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Prognostic Impact of Socioeconomic Status Compared to Overall Stage for HPV-negative Head and Neck Squamous Cell Carcinoma

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Abstract

Objective: To estimate the relative prognostic ability of socioeconomic status (SES) compared to overall stage for HPV-negative head and neck squamous cell carcinoma (HNSCC)

Materials and Methods: Data were obtained from the Carolina Head and Neck Cancer Epidemiology Study (CHANCE). An empiric 4-category SES classification system was created. Cox proportional hazards models, survival gradients, Bayesian information criterion (BIC), and Harrell's C index were used to estimate the effects of SES and stage on overall survival (OS).

Results: The sample consisted of 1229 patients with HPV-negative HNSCC. Patients with low SES had significantly increased risk of mortality at 5 years compared to patients with high SES (HR 3.11, 95% CI 2.07 to 4.67; $p<0.001$), and the magnitude of effect was greater than for overall stage (HR 3.01, 95% CI 2.35 to 3.86; $p<0.001$ for stage IV versus I). Compared to overall stage, the SES classification system had a larger total survival gradient (35.8% vs. 29.1%), similar model fit (BIC statistic of 7412 and 7388, respectively), and similar model discriminatory

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ability (Harrell's C index of 0.61 and 0.64, respectively). The association between low SES and OS persisted after adjusting for age, sex, race, alcohol, smoking, overall stage, tumor site, and treatment in a multivariable model (HR 2.96, 95% CI 1.92 to 4.56; p<0.001).

Conclusion: SES may have a similar prognostic ability to overall stage for patients with HPV-negative HNSCC. Future research is warranted to validate these findings and identify evidence-based interventions for addressing barriers to care for patients with HNSCC.

Keywords

Socioeconomic factors; head and neck neoplasms; prognosis; survival; neoplasm staging

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) contributes to a significant burden of cancer in the United States, accounting for approximately 65,410 new cases and 14,620 deaths in 2019.[1,2] Overall stage is consistently found to be one of the strongest predictors of mortality in HNSCC, with advanced stage patients having up to three-times the risk of 5-year mortality compared to early stage patients.[3,4] As such, cancer stage is considered to be the gold standard prognostic indicator for HNSCC and is the primary tool used to inform treatment decisions. Despite advancements in treatment, survival for HPV-negative HNSCC has remained relatively poor and unchanged over the past several decades, with 5-year overall survival (OS) estimates around 50-60% based on national database studies.[3,5,6] Research is warranted to identify new evidence-based interventions aimed at reducing this burden of HNSCC in the United States.

One promising but often overlooked target for interventions in HNSCC is socioeconomic status (SES). Low socioeconomic status (SES), as defined by household income, insurance status, and education level, is an established risk factor for poor OS in HNSCC.[7–10,11,12] One study found that compared to patients with other types of cancer, patients with head and neck cancer in the United States have significantly lower socioeconomic status while also incurring higher medical expenses.[13] Low income, lack of insurance, and poor education are associated with HNSCC risk factors such as tobacco and alcohol use,[14,15] and they can plausibly lead to barriers across the continuum of care of head and neck cancer patients. This care continuum extends from the initial diagnosis to treatment to active surveillance and intervention to address treatment-related morbidities as well as patient behaviors that impact health (e.g., tobacco use). Despite this, SES has received considerably less attention than cancer stage as a potential target for interventions aimed at mitigating poor survival outcomes in HNSCC.

Although it is known that low SES is associated with worse OS in HNSCC, the magnitude of this relationship compared to cancer stage, the gold-standard prognostic system, has not been reported. This comparison could be useful for: (1) quantifying the relative impact of SES on HNSCC survival outcomes, (2) identifying patients most at-risk of poor outcomes, and (3) guiding new population and policy interventions to reduce the burden of HNSCC in the United States. To help fill this gap in knowledge, we developed a novel SES

classification system using a population-based cohort of HPV-negative HNSCC patients and compared its prognostic ability to overall stage.

