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Health-related quality of life before and after head and neck squamous cell carcinoma: Analysis of the SEER-MHOS Linkage

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Abstract

Background—Understanding health-related quality of life (HRQOL) is crucial to providing high-quality survivorship care for head and neck squamous cell carcinoma (HNSCC) patients. Trends in and prognostic significance of HRQOL before and after HNSCC have not been well described.

Methods—HRQOL for older individuals with HNSCC was examined using the linked Surveillance, Epidemiology and End Results (SEER)-Medicare Health Outcomes Survey (MHOS) database. Surveys assessing HRQOL five years pre- to ten years post-diagnosis were included. HRQOL over time was modeled using multilevel linear regression with restricted cubic splines, and reported as either total HRQOL or change in HRQOL (denoted Δ). The association of pre-diagnosis HRQOL with survival was examined.

Results—1653 individuals were included. 61% completed one survey and 39% multiple surveys. Overall HRQOL decreased progressively until 13 months post-diagnosis, then recovered towards baseline between 2-5 years. However, after stratification by survival group, the post-diagnosis recovery was not observed. Individuals with shorter survival had lower HRQOL pre-diagnosis (<2-year survivors: 87.3; >5-year survivors: 96.4; $p=0.004$) with a steeper decline in HRQOL during diagnosis/treatment (<2-year survivors: -16.6 , 95% confidence interval [CI]= $[-23.8, -9.4]$; >5-year survivors: -0.9 , 95% CI= $[-1.8, 0.08]$). Radiotherapy and advanced stage were associated with greater declines in HRQOL during diagnosis/treatment ($p<0.001$). Higher pre-diagnosis HRQOL was independently associated with improved overall survival (adjusted hazard ratio for 10-point increase: 0.91, 95% CI=0.85-0.97).

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Conclusions—HRQOL declines before and after HNSCC, while any observed post-treatment recovery is likely an artifact of shorter survival among individuals with lowest HRQOL. The prognostic implication of pre-diagnosis HRQOL may inform patient counseling.

Keywords

Quality of Life; Head and Neck Cancer; Oropharynx; Survival; Radiotherapy

Introduction

Cancer survivorship has emerged as a healthcare priority in the United States since the Institute of Medicine consensus report in 2005.¹ Historically, health-related quality of life (HRQOL) was not a component of either medical education curricula or cancer treatment and surveillance guidelines. However, the aging population and improving cancer treatment outcomes have highlighted the need to describe the spectrum and determinants of cancer survivors' HRQOL, and to educate providers accordingly. Additionally, the need to accurately measure health-related quality of life (HRQOL) has been underscored.¹ The growing appreciation that HRQOL is paramount to improved cancer survivorship care is manifested by a growing literature of rigorous HRQOL evaluation in prostate and breast cancer survivors.^{2, 3}

HRQOL is particularly important in the current era of head and neck cancer, as the incidence of new diagnoses among young individuals with relatively few co-morbidities and expected long-term survival has increased significantly in recent years, and is expected to continue increasing.⁴⁻⁶ In the context of these incidence and survival trends and the short- and long-term morbidities of head and neck cancer therapy that range from speech and swallowing disruption to cosmetic deformity, understanding HRQOL is increasingly essential. Indeed, the prospective evaluation of HRQOL was recently identified as a priority in head and neck cancer clinical trials.⁷

Despite an expanding HRQOL literature for head and neck cancer, HRQOL trends prior to diagnosis have not been explored and our understanding of HRQOL trajectory after treatment is limited. In the present study trends in HRQOL over time relative to head and neck cancer diagnosis, its determinants and prognostic significance were examined using population-based HRQOL data from older individuals with head and neck squamous cell carcinoma (HNSCC).

Methods

SEER-MHOS database

The Medicare Health Outcomes Survey (MHOS) has been administered yearly since 1998 to a nationwide sample of individuals 65 years or older enrolled in U.S. Medicare Advantage Organizations (MAOs). Baseline and two-year follow-up MHOS surveys are administered by mail or phone to 1000 randomly selected enrollees from each participating MAO.⁸ MHOS response rates are 66% for baseline and 81% for follow-up surveys.⁹

MHOS has been linked to the Surveillance, Epidemiology and End Results (SEER) national cancer registry to create the SEER-MHOS database for use in studying HRQOL of older cancer survivors. The database has been described in detail elsewhere.^{8, 10} External investigators may access the data through an application process (<http://healthcaredelivery.cancer.gov/seer-mhos/>).

