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Health-related quality of life of patients treated with chemoradiotherapy plus or minus prophylactic antibiotics to reduce the number of pneumonias for locally advanced head and neck cancer, the PANTAP study

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ABSTRACT

Objectives: The recent PANTAP trial showed that administration of prophylactic antibiotics in locally advanced head and neck carcinoma (LAHNC) patients treated with chemoradiotherapy reduced fever, hospitalization and costs. The current study describes the effect of prophylactic antibiotics on health-related quality of life (HRQoL), another secondary endpoint of the trial.

Materials and methods: In this multicenter randomized trial, LAHNC patients treated with chemoradiotherapy received prophylactic antibiotics or standard care. HRQoL was assessed at baseline (before chemoradiotherapy), day 28 of chemoradiotherapy (one day before starting prophylactic antibiotics), the final day of radiotherapy, and 3.5 months after the end of chemoradiotherapy, using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC H&N35 module, and the Performance Status Scale for Head & Neck cancer patients (PSS-HN).

Results: Ninety-five patients were randomized: 48 patients were allocated to the standard group and 47 patients to the prophylaxis group. Thirty-four patients in the standard group (70.8%) and 28 patients in the prophylaxis group (59.6%) completed the questionnaires at baseline and at follow-up. No significant differences in HRQoL were found at baseline and at day 28. At the end of radiotherapy, the prophylaxis group performed better on almost all functional subscales of the EORTC QLQ-C30 and reported less symptoms. At the end of follow up, almost no differences were seen between the two treatment groups.

Conclusion: Prophylactic antibiotics during chemoradiotherapy for LAHNC patients improved HRQoL at the end of the radiotherapy, however no differences were found 3.5 months after the end of chemoradiotherapy.

Introduction

Head and neck cancer is the sixth most common type of cancer with an annual incidence of 686,328 new cases worldwide [1,2]. Locally advanced head and neck cancer (LAHNC) itself, as well as the side effects of treatment, can negatively influence health-related quality of life (HRQoL). Social and emotional interactions are important aspects of an individual's HRQoL and largely depend on structural and functional capacity of organs in the head and neck region that are affected by the tumour and its treatment [3]. Rettig et al. showed that HRQoL begins to decline in the 2–5 years before a diagnosis of LAHNC with a steep reduction in the 24 months before diagnosis [4]. At presentation, disease-related symptoms may comprise of hoarseness, pain, otalgia, dysphagia, cough and stridor [5], which likely to account for decreased HRQoL prior to diagnosis.

The treatment for LAHNC often consists of concomitant platinum-based chemoradiotherapy. However, this treatment is associated with a high rate of acute toxicities. Radiotherapy causes mucositis, dermatitis, dysphagia, anorexia and pain [6,7], whereas chemotherapy may cause nausea, neutropenia and thrombocytopenia and worsen radiotherapy-related toxicities, in particular mucositis and dysphagia [6]. In a previous study, the incidence of grade 3 or 4 acute toxicities among LAHNC patients treated with radiotherapy alone was 47%, while this was 77% among patients treated with concomitant chemoradiotherapy [6]. Due to these acute adverse events, there is a significant deterioration of HRQoL during treatment [8], that may be worse for

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patients treated with chemoradiotherapy compared to those treated with radiotherapy alone [9]. Immediately (4–6 weeks) after radiotherapy HRQoL declines even further [10,11], however gradual improvement is during the following period [4,9–12]. In general, most HRQoL domains recover to baseline levels around 12 months after treatment [9,13].

Dysphagia and aspiration during-and after chemoradiotherapy for head and neck cancer are usually underreported [14–16]. In LAHNC patients, the incidence of aspiration at diagnosis ranges from 9% to 53% [14,17], and the aspiration rate during and after chemoradiotherapy is between 13% and 69% [16–18]. As a consequence, aspiration pneumonia during chemoradiotherapy is a relatively frequent complication (46%) [19]. In the recently conducted PANTAP-trial, prophylactic antibiotics during chemoradiotherapy in LAHNC did not result in a reduction in the number of patients with a pneumonia (45.8% of the patients in the standard group versus 46.8% of the patients in the prophylaxis group), however prophylactic antibiotics led to a significant reduction in the rate of hospitalization, episodes of fever and costs per patient [19,20]. It could be hypothesized that prophylactic antibiotics have a protective effect on HRQoL as they may reduce acute toxicities such as mucositis and pain, which were previously shown to have a negative impact on HRQoL [21]. One of the secondary objectives of the PANTAP trial, and the aim of the current study, was to assess the effects of prophylactic antibiotics during chemoradiotherapy on the HRQoL among LAHNC patients compared with those who did not receive prophylactic antibiotics. We hypothesized that the group receiving prophylactic antibiotics would report a better HRQoL at the end of radiotherapy due to the positive effects of prophylactic antibiotics. In addition, our study aims to describe HRQoL changes during treatment in both treatment groups.

Methods

Patients and study design

The PANTAP-study was a randomized, multicenter phase II study for patients with LAHNC who were treated with chemoradiotherapy, either as primary treatment or postoperative treatment. Chemotherapy consisted of cisplatin, given at a dose of 100 mg/m^2 every 3 weeks for 3 cycles, or 40–50 mg/m^2 given every week for 6 or 7 cycles. Radiotherapy was given with intensity-modulated radiation therapy and an accelerated (68 Gy in 34 fractions of 2 Gy over 5.5 weeks) or conventional scheme (70 Gy in 35 fractions of 2 Gy over 7 weeks) [6,7] Patients were enrolled before start of the chemoradiotherapy. Exclusion criteria for registration included an allergy to amoxicillin, the use of maintenance antibiotics or immunodeficiency. Patients were randomized after 21–28 days of chemoradiotherapy, unless complications such as pneumonia, other infections or antibiotic treatment had occurred within the 14 days preceding randomization. Patients were randomized to receive either standard care alone, (the standard group), or to receive prophylactic oral amoxicillin/clavulanic acid 625 mg three times daily from day 29 until 14 days after the end of chemoradiotherapy in addition to standard care (the prophylaxis group). Patients were allocated equally to the two treatment groups by minimization, which is a method of adaptive stratification allowing a higher numbers of stratification factors: smoking, Chronic Obstructive Pulmonary Disease (Gold 0–2 or Gold 3–4), weight loss (more than 10% versus less than 10%), primary site of the tumour (oral cavity, oropharyngeal, or hypopharyngeal and laryngeal cancer), participating centre, and human papillomavirus positivity [22].

