ORIGINAL ARTICLE

HEALTH-RELATED QUALITY OF LIFE PROFILES BASED ON SURVIVORSHIP STATUS FOR HEAD AND NECK CANCER PATIENTS

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Abstract: *Background.* As the methodologies for evaluating health-related quality of life (HRQOL) in head and neck cancer patients have matured over the past 10 years, there has been an increasing focus on reporting longitudinal data. These studies have primarily focused on long-term survivors. This study addresses the HRQOL of both long-term and short-term survivors.

Methods. This is a prospective, longitudinal study of 479 head and neck cancer patients followed for at least 3 years after diagnosis. Analysis of longitudinally collected HRQOL scores was based on survivorship status.

Results. The HRQOL for 3 survivorship groups: short-term (died <1 year), intermediate-term (died 1-3 years), and long-term survivors (alive >3 years) were different at all time points (pretreatment, 3, 6, and 12 months). Differences were greatest between the short-term and long-term survivors. Long-term survivors demonstrated the best HRQOL and an improving HRQOL trajectory at 12 months. The HRQOL of short-term survivors declined precipitously throughout all available follow-up. Intermediate-term survivors did show some improvement following treatment but had a declining HRQOL trajectory at 12 months.

Conclusion. The HRQOL profiles of head and neck cancer patients differed significantly depending on survivorship status. Long-term HRQOL results should be analyzed within the context of the results for all of the patients eligible to have been included in the initial study cohort. ©2006 Wiley Periodicals, Inc. *Head Neck* **29:** 221–229, 2007

Keywords: health status assessment; health-related quality of life; head and neck cancer; cancer survivorship

The number of longitudinal studies assessing health-related quality of life (HRQOL) in patients with head and neck cancer has steadily increased over the past 10 years. This has paralleled a maturation of methodologies used in outcome studies in this patient population and the increased focus of attention on HRQOL in the management of head and neck cancer.[1] One of the general conclusions drawn from these studies has been that HRQOL in head and neck cancer patients worsens during and shortly after treatment and then gradually improves, approaching or reaching baseline levels 12 months after diagnosis. In general, global measures of quality of life, emotional distress, and pain seem to show the most consistent improvements, despite residual treatment effects

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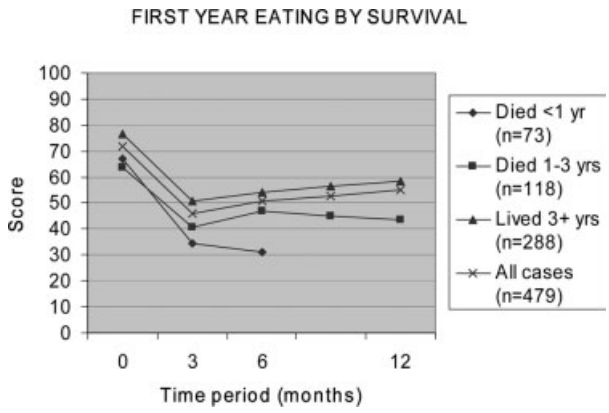


FIGURE 1. Eating score profiles across the first year by survival status and for all cases.

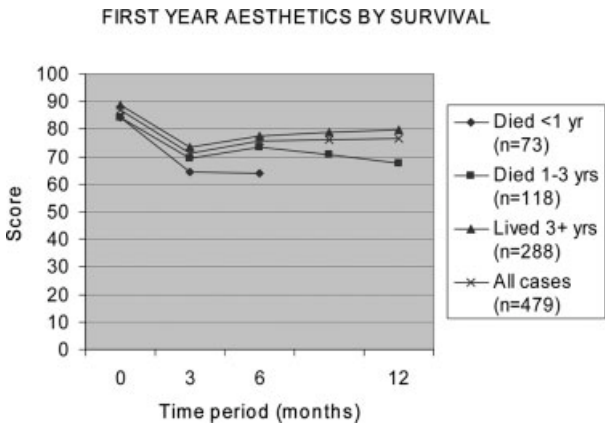


FIGURE 3. Aesthetic score profiles across the first year by survival status and for all cases.

such as xerostomia, compromised diet, and speech disturbances.[1–4]

