Quality of life in patients with head and neck cancer treated by radiotherapy: a prospective self-assessment with the EORTC QLQ-C30 and QLQ-H&N35 questionnaires

Kakovost življenja bolnikov z rakom glave in vratu, zdravljenih z radioterapijo: prospektivna samoocena z vprašalnikoma EORTC QLQ-C30 in QLQ-H&N35

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Abstract

Background: The quality of life (QoL) of Slovenian patients with head and neck cancer (HNC) treated by radiotherapy (RT) has not yet been systematically evaluated with internationally established tools, which would allow comparison with the study results from abroad.

Methods: Forty patients with HNC treated by definitive (N=23) or postoperative (N=17) RT completed two questionnaires of the European Organization for Research and Treatment of Cancer (EORTC), validated and translated into Slovenian, before RT, at the end of RT and 10-12 weeks after the end of treatment: general QLQ-C30 questionnaire for patients with different types of cancer and QLQ-H&N35 questionnaire for patients with HNC. Statistically significant differences between the two measurements of 10 points or more were defined as clinically significant.

Results: Prior to RT, patients with tracheostomy or feeding tube, smokers, patients with comorbidities and human papillomavirus-unrelated cancers had poorer QoL. The intensity of treatment (higher RT dose, addition of chemotherapy to RT) had a significant effect on QoL at the end of RT, but not 10-12 weeks after treatment. The analysis of the dynamics of changes in QoL items confirmed that in most cases the scores return to the level before the start of RT. The exceptions were items related to RT-specific gustatory and salivary apparatus failures: their final score was significantly worse than the pre-RT score.

Conclusion: Estimates of different QoL items in Slovenian patients with HNC before, during and after RT are comparable to the results of similar analyses abroad. After RT treatment, QoL depends mainly on the degree of damage to the gustatory and salivary apparatus, which also affects swallowing.

Izvleček

Izhodišče: Kakovost življenja (KŽ) slovenskih bolnikov z rakom glave in vratu (RGV), zdravljenih z radioterapijo (RT), še ni bila sistematično ovrednotena z mednarodno uveljavljenimi orodji, kar bi omogočilo primerjavo z rezultati tujih raziskav.

Metode: 40 bolnikov z RGV, zdravljenih s primarno (N=23) RT ali RT po operaciji (N=17), je pred pričetkom RT, ob koncu RT in 10–12 tednov po zaključku zdravljenja izpolnilo dva validirana in v slovenščino prevedena vprašalnika Evropske organizacije za raziskovanje in zdravljenje raka.


1 Introduction

Head and neck cancer (HNC) is the 8th most commonly diagnosed cancer and cause of cancer death worldwide (1). In Slovenia, 473 new cases and 225 deaths of HNC were registered in 2016 (2). With some exceptions, men from a lower socioeconomic background in their 6th and 7th decades of life with a history of smoking and alcohol consumption and consequently burdened with comorbidities such as arterial hypertension, diabetes, chronic obstructive pulmonary disease and liver disease are most commonly diagnosed with HNC (3). Due to the denial of objective problems and poorer social inclusion, such patients enter the healthcare system late, so at the time of diagnosis the disease had already progressed locally in as many as two thirds (2,4). Depending on its location and size, the tumour itself can cause various anatomical deformations and consequently functional disorders, which are worsened by surgery, radiotherapy (RT) and systemic therapy with their side effects. The problems such patients face include minor or major dysfunction in feeding, breathing and speech, which are sometimes accompanied by changes in the appearance of the face and neck, especially as sequelae of surgery (5,6).

Facing a cancer diagnosis, its associated problems and the long and aggressive oncological treatment have an important effect on patient's quality of life. Therefore, in addition to the response to treatment and duration of survival, traditionally the most important parameters in determining treatment success,
an assessment of a patient’s quality of life has recently become an important indicator of the actual value of treatment (7). Quality of life (QoL) is a multifaceted concept that includes numerous aspects of an individual’s life – their physical and mental condition, level of social connections, dependence on the help of relatives and perception of their own illness. It is based on subjective experience (8). HNC can cause somatic symptoms as well as problems in social contact, which makes the patient’s daily functioning difficult, lowers self-esteem and self-confidence and affects the patient’s attitude towards his or her own future (8,9).

