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Health-related quality of life in oropharyngeal cancer survivors – a population-based study

Thomas Guenzel, Ute Walliczek-Dworschak , Afshin Teymoortash, Susanne Singer, Martin Eichler, Thomas Wilhelm, Mike Schimmer, Achim Franzen

Department of Otorhinolaryngology, Head and Neck Surgery, Leer, Germany

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ABSTRACT:

Objective: The aim of this study was to compare QoL of oropharyngeal cancer survivors who had received different treatments.

Subjects and methods: We contacted 954 survivors. Each survivor received the QoL questionnaires EORTC QLQ-C30 and EORTC QLQ-H&N35.

Results: A total of 263 survivors completed the questionnaires (28% responses). Forty-five of them had undergone surgery, 20 had received definitive radiotherapy or chemo-radiotherapy, 85 surgery plus adjuvant radiotherapy, and 111 surgery plus adjuvant chemo-radiotherapy. Survivors who had received adjuvant radiotherapy and surgery reported significantly more problems with swallowing (B=13.43 [95% Confidence Interval (CI) 1.83-25.03]), senses (B=24,91 [CI 11.86-37.97]), eating (B=16.91 [CI 3.46-30.36]), dry mouth (B=26.42 [CI 12.17-40.67]), sticky saliva (B=22.37 [CI 6.23-38.50]) and nutritional supplements (B=18.59 [CI 0.62-36.56]) than those who had received surgery only. Survivors who had received adjuvant chemo-radiotherapy and surgery reported significantly many more problems with dry mouth (B=34.15 [CI 18.91-49.39]) and sticky saliva (B=22.90 [CI 5.65-40.16]), and fewer problems with physical functioning (B=-12.07 [CI 0.49-23-64]).

Conclusion: Survivors who participated in this survey and who had undergone surgery alone reported in some head- and neck-specific domains a better health-related quality of life than patients who had undergone multimodal treatment or adjuvant radiotherapy.

KEYWORDS: EORTC, oropharynx, tonsil, tongue, cancer, head and neck, quality of life

OBJECTIVE

Oropharyngeal carcinomas belong to the most frequent carcinomas of the head and neck[1,2]. The disease itself as well as the necessary therapy may lead to problems concerning swallowing, breathing, and articulation, resulting in decreased quality of life. Many patients suffer from impaired physical and emotional functioning[3]. In recent years, therefore, quality of life has received more attention as an important outcome in clinical trials as well as in daily clinical decision making[3-5].

Different tumour entities in the head and neck vary significantly regarding symptoms, therapy, prognosis, and thus quality of life[6]. For example, in one study, patients with laryngeal and hypo-pharyngeal cancer had a 3.3 times higher chance to improve global Quality of Life after primary radiotherapy compared to patients with oral cavity and oropharyngeal cancer[7].

The clinical characteristics and treatment regimens of oropharyngeal cancer have changed considerably during the past years. Survival, particularly among HPV-positive patients, has improved significantly with the use of chemo-radiotherapy[8]. Although patients survive longer now, their long-term quality of life is not well known[9-13]. The aim of the present study was therefore to assess the quality of life of oropharyngeal cancer survivors and to compare them concerning different treatment regimens they had received while adjusting for tumour stage at diagnosis.

SUBJECTS AND METHODS

Sampling and data collection

Patients were sampled from the population-based cancer re-

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gistry of the Federal State of Brandenburg, Germany. All patients with squamous cell carcinoma of the oropharynx treated between 2000 and 2009 who were known to be still alive were eligible for this study. Other tumour entities of the oropharynx as well as other locations were excluded.

Survivors received a mailed envelope with a questionnaire and written information about the study. Participation was voluntary, and written informed consent was obtained from each participant.

The study protocol was approved by the Ethics Committee of the Medical Association Brandenburg.

Questionnaire

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Core Questionnaire (EORTC QLQ-C30) and the disease-specific head and neck cancer module (EORTC QLQ-H&N35).

