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Dysphagia, trismus and speech impairment following radiation-based treatment for advanced stage oropharyngeal carcinoma: a one-year prospective evaluation

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Abstract
Objective The objective was to assess swallowing, mouth opening and speech function during the first year after radiation-based treatment (RT(+)) after introduction of a dedicated preventive rehabilitation program for stage III–IV oropharyngeal carcinoma (OPC).
Methods Swallowing, mouth opening and speech function were collected before and at six- and twelve-month follow-up after RT(+) for OPC as part of ongoing prospective assessments by speech-language pathologists.
Results Objective and patient-perceived function deteriorated until 6 months and improved until 12 months after treatment, but did not return to baseline levels with 25%, 20% and 58% of the patients with objective dysphagia, trismus and speech problems, respectively. Feeding tube dependency and pneumonia prevalence was low.
Conclusion Despite successful implementation, a substantial proportion of patients still experience functional limitations after RT(+) for OPC, suggesting room for improvement of the current rehabilitation program. Pretreatment sarcopenia seems associated with worse functional outcomes and might be a relevant new target for rehabilitation strategies.

Keywords Oropharyngeal carcinoma · Chemoradiotherapy · Radiotherapy · Dysphagia · Trismus · Speech · Sarcopenia

Introduction

The incidence of oropharyngeal cancer (OPC) has risen over the past decades, partially due to the rising incidence of human papilloma virus (HPV) associated cases [1]. In early stage OPC, surgery as well as radiotherapy (RT) are curative treatment options. In more advanced stages, especially when the disease is technically and functionally irresectable [2], organ preserving concurrent radiotherapy and systemic therapy (RT(+)) has become the common treatment modality.

Despite advancement in treatment, e.g. Intensity Modulated RT (IMRT) and Volumetric Modulated Arc Therapy (VMAT), and rehabilitation, e.g. the addition of prophylactic swallowing exercises to ameliorate functional sequelae related to the tumor and its treatment, negative side effects still do occur. Multiple studies have shown that RT(+) for OPC, although organ preserving, is accompanied with serious functional impairment and a decreased quality of life in the short- and long-term [3–6]. Apart from xerostomia, swallowing impairment (dysphagia), is the most important side effect,
which can worsen over time or even develop years after treatment [4, 7–10]. Impaired mouth opening (trismus), also commonly occurs after radiation-based treatment for OPC. Incidence rates of trismus vary across studies including patients with head and neck cancer sites treated with surgery and/ or RT(+), but oropharyngeal localization of the tumor consistently seems a significant risk factor [11–16]. Besides, RT(+) of the oropharynx also may affect articulation and speech [17]. Finally, a potential increased risk of carotid stenosis and cerebrovascular accidents has also been documented after RT(+) [18]. These negative side effects and the prolonged survival achieved with the improved treatment technologies over the last decades demand an increased awareness of functionality and quality of life after OPC treatment.

Most functional results at one-year post-treatment stay stable up until 5 years posttreatment, which makes functional status at 1 year posttreatment predictive of the 4 year thereafter [19]. Thorough knowledge on the course of functional limitations during the first year after RT(+) for OPC will thus aid in adequate pretreatment patient counseling, and the development and optimization of targeted and patient specific (preventive) rehabilitation protocols. Moreover, identification of risk factors might aid in the development of individualized rehabilitation programs. For example, the correlation of HPV status with functional outcome has never been studied, but might be a factor. Also, pretreatment sarcopenia, i.e. low skeletal muscle mass, is associated with unfavorable outcomes after treatment for head and neck cancer, including decreased survival and increased long-term feeding tube dependency, and might also be related to other post-treatment functional impairments [20, 21].

The objective of this study was to present OPC patients’ objective and subjective swallowing function, mouth opening and speech data before and at 6 and 12 months after RT(+) (IMRT) after introduction of a dedicated preventive rehabilitation program, with special attention for the possible role of HPV and pretreatment sarcopenia. These data are relevant for the optimization of current rehabilitation protocols.

Methods

Ethical considerations

This study was approved by the Institutional Review Board of the Netherlands Cancer Institute—Antoni van Leeuwenhoek (NKI-AVL) (IRBd19044).

Patient selection

All patients diagnosed with head and neck cancer in the NKI-AVL, a tertiary cancer center, are followed up in ongoing prospective assessments by speech-language pathologists, who intensively monitor functional limitations before, during and after treatment and start (additional) targeted rehabilitation.

For this analysis, Dutch speaking patients were included who were curatively treated with primary RT or RT + (RT with cisplatin or cetuximab) for a stage III-IV squamous cell carcinoma of the oropharynx between January 2013 and September 2018. Patients were excluded in case of distant metastases, a synchronous primary tumor elsewhere, prior treatment of the head and neck area (except neck dissection or skin lesions), missing pre-treatment assessment data or if only pretreatment assessment data were available. Patients were excluded from follow-up of this study when additional oncological treatment was given due to residual or recurrent disease.

Radiotherapy based treatment

According to protocol, the treatment consisted of radiotherapy given with 6 MV photons up to 70 Gy in 35 fractions in 6 weeks in case of RT alone and 7 weeks in case of RT + using sequential of simultaneous integrated boost (SIB) according to the IMRT technique (either step and shoot or VMAT). Patients receiving sequential integrated boost were given an elective dosage of 46 Gy (23 fractions of 2 Gy) with a total dosage of 70 Gy (35 fractions of 2 Gy). Patients receiving simultaneous integrated boost were given an elective dosage of 54.25 Gy (35 fractions of 1.55 Gy) with a total dosage of 70 Gy (35 fractions of 2 Gy).

Concurrent systemic treatment (which was indicated in case of stage N2b or higher or extranodal spread) consisted of cisplatin or cetuximab. Cisplatin was administered intravenously either in high-dose (100 mg/m² at day 1, 22 and 43 of radiotherapy), intermediate-dose (40 mg/m² every week), or low-dose (6 mg/m² daily during the first 5 weeks of radiotherapy). Cetuximab was given when patients were unfit for cisplatin. One week before the start of RT, a loading dose of 400 mg/m² was administered, followed by 250 mg/m² weekly during 7 weeks.

Preventive rehabilitation protocol

Since studies have suggested benefit of preventive rehabilitation during RT(+), in April 2008 a preventive rehabilitation trial was conducted in the NKI-AVL, comparing preventive rehabilitation with and without the TheraBite Jaw Motion Rehabilitation System™ [22]. Despite the fact that in a subsequent study the cost-effectiveness of the protocol with the TheraBite was shown [23], reimbursement of this rehabilitation tool unfortunately was not achieved due to small differences in effectiveness compared to standard rehabilitation without the TheraBite. In 2011 reimbursement was achieved.
for a preventive rehabilitation program including standard swallowing rehabilitation only, which was clinically implemented during 2012, with 2013 as the first full year of its implementation [24]. All patients in the present study were instructed to perform preventive swallowing and mouth opening exercises daily from the start of treatment up until at least 3 months afterwards. In short, this included performing the following set of exercises three times a day: range-of-motion (stretch) exercises and three muscle strengthening exercises (i.e., effortful swallow, Masako maneuver, and super-supraglottic swallow). No data on adherence to the protocol was collected.

**Data collection**

Baseline characteristics collected included gender, age at start treatment, comorbidity according to the Adult Comorbidity Evaluation-27 (ACE-27) index, body mass index (BMI), tumor site, T and N classification (AJCC 7th edition, used at time of diagnosis), AJCC stage, HPV status and treatment modality. HPV status was determined using immunohistochemistry for p16 and p53. In case immunohistochemistry did not provide a definite result, polymerase chain reaction was used. Skeletal muscle mass was assessed at baseline. This was performed by measuring the total cross-sectional muscle areas (CSMA) of the bilateral paravertebral and sternocleidomastoid muscles on a single CT slice at the level of C3 using the software tool SliceOmatic, as described previously [20, 25, 26]. Routine pretreatment CT- of PET/CT scans were used for this purpose. The transformation formula of Swartz et al. was used to estimate CSMA at L3 level [25]. The lumbar skeletal muscle mass (LSMI) was calculated by normalizing the CSMA for height, from here level [25]. The lumbar skeletal muscle mass (LSMI) was calculated by normalizing the CSMA for height, from here called the skeletal mass index (SMI). Lower values of the lumbar SMM indicate lower skeletal muscle mass with values below 43.2 cm²/m² indicating sarcopenia [26].