QoL of Slovenian patients with HNC treated with RT has not yet been systematically evaluated. On the other hand, the relevance and practical value of the conclusions of studies conducted in different settings is often limited or even questionable. In assessing the results of similar foreign studies, the specifics of the social and cultural environment of their enrolled patients and the connected value systems should be taken into account (10). Therefore, we have decided to evaluate QoL of Slovenian patients before and after RT with internationally established tools in a prospective study and compare our results to foreign studies.

2 Materials and methods

Our study was planned and conducted at the Institute for Oncology in Ljubljana as a prospective and observational study. The inclusion of 40 patients with operable or inoperable histologically confirmed locally and/or regionally advanced (stage TNM II-IVB (11)) squamous cell carcinoma of the head and neck was planned. The inclusion criteria were: age of 18 or above; male sex; cure as the treatment goal, including primary or postoperative irradiation of the mucosa of the larger part of the oral cavity, throat and larynx (75% and more) and tissues of both sides of the neck with a dose of 50 Gy or higher; written consent for participation in the study. The exclusion criteria were concomitant or previously treated HNC or other cancers (apart from basal cell carcinoma of the skin); palliation as the treatment goal; a medical condition that would preclude the safety of planned treatment. When treatment started with surgery, it included the removal of the primary tumour with a safety margin and removal of regional neck lymph nodes. All patients were irradiated on a linear accelerator with Intensity Modulated Radiation Therapy (IMRT) technique. Patients at higher risk of recurrence received chemotherapy (ChT) with cisplatin (40 mg/m²/week) during RT. Their state of nutrition was evaluated prior to treatment and weekly during treatment, together with acute side effects or RT and ChT.

The data on patients, their disease and treatment were obtained from medical documentation. QoL was evaluated three times in each patient: during RT treatment planning on CT-simulator (10-14 days prior to treatment with RT (evaluation 1)), at the end of RT (evaluation 2) and 10–12 weeks after treatment (evaluation 3). QoL was evaluated using the internationally established questionnaires EORTC QLQ C-30 version 3.0 and EORTC QLQ-H&N35 (module for HNC), validated and translated into Slovenian according to the procedure required by the European Organisation for Research and Treatment of Cancer (EORTC) (12). The questionnaire was completed by the patients themselves and only in case of problems did one of
the researchers help them to read and explain the questions (MG, KG).

Both questionnaires referred to the previous week. The EORTC QLQ-C30 is a general questionnaire for patients with different types of cancer. It consists of 30 questions: five functional scales (physical, role, cognitive, emotional, social), three symptom scales (fatigue, pain, nausea and vomiting), and one global health status and QoL scale; 8 individual questions are added to address other common symptoms of cancer patients and one addresses their financial situation. Questions are evaluated using a four-point Likert scale and a seven-point scale is used by patients to answer the questions about the state of their health and QoL (13).

The EORTC QLQ-H&N35 is a module of the basic EORTC QLQ-C30 questionnaire, intended for patients with HNC (14). It consists of 35 questions organized into 7 sets with 11 additional individual questions. Patients are asked about their symptoms and characteristic side effects of HNC treatment, their social contact and sex life. The questions are evaluated in the same manner as for the EORTC QLQ-C30 questionnaire (four-point Likert scale) except for the final 5 questions that have yes/no answers (14).

### 2.1 Statistical analysis

The collected data were statistically processed with the SPSS software platform (version 21.0, SPSS Inc., Chicago, Illinois, USA). We followed the EORTC instructions with questionnaire evaluation and interpretation and in case of missing answers (15). Numbers of points achieved in independent questions or the average score of all questions within each group (i.e. raw score) was standardized with a linear transformation using a 0–100 scale to calculate the score for an individual question or set. In questions about symptoms, a higher value represents a high level of symptomatology/problems, and in questions about functioning the reverse is true: a higher score represents a higher level of functioning (15). Only statistically significant differences of 10 points or more were deemed clinically important (16).

The scores were presented with a mean value and standard deviation or a median and range. The effect of patient characteristics, tumour and treatment on baseline QoL values was calculated using the Mann-Whitney U-test and the differences between scores measured at two time points with the Wilcoxon signed-rank test. To check for differences in the distribution of patients between treatment groups according to individual clinical characteristics, we used the chi-square test or Fisher’s exact test. All statistical tests were two-sided. Differences at p <0.05 were marked as statistically significant. The study was approved by the Republic of Slovenia National Medical Ethics Committee (46/02/15, 23. 3. 2015).

