Title

Changing functional status within 6 months posttreatment is prognostic of overall survival in patients with head and neck cancer: NRG Oncology Study

Journal

Head & Neck, 41(11)

ISSN

1043-3074

Authors

Eldridge, Ronald C
Pugh, Stephanie L
Trotti, Andy
et al.

Publication Date

2019-11-01

DOI

10.1002/hed.25922

Peer reviewed

HHS Public Access

Author manuscript

Head Neck. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

Head Neck. 2019 November ; 41(11): 3924–3932. doi:10.1002/hed.25922.

Changing Functional Status within Six Months Post-treatment is Prognostic of Overall Survival in Head and Neck Cancer Patients: an NRG Oncology Study

Ronald Curtis Eldridge, PhD[1], **Stephanie L Pugh, PhD**[2], **Andy Trotti, MD**[3], **Kenneth Hu, MD**[4], **Sharon Spencer, MD**[5], **Sue Yom, MD**[6], **David Rosenthal, MD**[7], **Nancy Read, MD**[8], **Anand Desai, MD**[9], **Elizabeth Gore, MD**[10], **George Shenouda, MD**[11], **Mark V Mishra, MD**[12], **Deborah Bruner, PhD**[1], **Canhua Xiao, PhD**[1]

[1]Emory University/Winship Cancer Center

[2]NRG Oncology Statistics and Data Management Center

[3]Moffitt Cancer Center

[4]Laura and Isaac Perlmutter Cancer Center at NYU Langone

[5]University of Alabama at Birmingham Medical Center

[6]UCSF Medical Center-Mount Zion

[7]University of Texas MD Anderson Cancer Center

[8]London Regional Cancer Program

[9]Akron City Hospital

[10]*Zablocki VA Medical Center* (accruals under *Froedtert and the Medical College of Wisconsin*)

[11]McGill University

[12]University of Maryland/Greenebaum Cancer Center

Abstract

Background: Is post-treatment functional status prognostic of overall survival in head and neck cancer (HNC) patients.

Methods: In an HNC clinical trial, 495 patients had two post-treatment functional assessments measuring diet, public eating, and speech within 6 months. Patients were grouped by impairment (highly, moderately, modestly, or not impaired) and determined if they improved, declined, or did not change from the first assessment to the second. Multivariable Cox models estimated overall mortality.

Results: Across all three scales, the change in post-treatment patient function strongly predicted overall survival. In diet, patients who declined to highly impaired had three times the mortality of patients who were not impaired at both assessments (hazard ratio=3.60; 95% confidence interval:

Corresponding author: Canhua Xiao, canhua.xiao@emory.edu, Address: 1520 Clifton Rd, Room 234, Atlanta, GA, 30322, Phone: (404) 712-9823.

2.02, 6.42). For patients improving from highly impaired, mortality was statistically similar to patients with no impairment (HR=1.38, 95% CI: 0.82, 2.31).

Conclusions: Post-treatment functional status is a strong prognostic marker of survival in HNC patients.

Keywords

Head and Neck Cancer Survival; Functional Status; Post-treatment; Longitudinal change; Quality of Life

INTRODUCTION

Cancer can negatively affect a patient's functional ability. In head and neck cancer (HNC), patients generally suffer a severe decline in physical and/or psychosocial function followed by a long recovery period [1,2]. Due to the anatomical sites of HNC, impaired function in a patient's ability to eat, speak, swallow, and smell can have dramatic effects on the patient's health-related quality of life (HRQOL). Instruments measuring patient functional status and HRQOL have been important secondary outcomes in HNC clinical trials [3–5]; the Performance Status Scale for Head and Neck Cancer Patients (PSS-HN) is a functional status measure [6]. More recently, functional status and HRQOL have been used as prognostic markers of patient survival.

A recent review of 19 prospective studies reported that a patient's pre-treatment physical function had strong evidence of an association with overall survival but other HRQOL subscales (Emotional, Cognitive, Social, Mental, and Role), and global HRQOL, had insufficient evidence [7]. Fewer papers in the review reported HRQOL during or after treatment but post-treatment HRQOL may be an indicator of patient response and recovery, possibly identifying a patient who may benefit from additional clinical management. In that case, the change in physical function over time may be more informative than a single baseline measure but few studies have assessed change. One study reported that change in a patient's physical functioning between pre-treatment and 6 months post-treatment was significantly associated with overall survival [8]. No prior study has focused exclusively on changes during post-treatment recovery. One issue is identifying meaningful timepoints to assess functional status that are early enough to aid clinical management.

In this secondary analysis of a large randomized clinical trial of HNC patients, we examined whether longitudinal change in post-treatment patient functional status, as measured by the PSS-HN, was associated with overall survival. A patient's PSS-HN response at two timepoints – 1) within the first 90 days post-treatment and 2) within 91 days to 6 months post-treatment – was used to determine whether the patient's functional status improved, declined, or stayed the same. That change was then fit to a regression model of overall survival. The goal of this analysis was to assess the potential benefit for monitoring post-treatment patient performance and to provide simple, concrete timepoints for future studies.

MATERIALS and METHODS

Study Population

The analysis consisted of patients enrolled in NRG Oncology's RTOG 9003 trial. RTOG 9003 was a randomized phase III clinical trial of stage III/IV HNC patients that activated in 1991, closed in 1997, and collected data through 2013; informed consent was obtained from all patients and the Institutional Review Boards of the National Cancer Institute and each study site approved the protocol [9]. The trial evaluated standard fractionated radiotherapy versus three other radiotherapy interventions: i) hyperfractionated, ii) accelerated fractionated split course, iii) accelerated fractionated with concomitant boost. The follow-up protocol was weekly during treatment, every 3 months for 1.5 years post-treatment, every 4 months from 1.5 to 3 years, every 6 months from 3 to 5 years, and then annually.