Many of the longitudinal HRQOL studies evaluating head and neck cancer patients have focused primarily on the results obtained from long-term survivors. It is from this group of patients that the general concept of HRQOL deterioration with treatment and subsequent recovery has emerged. In many of these studies, the patients who do not survive long enough to be included in the final analyses are acknowledged, however, a detailed analysis of their HRQOL outcome has not been presented.[1–7] In this paper we will refer to "HRQOL profiles." This term is used to describe not just the HRQOL outcome at a point in time, but also how the HRQOL scores for a particular group of patients increases or decreases over the course of time. In addition to HRQOL scores at defined points, the HRQOL profiles have a definable shape or form (Figures 1–5). There is evidence to suggest that head and neck cancer patients who do not survive long-term have substantially different HRQOL profiles than long-term survivors. Hammerlid et al[1] found that in a group of 232 head and neck cancer patients reporting serial HRQOL, those patients that dropped out or died during the study had consistently worse HRQOL than the 3-year survivors, including the HRQOL measured at baseline. De Graeff et al[2] and Bjordal et al[5] have reported similar results. Bjordal et al[5] pointed out that this renders direct comparison between mean HRQOL scores at 2 separate time points in a longitudinal study invalid, unless only the data for the patients that complete the study are used and the data for those patients that drop out or die during the study are excluded. Low HRQOL scores from poor performing patients who die early in a study will result in lower cohort mean HRQOL scores at the short-term follow-up points and therefore an inflated apparent improvement in long-term follow-up cohort mean HRQOL scores due to the ab-

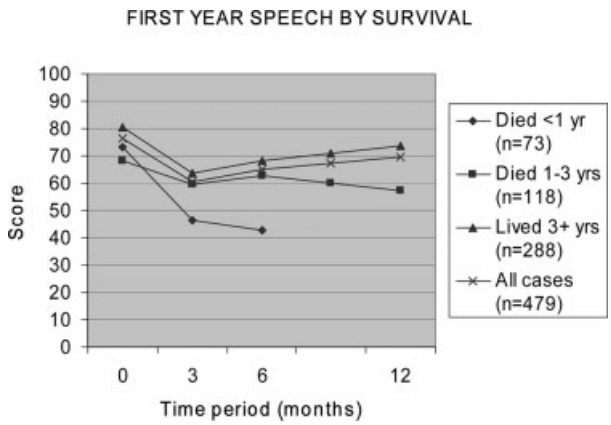


FIGURE 2. Speech score profiles across the first year by survival status and for all cases.

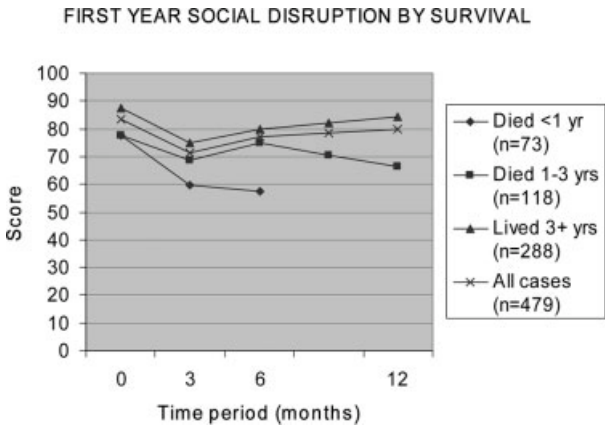


FIGURE 4. Social disruption score profiles across the first year by survival status and for all cases.

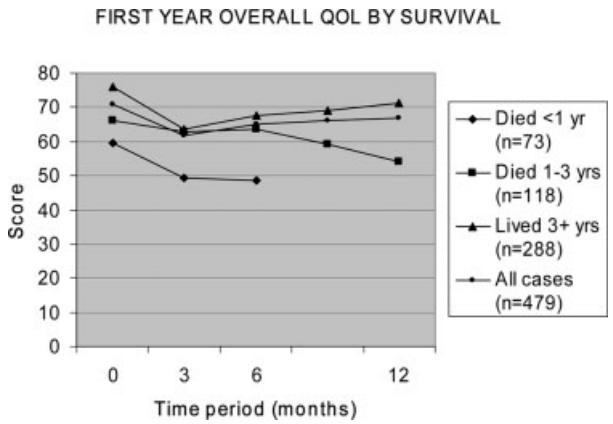


FIGURE 5. Overall quality of life item profiles across the first year by survival status and for all cases.

sence of contributions from the poor performing patients. The converse of this is also true, the scores contributed by the high performing patients will tend to mask the low scores of the poor performing patients early in a longitudinal study if the data from all available patients in the cohort are averaged (a cross-sectional evaluation).