Materials and Methods

Patient Sample

Data for this analysis were obtained from the Carolina Head and Neck Cancer Epidemiology Study (CHANCE); a population-based study in North Carolina. Methods of the CHANCE study are described in detail elsewhere.[16] Briefly, cases were eligible to participate in CHANCE if they had been diagnosed with a first primary squamous cell carcinoma of the oral cavity, pharynx, or larynx between January 1, 2002, and February 28, 2006; were ages 20 to 80 years at diagnosis; and resided in a 46-county region in central North Carolina. Case ascertainment relied on rapid identification of newly diagnosed cancer cases through the North Carolina Central Cancer Registry (NCCCR). The cancer registrars of 54 hospitals in the study area were contacted monthly to identify potentially eligible cases. Potentially eligible study subjects were mailed a brochure describing the purpose of the study, and upon consent, a study nurse conducted an at-home in-person interview. There were 1,381 cases in CHANCE. Cases were excluded from this study if they had a diagnosis of p16-positive oropharyngeal cancer (n=152). This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill, and all study participants provided written informed consent.

Exposure Assessment and Classification

Trained nurse-interviewers used a structured questionnaire during an in-home visit to obtain self-reported demographic and socioeconomic information from the cases. Socioeconomic information included health insurance status, household income category (<$20,000, $20,000 to $50,000, or >$50,000), and level of educational attainment (less than high school, high school graduate, or beyond high school). Cases were interviewed soon after cancer diagnosis (the average time between diagnosis and interview was 5.3 months).[17] Clinical information such as tumor site and treatment was abstracted from medical records and reviewed independently by a pathologist and a head neck cancer surgeon. Tumors were classified by site according to International Classification of Diseases for Oncology, third edition (ICD-O-3).[18] Stage at diagnosis was abstracted from medical records specifying the initial treatment plan. All staging used 7th edition AJCC guidelines as these were in use at the time of data collection. HPV-status was determined with p16 immunohistochemistry using a previously described protocol.[19,20]

An empiric 4-category SES classification system was developed for direct prognostic comparison to the traditional 4-category overall stage classification system (I-IV). The numeric SES classification system was based on tiers of education, income, and insurance status defined in the CHANCE questionnaire. Patients were assigned 2 points for each of the following: <high school education, <$20,000 household income, and no insurance. Patients were assigned 1 point for each of the following: high school graduate (but no school beyond), $20,000 to $50,000 household income, and Medicaid/Medicare/Other insurance. Patients were assigned 0 points for each of the following: education beyond high school,

>$50,000 household income, and private insurance. Patients were classified into an SES category based on their cumulative points for education, income, and insurance with more points representing lower SES: high (0 points), middle high (1-2 points), middle low (3-4 points), and low (5-6 points).

Outcome Measure

The primary outcome of interest was overall survival (OS). Overall survival was calculated from the date of diagnosis to either the date of death due to any cause or censoring at 5 years. CHANCE data were linked to the National Death Index (NDI) based on name, social security number, date of birth, sex, race, and state of residence to identify deaths through December 31, 2013. Disease-specific survival was not examined because the cause of death was not available for the majority of CHANCE patients.

Statistical Analysis

Descriptive statistics were used to examine demographic, clinical, and socioeconomic characteristics of the sample. Bivariate testing methods include Chi-square and two-sided t-tests. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality at 5 years in relation to SES and overall stage classifications. All models were minimally adjusted for demographic variables (age, sex, and race). A multivariable Cox proportional hazards model was used to estimate the independent effect of SES on mortality after adjusting for age, sex, race, alcohol, smoking, overall stage, tumor site, and treatment. Bayesian information criterion (BIC) was used to compare the two classification systems, with a lower BIC representing a better model fit. Harrell's C index was used to compare the discriminatory ability of the two classification systems, with a value closer to 1 representing better model discrimination between categories. Survival gradients were also calculated to compare the two classification systems.[21] These included the total survival gradient (difference in OS between highest and lowest category) as well as survival gradients between each category to assess monotonicity. Kaplan Meier curves were created to compare overall survival for SES and overall stage categories. The log-rank test was used to compare Kaplan Meier curves for dichotomized SES and overall stage categories. A statistical significance criterion of $p<0.05$ was used for all testing. Stata 16.0 (StataCorp LP, College Station, TX) was used for all analyses.

