Emerging understanding of dosimetric factors impacting on dysphagia and nutrition following radiotherapy for oropharyngeal cancer

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ABSTRACT

Background: Preliminary research has reported relationships between three-dimensional (3D) radiation dose to head and neck structures and consequential swallowing/nutritional outcomes. The current study aimed to identify which reported dose constraints identified functional impairment at 6 months post-treatment.

Materials and Methods: Dose constraints with reported relationships to swallowing/nutrition were identified through a systematic literature review. Dose volume histograms for 12 patients with T1-T3 oropharyngeal cancer treated with 3D conformal radiotherapy determined dosages delivered to specific structures. Doses were examined in relation to published dose constraints and swallowing/nutritional outcomes at 6 months post-treatment.

Results: Sixty-six percent of the reported mean, maximum and partial doses to eight structures correctly identified swallowing and nutrition outcomes at 6 months.

Discussion: The relationships observed between dosimetric constraints and functional outcomes highlight the potential for dosimetric data to assist in prognosis and treatment. Systematic research is required to refine dosimetric parameters and the impact on outcomes.

INTRODUCTION

The move from 2D radiotherapy planning to 3D planning has allowed more detailed reporting of radiation dose in relation to tissue volumes, i.e. the amount of radiation provided as a percentage volume to a structure of interest, such as the base of tongue (BOT). In the past, maximum point doses were stipulated by normal tissue tolerances and these were typically applied only to critical normal tissues, such as the spinal cord. In the past 10 years however, there has been a concerted effort to achieve greater understanding of the possible relationship between submaximal point dosages provided to various other structures, such as those specifically involved in swallowing, in an attempt to better understand the consequential impact of radiation dose on swallowing, and subsequently nutrition.

Treatment intensification (with altered fractionation radiotherapy, chemotherapy or targeted therapy [eg. cetuximab]) for head and neck cancer has been shown to improve survival compared with conventional radiotherapy treatment [(1-3)]. These approaches however have been associated with increased acute toxicity which has resulted negative functional sequelae for both swallowing and nutrition [(4)]. Improved treatment delivery with 3D conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT) has allowed intensified treatment to be delivered whilst allowing more of the normal tissue to be spared [(5)], with the potential to optimize the functional outcomes of swallowing and nutrition. Previously, swallowing dysfunction has been reported in 30-50% of patients treated with intensive non-surgical regimens [(6, 7)] and has been negatively correlated with quality of life 12 months post-treatment [(8)]. Dysphagia has also been associated with anxiety and depression in head and neck

cancer survivors [9]. Determining which patients will develop swallowing dysfunction following non-surgical treatment for head and neck cancer however is challenging. Recent evidence has examined the dosimetric parameters of specific swallowing organs at risk and their impact on post-treatment dysphagia and nutrition [10-23]. Dose volume histograms (DVHs) are routinely used in the 3D planning of radiotherapy for the assessment and reporting of dose to treatment volumes and OAR, and to ensure quality assurance, adequate dose to target structures, and avoidance of dose to nearby anatomical structures [24]. DVHs can also be generated post-treatment to determine the specific radiotherapy mean, maximum and partial doses received by each swallowing OAR within the treatment field. Each OAR can have a DVH generated for it, which demonstrates the volume of that organ receiving the dose. For example, a V_{45} of 80% to the inferior pharyngeal constrictor (see dashed line DVH in Figure 1) would indicate that 80% (Y axis) of the inferior pharyngeal constrictor received a total of 45Gy (X axis).

It has been hypothesized that the mean, maximum, and partial doses delivered to particular swallowing OAR may have a long-term impact on swallowing function, and that reduction of dose to these structures may help to minimise dysphagia and poor nutrition post-treatment [10-23, 25]. Eisbruch et al. (2004) [4] were the first to question an association between dose-volume parameters and dysphagia. They studied 32 patients with locally advanced head and neck cancer who were treated with two chemoradiation protocols associated with high rates of dysphagia and found a significant increase in tissue thickness of the pharyngeal constrictors, supraglottic larynx, and glottic larynx post-treatment. This enabled these authors to label these OAR as “dysphagia/aspiration related structures”, and an initial dose limitation of

50Gy to the pharynx was suggested to avoid stricture at this site [4]. Subsequent studies have utilized the anatomic swallowing OAR and contouring recommendations suggested by Eisbruch et al. (2004)[4] to provide further evidence for minimizing dysphagia Literature published recently has also indicated relationships between the requirement of alternative feeding and dose-volume parameters [21]. Investigations of additional critical parameters such as nutritional status or percentage weight loss and their relation to dose delivered to the swallowing OAR are still yet to be explored.

Enhanced understanding of the relationships between certain radiation dose levels and potential negative treatment effects will ultimately lead to informed treatment planning, optimisation of patient outcomes and greater prognostic decision making regarding patients most at risk for dysphagia and nutritional compromise following treatment. However, as yet this area of research is in the early preliminary stages. Hence the aims of the current paper are twofold: (1) to critically review the current literature and compile the published mean, maximum, and partial dosimetric parameters to OAR that have been implicated in swallowing outcomes to date, and (2) to examine the radiation dose information of a cohort who received 3D conformal AFRT-CB for oropharyngeal cancer with a range of functional outcomes assessed at 6 months post-treatment. The purpose of this will be to highlight how well the dose constraints reported in the literature to date relate to a range of detailed swallowing and nutritional outcomes at 6 months post-treatment.