Patient Performance Status for Head and Neck Cancer (PSS-HN)

The PSS-HN was designed and validated to evaluate head and neck cancer patient functioning and performance in three scales: Normalcy of Diet, Eating in Public, and Understandability of Speech [6,10]. The assessment is an unstructured interview administered by a staff member (i.e., study data manager, nurse, or clinical staff) who asks the patient questions in the three scales.

Based on patient responses, the interviewer will ask questions that demonstrate progressively better patient function and will stop when the patient responds in the negative; for instance, if a patient responds she eats soft foods, the interviewer will ask the patient about "soft chewable foods", then "dry bread and crackers" and so forth, until the patient responds she does not eat the food in question. The assessment of Understandability of Speech is based on the interviewer's ability to understand the patient during the interview. Each scale ranges from 0-100 where ≤50 indicates moderate to severe impairment and 100 indicates no impairment. The RTOG 9003 protocol called for PSS-HN to be collected at 1, 3, and 6 months post-treatment, then every 3 months afterward until 1.5 years. The PSS-HN was collected until 2000 when it was discontinued due to study burden. For sample size and analytical considerations, this analysis considered the post-treatment change in PSS-HN assessments between the first follow-up within 90 days and a second follow-up within 91 days to 6 months.

Analysis of Patient Functional Status

For these analyses, we grouped raw PSS-HN responses based on similar levels of impairment and sample size considerations (Table 1); future studies may want to assess the continuous PSS-HN measures. Specifically, normalcy of diet and public eating grouped into four levels of impairment we call "highly impaired", "moderately impaired", "modestly impaired", and "not impaired". Clarity of speech was grouped into three levels called "highly impaired", "moderately impaired", and "not impaired". For each analysis, the referent category was the "not impaired" level. Patient functional status was evaluated as a prognostic marker of overall survival using two approaches. The first approach used the first follow-up assessment within 90 days post-treatment; this was included as a reference to prior research. The other approach, the primary analysis, was the longitudinal improvement,

decline, or lack of change in impairment between the first follow-up and a second follow-up assessment within 91 days to 6 months. The worst PSS-HN in each time interval was used if a patient had multiple. We identified eight categories of patients who either improved (n=2), declined (n=2), or had no change (n=4) in their levels of impairment (Figure 1). The two groups that improved were: i) patients who were highly impaired at the first assessment but moderately, modestly, or not impaired at the second, called “improved from highly impaired”; ii) patients who were moderately or modestly impaired at the first assessment and improved to either modestly or not impaired at the second, called “general improvement”. The two groups that declined were the reverse: iii) patients who were moderately, modestly, or not impaired at the first assessment, but highly impaired at the second, called “declined to highly impaired”; and iv) patients who were modestly or not impaired at their first assessment and declined but did not reach the highly impaired category, called “general decline”. The four groups with no change between their first and second assessments correspond to the four levels of impairment. Since Clarity of Speech had only 3 levels of impairment there were 7 rather than 8 change categories: 2 that improved, 2 that declined, and 3 with no change. In a post-hoc analysis, the joint effects of the three PSS-HN scales were assessed by classifying patients as high-risk (denoted with * in Table 3) in either zero, one, two, or all three scales then regressing those groups on overall survival.

Statistical Methods

Multivariable proportional hazards regression was used to model overall survival on the three performance scales separately for the two approaches above. The primary result of this analysis is the post-treatment change in PSS-HN with survival. All models were adjusted for assigned treatment, patient age at study entry, sex, race, cancer site, tumor stage and grade, Karnofsky Performance Status, patient toxicity, study interviewer (i.e., data manager, nurse, or other clinical staff), the patient’s smoking status, marital status, education level, prior household income, and the dates of each PSS-HN assessment relative to treatment. Adjusted hazard ratios (HR), 95% confidence intervals (CI), and *P* values for the functional status variables are reported. All significance tests used a <0.05 threshold. Analyses were performed using SAS 9.4 (Cary, NC, USA) [11].

RESULTS

Seven hundred forty four of the 1,076 patients underwent assessment of functional status and thus were eligible for this analysis. Selected characteristics of those patients are listed in Table 2. The median age at study entry was 60 years. Eighty percent of the sample was male and 73% was white. The distribution of primary site tumors of the oropharynx, hypopharynx, larynx, and oral cavity were 59%, 14%, 17% and 10%, respectively. Forty-eight percent of the sample were heavy smokers with >40 pack years. For the survival analyses, 61 patients were excluded because they did not have a functional status within 90 days post-treatment, and an additional 30 patients were excluded because of missing information on covariates. A further 158 patients were excluded from the longitudinal analyses because they had only one functional assessment or their second assessment occurred after 6 months post-treatment. Of the 495 patients in the longitudinal analytic sample, 59 (12%) were censored.

Table 1 shows the grouped PSS-HN response categories among all patients who had their first assessment within 90 days of treatment. For each response category, the frequencies, average follow-up in person-years, and average number of days after treatment when the PSS-HN assessment occurred are provided. On average, a patient had their first functional assessment 33 days after treatment, in line with the study protocol; 92% of the cohort had its first assessment within 90 days. The average follow-up was 4.6 years; the median was 2.2 years.