Results

Baseline Characteristics

There were 1229 patients with HPV-negative HNSCC in the sample with a mean age of 59.7 (SD 10.4) years. The majority of patients were male (75.3%) and white (70.4%), and most patients had at least a 10 pack-year smoking history (81.4%) and a history of drinking alcohol (86.0%). There were 544 patients (44.3%) diagnosed with early stage (I or II) HNSCC and 685 patients (55.7%) diagnosed with advanced stage (III or IV) HNSCC.

Baseline characteristics were compared for patients by SES category (Table 1). There were 719 patients (58.5%) with low to middle low SES and 510 patients (41.5%) with middle high to high SES based on the numeric classification system. Compared to patients with

middle high to high SES, patients with low to middle low SES were more likely to be older ($p<0.001$), black ($p<0.001$), diagnosed with advanced stage disease ($p<0.001$), and report at least a 10 pack-year smoking history ($p<0.001$). When further stratified into quartiles by SES category, there was a stepwise increase in tobacco use with decreasing SES. Specifically, 58.7% of high SES, 77.9% of middle high SES, 85.9% of middle low SES, and 90.4% of low SES patients had at least a 10 pack-year smoking history.

5-year OS for SES versus Overall Stage Classification Systems

Patients were categorized into 4 tiers for both SES and overall stage (Table 2). The 5-year OS decreased sequentially for each lower tier of SES: 78.3% for high, 66.7% for middle high, 47.7% for middle low, and 42.5% for low (Table 2 and Figure 1). Compared to patients with high SES, patients with middle high SES had an elevated but non-statistically significant risk of mortality (HR 1.44, 95% CI 0.96 to 2.16; $p=0.078$), and patients with middle low (HR 2.65, 95% CI 1.79 to 3.93; $p<0.001$) and low (HR 3.11, 95% CI 2.07 to 4.67; $p<0.001$) SES had a statistically significant increased risk of mortality at 5 years, adjusted for age, sex, and race.

The 5-year OS decreased sequentially for each tier of overall stage: 73.1% for stage I, 56.8% for stage II, 55.7% for stage III, and 44.0% for stage IV (Table 2 and Figure 2). Compared to patients with stage I disease, patients with stage II (HR 1.77, 95% CI 1.32 to 2.36; $p<0.001$), stage III (HR 2.05, 95% CI 1.52 to 2.77; $p<0.001$), and stage IV (HR 3.01, 95% CI 2.35 to 3.86; $p<0.001$) HNSCC had statistically significantly increased risk of mortality at 5 years, adjusted for age, sex, and race.

Prognostic Impact of SES versus Overall Stage Classification Systems

The prognostic impact of the two classification systems was compared using the total survival gradient, monotonicity, BIC statistic, and Harrell's C index (Table 3). The total survival gradient (difference in OS between highest and lowest category) was 35.8% for the SES classification compared to 29.1% for the Overall Stage classification. There was a similar degree of monotonicity between categories for SES (11.6, 19, 5.2) and Overall Stage (11.7, 1.1, 16.3) classification systems.

The model fit and discriminatory ability of each classification system was similar as determined by the BIC statistic and Harrell's C index, respectively. The SES and Overall Stage classification systems had a BIC statistic of 7412 and 7388, respectively, with a lower number representing better model fit. The SES and Overall Stage classification systems had a Harrell's C index of 0.61 and 0.64, respectively, with a number closer to 1 representing better discriminatory ability.

