ORIGINAL ARTICLE

ONLINE FIRST

Long-term Health-Related Quality of Life in Survivors of Head and Neck Cancer

Gerry F. Funk, MD; Lucy Hynds Karnell, PhD; Alan J. Christensen, PhD

Objective: To examine health-related quality of life (HRQOL) reported by 5-year head and neck cancer survivors and factors that predicted these long-term scores.

Design: Prospective, observational outcomes study.

Setting: Tertiary care institution.

Patients: A total of 337 patients diagnosed as having head and neck carcinoma between January 1995 and December 2004, who enrolled in the Outcomes Assessment Project and survived at least 5 years.

Interventions: While participating in the longitudinal Outcomes Assessment Project, patients filled out surveys measuring HRQOL at numerous points in time.

Main Outcome Measures: Outcomes included 5-year scores in eating, speech, aesthetics, social disruption, physical and mental health, depressive symptoms, and overall quality of life (QOL). In addition to analyzing patients' 5-year HRQOL outcomes, multivariate analyses were performed to determine which patient, clinical, treatment, and 1-year HRQOL factors independently predicted these 5-year outcomes.

Results: Overall, the cohort's long-term general health was similar to that to age-matched norms from the general population. But over 50% of these survivors had problems eating, 28.5% reported depressive symptoms, and 17.3% reported substantial pain. At long-term follow-up, 13.6% continued to smoke, and 38.9% used alcohol. Multivariate analyses demonstrated that 1-year pain and diet were the strongest independent predictors of 5-year HRQOL outcomes.

Conclusions: Eating problems due to poor oropharyngeal functioning and persistent pain are the most prevalent problems that these survivors face. Early interventions addressing eating issues, swallowing problems, and pain management will be a crucial component in improving this patient population's long-term QOL, especially in those who are functioning poorly 1 year after diagnosis.

Arch Otolaryngol Head Neck Surg. 2012;138(2):123-133.
Published online January 16, 2012.
doi:10.1001/archoto.2011.234

Author Affiliations
Departments of Otolaryngology–Head and Neck Surgery, University of Iowa College of Medicine (Drs Funk and Karnell) and Psychology (Dr Christensen), University of Iowa, and Center for Research in the Implementation of Innovative Strategies in Practice, Iowa City VA Health Care System (Dr Christensen), Iowa City, Iowa.

THE NUMBER OF PEOPLE IN THE United States living with a diagnosis of cancer has tripled since 1971. In 2006, cancer survivors made up 3.5% of the US population, and that percentage is increasing by approximately 2.0% per year.[1,2] Currently, over 50% of patients treated for cancer in the United States, including head and neck cancer (HNC), will be cured of that cancer and become long-term survivors (≥5 years).[3,4] This growing population of patients has prompted a number of public health initiatives to study cancer survivorship[5] and address the knowledge gaps that exist regarding the health status of cancer survivors in the United States.[6] Many issues of concern in the general area of cancer survivorship are particularly relevant to patients with HNC. The treatment of HNC may affect general health, mental health, appearance, employment, social functioning, and family interactions in addition to the recognized effects on upper aerodigestive tract functioning.[7-11]

The period of cancer survivorship, as defined by the National Cancer Institute's Office of Cancer Survivorship, begins with the diagnosis of cancer and ends with the death of the patient.[12] Cancer survivorship has been described as temporally overlapping phases, including acute (diagnosis to the completion of treatment, dominated by issues of treatment and its effects), extended (beginning at the end of treatment and encompassing a period of frequent follow-up evaluations to detect recurrence), and permanent or long-term survival (beginning when the chance of recurrence becomes relatively low).[13]

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

Our goal was to evaluate patients with HNC within the contemporary context of cancer survivorship, which emphasizes the identification and management of treatment-related problems and comorbidities, health promotion, appropriate cancer surveillance, and family issues.[6] This study focuses on health-related quality of life (HRQOL) in long-term HNC cancer survivors. For most cancers, including HNC, long-term survivorship is defined as beginning 5 years following diagnosis, with the implication that the index cancer has been cured.

Although this study addresses long-term outcomes, HRQOL may be altered by cancer treatment during any of the phases of cancer survivorship. Treatment-related effects may, in part, be defined by the time course of their occurrence. The acute effects of cancer treatment are seen during or soon after treatment and resolve over time. Long-term effects are those that persist, and late effects are those that are not initially present but appear at some point after cancer treatment.[6] Examples of these in the population of patients of HNC include mucositis (acute), xerostomia (long-term), and osteoradionecrosis of the mandible (late).

Many studies published over the past 15 years have evaluated HRQOL in patients with HNC. Most of these studies have addressed HRQOL issues in the acute and short-term periods of survivorship. Findings from these studies include a notable decline in nearly all the parameters of HRQOL during and immediately after treatment with improvements in overall quality of life (QOL), speech, and some aspects of oropharyngeal function beginning around 6 months after treatment.[14-17]

Compared with the number of studies that have evaluated short-term HRQOL, relatively few studies have specifically evaluated long-term HRQOL outcomes 5 or more years from diagnosis in patients with HNC. These studies are costly, subject to high participant attrition rates, and require a substantial research infrastructure. Many of these long-term studies have been conducted in patient cohorts outside the United States. The findings indicate that, although general measures of QOL stabilize after 1 year, little improvement in a number of treatment-related symptoms and oropharyngeal function has been demonstrated after 1 year.[17-23] Persistent symptoms of psychological distress have also been reported.[24-26] Although a number of the long-term studies have found stabilization of general measures of QOL at long-term follow-up, a decline in overall QOL 10 years after treatment was found in a small cohort of patients from New Zealand.[27,28] Terrell et al[29] reported the long-term HRQOL outcomes in patients from the Veterans Affairs cooperative laryngeal cancer study. Investigators at the University of Wisconsin published a series of cross-sectional studies evaluating a number of different HRQOL parameters in convenience samples of long-term HNC survivors (Meyer et al,[30] Duke et al,[31] Holloway et al,[32] and Campbell et al[33]), and several other groups have reported long-term outcomes in patients with HNC.[34-38]

There has historically been and currently remains a tremendous research focus on improving the survival results for patients with HNC. Over the past 10 to 15 years, the HRQOL outcomes following HNC treatments have also been the subject of considerable research. The current study focuses on patients with HNC as long-term cancer survivors. Within this context, the emphasis in this study is placed on the evaluation of long-term HRQOL and treatment-related problems, comorbidities, and health promotion. The utility of selected, case-mix variables as predictors of long-term HRQOL outcomes in this ongoing longitudinal study of long-term HNC survivors are presented. As the field of cancer survivorship continues to evolve, it will be crucial for HNC health care providers to evaluate their patients within the contemporary context of cancer survivorship in order to take advantage of this increasing body of knowledge and the interventions that will derive from it for the benefit of these patients.

METHODS

Patients whose upper aerodigestive tract carcinomas were treated in the Department of Otolaryngology–Head and Neck Surgery are asked to participate in an Outcomes Assessment Project. When first initiated in January of 1995, this project was designed to investigate outcomes by collecting data at diagnosis and then at 3, 6, 9, and 12 months after diagnosis. In September 2003, the protocol was revised to include data collected at 2, 3, 4, 5, 10, 15, and 20 years after diagnosis. Both the initial and current studies have been approved through the University of Iowa College of Medicine human subjects investigational review board. The current study included all Outcomes Assessment Project participants who were enrolled by December 2004, so that they were 5 or more years out from diagnosis, and who agreed to participate in the long-term protocol.

