

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

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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.

Izvelek

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

(EORTC): splošen vprašalnik QLQ-C30, namenjen bolnikom z različnimi vrstami raka, in vprašalnik QLQ-H&N35, namenjen bolnikom z RGV. Kot klinično pomembne smo opredelili statistično pomembne razlike med dvema meritvama, ki so znašale 10 točk ali več.

Rezultati: Pred RT so imeli slabšo KŽ bolniki s traheostomo ali hranilno sondo, kadilci, bolniki s pridruženimi boleznimi in s človeškim virusom papiloma nepovezanimi raki. Intenzivnost zdravljenja (višji odmerek RT, dodatek kemoterapije k RT) je pomembno vplivala na KŽ ob koncu RT, ne pa tudi 10–12 tednov po zdravljenju. Analiza dinamike spreminjanja kazalcev KŽ je potrdila, da se v večini primerov stanje vrne na raven pred začetkom RT. Izjema so bili kazalci, povezani z okvarami bolnikovega sistema okušanja in slinjenja, ki so specifične za RT: njihova končna ocena je bila pomembno slabša kot ocena pred RT.

Zaključek: Ocene različnih kazalcev KŽ pri slovenskih bolnikih z RGV pred, med in po RT so primerljive z rezultati podobnih analiz v tujini. KŽ po zdravljenju z RT je odvisna predvsem od stopnje okvar okušanja in slinjenja, kar vpliva tudi na požiranje.

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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 of 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 \pm 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.

Characteristic	Number (N=40)
Age	62.5 years (7,61)^d
Smoking	
◦ Active smokers ^a	22 (55 %)
◦ Former ^b /occasional/mild smokers	13 (32,5 %)
◦ Non-smokers	5 (12,5 %)
Comorbidities	22 (55 %)
◦ Arterial hypertension	15 (37,5 %)
◦ Chronic obstructive pulmonary disease	6 (15 %)
◦ Hyperlipidaemia	4 (10 %)
◦ Cardiovascular diseases	4 (10 %)
◦ Type 2 diabetes	3 (7,5 %)
◦ Gastroesophageal reflux disease	3 (7,5 %)

Characteristic	Number (N=40)
◦ St. post stroke	3 (7.5%)
◦ Peripheral occlusive arterial disease	2 (5%)
◦ Chronic kidney disease	1 (2.5%)
Tracheostomy (before RT)	6 (15%)
Feeding tube	
◦ Before treatment	5 (12.5%)
◦ During treatment	7 (17.5%)
◦ After treatment	4 (10%)
HPV-related oropharyngeal tumour^c	7 (33.3%)
Location of the primary tumour	
◦ Oral cavity	7 (17.5%)
◦ Oropharynx	21 (52.5%)
◦ Hypopharynx	7 (17.5%)
◦ Larynx	5 (12.5%)
TNM stage	
◦ II	2 (5%)
◦ III	5 (12.5%)
◦ IVA	27 (67.5%)
◦ IVB	6 (15%)
Surgery before RT	17 (42.5%)
RT dose	66.6 Gy (60–70) ^e
Duration of irradiation	46.9 days (38–55) ^e
Addition of ChT to RT	
◦ Yes	21 (52.5%)
◦ Number of CT cycles	6 (3–7) ^e

Legend:

^a \geq cigarettes daily for the past 10 years or more

^b Stopped smoking before 12 or more months

^c Primary oropharyngeal tumours

^d Mean value (standard deviation)

^e Median (range)

Abbreviations used in the table:

RT – radiotherapy, KT – chemotherapy.

Table 2: Results of the EORTC QLQ-C30 questionnaire.

Indicator	Eval. 1*	Eval. 2*	Eval. 3*	Comparisons (p-value)
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.

