Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer

Kraaijenga, S.A.C.; Oskam, I.M.; van der Molen, L.; Hamming-Vrieze, O.; Hilgers, F.J.M.; van den Brekel, M.W.M.

DOI
10.1016/j.oraloncology.2015.05.003

Publication date
2015

Document Version
Final published version

Published in
Oral Oncology

Oral Oncology 51 (2015) 787–794

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer

S.A.C. Kraaijenga [a,1], I.M. Oskam [a,1], L. van der Molen [a], O. Hamming-Vrieze [b], F.J.M. Hilgers [a,c,*], M.W.M. van den Brekel [a,c,d]

[a] The Netherlands Cancer Institute, Department of Head and Neck Oncology and Surgery, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
[b] The Netherlands Cancer Institute, Department of Radiation Oncology, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
[c] Institute of Phonetic Sciences/ACLC, University of Amsterdam, Spuistraat 210, 1012 VT Amsterdam, The Netherlands
[d] Academic Medical Center, Department of Oral and Maxillofacial Surgery, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 13 April 2015
Received in revised form 7 May 2015
Accepted 11 May 2015
Available online 28 May 2015

Keywords:
Head and neck cancer
Deglutition disorders
Dysphagia
Trismus
Long-term effects
Intensity modulated radiotherapy

SUMMARY

Objectives: Assessment of long term (10-years+) swallowing function, mouth opening, and quality of life (QoL) in head and neck cancer (HNC) patients treated with chemo-radiotherapy (CRT) for advanced stage IV disease.

Materials and Methods: Twenty-two disease-free survivors, participating in a multicenter randomized clinical trial for inoperable HNC (1999–2004), were evaluated to assess long-term morbidity. The prospective assessment protocol consisted of videofluoroscopy (VFS) for obtaining Penetration Aspiration Scale (PAS) and presence of residue scores, Functional Oral Intake Scale (FOIS) scores, maximum mouth opening measurements, and (SWAL-QOL and study-specific) questionnaires.

Results: At a median follow-up of 11-years, 22 patients were evaluable for analysis. Ten patients (46%) were able to consume a normal oral diet without restrictions (FOIS score 7), whereas 12 patients (54%) had moderate to serious swallowing issues, of whom 3 (14%) were feeding tube dependent. VFS evaluation showed 15/22 patients (68%) with penetration and/or aspiration (PAS $\geqslant$ 3). Fifty-five percent of patients (12/22) had developed trismus (mouth opening $\leqslant$ 35 mm), which was significantly associated with aspiration (p = .011). Subjective swallowing function (SWAL-QOL score) was impaired across almost all QoL domains in the majority of patients. Patients treated with IMRT showed significantly less aspiration (p = .011), less trismus (p = .035), and less subjective swallowing problems than those treated with conventional radiotherapy.

Conclusion: Functional swallowing and mouth opening problems are substantial in this patient cohort more than 10-years after organ-preservation CRT. Patients treated with IMRT had less impairment than those treated with conventional radiotherapy.

Introduction

Head and neck cancer (HNC) patients are at risk to develop substantial functional impairments after organ-preserving treatment with chemoradiotherapy (CRT) [1]. Dysphagia is commonly the most severe functional impairment following this treatment. Given its serious impact on quality of life (QoL), assessment of deglutition disorders has become an important functional endpoint measure [2]. It is therefore not surprising that prevention of dysphagia has become a major focus point in HNC research. In the past decade, improved radiotherapy protocols with intensity modulated radiotherapy (IMRT) have been introduced to reduce radiation dosage to swallowing musculature and structures, with the intention to decrease post-treatment dysphagia [3,4]. More recently, the prevalence of dysphagia also has led to the development of preventive exercise programs. These exercise programs are associated with better post-treatment swallowing function, in particular on the short-term [5–10], and probably also longer-term [11]. However, since dysphagia can develop and/or progress years after CRT [12,13], long term (10-years+)

* Corresponding author at: Dept. Head and Neck Surgery and Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31 205122550.
E-mail address: f.hilgers@nki.nl (F.J.M. Hilgers).
[1] Both authors contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.oraloncology.2015.05.003
1368-8375/

prospectively collected swallowing and mouth opening data are of great importance to assess deglutition in HNC survivors [14]. In this study the prospectively collected objective and subjective functional results at 10-years+ post-treatment will be reported in a patient cohort treated with CRT for advanced, anatomical and functional inoperable HNC.

Material and methods

This study concerns the long term follow-up of all disease-free and evaluable patients, who participated in a randomized clinical trial (M99RAD) on two different cisplatin-based chemoradiation treatment protocols for advanced HNC [15]. The original cohort consisted of 237 patients diagnosed with advanced (stage IV), anatomical or functional [16] inoperable squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx. Patients were included between December 1999 and November 2004. The chemotherapy protocol consisted either of 100 mg/m^2 cisplatin in a 40 min intravenous (IV) infusion on days 1, 22, and 43, or of a weekly high-dose intra-arterial (IA) injection of 150 mg/m^2 cisplatin in combination with intravenous sodium thiosulphate rescue in weeks 1, 2, 3, and 4. Radiotherapy (70 Gy in 35 fractions) was administered over seven weeks, starting concurrently with chemotherapy. Since IMRT had been gradually introduced in our Institute during the trial period, roughly one fourth of the original patient population was treated with IMRT [4,17], while the remaining patients were treated with conventional radiotherapy (RT). During treatment, patients were encouraged to maintain an oral diet for as long as possible and prophylactic tube feeding was not applied. A (nasogastric or gastric) feeding tube only was given when the carefully monitored intake became troublesome. In the period the trial was conducted (1999–2004), the concept of standard preventive swallowing rehabilitation was not yet developed, and swallowing exercises were given post-treatment 'on demand', when removal of a feeding tube appeared troublesome because of aspiration and/or when sufficient oral intake could not be regained.