Data collected

MHOS contains demographic, socioeconomic, health and HRQOL data. HRQOL was measured using the Medical Outcomes Study Short Form 36 (SF-36)¹¹ from 1998-2005. The SF-36 has been used extensively in HRQOL research¹² and yields a Physical Component Summary (PCS) and a Mental Component Summary (MCS). The Veterans RAND 12-item Health Survey (VR-12), which includes PCS and MCS scores and is highly correlated with the SF-36, was used from 2006-2009.¹³ In the SEER-MHOS database, PCS and MCS scores are each normalized to the general U.S. population with mean 50 and standard deviation 10.⁸ Higher scores represent better HRQOL. PCS and MCS were combined into a summary score for this analysis, hereafter referred to as 'HRQOL', in order to reflect global health status encountered in the clinical setting. Two questions about depressive symptoms from the MHOS that were included in all cohorts but did not contribute to HRQOL score were combined in this analysis as a screen for recent depression (Q38-39, MHOS-1998).¹⁴ Smoking status was determined from the question, 'Do you now smoke every day, some days, or not at all?' (Q43, MHOS-1998).¹⁴ The 12 comorbid conditions assessed in all MHOS cohorts were included in this analysis (hypertension, angina pectoris/coronary artery disease, congestive heart failure, myocardial infarction, other heart conditions, stroke, chronic lung conditions, inflammatory bowel disease, hip/knee arthritis, hand/wrist arthritis, sciatica, diabetes).¹⁴

The SEER database contains information about incident cancers in certain areas of the U.S. Cancer site, stage, treatment (radiotherapy and surgery) and vital status, with date of death, are included. This analysis used the SEER staging system¹⁵ rather than that of the American Joint Committee on Cancer¹⁶ because the SEER system has been employed since the database began. SEER stages include: in situ (no basement membrane penetration or stromal invasion); localized (limited to organ of origin); regional (extension beyond the organ of origin, by direct extension and/or regional lymph node involvement); and distant (tumor cells have broken away from the primary tumor and grown at a new location).¹⁵ This analysis did not include surgical treatment data because of the limited information available and the heterogeneity of HNSCC surgical treatment.

Study population

Individuals eligible for this analysis were diagnosed with HNSCC, participated in a MHOS cohort from 1998-2009, and completed 1 MHOS survey within five years before and/or ten years after HNSCC diagnosis. If multiple surveys were available for any individual, up to four were included, restricted to those most proximal to the time of cancer diagnosis. HNSCC sites included were (with International Classification of Disease for Oncology codes): larynx (C32.0-3;C32.8-9;D02.0); oral cavity (C02.0-3;C02.8-9;C03.0-1;C03.9;C04.0-1;C04.8-9;C05.0;C05.8-9;C06.0-2;C06.8-9);

oropharynx (C01;C02.4;C05.1-2;C09.0-1;C09.8-9;C10.0;C10.2-3;C10.8-9;C14.2); hypopharynx (C12;C13.0-2;C13.8-9); lip (C00.0-6;C00.8-9); nasopharynx (C11.0-3;C11.8-9); nasal cavity/paranasal sinuses (C30.0;C31.0-3;C31.8-9). Nasopharynx, nasal cavity, and paranasal sinuses were combined for this analysis. Individuals with histology other than squamous cell carcinoma (SEER histology codes 8050-8089) or with multiple primary head and neck cancers were excluded. Oropharyngeal squamous cell carcinoma ('OPSCC') was compared with non-oropharyngeal HNSCC ('non-OPSCC') for some analyses.

Statistical analysis

Summary statistics were reported as number and percent, mean and standard deviation or median and interquartile range. For individuals with multiple surveys, time-varying demographic information (e.g., age) was taken from the survey most proximal to HNSCC diagnosis for summarizing population characteristics. In the absence of a non-cancer control group, HRQOL was described in relation to time from HNSCC diagnosis, and HRQOL score at various times relative to diagnosis were compared. Multilevel linear regression¹⁷ with restricted cubic splines¹⁸ was used to model trends in HRQOL as a dependent variable over time relative to HNSCC diagnosis, accounting for clustering by individual and MAO with random-effects intercepts. Spline terms for time from diagnosis were selected as recommended by Harrell.¹⁹ Models were selected by comparison of fit to lowess smoothing functions, residuals, and Akaike Information Criteria (AIC). Similar models were applied after stratification for survival group, with three knots each for <2 year and 2-5 year survivors, and six knots for >5 year survivors. HRQOL at different times, and absolute changes in HRQOL over given time intervals (denoted by ' '), were reported with 95% confidence intervals (CIs).

The overall model was then used to examine the association of variables of interest with HRQOL, accounting for time from diagnosis. Difference in HRQOL relative to the reference group was reported with 95% CI. For variables that interacted significantly with time from diagnosis, changes in HRQOL relative to the reference group at three different time points (-24, 13, 60 months) were reported. A multivariable model was also constructed using variables that were significantly associated with HRQOL after adjustment for other factors and/or were deemed clinically relevant.

