced in previous population-based studies, we sought to describe the relationship between hospital safety-net burden and the nature of presentation, modalities of therapy, and survival of patients with esophageal cancer by using a large cancer database.

**Patients and Methods**

**Data Source**

Raw data for this study were obtained through Participant User Files (PUF) from the American College of Surgeons National Cancer Database (NCDB). The NCDB is a data set consisting of deidentified tumor registry data from Commission on Cancer–accredited institutions. Data are collected from approximately 1,500 accredited facilities, representing nearly 70% of newly diagnosed cancer cases in the United States. Clinical and pathologic oncologic information from diagnosis, staging, treatment course, and follow-up are collected and available for analysis. Institutional Review Board approval was waived because only deidentified data were used.

**Study Population**

All patients with a diagnosis of esophageal cancer were queried using PUF files. Using the International Classification of Diseases for Oncology (third edition) (ICD-O-3), 116,769 patients diagnosed with esophageal cancer (C15.0 to C15.9) between 2004 and 2013 were identified. Further selection of eligible patients is outlined in Figure 1. Analysis of demographics, nature of presentation, treatment characteristics, and survival was performed.

**Data Collection**

Demographic information collected included age, sex, race, ethnicity, primary insurance status, median household income (median household income for patient Zip Code from United States Census data), rurality, and distance to treatment facility. Patient comorbidities were collected using the abbreviated Charlson-Deyo comorbidity score (CDS) and were categorized as 0, 1, or 2+.

Tumor characteristics, including American Joint Committee on Cancer (AJCC sixth edition, 2004 to 2009; AJCC seventh edition, 2010 to 2013) clinical stage (I to IV), tumor histology, and tumor location, were collected. Treatment characteristics included the treatment facility type and modality of therapy.

**Hospital Safety-Net Burden**

The safety-net burden of treating hospitals was used as the primary independent variable in this analysis. Facilities were categorized by the percentage of uninsured or Medicaid-insured patients treated and placed into quartiles according to the relative burden of uninsured or Medicaid-insured patients. Low safety-net burden hospitals (LBH) treated the lowest quartile, medium safety-net burden hospitals (MBH) treated between the 25th and 75th percentiles, and high safety-net burden hospitals (HBH) treated the highest quartile of uninsured or Medicaid-insured patients. This categorization has been described in several previous studies to assess the impact of hospital safety-net status on patient care [18–22].

**Statistical Analysis**

LBH, MBH, and HBH cohorts were compared on the basis of patient-related, tumor, and treatment characteristics. Categorical dependent variables were compared using $\chi^2$ tests. The nonparametric Mann-Whitney test was used to assess for continuous variables. Median, 3-year, and 5-year actuarial overall survival rates were determined by the Kaplan-Meier method. The comparison of rates among the groups was performed using the two-tailed log rank test. Stage-specific median survival and actuarial overall survival were compared.

Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using Cox regression modeling, using LBH as a reference.

Clustering of patients within facilities was accounted for by consideration of robust sandwich covariance matrix estimates [24]. The following a priori variables were included in our multivariable model: age, sex, race, Spanish or Hispanic origin, median household income, CDS, AJCC stage, histologic type, site, facility type, treatment modality, and insurance status. Statistical computations were performed on SAS 9.3 system (SAS Institute, Cary, NC) or GraphPad prism software (version 3.0, GraphPad Software). All tests were two-sided, and a $p$ value of $<0.05$ was considered statistically significant.

**Results**

The study population included 56,115 patients from 1,215 facilities treated from 2004 to 2013. There were 306, 605, and 304 hospitals that met the LBH, MBH, and HBH criteria, respectively. The median percentage of uninsured or Medicaid-insured patients treated in hospitals among LBH, MBH, and HBH safety-net tiers was 2.1% (range, 0% to 3.9%), 8.8% (range, 4% to 16%), and 22.7% (range, 16.1% to 100%), respectively (Supplemental Table 1). The distribution of LBH, MBH, and HBH remained comparable throughout the time period studied.