Prognostic Ability SES Classification System Adjusted for Potential Confounders

A multivariable Cox proportional hazards model was used to assess the prognostic ability of SES after adjusting for age, sex, race, alcohol, smoking, overall stage, tumor site, and treatment (Table 4). Compared to patients with high SES, patients with middle high SES had an elevated but non-statistically significant risk of mortality (HR 1.50, 95% CI 0.98 to 2.30; $p=0.062$), and patients with middle low (HR 2.48, 95% CI 1.63 to 3.77; $p<0.001$) and low

(HR 2.96, 95% CI 1.92 to 4.56; p<0.001) SES had significantly increased risk of mortality at 5 years.

Discussion

This study used an empirical SES classification system to determine the prognostic impact of SES compared to overall stage for HPV-negative HNSCC. Our findings suggest that SES has comparable prognostic ability to overall stage based on parameters such as the total survival gradient (35.8% vs. 29.1%), BIC statistic (7412 and 7388), and Harrell's C index (0.61 and 0.64). It is well established that education, insurance status, and income play a role across the spectrum of cancer care, but this is the first study to directly quantify the prognostic impact of SES compared to overall stage for HNSCC.

In the United States, there has been little improvement in OS for HPV-negative HNSCC over the past several decades. Our data show that patients with low SES have over 3 times the risk of mortality at 5 years compared to patients with high SES, suggesting that SES is a promising target for policy interventions aimed at reducing the burden of HNSCC. In fact, in this cohort, SES appears to be a stronger prognosticator than overall stage (HR 3.01, p<0.001 for stage IV vs. I and HR 3.11, p<0.001 for low vs. high SES), which has traditionally been the focus of new interventions. An important question is whether the association between SES and overall survival is truly driven by differences in education, insurance status, and income, or whether there are confounding variables such as stage and tobacco use. In the adjusted model, patients with low SES still had significantly increased risk of mortality compared to patients with high SES (HR 2.96, p<0.001), suggesting that the effect is largely driven by SES.

The relationship between low SES and poor OS in cancer patients is likely complex and multifactorial. For any given patient it may involve a combination of factors such as a lack of sufficient resources to obtain adequate cancer surveillance, poor health literacy, poor access to care, environmental exposures, limited access to deal with treatment-related morbidities, and a higher burden of comorbidities.[22] Our study identifies a category of low SES patients who are at very high risk of poor outcomes. At the very least, providers could work with these high-risk patients to elucidate specific barriers of care so that these can be incorporated into the management plan. Patient navigators may be one solution to help bridge this gap. Studies have found that patient navigators in oncology are useful for identifying barriers as well as improving patient outcomes such as treatment completion and adherence to follow-up appointments.[23,24]

On the systemic level, policies aimed at improving health literacy, access to affordable health insurance, and adequate income have the potential to address SES-related disparities. Studies have found that low educational attainment is a proxy for poor health literacy[25,26], and these patients are less likely to adhere to treatment recommendations.[27] Health literacy campaigns for oral cancer in particular have shown promising results in raising patient awareness and compliance with treatment recommendations.[28–30] In terms of access to health insurance, North Carolina is one of the 14 states that did not expand Medicaid after passage of the Affordable Care Act (ACA).[31] It is estimated that an additional 4.4

million individuals in the U.S. and 357,000 in North Carolina would gain health insurance coverage if the remaining states expanded Medicaid eligibility under the ACA.[32] Finally, the minimum wage in North Carolina was $7.25 per hour in 2019 which falls well below the calculated living wage.[33] Health literacy campaigns, Medicaid expansion, and raising the minimum wage are just a few examples of how policy can be used to address gaps in SES at the state level.