Survival analysis was limited to individuals completing surveys within five years prior to HNSCC diagnosis. Survival rates were estimated using the Kaplan-Meier method.²⁰ Overall survival (OS) was time from diagnosis to death, with censoring at last known vital status. Survival curves were compared using log-rank tests. Risk factors for mortality were explored using univariable and multivariable Cox proportional hazards models.²¹ Log(-log) plots were inspected and statistical tests of the proportional hazards assumption were used to ensure validity of the proportional hazards model. To examine the association of HRQOL with survival, HRQOL from the survey most proximal to HNSCC diagnosis was considered both as a categorical variable by quartile, and as a continuous variable per 10-point increase, to obtain hazard ratios associated with clinically relevant differences in HRQOL (one-half of

one standard deviation, consistent with previous research²²). The multivariate model had 80% power to detect an 8% reduction in hazard of death per 10-point increase in HRQOL.

Statistical analysis was performed using STATA 11.2 (College Station, TX). Two-sided p-values of 0.05 were considered statistically significant. This study was exempted from review by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Results

Study population

The study population consisted of 1653 individuals. A single survey was available for 61% (N=1006) of individuals, with two or more available for 39% (N=647). Characteristics of the study population are summarized in Table 1.

Trends in HRQOL over time from HNSCC diagnosis

Overall, HRQOL decreased slowly in the 2-5 years preceding HNSCC diagnosis (-2.1, 95%CI[-5.4,1.3]; Figure 1a, Table 2). A steep decline was then observed beginning approximately 24 months pre-diagnosis and culminating in a nadir at 13 months post-diagnosis (-6.5, 95%CI=[-8.9,-4.1]). This was followed by an increase in HRQOL from 13 months until approximately five years post-diagnosis (+3.9, 95%CI=[2.0,5.9]), and finally a steady decline for the remaining five years of the study period (-3.4, 95%CI=[-6.9,0.1]).

When considering MCS and PCS separately (Figure S1), trends over time relative to HNSCC diagnosis were similar to overall HRQOL, with the exception that the increase in MCS was not significant in the 5-10 years post-diagnosis (+0.6, 95%CI=[-1.6,2.9]). MCS was significantly higher than PCS at all time points ($p<0.001$).

To explore whether HRQOL is a proxy of survival, individuals were stratified by OS (Figure 1b, Table 2). HRQOL trends were evaluated among <2 year (N=296), 2-5 year (N=209), and >5 year survivors (N=1081). HRQOL declined over time for each group. Individuals with shorter survival had lower HRQOL five years before HNSCC diagnosis (87.3 for <2 year survivors, versus 92.8 for 2-5 year [$p=0.16$] and 96.4 for >5 year-survivors [$p=0.004$], respectively), and experienced greater declines in HRQOL around the time of diagnosis than those with longer survival (24 months pre- to 13 months post-diagnosis: -16.6, 95%CI=[-23.8,-9.4] for <2 year survivors; -9.9, 95%CI=[-15.8,-3.9] for 2-5 years survivors; -0.9, 95%CI=[-1.8,0.08] for >5 years survivors). Notably, the significant increase in HRQOL observed in the overall study population between 13 months and five years post-diagnosis was not observed in any group after stratification by survival.

Determinants of HRQOL

Associations between characteristics of interest and HRQOL were examined (Table 3). In univariate analysis, factors significantly associated with HRQOL included: age at diagnosis, gender, smoking, marital status, education, household income, race, comorbidities, depression, tumor site, disease stage and radiotherapy. In multivariable analysis, variables

independently associated with HRQOL included age, household income, comorbidities, depression, disease stage and radiotherapy therapy ($p<0.01$ for all).

Interactions between characteristics of significance and HRQOL were explored. In univariate analysis, significant interactions with time from HNSCC diagnosis were observed for SEER stage ($p<0.001$) and radiotherapy ($p=0.001$). Individuals with late-stage disease experienced greater decreases in HRQOL around the time of diagnosis (24 months pre- to 13 month post-diagnosis) when compared to individuals with early-stage disease (-13.0 , 95% CI= $[-16.8,-9.2]$ versus -2.6 , 95% CI= $[-5.9,0.7]$; $p<0.001$). Similarly, individuals treated with radiotherapy had greater decreases in HRQOL than those who were not (-10.3 , 95% CI= $[-13.4,-7.2]$ versus -0.8 , 95% CI= $[-4.6,3.0]$; $p<0.001$). After adjustment for other factors, significantly greater declines in HRQOL around the time of diagnosis were still observed for individuals with late-stage disease ($p=0.002$) or who received radiotherapy ($p<0.001$).

MCS and PCS were analyzed separately (Tables S1-2). Although similar patterns were observed to HRQOL overall, radiotherapy was associated with MCS ($p<0.001$) but not PCS ($p=0.36$), while gender was associated with PCS ($p<0.001$) but not MCS ($p=0.91$).