The original (phase III) trial compared standard IV with IA cisplatin infusion on oncological outcomes in 237 patients [17] and QoL in 207 patients [18,19]. Regarding oncological outcomes and toxicities, results showed that CRT with IA infusion is not superior to CRT with IV infusion. Toxicity results were comparable in both arms, although site and degree of toxicity differed. In short, renal toxicity was significantly lower in the IA treatment arm, and neurological toxicity was significantly more prevalent in the IA arm [17]. Regarding QoL results, no statistically significant differences between the groups (IA, IV) were found, and no statistically significant changes over time (1-year versus 5-years post-treatment) were observed for the total patient group during follow-up assessments [19]. Therefore, in the present study, functional swallowing and mouth opening results are reported for the combined patient cohort still alive and evaluable at 10-years+ post-treatment. All patient data and reasons for exclusion after 5-years and 10-years+ follow-up are provided in a consort flow-chart (Fig. 1). As can be seen, at 10-years+ post-treatment, besides the 20 evaluable patients from the 5-year cohort, 4 additional survivors, who had been unresponsive or refused to participate at the 5-years evaluation point, were also willing to participate. Two patients had major salvage surgery for recurrent disease during follow-up, and were excluded from swallowing/mouth opening analysis, since the functional outcomes in these patients were no longer (only) attributable to the CRT. Furthermore, two patients had minor (laser) surgery for a second primary at the oropharynx (pharyngeal arch and alveolar process, respectively) at 10-years and 11-years post-treatment. Subsequently, due to a recurrence the alveolar process patient two years later additionally required local resection with bone grafting. These latter two patients were kept in the functional analysis of in total 22 patients.

Multidimensional assessment

Assessment of functional sequels was performed with standard, multidimensional objective and subjective outcome-measures [20,21]. First, the protocol included standard videofluoroscopy (VFS) to determine swallowing function. All VFS studies were carried out by an experienced speech language pathologist. Patients were seated upright and were asked to swallow different consistencies of varying amounts twice (1, 3, 5 and 10 cc thin liquid; 3 and 5 cc paste; as well as solid [Omnipaque coated cake]). Testing was discontinued if the clinicians judged the swallowing potentially harmful to the patient. All VFS studies were reviewed in real-time, slow motion, and frame-by-frame, and rated in consensus by two experienced researchers (authors SK and LM). Results were expressed in terms of the Penetration and Aspiration Scale (PAS), as well as an overall 'presence of residue' score. The PAS, a tool with an acceptable reliability, consists of a 8-points scale, ranging from 1 to 8 (score 1: material does not enter the airway; score 2: material enters the airway, remains above the vocal folds, and is ejected from the airway; score 3: material enters the airway, remains above the vocal folds, and is not ejected from the airway; score 4: material enters the airway, contacts the vocal folds, and is ejected from the airway; score 5: material enters the airway, contacts the vocal folds, and is not ejected from the airway; score 6: material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway; score 7: material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort; score 8: material enters the airway, passes below the vocal folds, and no effort is made to eject) [22]. The overall 'presence of residue' score ranges from 0–3 (score 0: no residue, to score 3: residue above and below the vallecula, with minimal residue judged as normal). To interpret and compare results, individual test results were clustered with the highest score representing the total PAS or residue score per patient. The PAS was also simplified by dividing it into three categories (1: normal; 2–5: penetration; 6–8: aspiration), which roughly corresponds to normal, mild-to-moderate, and severe performance [23].

Secondly, oral intake/nutritional status was assessed with the Functional Oral Intake Scale (FOIS; range from 1 to 7 with score 1: nothing by mouth, score 2: tube dependent with minimal/inconsistent oral intake, score 3: tube dependent with consistent oral intake, score 4: total oral diet of a single consistency, score 5: total oral intake of multiple consistencies requiring special preparation or compensations, score 6: total oral intake of multiple consistencies without special preparation but with specific food limitations, and score 7: total oral diet without restrictions), and with data on oral nutritional supplements, tube feeding dependency, weight changes, and Body Mass Index (BMI).

Furthermore, maximum interincisor (mouth) opening (MIO) was measured in mm to determine trismus. MIO was measured using disposable TheraBite range of motion scales (Atos Medical, Sweden), and trismus was defined as a MIO of $\leqslant$35 mm [24].

Patients' subjective swallowing and mouth opening impairment was assessed with quality of life (QoL) questionnaires. The first questionnaire was the Swallowing Quality of Life Questionnaire (SWAL-QOL), which was administered to assess patients' perceived swallowing disorder. The SWAL-QOL has been translated and validated for use with Dutch oral, oropharyngeal, and laryngeal cancer patients [25,26]. The SWAL-QOL consists of 44-items that assess the effects of swallowing difficulties on 10 QoL domains (30 items), including food selection, eating duration, eating desire, fear, burden, mental health, social functioning, communication, sleep, and