The EORTC QLQ-C30 is a valid and reliable instrument which has been in use since 1993 worldwide[14]. The questionnaire consists of 30 questions assessing general quality of life issues of cancer patients. For the first 28 items, response categories are not at all – a little – quite a bit – very much. The last two items refer to the overall health situation and overall quality of life. The patients are asked to evaluate these aspects on the linear scale from very poor to excellent. The EORTC QLQ-C30 includes 5 functional scales, measuring physical, role, emotional, cognitive, and social functioning, three multi-item symptom scales (fatigue, nausea/vomiting, and pain), and six single-item scales. High scores on the functional and global scales represent better quality of life. In contrast, high scores on the symptom scale indicate poor quality of life.

The EORTC QLQ-H&N35 is an additional module to be used in conjunction with the EORTC QLQ-C30 and is disease-specific concerning the quality of life of patients suffering from head and neck cancer[6]. It consists of 35 questions, assessing the symptoms and side effects of the treatment, but also social functioning, body image, and sexuality. High scores of the scales correspond to severe symptoms and thus indicate poor quality of life.

Statistical analysis

We conducted a multivariate linear regression to test for differences between the treatment regimens (surgery alone vs. primary radiotherapy or chemoradiotherapy vs. surgery plus adjuvant radiotherapy vs. surgery plus adjuvant chemoradiotherapy). As potentially confounding variables, gender, age at diagnosis (in groups of 30-49, 50-59, 60-69, 70-89), year of diagnosis (2000 to 2009), pT-stage (in situ/1, 2, 3, 4), and pN-stage (0, 1, 2/3) were included in the model and thus adjusted for. The treatment regimens were coded as dummy variables with "surgery alone" as the reference. Patients with missing data were excluded from the analysis (listwise deletion). No statistical correction regarding significance was used, due to the likelihood of increased Type II error. Statistical analysis was performed with SPSS, version 22.

Tab. I. Sample Characteristics

AVERAGE AGE AT FIRST DIAGNOSIS (YEARS)			57.6
		Frequency	Percentage
Gender	Male	221	84
	Female	42	16
Location	Base of the tongue	47	18.0
	Tonsil	120	46.0
	Posterior wall	1	0.4
	Soft palate/uvula	23	8.8
	Not specified	70	26.8
Tumour stage (UICC)	I	30	11.5
	II	28	10.7
	III	62	23.8
	IVa	94	36.0
	IVb	6	2.3
	Not specified	41	15.7
Therapy	Surgery alone	45	17.2
	Radio- +/- chemotherapy	20	7.7
	Surgery and radiotherapy	85	32.6
	Surgery and radiotherapy and chemotherapy	111	42.5

RESULTS

Sample

During the study period, 1394 patients with squamous cell carcinoma of the oropharynx had been treated in the Federal State of Brandenburg and were documented in the cancer re-

Tab. II. General quality of life in survivors of squamous cell carcinoma, stratified by treatment. Displayed are the differences in the quality of life of adjuvant and primary treatments compared to surgery alone. Linear regression analyses were adjusted for pT stage, pN stage, age group, year of diagnosis, and gender (The result of the unstandardized coefficient B in the surgery + constant column is not informative because of few cases.) Significant results (p<0.05) are highlighted.

