QUALITY OF LIFE IN ORAL CARCINOMA: A 5-YEAR PROSPECTIVE STUDY

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Abstract: Background. We conducted this prospective longitudinal multicenter study to evaluate the health-related quality of life (HRQL) of patients with oral carcinoma at diagnosis, and after 1 and 5 years in relation to tumour location and treatment modality.

Methods. One hundred twenty-two patients (mean age, 61; 62% males) with oral carcinoma were evaluated with standardized HRQL questionnaires, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core30 (EORTC QLQ-C30) and the EORTC Head and Neck Cancer Module (EORTC QLQ-H&N35).

Results. Problems with teeth, dry mouth, and sticky saliva got worse between diagnosis and 5 years after diagnosis. Problems with dry mouth remained a problem between 1 and 5 years after diagnosis, except for the patients treated with surgery only. This group had fewer problems over time compared with patients receiving other treatment regimes. Survivors reported better HRQL than the nonsurvivors at diagnosis and at the 1-year follow-up. HRQL at diagnosis was associated with survival.

Conclusions. HRQL at diagnosis for patients with oral carcinoma seems to be an important factor for the prognosis of both HRQL over time and survival. Treatment of oral carcinoma often results in long-term side effects such as dry mouth, problems with teeth, and sticky saliva.

Keywords: longitudinal HRQL; oral carcinoma; EORTC QLQ-C30; EORTC QLQ-H&N35; predictive factors

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Treatment of head and neck cancer has a tremendous impact on the patients’ everyday lives.1–4 Methods for estimating health-related quality of life of patients (HRQL) have been developed during the past 2 decades, and some generally accepted questionnaires are widely used.5–10 Many studies in the last years state the need for
further prospective longitudinal studies of HRQL in cancer patients.

A prospective longitudinal multicenter study of HRQL was carried out in Sweden and Norway between 1993 and 2000. Three hundred fifty-seven patients with newly diagnosed head and neck carcinoma were included. The patients’ HRQL was assessed at diagnosis, 5 times during the first year, and after 5 years using the standardized questionnaires, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) and the EORTC Head and Neck Cancer Module (EORTC QLQ-H&N35).

Results from the 5-year follow-up of the study population have been evaluated, with a special focus on patients with laryngeal and pharyngeal carcinoma. In the current study, the 122 patients with oral carcinoma will be described.

The aim of the study was to explore changes in HRQL between diagnosis, the 1-year and the 5-year follow-ups for patients with oral carcinoma, in relation to disease subsites and treatment. In addition, we compared HRQL at diagnosis between patients who survived 5 years and patients who died during the study period. Another aim was to explore the possible predictors at diagnosis, for survival and a high HRQL after 5 years.

PATIENTS AND METHODS

Design. In the initial study, 357 patients were asked to answer HRQL questionnaires on 6 occasions during 1 year: at diagnosis, and 1, 2, 3, 6, and 12 months after start of treatment. Five years after diagnosis, the surviving patients were asked to complete the same HRQL questionnaires again. Patients who dropped out during the first study year but were alive at the 5-year follow-up were also asked to participate. The questionnaires were mailed to the patients, and patients were reminded once by post if they did not answer. Clinical data related to the treatment given, relapse and survival were collected 1 and 5 years after start of treatment. The local ethics committees approved the study.

The 122 patients with oral carcinoma out of the initial study group of 357 patients with head and neck cancer, were divided into the following diagnostic categories according to International Classification of Disease—revision 9 (ICD-9): oral tongue (141), gingival carcinoma (143), floor of mouth carcinoma (144), and other oral cavity carcinoma (145).

Health-Related Quality of Life Questionnaires. The EORTC QLQ-C30 and the EORTC QLQ-H&N35 were used throughout the study. The EORTC questionnaires comprise functioning scales, symptom scales, and single items. All scales and single items range in score from 0 to 100. For the functioning scales, a high score corresponds to a healthy function level. For the symptom scales and the single items a high score means a high level of symptoms or problems. The scales were scored in accordance with the EORTC Scoring Manual.