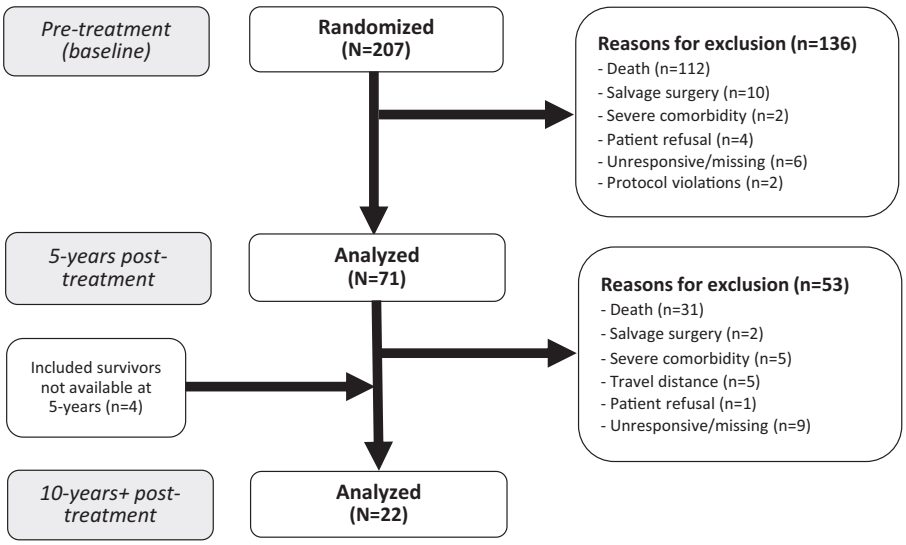

Fig. 1. Consort flowchart showing the number of patients participating at 10-years+ post-treatment and previous QoL assessments (baseline and 5-years post-treatment), including reasons for exclusion after 5-years and 10-years+ follow-up. At 10-years+ post-treatment, 4 additional survivors were willing to participate, who were unresponsive or refused to participate at 5-years post-treatment.

fatigue. Each domain ranges from 0 to 100 with a higher score indicating more impairment. Also a symptom scale (14 additional items) and a total SWAL-QOL score (the 23 items of the first seven scales listed above) can be calculated. Finally, the questionnaire includes three separate questions regarding nutrition intake, liquids intake, and general health [27]. A cut-off score of 14 points (or higher) has been established for identifying HNC patients with clinically relevant swallowing problems [25,26]. Additionally, a Dutch structured study-specific questionnaire was used, which aimed at assessing in more detail complaints during the last week concerning diet/swallowing and concerning mastication/mouth opening, in part based on the EORTC C30/HN35, as described earlier [20]. There were 6 questions in each category with mostly 4 possible, structured answers. For diet and swallowing these questions were: "What is the consistency of your diet?" "Do you have problems with swallowing solid food?" "Do you have problems with swallowing soft/minced food?" "Do you have problems with swallowing liquid food?" "Do you have to swallow repeatedly to get rid of the food?" "Is it painful to swallow?" For mastication and mouth opening these questions were: "Do you still have your own (set of) teeth?" "How often do you clean your teeth/dentures?" "How do you experience your mouth opening?" "Do you experience problems with eating, because of a limited mouth opening?" "Do you experience problems with speech, because of a limited mouth opening?" "Do you have problems with chewing your food?".

Statistical analysis

Descriptive statistics were generated for all continuous outcome measures (i.e. MIO, SWAL-QOL) at the 10-years+ assessment point. Data were summarised as medians with associated range. Spearman's rank correlation was used to determine significant associations between objective and subjective outcome variables (e.g. FOIS with SWAL-QOL score). The Mann–Whitney *U* test was used to compare outcome variables between two unpaired groups (IMRT vs. conventional RT). Percentages of reported/measured disorders were calculated for categorical outcome parameters, comparable to the methods described by Logemann et al. [28]. Pearson's Chi-Square test was used to test associations/differences in proportion between two or more groups. All data were collected and analyzed in SPSS (Chicago, Illinois; version 22.0), and a significance level of $p < 0.05$ was used.

Results

Patients' characteristics

At 10-years+ post-treatment (median 134 months; range 109–165 months), 22 patients (13 male, 9 female; current mean age: 62 years, range 42–74) were evaluable All patients were in complete remission. The majority of patients (82%) had a primary tumor located at the oropharynx. All patients were curatively treated with CRT for advanced (stage IV) HNC. Eight patients (36%) were treated with standard IV cisplatin infusion and 14 patients (64%) with high-dose IA cisplatin infusion. Ten patients (45%; IA/IV: 6/4) were treated with IMRT and 12 patients (55%; IA/IV: 8/4) with conventional RT. Regarding nutrition and oral intake, during treatment ultimately 19 of 22 patients (86%) needed nasogastric/gastric tube feeding (including 5 patients who already had a feeding tube at baseline), which was discontinued/ended after treatment as soon as nutritional requirements could be maintained orally again (see Table 1 for the number of patients with a feeding tube at the various assessment points).

The clinical patients' and tumor characteristics of the analyzed patient cohort at 10-years+ post-treatment ($n = 22$) and the original patient cohort at baseline ($n = 207$) are listed in Table 2. There were no significant differences in proportion between these two groups with respect to gender, tumor site, stage, or treatment ($p > .05$).

Functional results

Swallowing and mouth opening results per patient ($n = 22$) are summarized in Table 3.

Swallowing function and dietary intake

VFS evaluation of swallowing function showed more than normal post-swallow contrast residue in all patients, mainly at the vallecula and piriform sinus and already occurring after 1 cc sips of thin liquid. Safe oral intake was demonstrated in 7 patients (32%), whereas penetration and/or aspiration occurred in 15

Table 1
Number of patients with nasogastric or gastric feeding per assessment.