Survival analysis

Given the distinct trends in HRQOL by survival group, the prognostic implication of HRQOL for HNSCC was explored. Analysis was limited to individuals with surveys prior to HNSCC diagnosis ($N=664$). Median OS was 48.9 months (95% CI=38.5-54.6 months). Two-year survival was 62.5% (95% CI=58.7-66.1%), and 5-year survival was 43.9% (95% CI=40.1-47.7%).

OS was compared by quartiles of pre-diagnosis HRQOL. Higher HRQOL was significantly associated with improved OS ($p<0.001$, $p_{\text{trend}}<0.001$; Figure 2). Median OS for the highest HRQOL quartile was 79.1 months (95% CI=65.4-100.7), compared with only 22.5 months (95% CI=14.8-36.3) for the lowest quartile. Higher pre-diagnosis PCS and MCS scores were also associated with improved OS ($p<0.001$, $p_{\text{trend}}<0.001$ for PCS and $p=0.003$, $p_{\text{trend}}<0.001$ for MCS).

To account for the observed decline in HRQOL prior to diagnosis, survival was evaluated by timing of surveys prior to HNSCC diagnosis. Pre-diagnosis HRQOL quartile was significantly associated with overall survival after HNSCC diagnosis for surveys from 1-5 ($N=428$, $p<0.001$), 2-5 ($N=239$, $p<0.001$), and 3-5 ($N=155$, $p=0.006$) years prior to diagnosis.

The prognostic significance of clinically relevant 10-point changes in HRQOL was also evaluated. A 10-point increase in pre-diagnosis HRQOL was associated with 14% reduced risk of death (HR 0.86, 95% CI=0.82-0.91; Table 4). Even after adjustment for other factors associated with survival (age, smoking and marital status, comorbidities, household income, tumor site, stage, radiotherapy), each 10-point increase in pre-HRQOL was associated with a 9% reduction in risk of death (aHR 0.91, 95% CI=0.85-0.97).

OPSCC

Most OPSCCs in the U.S. are HPV-related, and HPV-OPSCC is considered a distinct disease from HPV-negative HNSCC.⁶ Therefore, trends in HRQOL and the prognostic significance of HRQOL among individuals with OPSCC compared to those with non-OPSCC were examined. Two years prior to HNSCC diagnosis, HRQOL of individuals with OPSCC (N=295) and non-OPSCC (N=1358) was similar (Figure S2, Table S3). However, 13 months after diagnosis HRQOL for individuals with OPSCC was significantly lower than those with non-OPSCC (difference: -5.4, 95%CI=[-9.0,-1.2]). At five and ten years after diagnosis, HRQOL was again similar between the two groups. Overall, HRQOL was not significantly different for OPSCC and non-OPSCC (p=0.13). Higher pre-diagnosis HRQOL quartile was non-significantly associated with improved survival after OPSCC among 131 individuals with pre-diagnosis surveys available (HR 0.95, p=0.32).

Discussion

This study is the first to examine both pre- and post-diagnosis HRQOL for individuals with HNSCC. A significant and progressive decline in HRQOL is observed prior to and after HNSCC diagnosis, and the magnitude of decline in HRQOL differs by survival group. HRQOL in the years leading up to HNSCC diagnosis has prognostic significance not previously appreciated; these large population-based data provide compelling evidence that pre-diagnosis HRQOL independently predicts survival.

These findings have relevance to patient care. While most studies to date have reported a decline in HRQOL after diagnosis followed by a recovery towards baseline after treatment,²³⁻²⁵ these data demonstrate that such recovery is not observed after stratification by survival group, and may actually represent an artifact of earlier deaths among individuals with lower HRQOL. Therefore, to counsel patients that overall HRQOL will certainly improve after therapy as suggested by previous studies is likely inaccurate, and providers should perhaps instead emphasize the importance of acclimatization to a new standard of emotional and physical health. Furthermore, the finding that individuals with lowest pre-diagnosis HRQOL suffer worse prognosis independent of other prognostic indicators should lend added gravity to treatment decisions for this subset of patients, such as when considering potentially morbid life-prolonging interventions versus high-quality palliative care.

The decline in HRQOL prior to impending HNSCC diagnosis has not been previously described, but is consistent with two longitudinal cohort studies that described significant declines in self-reported overall health prior to diagnosis of other cancer types.^{26, 27} We conclude from this that for a given individual, HRQOL at diagnosis is likely significantly lower than their true baseline. Studies that report baseline HRQOL as assessed at diagnosis, including most studies of head and neck cancer patients to date,²³⁻²⁵ should be interpreted with this discrepancy in mind. Notably, this also implies that in the clinical setting a rapid decline in HRQOL should be interpreted with caution, as it may herald a future diagnosis of malignancy or another significant health event.²⁶