The primary endpoint was to evaluate the number of patients who developed pneumonia. Secondary endpoints were to determine the number and duration of hospital admissions, to assess toxicity and adverse events including side effects of amoxicillin/clavulanic acid, to evaluate cost-effectiveness, and to explore HRQoL.

The study protocol was approved by the local ethical committee and registered at http://clinicaltrials.gov (NCT01598402).

Table 1
Patient characteristics at baseline (no statistically significant differences between the study groups).

	All patients		Patients with complete HRQoL questionnaires	
	Standard group (n = 48)	Prophylaxis group (n = 47)	Standard group (n = 34)	Prophylaxis group (n = 28)
Age-yr (range)	58.5 (43–68)	57.0 (23–68)	58.5 (48–68)	58.1 (29–68)
Sex – no. (%)				
Female	14 (29.2)	11 (23.4)	10 (29.4)	7 (25.0)
Male	34 (70.8)	36 (76.6)	24 (70.6)	21 (75.0)
WHO– no. (%)				
0	35 (72.9)	32 (68.1)	26 (76.5)	19 (67.9)
1	11 (22.9)	11 (23.4)	7 (20.6)	7 (25.0)
Unknown	2 (4.2)	4 (8.5)	1 (2.9)	2 (7.1)
Tumor site– no. (%)				
Oral cavity	14 (29.2)	13 (27.7)	9 (26.5)	6 (21.4)
Oropharynx	20 (41.7)	20 (42.6)	14 (41.2)	14 (50.0)
Hypopharynx	5 (10.4)	11 (23.4)	4 (11.8)	7 (25.0)
Larynx	8 (16.7)	3 (6.4)	7 (20.6)	1 (3.6)
Unknown primary	1 (2.1)	0	0	0
Indication CRT– no. (%)				
Primary treatment	26 (54.2)	34 (72.3)	19 (55.9)	20 (71.4)
Postoperative treatment	22 (45.8)	13 (27.7)	15 (44.1)	8 (28.6)

Assessments

HRQoL was assessed at baseline, day 28 of chemoradiotherapy (one day before starting prophylactic antibiotics), on the final day of radiotherapy, and 3.5 months after the end of chemoradiotherapy. Questionnaires included the 30-item core European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) [23], the EORTC QLQ Head and Neck Cancer-Specific Module (EORTC H&N35) [23], and the Performance Status Scale for Head & Neck cancer patients (PSS-HN) [24].

The EORTC QLQ-C30 is a 30-item questionnaire that assesses HRQoL in cancer patients across five functioning scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), three multi-item symptom scales (fatigue, pain, nausea and vomiting), six single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial problems) and global QoL [23]. Patients provide their answers on a 4-point scale (from 1 [not at all] to 4 [very much]), except for global QoL, which has a 7-point scale (from 1 [very poor] to 7 [excellent]). By linear transformation the raw scores are standardized, so that overall scores range from 0 to 100. A higher score on the functioning scales and on global QoL represent a better level of quality of life and functioning, and a higher score on the symptom scales means a worse level of symptoms [25]. According to EORTC Quality of Life Group guidelines, clinically important differences between the two treatment groups were divided into four classes based on size: large (representing unequivocal clinical relevance), medium (likely to be clinically relevant, but to a lesser extent), small (subtle but, nevertheless, clinically relevant) and trivial (circumstances unlikely to have any clinical relevance, or where there was no difference). For each subscale criteria to fit each of the four classes were composed [26]. Within each treatment group clinical relevant differences over time were defined as a difference of at least 10 points [27].

The EORTC H&N35, a disease-specific HRQoL questionnaire,

Table 2
Baseline scores in HRQoL measured by the EORTC QLQ-C30 and QLQ-H&N35. (N) after each subscales means the number of available questionnaires.

	Baseline				
	EORTC stage III-IV (mean)[F]	**Standard group (n = 34)**	**Prophylaxis group (n = 28)**	Δ	*p*
PSS-HN					
Normalcy of diet (N)	NA	77.5 (32)	68.8 (25)	−8.7	*0.253*
Eating in public(N)	NA	93.8 (32)	84.0 (25)	−9.8	*0.126*
Understandability of speech(N)	NA	89.8 (32)	90.0 (25)	0.2	*0.977*
QLQ-C30					
Physical functioning (N)	81.2	89.4 (34)	89.0 (28)	−0.4	*0.895*
Role functioning(N)	78.8	74.0 (34)	79.8 (28)	5.8	*0.413*
Emotional functioning(N)	71.2	77.7 (34)	82.1 (28)	4.4	*0.382*
Cognitive functioning(N)	86.4	89.7 (34)	94.0 (28)	4.3*	*0.267*
Social functioning (N)	82.2	79.4 (34)	88.7 (28)	9.3*	*0.104*
Global health status (N)	63.1	72.2 (33)	72.0 (28)	−0.2	*0.968*
Fatigue(N)	27.6	16.7 (34)	21.0 (28)	4.3	*0.415*
Nausea/vomiting (N)	5.2	0.5 (33)	5.4 (28)	4.9*	*0.075*
Pain(N)	24.9	18.1 (34)	18.5 (28)	0.4	*0.962*
Dyspnoea(N)	18.0	8.8 (34)	6.0 (28)	−2.8	*0.548*
Insomnia(N)	28.5	27.5 (34)	23.8 (28)	−3.7	*0.629*
Appetite loss(N)	19.4	10.8 (34)	19.0 (28)	8.2	*0.230*
Constipation(N)	11.7	12.7 (34)	10.7 (28)	−2	*0.719*
Diarrhea(N)	6.1	1.0 (34)	6.0 (28)	5*	*0.068*
Financial problems (N)	18.8	18.6 (34)	11.9 (28)	−6.7*	*0.289*
QLQ-H&N35[a]					
Pain(N)	NA	18.8 (34)	25.3 (27)	6.5	*0.203*
Swallowing(N)	NA	16.3 (34)	28.7 (27)	12.4†	*0.024*‡
Senses problems(N)	NA	16.2 (34)	7.4 (27)	−8.8	*0.090*
Speech problems(N)	NA	16.5 (33)	14.0 (27)	−2.5	*0.643*
Social eating(N)	NA	13.1 (33)	24.4 (26)	11.3†	*0.027*‡
Social contact(N)	NA	4.0 (33)	7.7 (27)	3.7	*0.302*
Sexuality(N)	NA	20.6 (30)	13.8 (23)	−6.8	*0.428*
Teeth(N)	NA	13.7 (34)	14.7 (25)	1	*0.891*
Opening mouth(N)	NA	26.5 (34)	24.4 (26)	−2.1	*0.800*
Dry mouth(N)	NA	17.6 (34)	18.5 (27)	0.9	*0.886*
Sticky saliva(N)	NA	21.6 (34)	20.5 (26)	−1.1	*0.887*
Coughing(N)	NA	24.5 (34)	22.2 (27)	−2.3	*0.704*
Felt ill(N)	NA	6.9 (33)	6.2 (26)	−0.7	*0.890*
Pain killers(N)	NA	48.5 (33)	37.0 (27)	−11.5†	*0.110*
Nutritional supplements(N)	NA	27.3 (33)	37.0 (27)	9.7	*0.427*
Feeding tube(N)	NA	9.1 (33)	7.7 (26)	−1.4	*0.851*

