Alcoholism: Independent Predictor of Survival in Patients With Head and Neck Cancer

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Background: **Despite recognition of the high prevalence of alcoholism among patients with head and neck cancer, the prognostic importance of alcoholism has not been evaluated adequately. Previous investigators have speculated that alcoholic patients may have a poorer prognosis than nonalcoholic patients because of more advanced stage of cancer, the immunosuppressive effects of alcohol, and an increased rate of death due to other alcohol-related diseases.** ***Purpose:*** **The goal of this population-based study was to identify the features of alcoholism that are associated with survival for patients with head and neck cancer and to develop an alcoholic severity staging system from a composite of the independent features of alcoholism.** ***Methods:*** **This prospective study included 649 patients who were diagnosed with cancer of the oral cavity, oropharynx, hypopharynx, or larynx during the period from September 1, 1983, through February 28, 1987, in a three-county area of western Washington state that participates in the Surveillance, Epidemiology, and End Results Program of the U.S. National Cancer Institute. Details on lifetime alcohol consumption, treatment for alcoholism, abstinence from alcohol prior to the diagnosis of cancer, and alcohol-related health problems were ascertained through in-person interviews near the time of diagnosis. Patients were classified as either nonalcoholics or alcoholics according to their responses to questions from the Michigan Alcoholism Screening Test. The measures of alcohol consumption and abuse that were found to be independently associated with 5-year survival by logistic regression analysis were combined using conjunctive consolidation to create a final composite variable, called an alcoholic severity stage. Cox proportional hazards regression analysis was done to estimate the relative risk (RR) of death within 5 years due to specific causes of death for each of the alcoholic severity stages.** ***Results:*** **Alcoholism (RR = 2.06; 95% confidence interval [CI] = 1.43-2.98) and a history of alcohol-related systemic health problems (i.e., liver disease, pancreatitis, delirium tremens, or seizures) (RR = 2.76; 95% CI = 1.69-4.49) were associated with an increased risk of death, whereas abstinence (i.e., the consumption of fewer than one drink per week at 1 year prior to the diagnosis of cancer) (RR = 0.62; 95% CI = 0.39-0.97) was associated with a decreased risk of death. These associations were independent of age, site of cancer, anatomical stage, histopathologic grade, smoking, and type of antineoplastic treatment. Patients in the two worst alcoholic severity stages had an increased risk of dying not only of head and neck cancer but also of cardiovascular disease, pulmonary disease, and other alcohol-related causes.** ***Conclusions:*** **Alcohol abuse, measured by alcohol consumption, functional impairment, a history of alcohol-related health problems, or abstinence, can provide important prognostic information for patients with head and neck cancer. Our results suggest that sobriety among alcoholic patients can lead to prolonged survival. [J Natl Cancer Inst 1996;88:542-9]**

Alcohol consumption is a well-known risk factor for the development of squamous cell carcinoma of the head and neck (*1*). Although the prevalence of alcoholism among patients with head and neck cancer has been estimated to be between 30% and 90% (*2,3*), little formal attention has been given to the evaluation of the prognostic importance of alcoholism. Three studies of patients with advanced head and neck cancer undergoing multimodality therapy (*4-6*) reported an association between alcohol consumption and decreased survival. With these exceptions, research on predictors of survival has focused mainly on the site of the primary tumor, the anatomical stage, and the type of antineoplastic therapy given. Reasons for this neglect may include belief in the exclusive prognostic importance of anatomical characteristics of the tumor, difficulty in identifying patients as alcoholics, and the absence of a taxonomy for classifying the severity of alcohol abuse that is prognostically relevant.

Alcoholic patients with head and neck cancer may have a poorer prognosis than other patients with head and neck cancer because of more advanced stage of disease in alcoholic patients (*2*), the immunosuppressive effects of alcohol (*7*), and an increased rate of death due to other alcohol-related diseases. The behavioral and personal characteristics of alcoholics, such as their cigarette-smoking habits, dietary habits, and emotional disturbances, may also contribute to a poorer prognosis. Some investigators (*8*) have speculated that treatment for alcoholism might improve prognosis if immunocompetence improves with abstinence, but this has not been evaluated.

The purpose of this study was to identify the features of alcoholism that are associated with survival for patients with head and neck cancer and to develop an alcoholic severity staging system from a composite of the independent features of alcoholism.

Subjects and Methods

Study Population

Patients for this study were identified through the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center in Seattle, WA. This is a population-based tumor registry that participates in the Surveillance, Epidemiology, and End Results (SEER) Program[1] of the U.S. National Cancer Institute (NCI). The registry covers a 13-county area in western Washington with an estimated population at the time of this study of 3 million. Eligible for inclusion were all persons with histologically confirmed primary squamous cell carcinoma of the oral cavity (International Classification of Diseases, Injuries, and Causes of Death, ninth revision [ICD-9],

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See "Notes" section following "References."

codes 140.0-140.9, 141.1-141.9, 143.0-145.2, and 145.5-145.9), oropharynx (ICD-9 codes 141.0, 145.3-145.4, 146.0-146.3, 146.5-146.9, 149.1, and 149.8), hypopharynx (ICD-9 codes 148.0-149.0), or larynx (ICD-9 codes 146.4 and 161.0-161.9) diagnosed during the period from September 1, 1983, through February 28, 1987, who were residents of King, Pierce, or Snohomish counties and were between the ages of 20 and 74 years (*9*).