	N IN THE MODEL	SURGERY + CONSTANT		RADIOTHERAPY +/- CHEMOTHERAPY		SURGERY + RADIOTHERAPY		SURGERY + RADIOTHERAPY + CHEMOTHERAPY
		N	unstandardized coefficient B	N	unstandardized coefficient B (95% CI)	N	unstandardized coefficient B (95% CI)	N	unstandardized coefficient B (95% CI)
Physical functioning	221	43	82.02	6	19.15 (-4.38 to 42.69)	76	5.33 (-5.51 to 16.17)	96	**12.07 (.49 to 23.64)**
Emotional functioning	221	43	81.70	6	12.24 (-15.39 to 39.86)	76	-2.37 (-15.09 to 10.36)	96	3.29 (-10.30 to 16.88)
Role functioning	220	42	81.67	6	28.10 (-2.67 to 58.87)	76	3.60 (-10.57 to 17.77)	96	9.56 (-5.60 to 24.71)
Cognitive functioning	221	43	66.46	6	14.71 (-9.97 to 39.40)	76	6.49 (-4.88 to 17.86)	96	7.61 (-4.53 to 19.76)
Social functioning	221	43	79.27	6	1.91 (-29.95 to 33.78)	76	-7.53 (-22.21 to 7.14)	96	.99 (-14.69 to 16.66)
Global quality of life	221	43	66.29	6	9.50 (-12.16 to 31.16)	76	-4.88 (-14.85 to 5.10)	96	6.90 (-3.75 to 17.56)
Fatigue	221	43	29.02	6	-26.09 (-54.70 to 2.52)	76	-7.28 (-20.46 to 5.89)	96	-13.94 (-28.01 to .13)
Nausea/vomiting	221	43	6.01	6	6.52 (-9.50 to 22.55)	76	.17 (-7.21 to 7.55)	96	-2.83 (-10.71 to 5.05)
Pain	221	43	24.01	6	-19.79 (-51.39 to 11.82)	76	-1.18 (-15.73 to 13.38)	96	-11.76 (-27.31 to 3.78)
Shortness of breath	220	42	35.50	6	-32.21 (-61.24 to -3.17)	76	-10.43 (-23.80 to 2.95)	96	-9.15 (-23.45 to 5.16)
Sleeplessness	221	43	29.23	6	-4.17 (-37.98 to 29.64)	76	.015 (-15.56 to 15.59)	96	-4.51 (-21.14 to 12.12)
Lack of appetite	221	43	-5.03	6	-4.80 (-37.34 to 27.75)	76	2.86 (-12.17 to 17.85)	96	.82 (-15.19 to 16.83)
Constipation	221	43	0.19	6	2.94 (-24.48 to 30.35)	76	3.35 (-9.28 to 15.98)	96	2.73 (-10.76 to 16.21)
Diarrhea	221	43	1.21	6	17.00 (-6.19 to 40.20)	76	2.28 (-8.41 to 12.96)	96	-1.04 (-12.50 to 10.37)
Financial difficulties	221	43	34.33	6	21.11 (-13.51 to 55.73)	76	11.59 (-4.35 to 27.54)	96	12.71 (-4.33 to 29.74)

gistry. Of them, 440 were deceased at the time of the survey. The remaining 954 patients were contacted and received the questionnaire.

A total of 263 survivors (28%) completed the questionnaire and sent it back.

Characteristics of the survivors

The average age of the survivors at the time of diagnosis was 57.6 years (standard deviation: 8.9). The majority of carcinomas were located in the palatine tonsil (46%), followed by the base of the tongue (18%). Carcinomas located in the area of the posterior wall and the soft palate or the uvula were found in 0.4% and 8.8% of cases, respectively (Tab 1).

Most survivors (38.3%) presented with an advanced tumour stage of IV (38.3%). The second most frequent tumour stage was stage III with 23.8%. Stages I and II occurred with nearly the same frequency, with respectively 11.5% and 10.7%.

Tab. III. Head-and-neck-cancer-specific quality of life in survivors of squamous cell carcinoma, stratified by treatment. Displayed are the differences in quality of life of adjuvant and primary treatments compared to surgery alone. Linear regression analyses were adjusted for pT stage, pN stage, age group, year of diagnosis, and gender (The result of the unstandardized coefficient B in the surgery + constant column is not informative because of few cases). Significant results (p<0.05) are highlighted.