Although the battery of surveys that Outcomes Assessment Project participants are asked to fill out has undergone small revisions over the years, 4 instruments are currently being used that measure general and HNC-specific health outcomes, depressive symptoms, and perceived social support. The 36-item Medical Outcomes Study Short-Form 36 (SF-36) is used to assess general health.[39,40] This well-validated method for scoring its 36 items includes 2 composite summary scores representing general physical and mental health. These scores are normalized on a range of 0 to 100, with higher scores representing better functioning. Based on his or her age, each patient was assigned a normative physical and mental health score that reflected the mean score for the general population of the same (individual-year) age. The distribution of this group of patients' normative data was used to determine cut-off scores for grouping patients' self-reported bodily pain scores and physical and mental health composite scores into 3 categories: low (patient scores that fell within the lowest quartile of the general population scores), intermediate (scores within the second and third quartiles), and high (scores within the highest quartile).

The HNC-specific outcomes were measured using the well-validated Head and Neck Cancer Inventory, a self-report instrument that consists of 4 domains: eating, speech, aesthetics, and social disruption (representing pain, socializing with friends and family, and employment) and 1 item addressing global QOL.[7] This survey's 30 items measure frequency and severity using a 5-point scale. The domain scores are normalized on a scale of 0 to 100, with higher scores representing better functioning. Based on prior work that correlated domain scores with relevant anchor health states,[41] these domain scores can be classified as low (0-30), intermediate (31-69), and high (70-100) functioning. Individuals in the high category have what would generally be regarded as relatively normal functioning, whereas those in the intermediate category have clearly abnormal functioning and those in the low category have severely

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

compromised functioning. For example, in the eating domain, scores in the intermediate group were based on the overall scores of patients whose diets were limited to soft food, and scores in the low group were based on the overall scores of patients with minimal or no oral intake. The magnitudes of small, intermediate, and large clinically important differences for the domain scores and the global QOL item were also determined to evaluate the clinical relevance of differences between scores.

The Beck Depression Inventory was used to quantify depressive symptoms.[42] This standardized instrument has been used in many different patient populations and has identified clinically significant depression in a group of patients receiving radiation therapy for their HNC.[43] The 0 to 3 ordinal responses of its 21 items result in a total score ranging from 0 to 63, with higher scores representing a larger (worse) number of depressive symptoms. Low, intermediate, and high categories for depressive symptoms are based on published norms that categorize this survey's outcomes as low (severe, ≥31), intermediate (mild or moderate, 10-30), or high (normal, 0-9).[44]

Perceived social support was measured using the Social Provisions Scale.[45] This validated survey has 24 items that measure both emotional and instrumental forms of support.

In addition to patient-provided data, demographic, disease, and treatment information was collected. Patient characteristics that potentially change over time, such as tobacco and alcohol use, were collected at pretreatment and at each follow-up period. Outcome information about recurrent disease and survival was routinely updated using data collected by the University of Iowa's cancer registry.

Comorbidity at the time of diagnosis was quantified using the Adult Comorbidity Evaluation–27 index (ACE-27), an adaptation of the Kaplan-Feinstein index for cogent comorbidity[46] that was developed for use with adult patients with cancer.[47] Based on information from medical records, patients are assigned a score on a 4-point scale representing no, mild, moderate, or severe comorbidities. Pain was measured using a visual analog scale with the ends labeled as "no pain" (0) and "worst possible pain" (10). These pain scores were categorized as no pain (0) or mild (1-3), moderate (4-6), and severe (7-10) pain.[48]

The data for this study were analyzed using SPSS Inc statistical software, version 15.0. Univariate analyses (Pearson correlations, independent sample *t* tests, and 1-way analysis of variance) were initially performed to determine which variables were significantly associated with the 8 outcomes representing 5-year HRQOL outcomes in eating, speech, aesthetics, social disruption, physical health, mental health, depressive symptoms, and overall QOL. The independent variables included information available at the time of treatment including age and comorbidity at diagnosis, site, stage, and treatment; 1-year HRQOL scores, including HNC-specific, general health, depressive symptom outcomes, and overall QOL; 1-year information about self-reported tobacco use, alcohol use, pain, and social support; and recurrence status.

Multivariate regression analyses were then performed, using variables with $P < .05$ in the univariate analyses, to determine which factors were independently predictive of the long-term HRQOL outcomes. One set of multivariate analyses was performed to determine which pretreatment variables predicted each of these 8 long-term outcomes. A second set of multivariate analyses was then performed that added 1-year HRQOL outcomes to a model that included the significant pretreatment variables. All values for site (oral cavity, oropharynx, hypopharynx, larynx, and other) and for 1-year tobacco and alcohol use (current, previous, never) were included in the univariate analyses. In the multivariate analyses, however, site was represented by 3 separate variables: oral cavity (yes or no), oropharynx (yes or no), and larynx-hypopharynx (yes or no). Tobacco and alcohol use were grouped so that current users were compared with previous users combined with those who never used. For all analyses, treatment was categorized as single or multimodality, and recurrence status was grouped so that patients who were never diagnosed as having recurrent disease were compared with those whose disease recurred at some point prior to their long-term follow-up.

RESULTS

Between January 1995 and December 2004, 1577 patients met the Outcomes Assessment Project's eligibility criteria. Of those 1577 eligible patients, 991 agreed to participate (a capture rate of 63%), while 308 refused and 278 were missed. The original Outcomes Assessment Project protocol captured data on patients through the first year after diagnosis. When the protocol was expanded in September 2003 to collect data up to 20 years after diagnosis, all surviving patients who had been enrolled in the initial protocol were asked to reenroll in the expanded protocol when they came for follow-up clinic visits. At the time this study was initiated, there were 337 participants who were diagnosed as of December 2004, had survived at least 5 years, and had been originally enrolled or reenrolled in the expanded protocol. The sample size reflects the capture rate at time of enrollment and reenrollment as well as the withdrawal rate due to death or termination of follow-up care.

The patient, disease, and treatment characteristics of the 337 patients are shown in **Table 1**. The median age at diagnosis was 57 years. Over half of the long-term survivors were initially diagnosed as having advanced-stage disease, and approximately 20% of these patients were classified as having moderate or severe levels of comorbid disease when first diagnosed with their HNC. That 10.7% of these patients received combined radiation and chemotherapy indicates that most of these patients were treated prior to the emergence of chemoradiation protocols. Recurrent disease had been diagnosed in 11.6% at some point prior to their long-term follow-up.

Long-term data based on self-report indicated that 13.6% of these long-term survivors were still smoking, 38.9% were still consuming alcohol, and 14.2% were experiencing moderate to severe pain (**Table 2**). Almost one-quarter had a restricted diet, ranging from no oral intake to soft foods only.

Of the 4 HNC-specific outcomes, eating had the lowest mean score (63.5), with less than half of the patients having scores in the high-functioning category (normal or near-normal ability to eat) (**Table 3**). Social disruption had the highest mean score (85.3) with 80.8% of patients in the highest performing group. The level of depressive symptoms for 70% of these patients was in the normal (high) range.