### 3 Results

Between February 2017 and January 2018, 40 patients were included in the study. Most were active smokers (55%) with a tumour of the oropharynx (52.5%) and stage IV disease (82.5%). At least 1 comorbidity requiring regular treatment with medication (range 1–4, mean value 2) was present in 22 (55%) patients, of whom 16 (72.7%) were active smokers (only 6 [33.3%] active smokers were present in the group of 18 patients...
without comorbidities, p=0.024). A tracheostomy was present in 6 patients prior to radiotherapy and 5 patients used a feeding tube. Due to uncontrolled weight loss during RT, 2 patients had a feeding tube inserted; at the final QoL evaluation, only 4 patients were dependent on a feeding tube. All patients finished their planned treatment. The data on patients, their disease and treatment are presented in Table 1.

All patients completed 3 pairs of questionnaires; there were no unanswered questions. Patients required 15–30 minutes to fill in both questionnaires. The interval between evaluation 1 and the beginning of RT was 15.2±3.6 days (mean value±standard deviation), between the end of RT and evaluation 2 0.8±0.3 days and 90.5±8.9 days for evaluation 3. The results of the analysis of the EORTC QLQ-C30 and EORTC QLQ-H&N35 are presented in Tables 2 in 3.

### Table 1: Characteristics of patients, tumours and treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.5 years (7,61)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
</tr>
<tr>
<td>Active smokers&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22 (55 %)</td>
</tr>
<tr>
<td>Former&lt;sup&gt;b&lt;/sup&gt;/occasional/mild smokers</td>
<td>13 (32.5 %)</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>5 (12.5 %)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>15 (37.5 %)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>6 (15 %)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>4 (10 %)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>4 (10 %)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>3 (7.5 %)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>3 (7.5 %)</td>
</tr>
<tr>
<td><strong>Tracheostomy (before RT)</strong></td>
<td>6 (15 %)</td>
</tr>
<tr>
<td><strong>Feeding tube</strong></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>5 (12.5 %)</td>
</tr>
<tr>
<td>During treatment</td>
<td>7 (17.5 %)</td>
</tr>
<tr>
<td>After treatment</td>
<td>4 (10 %)</td>
</tr>
<tr>
<td><strong>HPV-related oropharyngeal tumour</strong></td>
<td>7 (33.3 %)</td>
</tr>
<tr>
<td><strong>Location of the primary tumour</strong></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>7 (17.5 %)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>21 (52.5 %)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>7 (17.5 %)</td>
</tr>
<tr>
<td>Larynx</td>
<td>5 (12.5 %)</td>
</tr>
<tr>
<td><strong>TNM stage</strong></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>III</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>IVA</td>
<td>27 (67.5%)</td>
</tr>
<tr>
<td>IVB</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Surgery before RT</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>RT dose</td>
<td>66.6 Gy (60–70)</td>
</tr>
<tr>
<td>Duration of irradiation</td>
<td>46.9 days (38–55)</td>
</tr>
<tr>
<td><strong>Addition of ChT to RT</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (52.5%)</td>
</tr>
<tr>
<td>Number of CT cycles</td>
<td>6 (3–7)</td>
</tr>
</tbody>
</table>