Treatment. Patients were treated according to local protocol, but the treatment varied between the 4 centers involved. Patients with small cancers of the tongue and floor of the mouth were treated with surgery only, whereas those with larger tumours received combined treatment. Patients receiving hyperfractionated radiotherapy were treated 5 days a week, twice daily (1.7 Gy/fraction) up to a total dose of 64 to 68 Gy over 4 weeks and, in about 50% of the cases, in combination with brachytherapy. Brachytherapy was executed according to principles described by Lapeyre et al and Pernot et al. The doses varied between 12 and 55 Gy and, in about 80% of the patients, were given in addition to hyperfractionated radiotherapy.

Conventional radiotherapy was given with megavoltage (4–6 MV) irradiation from a linear accelerator. Usually, 2 upper opposing lateral portals with a separate anterior low-neck portal were used. The lateral fields were treated 5 days a week, once a day (2.0 Gy), up to a total dose of 62 to 70 Gy over 6 to 7 weeks. The anterior field received 2 Gy at 3-cm depth and was treated up to 50 Gy. Chemotherapy was given as a combination of cisplatinum and 5-fluorouracil, mostly in 2 cycles.

Statistical Methods. In the analyses of changes in HRQL over time, data from patients responding to all questionnaires was used. In comparison at a specific assessment point, data from all patients responding at that specific time point was used. Multivariate stepwise logistic regression was performed to predict HRQL at 5 years after diagnosis. To predict survival, the log-rank test was used for dichotomous and categorical variables, and for continuous variables Cox proportional hazard regression was used. Stepwise Cox proportional hazard regression was performed for multivariate purposes.
For descriptive purposes, mean and standard error of the mean (SEM) or a 95% confidence interval (CI) for the mean was used. For comparison between 2 groups, Fisher’s nonparametric permutation test was used; and for comparison over time within groups, Fisher’s nonparametric permutation test for matched pairs was used. All tests were 2-tailed and conducted at 5% significance level.

Missing values were imputed by the method advocated by the EORTC Quality of Life Group; if at least half of the items from a scale were completed, the mean value for these items was imputed for those missing. A difference of 10 points or more was regarded as clinically significant.

RESULTS

Patients Characteristics, Treatment, and Compliance. Of the 122 patients with oral cancer, 62% were male (Table 1). Approximately half of the patients had advanced disease (stage III/IV), varying between 41% and 68% in the various subsites. Ninety-one patients (75%) were alive after 1 year, and 64 patients (52%) were alive after 5 years. The 5-year survival rates varied between 30% and 72% among the 3 treatment groups. Most patients (67/122) received a combination of external radiotherapy and surgery; some of them also received brachytherapy and/or chemotherapy. Brachytherapy was given to 28 patients, mostly in combination with hyperfractionated radiotherapy (n = 20), and mostly to patients with carcinoma in the oral tongue (n = 17) and floor of mouth (n = 7) (Table 1, Figure 1). Chemotherapy was given to 14 patients, 80% of whom had stage III/IV disease, and most were given 2 cycles of cisplatinum/5-fluorouracil.

Of the 58 deceased patients at the 5-year follow-up, 38 patients had died of the index tumor, 2 from another malignancy, 9 from other diseases, and 9 from unknown causes.

The compliance with regard to the HRQL questionnaires in surviving patients was 77% at 1 year and 94% at 5 years.

The Longitudinal Results for All Patients.
patients reported a significantly improved emotional functioning between diagnosis and the 5-year follow-up. However, a significant deterioration was experienced in other dimensions; physical functioning, role functioning, dyspnea, problems with senses, teeth, opening mouth wide, dry mouth, and sticky saliva (Table 2, Figure 2).