**Patient Characteristics**

Demographic characteristics for the total cohort as well as each tier of safety-net burden are displayed in Table 1. The overall median age of the study population was 64 years (interquartile range, 57 to 73 years). Patients treated at HBH were younger (62 years) compared with MBH (65 years) and LBH (66 years) ($p < 0.0001$). Notably, there was a significantly higher proportion of black patients (21.5% vs 7.2% vs 4.2%; $p < 0.0001$) and Hispanic patients (6.5% vs 2.6% vs 2.7%; $p < 0.0001$) in HBH compared with MBH and LBH, respectively. Because uninsured and Medicaid-insured status was used to derive levels of safety-net burden, the mean of uninsured or Medicaid-insured patients treated within the HBH tier was significantly higher than in the MBH and LBH tiers (27.5% vs 9.2% vs 1.7%; $p < 0.0001$) (Supplemental Table 1). A significantly greater percentage of patients in the HBH tier (27%) were
classified in the lowest quartile of median household income compared with the MBH (11.3%) and LBH (8.1%) tiers ($p < 0.0001$). The burden of comorbidity was similar across all tiers of safety-net burden because 5.7%, 6.2%, and 5.8% of patients had a CDS of 2 or more in LBH, MBH, and HBH, respectively ($p = 0.008$).
Tumor and Treatment Characteristics

A greater percentage of patients within the HBH tier presented with later stages (29.2% stage III; 35.1% stage IV) compared with the MBH (27.3% stage III; 31.7% stage IV) and LBH (27.5% stage III; 31.3% stage IV) levels ($p < 0.0001$) (Table 2). More patients in the HBH category were diagnosed with squamous cell carcinoma compared with MBH and LBH (37.2% vs 24.3% vs 22.2%; $p < 0.0001$), and more patients in LBH (69.8%) and MBH (66.8%) presented with lower third esophageal tumors compared with those in high safety-net burden hospitals (57.2%; $p < 0.0001$).

With respect to treatment modalities, 15.8% of patients underwent surgical treatment alone, 22.7% underwent surgical treatment with perioperative therapy, 14.2% had chemotherapy alone, 8.3% had radiation therapy alone, and 39% had chemoradiation alone (Table 2). Fewer patients with potentially operable disease (stage 0 to III) from HBH underwent surgical treatment with or without perioperative therapy (44.3%), relative to those in LBH (56.9%) and MBH (55.3%; $p < 0.0001$).

Overall Survival

The median follow-up using the reverse Kaplan-Meier method was 61.7 months. The overall 5-year survival rate was 22.2%, and the overall median survival time was 15.9 months. The median survival and 5-year survival rates differed significantly among HBH, MBH, and LBH (13.1 months vs 16.2 months vs 18.1 months; 18.9% vs 22.6% vs 24.2%, respectively; $p < 0.0001$) (Fig 2). On pairwise comparison, survival was similar for MBH and LBH ($p = 0.230$). Results from a univariate stage-specific survival analysis are presented in Supplemental Table 2.

Multivariable Analysis

A multivariable analysis was performed adjusting for a priori selected patient-related, tumor, and treatment characteristics (Table 3). After adjusting for age, sex, race, and other factors, survival was similar for MBH and LBH ($p = 0.230$).
Spanish or Hispanic origin, median household income, CDS, AJCC stage, histologic type, site, facility type, treatment modality, and insurance status, a statistically significant increased risk of mortality was noted for patients treated at HBH (adjusted HR, 1.07; 95% CI, 1.04 to 1.11; \( p = 0.0001 \)) compared with patients treated at LBH. When performing both univariable (HR, 1.17; 95% CI, 0.99 to 1.39; \( p = 0.069 \)) and multivariable (HR, 1.06; 95% CI, 0.99 to 1.14; \( p = 0.093 \)) analysis by histologic type, however, there was no significant mortality risk for patients with adenocarcinoma at HBH relative to LBH. In contrast, there was a greater risk of mortality in patients with squamous cell carcinoma treated at HBH relative to LBH on multivariable analysis (adjusted HR, 1.11; 95% CI, 1.02 to 1.20; \( p = 0.014 \)).