To define a more comprehensive context within which to evaluate the likelihood that an individual will obtain a favorable long-term HRQOL result, the HRQOL, survival, and patient dropout data for all the patients within the original cohort of patients need to be accounted for in the evaluation of the HRQOL of the long-term survivors. Although long-term results will not be available for short-term survivors, the HRQOL data obtained from those patients can be extracted from the overall group results and evaluated. This type of analysis has not been reported in detail for a cohort of head and neck cancer patients.

In this study, the HRQOL data from a large cohort of head and neck cancer patients was segregated based on survivorship status. HRQOL profiles for each survivorship group were constructed. We operationally defined short-term survival as less than 1 year, long-term survival as 3 or more years, and designated survival of 1 to 3 years as intermediate-term. Three questions were addressed: (1) Do the HRQOL profiles for each of the 3 different survivorship groups differ? (2) How does the HRQOL change over time for the 3 different survivorship groups? (3) Is HRQOL data gathered at pretreatment and during the first post-treatment year related to survivorship out to 3 years? The focus of this paper was to evaluate the differences in HRQOL between these separate survivorship groups rather than analyze the case-mix variables associated with the different groups. In addition, this analysis will highlight the potential for misrepresenting the HRQOL for many patients within an overall cohort when a cross-sectional HRQOL analysis of all available patients at a point in time are combined.

PATIENTS AND METHODS

Patients in this study were drawn from the group of individuals enrolled in the University of Iowa's ongoing head and neck cancer Outcomes Assessment Program between June 6, 1997, and July 31, 2003. Patients 18 years or older with upper aerodigestive tract carcinomas evaluated in the Department of Otolaryngology—Head and Neck Surgery are eligible for enrollment in the Outcomes Assessment Project. The accrual rate of eligible patients during that time period was 71.2%.

Participants in the Outcomes Assessment Project filled out a battery of surveys prior to treatment and then at 3, 6, and 12 months following their diagnosis. One of the surveys that they completed is the Head and Neck Cancer Inventory (HNCI), a well-validated, 30-item instrument that measures head and neck cancer-specific outcomes in the areas of speech, eating, aesthetics, and social disruption. Higher scores on the HNCI indicate better outcome, domain scores are scaled from 0 to 100, and item no. 30 is a single, stand-alone question regarding overall quality of life (QOL).[8] Small, intermediate, and large clinically important differences (CIDs) have been published for the HNCI domain scores and are used in addition to traditional statistical methods for interpreting results.[9]

Information about participants' site and stage of cancer, demographics, comorbidities, treatment, and survival outcome are also collected as part of the Outcomes Assessment Project. Patients' date of last contact and oncologic status (dead/alive with/without cancer) is routinely updated based on information collected by the University of Iowa cancer registry.

On the basis of survival outcome, the patients in this study were placed into 1 of 3 survival-status groups: patients who died within 12 months of diagnosis (short-term survivors), patients who survived 1 year but died before 3 years (intermediate-term survivors), and patients who survived more than 3 years (long-term survivors). For short-term survivors, only outcome data through 6 months were available.

Descriptive statistics were used to illustrate HRQOL profiles across the first year of follow-up

Table 1. Patient characteristics and survival status ($N = 479$).