Indicator	Eval. 1*	Eval. 2*	Eval. 3*	Comparisons (p-value)
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 < 0.001
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

Indicator	Eval. 1*	Eval. 2*	Eval. 3*	Comparisons (p-value)
Feeding tube	12.5 ± 33.5	25.0 ± 43.9	10.0 ± 30.4	Evaluation 1 : evaluation 2 = 0.164 Evaluation 2 : evaluation 3 = 0.106 Evaluation 1 : evaluation 3 = 0.813
Weight loss	25.0 ± 43.9	70.0 ± 46.4	20.0 ± 40.5	Evaluation 1 : evaluation 2 < 0.001 Evaluation 2 : evaluation 3 < 0.001 Evaluation 1 : evaluation 3 = 0.670
Weight gain	27.5 ± 45.2	10.0 ± 30.4	45.0 ± 50.4	Evaluation 1 : evaluation 2 = 0.094 Evaluation 2 : evaluation 3 = 0.002 Evaluation 1 : evaluation 3 = 0.111

Legend: * Mean value ± standard deviation; Eval. – evaluation.

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 pathologic 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 (47.1±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 : 13.50±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

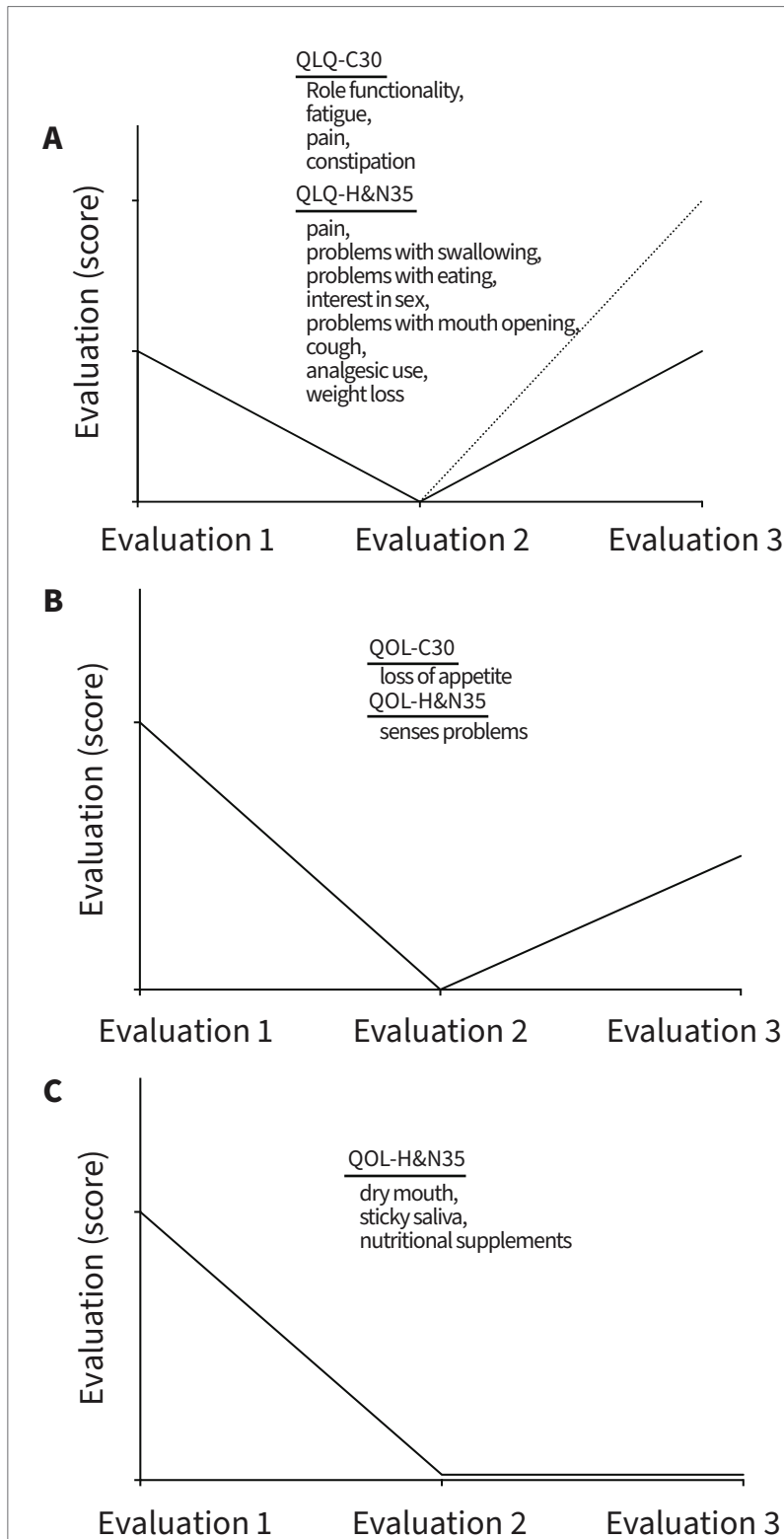


Figure 1: Patterns of statistically and clinically significant changes in the scores of some QoL indicators. (When evaluating the changes in scores of individual QoL indicators, it should be taken into account whether it is about evaluation of symptoms or functionality).

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

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

(26). 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: senses 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

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. DOI: [10.3322/caac.21492](https://doi.org/10.3322/caac.21492) PMID: [30207593](https://pubmed.ncbi.nlm.nih.gov/30207593/)
2. Rak v Sloveniji. Ljubljana: Onkološki inštitut Ljubljana; Epidemiologija in register raka; Register raka Slovenije; 2019.