Furthermore, swallowing, mouth opening and speech outcomes were collected from the speech-language pathologists’ records. For each domain an observer- as well as patient-rated outcome measure was collected before (t0) and 6 (t1) and 12 months (t2) post RT(+) as described below.

**Swallowing outcomes**

The primary observer-rated swallowing outcome was the functional oral intake scale (FOIS) which is a validated seven-point ordinal scale with lower scores indicating more intake problems [27]. As primary patient-rated swallowing outcome, the SWAL-QOL was used. This is a validated 44-item questionnaire on dysphagia and its influence on daily life. It includes ten domains: burden*, food selection*, eating duration*, eating desire*, fear*, sleep, fatigue, communication, mental health*, social functioning*, and symptom frequency. The total SWAL-QOL score is calculated from the subscales marked with an asterisk. All scores range from 0 to 100 with higher scores indicating more dysphagia-related problems [28, 29].

Secondary swallowing outcomes included feeding tube dependence and pneumonia during the past 6 months.

**Mouth opening outcomes**

The primary observer-rated trismus outcome was the mouth opening (maximum central inter-incisal opening) measured in millimeters using the TheraBite® Jaw Range of Motion Scale (Atos Medical AB, Hörby, Sweden). When a patient was missing the central incisors, 19 mm was subtracted from the score [30]. The patient-rated outcome was collected by means of a single item question on whether the patient experienced the mouth opening as limited.

**Voice and speech outcomes**

To assess observer-rated voice and speech outcomes, audio recordings were made of patients performing a set of speech tasks which included respectively reading aloud a 149 word long Dutch reading text called “Tachtig dappere fietsers” (Eighty brave cyclists), a word list, and sustained vowels (/a/,/i/,and/u/). All recordings were analyzes using the PRAAT program [31].

The primary observer-rated speech outcome was the vowel space area, a measure of articulation, for which the read text was used, or the word list if the text was not available. It was calculated as a percentage of the maximum total area of the vowel triangle [32]. In this study, values below 80% were used to indicate abnormal articulation.

The primary patient-rated speech outcome was the Speech Handicap Index (SHI). This is a thirty-item speech-related quality of life questionnaire on which a patient indicates the frequency of problems experienced on a five-point scale: never (=0), almost never (= 1), sometimes (= 2), almost always (= 3), and always (= 4). The score can range from 0 to 120 with higher scores indicating more speech-related problems. A psychosocial and a speech function subscale can be calculated from these thirty questions. The SHI also includes one global question indication the overall speech quality (excellent (=0), good (=30), average (=70), and bad (=100)) [33, 34].

Secondary speech outcomes were the articulation rate in syllables per second, which was measured from the reading text using a script in PRAAT [35]. The voice outcome measure was the acoustic voice quality index (AVQI), which was determined using a combination of 3 s of the sustained /a/ and 4 s of the read text [36, 37]. If no 3 s of /a/ was available, a combination of the sustained vowel records was used. If the read text was not present, 4 s of the word list was used.

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*A denotes values below 43.2 cm²/m² indicating sarcopenia [26].*
This outcome ranges from 1 to 10, with 1 being most equal to normal and 10 least equal to normal. A value of the AVQI less than 2.95 was considered a good voice quality [38].

**Statistical analysis**

Analyses were performed using IBM® SPSS® Statistics 25.0. Baseline characteristics were presented using descriptive statistics. To test whether patient and tumor characteristics of the patients at t0, t1 and t2 were different, the Kruskall–Wallis test was used for continuous data and the linear-by-linear approximation of the Pearson’s Chi-square test (exact two-sided p value) for dichotomous and ordinal data. To test differences in baseline characteristics of included patients and patients who were excluded because they either had only data at t0 available or did not have data at t0 available, the Mann Whitney U test for continuous data was used, the linear-by-linear approximation of the Pearson’s Chi-square test (exact two-sided significance) for ordinal data and the Fisher’s exact test for dichotomous data. Proportions and percentages were used to describe dichotomous outcomes and the median and range were used to describe all continuous outcomes. Differences between three timepoints were statistically analyzed by means of paired tests (i.e. Friedman test for continuous or ordinal data and a Cochran’s Q for dichotomous data) as well as the differences between two timepoints (i.e. Wilcoxon signed rank test for continuous or ordinal data and the McNemar test for dichotomous data). Univariable logistic regression analysis was used to explore factors related to dysphagia (FOIS < 7), trismus (mouth opening < 36 mm) and abnormal articulation (vowel space area > 80%) at t2. Differences in outcomes between HPV positive and negative patients and patients with and without pretreatment sarcopenia were assessed. Differences in baseline characteristics were assessed by means of the Mann–Whitney U test for continuous data, the linear-by-linear approximation of the Pearson’s Chi-square test (exact two-sided p value) for ordinal data and the Fisher’s exact test for dichotomous data. Associations were adjusted for confounders and mediators, chosen dependent on the outcome of interest (T and N classification, treatment and modified diet at t0 for differences in HPV classification; AJCC stage and modified diet at t0 for sarcopenia) by means of multivariable logistic or linear regression analyses. Overall, findings were considered statistically significant when the p value was less than 0.05. For all post-hoc pairwise comparisons, we considered a p value less than 0.01 statistically significant to account for multiple testing.

**Results**

Between January 2013 and September 2018, 248 patients with stage III-IV oropharyngeal squamous cell carcinomas were curatively treated with RT(+) at our institute of whom 106 patients were excluded from these analyses. Twenty-two patients were excluded because of previous treatment in the head and neck area (n = 7), a second primary tumor elsewhere (n = 14) or not speaking Dutch (n = 1). Eighty-four patients were eligible, but were excluded because of unavailable outcome data, due to several reasons: patient canceled pretreatment appointment (n = 4), appointment was not made (n = 40) or appointment was made, but assessments were not obtained (n = 40). Baseline characteristics of these 84 patients are shown in Table 1 and showed no significant differences with the included patients. Percentages of patients not included in the data assessment per accrual year are presented in Fig. 1. This figure also shows that the accrual increased from 19% in 2013 to 85% in 2018, with a slight decrease to 79% in 2019. Prevalence of functional impairment was comparable between patients included in 2013–2014 and 2017–2018 (appendix see Table 5).

In total, pretreatment data was assessed of 142 patients curatively treated with primary RT(+) for OPC. A further 34 patients had to be excluded due to missing follow-up data (11 patients withdrew, 3 patients did not receive a follow-up appointment, 15 had recurrent/residual disease, 1 developed second primary in the lung within the first 6 months post treatment, and 5 died (due to aspiration pneumonia, abdominal sepsis, sudden death, peritonitis or bleeding during alcohol abuse).

This left 108 patients for inclusion in the current analysis. Ninety-nine patients (92%) were present at t1 and 71 patients (66%) at t2 with 62 patients (57%) present at all three assessments. In appendix see Fig. 2 the reasons for loss to follow-up are presented. Median follow-up time at t1 was 6 months (range 2–9 months) and 12 months (range 8–18 months) at t2.