Characteristic	No. of patients (%)
Age, y	
<55	159 (33.2)
55–69	185 (38.6)
≥70	135 (28.2)
Sex	
Male	325 (67.8)
Female	154 (32.2)
Stage	
Early (I–II)	144 (30.1)
Advanced (III–IV)	296 (61.8)
Not stageable/Unknown	39 (8.1)
Site	
Oral cavity	192 (40.1)
Oropharynx	90 (18.8)
Hypopharynx	30 (6.3)
Larynx	111 (23.2)
Other site	56 (11.7)
Survival status	
Died within first year	73 (15.2)
Died in 2–3 years	118 (24.6)
Lived 3 or more years	288 (60.1)

for each of the groups. Mean scores for each of the HNCI's 4 domains and the overall QOL item were calculated for the different survival-status groups. One-way analysis of variance (ANOVA) were performed to determine whether the differences in these mean scores were significantly different across survival-status groups at pretreatment and at 3, 6, and 12 months follow-up. Post hoc analyses using Tukey's honestly significant difference were then performed to determine which pairwise comparisons were significant at $p < .05$. The observed differences between the mean scores of the various survival-status groups were also compared with the CID's for each domain to evaluate the clinical relevance of significant findings.[9]

RESULTS

This study included 479 patients who were enrolled in the longitudinal Outcomes Assessment Project between June 6, 1997, and July 31, 2003. Of the 589 patients enrolled during this time period, 108 were not eligible for inclusion in this study because they were alive at last contact but had less than 3 years of follow-up. Of the remaining 481 patients who were eligible, 1 lacked sufficient survival information, and 1 did not provide valid HNCI data while participating during this time frame. The remaining 479 patients were eligible even if they did not provide HNCI data at every time point during the first year. The accrual rates during the initiation of this study, and development of the Outcomes Assessment Project protocol, were lower than the accrual rates during the last 2 years of the study (83.1%).

As seen in Table 1, 73 patients died within the first year, 118 died within the second or third year, and 288 survived more than 3 years. These patients had a mean age of 60.9 years and most were male (67.8%). The majority of the patients (61.8%) presented with advanced (AJCC stage III or IV) disease. The oral cavity was the most common site (40.1%) followed, in frequency, by the larynx, oropharynx, and hypopharynx.

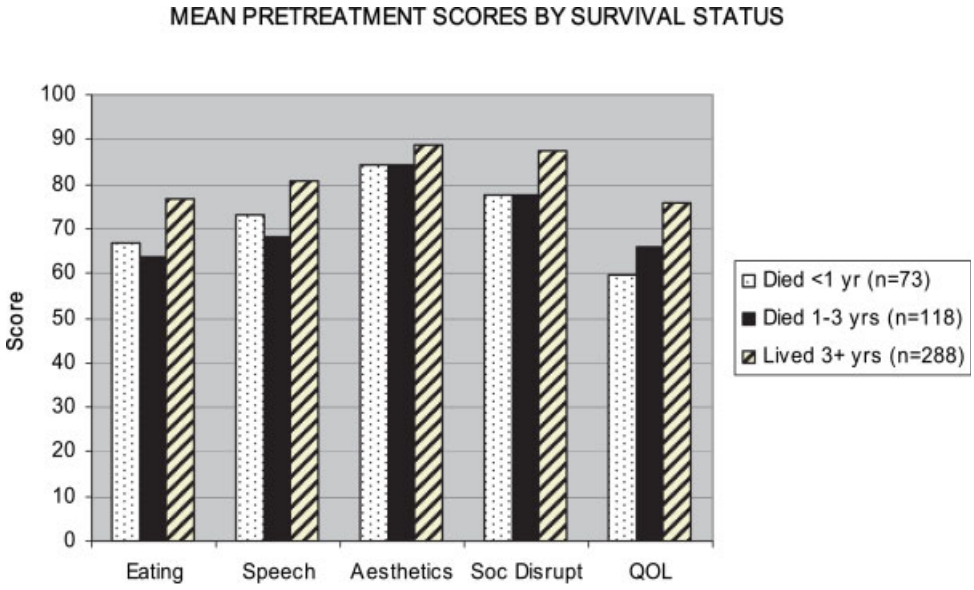
Figures 1 to 5 illustrate HRQOL changes across the first year in eating, speech, aesthetics, social disruption, and overall QOL for the 3 survival-status groups. Each of these groups (the short-term, intermediate-term, and long-term survivors) showed distinctly different HRQOL profiles from pretreatment through the 3-, 6-, and 12-month follow-up. The HRQOL was similar in appearance for each survival group across the different HRQOL domains.