3. Mehanna H, Paleri V, West CM, Nutting C. Head and neck cancer-part 1: epidemiology, presentation, and preservation. *Clin Otolaryngol*. 2011;36(1):65-8. DOI: [10.1111/j.1749-4486.2010.02231.x](https://doi.org/10.1111/j.1749-4486.2010.02231.x) PMID: [21414154](https://pubmed.ncbi.nlm.nih.gov/21414154/)
4. Primdahl H, Nielsen AL, Larsen S, Andersen E, Ipsen M, Lajer C, et al.; DAHANCA. Changes from 1992 to 2002 in the pretreatment delay for patients with squamous cell carcinoma of larynx or pharynx: a Danish nationwide survey from DAHANCA. *Acta Oncol*. 2006;45(2):156-61. DOI: [10.1080/02841860500423948](https://doi.org/10.1080/02841860500423948) PMID: [16546860](https://pubmed.ncbi.nlm.nih.gov/16546860/)
5. Strojjan P, Hutcheson KA, Eisbruch A, Beitler JJ, Langendijk JA, Lee AW, et al. Treatment of late sequelae after radiotherapy for head and neck cancer. *Cancer Treat Rev*. 2017;59:79-92. DOI: [10.1016/j.ctrv.2017.07.003](https://doi.org/10.1016/j.ctrv.2017.07.003) PMID: [28759822](https://pubmed.ncbi.nlm.nih.gov/28759822/)
6. Checcoli E, Bianchini C, Ciorba A, Candiani M, Riberti C, Pelucchi S, et al. Reconstructive head and neck surgery: oncological and functional results. *Tumori*. 2013;99(4):493-9. DOI: [10.1177/030089161309900409](https://doi.org/10.1177/030089161309900409) PMID: [24326838](https://pubmed.ncbi.nlm.nih.gov/24326838/)
7. Efficace F, Osoba D, Gotay C, Sprangers M, Coens C, Bottomley A. Has the quality of health-related quality of life reporting in cancer clinical trials improved over time? Towards bridging the gap with clinical decision making. *Ann Oncol*. 2007;18(4):775-81. DOI: [10.1093/annonc/mdl494](https://doi.org/10.1093/annonc/mdl494) PMID: [17259641](https://pubmed.ncbi.nlm.nih.gov/17259641/)
8. Leplège A, Hunt S. The problem of quality of life in medicine. *JAMA*. 1997;278(1):47-50. DOI: [10.1001/jama.1997.03550010061041](https://doi.org/10.1001/jama.1997.03550010061041) PMID: [9207338](https://pubmed.ncbi.nlm.nih.gov/9207338/)