**Baseline characteristics**

Baseline characteristics are presented in Table 1. Of the 108 included patients, 73 (67%) were male, 53 patients (49%) had an ACE-27 score > 0 indicating comorbidity, 49 patients (45%) had sarcopenia, 35 patients (32%) had a tumor located in the base of tongue, 80 (74%) had stage IV disease and 70 (68%) were HPV positive. There were no significant differences regarding these characteristics between the patients present at the different assessments. Patients who were excluded because only t0 data was available (n = 34), had higher tumor stages, and had more often a modified diet pre-treatment (FOIS < 7) and trismus. Patients who were eligible but not included in the study (n = 84) were comparable to the included patients with regard to patient, tumor and treatment characteristics. However, baseline BMI, SMM, presence of sarcopenia, FOIS and mouth opening were not available for these patients.
Table 1 Baseline characteristics of patients at t₀, t₁ and t₂

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<th>t₂</th>
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<td>2 (3)</td>
<td></td>
<td>2 (6)</td>
<td>6 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT + cetuximab</td>
<td>17 (16)</td>
<td>17 (17)</td>
<td>11 (16)</td>
<td></td>
<td>7 (21)</td>
<td>12 (14)</td>
<td></td>
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</tr>
<tr>
<td>RT + cisplatin</td>
<td>49 (45)</td>
<td>43 (43)</td>
<td>32 (45)</td>
<td></td>
<td>16 (47)</td>
<td>33 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified diet at t₀ (FOIS &lt;7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>89 (82)</td>
<td>81 (82)</td>
<td>66 (93)</td>
<td>0.090b</td>
<td>23 (72)</td>
<td>0.212d</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (18)</td>
<td>18 (18)</td>
<td>5 (7)</td>
<td></td>
<td>9 (28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>2</td>
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<td></td>
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<tr>
<td>Trismus at t₀</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>98 (94)</td>
<td>91 (96)</td>
<td>64 (94)</td>
<td>1.000b</td>
<td>21 (66)</td>
<td>&lt;0.001d</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (6)</td>
<td>4 (4)</td>
<td>4 (6)</td>
<td></td>
<td>11 (34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>4</td>
<td>3</td>
<td></td>
<td>2</td>
<td></td>
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</tr>
</tbody>
</table>

NB Not all percentages sum up exactly to 100% due to rounding

BMI body mass index, HPV human papilloma virus, FOIS functional oral intake scale, other soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT radiotherapy, SMM skeletal muscle mass, t₀ pretreatment, t₁ 6 months after treatment, t₂ 12 months after treatment, sarcopenia SMM below 43.2 cm²/m²

aP values shown for Kruskal–Wallis test
bLinear-by-linear approximation of the Pearson’s Chi-square test
cMann Whitney U test
dFisher’s exact test
Speech and voice outcomes

Speech and voice outcomes are presented in Fig. 3c and Table 4. The median vowel space area at \( t_1 \) was lower than at \( t_0 \). At \( t_2 \), the median vowel space area was lower than at \( t_1 \), suggesting worsening articulation. Articulation rate and voice quality (AVQI) did not change over time. More patients had speech-related problems in daily life, as assessed with the SHI, at \( t_1 \) compared to \( t_0 \).

Speech and voice outcomes stratified by treatment modality, resulting in relatively small numbers per group, are presented in appendix see Table 9.

Factors associated with functional limitations

Appendix see Table 10 shows the baseline characteristics stratified by patients who did or did not have a modified diet (FOIS < 7) at \( t_2 \). A modified diet at \( t_2 \) was univariably associated with pretreatment lower BMI, lower SMI, sarcopenia, and a T4 tumor.

Appendix see Table 11 shows the baseline characteristics stratified by patients who had trismus (mouth opening < 36 mm) at \( t_2 \). Trismus at \( t_2 \) was univariably associated with tumor site other than base of tongue and tonsil (i.e. soft palate, uvula, pharyngeal wall, vallecula, and pharyngeal arches).

Appendix see Table 12 shows the baseline characteristics stratified by patients who had a vowel space below 80%, indicating abnormal articulation, at \( t_2 \). A vowel space below 80% at \( t_2 \) was univariably associated with a pretreatment vowel space area below 80% only.

HPV status

Appendix see Table 13 shows the baseline characteristics stratified by HPV status. Compared to patients with an HPV negative tumor, patients with an HPV associated tumor had a higher BMI, higher SMI, lower T classifications, higher N classification, were more often treated with RT only, and had less often a modified diet at baseline.

Functional outcomes at \( t_0 \), \( t_1 \) and \( t_2 \) stratified by HPV status are presented in appendix see Table 14. At \( t_1 \) and \( t_2 \), patients with an HPV negative tumor more often had a modified diet compared to patients with an HPV positive tumor. Also, SWAL-QOL scores were higher in the HPV negative group at both \( t_1 \) and \( t_2 \). The prevalence of trismus was comparable between the HPV negative and positive patients at \( t_1 \). At \( t_2 \), however, trismus was less prevalent in HPV negative patients compared to HPV positive patients. Patients with an HPV negative tumor also had slightly worse speech and voice outcomes, especially at \( t_1 \). After adjusting for T and N classification, treatment and pretreatment modified diet, none of the differences were statistically significant.
except at $t_2$, patients with an HPV positive tumor had a smaller mouth opening.

**Sarcopenia**

Appendix see Table 15 shows the baseline characteristics stratified by pretreatment sarcopenia. Patients with pretreatment sarcopenia were more often female, had a lower BMI, higher T classifications, higher disease stages, more often an HPV negative tumor, and more often had a modified diet at baseline compared to patients without pretreatment sarcopenia.

All outcomes stratified by pretreatment sarcopenia are presented in appendix see Table 16. Pretreatment sarcopenia was associated with more modified diet at all time-points. Also, at $t_0$ and $t_1$, SWAL-QOL scores were higher in patients with sarcopenia, indicating more swallowing related problems. At $t_2$, SWAL-QOL scores were comparable.
Trismus outcomes were comparable between patients with and without sarcopenia at \( t_0 \), \( t_1 \) and \( t_2 \). Prevalence of objective speech problems (vowel space area below 80%) was comparable at \( t_0 \) and \( t_1 \), but higher in patients with sarcopenia at \( t_2 \). Patient reported speech problems, however, were more prevalent in patients with sarcopenia. After adjusting for AJCC stage and pretreatment modified diet, only modified diet and the total SWAL-QOL score at \( t_1 \) were significantly higher in patients with pretreatment sarcopenia.

**Discussion**

The objective of this study was to assess objective and subjective swallowing function, mouth opening and speech over a one-year period in a large cohort after RT(+) for advanced stage OPC treatment after introduction of a dedicated preventive rehabilitation program, also focusing on the role of HPV status and pretreatment sarcopenia. These results are relevant for the optimization of current rehabilitation protocols. Patients were treated with IMRT with or without systemic therapy and a concurrent preventive rehabilitation program. Data collection was part of a systematic, intensive routine monitoring program at our institute to evaluate outcomes after the implementation of this dedicated preventive rehabilitation program. Accrual to this study increased from 19% in 2013 to 85% in 2018, with a slight decrease to 79% in 2019, indicating increased awareness regarding the rehabilitation program and its evaluation amongst our medical staff. The study showed that the normalcy of oral intake and SWAL-QOL scores first deteriorated up to 6 months, and subsequently improved up until 12 months after treatment, but did not return to baseline levels. Rate of feeding tube dependency in this cohort was low, with none of the patients being feeding tube dependent at 1 year after treatment. Also, very few patients experienced pneumonia during the one-year follow-up. Trismus and speech problems showed the same trend as swallowing function, with increased prevalence of problems at six-month follow-up, and lower—but still above baseline—prevalence rates at one-year post-treatment. Patients treated with cisplatin-based RT+, HPV negative tumors, and patients with pretreatment sarcopenia were more likely to have functional limitations. Patients treated with RT+ had worse swallowing, trismus and speech and voice outcomes, compared to those treated with RT alone.