NA = not available.
* Small clinically important difference.
† Clinically relevant difference of more than 10 points.
‡ Statistically significant.
F EORTC reference data from patients with stage III or IV head and neck cancer [32].
[a] Weight gain and weight loss not reported due to difficult interpretation.

comprises 35 questions assessing symptoms and side effects of treatment, social function and body image/sexuality, and incorporates seven multi-item scales (pain, swallowing, senses (taste and smell), speech, social eating, social contact, sexuality), and 11 single item scales (teeth, opening mouth, dry mouth, sticky saliva, coughing, felt ill, pain killers, nutritional supplements, feeding tube, weight loss, weight gain). After linear transformation, all symptom scales range in score from 0 to 100, where a higher score means more complaints [23]. A difference of at least 10 points between the two treatment groups, as well as within the groups, was considered to be a clinically significant difference [27].

The PSS-HN was designed to measure unique disabilities of head and neck cancer patients. Surgery and/or systemic therapies in head and neck cancer patients often introduce cosmetic and functional deficits leading to problems with speech and eating [28]. The PSS-HN was developed as a simple and practical assessment and consists of three subscales: 'normalcy of diet', 'understandability of speech', and 'eating in public'. Each is rated from 0 to 100, with higher scores indicating better performance, and 100 representing normal function [24]. The 'normalcy of diet' subscale assesses the extent to which the patient is able to eat a regular diet. The 'understandability of speech' subscale rates the degree to which a listener is able to understand the patient's speech. The 'eating in public' subscale scores swallowing-related QoL issues by documenting the patient's ability to share a meal with others, and in which type of environment. The PSS-HN has been shown to have adequate inter-rater reliability and to be sensitive to differences in performance and change over time [24]. There are no studies performed to determine clinically relevant differences on the three subscales, as with the QLQ-C30 and QLQ-H&N35, however, a score of 50 or less on the different scales seems to correlate with a lower Karnofsky performance scale [24]. Norman's rule of thumb was used for the PSS-HN, whereby a ±0.5 standard deviation difference (i.e. 12.8 points) indicated a clinically relevant difference [29,30].

Statistics

Differences between the groups were calculated at every time point. Independent t-tests were performed to find any statistical significant differences between the two treatment groups for each symptom or functioning scale. For HRQoL during treatment compared with baseline (both groups) no statistical tests were performed and therefore results are descriptive. As described above, for all the separate questionnaires, we have not only reported statistical significant differences, but also (minimal) clinically important differences, because statistical significance does not provide information about clinical meaningfulness i.e. whether the observed effect is larger than the smallest clinically important effect [31,32].

The change in HRQoL and symptom burden (separate models for each scale) by treatment group was analyzed using linear mixed-effects models (i.e. covariance pattern model with an unstructured error variance matrix and maximum likelihood estimation) [33]. This technique uses data efficiently by including incomplete cases in the analysis. As a result, bias is limited and statistical power is preserved. Time was analyzed as a regular categorical predictor with four levels (i.e. four time points). The interaction of treatment group and time was tested separately. Analyses were performed in IBM SPSS 22.0 with a significance level of $\alpha = 0.05$.

Results

Patients

A total of 106 patients were included from six centres between January 2012 and July 2015. At randomization, 48 patients were allocated to standard group and 47 patients to the prophylaxis group. Nine included patients could not be randomized (e.g. due to the use of antibiotics 14 days prior to randomization). Both groups were well balanced with respect to baseline clinical and sociodemographic characteristics (Table 1).

HRQoL completion rate and baseline scores

Only patients who completed the questionnaires at baseline as well as at follow up were included in analyses (complete case analysis). Therefore, a total of 34 patients in the standard group (70.8%) and 28 patients in the prophylaxis group (59.6%) were included in final

Table 3
Scores in HRQoL at four time points during the study measured by the EORTC QLQ-C30 and QLQ-H&N35. (N) after each subscales means the number of available questionnaires. At baseline, 34 questionnaires in de standard group (70.8%) and 28 in the prophylaxis group (59.6%) could be analyzed, at day 28,70.8% and 55.3%, at the end of radiotherapy 52.1% and 40.4% and at follow up 70.8% and 69.6% in the standard group and prophylaxis group, respectively.