Legend:  
<sup>a</sup> ≥ cigarettes daily for the past 10 years or more  
<sup>b</sup> Stopped smoking before 12 or more months  
<sup>c</sup> Primary oropharyngeal tumours  
<sup>d</sup> Mean value (standard deviation)  
<sup>e</sup> Median (range)  
Abbreviations used in the table:  
RT – radiotherapy, KT – chemotherapy.
### Table 2: Results of the EORTC QLQ-C30 questionnaire.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Eval. 1*</th>
<th>Eval. 2*</th>
<th>Eval. 3*</th>
<th>Comparisons (p-value)</th>
</tr>
</thead>
</table>
| **Global health state/quality of life** | 62.3 ± 19.2 | 55.2 ± 23.0 | 68.1 ± 20.3 | Evaluation 1 : evaluation 2 = 0.078  
Evaluation 2 : evaluation 3 < 0.001  
Evaluation 1 : evaluation 3 = 0.050 |
| **Physical functioning**         | 86.8 ± 15.2 | 76.8 ± 23.0 | 82.2 ± 19.4 | Evaluation 1 : evaluation 2 = 0.049  
Evaluation 2 : evaluation 3 = 0.175  
Evaluation 1 : evaluation 3 = 0.217 |
| **Role functioning**             | 83.8 ± 27.9 | 63.3 ± 38.7 | 80.4 ± 27.7 | Evaluation 1 : evaluation 2 = 0.003  
Evaluation 2 : evaluation 3 = 0.003  
Evaluation 1 : evaluation 3 = 0.485 |
| **Emotional functioning**        | 82.5 ± 17.6 | 82.3 ± 18.1 | 88.8 ± 16.5 | Evaluation 1 : evaluation 2 = 0.849  
Evaluation 2 : evaluation 3 = 0.034  
Evaluation 1 : evaluation 3 = 0.023 |
| **Cognitive functioning**        | 96.3 ± 8.8 | 96.3 ± 8.0 | 96.7 ± 7.7 | Evaluation 1 : evaluation 2 = 0.844  
Evaluation 2 : evaluation 3 = 0.831  
Evaluation 1 : evaluation 3 = 0.844 |
| **Social functioning**           | 92.5 ± 16.9 | 86.3 ± 24.1 | 92.1 ± 19.2 | Evaluation 1 : evaluation 2 = 0.169  
Evaluation 2 : evaluation 3 = 0.191  
Evaluation 1 : evaluation 3 = 0.765 |
| **Fatigue**                      | 15.0 ± 16.0 | 33.1 ± 28.1 | 18.6 ± 19.9 | Evaluation 1 : evaluation 2 < 0.001  
Evaluation 2 : evaluation 3 < 0.001  
Evaluation 1 : evaluation 3 = 0.129 |
| **Nausea and vomiting**          | 0.8 ± 3.7 | 8.8 ± 16.5 | 3.3 ± 12.1 | Evaluation 1 : evaluation 2 = 0.003  
Evaluation 2 : evaluation 3 = 0.064  
Evaluation 1 : evaluation 3 = 0.313 |
| **Pain**                         | 17.1 ± 23.4 | 37.5 ± 27.9 | 14.6 ± 22.1 | Evaluation 1 : evaluation 2 < 0.001  
Evaluation 2 : evaluation 3 < 0.001  
Evaluation 1 : evaluation 3 = 0.476 |
| **Dyspnoea**                     | 6.7 ± 15.5 | 11.7 ± 26.7 | 12.5 ± 23.5 | Evaluation 1 : evaluation 2 = 0.240  
Evaluation 2 : evaluation 3 = 0.631  
Evaluation 1 : evaluation 3 = 0.148 |
| **Insomnia**                     | 21.7 ± 28.8 | 30.8 ± 34.1 | 17.5 ± 22.6 | Evaluation 1 : evaluation 2 = 0.168  
Evaluation 2 : evaluation 3 = 0.020  
Evaluation 1 : evaluation 3 = 0.205 |
| **Loss of appetite**             | 3.3 ± 10.1 | 55.8 ± 42.3 | 17.5 ± 27.2 | Evaluation 1 : evaluation 2 < 0.001  
Evaluation 2 : evaluation 3 < 0.001  
Evaluation 1 : evaluation 3 = 0.002 |
| **Constipation**                 | 9.2 ± 20.0 | 40.0 ± 38.6 | 13.3 ± 24.8 | Evaluation 1 : evaluation 2 < 0.001  
Evaluation 2 : evaluation 3 < 0.001  
Evaluation 1 : evaluation 3 = 0.553 |
| **Diarrhoea**                    | 0.8 ± 5.3 | 3.3 ± 12.6 | 0.0 ± 0.0 | Evaluation 1 : evaluation 2 = 0.375  
Evaluation 2 : evaluation 3 = 0.103  
Evaluation 1 : evaluation 3 = 0.324 |
| **Financial difficulties**       | 2.5 ± 8.9 | 3.3 ± 12.6 | 5.0 ± 16.1 | Evaluation 1 : evaluation 2 = 0.875  
Evaluation 2 : evaluation 3 = 0.500  
Evaluation 1 : evaluation 3 = 0.438 |