Most of the above summarized outcomes were in line with expectations and are comparable to those of other studies concluding that a substantial proportion of the patients have functional impairment after treatment. Although it is hard to compare the present results to other studies given the
Table 2 Swallowing outcomes at \( t_0 \), \( t_1 \) and \( t_2 \)

<table>
<thead>
<tr>
<th>Observer-rated outcome</th>
<th>Total</th>
<th>( t_0 )</th>
<th>( t_1 )</th>
<th>( t_2 )</th>
<th>( P ) value ( t_0 ) vs. ( t_1 )</th>
<th>( P ) value ( t_1 ) vs. ( t_2 )</th>
<th>( P ) value ( t_0 ) vs. ( t_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOIS</td>
<td></td>
<td>( n = 108 )</td>
<td>( n = 99 )</td>
<td>( n = 71 )</td>
<td>( n = 108 )</td>
<td>( n = 99 )</td>
<td>( n = 71 )</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>89 (82)</td>
<td>65 (66)</td>
<td>53 (75)</td>
<td>0.012(^a)</td>
<td>0.195(^c)</td>
<td>0.499(^b)</td>
<td>0.043(^c) ↑</td>
</tr>
<tr>
<td>6</td>
<td>8 (7)</td>
<td>24 (25)</td>
<td>14 (20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7 (7)</td>
<td>4 (4)</td>
<td>3 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>0 (0)</td>
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<td></td>
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<td>2</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>Unknown</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified diet (FOIS < 7)

| FOIS                  |       |        |        |        |          |          |          |
|                       | 89 (82) | 65 (66) | 53 (75) | 0.005\(^b\) | 0.012\(^d\) ↑ | 0.832\(^d\) | 0.004\(^d\) ↑ |
| No                    | 19 (18) | 33 (34) | 18 (25) |          |          |          |          |
| Yes                   | 0       | 1       | 0       |          |          |          |          |

Patient-rated outcome

<table>
<thead>
<tr>
<th>SWAL-QOL (0–100) median (range)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>General burden</td>
<td>0 (0–88)</td>
<td>0 (0–100)</td>
<td>0 (0–50)</td>
<td>0.004(^a)</td>
<td>0.001(^b) ↑</td>
<td>0.620(^c)</td>
<td>0.010(^c) ↑</td>
</tr>
<tr>
<td>Food selection</td>
<td>0 (0–88)</td>
<td>25 (0–100)</td>
<td>0 (0–50)</td>
<td>&lt; 0.001(^a)</td>
<td>&lt; 0.001(^b) ↑</td>
<td>0.031(^c) ↓</td>
<td>0.001(^c) ↑</td>
</tr>
<tr>
<td>Eating duration</td>
<td>13 (0–88)</td>
<td>38 (0–100)</td>
<td>38 (0–100)</td>
<td>&lt; 0.001(^a)</td>
<td>&lt; 0.001(^b) ↑</td>
<td>0.431(^c)</td>
<td>&lt; 0.001(^c) ↑</td>
</tr>
<tr>
<td>Eating desire</td>
<td>8 (0–92)</td>
<td>17 (0–83)</td>
<td>8 (0–67)</td>
<td>0.003(^a)</td>
<td>0.001(^c) ↑</td>
<td>0.245(^c)</td>
<td>0.002(^c) ↑</td>
</tr>
<tr>
<td>Fear</td>
<td>0 (0–69)</td>
<td>0 (0–69)</td>
<td>0 (0–38)</td>
<td>0.066(^c)</td>
<td>0.002(^c) ↑</td>
<td>0.490(^c)</td>
<td>0.031(^c) ↑</td>
</tr>
<tr>
<td>Sleep</td>
<td>38 (0–75)</td>
<td>38 (0–75)</td>
<td>25 (0–88)</td>
<td>0.044(^c)</td>
<td>0.307(^c)</td>
<td>0.003(^c) ↓</td>
<td>0.372(^c) ↑</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (0–67)</td>
<td>29 (0–75)</td>
<td>17 (0–83)</td>
<td>0.001(^a)</td>
<td>0.001(^c) ↑</td>
<td>0.177(^c)</td>
<td>0.055(^c) ↑</td>
</tr>
<tr>
<td>Communication</td>
<td>0 (0–75)</td>
<td>0 (0–75)</td>
<td>0 (0–63)</td>
<td>0.087(^a)</td>
<td>0.008(^c) ↑</td>
<td>0.780(^c)</td>
<td>0.065(^c) ↑</td>
</tr>
<tr>
<td>Mental health</td>
<td>0 (0–75)</td>
<td>0 (0–100)</td>
<td>0 (0–45)</td>
<td>0.138(^a)</td>
<td>0.002(^c) ↑</td>
<td>0.391(^c)</td>
<td>0.182(^c) ↑</td>
</tr>
<tr>
<td>Social functioning</td>
<td>0 (0–70)</td>
<td>0 (0–60)</td>
<td>0 (0–30)</td>
<td>0.215(^c)</td>
<td>0.002(^c) ↑</td>
<td>0.349(^c)</td>
<td>0.233(^c) ↑</td>
</tr>
<tr>
<td>Symptoms</td>
<td>7 (0–79)</td>
<td>16 (0–52)</td>
<td>13 (0–41)</td>
<td>0.003(^a)</td>
<td>&lt; 0.001(^b) ↑</td>
<td>0.032(^c)</td>
<td>0.003(^c) ↑</td>
</tr>
<tr>
<td>Total score</td>
<td>5 (0–69)</td>
<td>14 (0–77)</td>
<td>9 (0–43)</td>
<td>&lt; 0.001(^a)</td>
<td>&lt; 0.001(^b) ↑</td>
<td>0.342(^c)</td>
<td>&lt; 0.001(^c) ↑</td>
</tr>
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</table>

SWAL-QOL ≥ 14

| No                     | 52 (67) | 35 (52) | 38 (72) | 0.307\(^b\) | 0.057\(^d\) | 0.754\(^d\) | 0.388\(^d\) |
| Yes                    | 26 (33) | 32 (48) | 15 (28) |          |          |          |          |
| Unknown                | 30       | 32       | 18       |          |          |          |          |

Secondary outcomes

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<th>Feeding tube</th>
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<tbody>
<tr>
<td>No</td>
<td>106 (98)</td>
<td>93 (94)</td>
<td>71 (100)</td>
<td>0.018(^b)</td>
<td>0.289(^d)</td>
<td>0.125(^d)</td>
<td>1.000(^d)</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (2)</td>
<td>6 (6)</td>
<td>0 (0)</td>
<td></td>
<td></td>
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</tbody>
</table>

Pneumonia

| No | 98 (96) | 90 (97) | 67 (96) | 0.050\(^b\) | 1.000\(^d\) | 0.250\(^d\) | 1.000\(^d\) |
| Yes| 4 (4)   | 3 (3)   | 3 (4)   |          |          |          |          |

NB Not all percentages sum up exactly to 100% due to rounding

*FOIS* functional oral intake scale, *NGT* nasogastric tube, *PRG* percutaneous radiological gastrostomy, \( t_0 \) pretreatment, \( t_1 \) 6 months after treatment, \( t_2 \) 12 months after treatment

\(^a\)P values shown for Friedman test

\(^b\)Cochran’s Q test

\(^c\)Wilcoxon signed rank test

\(^d\)McNemar test

\(↑\)Indicating more problems

\(↓\)Indicating less problems
heterogeneity of cohorts and outcome measures currently used, some comparisons can be made. Starmer et al. evaluated 71 patients with OPC treated with IMRT with or without systemic therapy and preventive swallowing rehabilitation around 5 months post-treatment [9]. Probably because 92% of the patients received RT +, prevalence of a modified diet according to FOIS scores was higher in that study (86% compared to 34% in our study). Hunter et al. evaluated the two-year period after RT + without preventive swallowing rehabilitation for stage III-IV OPC in 72 patients [10]. At 6 and 12 months after treatment respectively, 6% and 2% had grade 2 dysphagia (modified diet) and 6% and 1% had grade 3 dysphagia (feeding tube dependence) according to the Common Toxicity Criteria Adverse Effects (CTCAE) scale. The significantly lower percentage of patients with a modified diet in that study may, in part, be because another outcome measure was used (CTCAE scale versus FOIS). Congruent with our finding, other studies also found that functional limitations worsened the first months after therapy and improved through 12 months after treatment with minimal improvement in the year thereafter [10, 39].