Of 856 eligible patients, interviews at or near the time of diagnosis were obtained for 697 (81.4%), including 107 interviews by proxy with next of kin of patients who had died or were too ill to be interviewed. Reasons for no interview included refusal by the subject's physician (n = 47), refusal by the subject (n = 69), inability to locate the subject (n = 36), and other reasons such as language barriers and incompetence (n = 7). Thirty-four interviewed patients with synchronous tumors and 14 interviewed patients without documented treatment were excluded, leaving an inception cohort of 649 patients. Patients with synchronous tumors were excluded because of the difficulty categorizing (i.e., controlling for) tumor variables for these patients. For example, a patient with a tumor of the oral cavity and a synchronous tumor of the larynx could be categorized as either a laryngeal cancer patient or an oral cavity cancer patient.

Data Collection

This study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Trained interviewers using a structured questionnaire conducted in-person interviews at the home of each study participant. Written informed consent was obtained from each study participant before being interviewed. All questions referred to the period of time before the reference date, which was 1 year prior to the date of diagnosis. The information collected included basic demographic data, occupational history, medical history (particularly focused on alcohol-related health problems), and information concerning alcohol consumption and tobacco use.

The SEER tumor registry provided information on primary site, stage at diagnosis, histopathologic grade, and first course of antineoplastic treatment, plus follow-up data on survival and cause of death. Causes of death were categorized as 1) head and neck cancer (ICD-9 codes 140.9-150.9, 161.9, 173.4, and 195.0), 2) lung cancer (ICD-9 code 162.9), 3) other cancer (ICD-9 codes 153.3-157.9, 171.9, 188.9, 189.2, 199.1, 202.8, 203.0, and 289.8), 4) cardiovascular disease (ICD-9 codes 394.9-429.2, 436.9, 440.9, 441.3, and 441.4), 5) pulmonary disease (ICD-9 codes 486.9, 496.9, 507.0, 518.5, and 518.8), 6) alcohol-related disease (ICD-9 codes 291.8, 571.1, 571.2, 571.5, and 577.1), 7) other cause (ICD-9 codes 38.9, 88.8, 250.0, 250.6, 335.2, 348.1, 578.9, 586.9, 785.5, 812.0, 955.0, 956.9, and 988.1), and 8) unknown cause (ICD-9 codes 777.7 and 779.9). The beginning of follow-up was defined as the date of the first antineoplastic therapy directed against the incident cancer.

All tumors were anatomically staged according to the staging system used for the SEER Program by the tumor registry staff (*10*). With this staging system, the extent of disease is based on combined clinical and surgical–pathologic assessment. Tumors are staged as being either in situ, local, regional, or distant cancers. Local tumors are invasive cancers confined to the site of origin. Regional tumors extend beyond the site of origin by direct extension to adjacent sites or to regional lymph nodes. Distant tumors either directly extend beyond adjacent sites, involve discontinuous or distant lymph nodes, or metastasize to other distant sites.

Statistics on survival of patients with head and neck cancer are usually reported according to the tumor, node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) (*11*). Tumors staged as local by the SEER staging system would be staged as stage I or II by AJCC criteria. Regional and distant tumors would be staged as stage III or IV by AJCC criteria.

Measures of Alcohol Consumption and Abuse

Interviewers asked all patients to describe their lifetime history of alcohol consumption, including the age they began to drink, the ages at which their drinking habits changed, and the average amounts of all alcoholic beverages (beer, wine, and liquor) that they drank during each time period in which their drinking habits were consistent. One drink was defined as 12 ounces of beer, 4 ounces of wine, or 1.5 ounces of liquor. Depending on the specific beverage, we estimate that the number of grams of ethanol in one drink varied from approximately 10 to 16 g. The unit of measurement, drink-year (i.e., the average number of drinks consumed per day during the years the subject drank × the number of years of drinking), was calculated to provide an index of lifetime alcohol consumption. Patients were also categorized according to their consumption of alcohol at the reference date (recency of alcohol consumption) as drinking one or more drinks per week (current drinkers) or as drinking fewer than one drink per week (abstainers).

Questions regarding lifetime functional impairment associated with alcohol consumption were modeled after the Michigan Alcoholism Screening Test (MAST) (*12,13*). In this study, we used 15 questions from the original 25-item MAST questionnaire. The MAST has widespread acceptance, and its psychometric properties of validity and reliability have been well established (*13,14*). MAST questions focus on whether or not the subject has ever had psychosocial problems (problems with personal relationships or work), legal problems (accidents or arrests), and help-seeking behavior (treatment or attendance at Alcoholics Anonymous meetings). Summary MAST scores are computed by applying a weighted scoring formula of 0, 1, 2, or 5 points to the response to each question and then adding the scores of all responses. A total score of 5 or more is considered diagnostic of alcoholism. Because of the wording of several questions (e.g., "have you *ever* gotten into trouble at work because of your drinking?"), the MAST measures lifetime problems with alcohol and does not distinguish between a current alcoholic and a recovering alcoholic with many years of sobriety. At the recommended cutpoint of 5, the MAST has a reported sensitivity for lifetime alcohol abuse and dependence of 90% and a specificity of 81% (*14*).