Short-term survivors had the lowest post-treatment HRQOL scores throughout the first year until their death. Their profiles showed a lower baseline HRQOL score than long-term survivors with a sharp decline in scores at both 3 and 6 months post-treatment with no recovery toward baseline after diagnosis and treatment.

Intermediate-term survivors had baseline scores similar to the short-term survivors (ie, lower than long-term survivors). Their profiles showed a decline in all domain scores at 3 months, a modest improvement at 6 months, then a downward slope between 6 and 12 months, indicating that in this group HRQOL had a negative trajectory at the end of the first year.

Long-term survivors had the highest mean HRQOL scores at all 4 time periods. Their HRQOL scores were the highest at baseline, followed by a decrease at 3 months, and then a gradual improvement across the remaining months, with scores approaching but not reaching pretreatment levels at 12 months follow-up. Unlike the other 2 survivor-status groups, long-term survivors showed a positive slope in HRQOL in all domains between 6 and 12 months, indicating that this group's HRQOL had a positive trajectory at the end of the first year.

When the mean scores for all patients in the cohort were combined and plotted at each time period, as they would be in a cross-sectional study that included all patient data available at a given point



Survival status	Mean HNCI domain score				Overall QOL
	Eating	Speech	Aesthetics	Social disruption	
Died <1 year	66.8	73.0	84.1	77.4	59.7
Died 1-3 years	63.5	68.1	84.2	77.7	66.1
Lived 3+ years	76.5	80.5	88.9	87.5	76.0
p value	<.001	<.001	.150	<.001	<.001

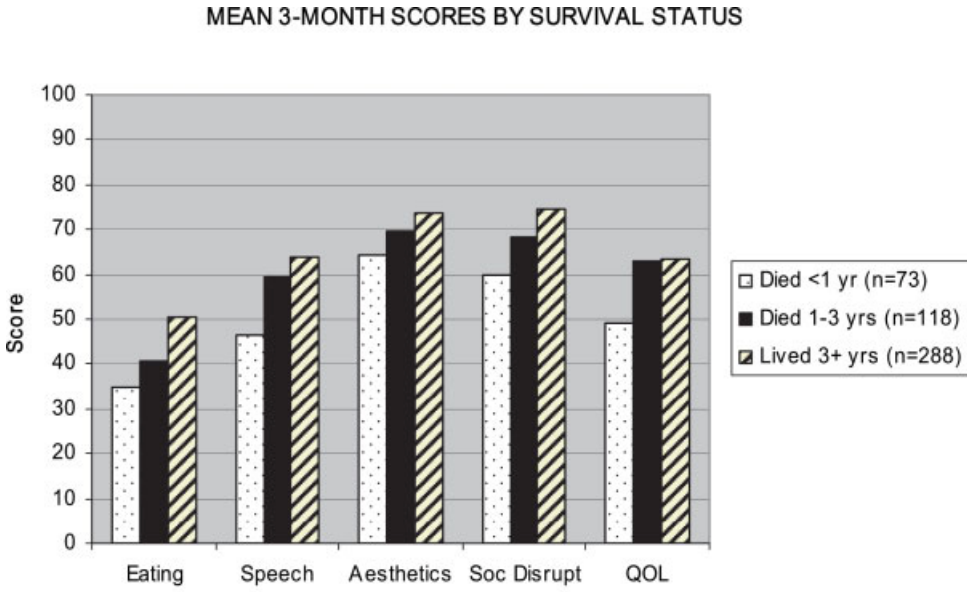
FIGURE 6. Mean pretreatment HNCI domain scores by survival status. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

in time, the resultant HRQOL profiles qualitatively resembled those of the long-term survivors.

Figures 6–9 show the head and neck cancer-specific and overall QOL scores, stratified by survival status, for the separate pretreatment, 3-, 6-, and 12-month time periods. Long-term survivors' scores were higher than those of the short-term and intermediate-term survivors. On the basis of the results of the ANOVAs, the differences between the 3 survival-status groups' pretreatment, 3-, 6-, and 12-month domain scores and overall QOL scores were significant for eating, speech, social disruption, and overall QOL. Differences in the aesthetic domain were not significantly different except at the 12-month period, when the long-term survivors had significantly better scores than the intermediate-term survivors.