Legend: * Mean value ± standard deviation; Eval. – evaluation.
Table 3: Results of the EORTC QLQ-H&N35 questionnaire.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Eval. 1*</th>
<th>Eval. 2*</th>
<th>Eval. 3*</th>
<th>Comparisons (p-value)</th>
</tr>
</thead>
</table>
| Pain                          | 12.7 ± 19.5 | 45.8 ± 30.7 | 16.0 ± 18.3 | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 < 0.001  
Evaluation 1: evaluation 3 = 0.416 |
| Swallowing problems           | 15.0 ± 20.0  | 50.0 ± 28.7  | 22.9 ± 26.0  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 < 0.001  
Evaluation 1: evaluation 3 = 0.201 |
| Senses problems               | 8.3 ± 20.0  | 53.3 ± 25.9  | 25.0 ± 26.7  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 < 0.001  
Evaluation 1: evaluation 3 = 0.201 |
| Speech problems               | 22.8 ± 27.2 | 31.9 ± 31.3  | 20.3 ± 24.5  | Evaluation 1: evaluation 2 = 0.168  
Evaluation 2: evaluation 3 = 0.030  
Evaluation 1: evaluation 3 = 0.658 |
| Social eating problems        | 6.9 ± 12.2  | 38.1 ± 29.5  | 13.1 ± 23.9  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 < 0.001  
Evaluation 1: evaluation 3 = 0.100 |
| Social contacts problems      | 3.7 ± 8.8   | 7.8 ± 17.3   | 5.5 ± 14.1   | Evaluation 1: evaluation 2 = 0.220  
Evaluation 2: evaluation 3 = 0.414  
Evaluation 1: evaluation 3 = 0.569 |
| Reduced interest in sex       | 10.0 ± 20.3 | 37.1 ± 40.0  | 15.0 ± 24.7  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 = 0.003  
Evaluation 1: evaluation 3 = 0.377 |
| Teeth problems                | 9.2 ± 26.1  | 10.0 ± 27.4  | 11.7 ± 25.7  | Evaluation 1: evaluation 2 = 0.846  
Evaluation 2: evaluation 3 = 0.688  
Evaluation 1: evaluation 3 = 0.375 |
| Mouth opening problems        | 10.0 ± 22.9 | 35.8 ± 42.3  | 12.5 ± 23.5  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 < 0.001  
Evaluation 1: evaluation 3 = 0.520 |
| Dry mouth                     | 23.3 ± 30.4 | 62.5 ± 39.4  | 51.7 ± 32.9  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 = 0.058  
Evaluation 1: evaluation 3 < 0.001 |
| Sticky saliva                 | 17.5 ± 30.2 | 70.8 ± 34.8  | 47.5 ± 32.8  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 = 0.002  
Evaluation 1: evaluation 3 < 0.001 |
| Cough                         | 16.7 ± 20.0 | 30.0 ± 32.7  | 15.0 ± 25.0  | Evaluation 1: evaluation 2 = 0.032  
Evaluation 2: evaluation 3 = 0.036  
Evaluation 1: evaluation 3 = 0.952 |
| Feeling ill                   | 12.5 ± 19.5 | 16.7 ± 27.2  | 10.0 ± 22.9  | Evaluation 1: evaluation 2 = 0.497  
Evaluation 2: evaluation 3 = 0.313  
Evaluation 1: evaluation 3 = 0.787 |
| Analgesic use                 | 42.5 ± 50.1 | 90.0 ± 30.4  | 52.5 ± 50.6  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 < 0.001  
Evaluation 1: evaluation 3 = 0.244 |
| Nutritional supplements       | 15.0 ± 36.2 | 62.5 ± 49.0  | 55.0 ± 50.4  | Evaluation 1: evaluation 2 < 0.001  
Evaluation 2: evaluation 3 = 0.622  
Evaluation 1: evaluation 3 < 0.001 |
### 3.1 The effect of patient characteristics and disease on QoL before RT (evaluation 1)

*EORTC QLQ-C30.* Physical activity was rated poorer by patients with HPV-unrelated tumours (84.6±15.6 : 97.1±7.6, p=0.018). Fatigue was expressed more in active smokers than in the group of former smokers and non-smokers (66.7±11.1 : 44.4±19.7, p=0.022), pain in patients with HPV-unrelated tumours (20.2±24.2 : 2.4±6.3, p=0.051) and dyspnoea in patients with a tracheostomy (22.2±17.2 : 3.9±13.6, p=0.032).