	N IN THE MODEL	SURGERY + CONSTANT		RADIOTHERAPY +/- CHEMOTHERAPY		SURGERY + RADIOTHERAPY		SURGERY + RADIOTHERAPY + CHEMOTHERAPY	
		N	unstandardized coefficient B	N	unstandardized coefficient B (95% CI)	N	unstandardized coefficient B (95% CI)	N	unstandardized coefficient B (95% CI)
Pains in the mouth	220	42	8.94	6	-17.25 (-43.20 to 8.71)	76	3.97 (-7.98 to 15.92)	96	-2.37 (-15.16 to 10.41)
Swallowing problems	220	42	1.93	6	-3.88 (-29.00 to 21.37)	76	**13.43 (1.83 to 25.03)**	96	10.42 (-1.98 to 22.83)
Problems with senses	220	42	3.59	6	14.42 (-13.92 to 42.77)	76	**24.91 (11.86 to 37.97)**	96	25.26 (11.30 to 39.22)
Speech problems	220	42	6.34	6	-11.87 (-37.00 to 13.26)	76	7.58 (-3.99 to 19.16)	96	-.08 (-12.46 to 12.30)
Trouble eating	220	42	-6.42	6	12.94 (-16.26 to 42.14)	76	**16.91 (3.46 to 30.36)**	96	12.62 (-1.76 to 27.00)
Social eating	220	42	-5.32	6	-8.61 (-31.45 to 14.22)	76	2.93 (-7.59 to 13.45)	96	-2.55 (-13.80 to 8.70)
Problems with sexuality	221	39	45.57	6	3.94 (-38.28 to 46.16)	69	-5.06 (-22.44 to 12.31)	89	-8.64 (-27.64 to 10.36)
Problems with teeth	220	42	15.74	6	-6.28 (-44.39 to 31.83)	76	13.64 (-3.92 to 31.19)	96	15.12 (-3.65 to 33.89)
Problems with opening mouth	220	42	20.21	6	-5.58 (-41.22 to 30.06)	76	15.45 (-.97 to 31.86)	96	9.61 (-7.94 to 27.17)
Dry mouth	220	42	33.27	6	18.11 (-12.83 to 49.05)	76	**26.42 (12.17 to 40.67)**	96	**34.15 (18.91 to 49.39)**
Sticky saliva	220	42	35.09	6	21.87 (-13.16 to 56.90)	76	**22.37 (6.23 to 38.50)**	96	**22.90 (5.65 to 40.16)**
Coughing	220	42	33.53	6	-4.52 (-36.19 to 27.15)	76	-.77 (-15.36 to 13.82)	96	-3.06 (-18.66 to 12.54)
Feeling ill	219	42	-1.67	6	-14.35 (-44.70 to 16.01)	75	3.76 (-10.26 to 17.77)	96	-3.20 (-18.15 to 11.75)
Pain killers	220	42	8.26	6	-7.46 (-50.25 to 35.33)	76	-5.84 (-25.54 to 13.87)	96	-14.53 (-35.61 to 6.54)
Nutritional supplements	220	42	-7.25	6	19.66 (-19.36 to 58.67)	76	**18.59 (.62 to 36.56)**	96	11.79 (-7.42 to 31.01)
Feeding tube	220	42	-6.50	6	11.08 (-19.15 to 41.32)	76	.987 (-12.94 to 14.91)	96	-.82 (-15.71 to 14.07)
Weight loss	220	42	9.15	6	-24.11 (-66.13 to 17.91)	76	.51 (-18.84 to 19.87)	96	-7.38 (-28.08 to 13.32)
Weight gain	220	42	27.00	6	-6.34 (-45.45 to 32.77)	76	-2.01 (-20.02 to 16.00)	96	9.04 (-10.22 to 28.31)

Most of the study participants had undergone surgical therapy with adjuvant radiotherapy or chemoradiotherapy, namely 111 (42.5%), while 85 survivors (32.6%) had been treated with surgery and adjuvant radiotherapy. Primary radiotherapy with or without chemotherapy had been applied in 7.7% of the survivors, and 45 (17.2%) had received surgery alone. None of the survivors had

received intensity-modulated radiation therapy (IMRT) as this had not yet been introduced in the clinics at that time. Chemotherapy protocols included cisplatin and 5-FU or carboplatin.