9. Rogers SN, Semple C, Babb M, Humphris G. Quality of life considerations in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016;130:S49-52. DOI: [10.1017/S0022215116000438](https://doi.org/10.1017/S0022215116000438) PMID: [27841117](https://pubmed.ncbi.nlm.nih.gov/27841117/)
10. Schwarz R, Hinz A. Reference data for the quality of life questionnaire EORTC QLQ-C30 in the general German population. *Eur J Cancer*. 2001;37(11):1345-51. DOI: [10.1016/S0959-8049\(00\)00447-0](https://doi.org/10.1016/S0959-8049(00)00447-0) PMID: [11435063](https://pubmed.ncbi.nlm.nih.gov/11435063/)
11. Sobin LH, Gospodarowicz M, Wittekind C, eds. International Union Against Cancer (UICC). TNM Classification of Malignant Tumours. 7th ed. Oxford (UK): Wiley-Blackwell; 2010. pp. 25-45.
12. European Organisation for Research and Treatment of Cancer. Quality of Life. Questionnaires. Brussels: EORTC; 2020 [cited 2020 Aug 10]. Available from: <https://qol.eortc.org/questionnaires/>.
13. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-76. DOI: [10.1093/jnci/85.5.365](https://doi.org/10.1093/jnci/85.5.365) PMID: [8433390](https://pubmed.ncbi.nlm.nih.gov/8433390/)
14. Singer S, Arraras JI, Chie WC, Fisher SE, Galalae R, Hammerlid E, et al. Performance of the EORTC questionnaire for the assessment of quality of life in head and neck cancer patients EORTC QLQ-H&N35: a methodological review. *Qual Life Res*. 2013;22(8):1927-41. DOI: [10.1007/s11136-012-0325-1](https://doi.org/10.1007/s11136-012-0325-1) PMID: [23188134](https://pubmed.ncbi.nlm.nih.gov/23188134/)
15. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A; EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
16. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139-44. DOI: [10.1200/JCO.1998.16.1.139](https://doi.org/10.1200/JCO.1998.16.1.139) PMID: [9440735](https://pubmed.ncbi.nlm.nih.gov/9440735/)
17. 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. DOI: [10.1016/j.oraloncology.2014.09.002](https://doi.org/10.1016/j.oraloncology.2014.09.002) PMID: [25262163](https://pubmed.ncbi.nlm.nih.gov/25262163/)