The survival results for a single PSS-HN assessment within 90 days post-treatment are reported as a reference to past research (Supplementary Table 1). In all three scales (normalcy of diet, public eating, and clarity of speech), the highly impaired group had the worst survival and was statistically significant from the not impaired group. For the normalcy of diet and public eating scales, the highly impaired groups were the only significant findings. However for the understandability of speech scale, the moderately impaired group also had significantly worse survival compared to the not impaired group.

For the primary analysis, the post-treatment change in a patient's PSS-HN between the first follow-up assessment within 90 days and a second follow-up within 91 days and 6 months was examined (Table 3 and Figure 2). Overall, patients who were highly or moderately impaired at both assessments had significantly higher mortality relative to patients who were not impaired at both assessments (referent group). Additionally, patients who declined in impairment from the first to the second assessment had significantly higher mortality. For instance, a patient who in their dietary restrictions was either moderately/modestly/not impaired at the first assessment but was highly impaired at the second assessment, had more than three times the mortality rate (HR=3.60; 95% CI: 2.02, 6.42). However if a patient showed the reverse, being highly impaired at <90 days but then improving to either moderately/modestly/not impaired at <6 months, that patient had statistically similar survival to patients reporting no impairment at both times (HR=1.38, 95% CI: 0.82, 2.31). Other noteworthy results are seen in patients who remained moderately impaired at the first and second assessment, among whom had roughly two times the mortality across the three scales (diet scale HR=2.49; 95% CI: 1.58, 3.92; public eating scale HR=1.47; 95% CI: 1.07, 2.00; speech scale HR=1.99; 95% CI: 1.31, 3.03). Also noteworthy are patients whose level of impairment declined but did not reach highly impaired, categorized as showing "general decline". Those patients had a diet scale HR=2.60 (95% CI: 1.67, 4.05), and a public eating scale HR=1.79 (95% CI: 1.26, 2.54). In separate sensitivity analyses, the cohort was stratified by primary site (oropharyngeal and non-oropharyngeal; supplementary tables 2 and 3) and conditional on patients who survived 1 year and 2 years (supplemental tables 4 and 5). In each, only modest differences to the pattern previously described were observed.

To highlight the importance of a patient's changing functional status during recovery, the results for one group that improved in the diet scale ("improved from highly impaired") and one group that declined ("general decline") are noted. For both groups of patients, survival would be mischaracterized if a single assessment was used. Additionally, at the second assessment (<6 months), both groups of patients had similar levels of impairment: 55% were moderately impaired, 39% modestly impaired, 6% not impaired in the "improved from highly impaired" group (n=33); and 69% were moderately impaired and 31% modestly

impaired in the “general decline” group (n=49). Despite having similar impairment levels at <6 months, the survival for each group appears quite different: HR=1.38 (95% CI: 0.82, 2.31) for the “improved from highly impaired” group, and HR=2.60 (95% CI: 1.67, 4.05) for the “general decline” group. This result demonstrates that survival for these patients depended on the trajectory of their post-treatment functional status more so than any individual assessment.

The joint contribution to mortality in the three PSS-HN scales was assessed by determining if a patient was high-risk (designated by * in Table 3), in either 1, 2, or all 3 scales; the referent group were patients who were not at high-risk in any of the three scales. Fifty-four percent of the cohort was determined high-risk in at least one scale (22% in one scale, 20% in two scales, 12% in three scales). A high-risk patient in one scale had an HR=1.64 (95% CI: 1.25, 2.14), while a high-risk patient in two scales had an HR=2.30 (1.72, 3.06), and a high-risk patient in all three scales had an HR=5.44 (95% CI: 3.79, 7.83). This result suggests there is a cumulative effect with each scale. The differences in survival are stark and persisted throughout follow-up (Figure 3).

DISCUSSION

In a secondary analysis of a large randomized clinical trial of head and neck cancer patients, a patient’s change in functional status in the 6 months post-treatment period was highly prognostic of overall survival. The association held for the initial functional assessment within 90 days post-treatment but improved dramatically when the patient’s improvement, or lack of, was considered in a second assessment from 91 days to 6 months. The prognostic ability persisted past the first and second year of follow-up and was independent of multiple other factors.

This study supports past research that finds the change in health related quality of life (HRQOL) in HNC patients is associated with survival [8,12–14]. However, where other studies estimated survival from the deterioration of HRQOL between pretreatment and post-treatment, in this study, survival was estimated based on the change in functional status exclusively during post-treatment recovery. The general characterization of HRQOL and functional status in HNC patients is a steep drop after treatment followed by a slow recovery period over the following year or two [1,2]. Identifying early and meaningful timepoints in the recovery period to assess HRQOL and functional status may have clinical benefit. Karvonen-Gutierrez et. al. recommended routine HRQOL assessments at pretreatment and at 6, 12, and 24 months post-treatment [15]. If the goal is predicting survival, our findings suggest this recommendation also include earlier post-treatment assessments – before 3 months and as early as 1 month in line with the RTOG 9003 protocol – because patient recovery from a severe decline in HRQOL may be more predictive of survival than the decline itself. Jameson et. al. and Verdonck-de Leeuw et. al. found that HRQOL recovery trajectories over 1 and 2 years post-treatment was associated with survival [13,14]. From the current study, patients who were highly impaired at <3 months post-treatment but showed modest improvement between 3-6 months had statistically the same survival as patients who experienced no impairment at both timepoints; and more than double the survival of patients who experienced little to no initial impairment but then modestly declined. Our analysis

suggests that patient recovery within the first 6 months is an important prognostic indicator though a trajectory analysis of patient recovery over a 1 or two year period may improve upon our results.