Depressive symptoms, income, number of comorbidities, and age were associated with HRQOL in a constant manner over time, while radiotherapy and advanced disease stage both greatly increased the magnitude of decline in HRQOL during HNSCC diagnosis and treatment. In ours and other studies, global HRQOL has been shown to decrease precipitously during the radiotherapy period, during which acute mucositis and other toxicities are common.^{25, 28} In long-term survivors however, although many irradiated patients experience chronic toxicities such as xerostomia and dysphagia,²⁹ global HRQOL was similar whether or not radiotherapy was received. It appears that while radiotherapy affects specific functions such as eating among long-term survivors of HNSCC, it does not have a durable impact on individuals' perceptions of their global health status, which is consistent with conclusions drawn from other groups.^{25, 30} Advanced disease stage appears to impact HRQOL in a manner similar to that of radiotherapy in ours and other studies.^{30, 31}

Emerging evidence suggests that HPV-OPSCC patients, who are generally younger and of higher socioeconomic status than their HPV-negative counterparts,^{6, 32} have a unique HRQOL trajectory. Despite higher pre-diagnosis scores, HPV-OPSCC patients experience a greater decline in HRQOL during treatment.³³ Although the HRQOL trends observed for OPSCC compared with non-OPSCC followed this general pattern, they did not reach statistical significance. However, HPV tumor status was unavailable, so the proportion of HPV-negative OPSCCs in this study was unknown. Interestingly, pre-diagnosis HRQOL was not associated with survival among individuals with OPSCC. Further investigation is required to determine whether the prognostic value of HRQOL is modified by HPV tumor status.

Limitations and strengths

This study is a secondary analysis of population-based data, and as such has several limitations and barriers to clinical application. The HRQOL assessment tools were not specific to head and neck cancer. No chemotherapy and limited surgery data were available, so treatment-related changes in HRQOL and survival differences could not be fully examined. The study population was heterogeneous, encompassing multiple sites and stages of head and neck cancer, and did not include a control group of individuals without cancer. Surveys were taken by adults 65 years of age and older, limiting generalizability to younger populations, although the majority of head and neck cancers arise in individuals in their 60s and 70s.³⁴ Selection bias is inevitable when analyzing data from voluntary questionnaires. Finally, two-thirds of individuals only completed one MHOS survey, restricting analysis of HRQOL trajectory over time. However, the unique access to pre-diagnosis HRQOL scores and large study population lend significance to the findings reported herein despite these drawbacks.

Conclusion

Understanding HRQOL is crucial to providing high-quality survivorship care for the growing population of HNSCC survivors. The prognostic implication of pre-diagnosis HRQOL should inform patient counseling. Further research is needed to further clarify trends in and determinants of HRQOL, and to examine the potential for targeted interventions to optimize HRQOL for HNSCC survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hewitt, ME.; Greenfield, S.; Stovall, E. National Cancer Policy Board (U.S.). Committee on Cancer Survivorship: Improving Care and Quality of Life. From cancer patient to cancer survivor : lost in transition. Washington, D.C: National Academies Press; 2006.
2. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008; 358:1250–1261. [PubMed: 18354103]
3. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst*. 2012; 104:386–405. [PubMed: 22271773]
4. Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. *Oncologist*. 2010; 15:994–1001. [PubMed: 20798198]
5. Fakhry C, Andersen KK, Eisele DW, Gillison ML. Oropharyngeal cancer survivorship in Denmark, 1977-2012. *Oral Oncol*. 2015
6. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011; 29:4294–4301. [PubMed: 21969503]
7. Chera BS, Eisbruch A, Murphy BA, et al. Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. *J Natl Cancer Inst*. 2014; 106
8. Ambs A, Warren JL, Bellizzi KM, Topor M, Haffer SC, Clauser SB. Overview of the SEER--Medicare Health Outcomes Survey linked dataset. *Health Care Financ Rev*. 2008; 29:5–21. [PubMed: 18773611]
9. [April 30, 2015.] The SEER-MHOS Data File: Response Rates. Available from URL: <http://healthcaredelivery.cancer.gov/seer-mhos/aboutdata/table.response.rates.html>
10. Reeve BB, Potosky AL, Smith AW, et al. Impact of cancer on health-related quality of life of older Americans. *J Natl Cancer Inst*. 2009; 101:860–868. [PubMed: 19509357]
11. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992; 30:473–483. [PubMed: 1593914]
12. Ware JE Jr. SF-36 health survey update. *Spine (Phila Pa 1976)*. 2000; 25:3130–3139. [PubMed: 11124729]
13. Selim AJ, Rogers W, Qian SX, Brazier J, Kazis LE. A preference-based measure of health: the VR-6D derived from the veterans RAND 12-Item Health Survey. *Qual Life Res*. 2011; 20:1337–1347. [PubMed: 21336657]
14. [June 2, 2015] Health of Seniors Survey. Available from URL: http://www.hosonline.org/surveys/hos/download/HOS_1998_Survey.pdf
15. Young, JL.; Roffers, SD.; Ries, LAG.; Fritz, AG.; Hurlbut, AAe. SEER Summary Staging Manual - 2000: Codes and Coding Instructions. Bethesda, MD: National Cancer Institute; 2001.
16. Edge, SB. American Joint Committee on Cancer AJCC cancer staging manual. 7th. New York: Springer; 2010.
17. Rabe-Hesketh, S.; Skrondal, A. Multilevel and longitudinal modeling using Stata. STATA press; 2008.