Table 3 also shows the percentage of these patients' physical and mental health composite scores within each functional category. These 3 categories represent the age-matched general population norms broken down into quartiles, with the high- and low-functioning groups representing the top and bottom 25% of the general population's scores. A substantially higher percentage of patients' scores fell into both the top and bottom quartiles

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

Table 1. Patient, Disease, and Treatment Characteristics of 337 Patients With a History of HNC Who Survived 5 or More Years

Characteristic	No. (%)
Age at diagnosis, median, y	57.0
≤58	191 (56.7)
≥59	146 (43.3)
Comorbidity at diagnosis	
None	91 (27.0)
Mild	121 (35.9)
Moderate	59 (17.5)
Severe	13 (3.9)
Unknown	53 (15.7)
Site	
Oral cavity	127 (37.7)
Oropharynx	75 (22.3)
Hypopharynx	7 (2.1)
Larynx	73 (21.7)
Other site[a]	55 (16.3)
"Combined" stage	
Early (0-2)	139 (41.2)
Advanced (3-4)	179 (53.1)
Unstageable	15 (4.5)
Unknown	4 (1.2)
Treatment type	
Surgery only	131 (38.9)
Radiation only	42 (12.5)
Surgery + RT (with or without chemo)	126 (37.4)
RT + chemo	36 (10.7)
Unknown	2 (0.6)
Recurrence status	
Recurred	39 (11.6)
Did not recur	279 (82.8)
Never disease free	6 (1.8)
Unknown	13 (3.9)

Abbreviations: Chemo, chemotherapy; HNC, head and neck cancer; RT, radiation therapy.

[a] The "other site" category includes lip (in 6 patients), parotid gland (15), submandibular gland (4), nasopharynx (6), pharynx, not otherwise specified (1), nasal cavity (6), maxillary sinus (5), ethmoid sinus (2), head and neck site, not otherwise specified (5), and unknown primary (5).

Table 2. Five-Year Lifestyle and Psychosocial Characteristics of 337 Patients With a History of HNC Who Survived 5 or More Years

Characteristic at 5 Years	No. (%)
Tobacco use	
Current	46 (13.6)
Previous	194 (57.6)
Never	75 (22.3)
Unknown	22 (6.5)
Alcohol use	
Current	131 (38.9)
Previous	134 (39.8)
Never	45 (13.4)
Unknown	27 (8.0)
Pain scale	
None (0)	211 (62.6)
Mild (1-3)	53 (15.7)
Moderate (4-6)	31 (9.2)
Severe (7-10)	17 (5.0)
Unknown	25 (7.4)
Depressive symptoms scale	
Normal (0-9)	233 (69.1)
Mild (10-20)	77 (22.8)
Moderate (21-30)	11 (3.3)
Severe (≥31)	5 (1.5)
Unknown	11 (3.3)
Diet	
Full	259 (76.9)
Soft/liquid	37 (11.0)
NPO-MOI	20 (5.9)
Unknown	21 (6.2)
Dentition	
Fully dentate	168 (49.9)
Partially edentulous	54 (16.0)
Edentulous	97 (28.8)
Unknown	18 (5.3)

Abbreviations: HNC, head and neck cancer; NPO-MOI, nil per os, minimum oral intake.

for physical and mental health, with over half in the high-functioning category (53.3% and 53.7%, respectively) and over one-third in the low-functioning category (36.7% and 39.3%, respectively). When evaluated as a group, an analysis comparing the participant cohort's average health scores with the age-matched general population scores indicated that, as a group, their reported physical health was significantly higher than the normative scores ($P=.003$). No significant difference was found, however, between their reported mental health and the normative scores ($P=.19$). A similarly skewed distribution was found for these patients' bodily pain scores, with 45.6% falling in the high-functioning category and 17.3% in the low-functioning category. An analysis comparing the participant cohort's average bodily pain scores with their normative scores indicated that these patients had significantly less pain ($P<.001$) than the age-matched general population.

To determine which factors predict long-term outcomes, an initial set of univariate and multivariate analyses were performed that included pretreatment variables only (**Table 4** and **Table 5**). In a second univariate and multivariate analysis, this examination was then broadened to include 1-year outcomes as possible predictors of long-term outcomes (**Table 6** and **Table 7**). Table 4 shows the significant univariate associations ($P<.05$) of various characteristics known at the time of treatment with the 8 dependent variables representing long-term HRQOL outcomes. Early stage was associated with better outcomes in all areas except physical health. Older age was associated with significantly better aesthetic, social disruption, and mental health outcomes and fewer depressive symptoms. Older age was also associated with significantly worse physical health. Physical health scores worsened (decreased) as the level of comorbidity at diagnosis increased. Oropharyngeal and hypopharyngeal tumors were associated with worse eating outcomes, whereas laryngeal tumors were associated with worse speech scores. The receipt of radiation therapy and chemotherapy was associated with worse outcomes in eating and social disruption, whereas radiation therapy was also associated with worse outcomes in speech.

When multivariate analyses were performed, which included the pretreatment variables that were significantly associated with the long-term outcomes ($P<.05$),

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

Table 3. Long-term HRQOL Level of Functioning and Mean Scores for 337 Patients With a History of HNC Who Survived 5 or More Years

Outcome	Functional Levels, %			Mean Score[a]	Count
	High	Intermediate	Low		
HNC-specific[b]					
Eating	48.4	35.4	16.1	63.5	316
Speech	66.9	28.4	4.7	75.0	320
Aesthetics	74.8	12.8	12.5	78.1	329
Social disruption	80.8	16.4	2.8	85.3	318
Depressive symptoms[c]	71.5	23.6	4.9	7.3	326
General health[d]					
Physical	53.3	10.0	36.7	47.6	300
Mental	53.7	7.0	39.3	50.4	300
Bodily pain[d]	45.6	37.2	17.3	52.0	315

Abbreviations: HNC, head and neck cancer; HRQOL, health-related quality of life.

[a] All outcomes are scored on a scale of 0 to 100, except depressive symptoms which is scored on a scale of 0 to 63.

[b] The HNC-specific functional levels are based on cut-off scores representing appropriate anchor states. See Funk et al.[41]

[c] Depressive symptoms levels are based on cut-off scores representing 0 to 9 symptoms (normal) for high, 10 to 20 for intermediate (mild), and 21 or greater for low (moderate or severe). See Kendall et al.[44]

[d] General physical, mental health, and bodily pain functional levels are based on cut-off scores representing age-matched normative data from the general population, with high indicating the top quartile of the general population's normative scores, intermediate indicating the second and third quartiles, and low indicating the bottom (worst) quartile.

advanced-stage disease was independently predictive of worse HNC-related outcomes as well as an increased level of depressive symptoms (Table 5). Oropharyngeal and hypopharyngeal tumors were associated with worse eating function, whereas laryngeal tumors were associated with worse speech function. Receipt of radiation therapy was independently predictive of worse eating function. Age remained an independent predictor, with older patients having significantly better aesthetic, social disruption, and mental health outcomes and fewer depressive symptoms, but worse physical health. The R^2 values for these multivariate models using pretreatment variables ranged from 0.05 for depressive symptoms to 0.23 for eating.

Univariate analyses of 1-year outcomes demonstrated that pain and diet were associated with long-term outcomes (Table 6). Higher levels of pain and more restrictive diets were associated with worse outcomes in all 8 HRQOL areas. Having a recurrence resulted in worse outcomes in 3 of the 4 HNC-related outcomes (eating, aesthetics, social disruption) and in mental health and overall QOL. Being edentulous was associated with worse eating, speech, aesthetics, and physical health.

The multivariate analyses that included the short-term outcomes as well as the pretreatment variables indicated that worse pain and restrictive diets at 1 year remained the strongest independent predictors of poor long-term outcomes (Table 7). (The influence of pain at 1 year on these 5-year outcomes is illustrated in the **Figure**.) These multivariate models also had higher R^2 values that ranged from 0.18 for depressive symptoms to 0.47 for eating. Once these short-term outcomes were included in the model, stage was no longer independently predictive of any long-term outcomes except eating. Age, comorbidity at diagnosis, and radiation therapy were the variables known during the original treatment phase that remained independent predictors. Older patients were more likely to have better mental health and worse physical health, patients with worse comorbidity were more likely to have worse physical health, and patients treated with irradiation were more likely to have worse eating function. Being edentulous was also independently predictive of worse eating and aesthetic outcomes.