	Baseline				Day 28				After RT				FU			
	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	*p*	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	*p*	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	*p*	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	*p*
PSS-HN																
Normalcy of diet(N)	77.5 (32)	68.8 (25)	−8.7	*0.253*	45.5 (31)	37.6 (25)	−7.9	*0.294*	39.2 (24)	28.9 (18)	−10.3	*0.210*	72.0 (32)	56.9 (26)	−15.1[#]	*0.090*
Eating in public(N)	93.8 (32)	84.0 (25)	−9.8	*0.126*	67.5 (30)	56.8 (22)	−10.7	*0.274*	69.6 (23)	68.8 (16)	−0.8	*0.946*	87.5 (32)	72.9 (24)	−14.6[#]	*0.094*
Understandability of speech(N)	89.8 (32)	90.0 (25)	0.2	*0.977*	79.8 (31)	80.0 (25)	0.2	*0.981*	71.9 (24)	84.7 (18)	12.8[#]	*0.175*	91.9 (31)	90.0 (25)	−1.9	*0.607*
QLQ-C30																
Physical functioning(N)	89.4 (34)	89.0 (28)	−0.4	*0.895*	82.0 (34)	84.2 (26)	2.2	*0.539*	76.0 (25)	83.2 (19)	7.2[*]	*0.167*	87.1 (34)	84.6 (28)	−2.5	*0.473*
Role functioning(N)	74.0 (34)	79.8 (28)	5.8	*0.413*	62.3 (34)	64.7 (26)	2.4	*0.708*	55.3 (25)	68.4 (19)	13.1[*]	*0.127*	73.5 (34)	73.8 (28)	0.3	*0.965*
Emotional functioning (N)	77.7 (34)	82.1 (28)	4.4	*0.382*	81.4 (34)	78.2 (26)	−3.2	*0.536*	78.7 (25)	83.8 (19)	5.1	*0.335*	85.9 (33)	81.3 (28)	−4.6	*0.304*
Cognitive functioning (N)	89.7 (34)	94.0 (28)	4.3[*]	*0.267*	81.9 (34)	86.5 (26)	4.6[*]	*0.382*	77.3 (25)	89.5 (19)	12.2[¥]	*0.047*[‡]	88.4 (33)	91.7 (28)	3.3[*]	*0.389*
Social functioning(N)	79.4 (34)	88.7 (28)	9.3[*]	*0.104*	73.0 (34)	75.6 (26)	2.6	*0.693*	66.7 (25)	86.0 (19)	19.3[F]	*0.023*[‡]	84.3 (33)	83.3 (28)	−1	*0.851*
Global QoL(N)	72.2 (33)	72.0 (28)	−0.2	*0.968*	57.4 (34)	59.6 (26)	2.2	*0.679*	50.3 (25)	59.6 (19)	9.3[*]	*0.194*	71.7 (33)	64.9 (28)	−6.8[*]	*0.179*
Fatigue(N)	16.7 (34)	21.0 (28)	4.3	*0.415*	41.5 (34)	41.9 (26)	0.4	*0.950*	46.7 (25)	38.6 (19)	−8.1[*]	*0.267*	28.9 (34)	27.0 (28)	−1.9	*0.736*
Nausea/vomiting(N)	0.5 (33)	5.4 (28)	4.9[*]	*0.075*	27.0 (34)	15.4 (26)	−11.6[¥]	*0.091*	29.3 (25)	27.2 (19)	−2.1	*0.808*	6.9 (34)	5.4 (28)	−1.5	*0.659*
Pain(N)	18.1 (34)	18.5 (28)	0.4	*0.962*	28.9 (34)	34.0 (26)	5.1	*0.440*	35.3 (25)	37.7 (19)	2.4	*0.782*	17.6 (34)	18.5 (28)	0.9	*0.897*
Dyspnoea(N)	8.8 (34)	6.0 (28)	−2.8	*0.548*	7.8 (34)	11.5 (26)	3.7	*0.390*	8.0 (25)	8.8 (19)	0.8	*0.864*	7.8 (34)	11.9 (28)	4.1[*]	*0.384*
Insomnia(N)	27.5 (34)	23.8 (28)	−3.7	*0.629*	22.2 (33)	18.7 (25)	−3.5	*0.642*	22.7 (25)	15.8 (19)	−6.9[*]	*0.443*	16.7 (34)	28.4 (27)	11.7[*]	*0.158*
Appetite loss(N)	10.8 (34)	19.0 (28)	8.2	*0.230*	49.0 (34)	50.7 (25)	1.7	*0.854*	53.3 (25)	42.1 (19)	−11.2	*0.284*	22.5 (34)	33.3 (28)	10.8	*0.176*
Constipation(N)	12.7 (34)	10.7 (28)	−2	*0.719*	22.5 (34)	23.1 (26)	0.6	*0.927*	29.3 (25)	29.8 (19)	0.5	*0.955*	6.9 (34)	9.5 (28)	2.6	*0.583*
Diarrhea(N)	1.0 (34)	6.0 (28)	5[*]	*0.068*	9.8 (34)	7.7 (26)	−2.1	*0.618*	10.7 (25)	15.8 (19)	5.1[*]	*0.390*	1.0 (33)	4.8 (28)	3.8[*]	*0.136*
Financial problems(N)	18.6 (34)	11.9 (28)	−6.7[*]	*0.289*	15.7 (34)	12.8 (26)	−2.9	*0.614*	20.0 (25)	12.3 (19)	−7.7[*]	0.343	17.2 (33)	21.4 (28)	4.2[*]	*0.552*
QLQ-H&N35[a]																
Pain(N)	18.8 (34)	25.3 (27)	6.5	*0.203*	39.2 (34)	44.3 (25)	5.1	*0.418*	46.2(24)	41.2 (18)	−5	*0.501*	26.5 (34)	28.7 (27)	2.2	*0.704*
Swallowing(N)	16.3 (34)	28.7 (27)	12.4[†]	*0.024*[‡]	45.9 (34)	46.7 (25)	0.8	*0.907*	53.8 (24)	47.2 (18)	−6.6	*0.396*	22.7 (34)	29.9 (27)	7.2	*0.263*
Senses problems(N)	16.2 (34)	7.4 (27)	−8.8	*0.090*	51.0 (34)	40.7 (25)	−10.3[†]	*0.159*	46.5 (24)	40.7 (18)	−5.8	*0.468*	28.4 (34)	30.9 (27)	2.5	*0.729*
Speech problems(N)	16.5 (33)	14.0 (27)	−2.5	*0.643*	25.7 (34)	28.4 (26)	2.7	*0.690*	42.4 (25)	26.9 (19)	−15.5[†]	*0.051*	14.4 (34)	19.0 (28)	4.6	*0.354*
Social eating(N)	13.1 (33)	24.4 (26)	11.3[†]	*0.027*[‡]	35.9 (34)	39.4 (26)	3.5	*0.487*	41.9 (25)	38.7 (19)	−3.2	*0.643*	17.6 (34)	34.3 (27)	16.7[†]	*0.017*[‡]
Social contact(N)	4.0 (33)	7.7 (27)	3.7	*0.302*	12.7 (34)	9.6 (26)	−3.1	*0.479*	22.1 (25)	9.4 (19)	−12.7[†]	*0.041*[‡]	6.3 (34)	8.8 (28)	2.5	*0.446*
Sexuality(N)	20.6 (30)	13.8 (23)	−6.8	*0.428*	38.0 (32)	41.7 (22)	3.7	*0.711*	43.5 (23)	42.2 (17)	−1.3	*0.908*	29.6 (31)	27.8 (24)	−1.8	*0.845*
Teeth(N)	13.7 (34)	14.7 (25)	1	*0.891*	13.7 (34)	14.5 (23)	0.8	*0.888*	26.4 (24)	21.6 (17)	−4.8	*0.616*	10.1 (33)	26.9 (26)	16.8[†]	*0.019*[‡]
Opening mouth(N)	26.5 (34)	24.4 (26)	−2.1	*0.800*	37.3 (34)	34.7 (25)	−2.6	*0.764*	47.2 (24)	35.2 (18)	−12	*0.165*	30.4 (34)	34.6 (27)	4.2	*0.583*
Dry mouth(N)	17.6 (34)	18.5 (27)	0.9	*0.886*	52.0 (34)	50.7 (25)	−1.3	*0.881*	52.8 (24)	48.1 (18)	−4.7	*0.643*	54.9 (34)	56.8 (27)	1.9	*0.835*
Sticky saliva(N)	21.6 (34)	20.5 (26)	−1.1	*0.887*	58.8 (34)	68.0 (25)	9.2	*0.255*	66.7 (24)	70.4 (19)	3.7	*0.682*	45.1 (34)	43.2 (27)	−1.9	*0.789*