All patients were asked if a doctor had ever told them that they had esophagitis, gastritis, ulcers, liver disease, pancreatitis, delirium tremens, or seizures due to alcohol. If they answered "yes," they were asked at what age the problem began or was first detected and if they required hospitalization for treatment. Patients who indicated that their liver disease was cirrhosis, fibrosis, hepatitis, inflammation, or ascites were considered to have a history of alcohol-related liver disease. Esophagitis, gastritis, and ulcers were classified as alcohol-related local health problems because they could be attributed to the direct effect of alcohol on gastrointestinal mucosa; liver disease, pancreatitis, delirium tremens, and seizures due to alcohol were classified as alcohol-related systemic health problems because they could be attributed to the toxic effect of alcohol on organs distant from the gastrointestinal system.

Creation of the Alcoholic Severity Staging System

To create a multivariate staging system for alcohol abuse, we used conjunctive consolidation, a statistical technique that has been used previously to form multivariate staging systems for cancers of the rectum (*15*), endometrium (*16*), lung (*17*), and larynx (*18*) The basis of this technique is to examine in tabular format the simultaneous impact of two variables on outcome and then to combine those categories with statistical isometry (i.e., similar survival) and biological similarity in order to create a new composite variable (*17*). The variables of alcohol abuse (i.e., MAST score, alcohol-related health problems, and recency of alcohol consumption) that were found to be independently associated with survival by logistic regression analysis were combined by conjunctive consolidation to create a final composite variable, called an alcoholic severity stage. Abstinent alcoholics without a history of alcohol-related systemic health problems had an overall 5-year survival estimate (62.8%, 27/43) similar to that for nonalcoholics (65.9%, 216/328). Therefore, these two groups of patients formed the composite alcoholic severity stage A. Abstinent alcoholics with a history of alcohol-related systemic health problems had an overall 5-year survival estimate (50.0%, 19/38) nearly identical to that for alcoholics currently drinking without a history of alcohol-related systemic health problems (49.2%, 65/132). Therefore, these two groups formed the composite alcoholic severity stage B. Alcoholics who were currently drinking and had a history of alcohol-related systemic health problems had an overall 5-year survival estimate of 25.0% (21/84) and formed alcoholic severity stage C. Twenty-eight patients with a history of liver disease and/or pancreatitis were not classified as alcoholics by their MAST score; however, because the mean weekly and lifetime alcohol consumption of this group of patients was not significantly different from that for patients with a MAST score indicating alcoholism (e.g., mean weekly alcohol consumption of 28.7 drinks per week versus 31.1 drinks per week; $P = .72$ by two-sample t test), these 28 patients were also categorized as alcoholics in the alcoholic severity staging system. For the creation of the alcoholic severity staging system, 11 patients with unknown data on recency of alcohol consumption and 13 patients lost to 5-year follow-up were excluded from analysis.

Statistical Analysis

To assess the association of 5-year survival with potential prognostic factors, contingency tables were constructed and analyzed by Pearson chi-squared tests for $R \times C$ tables and by the Mantel–Haenszel test for linear trend where appropriate (*19*). Two-sample (independent-sample) t tests were used to test for differences in means of weekly and lifetime alcohol consumption for independent groups of patients. The effects of alcohol consumption and abuse on 5-year survival were quantified by relative risk (RR) values. RR values and 95% confidence intervals (CIs) were estimated by logistic regression analysis (*20-22*). Models included terms for MAST score, alcohol-related health problems, recency of alcohol use, weekly alcohol consumption, and lifetime alcohol consumption, as well as terms for other potential predictors (i.e., smoking, age, site of cancer, histopathologic grade, anatomical stage, and type of antineoplastic treatment) of survival. Regression coefficients were based on the likelihood ratio test. When all demographic, tumor, alcohol, and smoking variables were entered in a forward-stepping or a backward-stepping logistic regression model with a P value set at .05 for acceptance and at .10 for removal, age, site of cancer, anatomical stage, cigarette smoking, MAST score, alcohol-related health problems, and recency of alcohol consumption were identified as statistically significant, independent predictors of survival. In addition to these variables, the final logistic model also included the histopathologic grade of the tumor and the type of antineoplastic treatment given because of the standard inclusion of these variables in predictions of prognosis.

The Kaplan–Meier method (*23*) was used to calculate the probability of survival from the date of initial therapy. Survival curves were generated according to the alcoholic severity stage. The logrank test was used to test for statistical significance of differences in survival curves. Cox proportional hazards regression analysis (*24*) was done to calculate the RR of death within 5 years and the RR of death due to specific causes for each of the alcoholic severity stages, unadjusted and adjusted for age, sex, site of cancer, anatomical stage, histopathologic grade, smoking, and type of antineoplastic treatment. The appropriateness of the proportional hazards assumption was assessed by examination of log-minus-log survival plots. Cross-product interaction terms (both two- and three-way) between alcohol, smoking, demographic, tumor, and treatment variables were forced into the regression models but were not included because they were not found to be statistically significant.