18. Marrie RA, Dawson NV, Garland A. Quantile regression and restricted cubic splines are useful for exploring relationships between continuous variables. *J Clin Epidemiol*. 2009; 62:511–517. e511. [PubMed: 19135859]
19. Harrell, FE, Jr. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer; 2001.
20. Kaplan E, M P. Nonparametric estimation from incomplete observations. *J Amer Statist Assn*. 1958:457–481.
21. Cleves, M. *An introduction to survival analysis using Stata*. Stata Press; 2008.
22. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003; 41:582–592. [PubMed: 12719681]
23. So WK, Chan RJ, Chan DN, et al. Quality-of-life among head and neck cancer survivors at one year after treatment--a systematic review. *Eur J Cancer*. 2012; 48:2391–2408. [PubMed: 22579456]
24. Bottomley A, Tridello G, Coens C, et al. An international phase 3 trial in head and neck cancer: quality of life and symptom results: EORTC 24954 on behalf of the EORTC Head and Neck and the EORTC Radiation Oncology Group. *Cancer*. 2014; 120:390–398. [PubMed: 24452673]
25. Klein J, Livergant J, Ringash J. Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: a systematic review. *Oral Oncol*. 2014; 50:254–262. [PubMed: 24559650]
26. Diehr P, Williamson J, Patrick DL, Bild DE, Burke GL. Patterns of self-rated health in older adults before and after sentinel health events. *J Am Geriatr Soc*. 2001; 49:36–44. [PubMed: 11207840]
27. Petrick JL, Foraker RE, Kucharska-Newton AM, et al. Trajectory of overall health from self-report and factors contributing to health declines among cancer survivors. *Cancer Causes Control*. 2014; 25:1179–1186. [PubMed: 24986768]
28. Egestad H, Emaus N. Changes in health related quality of life in women and men undergoing radiation treatment for head and neck cancer and the impact of smoking status in the radiation treatment period. *Eur J Oncol Nurs*. 2014; 18:339–346. [PubMed: 24877857]
29. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008; 26:3582–3589. [PubMed: 18559875]
30. Funk GF, Karnell LH, Christensen AJ. Long-term health-related quality of life in survivors of head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2012; 138:123–133. [PubMed: 22248560]
31. Hammerlid E, Silander E, Hornestam L, Sullivan M. Health-related quality of life three years after diagnosis of head and neck cancer--a longitudinal study. *Head Neck*. 2001; 23:113–125. [PubMed: 11303628]
32. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst*. 2008; 100:407–420. [PubMed: 18334711]
33. Sharma A, Mendez E, Yueh B, et al. Human papillomavirus-positive oral cavity and oropharyngeal cancer patients do not have better quality-of-life trajectories. *Otolaryngol Head Neck Surg*. 2012; 146:739–745. [PubMed: 22275190]
34. Howlader, N.; Noone, AM.; Krapcho, M., et al. [October 15, 2014] SEER Cancer Statistics Review, 1975-2011. Available from URL: http://seer.cancer.gov/csr/1975_2011/

Figure 1.
HRQOL over time from head and neck cancer diagnosis. a. Overall; b. Stratified by survival.

Figure 2. Overall survival by HRQOL quartile, assessed within five years before head and neck cancer diagnosis.

Table 1
Study population characteristics.^a

Characteristic	N (%)
Total N	
	1653
Number of surveys per individual	
1	1006 (61)
2	546 (33)
3	58 (4)
4	43 (3)
MHOS cohort	
1998-1999	456 (28)
2000-2001	379 (23)
2002-2003	183 (11)
2004-2005	156 (9)
2006-2007	179 (11)
2008-2009	300 (18)
Age at diagnosis (years)	
Mean (s.d.)	71.7 (8.5)
Gender	
Male	1175 (71)
Female	478 (29)
Smoking status	
Former/never	1103 (74)
Current	387 (26)
Marital status	
Married	917 (57)
Divorced/separated/never married	318 (20)
Widowed	372 (23)
Education	
Did not graduate high school	498 (31)
High school graduate/GED	506 (32)
Post-high school	597 (37)
Household income	

Characteristic	N (%)
<\$19,999	595 (36)
\$20,000-49,999	573 (35)
\$50,000	178 (11)
Don't know/missing	307 (19)
Race	
White	1299 (79)
Other	354 (21)
Recent depressive symptoms	
No	1134 (70)
Yes	483 (30)
Comorbidities	
0-1	557 (35)
2-3	573 (36)
4	478 (30)
Calendar period of diagnosis	
1988-1997	380 (23)
1998-2000	367 (22)
2001-2003	265 (22)
2004-2006	311 (19)
2007-2009	230 (14)
Primary site	
Larynx	625 (38)
Oral cavity	385 (23)
Lip	198 (12)
Oropharynx	295 (18)
Hypopharynx	71 (4)
Nasopharynx, nasal cavity, paranasal sinuses	79 (5)
SEER stage	
In situ	94 (6)
Local	822 (56)
Regional	426 (29)
Distant	119 (8)
Radiotherapy	
No	661 (41)
Yes	963 (59)

^aFor individuals with multiple surveys, time-varying demographic information is from survey most proximal to head and neck cancer diagnosis.