18. Terrell JE, Ronis DL, Fowler KE, Bradford CR, Chepeha DB, Prince ME, et al. Clinical predictors of quality of life in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 2004;130(4):401-8. DOI: [10.1001/archotol.130.4.401](https://doi.org/10.1001/archotol.130.4.401) PMID: [15096421](https://pubmed.ncbi.nlm.nih.gov/15096421/)
19. King SN, Dunlap NE, Tennant PA, Pitts T. Pathophysiology of radiation induced dysphagia in head and neck cancer. *Dysphagia*. 2016;31(3):339-51. DOI: [10.1007/s00455-016-9710-1](https://doi.org/10.1007/s00455-016-9710-1) PMID: [27098922](https://pubmed.ncbi.nlm.nih.gov/27098922/)
20. Han P, Suarez-Durall P, Mulligan R. Dry mouth: a critical topic for older adult patients. *J Prosthodont Res*. 2015;59(1):6-19. DOI: [10.1016/j.jpor.2014.11.001](https://doi.org/10.1016/j.jpor.2014.11.001) PMID: [25498205](https://pubmed.ncbi.nlm.nih.gov/25498205/)
21. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol*. 2010;11(8):781-9. DOI: [10.1016/S1470-2045\(10\)70017-6](https://doi.org/10.1016/S1470-2045(10)70017-6) PMID: [20451455](https://pubmed.ncbi.nlm.nih.gov/20451455/)
22. Rogers SN, Waylen AE, Thomas S, Penfold C, Pring M, Waterboer T, et al. Quality of life, cognitive, physical and emotional function at diagnosis predicts head and neck cancer survival: analysis of cases from the Head and Neck 5000 study. *Eur Arch Otorhinolaryngol*. 2020;277(5):1515-23. DOI: [10.1007/s00405-020-05850-x](https://doi.org/10.1007/s00405-020-05850-x) PMID: [32062743](https://pubmed.ncbi.nlm.nih.gov/32062743/)
23. Niska JR, Thorpe CS, Halyard MY, Tan AD, Atherton PJ, Dueck AC, et al. Patient-reported quality-of-life outcomes in relation to provider-assessed adverse events during head and neck radiotherapy. *J Patient Rep Outcomes*. 2020;4(1):60. DOI: [10.1186/s41687-020-00227-4](https://doi.org/10.1186/s41687-020-00227-4) PMID: [32677021](https://pubmed.ncbi.nlm.nih.gov/32677021/)
24. Al-Mamgani A, van Rooij P, Tans L, Verduijn GM, Sewnaik A, Baatenburg de Jong RJ. A prospective evaluation of patient-reported quality-of-life after (chemo)radiation for oropharyngeal cancer: which patients are at risk of significant quality-of-life deterioration? *Radiother Oncol*. 2013;106(3):359-63. DOI: [10.1016/j.radonc.2012.12.014](https://doi.org/10.1016/j.radonc.2012.12.014) PMID: [23395066](https://pubmed.ncbi.nlm.nih.gov/23395066/)
25. Karimi AM, Gairola M, Ahlawat P, Tandon S, Pal M, Sachdeva N, et al. Health-related quality of life assessment for head-and-neck cancer patients during and at 3 months after radiotherapy - A prospective, analytical questionnaire-based study. *Natl J Maxillofac Surg*. 2019;10(2):134-40. DOI: [10.4103/njms.NJMS_92_18](https://doi.org/10.4103/njms.NJMS_92_18) PMID: [31798246](https://pubmed.ncbi.nlm.nih.gov/31798246/)
26. Pezdirec M, Strojan P, Boltezar IH. Swallowing disorders after treatment for head and neck cancer. *Radiol Oncol*. 2019;53(2):225-30. DOI: [10.2478/raon-2019-0028](https://doi.org/10.2478/raon-2019-0028) PMID: [31194691](https://pubmed.ncbi.nlm.nih.gov/31194691/)
27. Sprangers MA, Schwartz CE. The challenge of response shift for quality-of-life-based clinical oncology research. *Ann Oncol*. 1999;10(7):747-9. DOI: [10.1023/A:1008305523548](https://doi.org/10.1023/A:1008305523548) PMID: [10470418](https://pubmed.ncbi.nlm.nih.gov/10470418/)
28. Abel E, Silander E, Nyman J, Björk-Eriksson T, Hammerlid E. Long-term aspects of quality of life in head and neck cancer patients treated with intensity modulated radiation therapy: A 5-year longitudinal follow-up and comparison with a normal population cohort. *Adv Radiat Oncol*. 2019;5(1):101-10. DOI: [10.1016/j.adro.2019.07.015](https://doi.org/10.1016/j.adro.2019.07.015) PMID: [32051896](https://pubmed.ncbi.nlm.nih.gov/32051896/)
29. Ge X, Liao Z, Yuan J, Mao D, Li Y, Yu E, et al. Radiotherapy-related quality of life in patients with head and neck cancers: a meta-analysis. *Support Care Cancer*. 2020;28(6):2701-12. DOI: [10.1007/s00520-019-05077-5](https://doi.org/10.1007/s00520-019-05077-5) PMID: [31673782](https://pubmed.ncbi.nlm.nih.gov/31673782/)
30. Li X, Lee A, Cohen MA, Sherman EJ, Lee NY. Past, present and future of proton therapy for head and neck cancer. *Oral Oncol*. 2020;110:104879. DOI: [10.1016/j.oraloncology.2020.104879](https://doi.org/10.1016/j.oraloncology.2020.104879) PMID: [32650256](https://pubmed.ncbi.nlm.nih.gov/32650256/)