COMMENT

The health-related, financial, and psychosocial issues confronting a growing number of cancer survivors in the United States has received relatively little public health attention until recently. A number of private and public organizations, such as the Lance Armstrong Foundation, together with the Centers for Disease Control and Prevention, the Office of Cancer Survivorship within the National Cancer Institute, the American Society of Clinical Oncology, the Institute of Medicine, and National Research Council, have brought attention to the need for research addressing the issues of cancer survivors.[5,49,50] However, the initiatives undertaken by these organizations are relatively recent, and it is evident that significant gaps in knowledge regarding the multifaceted issues of cancer survivorship exist. Despite calls for cancer survivor management guidelines, there is currently insufficient evidence-based information from which to create these guidelines.[51]

Patients treated for HNC share many of the challenges faced by other cancer survivors, including the risk of recurrence, the increased risk of second primary cancer, decreased physical and mental health, and detrimental effects on social functioning, employment, and family interactions.[9,10,25,52,53] In addition to these issues, survivors of HNC may be confronted with deficits in upper aerodigestive tract functioning and facial appearance. With the rapid evolution of HNC treatments over the past 20 years, from primarily surgery to combined

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

Table 4. Mean Long-term HRQOL Outcome Scores by Patient, Disease, and Treatment Characteristics, and Recurrence Status for 337 Patients With a History of HNC Who Survived 5 or More Years[a]

	Mean 5-y Scores[b]							
Characteristic	Eating	Speech	Aesthetics	Social Disruption	Physical Health	Mental Health	Depression[c]	Overall QOL
Age, y								
≤58	61.3	73.4	74.4	82.4	48.9	49.0	8.5	72.0
≥59	66.6	77.2	83.1	89.4	45.8	52.3	5.8	76.1
P value	NS	NS	.007	.001	.01	.003	<.001	NS
Comorbidity at diagnosis								
None (0)	68.0	78.7	78.1	85.9	50.9	50.5	7.3	77.6
Mild (1)	59.2	70.9	80.0	84.4	47.0	50.7	7.4	72.0
Moderate-severe (2-3)	63.1	74.9	76.0	86.2	42.6	50.4	8.3	70.7
P value	NS	NS	NS	NS	<.001	NS	NS	NS
Site[d]								
Oral cavity	63.3	76.9	77.6	87.2	48.7	50.0	6.9	74.6
Oropharynx	53.1	72.8	77.5	81.2	48.5	50.0	7.8	74.0
Hypopharynx	51.1	76.6	94.6	82.1	42.2	48.2	7.0	64.3
Larynx	71.1	66.0	80.7	85.0	45.6	50.1	8.1	70.4
P value	.001	.02	NS	NS	NS	NS	NS	NS
Stage								
Early	76.8	81.8	85.6	91.6	49.1	51.9	5.7	77.6
Advanced	52.5	68.3	71.4	80.2	46.9	49.2	8.7	70.6
P value	<.001	<.001	<.001	<.001	NS	.03	<.001	.007
Surgery performed								
Yes	64.5	74.9	76.7	85.8	47.5	50.2	7.1	74.4
No	60.3	75.2	82.4	83.7	47.9	51.0	8.1	71.8
P value	NS	NS	NS	NS	NS	NS	NS	NS
Radiation performed								
Yes	56.7	72.1	76.3	82.1	47.6	50.3	7.8	71.9
No	73.9	79.3	80.7	90.2	47.9	50.8	6.6	76.6
P value	<.001	.005	NS	<.001	NS	NS	NS	NS
Chemo performed								
Yes	51.3	73.2	80.2	79.6	49.9	49.9	6.8	73.5
No	66.1	75.6	77.9	85.6	47.4	50.7	7.2	74.1
P value	.001	NS	NS	.02	NS	NS	NS	NS

Abbreviations: Chemo, chemotherapy; HNC, head and neck cancer; HRQOL, health-related quality of life; NS, not significant; QOL, quality of life.

[a] Correlations were performed on the numeric variable of age, although this table shows mean scores within 2 groupings of these continuous variables for illustrative purposes. Analysis of variables and *t* tests were performed on the remaining categorical variables, grouped according to the categories shown in this table.

[b] *P* values for significant univariate associations are shown ($P < .05$).

[c] Higher scores for depression reflect more depressive symptoms (ie, worse function), whereas higher scores for the remaining HRQOL variables reflect better function.

[d] Omits 55 patients in the "other" site category.

surgery and adjunctive radiation to combinations of chemotherapy and radiation, there has been a tremendous focus on evaluating the oncologic outcomes of these new and developing treatments. There has also been an increase in HRQOL research directed at patients with HNC over this same time frame, most of which has focused on short-term, upper aerodigestive tract function. Relatively little attention has been given to patients with HNC within the context of contemporary cancer survivorship and particularly long-term cancer survivorship.

Most studies published over the past 10 years evaluating HRQOL in patients with HNC addressed outcomes during the acute and short-term periods of survivorship, from 3 months to 3 years following treatment, or have included patients with varying lengths of follow-up. Consistent short-term findings from these studies include a significant decline in nearly all the parameters of HRQOL during and immediately after treatment with gradual improvements in overall QOL, speech, some aspects of oropharyngeal function, depression, and pain beginning around 6 months after treatment, when the acute effects of mucositis, skin pain, and surgical pain have diminished.[14-17]

Studies that have specifically evaluated long-term HRQOL outcomes in patients with HNC 5 or more years from diagnosis are limited, and most have been conducted with patient cohorts outside the United States. The HNC-specific findings of studies examining 167 five-year survivors from a sample of 357 patients originally recruited from 5 hospitals in Norway and Sweden from 1993 to 1995 indicated that patients had persistent, late problems with poor oral and oropharyngeal function related to dental debilities, xerostomia, muscular fibrosis, and altered anatomy.[21] The results from a series of studies that categorized this cohort of 167 patients according to 3 anatomic sites indicated that these oropharyngeal problems tended to be more prevalent, with pharyngeal cancers than with laryngeal or oral cavity cancers.[22,23,54] Oropharyn-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

Table 5. Patient, Disease, and Treatment Characteristics Independently Associated With 5-Year HRQOL Scores for 337 Patients With a History of HNC Who Survived 5 or More Years

	P Values of Variables Predicting 5-Year Scores[b]							
Independent Variable[a]	Eating	Speech	Aesthetics	Social Disruption	Physical Health	Mental Health	Depressive Symptoms	Overall QOL[c]
Age, continuous variable	EM	EM	.002	.007	.006	<.001	.008	EM
Comorbidity at dx (0-3)	EM	EM	EM	EM	.001	EM	EM	EM
Site								
Oral cavity, Y/N	.003	.02	EM	EM	EM	EM	EM	EM
Oropharynx, Y/N	NS	NS	EM	EM	EM	EM	EM	EM
Hypopharynx, Y/N	NS	NS	EM	EM	EM	EM	EM	EM
Larynx, Y/N	NS	<.001	EM	EM	EM	EM	EM	EM
"Combined" stage[d] (0-4)	<.001	<.001	<.001	<.001	EM	NS	.002	NS
Radiation therapy, Y/N	.01	NS	EM	NS	EM	EM	EM	EM
Chemotherapy, Y/N	NS	EM	EM	NS	EM	EM	EM	EM
Adjusted R^2	.23	.12	.07	.09	.09	.05	.05	EM

Abbreviations: Dx, diagnosis; EM, excluded from model (variables that were not significant [$P < .05$ level] in the univariate analysis and were therefore not included in the multivariate analysis); HNC, head and neck cancer; HRQOL, health-related quality of life; NS, variables that were significant ($P < .05$ level) in the univariate analysis and were therefore included in the model but were not significant ($P < .05$ level) in the multivariate analysis.