Change in Health-Related Quality of Life Scores for All Patients between the 1-Year and the 5-Year Follow-Up. No improvement was seen in this period. A significant deterioration was reported for role function and for problems with sticky saliva and opening the mouth wide (Table 2, Figure 2). Dry mouth remained a problem on an unchanged level, between the 3-month and 5-year follow-ups.

Comparison of Health-Related Quality of Life of Survivors and Nonsurvivors. At diagnosis, survivors at the 5-year follow-up scored clinically significant better in 12 of 28 scales and single items compared with those who died during the study (Table 3, ΔB-A).

At the 1-year follow-up, patients who survived the first year but died before the 5-year follow-up reported clinically significantly worse HRQL in 21 scales and single items compared with the 5-year survivors (Table 3; ΔD-C). One scale had an exceptionally large difference of 47 points (sex-uality scale) in favor of the survivors. No scale or single item showed differences in favor of the non-survivors.

Results from the EORTC QLQ-C30 and QLQ-H&N35 for Subgroups of Patients.

Longitudinal Results in Relation to Treatment. Patients treated with surgery as the only mode of treatment had a stable and high HRQL at all assessment points and did not show any significant problems at the 5-year follow-up.

Patients treated with radiotherapy as the only mode of treatment showed a clinically significant improvement of sleep disturbance, pain QLQ-H&N35, social eating, and opening the mouth wide between diagnosis and the 5-year follow-up. This group also showed a clinically significant deterioration between diagnosis and the 5-year follow-up for physical function, role function, dyspnea, senses, and dry mouth (Figure 3).

The combined-treatment group showed a clinically significant improvement for emotional function and sleep disturbance, and a deterioration for role function, senses, opening the mouth wide, dry mouth, and sticky saliva, between diagnosis and the 5-year follow-up.

The radiotherapy group and the combined treatment group both showed persisting severe problems with dry mouth from the 3-month follow-up over time (Figure 3).

Predictors at Diagnosis for Health-Related Quality of Life after 5 Years and for 5-Year Survival. In a multivariate step-wise logistic regression analysis of all the HRQL variables that could possibly affect the global quality of life scale (QLQ-C30) 5 years after diagnosis, it was shown that the pain-C30 scale at diagnosis alone was the best predictor for a high quality of life after 5 years (Table 4).

A univariate analysis of all of the scales and single items at diagnosis as well as stage, comorbidity, and brachytherapy to predict death at 5 years, showed that advanced-stage disease (stage III/IV) and the presence of comorbidity were predictors for death at 5 years as well as 17 of the scales and single items at diagnosis (eg, physical functioning, cognitive functioning, social functioning, fatigue scale, pain [QLQ-C30] scale, pain [QLQ-H&N35] scale, sense scale, speech scale, teeth problems, opening the mouth wide, dry mouth, and sticky saliva) (Table 5).
A stepwise multivariate Cox regression analysis of predictors for death at 5 years, with HRQL scales, stage, comorbidity, and brachytherapy as possible predictors (chosen from the univariate analysis with p values of p < 0.10), showed that advanced-stage disease (stage III/IV), presence of comorbidity, and a high score on the sense scale (more symptoms) at diagnosis were the most important predictors (Table 6).

**DISCUSSION**

This prospective, longitudinal multicenter study has been ongoing for 5 years. The patients represented a nonselected patient group from certain areas of Sweden and Norway (i.e., those who met the inclusion criteria were included in the study continuously during the weekly tumor conferences).

The compliance improved during the study period. The lower compliance at the 1-year follow-up might be due to physical and mental tiredness after treatment but improved 5 years after treatment and could be due to a more positive perspective on the disease and treatment.

The study aimed to explore HRQL for different subgroups within the oral carcinoma group, to...
ascertain if any differences in HRQL existed between treatment groups over time and between survivors and nonsurvivors.