(*continued on next page*)

Table 3 (*continued*)

	Baseline				Day 28				After RT				FU			
	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	*p*	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	*p*	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	*p*	Standard group (n = 34)	Prophylaxis group (n = 28)	Δ	*p*
Coughing(N)	24.5 (34)	22.2 (27)	−2.3	*0.704*	35.3 (34)	38.7 (25)	3.4	*0.627*	29.2 (24)	29.6 (18)	0.4	*0.951*	24.5 (34)	29.6 (27)	5.1	*0.431*
Felt ill(N)	6.9 (33)	6.2 (26)	−0.7	*0.890*	32.4 (34)	25.3 (26)	−7.1	*0.329*	41.7 (25)	24.1 (19)	−17.6[¥]	*0.054*	12.7 (34)	14.8 (28)	2.1	*0.740*
Pain killers(N)	48.5 (33)	37.0 (27)	−11.5[†]	*0.110*	76.5 (34)	88.5 (26)	12	*0.224*	76.0 (25)	84.2 (19)	8.2	*0.515*	29.4 (34)	28.6 (28)	−0.8	*0.943*
Nutritional supplements (N)	27.3 (33)	37.0 (27)	9.7	*0.427*	72.7 (33)	76.0 (25)	3.3	*0.783*	72.0 (25)	57.9 (19)	−14.1[†]	*0.340*	41.2 (34)	46.4 (28)	5.2	*0.684*
Feeding tube(N)	9.1 (33)	7.7 (26)	−1.4	*0.851*	23.5 (34)	38.5 (26)	15[‡]	*0.227*	36.0 (25)	50.0 (18)	14[‡]	*0.371*	26.5 (34)	32.1 (28)	5.6	*0.632*

[*] Small clinical important difference.
[¥] Medium clinical important difference.
[F] Large clinical important difference.
[†] Clinical relevant difference of more than 10 points.
[‡] Statistically significant ($p < 0.05$).
[#] Clinical relevant difference of more than 12.8 points.
[a] Weight gain and weight loss not reported due to difficult interpretation.

analyses. At baseline 34 patients in the standard group and 28 patients in the prophylaxis group completed the questionnaires, before the start of prophylactic antibiotics (at day 28) 34 and 26 patients respectively, at the end of radiotherapy 25 and 19 patients and at the end of follow up 34 and 28 patients respectively. However, this could be different patients who completed the questionnaires at any time point.

At baseline, we found small clinically relevant differences between the two treatment arms in some of the EORTC QLQ-C30 scales. However, none of these were statistically significant.

Three items on the EORTC-HN35 were clinically relevant different with a difference of more than 10 points. The prophylaxis group scored higher on 'swallowing' (28.7 vs. 16.3) and 'social eating' (24.2 vs. 13.1) than the standard group and lower on 'painkillers' (37.0 vs. 48.5) than the standard group. However, only the differences on 'swallowing' ($p = 0.024$) and 'social eating' ($p = 0.027$) were statistically significant in favour of the standard group (Table 2).

The scores on the EORTC QLQ-C30 were comparable with EORTC reference data from patients with stage III or IV head and neck cancer [34].

HRQoL between treatment groups during treatment

At day 28 of chemotherapy, before the start of prophylactic antibiotics, there was no statistically significant difference between the standard and prophylaxis group (Table 3).

After radiotherapy, at which point the prophylaxis group were still taking antibiotics and acute toxicities of treatment are generally the highest, the prophylaxis group reported fewer symptoms on almost all subscales of the QLQ-C30, QLQ-H&N35 and PS-HN, though almost no items were significantly different to the 0.05 level (Table 3). 'Cognitive functioning' and 'social functioning' from the EORTC QLQ-C30 and 'social contact' from the QLQ-H&N35 were significantly different in favour of the prophylaxis group (Fig. 1).

At 3.5 months after the end of chemoradiotherapy, the standard group scored lower on 'social eating' (17.6 vs. 34.3, $p = 0.017$) and 'teeth' (10.1 vs. 26.9, $p = 0.019$) to a strong clinically relevant level compared to the prophylaxis group in favour of the standard group (Table 3).