The Patient Performance Status for Head and Neck Cancer (PSS-HN) was used to measure patient functional status. Unlike HRQOL, the PSS-HN is not self-administered. It is a short, simple interview by a nurse or other clinical staff. The PSS-HN has adequate reliability [10] and correlates with other measures such as the Functional Assessment for Cancer Therapy Head and Neck instrument and the Karnofsky Performance Scale [6], though the results of this study are independent of a patient's Karnofsky score. Normalcy of diet relates closely to physical functioning [6] and physical functioning may better represent underlying patient conditions that influence survival [7]. Since the PSS-HN was specifically designed to measure HNC patient function this may be one reason why we observed stronger results than previous reports. In our study, we found all three PSS-HN scales were prognostic of survival though the highest variability was in normalcy of diet making it a more reliable indicator for change over time. All three scales may be indicators of physical functioning but they also appear to capture unique information because we observed cumulative survival effects, as high-risk patients in multiple scales had much worse survival than patients who were high-risk in just one scale.

The study has some notable strengths and weaknesses. Human papillomavirus (HPV) status was not available because the parent study was conducted before widespread HPV testing. An HPV positive patient has a better prognosis and is likely to respond better to radiotherapy than an HPV negative patient [16,17]. If HPV positive patients report better post-treatment functional status, or better functional recovery, part of our results may be explained by HPV. However in a sensitivity analysis, our results held among non-oropharyngeal cancer patients, a population that is largely HPV negative [18]. The parent clinical trial enrolled patients from 1993 to 1997 and the standard treatment for HNC has changed [19–22]. In this study, assigned treatment was not associated with PSS-HN recovery and treatment was adjusted in the analysis. However, due to the elapsed time, this analysis should be replicated in a more recent cohort. The parent study was also a strength of this analysis. The extensive follow-up and large sample size allowed us to assess changes in PSS-HN over time that would have been underpowered with fewer subjects and more censoring.

In a large study of HNC patients receiving radiotherapy, a patient's decline and recovering functional status over 6 months post-treatment was strongly associated with overall patient survival. The association was independent of multiple prognostic factors, persisted throughout follow-up, and affected one third to one half of the study population. Trajectories of HNC patient function may be a useful metric incorporated into clinical decision support algorithms, providing evidenced-based point of care information for clinical management [23]. However, further evidence of the burden of collecting this information would be required before clinical implementation. The strength of the association combined with the ease of the assessment and the early time at which it can be administered, suggests that repeat post-treatment functional assessments may have clinical benefits for head and neck cancer patients and should be further studied.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This project was supported by grants UG1CA189867 (NCORP), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC) from the National Cancer Institute (NCI).

Conflicts of Interest: Dr(s). Bruner, Desai, Eldridge, Gore, Hu, Pugh, Read, Shenouda, Spencer, Trotti and Xiao disclose no conflicts of interest. Dr. Mishra discloses employment of an immediate family member of Orthofix, stock and other ownership with GE and Adverum, honoraria from Varian, speakers' bureau compensation from Varian, and travel, accommodations, or expenses from Varian. Dr. Rosenthal discloses stock or other ownership with Concordia, a consulting or advisory role from Merck, research funding from Merck, and travel, accommodations and expenses from Merck. Dr. Yom discloses research funding from Genentech, Merck, and Bristol-Myers Squibb.

REFERNCES

1. List MA, Siston A, Haraf D, et al. Quality of Life and Performance in Advanced Head and Neck Cancer Patients on Concomitant Chemoradiotherapy: A Prospective Examination. J Clin Oncol 1999;17(3):1020–1020. [PubMed: 10071297]
2. So WKW, Chan RJ, Chan DNS, et al. Quality-of-life among head and neck cancer survivors at one year after treatment: A systematic review. Eur J Cancer. 2012;48(15):2391–2408. [PubMed: 22579456]
3. Browman GP, Levine MN, Hodson DI, et al. The Head and Neck Radiotherapy Questionnaire: a morbidity/quality-of-life instrument for clinical trials of radiation therapy in locally advanced head and neck cancer. J Clin Oncol 1993;11(5):863–872. [PubMed: 8487051]
4. 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. International Journal of Radiation Oncology • Biology • Physics. 1994;28(4):847–856.
5. Langendijk JA, Doornaert P, Leeuw IMV-d, Leemans CR, Aaronson NK, Slotman BJ. Impact of Late Treatment-Related Toxicity on Quality of Life Among Patients With Head and Neck Cancer Treated With Radiotherapy. J Clin Oncol 2008;26(22):3770–3776. [PubMed: 18669465]
6. List MA, D'Antonio LL, Cella DF, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale: A study of utility and validity. Cancer. 1996;77(11):2294–2301. [PubMed: 8635098]
7. van Nieuwenhuizen AJ, Buffart LM, Brug J, Leemans CR, Verdonck-de Leeuw IM. The association between health related quality of life and survival in patients with head and neck cancer: a systematic review. Oral Oncol 2015;51(1):1–11. [PubMed: 25262163]
8. Meyer F, Fortin A, Gélinas M, et al. Health-Related Quality of Life As a Survival Predictor for Patients With Localized Head and Neck Cancer Treated With Radiation Therapy. J Clin Oncol 2009;27(18):2970–2976. [PubMed: 19451440]
9. Beitler JJ, Zhang Q, Fu KK, et al. Final Results of Local-Regional Control and Late Toxicity of RTOG 9003: A Randomized Trial of Altered Fractionation Radiation for Locally Advanced Head and Neck Cancer. International Journal of Radiation Oncology*Biology*Physics. 2014;89(1):13–20.
10. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Cancer. 1990;66(3):564–569. [PubMed: 2364368]
11. SAS, Institute, Inc. Base SAS 9.4 Procedures Guide. Second ed. Cary, NC: SAS Institute Inc.; 2012.
12. Oskam IM, Verdonck-de Leeuw IM, Aaronson NK, et al. Quality of life as predictor of survival: A prospective study on patients treated with combined surgery and radiotherapy for advanced oral and oropharyngeal cancer. Radiother Oncol 97(2):258–262. [PubMed: 20189668]