To control for smoking in the logistic and Cox regression analyses, we evaluated several variables related to smoking status and history; these variables included number of cigarettes smoked per day, number of years of smoking, and recency of smoking (i.e., current versus never and former). We decided to use a summary cigarette-use variable (cigarette smoking), which categorized persons by those who never smoked or quit 15 or more years previously, those who quit less than 15 years previously, and current smokers who smoked fewer than 20 cigarettes per day or 20 or more cigarettes per day. The substitution of other smoking variables or combinations of other smoking variables in the multivariate regression models for the variable cigarette smoking had little or no impact on the RR estimates of the alcohol variables of MAST score, alcohol-related health problems, recency of alcohol consumption, and alcoholic severity stage. Age was entered as a continuous variable in all logistic and Cox regression models.

All analyses were done with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL) software (*22*). All tests of statistical significance were two-sided.

Results

Table 1 shows that 5-year survival estimates were associated with age, site of cancer, anatomical stage, histopathologic grade, antineoplastic treatment, education, marital status, and employment status. After adjustment for age, site of cancer, anatomical stage, histopathologic grade, and antineoplastic treatment, survival remained associated with several measures of alcohol consumption and abuse and with cigarette smoking (Table 2). MAST score, a history of alcohol-related systemic health problems, and recency of alcohol consumption remained independently associated with 5-year survival, after further adjustment was made for each other and for cigarette smoking.

In the group of patients classified as alcoholics by MAST score, abstinence at the reference date was independently associated with increased survival. The 5-year survival estimate for abstinent alcoholics was 57.1% (44/77), whereas that for alcoholics currently drinking was 40.9% (79/193; P = .016 by chi-squared test). In this analysis, seven patients without data on recency of alcohol consumption and seven patients lost to follow-up were excluded. This difference in survival remained statistically significant after adjustment was made for age, site of cancer, histopathologic grade, anatomical stage, smoking, and antineoplastic treatment (RR = 0.44; 95% CI = 0.23-0.85). Sixty-three (81.8%) of the 77 abstinent alcoholics had received treatment for their alcoholism either through Alcoholics Anonymous or through inpatient treatment. For these 77 patients, the median number of years of abstinence before the date of diagnosis of cancer was 6.0 (standard deviation = 5.8 years).

In the group of patients with a history of alcohol-related systemic health problems, abstinence remained independently associated with increased survival. The 5-year survival estimate for abstinent patients with a history of alcohol-related systemic health problems was 50.0% (19/38), whereas it was 25.0% (21/84; P = .006 by chi-squared test) for nonabstinent patients with a history of alcohol-related systemic health problems. For this analysis, three patients without data on recency of alcohol consumption and five patients lost to follow-up were excluded. This difference also remained statistically significant after adjustment was made for age, site of cancer, histopathologic grade, anatomical stage, smoking, and antineoplastic treatment (RR = 0.17; 95% CI = 0.05-0.57).

Alcoholism was associated with advanced anatomical stage and increased smoking: 51.6% (143/277) of the patients classified as alcoholics by MAST score versus 38.6% (137/355) of the patients classified as nonalcoholics presented with regional or distant cancer (P<.01 by chi-squared test); 69.1% (188/272) of the alcoholics were currently smoking 20 or more cigarettes per day, whereas 47.3% (165/349) of the nonalcoholics were currently smoking 20 or more cigarettes per day (P<.00001 by chi-squared test). For alcoholics, abstinence from alcohol was associated with decreased smoking: 55.3% (42/76) of the abstinent alcoholics were currently smoking 20 or more cigarettes per day, whereas 73.7% (140/190) of the nonabstinent alcoholics were currently smoking 20 or more cigarettes per day (P<.01 by chi-squared test). The percentage of patients categorized as alcoholics by site of cancer was 40.0% (86/215) for larynx, 39.6% (91/230) for oral cavity, 54.3% (76/140) for oropharynx, and 48.4% (31/64) for hypopharynx.

Survival and Cause of Death in the Alcoholic Severity Staging System

Fig. 1 shows Kaplan–Meier survival curves for 7 years of follow-up. Survival was clearly most favorable for patients in stage A and least favorable for those in stage C, regardless of anatomical stage. Patients in alcoholic severity stages B and C (Table 3) had an increased risk of dying not only of head and neck cancer but also of cardiovascular disease, pulmonary disease, and alcohol-related causes, both before and after adjustment for other potential predictors of survival.

Table 1. Five-year survival estimates according to demographic and tumor characteristics