	Baseline Pre-CRT	7-weeks During CRT	12-weeks Post-CRT	1-year Post-CRT	5-years Post-CRT	10-years Post-CRT
Yes	5	19	12	5	3	3
No	17	3	10	17	19	19

Abbreviations: CRT = chemo-radiotherapy.

patients (68%). Specifically, penetration (PAS score 2–5) was demonstrated in 2 patients (9%), and aspiration (PAS score 6–8) was shown in 13 patients (59%), with 10 of 13 patients making no effort to eject (silent aspiration). Aspiration (PAS $\geqslant$ 6) occurred significantly less in patients treated with IMRT (3 of 10 patients) compared to patients treated with conventional RT (10 of 12 patients; $p = .011$; Chi-Square test).

Regarding oral intake, 10 patients (46%) were able to consume a normal oral diet without restrictions (FOIS score 7), whereas 12 patients (54%) had restrictions: 10 patients were only able to consume an oral diet with specific food limitations (FOIS score 6; $n = 6$) or with special preparation (FOIS score 5; $n = 3$), and 3 patients were feeding-tube dependent (FOIS score 1–3). Three patients (2 of 3 with a feeding tube) had a history of repeated ($\geqslant$2) aspiration pneumonia and/or other recurring pulmonary problems in the last 6 months. Moreover, according to the study-specific questionnaire, 13 patients (59%) reported swallowing difficulties, of whom 4 patients also reported painful swallowing.

Results of the SWAL-QOL questionnaire ($n = 22$) are described in Table 4. Signs of impaired swallowing function (score > 14) were found across all QoL domains with exception of the domains sleep and mental health. Especially eating duration was severely impaired (median score = 63; mean score ± SD = 58 ± 32), and significantly associated with lower FOIS scores ($r_s = -.61$, $p = .002$). Similarly, social functioning ($r_s = -.50$, $p = .019$) and fear of eating ($r_s = -.48$, $p = .025$) were associated with restricted oral intake (FOIS score). General burden ($r_s = -.54$, $p = .010$), and fear of eating ($r_s = -.58$, $p = .005$) correlated with repeated pneumonia. Patients treated with IMRT showed significant better scores on the domains food selection, eating desire, communication, mental health, and social functioning (Mann–Whitney U test; see Fig. 2 and/or Table 5). No associations between swallowing outcomes and tumor site or stage were found.

Mouth opening and mastication

Mean maximum mouth opening at 10-years+ post-treatment ($n = 22$) was 32 mm (median 33 mm, range 8–58 mm) with 12 patients (55%; CONV/IMRT: 9/3) showing trismus (as defined as a MIO $\leqslant$ 35 mm) at this assessment point. This concerned mainly oropharyngeal cancer patients ($n = 11$; CONV/IMRT: 9/2). Ten patients (46%) reported besides swallowing problems also difficulties with mastication and 4 patients (18%) reported also pain during mastication. There was a significant lower incidence of trismus in patients treated with IMRT (3/10) versus patients treated with conventional RT (9/12; $p = .035$; Chi-Square test). Trismus was significantly associated with aspiration ($p = .011$).

Discussion

This is one of the first studies prospectively investigating long term (10-years+) QoL, swallowing function, and mouth opening in HNC patients treated with CRT for advanced disease. Regarding swallowing function, both observer-rated and patient-reported severe functional disorders and related morbidity problems were common in this patient cohort. Results showed occurrence of penetration and/or aspiration in almost 70% of patients and profound pharyngeal residue in all patients. Moreover, four patients were still feeding tube dependent and/or had developed frequent aspiration pneumonias and/or other recurring pulmonary problems. Forty-six percent of patients were able

Table 2
Clinical patient-, tumor- and treatment characteristics for the long term analysed patient cohort ($n = 22$) and the original patient cohort ($n = 207$).

Characteristic	207 patients at baseline	22 patients 10-years+	Statistics	
	n (%)	*n* (%)	Chi-Square	*P* value
Mean age, *y* (range)	55 (24–81)	62 (42–74)	NA	NA
Gender				
Male	153 (74%)	13 (59%)	2.191	.139
Female	54 (26%)	9 (41%)		
Tumor site				
Oral cavity	33 (16%)	1 (4.5%)	2.755	.252
Oropharynx	136 (66%)	18 (82%)		
Hypopharynx	38 (18%)	3 (14%)		
T stage				
T2	4 (2%)	1 (4.5%)	3.291	.193
T3	61 (29%)	10 (45%)		
T4	142 (69%)	11 (50%)		
N stage				
N0	37 (18%)	9 (41%)	8.177	.147
N1	25 (12%)	3 (14%)		
N2a	10 (5%)	0 (0%)		
N2b	55 (27%)	5 (23%)		
N2c	60 (29%)	3 (14%)		
N3	20 (10%)	2 (9%)		
Chemotherapy				
IV	103 (50%)	8 (36%)	1.429	.232
IA	104 (50%)	14 (64%)		
Radiotherapy				
IMRT	(± 25%)	10 (45%)	NA	NA
CONV	(± 75%)	12 (55%)		

Abbreviations: *y* = years; IV = intravenous; IA = intra-arterial; IMRT = Intensity-Modulated Radiotherapy; CONV = conventional radiotherapy.

Table 3
Swallowing and mouth opening data collection per patient.