Only few studies have investigated trismus within the first year after radiation-based treatment and a preventive rehabilitation protocol for advanced stage OPC. Kraaijenga et al. found that 9 of 24 patients (27%) after RT + for OPC had trismus at a median follow-up of 13 weeks [16]. In our study this concerned 23% at six-month follow-up and 20% at twelve-month follow-up. Incidence rates of trismus in other studies including all head and neck cancer localizations treated with surgery and/or radiation vary, but oropharyngeal localization of the tumor consistently seems a risk factor [11–15, 40]. This is probably because treatment of the oropharynx causes fibrosis in the mastication musculature [16]. This hypothesis is also supported by our results showing that patients with tumor localizations within the oropharynx other than base of tongue have trismus more often.

Apparently, despite trismus preventing measures in our preventive rehabilitation program, trismus is still a prevalent problem in this cohort. Therefore, extra measures could be taken to prevent and treat trismus, for example, by selecting high risk patients for more intensive guidance, and emphasizing the need for trismus prevention stronger, prior to treatment. The consistent use of mouth opening exercises (e.g. with tongueblades or TheraBite®) in this patient group might have been advantageous [41]. The lack of reimbursement for TheraBite® in the Netherlands, preventing regular use of this medical device in our patient population, is noteworthy in this respect.

With respect to speech and voice outcomes, according to our results, observer-rated intelligibility was deteriorated.
Subjective speech outcomes, however, deteriorated up until 6 months and returned to baseline levels at twelve-month follow-up. This is most likely because patients get used to the altered speech. Vainshtein et al. found the same trend in patient-reported voice quality, which decreased maximally at 1 month after treatment and recovered to baseline after 12 to 18 months [42]. In an earlier study from our institute, Jacobi et al. found comparable results. They reported that computer analyzed articulation and sound quality was impaired in head and neck cancer patients after RT + , especially with oral and oropharyngeal cancer sites [43].

The policy evaluated in this study was comparable to that applied in the control arm of the randomized trial by van der Molen et al. [22]. The proportion of patients with functional limitations at one-year follow-up of that study are substantially lower than observed in the current cohort [44]. Only 7% of the 49 included patients had a modified diet (FOIS < 7) at one-year follow-up, compared to 25% of the patients in our study. Also, only 3% had trismus, compared to 20% in our study. The first explanation obviously is the heterogeneity of the patient cohorts. In our study, only OPC patients treated with radiotherapy-based treatment were included, while only 37% of the patients included in the randomized study had OPC, and all received chemoradiotherapy. Another, more important explanation is that in the setting of a randomized study, adherence to the rehabilitation protocol is likely to be higher, which might have resulted in better functional outcomes, supporting the benefit of the rehabilitation protocol, but also highlighting the challenges of achieving similar outcomes in regular practice.

Our results suggest that patients treated with concomitant systemic therapy have more functional limitations than patients treated with RT alone, although numbers were small. This might be due to the toxicity of systemic therapy, but might also be because of the higher tumor stages, and therefore also larger radiotherapy fields. Only 17 (16%) of the 108 included patients

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Speech and voice outcomes at t₀, t₁ and t₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Observer-rated outcomes</td>
<td></td>
</tr>
<tr>
<td>Vowel space area (%) (median)</td>
<td>85 (51–129)</td>
</tr>
<tr>
<td>Vowel space area &lt; 80%</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Patient-rated outcomes</td>
<td></td>
</tr>
<tr>
<td>SHI median (range)</td>
<td>0 (0–42)</td>
</tr>
<tr>
<td>Speech domain (0–56)</td>
<td>0 (0–39)</td>
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<tr>
<td>Psychosocial domain (0–56)</td>
<td>0 (0–83)</td>
</tr>
<tr>
<td>Total score (0–120)</td>
<td>0 (0–60)</td>
</tr>
<tr>
<td>SHI ≥ 6</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
</tr>
<tr>
<td>Articulation rate (syllables/s) (median)</td>
<td>2.3 (0.2–7.7)</td>
</tr>
<tr>
<td>AVQI median (range)</td>
<td>4.5 (3.3–5.3)</td>
</tr>
</tbody>
</table>

NB Not all percentages sum up exactly to 100% due to rounding

AVQI acoustic voice quality index, FOIS functional oral intake scale, NGT nasogastric tube, PRG percutaneous radiological gastrostomy, SHI speech handicap index, t₀ pretreatment, t₁ 6 months after treatment, t₂ 12 months after treatment

a P values shown for Friedman test
b Cochran’s Q test
c Wilcoxon signed rank test
d McNemar test
† Indicating more problems
↓ Indicating less problems
were treated with cetuximab based RT+ and therefore there is a high risk of atypical sampling and conclusions on functional outcomes relative to RT only or cisplatin-based RT+ based on these analyses should be made with caution. A recently published randomized study concluded that the degree of toxicities, including dysphagia, between cisplatin and cetuximab in HPV positive OPC was comparable [5].

In our cohort, although HPV status was not associated with trismus and speech outcomes, patients with HPV positive tumors had less objective and subjective functional impairment. However, patients with HPV positive tumors also had more favorable baseline characteristics, including higher pretreatment SMI (as also reported by Chargi et al. [45]), lower T classification, were more often treated with RT only and less often had a modified diet before treatment. When adjusting for baseline characteristics in multivariable analyses, HPV status was not significantly associated with functional limitations, except for a smaller mouth opening at one-year post-treatment. Although no definite conclusions can be drawn, it seems that HPV status itself does not influence post-treatment functional limitations.

Results in literature have contrasting results regarding the association of HPV status with functional limitations after RT(+). Vangelov et al. evaluated 100 patients with OPC treated with RT(+) and found that after adjusting for baseline characteristics (i.e. smoking, nodal stage, IMRT, and oropharyngeal RT dose), patients with an HPV positive tumor more often had tube feeding and weight loss, compared to patients with an HPV negative tumor [46]. Again, adjusted for baseline characteristics (i.e. age, gender, stage, treatment modality, RT dose, neck node irradiation, and pretreatment weight loss), Vatca et al., on the other hand, evaluated 228 OPC patients and found that patients with an HPV positive tumor had more mucositis and weight loss during treatment [47]. Sharma et al. evaluated 228 OPC patients and found that quality of life in HPV positive patients was lower shortly after treatment but became comparable by 1 year after treatment, also adjusted for baseline differences [48], which is similar to our findings.

A low skeletal muscle mass, or sarcopenia, before treatment, was associated with an impaired diet before and after treatment. This is in line with results of a previous study performed at our institute which demonstrated that sarcopenia is a strong determinant for feeding tube use after RT+ for head and neck cancer [20]. Skeletal muscle loss is thought to be related to swallowing muscle loss, causing swallowing difficulties which might result in a modified diet or eventually tube dependency. Moreover, swallowing problems itself may result in skeletal muscle loss due to insufficient nutritional intake. Therefore, these results support the hypothesis that sarcopenia might be a relevant target to optimize patients’ condition before as well as after treatment to improve functional status. Apparently, our current preventive rehabilitation protocol does not target muscle mass sufficiently and/or not sufficiently long enough to close the gap between sarcopenic and non-sarcopenic patients with regard to swallowing impairment. In view of the association between pretreatment sarcopenia and functional outcomes, integrating SMI determination before treatment is warranted.

**Limitations**

A limitation of this study is the suboptimal accrual during the first years of the data collection. These analyses were performed on data collected as part of standard care. Collecting data in this way usually introduced a risk for suboptimal inclusion especially during startup. Although at first inclusion rates were low, they improved over time with current inclusion rates between 79 and 85%, making it likely that this cohort is representative for the entire cohort. In addition, because baseline characteristics between included patients and not included patients were similar, no selection bias due to (non-)inclusion seems present. Another limitation of this study is that no data on adherence to the preventive rehabilitation protocol was collected, as this is not routinely registered in usual care. However, the observed outcomes thus realistically reflect the outcomes as they occur in clinical practice.