Variable	No. of patients	No. of 5-y survivors	No. of patients lost to follow-up at 5 y	%*	P†
Total	649	350	13	55.0	
Sex					
Male	462	251	9	55.4	.76
Female	187	99	4	54.1	
Race					
White	622	339	13	55.7	.13
Nonwhite	27	11	0	40.7	
Age, y					
≤55	146	98	6	70.0	<.001
56-71	426	216	6	51.4	
≥72	77	36	1	47.4	
Site of cancer					
Larynx	215	148	4	70.1	<.00001
Oral cavity	230	129	5	57.3	
Oropharynx	140	51	4	37.5	
Hypopharynx	64	22	0	34.4	
Anatomical stage					
In situ	28	23	0	82.1	<.00001
Local	324	224	7	70.7	
Regional	228	88	5	39.5	
Distant	52	9	1	17.6	
Unknown	17	6	0	35.3	
Histopathologic grade					
Well differentiated	150	89	6	61.8	.014
Moderately differentiated	272	138	2	51.1	
Poorly differentiated	114	50	4	45.5	
Other	5	3	0	60.0	
Unknown‡	108	70	1	65.4	
Antineoplastic treatment					
Surgery	250	164	4	66.7	<.00001
Radiation therapy	130	74	3	58.3	
Surgery and radiation therapy	178	85	3	48.6	
Combination therapy with chemotherapy§	77	27	2	36.0	
Chemotherapy only	14	0	1	0.0	
Education					
College	237	142	2	60.4	.003
High school	325	175	9	55.4	
Grade school	82	32	2	40.0	
Unknown	5	1	0	20.0	
Marital status					
Married	405	242	2	60.0	.001
Single‖	239	107	11	46.9	
Unknown	5	1	0	20.0	
Employment status					
Employed	251	156	7	63.9	.003
Unemployed¶	373	190	6	51.8	
Unknown	25	4	0	16.0	

*% (percent alive at 5 years) = number of 5-year survivors/(number of patients – number of patients lost to follow-up at 5 years).

†Significance levels given by chi-squared test. Chi squared for linear trend was used where appropriate (e.g., age, stage, grade, and education). Unknown values were excluded from analysis.

‡The group of patients with unknown histopathologic grade had a 5-year survival estimate of 65.4%, most likely because 80 (74%) of the 108 patients had in situ or local tumors.

§Includes surgery with chemotherapy; radiation therapy with chemotherapy; and surgery, radiation therapy, and chemotherapy.

‖Includes divorced, widowed, separated, and never married.

¶Includes retired workers, housewives, and unemployed persons.

Discussion

This study demonstrates that alcohol abuse, measured by alcohol consumption, functional impairment, a history of alcohol-related health problems, or abstinence from alcohol consumption, can provide important prognostic information for patients with head and neck cancer. Alcoholism and a history of alcohol-related liver disease, pancreatitis, delirium tremens, or seizures (e.g., alcohol-related systemic health problems) were associated with an increased risk of death, whereas abstinence from alcohol consumption was associated with a decreased risk of death. These associations were independent of age, tumor site, anatomical stage, histopathologic grade, antineoplastic treatment, and smoking. Alcoholics who were abstinent prior to the diagnosis of their tumor and who did not have a history of alcohol-related systemic health problems had an overall 5-year survival estimate nearly identical to that found for nonalcoholics. Alcoholics with a history of alcohol-related systemic health problems had the worst prognosis; however, even for this group of patients, abstinence prior to tumor diagnosis was associated with increased survival. Because alcoholism, a history of alcohol-related systemic health problems, and abstinence predicted survival independently of each other, they were combined to create a classification system called the alcoholic severity staging system.

Our findings may be explained in part by the effects of alcohol on the immune system. Alcohol consumption could decrease survival by causing immunosuppression that could impair the patient's ability to destroy cancer cells. Alcoholics have been shown to have numerous immunologic alterations, including granulocytopenia, lymphopenia, T-cell depression, delayed hypersensitivity, and decreased cytotoxicity of natural killer cells (*25-30*). Alcoholics with liver disease have been shown to have elevated levels of immunoglobulin A (IgA) (*31*) and an even greater reduction in natural killer cell cytotoxicity than alcoholics without liver disease (*32,33*). In patients with head and neck cancer, elevated levels of IgA have been shown to correlate inversely with disease-free survival (*7,34*), and decreased natural killer cell function has been associated with increased rates of metastases (*35-38*). Alcohol consumption could also impair the absorption, utilization, and storage of nutrients and thereby may induce malnutrition, which in turn could cause further immunosuppression (*39*). Alternatively, alcoholics may also have poorer diets and

Table 2. Five-year survival estimates and relative risks of death according to measures of cigarette smoking and alcohol consumption

Variable	No. of patients	%*	Adjusted for age, site of cancer, histopathologic grade, anatomical stage, and antineoplastic treatment† Relative risk (95% confidence interval)	*P*	Final logistic model‡ Relative risk (95% confidence interval)	*P*
Michigan Alcoholism Screening Test score						
<5 (nonalcoholic)	365	63.0	1.00 (reference)		1.00 (reference)	
≥5 (alcoholic)	284	44.8	2.06 (1.43-2.98)	<.001	1.66 (1.09-2.52)	.018
Alcohol-related health problems§						
None	416	60.1	1.00 (reference)		1.00 (reference)	
Local	103	62.7	0.94 (0.57-1.55)	.81	0.74 (0.44-1.26)	.27
Systemic	130	32.0	2.76 (1.69-4.49)	<.0001	2.27 (1.33-3.89)	.003
Recency of alcohol use‖						
Current drinkers	502	54.1	1.00 (reference)		1.00 (reference)	
Abstainers	136	61.5	0.62 (0.39-0.97)	.038	0.56 (0.34-0.91)	.019
Cigarette smoking¶						
Current ≥20 cigarettes/day	353	50.0	1.00 (reference)		1.00 (reference)	
Current <20 cigarettes/day	80	64.1	0.58 (0.33-1.04)	.066	0.68 (0.38-1.24)	.21
Quit <15 y ago	76	58.7	0.82 (0.46-1.46)	.50	0.99 (0.54-1.80)	.97
Never or quit ≥15 y ago	112	71.2	0.34 (0.20-0.59)	<.001	0.42 (0.24-0.74)	.003
Weekly alcohol consumption#						
<7 drinks/wk	218	70.2	1.00 (reference)		Not included	
7-13 drinks/wk	117	56.3	1.73 (1.01-2.94)	.044		
14-41 drinks/wk	180	52.2	2.04 (1.27-3.26)	.003		
≥42 drinks/wk	73	47.2	2.03 (1.08-3.82)	.028		
Lifetime alcohol consumption**						
≤40 drink-years	245	68.8	1.00 (reference)		Not included	
41-120 drink-years	182	55.6	1.58 (1.01-2.47)	.045		
≥121 drink-years	161	48.4	1.84 (1.15-2.93)	.010		