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Table 2
Trends in HRQOL at various times relative to head and neck cancer diagnosis, overall and stratified by survival group

Time	Overall N=1653		<2 year survivors N=296		2-5 year survivors N=209		>5 year survivors N=1081	
	HRQOL score (95%CI)	Change from baseline (95%CI)	HRQOL score (95%CI)	Change from baseline (95%CI)	HRQOL score (95%CI)	Change from baseline (95%CI)	HRQOL score (95%CI)	Change from baseline (95%CI)
5 years pre-diagnosis ('baseline’)	92.3 (89.3,95.2)		87.3 (92.7,91.9)		92.8 (85.1,100.5)		96.4 (91.8,100.9)	
2 years pre-diagnosis	90.2 (88.4,92.0)	-2.1 (-5.4,1.3)	86.3 (83.4,89.2)	-1.0 (-6.7,4.8)	89.8 (85.3,94.2)	-3.1 (-12.4,6.3)	94.5 (91.9,97.1)	-1.9 (-6.9,3.1)
Diagnosis	85.0 (83.4,86.6)	-7.2 (-10.4,-4.0)	73.9 (70.3,77.6)	-13.4 (-18.6,-8.2)	82.9 (79.0,86.9)	-9.9 (-18.3,-1.5)	91.5 (89.4,93.5)	-4.9 (-9.8,0.04)
13 months post-diagnosis	83.7 (82.0,85.4)	-8.5 (-11.6,-5.4)	69.7 (62.8,76.7)	-17.6 (-26.1,-9.0)	79.9 (76.1,83.7)	-12.9 (-20.9,-4.9)	90.1 (87.9,92.2)	-6.3 (-11.1,-1.6)
2 years post-diagnosis	84.1 (82.4,85.8)	-8.2 (-11.2,-5.2)	63.8 (35.9,91.7)	-23.5 (-51.6,4.5)	78.0 (73.6,82.5)	-14.8 (-23.2,-6.3)	89.2 (87.2,91.2)	-7.2 (-11.7,-2.7)
5 years post-diagnosis	88.0 (86.2,89.7)	-4.3 (-7.5,-1.0)			52.1 (14.9,89.3)	-40.7 (-79.1,-2.3)	88.6 (86.8,90.3)	-7.8 (-12.5,-3.2)
10 years post-diagnosis	84.6 (81.6,87.6)	-7.7 (-11.9,-3.5)					84.2 (81.4,87.1)	-12.1 (-17.5,-6.8)

CI, confidence interval

Table 3
Characteristics significantly associated with HRQOL among individuals diagnosed with head and neck cancer

Characteristic	Difference in HRQOL, Univariate ^d (95%CI)	p-value	Difference in HRQOL, Multivariate ^{d,b} (95%CI)	p-value
A. Characteristics for which association with HRQOL does not significantly vary with time from diagnosis:				
Age at diagnosis, by quartile (years)		<0.001		0.01
<67 years	REF		REF	
68-72 years	3.9(1.5,6.3)		1.9(-0.1,3.9)	
73-77 years	2.6(-1.5,1)		1.0(-1.0,3.0)	
>78 years	-2.0(-4.6,0.5)		-1.3(-3.4,0.9)	
Gender		0.006		
Male	REF			
Female	-2.6(-4.4,-0.7)			
Smoking		<0.001		
Former/never	REF			
Current	-3.6(-5.5,-1.8)			
Marital status		0.001		
Married	REF			
Not married	-2.7(-4.4,-1.1)			
Education		<0.001		
<High school graduate	REF			
High school graduate/GED	3.8(1.9,5.8)			
Post-high school	7.1(5.1,9.1)			
Household income		<0.001		<0.001
<\$19,999	REF		REF	
\$20,000-49,999	5.6(3.9,7.3)		3.7(2.3,5.2)	