**Conclusion**

Objective and patient-perceived swallowing, mouth opening, and speech function of patients treated with IMRT with or without systemic therapy combined with a preventive rehabilitation program for OPC deteriorate up until 6 months and improve until 12 months after treatment, but do not return to baseline levels. Patients treated with cisplatin-based CRT, HPV negative tumors and patients with pretreatment sarcopenia were more likely to have functional limitations. HPV negative status itself is not likely to be a cause of functional limitations, but the associated unfavorable patient and tumor characteristics are. Pretreatment sarcopenia might be a relevant target for prehabilitation strategies. Although for most patients in this cohort organ preserving treatment resulted in function preservation, there is a proportion of patients with functional problems, suggesting room for improvement of the current rehabilitation program.
Appendix

See Table 5,6,7,8,9,10,11,12,13,14,15,16

Table 5  Functional outcomes at t1 and t2 stratified by inclusion year

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<td><strong>Swallowing outcomes</strong></td>
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<tr>
<td>Modified diet (FOIS &lt; 7)</td>
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<td>9 (64)</td>
<td>26 (67)</td>
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<td>SWAL-QOL total score (0–100) median (range)</td>
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<tr>
<td>No</td>
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<td>20 (0–77)</td>
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<td>3 (43)</td>
<td>10 (42)</td>
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<td>7</td>
<td>16</td>
<td>2</td>
<td>7</td>
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<td>5 (17)</td>
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<td>24</td>
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<tr>
<td><strong>Trismus outcomes</strong></td>
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<td></td>
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<tr>
<td>Mouth opening in mm median (range)</td>
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<tr>
<td>No</td>
<td>46 (30–59)</td>
<td>44 (27–52)</td>
<td>44 (10–58)</td>
<td>43 (25–52)</td>
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<td>28 (76)</td>
<td>11 (79)</td>
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<td>Perceived trismus</td>
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<td>9 (82)</td>
<td>28 (78)</td>
<td>11 (85)</td>
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<td>2 (18)</td>
<td>8 (22)</td>
<td>2 (15)</td>
<td>2 (7)</td>
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<td>0</td>
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<td><strong>Speech and voice outcomes</strong></td>
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<td></td>
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<tr>
<td>Vowel space area (%) median (range)</td>
<td>81 (59–99)</td>
<td>75 (49–100)</td>
<td>86 (58–96)</td>
<td>71 (51–102)</td>
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<tr>
<td>Vowel space area &lt; 80%</td>
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<td></td>
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<td>5 (50)</td>
<td>14 (39)</td>
<td>7 (58)</td>
<td>6 (24)</td>
</tr>
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<td>5 (50)</td>
<td>22 (61)</td>
<td>5 (42)</td>
<td>19 (76)</td>
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<tr>
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<td>4</td>
<td>4</td>
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<td>4</td>
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<td>SHI total score (0–120) median (range)</td>
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<tr>
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<td>4 (0–60)</td>
<td>0 (0–22)</td>
<td>0 (0–40)</td>
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<td>9 (56)</td>
<td>9 (82)</td>
<td>12 (92)</td>
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<td>71 (44)</td>
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<td>1 (8)</td>
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<td>SHI ≥ 6</td>
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<td>7</td>
<td>24</td>
<td>3</td>
<td>16</td>
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</tbody>
</table>

P values shown for multivariable regression adjusted for AJCC stage and modified diet at t0

NB Not all percentages sum up exactly to 100% due to rounding

FOIS functional oral intake scale, HPV human papillomavirus, SHI speech handicap index, t1 6 months after treatment, t2 12 months after treatment
### Table 6: Baseline characteristics stratified by treatment modality

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<tr>
<th></th>
<th>Number of patients (%)</th>
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<tbody>
<tr>
<td></td>
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<td>RT + cetuximab n = 17</td>
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<tr>
<td><strong>Gender</strong></td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (69)</td>
<td>14 (82)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (31)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Age at baseline median (range)</td>
<td>61 (39–81)</td>
<td>64 (56–79)</td>
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<tr>
<td><strong>ACE-27</strong></td>
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<td></td>
</tr>
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<td>0</td>
<td>19 (45)</td>
<td>4 (24)</td>
</tr>
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<td>1</td>
<td>14 (33)</td>
<td>7 (41)</td>
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<tr>
<td>2</td>
<td>7 (17)</td>
<td>5 (29)</td>
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<td>3</td>
<td>2 (5)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>BMI median (range)</strong></td>
<td>26 (17–44)</td>
<td>25 (18–33)</td>
</tr>
<tr>
<td><strong>SMM median (range)</strong></td>
<td>45 (22–64)</td>
<td>45 (28–54)</td>
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<tr>
<td><strong>Sarcopenia</strong></td>
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<tr>
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<td>27 (64)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Yes</td>
<td>15 (36)</td>
<td>8 (47)</td>
</tr>
<tr>
<td><strong>Oropharyngeal tumor site</strong></td>
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<tr>
<td>Base of tongue</td>
<td>16 (38)</td>
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<td>Tonsil</td>
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<td>T2</td>
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<td>7 (47)</td>
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<td>RT</td>
<td>39 (93)</td>
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</tr>
<tr>
<td>RT unfit for RT +</td>
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<td>0 (0)</td>
</tr>
<tr>
<td>RT + cetuximab</td>
<td>0 (0)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>RT + cisplatin</td>
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<td>0 (0)</td>
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<tr>
<td><strong>Modified diet at t0 (FOIS &lt; 7)</strong></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>36 (86)</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (14)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>Trismus at t0</strong></td>
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<td></td>
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<tr>
<td>No</td>
<td>39 (93)</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (7)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

NB Not all percentages sum up exactly to 100% due to rounding

BMI body mass index, FOIS functional oral intake scale, HPV human papilloma virus, other soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT radiotherapy, SMM skeletal muscle mass
Table 7 Swallowing outcomes at $t_0$, $t_1$ and $t_2$ stratified by treatment modality

<table>
<thead>
<tr>
<th>Observer-rated outcome</th>
<th>RT ($n=42$)</th>
<th>RT + cetuximab ($n=17$)</th>
<th>RT + cisplatin ($n=49$)</th>
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<tr>
<td>FOIS</td>
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<tr>
<td>7</td>
<td>36 (86)</td>
<td>16 (94)</td>
<td>37 (76)</td>
</tr>
<tr>
<td>6</td>
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<td>36 (86)</td>
<td>16 (94)</td>
<td>37 (76)</td>
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<tr>
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<tr>
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Patient-rated outcome

<table>
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<tr>
<th>SWAL-QOL (0–100) median (range)</th>
<th>rt0</th>
<th>rt1</th>
<th>rt2</th>
</tr>
</thead>
<tbody>
<tr>
<td>General burden</td>
<td>0 (0–88)</td>
<td>0 (0–50)</td>
<td>0 (0–38)</td>
</tr>
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<td>Food selection</td>
<td>0 (0–88)</td>
<td>0 (0–50)</td>
<td>0 (0–38)</td>
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<td>Eating duration</td>
<td>0 (0–88)</td>
<td>0 (0–50)</td>
<td>0 (0–38)</td>
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<tr>
<td>Eating desire</td>
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<td>9 (0–50)</td>
<td>38 (0–88)</td>
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<td>Fear</td>
<td>0 (0–69)</td>
<td>25 (0–69)</td>
<td>13 (0–100)</td>
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<tr>
<td>Sleep</td>
<td>38 (0–100)</td>
<td>25 (0–88)</td>
<td>25 (0–69)</td>
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<tr>
<td>Fatigue</td>
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<td>17 (0–83)</td>
<td>25 (0–88)</td>
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<td>Communication</td>
<td>0 (0–50)</td>
<td>0 (0–25)</td>
<td>7 (0–75)</td>
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<td>Mental health</td>
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<td>0 (0–63)</td>
<td>0 (0–38)</td>
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<td>Social functioning</td>
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<td>0 (0–38)</td>
<td>0 (0–50)</td>
</tr>
<tr>
<td>Symptoms</td>
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<td>13 (0–27)</td>
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<tr>
<td>Total score</td>
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<td>3 (0–28)</td>
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SWAL-QOL $\geq 14$