	Patient			Tumor		Treatment			Objective outcomes 10-years							Subjective outcomes 10-years				
	Sex	Age	Baseline weight	Site	Stage	CTx	RTx	Feeding tube	Nutrition/intake			VFS		Mouth opening		Swallowing		Mastication		Pneumonia (⩾2 half y)
					TNM				Weight	FOIS	Tube	PAS	Residue	MIO	Trismus	Difficulty	Pain	Difficulty	Pain	
1	M	70	106 kg	Oroph	T3N0	IV	IMRT	Yes	105 kg	7	No	1	Yes	46 mm	No	No	No	No	No	No
2	M	65	95 kg	Oroph	T4N2c	IV	IMRT	Yes	80 kg	7	No	5	Yes	58 mm	No	Yes	No	Yes	No	No
3	M	64	75 kg	Oroph	T3N0	IA	IMRT	Yes	68 kg	6	No	3	Yes	41 mm	No	No	No	No	No	No
4	M	64	79 kg	Oroph	T4N2b	IA	IMRT	Yes	80 kg	7	No	1	Yes	10 mm	Yes	No	No	No	No	No
5	M	63	93 kg	Oroph	T3N2b	IV	IMRT	Yes	96 kg	6	No	1	Yes	40 mm	No	No	No	No	No	No
6	F	58	66 kg	Oroph	T3N2c	IV	IMRT	Yes	65 kg	2	Yes	6	Yes	10 mm	Yes	Yes	No	Yes	No	Yes
7	M	58	70 kg	Hypo	T3N1	IA	IMRT	Yes	78 kg	6	No	8	Yes	52 mm	No	Yes	No	No	No	No
8	M	57	89 kg	Hypo	T2N0	IA	IMRT	Yes	102 kg	7	No	8	Yes	40 mm	No	No	No	No	No	No
9	M	56	88 kg	Oroph	T3N2b	IA	IMRT	No	90 kg	7	No	1	Yes	40 mm	No	Yes	Yes	Yes	Yes	No
10	F	42	65 kg	Oral	T3N0	IA	IMRT	Yes	67 kg	7	No	1	Yes	21 mm	Yes	No	No	No	No	No
11	F	67	83 kg	Oroph	T4N0	IA	CONV	Yes	60 kg	6	No	8	Yes	32 mm	Yes	No	No	No	No	No
12	M	64	68 kg	Oroph	T4N1	IA	CONV	Yes	69 kg	7	No	8	Yes	25 mm	Yes	Yes	Yes	Yes	Yes	No
13	F	67	62 kg	Oroph	T4N2b	IA	CONV	Yes	64 kg	7	No	8	Yes	23 mm	Yes	No	No	No	No	No
14	M	69	64 kg	Oroph	T4N0	IV[a]	CONV	Yes	78 kg	1	Yes	8	Yes	15 mm	Yes	Yes	Yes	Yes	Yes	No
15	F	63	43 kg	Oroph	T3N0	IA	CONV	Yes	44 kg	6	No	8	Yes	34 mm	Yes	Yes	Yes	Yes	Yes	No
16	F	62	45 kg	Oroph	T4N1	IV	CONV	Yes	45 kg	5	No	6	Yes	23 mm	Yes	Yes	No	No	No	No
17	F	62	54 kg	Oroph	T4N3	IV	CONV	Yes	56 kg	2	Yes	7	Yes	40 mm	No	Yes	No	No	No	Yes
18	M	70	90 kg	Oroph	T3N0	IA[b]	CONV	Yes	92 kg	6	No	8	Yes	27 mm	Yes	Yes	No	Yes	No	No
19	F	60	54 kg	Oroph	T3N2c	IV	CONV	Yes	54 kg	5	No	8	Yes	8 mm	Yes	Yes	No	Yes	No	No
20	F	60	62 kg	Oroph	T4N2b	IA	CONV	Yes	63 kg	5	No	8	Yes	23 mm	Yes	Yes	No	Yes	No	Yes
21	M	74	78 kg	Hypo	T4N0	IA	CONV	No	77 kg	7	No	1	Yes	46 mm	No	No	No	No	No	No
22	M	50	84 kg	Oroph	T4N3	IA	CONV	Yes	84 kg	7	No	1	Yes	45 mm	No	Yes	No	Yes	No	No

Abbreviations: TNM = Tumor Node Metastasis; CTx = chemotherapy treatment; RTx = radiotherapy treatment; FOIS = Functional Oral Intake Scale; VFS = Videofluoroscopy; PAS = Penetration and Aspiration Scale; MIO = Maximal Interincisor Opening; M = male; F = female; hypo = hypopharynx; oroph = oropharynx; oral = oral cavity; IA = intra-arterial; IV = intravenous; IMRT = Intensity-Modulated Radiotherapy; CONV = conventional radiotherapy; kg = kilograms; mm = millimetres; NA = not applicable.

[a] This patient had required laser surgery for second primary at the pharyngeal arch at 10-years post-treatment.

[b] This patient had required laser surgery for second primary at the alveolar process at 11-years post-treatment, subsequently followed by local resection with bone grafting due to recurrent disease at 13-years post-treatment.

Table 4
Distribution of domains by SWAL-QOL questionnaire variables in 22 HNC patients at 10-years+ post-treatment.

Variable	N valid	Min - Max	Median	Mean ± SD
General burden	22	0–100	31.5	36 ± 33
Food selection	22	0–75	25	27 ± 24
Eating duration	22	0–100	63	58 ± 32
Eating desire	22	0–42	29	25 ± 15
Fear of eating	22	0–100	56.5	44 ± 36
Sleep	22	0–75	13	19 ± 22
Fatigue	22	0–67	21	25 ± 22
Communication	22	0–88	25	34 ± 27
Mental Health	22	0–55	10	20 ± 19
Social Function	22	0–65	25	23 ± 19
Symptom score	22	0–75	41	41 ± 23

Abbreviations: Min = minimum; Max = maximum; SD = standard deviation.

to consume a normal oral diet without restrictions, but four of them still reported having swallowing difficulties. Patients' perceived swallowing function, as assessed with the SWAL-QOL questionnaire, was impaired across most QoL domains (score >14) too, indicating clinically relevant swallowing problems with significant impact on QoL [25,26]. We did not find an association between site of disease and dysphagia severity. However, all patients had advanced (stage IV) disease and were predominantly treated with large radiation fields, encompassing several organs at risk involved in swallowing, regardless of disease site.