13. Jameson MJ, Karnell L, Christensen AJ, Funk GF. First-year trends in self-reported general health predict survival in patients with head and neck cancer. Archives of Otolaryngology–Head & Neck Surgery. 2008;134(9):958–964. [PubMed: 18794441]
14. Verdonck-de Leeuw IM, Buffart LM, Heymans MW, et al. The course of health-related quality of life in head and neck cancer patients treated with chemoradiation: A prospective cohort study. Radiother Oncol 2014;110(3):422–428. [PubMed: 24582144]
15. Karvonen-Gutierrez CA, Ronis DL, Fowler KE, Terrell JE, Gruber SB, Duffy SA. Quality of Life Scores Predict Survival Among Patients With Head and Neck Cancer. J Clin Oncol 2008;26(16): 2754–2760. [PubMed: 18509185]
16. Ang KK, Harris J, Wheeler R, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. N Engl J Med 2010;363(1):24–35. [PubMed: 20530316]
17. Lassen P The role of Human papillomavirus in head and neck cancer and the impact on radiotherapy outcome. Radiother Oncol 95(3):371–380. [PubMed: 20493569]
18. Combes J-D, Franceschi S. Role of human papillomavirus in non-oropharyngeal head and neck cancers. Oral Oncol50(5):370–379. [PubMed: 24331868]
19. Pignon J-P, Maître AI, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 92(1):4–14. [PubMed: 19446902]
20. Al-Sarraf M Treatment of Locally Advanced Head and Neck Cancer: Historical and Critical Review. Cancer Control. 2002;9(5):387–399. [PubMed: 12410178]
21. Vermorken JB, Mesia R, Rivera F, et al. Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. N Engl J Med 2008;359(11):1116–1127. [PubMed: 18784101]
22. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. The Lancet Oncology. 2010;11(1):21–28. [PubMed: 19897418]
23. Lobach DF, Johns EB, Halpenny B, et al. Increasing Complexity in Rule-Based Clinical Decision Support: The Symptom Assessment and Management Intervention. JMIR Medical Informatics. 2016;4(4):e36. [PubMed: 27826132]

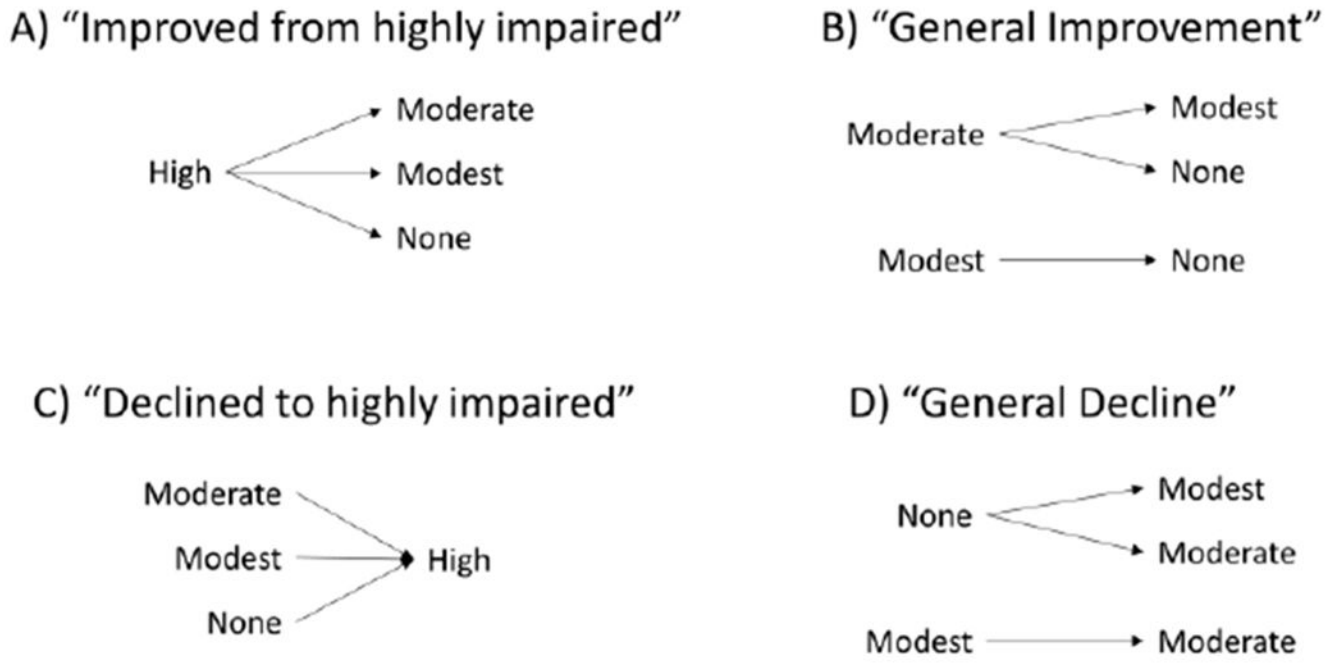

Figure 1.