[a] Values used in multivariate analysis.

[b] *P* values for significant independent predictors of outcomes are shown.

[c] No multivariate analysis performed for overall QOL since there was only 1 pretreatment variable associated with this outcome.

[d] Stage is missing 19 cases that were unstageable or for whom stage was unknown.

geal functional problems were also the most frequent HNC-specific HRQOL deficits 7 to 11 years after treatment for 204 survivors representing 25% of the 821 Norwegian patients who had participated in a trial of conventional and hypofractionated radiation.[24,26]

Several long-term studies have indicated that the general health of survivors tends to be worse than that of the general population. The 204 long-term survivors who had participated in the Norwegian radiation therapy trial responded to a single-item query about their general health with significantly lower ratings than matched controls from the general population.[25] Similar results using a more sophisticated instrument were found in the United States in an outcomes study of 46 survivors with advanced-stage laryngeal cancer, representing 14% of the 332 original patients who participated in the Veterans Affairs Laryngeal Cancer Cooperative Study.[55] The findings of Terrell et al[29] indicated that these survivors, who were 8 to 12 years posttreatment, reported worse scores in 7 of 8 domains of the SF-36 when compared with general population norms for men aged 55 to 64 years.

Previous results for pain indicated that, while the mean SF-36 bodily pain scores for the 46 survivors from the advanced-stage laryngeal cancer clinical trial were comparable with normative data for men aged 55 to 64 years,[29] 14% of the 204 survivors from a radiation therapy clinical trial reported high levels of pain symptoms, defined by the authors as EORTC pain scale scores of 50 or higher on a scale of 0 to 100.[26] Previous results for mood disorders have indicated that 25% of the 204 patients who had undergone radiation therapy demonstrated psychological distress on a screening instrument used to measure psychiatric disorders.[26]

As found in these previously published studies, the present study demonstrated that poor oral and oropharyngeal function was a persistent problem in long-term survivors, with over 50% reporting problems with eating. These oral deficits may be due to neuromuscular changes, anatomic deficits following surgery, soft-tissue fibrosis, xerostomia, pain, and dental deficits. In addition, poor swallowing function may exert more than a detrimental effect on HRQOL.[33] Unrecognized aspiration following chemoradiation to treat HNC may also contribute to mortality. Aspiration pneumonia may add substantially to the morbidity and mortality associated with HNC treatment, although this long-term adverse effect may not be easily identified as a result of cancer therapy.[56]

The present study's results dealing with pain in long-term survivors were also similar to those of previous findings. The mean bodily pain scores for the participant cohort in the present study were statistically higher than age-matched normative data, but the difference was not clinically meaningful; the study by Terrell et al[29] indicated no significant difference between the overall bodily pain scores of their long-term survivors and age-matched norms. But on an individual basis, the rather substantial 15% who reported having moderate or severe pain in the present study was in close agreement with the 14% of the 204 survivors from a radiation therapy clinical trial that reported high levels of pain symptoms.[26]

Unlike the 2 previously cited studies that indicated that long-term survivors have poorer general health than matched controls,[26,29] the average general health of the long-term survivors in the present study was equivalent to age-matched norms from the general population. (Although patient-reported physical health scores were significantly higher than normative scores from a statistic standpoint, the difference was not a clinically relevant one.) The most probable reason for the current finding of equivalent health, vs the previous finding of worse health, is that the present study was able to compare each patient with his or her age-matched general population norm rather than having to use grouped general population norms for the 55- to 64-year-old group. These cur-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

Table 6. Mean Long-term HRQOL Outcome Scores by 1-Year Characteristics for 337 Patients With a History of HNC Who Survived 5 or More Years[a]

	Mean 5-y Scores[b]							
1-Year Factor	Eating	Speech	Aesthetics	Social Disruption	Physical Health	Mental Health	Depression[c]	Overall QOL
Pain scale								
None (0)	70.3	82.4	85.8	91.7	50.4	53.4	5.4	79.9
Mild (1-3)	59.0	70.3	75.0	86.2	47.4	49.6	7.3	72.4
Moderate/severe (4-10)	45.7	56.9	56.8	61.7	39.4	40.9	15.6	51.1
P value	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Tobacco use								
Current	58.3	73.7	71.5	79.4	46.6	46.4	10.1	67.2
Previous	65.1	75.6	82.2	86.8	48.1	51.9	7.1	74.4
Never	64.5	77.9	78.7	88.5	47.9	50.6	6.5	76.2
P value	NS	NS	NS	NS	NS	.03	NS	NS
Alcohol use								
Current	67.8	80.0	83.9	87.3	49.3	51.2	7.0	76.8
Previous	60.9	71.5	76.7	84.5	47.8	50.0	7.8	72.1
Never	63.7	75.8	77.2	87.8	45.6	52.2	6.7	75.0
P value	NS	.02	NS	NS	NS	NS	NS	NS
Social support score								
≤59	62.7	74.7	78.6	84.7	45.8	50.1	7.1	72.6
>60	66.2	78.2	80.9	88.2	49.8	50.7	6.4	76.3
P value	NS	NS	NS	NS	NS	NS	NS	NS
Diet								
Full	72.1	80.6	85.2	90.4	48.9	52.3	6.4	76.6
Soft/liquid	32.6	60.4	57.8	73.5	44.1	46.5	10.5	66.9
NPO-MOI	34.2	53.6	61.9	65.5	44.4	46.7	11.6	64.5
P value	<.001	<.001	<.001	<.001	.02	.001	<.001	.007
Dental status								
Fully dentate	72.5	79.5	86.3	88.6	49.7	52.3	5.9	77.4
Partially edentulous	60.4	83.4	78.7	86.6	49.7	49.4	6.9	77.4
Edentulous	52.9	70.1	69.9	85.4	45.2	49.9	7.9	72.0
P value	<.001	.002	.002	NS	.02	NS	NS	NS
Recurrence status								
Recurred	53.9	68.1	62.5	77.0	45.2	46.6	9.0	66.4
Did not recur	65.3	75.6	80.1	86.7	48.3	50.9	7.1	74.4
P value	.02	NS	.004	.02	NS	.04	NS	.04

Abbreviations: HNC, head and neck cancer; HRQOL, health-related quality of life; NPO-MOI; nil per os, minimum oral intake; NS, not significant; QOL, quality of life.

[a] Correlations were performed on these numeric variables, although this table shows mean scores within various groupings of the 1-year HRQOL variables for illustrative purposes.

[b] *P* values for significant univariate associations are shown ($P < .05$).

[c] Higher scores for depression reflect more depressive symptoms (ie, worse function), whereas higher scores for the remaining HRQOL variables reflect better functioning.

rent results indicate that, in general, the overall level of general health in this relatively contemporary sample of patients was comparable with the overall health of others their age.