On a positive note, impairments were significantly less profound in patients treated with IMRT – a treatment modality that during the trial period had gradually been introduced in our Institute. Although the patient population was rather small in the current study, results are in concordance with a previous, larger-scale study from our Institute, that also showed better xerostomia related QoL 2–3-years post-treatment in patients treated with IMRT compared to conventional RT [4]. Interestingly, another article from our Institute on late efficacy/toxicity in the same patient population recently reported that treatment protocol (IV versus IA cisplatin infusion) might also play a role in this. After a median follow-up of 7.5 years, dysphagia according to the RTOG toxicity criteria was reported to be worse in the IV arm [29]. However, the present and previous studies on swallowing function and dietary intake did not reveal any significant differences between the two IA and IV chemotherapy protocols in this respect [18,19]. The authors in the '7.5-years study' did not take into account the effects of the changes in radiation treatment (IMRT versus conventional RT) during the trial. Having those IMRT–conventional RT data taken into consideration now [30], it therefore seems more likely that treatment with IMRT instead of the IV cisplatin infusion has been causing the more favourable swallowing outcomes in this patient cohort.

Regarding mouth opening problems, trismus was observed in more than fifty percent of patients. This is substantially higher than the weighted prevalence of 31% following conventional RT with chemotherapy, as recently determined in a review of several studies where trismus was appropriately assessed [31]. The population of this study, with mainly advanced primaries located at the oropharynx [32], might be a reason for this difference. Limited mouth opening may make proper mastication of food more difficult, which is in accordance with half of our patients complaining about mastication difficulty. Furthermore, trismus may result in compromised airway clearance with poor bolus organization that – together with increased pharyngeal residue – has the potential to lead to aspiration problems [31]. Also in our patient cohort a relationship between trismus and aspiration was found. An explanation might be that the patients who developed both functional deficits (trismus and aspiration) received higher RT doses on the muscles critical to mastication and swallowing [33]. The fact that trismus occurred significantly more in patients treated with conventional RT compared to patients treated with IMRT confirms such a dose–effect relationship.

To prevent CRT-induced swallowing disorders, maintenance of oral intake throughout CRT treatment and/or preventive swallowing exercises ("eat or exercise" principle) have independently been associated with better post-treatment swallowing outcomes directly after treatment and at short-term follow-up [34,35]. Also in a recent prospective clinical trial from our institute, with a

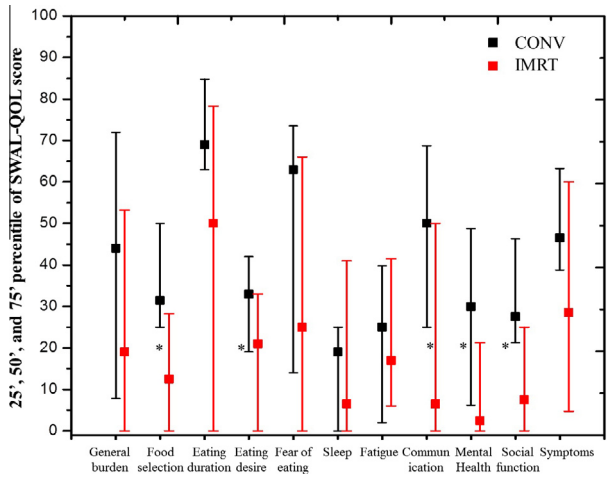

Fig. 2. Distribution of domains by SWAL-QOL questionnaire variables in 22 HNC patients at 10-years+ post-treatment, associated by radiotherapy treatment protocol (Intensity-Modulated Radiotherapy [IMRT] versus conventional radiotherapy [CONV]). Asterisk means statistical difference based on a p value < 0.05 according to Mann–Whitney U test.

Table 5
Distribution of domains by SWAL-QOL questionnaire variables in 22 HNC patients at 10-years+ post-treatment, divided by radiotherapy treatment (Intensity-Modulated Radiotherapy [IMRT] versus conventional radiotherapy [CONV]).

Variable	RTx	N valid	Min–Max	Median	Mean ± SD	Statistic
General burden	IMRT	10	0–75	19	26.4 ± 28.6	p = .203
	CONV	12	0–100	44	44.1 ± 34.6	
Food selection	IMRT	10	0–50	12.5	16.3 ± 18.7	p = .043*
	CONV	12	0–75	31.5	36.6 ± 24.6	
Eating duration	IMRT	10	0–100	50	41.3 ± 39.2	p = .059
	CONV	12	50–100	69	72.1 ± 16.9	
Eating desire	IMRT	10	0–42	21	17.5 ± 16.4	p = .050*
	CONV	12	17–42	33	31.3 ± 10.1	
Fear of eating	IMRT	10	0–100	25	35.1 ± 39.1	p = .314
	CONV	12	0–94	63	50.8 ± 33.0	
Sleep	IMRT	10	0–63	6.5	18.9 ± 23.9	p = .923
	CONV	12	0–75	19	18.8 ± 22.3	
Fatigue	IMRT	10	0–67	17	24.2 ± 24.8	p = .821
	CONV	12	0–67	25	25.0 ± 21.4	
Communication	IMRT	10	0–50	6.5	18.8 ± 23.0	p = .014*
	CONV	12	25–88	50	46.9 ± 22.8	
Mental health	IMRT	10	0–40	2.5	10 ± 13.9	p = .014*
	CONV	12	5–55	30	27.9 ± 20.1	
Social function	IMRT	10	0–45	7.5	13 ± 15.7	p = .017*
	CONV	12	0–65	27.5	31.3 ± 18.0	
Symptom score	IMRT	10	0–75	28.5	31.1 ± 28.1	p = .123
	CONV	12	21–68	46.5	48.8 ± 14.8	

Abbreviations: RTx = radiotherapy treatment; Min = minimum; Max = maximum; SD = standard dev* p-value according to Mann–Whitney U test; significance level at p < 0.05.iation; IMRT = Intensity–Modulated Radiotherapy; CONV = conventional radiotherapy.