These statistical analyses indicated that at least 2 of the scores differed significantly at each time point. Post hoc, pairwise analyses of the pretreatment eating, speech, and social disruption scores (Figure 6) indicated that long-term survivors had significantly higher scores at presentation than the other 2 groups. The single exception was in speech, where no significant difference was found between short-term and long-term survivors' scores. Pretreatment scores did not differentiate the short-term from the intermediate-term survivors. Although the former had slightly higher scores, the differences were not significant in any domain. Pretreatment overall QOL followed the same pattern, with long-term survivors having significantly higher scores than the short-term and intermediate-term survivors, but the short-term and intermediate-term survival groups were not significantly different from each other.

Post-hoc analysis of 3- and 6-month eating, speech, and social disruption scores indicated that scores for short-term survivors were significantly worse than those of long-term survivors (Figures 7 and 8). At 3 months, when all groups' mean HRQOL scores were at their lowest, intermediate-term survivors were not significantly different from the short-term survivors and were not significantly different from the long-term survivors except in the eating domain. At 6 months, when the intermediate-term and long-term survivor groups' scores began to increase, those 2 groups



Survival status	Mean HNCI domain score				Overall QOL
	Eating	Speech	Aesthetics	Social disruption	
Died <1 year	34.6	46.4	64.4	59.8	49.3
Died 1-3 years	40.7	59.4	69.5	68.5	62.8
Lived 3+ years	50.6	63.8	73.5	74.7	63.4
p value	.004	.003	.272	.002	.004

FIGURE 7. Mean 3-month HNCI domain scores by survival status. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

were not significantly different from each other. However, the short-term survivors falling scores were significantly worse than the 2 other groups, except in the eating domain where no significant difference was found between them and the intermediate-term survivors. For the 3- and 6-month overall QOL item, short-term survivors were significantly worse than both the intermediate-term and long-term survivors, but the latter 2 groups were not significantly different from each other.

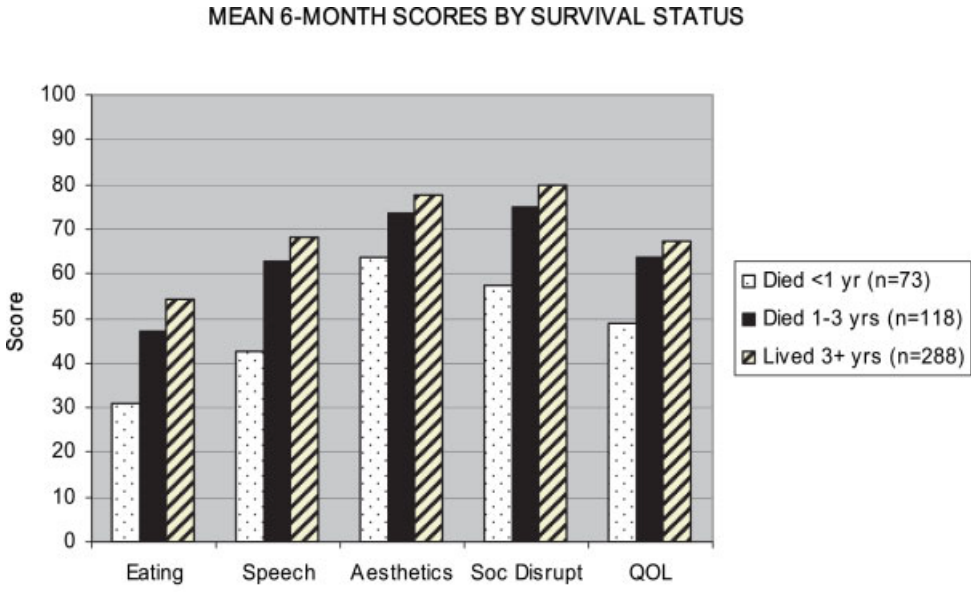
The 12-month scores, which compared only the intermediate-term and long-term survivors, showed the long-term to be significantly better than the intermediate-term survivors in all domains and overall QOL.

On the basis of the CID benchmark values (small ~4–5, intermediate ~9–12, and large ~14–20) for the HNCI domain scores,[9] the magnitude of the significant differences in all the pretreatment and posttreatment domain scores between the survival groups were clinically relevant. These differences were larger than a small CID. The differences were larger in the later time periods.