The four classifications of patients whose Performance Status Scale for Head and Neck impairment level changed from the 1st follow-up at <90 days to the 2nd follow-up at 91 days to <6 months. Panels A and B show patients who improved from the 1st to the 2nd assessment, and panels C and D show patients who declined from the 1st to the 2nd assessment. Not shown are the four groups of patients whose impairment status did not change between the first and second follow-up: highly impaired, no change; moderately impaired, no change; modestly impaired, no change; and not impaired, no change.

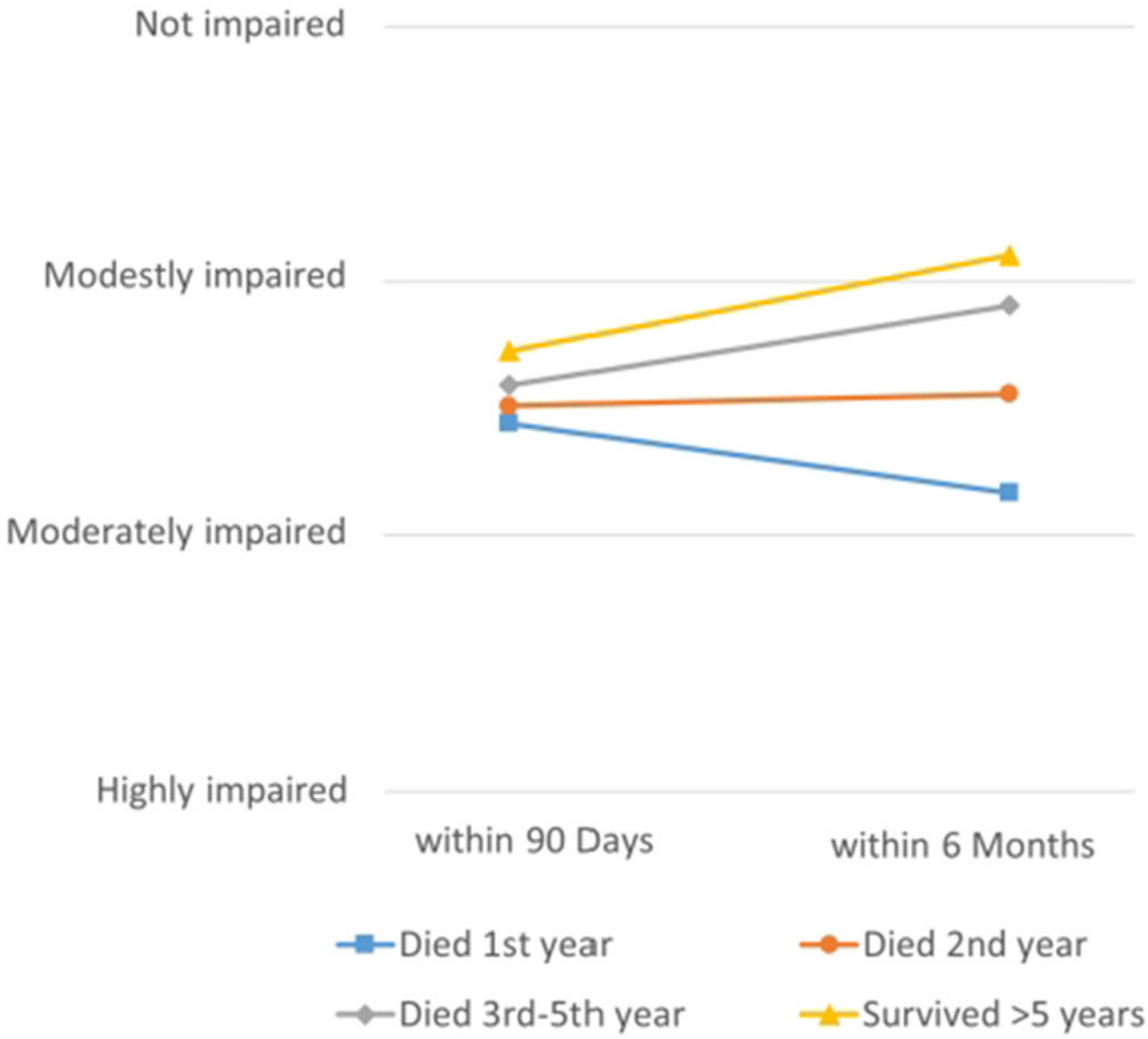

Figure 2.

Average level of impairment in the “normalcy of diet” scale of the Performance Status Scale for Head and Neck at a first assessment within 90 days of treatment and at a follow-up assessment within 6 months of treatment stratified by duration of overall survival in 493 head and neck cancer patients.