* p-value according to Mann–Whitney U test; significance level at p < 0.05.

cisplatin-based CRT with IMRT therapy protocol, results showed minimal swallowing disorders at 6-years follow-up in patients, who were treated with preventive swallowing exercises [11]. In that study cohort, none of the twenty-two patients was dependent on tube feeding at 6-years post-treatment, and it is likely that the favourable swallowing outcomes can be attributed both to the organ-sparing IMRT and to the preventive and continued post-treatment rehabilitation programs which were applied. It is not clear whether the poor outcome in the current cohort is mainly caused by the lack of preventive rehabilitation, the larger radiation fields, or the progressive fibrosis at long term following RT. However, results probably would have been even more dismal if not 45% of these long term survivors had received IMRT.

Regarding oral intake during treatment, the usefulness of prophylactic gastric tube placement to maintain weight and nutrition during treatment is currently under debate [36]. The controversy is mainly about maintaining weight during treatment versus maintaining swallowing function by training oral intake [37]. As supported by several studies [28,35,38,39], it seems reasonable to assume that prophylactic gastric tube placement leads to worse post-treatment swallowing and diet outcomes, since the swallowing muscles are no longer actively used and may atrophy (the "use it or loose it" principle) [39]. Weight loss during treatment is associated with worse oncological outcome [37], but it is not clear what loss is acceptable. However, initial body mass index (BMI) may play a role in that, since oropharyngeal cancer patients with a BMI > 25 at the start of treatment may have a better overall survival [37].

Conclusion

Functional problems in this patient cohort at 10-years+ post CRT treatment are substantial, with noticeable occurrence of dysphagia, recurrent aspiration pneumonia, feeding tube dependency, and trismus. IMRT patients showed less swallowing impairment and trismus, though, than patients treated with conventional RT.

Conflict of interest statement

This study has no conflict of interest.

Acknowledgements

Wilma van Heemsbergen, epidemiologist and clinical researcher at the Department of Epidemiology & Biostatistics at the Netherlands Cancer Institute, is greatly acknowledged for her support and advice in the statistical analysis. This study was made possible by grants provided by "Stichting de Hoop" and the "Verwelius Foundation".