Supplemental Table 3 describes the impact of each component of our multivariable model. There was no mortality risk associated with black race (HR, 1.00; 95% CI, 0.96 to 1.05; \( p = 0.908 \)), and there was a decreased risk of mortality for patients of Hispanic ethnicity (HR, 0.82; 95% CI, 0.77 to 0.88; \( p < 0.0001 \)). A likely driving factor behind the increased risk of mortality for HBH is the independent risk of mortality associated with being uninsured or Medicaid insured (HR 1.27; 95% CI, 1.22 to 1.32; \( p < 0.0001 \)).

Of note, there was a substantial number of patients with missing data in this cohort. After applying exclusion criteria to the initial cohort of 116,769 patients, we identified 16,730 patients with missing information on following covariates: race, ethnicity, income, facility type, rurality, distance to treatment facility, and AJCC stage.

Comment

We have shown that HBH are associated with an increased risk of mortality in patients with esophageal cancer compared with LBH. Disparities in cancer care and outcomes can be attributed to social determinants of health \[5–21, 25–27\]. Specifically, studies using the Nationwide Inpatient Sample, the Surveillance, Epidemiology, and End Results database, and data from the Veteran’s Administration have shown that black race, Hispanic ethnicity, and low socioeconomic status have been associated with decreased use of curative therapy and survival \[5–17\]. Patients at risk for experiencing these disparities often receive care at safety-net hospitals. Many
of these institutions are located closer to vulnerable populations and have developed targeted services to improve delivery of care for these vulnerable populations [25, 28]. It remains to be seen whether treatment and survival disparities are mitigated in HBH, where such services may exist.

Few studies have investigated treatment and outcome disparities in relation to the safety-net burden of the institutions administering care, and these have reported conflicting findings [18–23, 29, 30]. HBH have been the subject of scrutiny with regard to the provision of high-quality complex cancer care and ancillary clinical services, and they have been held accountable for relatively poor immediate postoperative outcomes in esophageal cancer [21, 23]. In contrast, analyses of patients with pancreatic cancer and patients with head and neck cancer did not show any difference in perioperative morbidity and mortality between HBH and LBH despite high burden safety nets having a greater volume of racial minorities, more emergency procedures, and patients with more comorbidities [18, 20].

Importantly, we have shown that HBH are not associated with survival differences in patients with esophageal adenocarcinoma, which is responsible for more than 80% of esophageal cancers in the United States [31]. Additionally, in contrast to previous studies, we did not identify a mortality risk associated with race or ethnicity. We observed that patients presented at a later stage in HBH and that a greater percentage of patients in LBH underwent surgical treatment compared with their counterparts. Although our analysis of stage-specific survival was a univariable, unadjusted analysis, the AJCC stage was a component of our multivariable model. We observed that patients with stage I to III disease in LBH underwent surgical treatment with or without perioperative therapy more often than primary chemotherapy or radiation. Despite these observations, we cannot draw conclusions regarding the comparative use of therapy on the basis of safety net status. Such an investigation was not our focus and was beyond the scope of this study.

A greater proportion of patients with tumors of squamous histologic type were treated at HBH. Adenocarcinoma and squamous cell carcinoma represent distinct entities with different biology, treatment, and outcomes.