The distribution of patients according to functional levels, however, indicated that the percentage in the low-functioning category (representing the bottom 25% of the general population's scores) was relatively high for physical health (36.7%) and mental health (39.3%). Although the mean general health scores for these patients are offset by the large percentage in the high-functioning category, the sizable number of long-term survivors with poor physical and mental health is most likely due to comorbidities, continued use of alcohol and tobacco, and poor diet in this segment of the survivor cohort.[47,57-62]

In the present study, the best predictors of 5-year outcomes were level of pain and type of diet reported by patients at 1 year. Pain and diet at 1 year after treatment, reflective of how well the patient is functioning in numerous health-related areas after the acute toxic effects have subsided, accounted for more of the variance in long-term outcomes (ie, were stronger predictors, with higher adjusted R^2 values) than pretreatment variables such as stage, site, and age. Previous studies have noted that HRQOL scores tend to increase after treatment, then level off at 1 year with little subsequent improvement. But the findings in the present study speak to the need for very early intervention done concurrently with treatment to maximize the early swallowing function and to address pain.

Another significant predictor of long-term eating functioning for these survivors was dental status at 1 year. This finding is similar to that of a 2005 study[31] that demonstrated a direct relationship between inadequate dental rehabilitation in long-term HNC survivors and poor

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

Table 7. Patient, Disease, and Treatment Characteristics and 1-Year Data Independently Associated With 5-Year HRQOL Scores for 337 Patients With a History of HNC Who Survived 5 or More Years

	P Values of Variables Predicting 5-y Scores[b]							
Independent Variable[a]	Eating	Speech	Aesthetics	Social Disruption	Physical Health	Mental Health	Depressive Symptoms	Overall QOL
Age, continuous variable	EM	EM	NS	NS	.01	.02	NS	EM
Comorbidity at dx (scores 0-3)	EM	EM	EM	EM	.01	EM	EM	EM
Site								
Oral cavity, Y/N	NS	NS	EM	EM	EM	EM	EM	EM
Oropharynx, Y/N	NS	NS	EM	EM	EM	EM	EM	EM
Hypopharynx, Y/N	NS	NS	EM	EM	EM	EM	EM	EM
Larynx, Y/N	NS	NS	EM	EM	EM	EM	EM	EM
"Combined" stage[c] (stages 0-4)	.04	NS	NS	NS	EM	NS	NS	NS
Radiation therapy, Y/N	.03	NS	EM	NS	EM	EM	EM	EM
Chemotherapy, Y/N	NS	EM	EM	NS	EM	EM	EM	EM
Pain at 1 y, continuous variable	.01	.001	.008	<.001	<.001	<.001	<.001	<.001
Tobacco use at 1 y, current vs previous/never	EM	EM	EM	EM	EM	NS	EM	EM
Alcohol use at 1 y, current vs previous/never	EM	NS	EM	EM	EM	EM	EM	EM
Diet at 1 y, full/soft-liquid/NPO-MOI	<.001	<.001	.01	<.001	.03	NS	.02	NS
Dentures at 1 y, full/partial/edentulous	<.001	NS	.001	EM	NS	EM	EM	EM
Recurrence status, recurred vs did not recur	NS	EM	NS	NS	EM	NS	EM	NS
Adjusted R^2	.47	.30	.21	.35	.26	.20	.21	.18

Abbreviations: Dx, diagnosis; HNC, head and neck cancer; EM, excluded from model (variables that were not significant [$P < .05$ level] in the univariate analysis and were therefore not included in the multivariate analysis); HRQOL, health-related quality of life; N, no; NS, variables that were significant ($P < .05$ level) in the univariate analysis and were therefore included in the model, but were not significant ($P < .05$ level) in the multivariate analysis; NPO-MOI, nil per os, minimum oral intake; QOL, quality of life; Y, yes.

[a] Values used in multivariate analysis.

[b] *P* values for significant independent predictors of outcomes are shown.

[c] Stage is missing in 19 cases that were unstageable or for whom stage was unknown.

HRQOL in a number of domains including eating and pain. Dental extractions and full-mouth edentulation are frequently performed in this patient population prior to radiation therapy to prevent osteonecrosis of the mandible. Routine denture use may be complicated by xerostomia following radiation therapy, rendering some patients edentulous and with no means of satisfactory dental rehabilitation following treatment. Unfortunately, financial barriers to dental rehabilitation may exist for many patients. Medicare and many insurance policies do not cover any denture or dental-related costs, despite the fact that the oral rehabilitative needs are a direct result of cancer care. Many insurance policies that do provide some coverage only provide partial coverage for denture costs.

Almost 15% of the survivors in the present study were continuing to smoke and 40% were continuing to drink alcohol by self-report at their 5-year follow up. These percentages suggest that aggressive smoking and alcohol use education and interventions are warranted. This is important not only from an oncologic standpoint but also from a comorbid illness and general health maintenance perspective.[9]

Conducting HRQOL studies on long-term cancer survivors is difficult for a number of reasons. The accuracy of the results may be compromised by the loss of patients to follow-up for a variety of reasons.[14] Drawing conclusions can be problematic because the evolutions in treatment are occurring so rapidly that the posttreatment cohort is a moving target. The treatment modalities for HNC have undergone substantial changes over the past 20 years. There has been an emergence of chemotherapy and epidermal growth factor receptor inhibitor use as well as an abandonment of more radical, function-disrupting surgery for function-sparing approaches accompanied by considerable improvement in the ability to reconstruct and rehabilitate surgical defects.[8,63-66] Also, comparing across studies is complicated by the different methods used to evaluate and define HRQOL.[67]

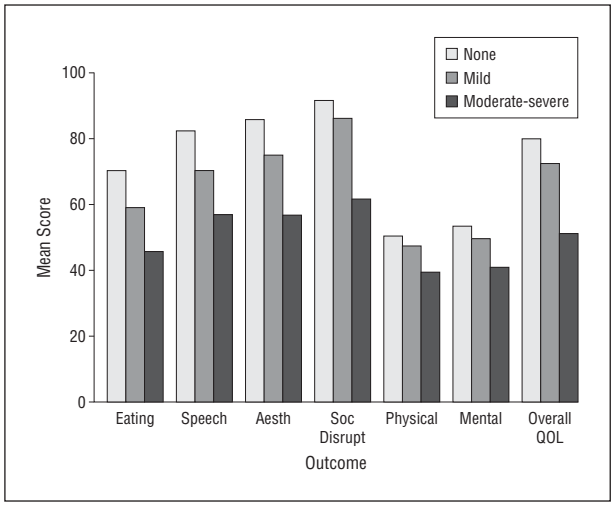

Figure. Mean 5-year scores for head and neck cancer–specific and general health outcomes by level of pain at 1 year. Aesth indicates aesthetics; QOL, quality of life; and Soc Disrupt, social disruption.

Despite these difficulties, the population of patients with HNC needs to be included in the expanding evaluation of cancer survivorship issues for a number of rea-

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

sons. First, it is frequently said and written that the survival of HNC has not improved for decades. However, as with many other types of cancer, the site- and histology-specific survival rates for many cancers of the head and neck have significantly improved over the past 20 years.[3] Second, owing to the emergence of function- and structure-sparing surgery, tremendous advances in reconstructive techniques as well as the increased use of nonoperative interventions, the external stigma of facial deformity following HNC treatment is less than in years past. These new therapeutic approaches have aided in the return of many of these patients to mainstream society. Despite these advancements, patients still confront the same issues as other cancer survivors. For example, the most frequently reported reason for discontinuing employment after treatment of an HNC is fatigue, and the least frequent is appearance.[9] Third, the demographics of patients with HNC are changing and vulnerable patient groups (elderly, minority, poor socioeconomic status) are now overrepresented among patients with HNC.[57] Fourth, the late and long-term toxic effects of a wide range of rapidly evolving treatment protocols are poorly reported, with very little or no long-term, comprehensive, HRQOL data available.[68,69] Fifth, HNC is strongly associated with the use of alcohol and tobacco, and a high percentage of patients with HNC experience comorbid illnesses related to the use of these substances, which puts them at increased risk of recurrent or second primary tumors.[47,70] Finally, the number of potential areas for survivorship investigation and intervention in this patient population presents opportunities for improvements in HRQOL and even improved overall survival. For these reasons, outcome evaluation from a global survivorship perspective, including HRQOL, late and long-term treatment effects, impact of comorbidities, health promotion, health care utilization, and family issues, is extremely pertinent to many of the challenges confronting HNC survivors.