Quality of Life

There were only a few significant differences in the general quality of life between the different therapeutic approaches when adjusting for tumour stage, age, gender, and year of diagnosis (Table 2). Patients who had received surgery and adjuvant chemoradiation (S+R+C) reported better physical functioning than patients who had received surgery alone (difference 12.1 points [95% confidence interval (CI) 0.5-23.6]). Survivors who had received definitive radiotherapy or chemoradiotherapy reported fewer problems with shortness of breath (-32.2 [CI -61.2 to -3.2]).

Head-and-neck-cancer-specific quality of life differed more often (Table 3). Survivors who had received surgery with adjuvant radiotherapy had significantly many more problems with swallowing (+13.4 [CI 1.8 to 25.0]), more problems with tasting and smelling (+24.9 [CI 11.9 to 38.0]), more problems with social eating (16.9 [CI 3.5 to 30.4]), and more often had dry mouth (+26.4 [CI 12.2 to 40.7]) and sticky saliva (+22.4 [CI 6.2 to 38.5]) compared to survivors who had been treated with surgery alone. They also needed nutritional supplements more often (+18.6 [CI 0.6 to 36.6]).

Survivors who had received surgery with adjuvant chemoradiation reported problems with tasting and smelling more often (+25.3 [CI 11.3 to 39.2]), and they had problems with dry mouth (+34.2 [CI 18.9 to 49.4]) and sticky saliva more often (+22.9 [5.6 to 40.2]) compared to survivors who had only received surgery.

There were no statistically significant differences between survivors who had received surgery alone and those who had had definitive radiotherapy or chemoradiotherapy

Discussion

This study examined potential differences in the quality of life of oropharyngeal cancer survivors regarding different treatment regimens when tumour stage, age at diagnosis, sex, and time since diagnosis are taken into account.

We found that survivors who had undergone surgery alone had fewer problems with quality of life in a variety of domains than those who had received surgery plus adjuvant treatment, especially concerning swallowing-related issues, dry mouth, and sticky saliva. The differences were not only statistically significant but also clinically relevant as the mean scores differed by more than 10 points, which is considered to be a meaningful clinical difference[15]. Those problems are the typical symptoms occurring after irradiation of the head and neck region[16].

The results of our study should be interpreted in the light of its limitations. Most importantly, only 28% of the survivors completed the quality of life questionnaires. Furthermore, we had to exclude 42 patients from our analysis because of missing data with respect to disease stage.

This may have introduced a selection bias if, for example, only those survivors participated who experienced relatively good quality of life. However, as our aim was to compare the different treatment regimens, the comparison would only be biased if the participation rates were different between the four groups, which was not the case.

Another limitation is that the patients' HPV status and co--morbidities were not documented in the cancer registry and could therefore not be taken into account in the analyses. Co--morbidities are a known confounding factor for treatment decisions und treatment outcomes.

We were also not able to research patients who received IMRT, as this had not yet been introduced in the clinics at that time. Moreover, the group of survivors with definitive radiotherapy or chemoradiotherapy was very small. The fact that we did not find any statistically significant differences between them and the group of survivors with surgery alone is therefore most likely due to not sufficient power, and the differences themselves may be the result of random variation within the groups.

We did not perform an a priori power calculation for the analysis, which is another limitation.

The strength of our study is its population-based approach and a multivariate nature of the statistical analysis. This enables us to compare the treatments despite the fact that, of course, different treatments are indicated based on different disease and patient characteristics.

CONCLUSION

Bearing the limitations and strengths in mind, we can cautiously conclude that multimodal treatments and surgery with adjuvant radiotherapy may result in a long-term decreased quality of life. The patients, in the consultation with the doctor, should therefore be prepared for these possible changes in quality of life, and supportive care measures should be offered to them if available.

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Corresponding author: Dr Thomas Guenzel, MD; Department of Otorhinolaryngology, Head and Neck Surgery, Kirchstrasse 61, 26789 Leer, Germany; Phone: +49 491 65840; Fax: +49 491 65859; E-mail: info@hno-praxis-leer.de

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