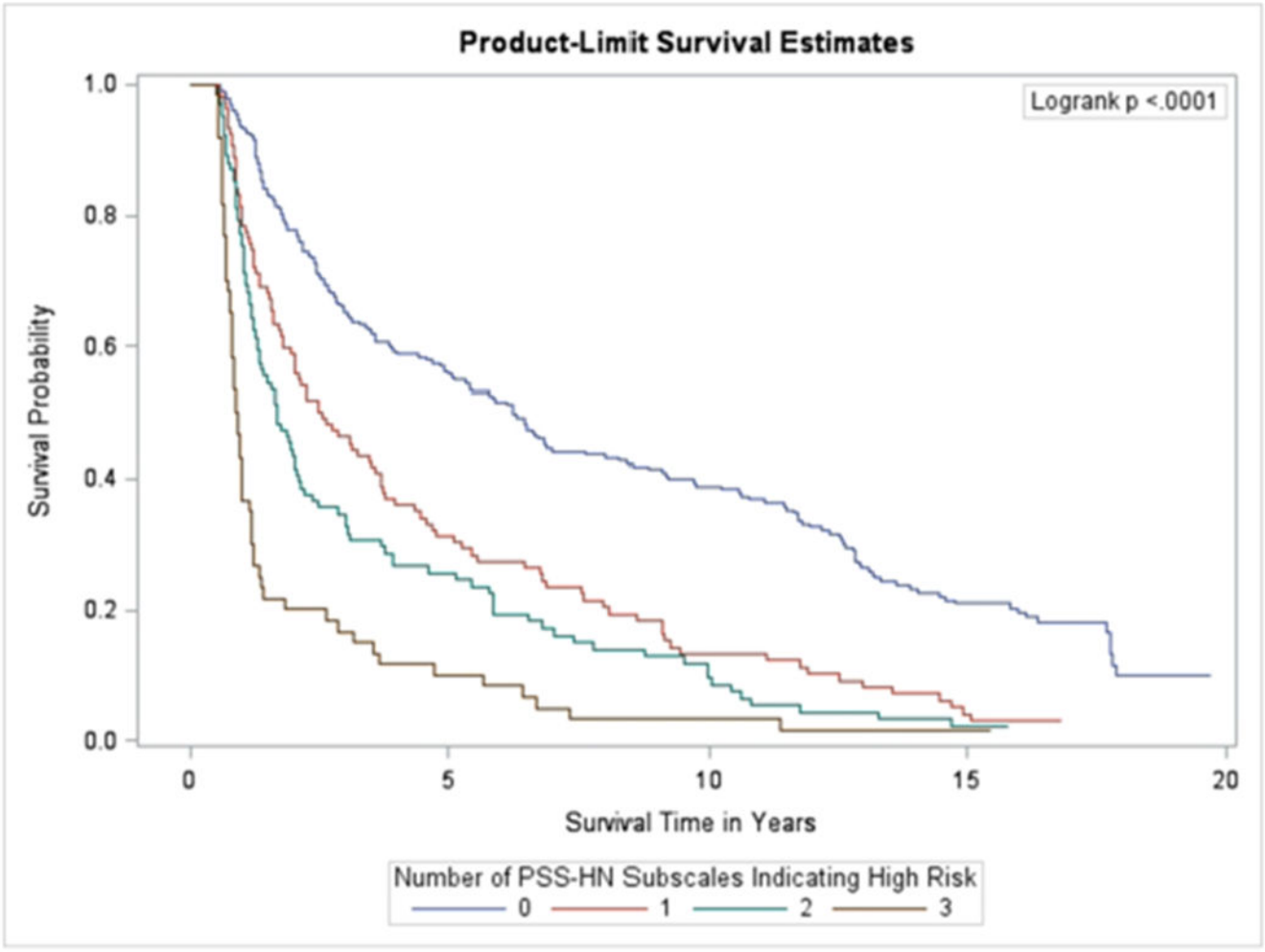

Figure 3.

Kaplan-Meier overall survival curve of head and neck cancer patients classified as high-risk (denoted with a * in Table 3) in either zero, one, two, or all three Performance Status Scale for Head and Neck (PSS-HN) scales in the Radiation Therapy Oncology Group 9003 study (N=495). For patients high-risk in zero scales (N=226) as the referent category, we observed statistically significant increased risks for patients high-risk in one scale (N=107, hazard ratio=1.64, 95% confidence interval: 1.25, 2.14), two scales (N=101, HR=2.30, 95% CI: 1.72, 3.06), and all three scales (N=61, HR=5.44, 95% CI: 3.79, 7.83).

Table 1.

Frequency table, average follow-up time, and average date of functional assessment within the first 90 days after treatment for response categories of the three measures in the PSS-HN assessment in the RTOG 9003 study

	Levels of Impairment[a]	No. of Patients	Avg number of PY	% of total PY per scale	PSS-HN Assessment date (SD)[b]
Normalcy of Diet (N=650)					
Non-oral feeding	Highly impaired	98	3.4	10.9	30.8 (13.2)
Cold liquids	Moderately impaired	27	4.6	4.0	29.1 (13.9)
Warm liquids	“ ”	44	3.6	5.1	30.5 (15.8)
Pureed foods	“ ”	30	4.2	4.1	33.6 (15.2)
Soft foods requiring no chewing	“ ”	86	4.4	12.4	30.9 (15.1)
Soft chewable foods	Modestly impaired	186	5.3	32.0	35.1 (13.6)
Dry bread and crackers	“ ”	34	4.8	5.3	30.3 (15.2)
Carrots, celery	“ ”	10	6.3	2.1	36.7 (19.2)
All meat	“ ”	36	4.9	5.8	39.4 (18.4)
Peanuts	“ ”	4	3.7	0.5	29.3 (8.1)
Full Diet	Not impaired	95	5.7	17.7	35.3 (14.2)
Public Eating (N=633)					
Always eats alone	Highly impaired	48	2.2	3.4	32.8 (15.7)
Eats only at home with select persons	Moderately impaired	172	4.2	24.3	30.3 (14.9)
Eats only in select places	“ ”	95	4.5	14.2	33.9 (14.4)
Eats anywhere, may limit intake	Modestly impaired	108	5.7	20.6	33.8 (15.3)
No restriction of place or food	Not impaired	210	5.4	37.4	35.2 (13.8)
Understandability of Speech (N=645)					
Never understandable	Highly impaired	12	1.3	0.5	36.5 (24.4)
Difficult to understand	“ ”	14	0.8	0.4	41.4 (15.0)
Usually understandable, face to face	“ ”	34	1.5	1.7	31.2 (17.7)
Understandable most of the time, some repetition	Moderately Impaired	113	3.0	11.4	32.0 (14.2)
Always understandable	Not impaired	472	5.5	86.1	33.3 (14.3)