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<tr>
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<td>21 (91)</td>
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<td>9 (32)</td>
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<td>Unknown</td>
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<td>17</td>
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Secondary outcomes

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<th>Feeding tube</th>
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<tr>
<td>No</td>
<td>41 (98)</td>
<td>28 (100)</td>
<td>15 (88)</td>
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<tr>
<td>Yes NGT</td>
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Pneumonia

<table>
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<td>No</td>
<td>40 (95)</td>
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<td>1 (4)</td>
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<td>Unknown</td>
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</table>

NB Not all percentages sum up exactly to 100% due to rounding

FOIS functional oral intake scale, $t_0$ pretreatment, $t_1$ 6 months after treatment, $t_2$ 12 months after treatment

$^a$P values shown for Friedman test

$^b$Cochran’s Q test
### Table 8  Trismus outcomes at $t_0$, $t_1$ and $t_2$ stratified by treatment modality

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT + cetuximab</th>
<th>RT + cisplatin</th>
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<tbody>
<tr>
<td></td>
<td>$t_0$</td>
<td>$t_1$</td>
<td>$t_2$</td>
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<tr>
<td>$n$</td>
<td>42</td>
<td>39</td>
<td>28</td>
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</tbody>
</table>

**Observer-rated outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Mouth opening in mm median (range)</th>
<th>Trismus</th>
<th>Patient-rated outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
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<td>Yes</td>
</tr>
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<td></td>
<td></td>
<td>Unknown</td>
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</tbody>
</table>

**Trismus**

- No
- Yes
- Unknown

**Patient-rated outcomes**

- Perceived trismus
- Unknown

---

### Table 9  Speech outcomes at $t_0$, $t_1$ and $t_2$ stratified by treatment modality

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<th></th>
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<th>RT + cetuximab</th>
<th>RT + cisplatin</th>
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</thead>
<tbody>
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**Observer-rated outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Vowel space area (%)</th>
<th>Vowel space area &lt;80%</th>
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<tr>
<td></td>
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**Patient-rated outcomes**

<table>
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<th>SHI median (range)</th>
<th>SHI ≥6</th>
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<tbody>
<tr>
<td></td>
<td>Speech domain (0–56)</td>
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<td></td>
<td>Psychosocial domain (0–56)</td>
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<td>Total score (0–120)</td>
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**Secondary outcomes**

<table>
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<tr>
<th></th>
<th>Articulation rate (syllables/s) median (range)</th>
<th>AVQI median (range)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

*NB* Not all percentages sum up exactly to 100% due to rounding

*FOIS* functional oral intake scale, *NGT* nasogastric tube, *PRG* percutaneous radiological gastrostomy, $t_0$ pretreatment, $t_1$ 6 months after treatment, $t_2$ 12 months after treatment
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal diet (FOIS 7) at t1 n = 53</th>
<th>Modified diet (FOIS &lt; 7) at t2 n = 18</th>
<th>Univariable logistic regression analysis</th>
<th>OR (95% CI)</th>
<th>P value</th>
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<tr>
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<td>41 (30–54)</td>
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<td>Treatment modality</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>RT</td>
<td>23 (43)</td>
<td>5 (28)</td>
<td>1.0</td>
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</tr>
<tr>
<td>RT + cetuximab</td>
<td>7 (13)</td>
<td>4 (22)</td>
<td>2.6 (0.6–12.6)</td>
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</tr>
<tr>
<td>RT + cisplatin</td>
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<td>9 (50)</td>
<td>1.8 (0.5–6.2)</td>
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</tr>
<tr>
<td>Pretreatment modified diet (FOIS &lt; 7)</td>
<td></td>
<td></td>
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<td>2 (11)</td>
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</table>

NB Not all percentages sum up exactly to 100% due to rounding

BMI body mass index, CI confidence interval, HPV human papilloma virus, FOIS functional oral intake scale, OR odds ratio, other soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT radiotherapy, sarcopenia SMM below 43.2 cm²/m², SMM skeletal muscle mass
Table 11 Baseline characteristics by trismus at t2 and univariable analysis

<table>
<thead>
<tr>
<th></th>
<th>No trismus at t1</th>
<th>Trismus at t1</th>
<th>Univariable logistic regression analysis</th>
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<td>n = 14</td>
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<td>P value</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>39 (71)</td>
<td>12 (86)</td>
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</tr>
<tr>
<td>Female</td>
<td>16 (29)</td>
<td>2 (14)</td>
<td>0.4 (0.1–2.0) 0.272</td>
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<td>Age at baseline median (range)</td>
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<td>64 (42–73)</td>
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<tr>
<td>1</td>
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<td>7 (50)</td>
<td>1.6 (0.5–5.4) 0.421</td>
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<td>3</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>BMI median (range)</td>
<td>26 (17–44)</td>
<td>24 (18–30)</td>
<td>0.9 (0.7–1.0) 0.073</td>
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<tr>
<td>SMM median (range)</td>
<td>45 (22–64)</td>
<td>44 (34–50)</td>
<td>1.0 (0.9–1.1) 0.617</td>
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<tr>
<td>No</td>
<td>35 (64)</td>
<td>8 (57)</td>
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</tr>
<tr>
<td>Yes</td>
<td>20 (36)</td>
<td>6 (43)</td>
<td>1.3 (0.4–4.3) 0.655</td>
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<tr>
<td>Tumor site</td>
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<td></td>
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</tr>
<tr>
<td>Base of tongue</td>
<td>23 (42)</td>
<td>2 (14)</td>
<td>1.0</td>
</tr>
<tr>
<td>Tonsil</td>
<td>25 (46)</td>
<td>8 (57)</td>
<td>3.7 (0.7–19.2) 0.122</td>
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<td>4 (29)</td>
<td>6.6 (1.0–43.8) 0.052</td>
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<td>T2</td>
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<td>2 (14)</td>
<td>1.0 (0.1–7.9) 1.000</td>
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<td>3 (21)</td>
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<tr>
<td>RT</td>
<td>24 (44)</td>
<td>4 (29)</td>
<td>1.0</td>
</tr>
<tr>
<td>RT + cetuximab</td>
<td>9 (16)</td>
<td>1 (7)</td>
<td>0.7 (0.1–6.8) 0.732</td>
</tr>
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<td>22 (40)</td>
<td>9 (64)</td>
<td>2.5 (0.7–9.1) 0.180</td>
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<td>2 (17)</td>
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NB Not all percentages sum up exactly to 100% due to rounding

BMI body mass index, CI confidence interval, HPV human papilloma virus, FOIS functional oral intake scale, OR odds ratio, other soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT radiotherapy, sarcopenia SMM below 43.2 cm²/m², SMM skeletal muscle mass
Table 12  Baseline characteristics by vowel space area below 80% at t1 and univariable analysis