References

[1] van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Hilgers FJ. Functional outcomes and rehabilitation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol 2009;266:889–900.
[2] Kraaijenga SA, van der Molen L, van den Brekel MW, Hilgers FJ. Current assessment and treatment strategies of dysphagia in head and neck cancer patients: a systematic review of the 2012/13 literature. Curr Opin Support Palliat Care 2014;8:152–63.
[3] Eisbruch A, Kim HM, Feng FY, Lyden TH, Haxer MJ, Feng M, et al. Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys 2011;81:e93–9.
[4] van Rij CM, Oughlane-Heemsbergen WD, Ackerstaff AH, Lamers EA, Balm AJ, Rasch CR. Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. Radiat Oncol 2008;3:41.
[5] Kulbersh BD, Rosenthal EL, McGrew BM, Duncan RD, McColloch NL, Carroll WR, et al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope 2006;116:883–6.
[6] Carroll WR, Locher JL, Canon CL, Bohannon IA, McColloch NL, Magnuson JS. Pretreatment swallowing exercises improve swallow function after chemoradiation. Laryngoscope 2008;118:39–43.
[7] van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. Dysphagia 2011;26:155–70.
[8] Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. Int J Radiat Oncol Biol Phys 2012;83:210–9.
[9] Kotz T, Federman AD, Kao J, Milman L, Packer S, Lopez-Prieto C, et al. Prophylactic swallowing exercises in patients with head and neck cancer undergoing chemoradiation: a randomized trial. Arch Otolaryngol Head Neck Surg 2012;138:376–82.
[10] van der Molen L, van Rossum MA, Rasch CR, Smeele LE, Hilgers FJ. Two-year results of a prospective preventive swallowing rehabilitation trial in patients treated with chemoradiation for advanced head and neck cancer. Neck cancer. Eur Arch Otorhinolaryngol 2014;271(5):1257–70.
[11] Kraaijenga SA, van der Molen L, Jacobi I, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Prospective clinical study on long-term swallowing function and voice quality in advanced head and neck cancer patients treated with concurrent chemoradiotherapy and preventive swallowing exercises. Eur Arch Otorhinolaryngol 2015 (Epub).
[12] 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.
[13] Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW, et al. Late dysphagia after radiotherapy-based treatment of head and neck cancer. Cancer 2012;118:5793–9.
[14] Hutcheson KA, Lewin JS, Holsinger FC, Steinhaus G, Lisec A, Barringer DA, et al. Long-term functional and survival outcomes after induction chemotherapy and risk-based definitive therapy for locally advanced squamous cell carcinoma of the head and neck. Head Neck 2014;36:474–80.
[15] Balm AJ, Rasch CR, Schornagel JH, Hilgers FJ, Keus RB, Schultze-Kool L, et al. High-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer. Head Neck 2004;26:485–93.
[16] Kreeft AM, van der Molen L, Hilgers FJ, Balm AJ. Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature. Eur Arch Otorhinolaryngol 2009;266:1687–98.
[17] Rasch CR, Hauptmann M, Schornagel J, Wijers O, Buter J, Gregor T, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: results of a randomized phase 3 trial. Cancer 2010;116:2159–65.
[18] Ackerstaff AH, Balm AJ, Rasch CR, de Boer JP, Wiggenraad R, Rietveld DH, et al. First-year quality of life assessment of an intra-arterial (RADPLAT) versus intravenous chemoradiation phase III trial. Head Neck 2009;31:77–84.
[19] Ackerstaff AH, Rasch CR, Balm AJ, de Boer JP, Wiggenraad R, Rietveld DH, et al. Five-year quality of life results of the randomized clinical phase III (RADPLAT) trial, comparing concomitant intra-arterial versus intravenous chemoradiotherapy in locally advanced head and neck cancer. Head Neck 2012;34:974–80.
[20] van der Molen L, van Rossum MA, Ackerstaff AH, Smeele LE, Rasch CR, Hilgers FJ. Pretreatment organ function in patients with advanced head and neck cancer: clinical outcome measures and patients' views. BMC Ear Nose Throat Disord 2009;9:10.
[21] van der Molen L, van Rossum MA, Jacobi I, van Son RJ, Smeele LE, Rasch CR, et al. Pre- and posttreatment voice and speech outcomes in patients with advanced head and neck cancer treated with chemoradiotherapy: expert listeners' and patient's perception. J Voice 2012;26:e25–33. 664.
[22] Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia 1996;11:93–8.
[23] McHorney CA, Martin-Harris B, Robbins J, Rosenbek J. Clinical validity of the SWAL-QOL and SWAL-CARE outcome tools with respect to bolus flow measures. Dysphagia 2006;21:141–8.
[24] Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. Int J Oral Maxillofac Surg 2006;35:337–42.
[25] Rinkel RN, Verdonck-de Leeuw IM, Langendijk JA, van Reij EJ, Aaronson NK, Leemans CR. The psychometric and clinical validity of the SWAL-QOL questionnaire in evaluating swallowing problems experienced by patients with oral and oropharyngeal cancer. Oral Oncol 2009;45:e67–71.
[26] Rinkel RN, Verdonck-de Leeuw IM, van den Brakel N, de Bree R, Eerenstein SE, Aaronson N, et al. Patient-reported symptom questionnaires in laryngeal cancer: voice, speech and swallowing. Oral Oncol 2014;50:759–64.
[27] McHorney CA, Robbins J, Lomax K, Rosenbek JC, Chignell K, Kramer AE, et al. The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. Dysphagia 2002;17:97–114.
[28] Logemann JA, Pauloski BR, Rademaker AW, Lazarus CL, Gaziano J, Stachowiak L, et al. Swallowing disorders in the first year after radiation and chemoradiation. Head Neck 2008;30:148–58.

[29] Heukelom J, Lopez-Yurda M, Balm AJ, Wijers OB, Buter J, Gregor T, et al. Late follow-up of the randomized radiation and concomitant high-dose intra-arterial or intravenous cisplatin (RADPLAT) trial for advanced head and neck cancer. Head Neck 2015 (Epub).
[30] Gupta T, Agarwal J, Jain S, Phurailatpam R, Kannan S, Ghosh-Laskar S, et al. Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: a randomized controlled trial. Radiother Oncol 2012;104:343–8.
[31] Bensadoun RJ, Riesenbeck D, Lockhart PB, Elting LS, Spijkervet FK, Brennan MT. A systematic review of trismus induced by cancer therapies in head and neck cancer patients. Support Care Cancer 2010;18:1033–8.
[32] Kamstra JI, Dijkstra PU, van Leeuwen M, Roodenburg JL, Langendijk JA. Mouth opening in patients irradiated for head and neck cancer: a prospective repeated measures study. Oral Oncol 2015 (Epub).
[33] van der Molen L, Heemsbergen WD, de Jong R, van Rossum MA, Smeele LE, Rasch CR, et al. Dysphagia and trismus after concomitant chemo-Intensity-Modulated Radiation Therapy (chemo-IMRT) in advanced head and neck cancer; dose-effect relationships for swallowing and mastication structures. Radiother Oncol 2013;106:364–9.
[34] Langmore S, Krisciunas GP, Miloro KV, Evans SR, Cheng DM. Does PEG use cause dysphagia in head and neck cancer patients? Dysphagia 2012;27:251–9.
[35] Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY, et al. Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. JAMA Otolaryngol Head Neck Surg 2013;139:1127–34.
[36] Wopken K, Bijl HP, van der Schaaf A, van der Laan HP, Chouvalova O, Steenbakkers RJ, et al. Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/chemo-radiotherapy in head and neck cancer. Radiother Oncol 2014;113:95–101.
[37] Ottosson S, Soderstrom K, Kjellen E, Nilsson P, Zackrisson B, Laurell G. Weight and body mass index in relation to irradiated volume and to overall survival in patients with oropharyngeal cancer: a retrospective cohort study. Radiat Oncol 2014;9:160.
[38] Mekhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, Lavertu P. Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? Cancer 2001;91:1785–90.
[39] Chen AM, Li BQ, Lau DH, Farwell DG, Luu Q, Stuart K, et al. Evaluating the role of prophylactic gastrostomy tube placement prior to definitive chemoradiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2010;78:1026–32.