Abbreviations: RTOG=radiation therapy oncology group, PSS-HN=Performance Status Scale for Head and Neck cancer patients, AVG=average, PY=person-years, SD=standard deviation;

[a] The levels correspond to the analytical groups used in proportional hazards modeling. The shading indicates where multiple PSS-HN response categories were grouped for analytical purposes.

[b] The average number of days between the end of treatment and the first functional assessment by the PSS-HN.

Table 2.

Selected characteristics of the RTOG protocol 9003 study population with a PSS-HN (N=744)

Age, median (IQR)	60	(53, 66)
Sex	*No. of Patients*	*% of total*
Male	597	80.2
Female	147	19.8
Race		
White	541	72.7
Hispanic	40	5.4
Black	145	19.5
Other	12	1.6
Protocol RX		
standard	191	25.7
HFX arm	195	26.2
AFX-C arm	177	23.8
AFX-S arm	181	24.3
Education		
Grade 1-8, or none	107	14.4
Some high school	180	24.2
High school graduate	211	28.4
Some college/technical	208	28.0
Marital Status		
Married	370	49.7
Not married	356	47.8
Smoking		
Non-smoker	72	9.7
<20 pack years	86	11.6
20-40 pack years	180	24.2
>40 pack years	356	47.8
Unknown, unanswered	50	6.7
Cancer site		
Oral cavity	76	10.2
Oropharynx	441	59.3
Hypopharynx	104	14.0
Supraglottic larynx	123	16.5
KPS		
60	28	3.8
70	76	10.2
80	158	21.2
90	347	46.6
100	135	18.1
Tumor classification		

T1	43	5.8
T2	202	27.2
T3	277	37.2
T4	222	29.8
Lymph node classification		
N0	158	21.2
N1	150	20.2
N2	349	46.9
N3	87	11.7
Highest grade toxicity within 6 months post-treatment		
0-2	328	44.1
3-5	416	55.9

Abbreviations: RTOG=radiation therapy oncology group, PSS-HN=Performance Status Scale for Head and Neck cancer patients, IQR=interquartile range, RX=radiation treatment, HFX=hyperfractionated, AFX-C=accelerated fractionated with concomitant boost, AFX-S=accelerated fractionated with a split

Table 3.

Change in PSS-HN from initial assessment within 90 days of treatment to follow-up assessment within 6 months for overall survival

Normalcy of Diet (n=493)	No. of Patiens	HR	95% CI	*P* value
*Highly impaired, no change	33	3.32	(1.91, 5.77)	<0.001
*Declined to highly impaired	28	3.60	(2.02, 6.42)	<0.001
Improved from highly impaired	33	1.38	(0.82, 2.31)	0.221
*Moderately impaired, no change	61	2.49	(1.58, 3.92)	<0.001
*General decline	49	2.60	(1.67, 4.05)	<0.001
General improvement	116	0.98	(0.66, 1.45)	0.908
Modestly impaired, no change	120	1.12	(0.76, 1.65)	0.580
Not impaired, no change	53	1	ref	
Public Eating (n=474)				
*Highly impaired, no change	16	3.56	(1.96, 6.47)	<0.001
*Declined to highly impaired	25	1.82	(1.03, 3.21)	0.038
Improved from highly impaired	14	1.29	(0.67, 2.51)	0.446
*Moderately impaired, no change	116	1.47	(1.07, 2.00)	0.017
*General decline	58	1.79	(1.26, 2.54)	0.001
General improvement	94	0.78	(0.57, 1.08)	0.132
Modestly impaired, no change	32	0.97	(0.61, 1.54)	0.886
Not impaired, no change	119	1	ref	
Understandability of Speech (N=481)				
*Highly impaired, no change	18	2.30	(1.26, 4.21)	0.007
*Declined to highly impaired	36	3.01	(2.02, 4.48)	<0.001
*Improved from highly impaired	16	2.12	(1.21, 3.70)	0.008
*Moderately impaired, no change	36	1.99	(1.31, 3.03)	0.001
General decline	27	1.09	(0.68, 1.73)	0.734
General improvement	28	1.04	(0.67, 1.63)	0.852
Not impaired, no change	320	1	ref	

Abbreviations: RTOG=radiation therapy oncology group, PSS-HN=Performance Status Scale for Head and Neck cancer patients, HR=hazard ratio, CI=confidence interval, ref=referent group

HRs adjusted for age, sex, race, assigned treatment, tumor stage and grade, tumor site, Karnofsky performance, patient toxicity, smoking status, marital status, education level, income level, PSS-HN administrator and dates of assessments

*Denotes high-risk group