HRQoL during treatment compared with baseline in both groups

The standard group had a lower score to a clinically relevant level on all functional subscales of the EORTC-QLQ-C30, except for 'emotional functioning,' at the end of radiotherapy compared to baseline, while the prophylaxis group had a lower score to a clinically relevant level only on 'role functioning' and 'global QoL' (Fig. 1). Scores on all functional subscales returned to baseline values at 3.5 months follow up for both treatment groups. In both groups, patients experiences a clinically relevant increase in symptoms after chemoradiotherapy compared to baseline that persisted until 3.5 months follow up on the items 'senses problems', dry mouth', 'sticky saliva', and 'feeding tube' (Table 3). On the other symptom subscales of the EORTC QLQ-C30 and QLQ-H&N35, there was a clinically meaningful increase in scores during chemoradiotherapy measured at day 28 and at the end of radiotherapy compared with baseline, which recovered to baseline levels at 3.5 months follow up for both groups (Table 3).

Course of HRQoL

At a group level, the EORTC QLQ-C30 functioning scales 'physical functioning', 'role functioning', and 'global QoL' significantly decreased between baseline and the end of chemoradiotherapy, indicating problems increased by the end of chemoradiotherapy. These changes were similar in both treatment groups (Table 4). Patients scored statistically significantly higher on 'fatigue', 'pain', 'constipation', and 'diarrhea' of the EORTC QLQ-C30 at the end of radiotherapy compared to baseline

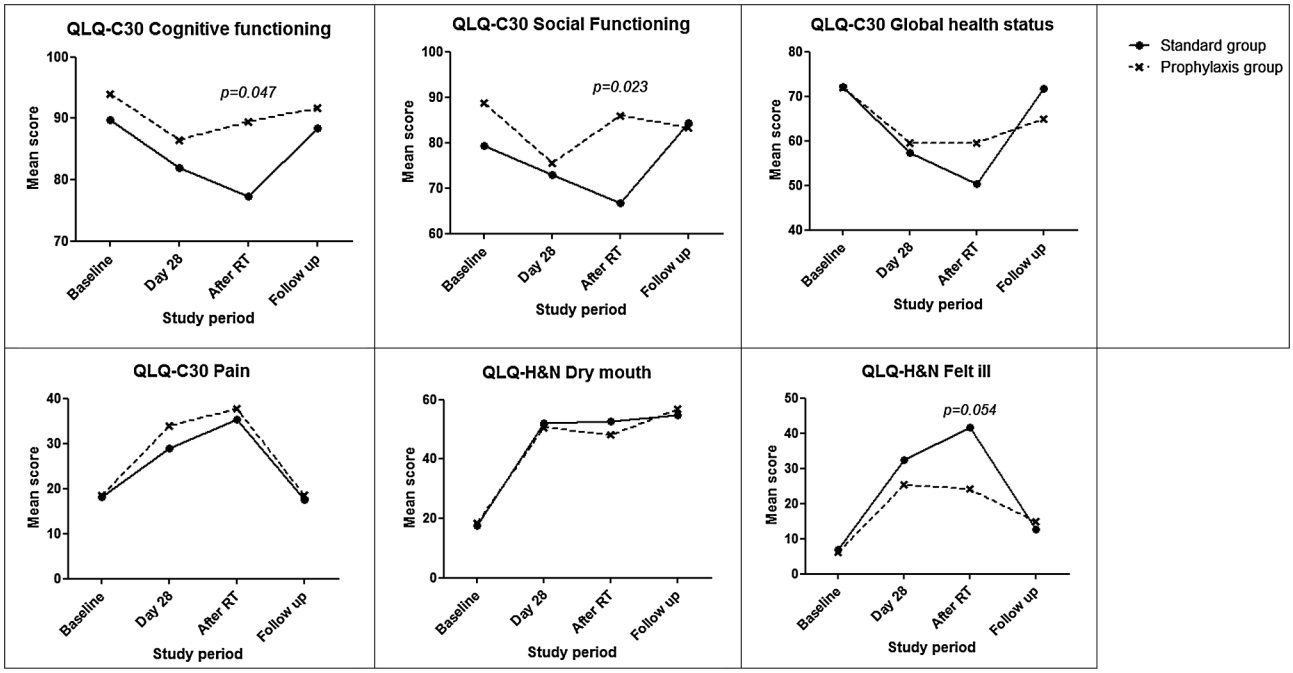

Fig. 1. On the top three functional items of the QLQ-C30 showing a decrease during chemoradiotherapy, and an increase at follow up, whereas the prophylaxis group in general had a less steeper decline after radiotherapy compared with the standard group. On the bottom three symptom subscales, showing an increase in symptoms during radiotherapy, with improvement of symptoms at follow up, except for some specific subscales like dry mouth. The prophylaxis group felt less ill during chemoradiotherapy.

and 3.5 months follow-up, with no difference between the two treatment groups. Patients also scored significantly higher on 'Nausea and vomiting' at the end of radiotherapy compared with all other time-points. The symptoms of the EORTC QLQ-H&N35 'pain', 'swallowing', 'sticky saliva', changed significantly between the end of radiotherapy and baseline and end of radiotherapy and end of follow-up, with significantly higher scores at the end of radiotherapy. The symptoms 'senses problems', 'speech problems', 'social eating', 'sexuality', 'dry mouth', 'coughing', 'felt ill' and the need of 'a feeding tube' scores all significantly higher at the end of radiotherapy compared with baseline. On the 'cognitive functioning' and 'social functioning' scales of the EORTC QLQ-C30 and the 'social contact' and 'feeling ill' symptom scales of the EORTC QLQ-H&N35 the standard group experienced significantly more problems over time compared to the prophylaxis group (Table 4).

Discussion

HRQoL was an important secondary objective of the PANTAP-study, which showed that prophylactic administration of amoxicillin/clavulanic acid reduced the number of hospital admissions, episodes of fever and healthcare costs without lowering the incidence of pneumonias. This study showed that prophylactic antibiotics also seemed to improve most aspects of HRQoL at the end of radiotherapy compared to standard care alone, although not all subscales were statistically significantly different.