*% (percent alive at 5 years) = number of 5-year survivors/(number of patients – number of patients lost to follow-up at 5 years).

†Adjusted by logistic regression.

‡Final logistic model included age, site of cancer, histopathologic grade, anatomical stage, antineoplastic treatment, Michigan Alcoholism Screening Test score, recency of alcohol use, alcohol-related health problems, and cigarette smoking. The categories used to adjust for smoking were 1) never smoked or quit ≥15 years ago, 2) quit <15 years ago, 3) currently smoking fewer than 20 cigarettes a day, and 4) currently smoking 20 or more cigarettes a day.

§Local includes patients with a history of gastritis, ulcers, or esophagitis without a history of systemic problems. Systemic includes patients with a history of liver disease, pancreatitis, delirium tremens, or seizures due to alcohol. Five-year survival estimates by type of systemic health problem were as follows: liver disease—40.0% (28/70); pancreatitis—18.8% (3/16); and delirium tremens or seizures due to alcohol—30.4% (17/56, four patients lost to follow-up).

‖Drinking status at the reference date, which was 1 year prior to the diagnosis of cancer; data missing for 11 patients.

¶Data missing for 28 patients.

#Average consumption during the years the subject drank; data missing for 61 patients.

**Average consumption during the years the subject drank × years drinking; data missing for 61 patients.

consume fewer nutrients than nonalcoholics. Because information on nutritional status and dietary intake at the time of diagnosis was not collected as part of this study, we could not compare the nutritional status of alcoholic patients with that of nonalcoholic patients.

As defined by the MAST questionnaire, alcoholism was a prognostically more important variable than level of alcohol consumption. The MAST score may be a more accurate assessment of alcohol consumption than the patient's report of quantities of alcohol consumed. In addition, the MAST questionnaire is a measure of impaired functional status, and multiple studies have demonstrated that functional status [defined by other functional measures, such as the Karnofsky (*40*) or Eastern Cooperative Oncology Group (*41*) performance scale] is a predictor of outcome in cancer.

Investigators (*42*) have demonstrated that alcoholic patients without cancer but with a history of liver disease, pancreatitis, delirium tremens, or seizures due to alcohol have a higher mortality rate than alcoholics without these illnesses. In this study, we demonstrated that this is also true for patients with head and neck cancer.

Perhaps the most important finding of our study was that abstinence from alcohol prior to the diagnosis of cancer was associated with a statistically significant increase in survival. This finding suggests that sobriety among alcoholic patients with head and neck cancer can lead to prolonged survival. The immunosuppression present in alcoholic patients without cancer does seem to improve in those patients who quit drinking (*43*). Thus, it is possible that the improved prognosis for abstinent alcoholics in our study was partially a consequence of increased immunocompetence. Our results are consistent with those obtained in studies of patients without cancer that have demonstrated that alcoholics in remission have improved life expectancy compared with alcoholics who continue to drink (*44-46*). For example, a study with a follow-up period from 1 through 11 years (*46*) reported that abstinent alcoholics without major medical illnesses (e.g., without