<table>
<thead>
<tr>
<th></th>
<th>VSA &gt; 80% at t1 n=24</th>
<th>VSA &lt; 80% t1 n=33</th>
<th>Univariable logistic regression analysis</th>
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<tbody>
<tr>
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<td>P value</td>
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</tr>
<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>20 (83)</td>
<td>24 (73)</td>
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</tr>
<tr>
<td>Female</td>
<td>4 (17)</td>
<td>9 (27)</td>
<td>1.9 (0.5–7.0)</td>
</tr>
<tr>
<td>Age at baseline median (range)</td>
<td>61 (44–75)</td>
<td>60 (39–75)</td>
<td>1.0 (1.0–1.1)</td>
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<td>12 (50)</td>
<td>21 (64)</td>
<td>1.0</td>
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<td>1</td>
<td>11 (46)</td>
<td>8 (24)</td>
<td>0.4 (0.1–1.3)</td>
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<td>3</td>
<td>1 (4)</td>
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<td>1.1 (0.1–14.0)</td>
</tr>
<tr>
<td>BMI median (range)</td>
<td>26 (20–44)</td>
<td>25 (18–33)</td>
<td>1.0 (0.8–1.1)</td>
</tr>
<tr>
<td>SMM median (range)</td>
<td>46 (32–64)</td>
<td>45 (30–54)</td>
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<tr>
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<td>18 (75)</td>
<td>20 (61)</td>
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<tr>
<td>Yes</td>
<td>6 (25)</td>
<td>13 (39)</td>
<td>2.0 (0.6–6.2)</td>
</tr>
<tr>
<td>Tumor site</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Base of tongue</td>
<td>8 (33)</td>
<td>14 (42)</td>
<td>1.0</td>
</tr>
<tr>
<td>Tonsil</td>
<td>12 (50)</td>
<td>15 (46)</td>
<td>0.7 (0.2–2.3)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (17)</td>
<td>4 (12)</td>
<td>0.6 (0.1–2.9)</td>
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<tr>
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<td>1.3 (0.3–5.1)</td>
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<tr>
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<td>2 (8)</td>
<td>7 (21)</td>
<td>5.1 (0.8–30.2)</td>
</tr>
<tr>
<td>RT + cisplatin</td>
<td>9 (38)</td>
<td>17 (52)</td>
<td>2.7 (0.8–8.8)</td>
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<td>Pretreatment VSA &lt; 80%</td>
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<tr>
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<td>14 (48)</td>
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<tr>
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<td>4 (24)</td>
<td>15 (52)</td>
<td>4.6 (1.2–16.9)</td>
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<tr>
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<td>4</td>
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</tbody>
</table>

NB Not all percentages sum up exactly to 100% due to rounding

BMI body mass index, CI confidence interval, HPV human papilloma virus, FOIS functional oral intake scale, OR odds ratio, other soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT radiotherapy, sarcopenia SMM below 43.2 cm²/m², SMM skeletal muscle mass, VSA vowel space area
Table 13 Baseline characteristics stratified by HPV status

<table>
<thead>
<tr>
<th></th>
<th>HPV − (n=33)</th>
<th>HPV + (n=70)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>20 (61)</td>
<td>50 (71)</td>
<td>0.366(^c)</td>
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<tr>
<td>Female</td>
<td>13 (39)</td>
<td>20 (29)</td>
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</tr>
<tr>
<td>Age at baseline median (range)</td>
<td>62 (44–75)</td>
<td>62 (39–79)</td>
<td>0.511(^a)</td>
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<td>ACE-27</td>
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<tr>
<td>0</td>
<td>14 (42)</td>
<td>38 (54)</td>
<td>0.151(^b)</td>
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<td>24 (34)</td>
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<tr>
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<td>3 (9)</td>
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NB: Not all percentages sum up exactly to 100% due to rounding

BMI body mass index, HPV human papilloma virus, other soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT radiotherapy, sarcopenia SMM below 43.2 cm²/m², SMM skeletal muscle mass

\(^a\)\(P\) values shown for Mann–Whitney \(U\) test

\(^b\)Linear-by-linear approximation of the Pearson’s Chi-square test

\(^c\)Fisher’s exact test
Table 14  Functional outcomes at t1 and t2 stratified by HPV status.

|                      | HPV −  
|                      |   n = 31 | HPV +  
|                      |   n = 64 | Adjusted p value | HPV −  
|                      |   n = 18 | HPV +  
|                      |   n = 51 | Adjusted p value |
|----------------------|---------|---------------|--------------|
| Swallowing outcomes  |         |               |              |
| Modified diet (FOIS < 7) |         |               |              |
| No                   | 19 (61) | 43 (68)       | 0.206        | 13 (72) | 39 (77)       | 0.460 |
| Yes                  | 12 (39) | 20 (32)       | 5 (28)       | 12 (24) |
| Unknown              | 0       | 1             | 0            |         |
| SWAL-QOL total score (0–100) median (range) | 21 (0–77) | 8 (0–52) | 0.492 | 14 (0–32) | 5 (0–43) | 0.652 |
| No                   | 9 (38)  | 26 (65)       | 8 (62)       | 29 (76) | 0.292 |
| Yes                  | 15 (63) | 14 (35)       | 5 (39)       | 9 (24)  |
| Unknown              | 7       | 24            | 5            | 13      |
| SWAL-QOL ≥ 14        |         |               |              |
| No                   | 25 (86) | 40 (80)       | 15 (94)      | 39 (87) | 0.996 |
| Yes                  | 4 (14)  | 10 (20)       | 1 (6)        | 6 (13)  |
| Unknown              | 2       | 14            | 2            | 6       |
| Trismus outcomes     |         |               |              |
| Mouth opening in mm median (range) | 42 (18–54) | 45 (16–63) | 0.627 | 45 (27–53) | 43 (10–64) | 0.046 |
| No                   | 23 (77) | 43 (78)       | 15 (88)      | 38 (76) | 0.086 |
| Yes                  | 7 (23)  | 12 (22)       | 2 (12)       | 12 (24) |
| Unknown              | 1       | 9             | 1            | 1       |
| Perceived trismus    |         |               |              |
| No                   | 25 (86) | 40 (80)       | 15 (94)      | 39 (87) | 0.996 |
| Yes                  | 4 (14)  | 10 (20)       | 1 (6)        | 6 (13)  |
| Unknown              | 2       | 14            | 2            | 6       |
| Speech and voice outcomes |         |               |              |
| Vowel space area (%) median (range) | 77 (58–100) | 82 (49–107) | 0.913 | 77 (51–102) | 76 (53–112) | 0.528 |
| Vowel space area <80% |         |               |              |
| No                   | 13 (48) | 43 (78)       | 7 (44)       | 16 (41) | 0.463 |
| Yes                  | 14 (52) | 12 (22)       | 9 (56)       | 23 (59) |
| Unknown              | 4       | 9             | 2            | 12      |
| SHI total score (0–120) median (range) | 4 (0–61) | 3 (0–52) | 0.896 | 1 (0–10) | 0 (0–40) | 0.151 |
| SHI ≥ 6              |         |               |              |
| No                   | 12 (60) | 25 (69)       | 11 (85)      | 24 (92) | 0.325 |
| Yes                  | 8 (40)  | 11 (31)       | 2 (15)       | 2 (8)   |
| Unknown              | 11      | 28            | 5            | 25      |

P values shown for multivariable regression adjusted for T and N classification, treatment and modified diet at t0

NB Not all percentages sum up exactly to 100% due to rounding

FOIS functional oral intake scale, HPV human papillomavirus, SHI speech handicap index, t1 6 months after treatment, t2 12 months after treatment
Table 15 Baseline characteristics stratified by pretreatment sarcopenia

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<th>Sarcopenia N=49</th>
<th>P value</th>
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<td>16 (33)</td>
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<td>1 (2)</td>
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<td>BMI median (range)</td>
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<td>8 (16)</td>
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NB Not all percentages sum up exactly to 100% due to rounding
BMI body mass index, HPV human papilloma virus, other soft palate, uvula, oropharyngeal wall, vallecula or pharyngeal arch, RT radiotherapy, sarcopenia skeletal muscle mass below 43.2 cm²/m²²

*a* P values shown for Mann-Whitney U test

*b* Linear-by-linear approximation of the Pearson’s Chi-square test

*c* Fisher’s exact test
### Table 16  Functional outcomes at t1 and t2 stratified by pretreatment sarcopenia

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P values shown for multivariable regression adjusted for AJCC stage and modified diet at t0

NB Not all percentages sum up exactly to 100% due to rounding

FOIS functional oral intake scale, HPV human papillomavirus, SHI speech handicap index, sarcopenia skeletal muscle mass below 43.2 cm²/m², t1 6 months after treatment, t2 12 months after treatment
Acknowledgements We would like to acknowledge the speech-language pathologists at our institute Anne Kornman, Merel Latenstein, Klaske van Sluis, and Nadya van Gent for the data collection. Jasmine de Jong is acknowledged for her contribution to building the database. The Netherlands Cancer Institute receives a research grant from Atos Medical Sweden, which contributes to the existing infrastructure for health-related, quality-of-life research in the Department of Head and Neck Oncology and Surgery.

References


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