At baseline some small clinically relevant differences were found between the two treatment groups, though most disappeared before the start of the prophylactic antibiotics at day 28. However, at the end of radiotherapy, when patients in the prophylaxis group were still taking the prophylactic antibiotics, the prophylaxis group reported a better HRQoL on most items compared to the standard group. At the end of follow up, 3.5 months after the end of chemoradiotherapy, few differences still existed between the two treatment groups. This suggests the advantage of the prophylaxis, with respect to the HRQoL, is experienced between the start of the antibiotics and the end of radiotherapy, as seen in the decreased decline in functional subscales. During the study, HRQoL deteriorated from baseline to day 28 and the end of radiotherapy; patients experienced a significantly higher symptom burden at the end of radiotherapy compared to baseline on 10 of the 18 symptoms covered by the EORTC QLQ-H&N35 reflects the high level of toxicity at the end of chemoradiotherapy. This confirms findings in the literature that show a decline in HRQoL during and at the end of (chemo)radiotherapy [9,11]. This deterioration can be explained by treatment toxicities.

Interestingly, we observed no difference in reported levels of diarrhoea in the prophylaxis group compared to the standard group. This is surprising given the relatively long use of antibiotics in the prophylaxis group.

At follow-up, 3.5 months after the end of chemoradiotherapy, most subscales returned to baseline-values or better, which has been previously described in other studies [4,9,12]. Only the 'senses problems', 'dry mouth', and 'sticky saliva' symptom scales saw no improvement at follow up. This is also agrees with previous studies by Vergeer et al. and Jellema et al. that showed dry mouth, sticky saliva and diminished taste can be long lasting or even permanent [10,35], due to permanent damage to the salivary glands caused by the radiotherapy. The fact that patients in the prophylaxis group scored significantly higher on the subscales 'social eating' and 'teeth' at follow-up, cannot be explained by the use of prophylactic antibiotics. This may be due to statistical issues related to the small number of completed questionnaires.

Slightly more patients included in the prophylaxis group had hypopharyngeal cancer, although not statistically different. Hypopharyngeal cancer is associated with a greater risk of aspiration and pneumonia. This may have influenced the number of aspiration pneumonias in both groups. But as the number of pneumonias were not different between the two groups, it likely would not have had any consequence on the HRQoL outcomes.

To the best of our knowledge, the PANTAP study is the first study to investigate the effect of prophylactic antibiotics on the occurrence of pneumonias, the number of hospital admissions and healthcare costs in LAHNC patients treated with chemoradiotherapy. The strength of the

Table 4
Linear mixed-effects model of the functional scales of the EORTC QLQ-C30 (4a) and the EORTC QLQ-H&N35 (4b). The item financial problems of the EORTC QLQ-C30 and the items nutritional supplements, feeding tube, weight loss and weight of the EORTC H&N-35 are not reported, because they are based on single item-questions, and in that way difficult to interpret and because of the small number of patients easy to vary in outcome.

4a.	Physical functioning Beta	Role functioning Beta	Emotional functioning Beta	Cognitive functioning Beta	Social functioning Beta	Global QoL Beta	Fatigue Beta	Nausea Beta	Pain Beta	Dyspnoea Beta	Insomnia Beta	Appetite loss Beta	Constipation Beta	Diarrhea Beta
Time variables														
Time														
T3 versus T1	6.69*	13.14*	−1.45	4.74	4.90	13.06*	−19.27*	−21.17*	−19.30*	−3.92	6.52	−27.01*	−19.17*	−9.05*
T3 versus T2	1.88	−2.92	−5.65	−3.05	−7.81	−0.04	1.59	−11.20*	−4.56	1.50	1.30	4.67	−6.64	−7.04
T3 versus T4	2.34	7.19	−2.34	2.36	−0.45	5.92	−13.32*	−21.17*	−19.30*	2.04	11.16	−12.72	−20.36*	−10.24*
Treatment														
Arm B versus Arm A	−6.16	−10.30	−5.67	−11.91*	−16.37*	−7.78	6.71	4.02	−3.06	−2.03	4.63	8.66	0.64	−3.58

4b.	Pain Beta	Swallowing Beta	Senses problems Beta	Speech problems Beta	Social eating Beta	Social contact Beta	Sexuality Beta	Teeth Beta	Opening mouth Beta	Dry mouth Beta	Sticky saliva Beta	Coughing Beta	Felt ill Beta	Pain killers Beta
Time variables														
Time														
T3 versus T1	−15.44*	−20.60*	−35.79*	−14.33*	−16.95*	−2.52	−29.21*	−3.08	−12.26	−28.47*	−49.40*	−11.05*	−19.98*	−14.59
T3 versus T2	3.04	−2.73	−0.15	−0.24	−1.88	−0.82	−1.30	−4.43	−2.33	6.01	−0.53	5.92	−0.14	1,97
T3 versus T4	−12.31*	−19.26*	−11.30	−9.52	−6.56	−1.20	−15.28	6.68	−1.66	10.99	−26.22*	−2.78	−10.48	−55.98*
Treatment														
Arm B versus Arm A	4.03	4.63	7.81	13.36	1.19	11.51*	0.50	5.83	5.95	7.38	−3.44	−2.87	16.24*	−6.97

* Indicating a clinically significant difference (<0.05).

current study is the focus on the effect of prophylactic antibiotics on HRQoL in this patient group. As far as we know, only one other study has looked at the effect of antibiotics on HRQoL. Braimah et al. investigated the effect of oral antibiotics on HRQoL after mandibular third molar surgery and showed that extended oral use of amoxicillin/clavulanic acid was correlated with a better, though not statistically significant, HRQoL [36].

A limitation of this study is the relative low compliance of completed HRQoL questionnaires, particularly at the end of radiotherapy. In addition, fewer questionnaires were completed by the prophylaxis group (at baseline 70.8% versus 59.6% for standard versus prophylaxis groups, respectively). Because of this, the number of included questionnaires was too low to perform multivariate analyses and no conclusions could be drawn on the impact of pneumonia or hospital admission on HRQoL. The explorative nature of this study also made it impossible to correct for multiple comparisons or confounders such as comorbidity. Furthermore, the last follow-up questionnaire was at 3.5 months after the end of chemoradiotherapy, limiting our ability to assess the long-term effects of prophylactic antibiotics on HRQoL. However, as HRQoL largely returned to baseline values at 3.5 months follow up with almost no differences between the groups, no large clinically relevant differences would be expected in future.