*EORTC QLQ-H&N35.* Problems with speech were greater in smokers (32.3±30.1 : 11.1±17.9, p=0.018), patients with a tracheostomy (46.3±28.5 : 18.6±25.2, p=0.041) and tumour of the larynx/hypopharynx (39.8±29 : 15.5±24.5, p=0.008); problems with social eating in patients with a feeding tube (18.3±10.9 : 5.2±11.6, p=0.026); problems with social contact in patients with a tracheostomy (17.8±16.2 : 1.2±3.1, p=0.019); dry mouth in patients with multiple comorbidities (31.8±30 : 13±28.3, p=0.022); problems with cough with tumour of the larynx/hypopharynx (30.5±22.3 : 10.7±15.8, p=0.017).

There were no differences in QoL between patients with or without prior surgery before the start of RT.

### 3.2 The effect of treatment on QoL (evaluations 2 and 3)

We evaluated what effect the dose of radiation and addition of ChT to RT has on QoL. In all patients with RT as their first treatment, the total dose directed at the primary tumour and pathological lymph nodes was 70 Gy. The range of the total dose received by patients after surgery was 60–66 Gy (median, 60 Gy). All 6 patients with a tracheostomy had surgery performed first (surgery first 6/17, RT first 0/23, P=0.003). Adjuvant ChT with RT was received by 21 patients (52.5%), 17/23 (73.9%) in patients with primary RT (surgery 4/17, P=0.003). In the group that received ChT, 17/21 (81%) of tumours were T3-T4 stages and only 9/19 (47%, p=0.046) in the group without ChT. Therapeutic groups did not differ in other clinical factors (location of the primary tumour, TNM stage, tube feeding, HPV-related oropharyngeal cancer, comorbidities).

*EORTC QLQ-C30.* At the end of treatment (evaluation 2), we identified lower scores in everyday activities in patients who received primary RT than in patients with RT after surgery (50.7±42.2 : 80.4±25.8, p=0.034); these patients had higher rates of fatigue.
(46.8±26.6 : 14.4±17.4, p<0.001), pain (46.6±30.2 : 26.5±20.5, p=0.048) and loss of appetite (73.9±38.9 : 31.4±34.3, p=0.003). The addition of ChT to RT (unrelated to the type or RT) had a negative effect on role functioning (48.4±39.1 : 79.8±31.7, p=0.008), emotional functioning (76.2±20.5 : 89±12.4, p=0.037), fatigue (46±28.8 : 18.7±19.3, p=0.003), nausea and vomiting (15.9±20.1 : 0.9±3.8, p=0.016), pain (49.2±29.1 : 24.6±20.3, p=0.008) and sleep (insomnia: 43.9±35.2 : 17.5±28, 0.018). Patients who received primary ChT-RT (total RT dose 70 Gy with concurrent ChT) scored poorer in role functioning (41.2±39.6 : 79.7±29.3, p=0.004), emotional functioning (74±21.6 : 88.4±12.2, p=0.028), fatigue (52.3±26.9 : 18.8±19.4, p<0.001), nausea and vomiting (16.7±21.2 : 2.9±8.2, p=0.045), pain (54.9±28.1 : 24.6±20, p=0.001), insomnia (47±37.4 : 18.8±26.3, p=0.017) and loss of appetite (72.6±39.5 : 43.5±40.8, p=0.043) than other patients who received less aggressive treatment.

After the end of treatment (evaluation 3), patients who were treated with primary RT with a total dose of 70 Gy reported higher rates of fatigue than patients who were treated with RT after surgery and with a lower total dose (24.1±22.9 : 11.1±11.8, p=0.065). Patients who received concurrent ChT in addition to RT scored poorer in role functioning (71.4±28 : 90.4±24.4, p=0.012), those treated with primary ChT-RT also scored poorer in role functioning (68.6±29.4 : 89.1±23.4, p=0.013) and had higher rates of fatigue (25.5±20.7 : 13.5±18, p=0.035) than other patients.

**EORTC QLQ-H&N35.** At the end of treatment (evaluation 2), patients with primary RT (70 Gy) had more problems with social eating (51.4±30.2 : 20.1±16.4, p<0.01), sex (47.8±40.6 : 22.6±35.3, p=0.057), weight loss (91.3±28.8 : 47.1±52.5, p=0.017) than patients who were treated with RT after surgery who also received a lower dose of RT. The addition of ChT to RT (unrelated to the type of RT) had a negative effect on swallowing (60.3±26.6 : 38.6±27.3, p=0.025) and cough (46±35.7 : 12.3±16.5, p=0.003).