DISCUSSION

This study demonstrated that head and neck cancer patients' HRQOL profiles constructed over the first posttreatment year are clearly related to survivorship status extending out at least 3 years from diagnosis. Three groups of patients with distinctly different HRQOL profiles were defined by their survivorship status.

Long-term survivors consistently had the highest HRQOL scores from pretreatment out to 12 months. This group of high performing patients (based on survival and HRQOL outcomes) is frequently the focus of analyses carried out in long-term or prospective, longitudinal studies of head and neck cancer outcomes.[2,10–13] However, at long-term follow-up, these high performing patients often represent only a minority of the original inception cohort.[10,14–16] When the data for the short-term survivors with poor HRQOL are excluded, it must be recognized that the resultant HRQOL is specific to this high performing group of patients and may not be generalized to the majority of the head and neck cancer patients within the original cohort. The HRQOL profiles in Figures 1 to 5 clearly demonstrate a different



Survival status	Mean HNCI domain score				Overall QOL
	Eating	Speech	Aesthetics	Social disruption	
Died <1 year	30.9	42.8	63.9	57.2	48.7
Died 1-3 years	46.9	62.6	73.4	74.8	63.7
Lived 3+ years	54.3	68.2	77.7	79.8	67.4
p value	.005	<.001	.136	<.001	.002

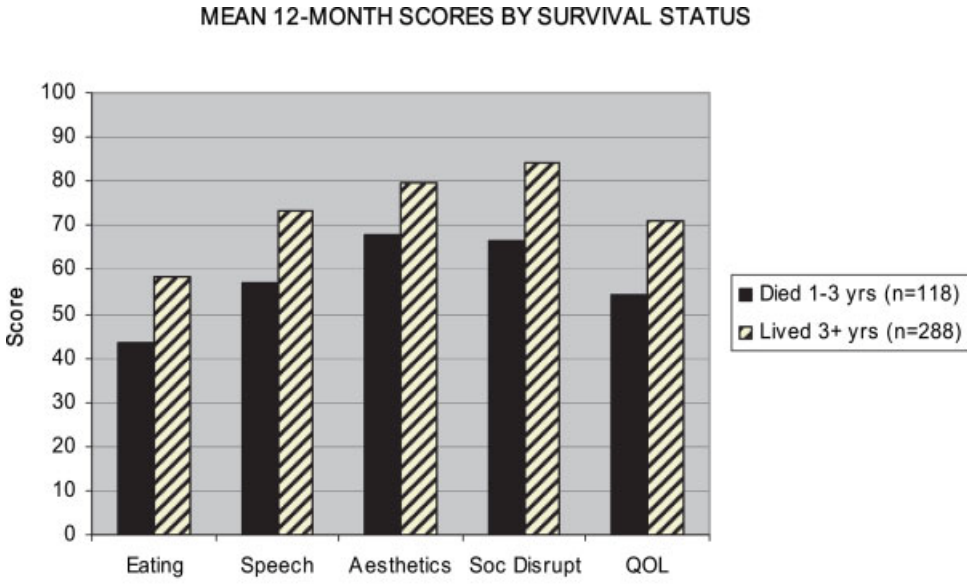
FIGURE 8. Mean 6-month HNCI domain scores by survival status. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

HRQOL experience during the course of management for the long-term survivors when compared with the other 2 survivorship groups.

Although the short-term survivors and consequently poor performing patients are often acknowledged to have lower HRQOL than the long-term survivors or those that completed a course of evaluation,[1,2] a detailed picture of their HRQOL profile from pretreatment out to last available data prior to death has not previously been delineated. The scores at nearly every point on the HRQOL profile of short-term survivors in our study were significantly below those of the long-term survivors. Most striking was the different shape of the HRQOL profile for the short-term survivors, which was essentially a downward sloping line from pretreatment onward. This profile is a graphic demonstration that for a substantial fraction of head and neck cancer patients, treatment offers little improvement in survival when compared with supportive care alone,[17] and the HRQOL of these patients deteriorates throughout their interaction with the health care system.