Characteristic	Difference in HRQOL, Univariate ^a	(95%CI)	p-value	Difference in HRQOL, Multivariate ^{a,b}	(95%CI)	p-value
\$50,000	12.3(9.8,14.9)			8.5(6.3,10.7)		
Don't know/missing	3.5(1.6,5.4)			3.9(2.1,5.8)		
Race			0.008			
White	REF					
Other	-2.8(-4.9,-0.7)					
Comorbidities			<0.001			<0.001
0-1	REF			REF		
2-3	-9.3(-10.9,-7.7)			-7.3(-8.8,-5.8)		
4	-17.9(-19.6,-16.1)			-14.9(-16.5,-13.2)		
Depression in past year			<0.001			<0.001
No	REF			REF		
Yes	-20.2(-21.6,-18.8)			-16.8(-18.2,-15.4)		
Primary site			0.03			
Larynx/hypopharynx	REF					
Oral cavity	-0.9(-3.0,1.3)					
Oropharynx	-0.6(-2.9,1.8)					
Other ^c	2.9(0.4,5.3)					
B. Characteristics for which association with HRQOL significantly varies by time from diagnosis:						
	2 years pre-diagnosis	13 months post-diagnosis	5 years post-diagnosis	2 years pre-diagnosis	13 months post-diagnosis	5 years post-diagnosis
Stage						
			<0.001			<0.001
Early	REF	REF	REF	REF	REF	REF
Late	0.3(-3.2,3.7)	-10.1(-13.5,-6.7)	-0.5(-4.1,3.0)	0.2(-2.8,3.1)	-6.8(-9.8,-3.8)	1.5(-1.5,4.4)
Radiotherapy			0.001			0.01
No	REF	REF	REF	REF	REF	REF

Characteristic	Difference in HRQOL, Univariate ^a	(95%CI)	p-value	Difference in HRQOL, Multivariate ^{a,b}	(95%CI)	p-value
Yes	2.2(-1.2,5.6)	-7.3(-10.6,-4.0)	-0.8(-3.9,2.2)	1.9(-1.1,4.9)	-5.1(-8.1,-2.2)	-1.2(-3.9,1.5)

^aModels include cubic spline terms for time relative to HNSCC diagnosis.

^bModel includes all characteristics for which results are reported, survey by proxy and calendar year of diagnosis.

^cOther: includes nasopharynx, nasal cavity, paranasal sinuses, and lip.

CI, confidence interval

Table 4
Risk factors for mortality among 664 individuals for whom HRQOL was assessed within 5 years before head and neck cancer diagnosis

Characteristic	N (%)	Univariate HR (95%CI)	Multivariate HR ^a (95%CI)
Pre-diagnosis HRQOL(per 10-point increase)			
Median (IQR)	90.1 (74.4-106.0)	0.86(0.82-0.91)	0.91(0.85-0.97)
Age at diagnosis (years)			
Mean (standard deviation)	75.2 (7.5)	1.04(1.03-1.06)	1.07(1.05-1.09)
Gender			
Male	466 (70)	REF	
Female	198 (30)	1.12(0.92-1.37)	
Smoking status			
Former/never	405 (68)	REF	REF
Current	190 (32)	1.24(1.02-1.52)	1.48(1.15-1.91)
Marital status			
Married	369 (57)	REF	REF
Not married	279 (43)	1.41(1.17-1.69)	1.18 (0.92-1.50)
Education			
Did not graduate high school	205 (32)	REF	
High school graduate/GED	204 (32)	0.86(0.68-1.08)	
Post-high school	235 (36)	0.77(0.61-0.96)	
Household income			
<\$19,999	241 (36)	REF	REF
\$20,000-49,999	220 (33)	0.74(0.60-0.92)	1.08(0.83-1.42)
\$50,000	73 (11)	0.50(0.35-0.71)	0.64(0.42-0.97)
Don't know/missing	130 (20)	0.86(0.66-1.11)	0.83(0.59-1.17)
Race			
White	530 (80)	REF	
Other	134 (20)	1.14(0.89-1.44)	
Comorbidities			
0-1	215 (33)	REF	REF
2-3	237 (37)	1.11(0.88-1.39)	0.99(0.76-1.31)
4	196 (30)	1.46(1.16-1.82)	1.19(0.89-1.59)

Characteristic	N (%)	Univariate HR (95%CI)	Multivariate HR ^a (95%CI)
Primary site			
Larynx, hypopharynx	267 (40)	REF	REF
Oral cavity	170 (26)	1.24(0.99-1.56)	0.98(0.73-1.30)
Oropharynx	131 (20)	1.59(1.25-2.03)	1.08(0.79-1.46)
Other ^b	96 (14)	1.48(0.90-2.41)	0.88(0.61-1.28)
Stage			
Early	338 (54)	REF	REF
Late	284 (46)	2.30(1.90-2.79)	2.50(1.95-3.19)
Radiotherapy			
No	257 (39)	REF	REF
Yes	397 (61)	1.20(1.00-1.45)	1.20(0.94-1.54)

^aModel includes survey by proxy.

^b'Other' includes nasopharynx, nasal cavity, paranasal sinuses, and lip.

HR, hazard ratio; CI, confidence interval; IQR, interquartile range