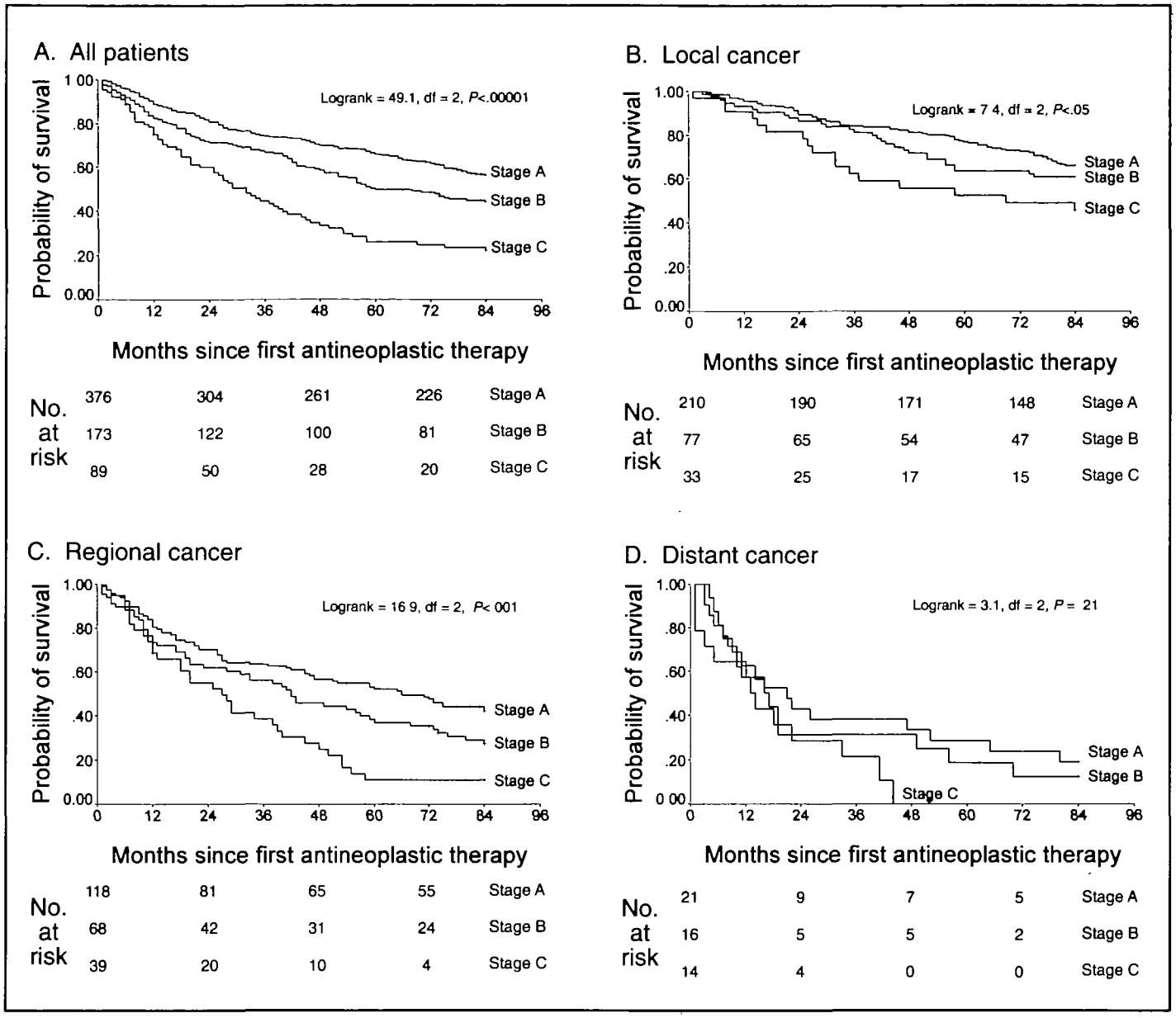

Fig. 1. Kaplan–Meier survival curves for 7 years of follow-up for patients with head and neck cancer according to alcoholic severity stage. A three-level composite alcoholic severity staging system demarcated a distinct prognostic gradient for the entire study cohort (**A**) and for patients with local cancer (**B**), regional cancer (**C**), and distant cancer (**D**). The categories of patients within each alcoholic severity stage were as follows: stage A—1) nonalcoholics and 2) abstinent alcoholics without a history of alcohol-related systemic health problems; stage B—1) abstinent alcoholics with a history of alcohol-related systemic health problems and 2) alcoholics currently drinking without a history of alcohol-related systemic health problems; and stage C—alcoholics currently drinking with a history of alcohol-related systemic health problems. Alcoholism was defined as having a MAST score ≥5 (*see* "Subjects and Methods" section for details) or a history of alcohol-related systemic health problems (e.g., liver disease, pancreatitis, delirium tremens, or seizures due to alcohol). Abstaining and currently drinking refer to whether patients were drinking at the reference date, which was 1 year prior to the diagnosis of cancer.

"clinically significant liver dysfunction" or cancer) did not have a mortality experience different from that of nonalcoholics.

Compared with patients in alcoholic severity stage A, patients in alcoholic severity stages B and C had an increased risk of dying not only of head and neck cancer but also of cardiovascular disease, pulmonary disease, and other alcohol-related causes. Multiple mechanisms (*47-50*), such as alcohol-induced cardiomyopathy, arrhythmia, or hypertension, can perhaps explain the observed increased risk of mortality from cardiovascular disease. The increased risk of death due to pulmonary disease (in particular, pneumonia) can perhaps be explained by the known defects in cellular and humoral immunity seen in chronic alcoholics. Not unexpectedly, patients in alcoholic severity stage C had a very high risk (adjusted RR = 49.60) of dying of alcohol withdrawal, hepatitis, cirrhosis, or pancreatitis.