Patients treated with primary ChT-RT had more problems with swallowing (63.2±24.5 : 40.2±28.2, p=0.019), social eating (51±31.3 : 28.6±24.7, p=0.013), sex (56.9±38.2 : 22.5±35.4, p=0.014), cough (49±37.5 : 15.9±19.8, p=0.006) and weight loss (94.1±24.3 : 56.5±50.7, p=0.040) than other patients.

The evaluation 10–12 weeks after treatment (evaluation 3) did now show significant differences between therapeutic groups in any activity or symptoms included in the EORTC QLQ-H&N35 questionnaire.

### 3.3 The dynamic of QoL changes
#### (comparing evaluations 1–3)

We identified three patterns of statistically and at the same time clinically significant changes in the scores of some QoL indicators (Tables 2 and 3): after temporary worsening due to RT (between evaluations 2 and 3), there was significant improvement after treatment (between evaluations 2 and 3), which was comparable to or even better than before RT (Figure 1A) or did not reach the level before the start of RT but still improved compared to evaluation 2 (Figure 1B); significant worsening during RT was not followed by improvement (Figure 1C). The difference between individual scores was less than 10 points and/or statistically significant in other QoL indicators. Of course, when evaluating the changes...
in scores of individual QoL indicators, it should be taken into account whether it is about evaluating symptoms or functionality.

**EORTC QLQ-C30.** Indicators in which the score temporarily worsened due to treatment but did not deviate from the baseline at the end were “role functionality”, “fatigue” and “constipation” (Figure 1A); with loss of appetite, the final improvement did not reach the level before the start of RT (Figure 1B).

**EORTC QLQ-H&N35.** After temporary and significant worsening of the score, it returned to the baseline in the indicators “pain”, “dysphagia”, “social eating”, “interest in sex”, “opening mouth”, “cough”, “analgesic use”, and “weight loss” (Figure 1A). With the “senses problems” indicator, the temporary score worsening was followed by significant improvement, which did not reach the level before the start of RT (Figure 1B). With indicators “dry mouth”, “sticky saliva” and “nutritional supplements”, the score worsening caused by treatment persisted even after treatment’s end (Figure 1C).

Due to the sample size, we did not analyze the dynamics of QoL changes within individual subgroups of patients (clinical, therapeutic).

**4 Discussion**

In our group of patients with HNC, QoL before RT was especially affected by the presence of a tracheostomy and feeding tube. During RT, individual QoL indicators significantly worsened, also depending on treatment intensity (total RT dose, adjuvant ChT), which coincided with the development of acute side effects of RT and ChT. After treatment, most indicators returned to the baseline, except those that reflect RT-specific

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**Figure 1:** Patterns of statistically and clinically significant changes in the scores of some QoL indicators. (When evaluating the changes in scores of individual QoL indicators, it should be taken into account whether it is about evaluation of symptoms or functionality).
tissue injury (glandular tissue, taste).

Currently, there is no "gold standard" with which we could measure QoL, even though it is one of the key components in assessing treatment success (7). It evaluates the patient's perception of their disease, treatment and its consequences, and at the same time significantly coincides with the prognosis of HNC (17). The unexplored nature of this area in the Slovenian population of patients with HNC and therefore the unverified validity of the conclusions of similar foreign studies were the initiative for conducting our study. We used the EORTC QLQ-C30 and QLQ-H&N35 questionnaires, the most commonly used established tools in clinical practice, to evaluate QoL (13,14).

As expected, in the first evaluation of QoL before RT, we found less problems in patients without a tracheostomy or feeding tube, vices (non-smokers and former smokers), comorbidities or with HPV-related oropharyngeal tumours. It is known that a tracheostomy and in particular a feeding tube and its associated problems with feeding are the conditions that lower QoL in patients with HNC the most, especially in social environments and outside the home (18). A tracheostomy as the reason for dyspnoea, cough and problems with communication and social contact was the consequence of laryngectomy due to a primary hypopharyngeal or laryngeal tumour in all 6 patients, while a feeding tube was inserted prior to surgery due to dysphagia. This was the result of either a tumorectomy or injury to tissues and structures involved in swallowing due to a tumour (19). Comorbidity is an important indicator of a lower functional reserve of the body or its ability to compensate for the harmful effects of another disease (e.g. cancer) and/or its treatment. In our group, the burden of comorbidity significantly correlated with smoking, which, along with numerous drugs that reduce the symptoms of comorbidities, is known to have a negative effect on saliva production and can cause the sensation of a dry mouth (20). The favourable QoL indicator scores in patients with HPV-related oropharyngeal tumours compared to others reflect the lower age, absence of vices and comorbidities, higher economic status and better cooperation during treatment in this patient group (21,22).