Strengths of this study include a large, population-based dataset with individual-level data on key indicators of SES. Individual-level data on SES is not available in most national cancer databases, so there has been a paucity of research that quantifies the prognostic impact of SES in HNSCC. If validated by other HNSCC studies, our SES classification system could be used to help risk stratify HNSCC patients at initial diagnosis, identifying those who may benefit most from a holistic management strategy. The numeric SES classification system presented here is simple and reproducible across a wide range of clinical settings. Additionally, the evidence presented in this study provides an impetus for further research into novel interventions aimed at addressing barriers to care in HNSCC patients.

Our study has several limitations. Staging information was based on AJCC 7th edition guidelines due to lack of information on variables such as extracapsular extension and depth-of-invasion, which were not routinely included in pathological reports during the time period of this study. Validation studies for this classification system should use the updated AJCC 8th edition staging as a comparator, if available. Additionally, the household income categories for our SES classification system were based on federal poverty levels (FPL) for a family of four at the time of the study in 2006 (100% of FPL was $20,000; 250% of FPL was $50,000), so they may not be representative of modern income brackets. Future validation studies should ideally use income cutoffs that best reflect the sample period under investigation. Finally, our data were from a single state and may not be representative of all HNSCC patients in the United States. Additional research is needed to verify these findings.

Conclusion:

In a large, population-based cohort of HPV-negative HNSCC patients, SES appears to have similar prognostic ability to cancer stage. Socioeconomic status can be used as a metric to help risk-stratify patients and guide additional interventions in select patients. Additional research is warranted to validate the impact of SES on the prognosis of HNSCC patients and to identify evidence-based strategies for mitigating barriers to care in HSNCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

HPV	human papillomavirus
HNSCC	head and neck squamous cell carcinoma
SES	socioeconomic status
OS	overall survival
CHANCE	Carolina Head and Neck Cancer Epidemiology Study
NCCCR	North Carolina Central Cancer Registry
BIC	Bayesian information criterion

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Highlights:

- Low socioeconomic status (SES) predicts poor overall survival (OS) in HNSCC
- Cancer stage has been considered the gold-standard prognosticator in HNSCC
- Low SES may have similar prognostic ability to stage in HNSCC