We did identify a group of intermediate-term survivors who demonstrated a brief recovery of HRQOL following treatment. However, between 6 and 12 months, this group's HRQOL profile resumed a downward slope as would be expected for patients who are destined to die within a year. As with other reported long-term studies, these relatively poor performing patients made up a substantial fraction of the accrued cohort of patients in this study. At nearly every data point, the intermediate-term survivorship group had worse scores than the long-term survivors, and the divergence in scores grew at the later time points.

When the HRQOL scores were plotted with the inclusion of all available patients at each time point, the resulting composite profile was qualitatively similar in form to the profile of the long-term survivors. Presentation of this type of composite profile in the reporting of long-term head and neck cancer HRQOL results, as would be obtained in a cross sectional analysis, is somewhat misleading because only the long-term survivors have a true HRQOL profile that is qualitatively represented by a composite profile that demonstrates decline and sustained improvement with a positive trajectory out to 12 months (Figures 1–5).



Survival status	Mean HNCI domain score				Overall QOL
	Eating	Speech	Aesthetics	Social disruption	
Died 1-3 years	43.5	57.2	67.7	66.5	54.2
Lived 3+ years	58.4	73.5	79.7	84.2	71.1
p value	.002	<.001	<.004	<.001	<.001

FIGURE 9. Mean 12-month HNCI domain scores by survival status. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

In addition, the dramatic decline with no evident benefit for the short-term survivors, and the negative slope of the intermediate-term survivors' scores is masked within the HRQOL profile constructed with data from all patients available at each time point.

Clearly, long-term data will not be available for patients who die during the course of longitudinal studies. However, the most comprehensive results available should be reported in order to more accurately define the likelihood of attaining a particular long-term, HRQOL endpoint for the head and neck cancer patients within a particular cohort and in order to more clearly frame conclusions drawn regarding the long-term survivors from that cohort. It is very beneficial if these data are reported in a format that is as close as possible to the format used to present the long-term patients' results in order to facilitate direct comparison. In the same way that randomized trials are most rigorously evaluated based on the initial study group assignment and intent to treat, prospective, longitudinal outcomes studies should be evaluated based on initial intent to enroll with an accounting for all accrued patients.[18]

Currently little is reported on the long-term trends in HRQOL for head and neck cancer patients. Hammerlid et al[1] reported on HRQOL obtained longitudinally out to 3 years in head and neck cancer patients and found that the HRQOL of long-term survivors changed relatively little between 1 and 3 years for that group. Deficits in oral function and improvements in emotional function and overall quality of life were relatively stable. Mehanna et al[4] presented data suggesting a significant fall in quality of life (life satisfaction) when compared with pretreatment, 12-month, and 24-month scores in a long-term study of head and neck cancer patients followed 10 years. On the basis of their data, it is unclear exactly when, during the time period from 2 to 10 years, that the fall occurred. Together with the data of Hammerlid et al and long-term data from others,[10,11,16] it is suggested that at least the general QOL for long-term survivors of head and neck cancer does eventually fall. Although the point at which this occurs remains unclear, and it is likely to be sometime before10 years out from diagnosis. Mehanna et al[4] did not have data to provide a clear reason for the decline in quality of life seen in their long-term survivors. They speculated, however, that

possible reasons included advanced age, residual treatment effects, late-onset treatment effects, comorbidity, and loss of contact with the health care system.

Through an aggressive reenrollment of head and neck cancer patients who have previously provided longitudinal data for the Outcomes Assessment Project, the current outcomes program at the University of Iowa has been gathering data out to 10 years and beyond for head and neck cancer patients. This work is ongoing and will be presented in a series of studies addressing the long-term, longitudinal changes in HRQOL in this patient group.

CONCLUSIONS

Survivorship status extending out to at least 3 years beyond diagnosis is significantly related to the HRQOL profiles of head and neck cancer patients from pretreatment through 12 months of follow-up. The HRQOL profiles of patients with short-term, intermediate-term, and long-term survival are qualitatively and quantitatively different. Long-term survivors have superior HRQOL at all assessment points including pretreatment. The HRQOL of short-term survivors drops with treatment and never improves. In reporting long-term HRQOL results from prospective, longitudinal studies of head and neck cancer patients, as much information as possible regarding all patients eligible to participate in the study is essential in order to provide an accurate context within which to evaluate and discuss the HRQOL results of the long-term survivors.

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