The results from the whole group of oral carcinoma patients showed that some treatment-related side effects got significantly worse between 1 and 5 years. A few scales improved between diagnosis and 5 years, but no improvement was shown between 1 and 5 years (Table 2). The worsening of sticky saliva and problems with opening mouth wide 5 years after diagnosis was also found for pharyngeal cancer patients within the same longitudinal study.15 Similar results have been found in other studies of shorter duration.2,3

Except for increasing problems with treatment-related side effects, no change in HRQL between 1 and 5 years after diagnosis was found, in accordance with Rogers et al, who reported no further dynamics after 1 year.25,26 Therefore, the patients’ HRQL 1 year after diagnosis could be a good indication of the patients’ future HRQL.

The survival rate was markedly less in the radiotherapy group compared with the other 2 treatment groups and could probably be explained by the fact that the radiotherapy group consisted mostly of patients with advanced-stage (stage III/IV) tumors. This group had a tendency toward more heart problems and had more smokers among the patients but was in other aspects such as age, sex, and social background similar to the other 2 treatment groups. In the group of patients with surgery as the only treatment, 80% had early-stage (stage I/II) tumors and 56% were nonsmokers (not all data shown) (Table 1).

In comparison with population norms, our patients showed significantly worse values according to the EORTC QLQ-H&N35 questionnaire,27 which is similar to results reported earlier for patients within the same longitudinal study.12,15–17 This result is in contrast to the scores from the EORTC QLQ-C30 questionnaire, which showed similar values compared with the population norms presented by Michelson et al.28 It seems rational to believe that the difference in HRQL between the head and neck cancer patients and the normal population at the 1-year and 5-year follow-ups mostly depends on treatment-related problems and not on older patient age.

In a 1-year prospective study of 83 patients with oral and oropharyngeal carcinoma treated with surgery only, Schliephake et al showed that the HRQL changes during the first year reached almost diagnostic levels after 1 year. No significant problems with dry mouth and sticky saliva were found; this could probably be explained by the fact that all patients were treated with sur-
This corresponds well to the findings in this study.

In a retrospective study by Klug et al in 2002, 181 patients with oral or oropharyngeal carcinoma were evaluated by the EORTC QLQ-C30 and QLQ-H&N35. That study concluded that a combined treatment offered the best chances of survival and that patients’ HRQL was equivalent to other forms of therapy. The results are opposite to this study, in which patients given combined treatment often had persisting problems even 5 years after diagnosis.

Van Cann et al evaluated 105 patients retrospectively between 2 and 7 years after diagnosis with oral and oropharyngeal cancer, treated with radiotherapy as well as combined treatment. The patients filled in the EORTC QLQ-C30 and QLQ-H&N35 questionnaires and radiotherapy seemed to be the parameter affecting the HRQL the most; the authors stress the need for radical primary surgery in order to avoid radiotherapy, which is in accordance with the results from this HRQL study, without considering possible benefits of survival.
Fang et al evaluated 102 patients with advanced carcinoma in the oral, oropharyngeal, hypopharyngeal and laryngeal region, treated with radiotherapy only, and explored predictors for survival, using the same questionnaires as in this study. They found that the fatigue scale from the EORTC QLQ-C30 as well as lymph node status according to American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC)-predicted survival. In our study, fatigue was shown to be a predictor for survival in a univariate analysis of all the variables, among several other scales and single items as well as stage and comorbidity; but in a multivariate analysis, only a few factors were identified as independent predictors for survival 5 years (ie, stage, comorbidity, and sense scale) (Tables 5 and 6). The presence of the sense scale in the outcome of this analysis could be explained by the fact that large tumors affect both the taste and smell, and the patients with large tumors have poorer survival. In this study, the patients who reported the worst problems with smell and taste at diagnosis also had the largest tumors.

A high score on the global quality of life scale (QLQ-C30) at the 5 year follow-up was predicted by a low score (less symptom) on the pain QLQ-C30 scale at diagnosis, in this study, (Table 4). Similar analyses were performed in 2 other papers emanating from the 357 head and neck cancer

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### Table 4. A stepwise multivariate logistic regression analysis of stage, comorbidity, brachytherapy, and all health-related quality of life variables as predictors for a high health-related quality of life 5 years after diagnosis.