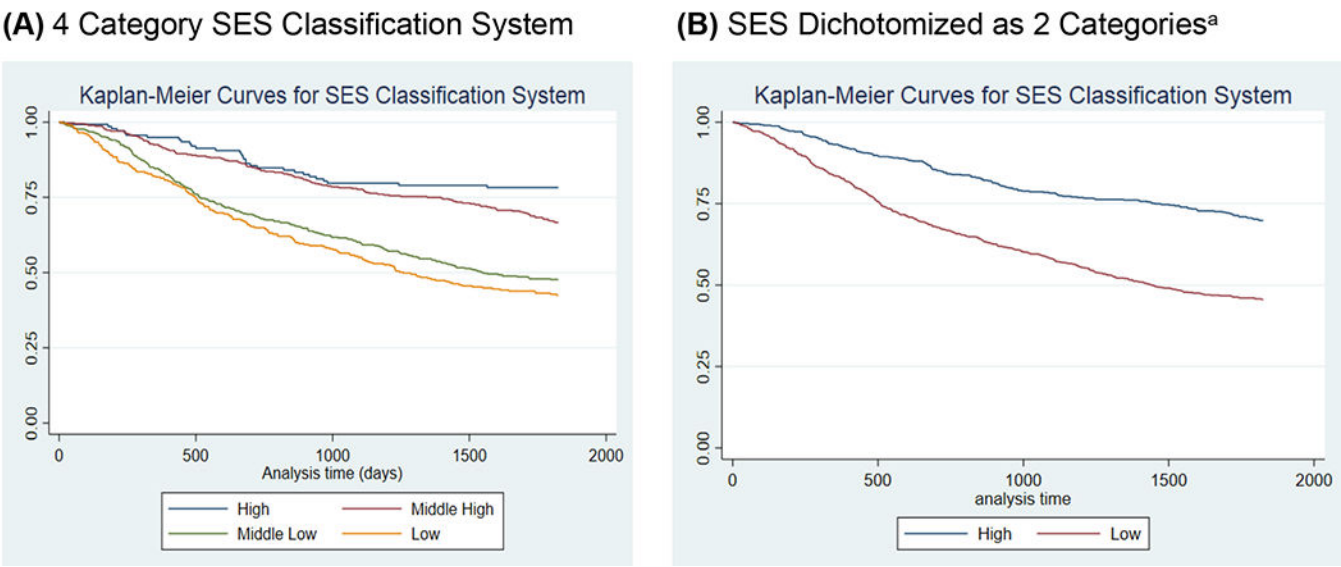

Figure 1: Kaplan-Meier curves for SES Classification System

[a]High=Patients classified as high or middle high; Low= Patients classified as low or middle low; log-rank test p-value<0.001 for high vs. low SES

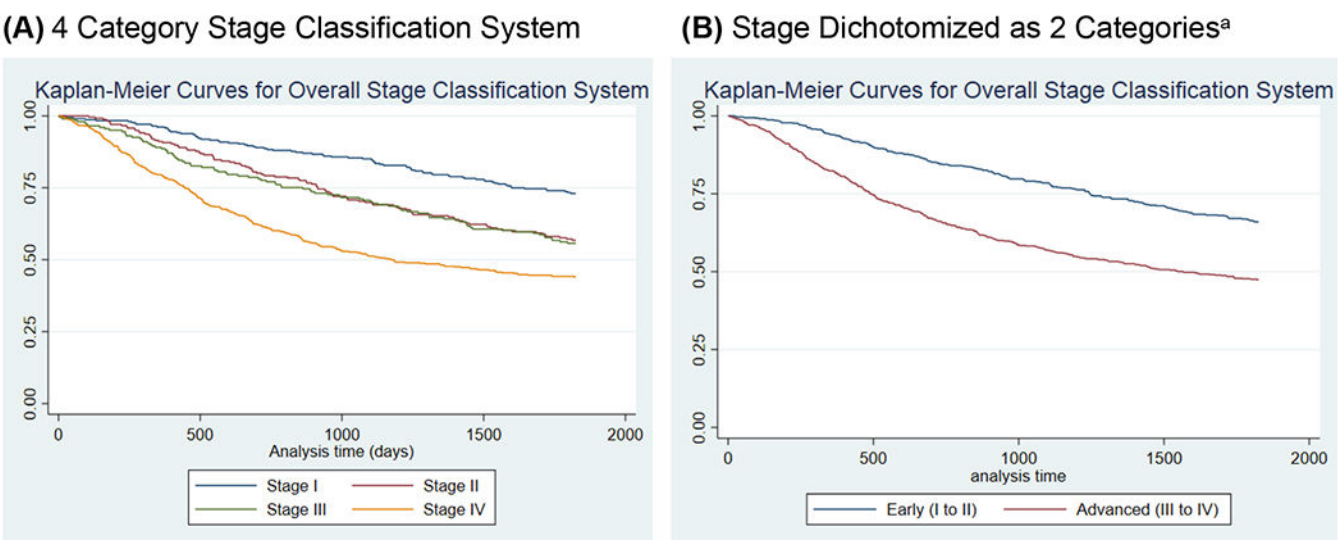

Figure 2: Kaplan-Meier curves for Overall Stage Classification System

[a]log rank test p-value<0.001 for early vs. advanced overall stage

Table 1:

Baseline characteristics of the sample

Characteristic	Low SES[a] (n=719)	High SES (n=510)	p-value
Age (mean, SD)	60.8 (10.1)	58.1 (10.6)	<0.001
Sex			0.078
Male	528 (73)	379 (78)	
Female	191 (27)	113 (22)	
Race			<0.001
White	424 (59.0)	441 (86.5)	
Black	281 (39.1)	61 (12.0)	
Other	14 (1.9)	8 (1.5)	
Education			<0.001
Less than high school	435 (60.5)	20 (3.9)	
High school graduate	209 (29.1)	142 (27.8)	
Beyond high school	75 (10.4)	348 (68.2)	
Household income			<0.001
< $20,0000	459 (66.0)	6 (1.2)	
$20,000 to $50,000	221 (31.7)	195 (41.0)	
> $50,000	16 (2.3)	275 (57.8)	
Insurance			<0.001
Uninsured	147 (21.2)	2 (0.4)	
Medicaid/Medicare/Other	476 (68.7)	172 (35.3)	
Private	70 (10.1)	313 (64.3)	
Tumor Site			0.001
Larynx	299 (41.6)	182 (35.7)	
Oral Cavity	321 (44.6)	279 (54.7)	
Oropharynx	99 (13.8)	49 (9.6)	
Overall Stage (AJCC 7th edition)			<0.001
I	145 (20.2)	163 (32.0)	
II	145 (20.2)	91 (17.8)	
III	122 (16.9)	79 (15.5)	
IV	307 (42.7)	177 (34.7)	
T Classification			<0.001
T1	181 (25.2)	212 (41.6)	
T2	223 (31.0)	161 (31.6)	
T3	156 (21.7)	72 (14.1)	
T4	159 (22.1)	65 (12.8)	
N Classification			0.026
N0	410 (57.0)	308 (60.4)	
N1	81 (11.3)	60 (11.8)	
N2	192 (26.7)	133 (26.1)	
N3	36 (5.0)	9 (1.8)	

Characteristic	Low SES[a] (n=719)	High SES (n=510)	p-value
M Classification			0.459
M0	712 (99.0)	507 (99.4)	
M1	7 (1.0)	3 (0.6)	
Prior history of alcohol use	591 (86.4)	419 (85.3)	0.603
Smoking history (>10 pack years)	623 (87.6)	367 (72.7)	<0.001
Treatment			0.019
Surgery Only	161 (22.8)	155 (30.5)	
Surgery + Radiation	135 (19.2)	94 (18.5)	
Surgery + Chemoradiation	54 (7.7)	40 (7.9)	
Radiation Only	354 (50.3)	219 (43.1)	

[a]Low SES includes patients classified as low or middle low; High SES includes patients classified as high or middle high

Table 2:

5-year Overall Survival and Cox proportional hazards model for each classification system

Classification	No. Patients	5-year OS	HR and 95% CI[a]	P-value
SES				
High	138	78.3	Reference	
Middle High	372	66.7	1.44 (0.96 to 2.16)	0.078
Middle Low	434	47.7	2.65 (1.79 to 3.93)	<0.001
Low	285	42.5	3.11 (2.07 to 4.67)	<0.001
Overall Stage				
I	308	73.1	Reference	
II	236	56.8	1.77 (1.32 to 2.36)	<0.001
III	201	55.7	2.05 (1.52 to 2.77)	<0.001
IV	484	44.0	3.01 (2.35 to 3.86)	<0.001

[a]All hazard ratios are adjusted for age, sex, and race

Table 3:

Comparison of Model Prognostic Measures for SES and Overall Stage Classification Systems

Prognostic Measures	SES	Overall Stage
Total Survival Gradient	35.8%	29.1%
Monotonicity	11.6, 19, 5.2	11.7, 1.1, 16.3
BIC statistic	7412	7388
Harrell's C index	0.61	0.64

Table 4:

Multivariable Cox Proportional Hazards Model for SES Classification System Adjusted for Potential Confounders

Classification	HR and 95% CI[a]	P-value
High	Reference	
Middle High	1.50 (0.98 to 2.30)	0.062
Middle Low	2.48 (1.63 to 3.77)	<0.001
Low	2.96 (1.92 to 4.56)	<0.001

[a]Model adjusted for age, sex, race, alcohol, smoking, overall stage, tumor site and treatment