In conclusion, the present study's results suggest that a large percentage of long-term survivors of HNC have poor oropharyngeal functioning. The efficacy of preventive and rehabilitative interventions in this area should be a focus of future research. Our findings indicate that long-term survivors as a group maintain their general health. However, every effort should be made to address the substantial subgroup of these patients with poor health and high levels of pain.

Submitted for Publication: January 19, 2011; final revision received August 31, 2011; accepted October 22, 2011.
Published Online: January 16, 2012. doi:10.1001/archoto.2011.234
Correspondence: Gerry F. Funk, MD, Department of Otolaryngology–Head and Neck Surgery, University of Iowa Hospitals and Clinics, 200 Hawkins Dr, Room 21202 PFP, Iowa City, IA 52242 (gerry-funk@uiowa.edu).
Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Funk, Karnell, and Christensen. *Acquisition of data:* Funk and Karnell. *Analysis and interpretation of data:* Funk, Karnell, and Christensen. *Drafting of the manuscript:* Funk and Karnell. *Critical revision of the manuscript for important intellectual content:* Funk, Karnell, and Christensen. *Statistical analysis:* Funk and Karnell. *Obtained funding:* Funk and Karnell. *Administrative, technical, and material support:* Funk and Karnell. *Study supervision:* Funk and Christensen.
Financial Disclosure: None reported.
Funding/Support: This work was supported by National Institutes of Health grant R01 CA106908 through the Office of Cancer Survivorship.
Previous Presentation: This study was presented at the Seventh International Conference on Head and Neck Cancer; July 20, 2008; San Francisco, California.
Additional Contributions: Amy Trullinger, BA, enrolled eligible patients and collected their data for this study.

REFERENCES

1. Travis LB, Rabkin CS, Brown LM, et al. Cancer survivorship: genetic susceptibility and second primary cancers: research strategies and recommendations. *J Natl Cancer Inst*. 2006;98(1):15-25.
2. Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: age, health, and disability. *J Gerontol A Biol Sci Med Sci*. 2003;58(1):82-91.
3. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer*. 2005;114(5):806-816.
4. Trask PC, Rabin C, Rogers ML, et al. Cancer screening practices among cancer survivors. *Am J Prev Med*. 2005;28(4):351-356.
5. Hewitt M, Greenfield S, Stovall E, eds. *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, DC: National Academies Press; 2005.
6. Aziz NM. Cancer survivorship research: state of knowledge, challenges and opportunities. *Acta Oncol*. 2007;46(4):417-432.
7. Funk GF, Karnell LH, Christensen AJ, Moran PJ, Ricks J. Comprehensive head and neck oncology health status assessment. *Head Neck*. 2003;25(7):561-575.
8. El-Deiry M, Funk GF, Nalwa S, et al. Long-term quality of life for surgical and nonsurgical treatment of head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2005;131(10):879-885.
9. Buckwalter AE, Karnell LH, Smith RB, Christensen AJ, Funk GF. Patient-reported factors associated with discontinuing employment following head and neck cancer treatment. *Arch Otolaryngol Head Neck Surg*. 2007;133(5):464-470.
10. Karnell LH, Funk GF, Christensen AJ, Rosenthal EL, Magnuson JS. Persistent posttreatment depressive symptoms in patients with head and neck cancer. *Head Neck*. 2006;28(5):453-461.
11. Karnell LH, Christensen AJ, Rosenthal EL, Magnuson JS, Funk GF. Influence of social support on health-related quality of life outcomes in head and neck cancer. *Head Neck*. 2007;29(2):143-146.
12. Pollack LA, Greer GE, Rowland JH, et al. Cancer survivorship: a new challenge in comprehensive cancer control. *Cancer Causes Control*. 2005;16(suppl 1):51-59.
13. Mullan FS. Seasons of survival: reflections of a physician with cancer. *N Engl J Med*. 1985;313(4):270-273.
14. Goldstein DP, Hynds Karnell L, Christensen AJ, Funk GF. Health-related quality of life profiles based on survivorship status for head and neck cancer patients. *Head Neck*. 2007;29(3):221-229.
15. de Graeff A, de Leeuw JR, Ros WJG, Hordijk GJ, Blijham GH, Winnubst JAM. Long-term quality of life of patients with head and neck cancer. *Laryngoscope*. 2000;110(1):98-106.
16. Magné N, Marcy PY, Chamorey E, et al. Concomitant twice-a-day radiotherapy and chemotherapy in unresectable head and neck cancer patients: a long-term quality of life analysis. *Head Neck*. 2001;23(8):678-682.
17. Bjordal K, Ahlner-Elmqvist M, Hammerlid E, et al. A prospective study of quality of life in head and neck cancer patients, part II: longitudinal data. *Laryngoscope*. 2001;111(8):1440-1452.
18. Hammerlid E, Ahlner-Elmqvist M, Bjordal K, et al. A prospective multicentre study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. *Br J Cancer*. 1999;80(5-6):766-774.
19. Hammerlid E, Silander E, Hörnestam L, Sullivan M. Health-related quality of life