<table>
<thead>
<tr>
<th>p value</th>
<th>Odds ratio (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low score on the pain EORTC QLQ-C30 scale at diagnosis = less symptoms at diagnosis</td>
<td>.022</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30.

### Table 5. A univariate survival analysis of stage, comorbidity, brachytherapy and all of the health-related quality of life variables at diagnosis as predictors for death at 5 years.

<table>
<thead>
<tr>
<th>p value</th>
<th>Hazard ratio (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced-stage disease (stage III/IV)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comorbidity present</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical functioning scale</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fatigue scale</td>
<td>.037</td>
</tr>
<tr>
<td>Pain-C30 scale</td>
<td>.010</td>
</tr>
<tr>
<td>Pain-HN35 scale</td>
<td>.002</td>
</tr>
<tr>
<td>Sense scale</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Speech scale</td>
<td>.007</td>
</tr>
<tr>
<td>Teeth problems</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Opening mouth wide</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>.009</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; HN35, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck module.

Note: Not all scales analyzed are reported here.

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### Table 6. A stepwise multivariate Cox regression analysis of stage, comorbidity, brachytherapy, and health-related quality of life variables at diagnosis as predictors for death at 5 years.

<table>
<thead>
<tr>
<th>p value*</th>
<th>Hazard ratio (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced-stage disease (stage III/IV)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comorbidity present</td>
<td>*.001</td>
</tr>
<tr>
<td>High score on the sense scale</td>
<td>.007</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Note: Not all scales analyzed are reported here.

*Only p values <.10 from the univariate analysis.
patients from the initial study. In both papers reporting the HRQL for laryngeal and pharyngeal carcinoma, a high score on the global quality of life scale (QLQ-C30) at diagnosis was found to predict a high score on the global quality of life scale (QLQ-C30) at the 5-year follow-up.\textsuperscript{16,17}

Hence, less pain at diagnosis was correlated with both smaller tumors (T1-2) and a high score on the global quality of life scale (QLQ-C30) at diagnosis, (data not shown). Less pain (a low score on the pain QLQ-C30 scale) at diagnosis was also correlated with a high score on the global quality of life scale (QLQ-C30) after 5 years, as shown in our multivariate logistic regression analysis (Table 4).

In a retrospective study by Wijers et al, dry mouth syndrome was evaluated in long-term head and neck cancer survivors between 1965 and 1995. Of 1750 patients with different types of head and neck cancer, 39 were alive after 30 years and answered the questionnaires. It was found that 64% of the long-term survivors experienced moderate to severe problems with dry mouth.\textsuperscript{33} The result corresponds well to the results in this study that showed persistent problems with dry mouth accompanied by sticky saliva and problems with opening the mouth wide after 5 years. Therefore intensity-modulated radiation therapy (IMRT) seems promising as a future treatment option to avoid these long-term problems.

\textbf{CONCLUSIONS}

Surgery as the only treatment results in a HRQL level almost at diagnosis level already after 3 months and stays there even after 1 and 5 years. Combined treatment, however, results in a marked worsening of treatment-related side-effects at the 1-year follow-up as well as at the 5-year follow-up. There should be an incitement to detect the cancers at early stages to be able to avoid radiation therapy and to succeed in treating the patients with surgery only.

The use of IMRT should be considered, to minimize known side effects of dry mouth and teeth problems that are common in the standard radiation therapy.

HRQL evaluation 1 year after diagnosis is stable with a few exceptions and could be used to predict future HRQL in most patients. Accordingly, high scores of HRQL functioning scales (EORTC QLQ-C30) and low scores on the symptom scales and single items (EORTC QLQ-C30 and QLQ-H\&N35) at the 1-year follow-up seems to predict a high survival 5 years (Table 3).

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\textbf{REFERENCES}