Table 3. Univariate and Multivariate Analysis of Overall Survival by Low, Medium, and High Burden Safety-Net Hospitals: Overall and Stratified by Histologic Type

<table>
<thead>
<tr>
<th>Burden</th>
<th>n</th>
<th>Events</th>
<th>Univariable</th>
<th>Multivariablea</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>9,188</td>
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<tr>
<td>Medium</td>
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<tr>
<td>High</td>
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<td>7,807</td>
<td>1.24 (1.06–1.46)</td>
<td>0.008</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>2,035</td>
<td>1,488</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
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<td>6,959</td>
<td>1.12 (0.98–1.26)</td>
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<tr>
<td>High</td>
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<td>1.29 (1.13–1.46)</td>
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<tr>
<td>Low</td>
<td>6,323</td>
<td>4,361</td>
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<tr>
<td>Medium</td>
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<td>17,768</td>
<td>1.06 (0.90–1.25)</td>
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<td>1.17 (0.99–1.39)</td>
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<td>Other histologic type</td>
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<tr>
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<tr>
<td>Medium</td>
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<td>1.02 (0.80–1.29)</td>
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</tr>
<tr>
<td>High</td>
<td>773</td>
<td>621</td>
<td>1.28 (1.01–1.61)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

a Multivariate model includes the following factors: age, sex, race, Spanish or Hispanic origin, median household income, Charlson-Deyo score, American Joint Committee on Cancer stage, histologic type, site, facility type, treatment modality and insurance status. b Multivariate model includes all factors from overall analysis except histologic type.

CI = confidence interval; HR = hazard ratio; Ref = reference.
Interestingly, we have shown an adjusted risk for mortality for patients treated at HBH for squamous cell carcinoma only. HBH were associated with an 11% increase in mortality risk for patients with squamous cell carcinoma versus LBH (p = 0.014). Given that these entities can have different risk factors, associated comorbidities, and treatment algorithms, studies should examine the use, efficacy, and sequence of treatment for squamous cell carcinoma within the HBH population.

Although our findings may suggest that the mortality risk associated with HBH may be attributable to these facilities, the limitations of this analysis should temper this interpretation. Unadjusted and potentially impactful variables related to the HBH, Medicaid-insured, and uninsured populations that could not be ascertained from the NCDB such as performance status, frailty, housing status, immigration status, access to follow-up care, supportive care, and others were not included in our multivariable model. The final population analyzed did not include approximately 20,000 patients with a previous diagnosis of cancer, thereby limiting the generalizability of these results. Additionally, we excluded nearly 17,000 patients with missing covariate data. The inclusion of this cohort could significantly attenuate, and perhaps nullify, the association of mortality with HBH. Although the NCDB provides information regarding overall survival, it does not include cancer-specific survival. Importantly, differences in overall survival at HBH may be attributed at least partially to other comorbidities associated with this population of patients. Additionally, the CDS provided by the NCDB represents a truncated version of the true CDS, thereby clouding the comparison of comorbid conditions across safety-net burden.

Additional studies of care delivered at HBH, among the Medicaid-insured or uninsured population, or among patients with squamous cell carcinoma would yield granular data regarding variables that are not captured in large databases and elucidate specific obstacles impeding complex cancer care at HBH. To illustrate this point, a qualitative study in which patients from vulnerable populations were interviewed identified communication, trust, personal financial difficulty, and health literacy as patient-identified issues that affected the quality of care [12]. To our knowledge, there has not been published literature demonstrating that addressing both patient identified-barriers and other known social determinants of health affects presentation, treatment, and outcomes in esophageal cancer. It is possible that the incorporation of resources such as patient navigators, interpreter services, transportation support, food pantries, and community health networks may further attenuate the differences in survival and use of care observed between HBH and LBH. Safety nets within the HBH tier likely share resource-driven challenges and may find pathways implemented at similar institutions more achievable than those care pathways at lower burden centers.

Conclusion
We analyzed esophageal cancer presentation, treatment, and outcomes at hospitals with varying safety-net burden. The risk of mortality was increased for patients with esophageal squamous cell carcinoma in safety-net hospitals treating a relatively high burden of Medicaid-insured and uninsured patients. Further studies must examine the delivery of care at HBH as well as patient-specific comorbidities and social determinants of health that influence outcomes for patients with esophageal squamous cell cancer.

References