In conclusion, prophylactic antibiotics in LAHNC patients treated with chemoradiotherapy may mitigate deterioration of HRQoL at the end of the radiotherapy compared to standard care alone. However, no differences were found between groups at the end of follow up. This study should be replicated with larger numbers and more potential covariates. However, given the fact that prophylactic antibiotics, compared to standard treatment, reduced the number of hospital admissions and costs and also seemed to help maintain HRQoL at the end of the chemoradiotherapy, prophylactic antibiotics in this patients group can be considered.

Declaration of Competing Interest

None declared.

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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: Cancer J Clin 2018;68:7–30.
[2] Ferlay JSI, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide; IARC Cancerbase No. 11; 2012.
[3] Bottomley A, Tridello G, Coens C, Rolland F, Tesselaar ME, Leemans CR, et al. An international phase 3 trial in head and neck cancer: quality of life and symptom results: EORTC 24954 on behalf of the EORTC head and neck and the EORTC radiation oncology group. Cancer 2014;120:390–8.
[4] Rettig EM, D'Souza G, Thompson CB, Koch WM, Eisele DW, Fakhry C. Health-related quality of life before and after head and neck squamous cell carcinoma: analysis of the surveillance, epidemiology, and end results-medicare health outcomes survey linkage. Cancer 2016;122:1861–70.
[5] Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet 2008;371:1695–709.
[6] Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. New Engl J Med 2003;349:2091–8.
[7] Driessen CM, Janssens GO, van der Graaf WT, Takes RP, Merkx TA, Melchers WJ, et al. Toxicity and efficacy of accelerated radiotherapy with concurrent weekly cisplatin for locally advanced head and neck carcinoma. Head Neck 2016;38(Suppl 1):E559–65.
[8] Kelly C, Paleri V, Downs C, Shah R. Deterioration in quality of life and depressive symptoms during radiation therapy for head and neck cancer. Otolaryngol–Head Neck Surg: Off J Am Acad Otolaryngol-Head Neck Surg 2007;136:108–11.
[9] Klein J, Livergant J, Ringash J. Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: a systematic review. Oral Oncol 2014;50:254–62.
[10] Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys 2009;74:1–8.
[11] Epstein JB, Robertson M, Emerton S, Phillips N, Stevenson-Moore P. Quality of life and oral function in patients treated with radiation therapy for head and neck cancer. Head Neck 2001;23:389–98.
[12] de Graeff A, de Leeuw JR, Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA. Long-term quality of life of patients with head and neck cancer. Laryngoscope 2000;110:98–106.
[13] List MASA, Haraf D, Schumm P, Kies M, Stenson K, Vokes EE. Quality of life and performance in advanced head and neck cancer patients on concomitant chemoradiotherapy: a prospective examination. J Clin Oncol 1999;17(3):1020–8.
[14] Denaro N, Merlano MC, Russi EG. Dysphagia in head and neck cancer patients: pretreatment evaluation, predictive factors, and assessment during radio-chemotherapy, recommendations. Clin Exp Otorhi 2013;6:117–26.
[15] Xu B, Boero IJ, Hwang L, Le QT, Moiseenko V, Sanghvi PR, et al. Aspiration pneumonia after concurrent chemoradiotherapy for head and neck cancer. Cancer 2015;121:1303–11.
[16] Rutten H, Pop LA, Janssens GO, Takes RP, Knuijt S, Rooijakkers AF, et al. Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. Int J Radiat Oncol Biol Phys 2011;81:923–9.
[17] Langerman A, Maccracken E, Kasza K, Haraf DJ, Vokes EE, Stenson KM. Aspiration in chemoradiated patients with head and neck cancer. Arch Otolaryngol–Head Neck Surg 2007;133:1289–95.
[18] Nguyen NP, Smith HJ, Dutta S, Alfieri A, North D, Nguyen PD, et al. Aspiration occurence during chemoradiation for head and neck cancer. Anticancer Res 2007;27:1669–72.
[19] Ham J, Driessen C, Hendriks MP, Fiets WE, Kreike B, Hoeben A, et al. Prophylactic antibiotics to prevent pneumonia in patients treated with chemoradiotherapy (CRT) for locally advanced head and neck carcinoma (LAHNC). J Clin Oncol 2016;34:6079-.
[20] Ham J, Driessen C, Hendriks MP, Fiets WE, Kreike B, Hoeben A, et al. Cost-effectiveness of prophylactic antibiotics to prevent pneumonia in patients treated with chemoradiotherapy (CRT) for locally advanced head and neck carcinoma (LAHNC). J Clin Oncol 2017;35:6075.
[21] Husson O, Haak HR, Buffart LM, Nieuwlaat WA, Oranje WA, Mols F, et al. Health-related quality of life and disease specific symptoms in long-term thyroid cancer survivors: a study from the population-based PROFILES registry. Acta Oncol (Stockholm, Sweden) 2013;52:249–58.
[22] Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials. A review. Control Clin Trials 2002;23:662–74.
[23] 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;85:365–76.
[24] List MA, D'Antonio LL, Cella DF, Siston A, Mumby P, Haraf D, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale. A study of utility and validity. Cancer 1996;77:2294–301.
[25] Fayers PM AN, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC quality of life group. The EORTC QLQ-C30 scoring manual, 3rd ed.; 2001.
[26] Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol: Off J Am Soc Clin Oncol 2011;29:89–96.
[27] 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: Off J Am Soc Clin Oncol 1998;16:139–44.
[28] List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Cancer 1990;66:564–9.
[29] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582–92.
[30] Norman GR, Sridhar FG, Guyatt GH, Walter SD. Relation of distribution-and anchor-based approaches in interpretation of changes in health-related quality of life. Med Care 2001;39:1039–47.
[31] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Contr Clin Trials 1989;10:407–15.
[32] King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Qual Life Res: Int J Qual Life Aspects Treat, Care Rehab 1996;5:555–67.
[33] Liu LC, Hedeker D. A mixed-effects regression model for longitudinal multivariate ordinal data. Biometrics 2006;62:261–8.
[34] Scott NW FP, Aaronson NK, Bottomley A et al. EORTC QLQ-C30 reference values manual; 2008.
[35] Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:751–60.
[36] Braimah RO, Ndukwe KC, Owotade JF, Aregbesola SB. Impact of oral antibiotics on health-related quality of life after mandibular third molar surgery: an observational study. Nig J Clin Pract 2017;20:1189–94.