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013

three years after diagnosis of head and neck cancer—a longitudinal study. *Head Neck*. 2001;23(2):113-125.
20. Hammerlid E, Taft C. Health-related quality of life in long-term head and neck cancer survivors: a comparison with general population norms. *Br J Cancer*. 2001; 84(2):149-156.
21. Abendstein H, Nordgren M, Boysen M, et al. Quality of life and head and neck cancer: a 5 year prospective study. *Laryngoscope*. 2005;115(12):2183-2192.
22. Nordgren M, Abendstein H, Jannert M, et al. Health-related quality of life five years after diagnosis of laryngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2003; 56(5):1333-1343.
23. Nordgren M, Jannert M, Boysen M, et al. Health-related quality of life in patients with pharyngeal carcinoma: a five-year follow-up. *Head Neck*. 2006;28(4):339-349.
24. Bjordal K, Kaasa S, Mastekaasa A. Quality of life in patients treated for head and neck cancer: a follow-up study 7 to 11 years after radiotherapy. *Int J Radiat Oncol Biol Phys*. 1994;28(4):847-856.
25. Bjordal K, Mastekaasa A, Kaasa S. Self-reported satisfaction with life and physical health in long-term cancer survivors and a matched control group. *Eur J Cancer B Oral Oncol*. 1995;31B(5):340-345.
26. Bjordal K, Kaasa S. Psychological distress in head and neck cancer patients 7-11 years after curative treatment. *Br J Cancer*. 1995;71(3):592-597.
27. Mehanna HM, Morton RP. Does quality of life predict long-term survival in patients with head and neck cancer? *Arch Otolaryngol Head Neck Surg*. 2006; 132(1):27-31.
28. Mehanna HM, Morton RP. Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. *Clin Otolaryngol*. 2006;31(3):204-211.
29. Terrell JE, Fisher SG, Wolf GT; Veterans Affairs Laryngeal Cancer Study Group. Long-term quality of life after treatment of laryngeal cancer. *Arch Otolaryngol Head Neck Surg*. 1998;124(9):964-971.
30. Meyer TK, Kuhn JC, Campbell BH, Marbella AM, Myers KB, Layde PM. Speech intelligibility and quality of life in head and neck cancer survivors. *Laryngoscope*. 2004;114(11):1977-1981.
31. Duke RL, Campbell BH, Indresano AT, et al. Dental status and quality of life in long-term head and neck cancer survivors. *Laryngoscope*. 2005;115(4):678-683.
32. Holloway RL, Hellewell JL, Marbella AM, Layde PM, Myers KB, Campbell BH. Psychosocial effects in long-term head and neck cancer survivors. *Head Neck*. 2005;27(4):281-288.
33. Campbell BH, Spinelli K, Marbella AM, Myers KB, Kuhn JC, Layde PM. Aspiration, weight loss, and quality of life in head and neck cancer survivors. *Arch Otolaryngol Head Neck Surg*. 2004;130(9):1100-1103.
34. Zelefsky MJ, Gaynor J, Kraus D, Strong EW, Shah JP, Harrison LB. Long-term subjective functional outcome of surgery plus postoperative radiotherapy for advanced stage oral cavity and oropharyngeal carcinoma. *Am J Surg*. 1996;171 (2):258-262.
35. Rogers SN, Hannah L, Lowe D, Magennis P. Quality of life 5-10 years after primary surgery for oral and oro-pharyngeal cancer. *J Craniomaxillofac Surg*. 1999; 27(3):187-191.
36. Laccourreye O, Hans S, Borzog-Grayeli A, Maulard-Durdux C, Brasnu D, Housset M. Complications of postoperative radiation therapy after partial laryngectomy in supraglottic cancer: a long-term evaluation. *Otolaryngol Head Neck Surg*. 2000;122(5):752-757.
37. Evensen JF, Bjordal K, Knutsen BH, Olsen DR, Støre G, Tausjø JE. Side effects and quality of life after inadvertent radiation overdosage in brachytherapy of head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2002;52(4):944-952.
38. Wijers OB, Levendag PC, Braaksma MMJ, Boonzaaijer M, Visch LL, Schmitz PIM. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. *Head Neck*. 2002;24(8):737-747.
39. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36), I: conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.
40. Ware JE, Kosinski M, Dewey JE. *How to Score Version Two of the SF-36 Health Survey*. Lincoln, RI: Quality Metric Inc; 2000:75.
41. Funk GF, Karnell LH, Smith RB, Christensen AJ. Clinical significance of health status assessment measures in head and neck cancer: what do quality-of-life scores mean? *Arch Otolaryngol Head Neck Surg*. 2004;130(7):825-829.
42. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561-571.
43. Katz MR, Kopek N, Waldron J, Devins GM, Tomlinson G. Screening for depression in head and neck cancer. *Psychooncology*. 2004;13(4):269-280.
44. Kendall PC, Hollon SD, Beck AT, Mammen CL, Ingram RE. Issues and recommendations regarding use of the Beck Depression Inventory. *Cognit Ther Res*. 1987;11(3):289-299.
45. Cutrona CE, Russell DW. The provisions of social relationships and adaptation to stress. In: Jones WH, Perlman D, eds. *Advances in Personal Relationships*. Vol 1. Greenwich, CT: JAI Press; 1987:37-67.
46. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *J Chronic Dis*. 1974;27(7-8):387-404.
47. Piccirillo JF. Importance of comorbidity in head and neck cancer. *Laryngoscope*. 2000;110(4):593-602.
48. Foley KM. Pain assessment and cancer pain syndromes. In: Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Textbook of Palliative Medicine*. 2nd ed. New York, NY: Oxford University Press Inc; 1998:310-331.
49. Herbst RS, Bajorin DF, Bleiberg H, et al; American Society of Clinical Oncology. Clinical cancer advances 2005: major research advances in cancer treatment, prevention, and screening: a report from the American Society of Clinical Oncology. *J Clin Oncol*. 2006;24(1):190-205.
50. Centers for Disease Control and Prevention. *A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies*. Atlanta, GA: Dept of Health and Human Services; 2004.
51. Earle CC. Cancer survivorship research and guidelines: maybe the cart should be beside the horse. *J Clin Oncol*. 2007;25(25):3800-3801.
52. Funk GF, Karnell LH, Dawson CJ, et al. Baseline and post-treatment assessment of the general health status of head and neck cancer patients compared with United States population norms. *Head Neck*. 1997;19(8):675-683.
53. Grignon LM, Jameson MJ, Karnell LH, Christensen AJ, Funk GFF. General health measures and long-term survival in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2007;133:471-476.
54. Nordgren M, Hammerlid E, Bjordal K, Ahlner-Elmqvist M, Boysen M, Jannert M. Quality of life in oral carcinoma: a 5-year prospective study. *Head Neck*. 2008; 30(4):461-470.
55. Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*. 1991;324(24):1685-1690.
56. Nguyen NP, Frank C, Moltz CC, et al. Aspiration rate following chemoradiation for head and neck cancer: an underreported occurrence. *Radiother Oncol*. 2006; 80(3):302-306.
57. Sikora AG, Toniolo P, DeLacure MD. The changing demographics of head and neck squamous cell carcinoma in the United States. *Laryngoscope*. 2004;114 (11):1915-1923.
58. Allison PJ. Factors associated with smoking and alcohol consumption following treatment for head and neck cancer. *Oral Oncol*. 2001;37(6):513-520.
59. Hoffman HT, Karnell LH, Funk GF, Robinson RA, Menck HR. The National Cancer Data Base report on cancer of the head and neck. *Arch Otolaryngol Head Neck Surg*. 1998;124(9):951-962.
60. Dikshit RP, Boffetta P, Bouchardy C, et al. Lifestyle habits as prognostic factors in survival of laryngeal and hypopharyngeal cancer: a multicentric European study. *Int J Cancer*. 2005;117(6):992-995.
61. Falciglia GA, Whittle KM, Levin LS, Steward DL. A clinical-based intervention improves diet in patients with head and neck cancer at risk for second primary cancer. *J Am Diet Assoc*. 2005;105(10):1609-1612.
62. Steward DL, Wiener F, Gleich LL, Falciglia G. Dietary antioxidant intake in patients at risk for second primary cancer. *Laryngoscope*. 2003;113(9):1487-1493.
63. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003; 349(22):2091-2098.
64. Pignon JP, le Maître A, Bourhis J; MACH-NC Collaborative Group. Meta-analyses of chemotherapy in head and neck cancer(MACH-NC): an update. *Int J Radiat Oncol Biol Phys*. 2007;69(2)(Suppl):S112-S114.
65. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck*. 2005;27(10):843-850.
66. Forastiere AA, Burtness BA. Epidermal growth factor receptor inhibition in head and neck cancer: more insights, but more questions. *J Clin Oncol*. 2007;25 (16):2152-2155.
67. Pusic A, Liu JC, Chen CM, et al. A systematic review of patient-reported outcome measures in head and neck cancer surgery. *Otolaryngol Head Neck Surg*. 2007;136(4):525-535.
68. Denis F, Garaud P, Bardet E, et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *Int J Radiat Oncol Biol Phys*. 2003;55(1):93-98.
69. Munker R, Purmale L, Aydemir U, et al. Advanced head and neck cancer: long-term results of chemo-radiotherapy, complications and induction of second malignancies. *Onkologie*. 2001;24(6):553-558.
70. Do KA, Johnson MM, Lee JJ, et al. Longitudinal study of smoking patterns in relation to the development of smoking-related secondary primary tumors in patients with upper aerodigestive tract malignancies. *Cancer*. 2004;101(12):2837-2842.

©2012 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/24/2013