We included the dose of radiation and addition of ChT to RT in our evaluation of the effect of treatment on QoL. As the radiation dose is dictated by the type of RT (primary/after surgery), we also assessed the effect of surgery on QoL. As expected, at the end of treatment, when the acute side effects of RT and ChT are most severe (23), patients with more intensive treatment (e.g. higher dose of RT and addition of ChT) had more problems; patients with primary ChT-RT gave the worst scores. Other authors have also concluded that most QoL indicator scores are lowest at the end of treatment (23,24). After the end of treatment, the negative influence of treatment intensity on QoL had subsided: the difference between the more and less intensively treated patients was only manifested in the degree of fatigue and normal activities.

The analysis of the dynamics of changes in QoL indicators in our study, as well as findings of foreign authors, confirm that in most cases the situation returns to the state before the start of RT (24,25). In our study, this was true for the indicators: role functioning, fatigue, pain, constipation, sexual functioning, cough, analgesic use, mouth opening and social eating. In the last two indicators in particular, we would expect that patients to rate them as worse as a recent study found the presence of dysphagia in as many as 41% of Slovenian patients with HNC.
The patient tendency to rate certain QoL indicators after the end of oncological treatment similarly to before the start of treatment is a known phenomenon. Experts attribute it to the re-evaluation of the concept of QoL, including the value system and personal standards, which is characteristic of oncological patients and others facing a potentially deadly disease (27). A poorer final score was recorded for indicators associated with RT-specific defects, i.e., defects in the patient’s gustatory and salivary apparatus: sense problems, dry mouth, sticky saliva, loss of appetite, nutritional supplements. By increasing the intake of nutritional supplements, patients alleviate the harmful effects of difficult eating and loss of appetite, which can both be the results of taste disturbances, lack of saliva and changes in its consistency (26).

These unwanted sequelae of RT cannot be completely avoided by using modern irradiation techniques such as IMRT or proton beam therapy (28-30). The degree of these sequelae is dependent on the location and size of the tumour (target) and/or the extent of injury to the glandular tissue due to invasive tumour growth or surgery; we do not know of an effective method to alleviate or even remove such phenomena (5).

The presented results of the study should be judged in the light of its limitations. The first is the sample size, which was chosen arbitrarily, aware of the logistical difficulty of data collection. Therefore, interpretation requires a degree of caution. A small sample size also prevented the use of multivariate analysis, which would evaluate the independent significance of the studied QoL indicators. The study was limited to only male patients, which represent the majority of patients with HNC: by excluding women, the number of possible factors that could affect the results was reduced, but unfortunately, the validity of results for the entire population of patients with HNC in Slovenia treated with RT was also reduced. We also did not analyse the effect of factors that could affect QoL, such as the state of family life, social status, level of education, employment and mental state. Analyses of the role of these factors were not planned, not only because of the number of patients involved but also because of the expected difficulties in collecting reliable data. The last evaluation of QoL was performed at 10–12 weeks after treatment, which does not mean that QoL of patients does not change in the following months and years. Regeneration of the gustatory and salivary apparatus is supposed to take up to 2 years after the end of RT and fibrotic transformation of irradiated tissues several years before the final state is achieved (5). Last but not least, we noticed that patients often ran out of patience in completing the questionnaires, despite the standardized translation into Slovene, and they completed the last part of the 68 questions that both questionnaires together consist of in a hurry. Some questions were more difficult for individual patients to understand and required further clarification from the researchers.

5 Conclusion

The evaluation of different QoL indicators in Slovenian patients with HNC before, during and after RT are comparable to similar foreign analyses. After treatment with RT, QoL is particularly dependent on the functional state of the gustatory and salivary apparatus, which, together with the tumour and treatment-induced damage to the swallowing muscles and other anatomical structures, leads to differently expressed swallowing
disorders. Therefore, accurately informing patients about what they can expect from the proposed treatment, not only in terms of cure but also side effects, is crucial.

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References

2. Rak v Sloveniji. Ljubljana: Onkološki inštitut Ljubljana; Epidemiologija in register raka; Register raka Slovenije; 2019.