Some limitations of our study must be acknowledged. The first limitation was our inability to characterize antineoplastic treatment with any greater detail than surgery, radiation therapy, chemotherapy, or combination therapy. Antineoplastic treatment was entered as a separate variable in the logistic and Cox regression models, but we were not able to obtain finer control for therapy, by adding such variables as neck dissection, laryngectomy, or radiation dosage. One might also

Table 3. Relative risk of death by cause of death in the alcoholic severity staging system*

Cause of death†	No. of deaths within alcoholic severity stage			Crude		Cox regression model‡	
	A	B	C	Alcoholic severity stage B: relative risk (95% confidence interval)	Alcoholic severity stage C: relative risk (95% confidence interval)	Alcoholic severity stage B: relative risk (95% confidence interval)	Alcoholic severity stage C: relative risk (95% confidence interval)
Head and neck cancer§	55	42	34	1.87 (1.25-2.79)	3.57 (2.32-5.49)	1.51 (0.99-2.32)	2.17 (1.32-3.57)
Lung cancer	15	6	2	1.04 (0.40-2.68)	1.00 (0.23-4.41)	0.87 (0.31-2.44)	1.10 (0.23-5.31)
Other cancer	15	4	2	0.68 (0.23-2.06)	0.91 (0.21-4.00)	0.66 (0.21-2.13)	0.48 (0.06-3.74)
Cardiovascular disease	15	12	8	2.02 (0.95-4.32)	3.48 (1.47-8.24)	2.18 (0.94-5.06)	2.69 (0.94-7.76)
Pulmonary disease	3	6	2	5.01 (1.25-20.1)	4.64 (0.77-28.1)	4.54 (1.02-20.3)	6.32 (0.83-48.40)
Alcohol-related disease	1	1	4	2.52 (0.16-40.4)	26.33 (2.91-238.0)	5.06 (0.19-138.3)	49.60 (1.62-1517.9)
Other disease	5	4	3	1.73 (0.66-4.53)	4.76 (1.87-12.1)	1.67 (0.61-4.54)	3.70 (1.26-10.80)
Unknown	4	1	3	1.85 (0.66-5.19)	3.18 (0.85-11.8)	1.92 (0.59-6.24)	3.17 (0.72-14.00)
All causes	113	76	58	1.71 (1.30-2.26)	3.25 (2.39-4.41)	1.52 (1.13-2.04)	2.25 (1.57-3.20)
Total person-months	17 188	6882	2682				

*52 patients with unknown alcoholic severity stage, unknown cigarette consumption, or unknown anatomical stage were excluded from analysis.

†For International Classification of Diseases, Injuries, and Causes of Death, ninth revision (ICD-9), codes, *see* "Subjects and Methods" section.

‡Model included age, sex, site of cancer, anatomical stage, histopathologic grade, smoking, antineoplastic treatment, and alcoholic severity stage The categories used to adjust for smoking were 1) never smoked or quit ≥15 years ago, 2) quit <15 years ago, 3) currently smoking fewer than 20 cigarettes a day, and 4) currently smoking 20 or more cigarettes a day. Alcohol severity stage A is the reference category (relative risk = 1.00) for the Cox regression model and for the (crude) unadjusted analysis.

§Twelve (9.2%) of the 131 patients who died of head and neck cancer had developed a second head and neck primary tumor. ICD-9 codes for cause of death did not indicate whether these patients died of their index tumor or of their second primary tumor.

expect that patients with alcohol-related systemic health problems would be poor surgical candidates and consequently would receive radiation therapy more often than surgery. However, when we compared rates of surgery and radiation therapy among patients in alcoholic severity stages A, B, and C, we found no statistically significant difference after controlling for anatomical stage (data not presented), suggesting that this possibility is not an explanation of our results. The strongest determinant of treatment was anatomical stage.

A second limitation of our study was the lack of follow-up information on alcohol consumption and smoking after the diagnosis of cancer. We speculate that there may be an association between prior and subsequent drinking behavior and that any change in patients' drinking behavior after the diagnosis of cancer may affect their survival. For example, if alcoholics previously in remission returned to drinking after the diagnosis of cancer, then their survival rate would decrease; if alcoholics who were drinking at the time of diagnosis became abstinent after diagnosis, then their survival rate would increase. If these changes had occurred, they would have lowered our RR estimates and would have made it more difficult to detect an association between abstinence and improved survival. Thus, they are unlikely explanations of our results. Similar considerations would also apply to any effects on survival that might be associated with changes in smoking behavior.

With the proposed new alcoholic severity staging system, clinicians will be better able to classify patients according to the severity of their alcohol abuse and, consequently, will be better able to compare treatment strategies and outcome and to identify patients at high risk of dying of alcohol-related health problems other than cancer. The only other study that offers a classification system for alcoholism to evaluate outcome is the Kaplan–Feinstein classification system of comorbidity (*51*). This classification system was developed for patients with diabetes mellitus and classifies only alcoholism that is characterized by severe decompensation (e.g., "more than one episode of delirium tremens or alcoholic seizures") as prognostically important (*18,51*).

Treatment for alcoholism is presently not a routine part of head and neck cancer therapy. Since abstinence may improve survival, alcoholics ought to be offered treatment for alcoholism at the time of diagnosis of cancer. Individualized interventions (*52*) should be designed to educate patients about the specific health benefits of abstaining from drinking, to encourage patients to try abstaining again, and to teach behavioral skills that reinforce drinking cessation. Future research should be conducted to clarify the biological and psychosocial reasons why alcoholics with head and neck cancer have decreased survival compared with other patients with head and neck cancer.

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Notes

[1] *Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the NCI. Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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