MATERIALS AND METHODS

Review of the Current Literature

Identification of verified dosimetric parameters associated with swallowing and nutritional outcomes post-treatment was conducted through a systematic review of the literature. Electronic publications in English between January 1990 and May 2011 were searched for by the first author (BC). CINAHL, Pre-CINAHL, EMBASE, Medline and PubMed databases were searched using keywords, subject heading words, titles and abstracts. The following Medical Subject Headings (MeSH) search terms were used: deglutition, deglutition disorders, intensity modulated radiotherapy, radiotherapy and head and neck neoplasms. Additional search terms included swallowing, dysphagia, aspiration, videofluoroscopy, dosimetry, dose-volume constraints, dose-volume histogram, and head and neck cancer. Studies were included if: 1) participants were diagnosed with head and neck cancer; 2) specific swallowing-related structures were outlined; 3) total, mean, median, maximum, or partial doses of radiotherapy to specific swallowing-related structures were reported; 4) "dysphagia outcomes" were reported at one or more time points post-treatment and included at least one of the following: dysphagia toxicity, aspiration, physiological swallowing impairment, stricture, patient-reported swallowing function, diet tolerance, swallowing-related or general quality of life, and/or dependence on alternative feeding. Studies were excluded if: 1) participants were diagnosed with cancer other than that defined to the head and neck area; 2) anatomical structures outlined related specifically to outcomes other than swallowing (ie. saliva, skin, voice, edema, anatomical change); 3) dysphagia outcome was not reported; 4) radiotherapy dose to swallowing-related structures was not reported; or 5) the relationship between the dysphagia outcome and radiotherapy dose was not reported.

Following this search strategy, the reference lists of identified articles were manually searched for additional relevant publications. All relevant publications were reviewed by two researchers (BC and RN) and rated for methodological quality based on the Transparent Reporting of Evaluations with Non-randomized Designs (TREND) checklist, developed to be consistent with the Consolidated Standards or Reporting Trials (CONSORT) statement for randomized controlled trials [(26)]. The 22 criteria specified by TREND were given a rating of one (satisfies the criteria), or zero (does not satisfy the criteria), yielding a possible total quality rating of 22.

A total of 18 studies met the criteria to be included in this review, of which one was a systematic review and another of these papers was a review of results reported by two other studies, and was therefore excluded [(15)]. The remaining 16 were a variety of non-randomized evaluation designs, and were evaluated in detail and given a quality rating using the 22 item TREND checklist [(26)]. The two researchers (BC and RN) subsequently met to compare their ratings and an agreed consensus was reached. Analysis revealed that the average score for quality of methodology was 14.6 (range = 11-17), with higher scores representative of an article meeting a greater number of methodological criteria (Table 1).

Dosimetric data was collated from the articles regarding specific swallowing structures. These included of the base of tongue (BOT), pharyngeal constrictors (PC, as a single structure), as well as superior (SPC), middle (MPC) and inferior (IPC) pharyngeal constrictors, glottic/supraglottic larynx (GSL), upper esophageal sphincter (UES), and esophagus (ES). From this, only the most conservative evidence based dose constraints for these swallowing structures were collated from the literature

reviewed (Figure 2). For example, if dose constraints of V_{50} < 50Gy, V_{50} < 55Gy or V_{60} < 50Gy to the BOT were reported in separate studies, then V_{50} < 50Gy was included in the summary as the most conservative dose reported.

Application of Known Dosimetric Parameters

The second component of the current study aimed to determine whether those dose constraints identified in the literature as associated with swallowing outcomes post-treatment were accurate at identifying swallowing, nutrition, and patient-rated functional impairment. As such, the dosimetric details of a homogenous cohort of patients who received 3D conformal AFRT-CB for T1-T3 oropharyngeal SCC were generated and applied to their swallowing, nutrition, and patient-rated outcomes.

Participants

The cohort included 12 participants taken from a group of 14 participants described previously in a prospective study examining functional outcomes [27]. Demographic details are reported in Table 2, and maximum, mean and V_{40}, V_{50}, and V_{60} partial doses received by this cohort are reported in Table 3. Two participants from the original cohort were excluded as one participants' radiotherapy planning data was unable to be restored (AF05), and for another the imaging was of insufficient quality to accurately delineate the target structures (AF04). Data analysis was, therefore, completed on the 12 participants who completed treatment and follow-up at 6 months post-treatment, and for whom accurate DVHs could be generated. No patient received chemotherapy or targeted therapies. All patients received their treatment at the Metro South Radiation Oncology Service in Brisbane, Australia. Ethics approval was obtained from the Princess Alexandra Hospital and The University of Queensland

Human Research and Ethics Committees, and all participants provided written consent prior to their involvement.

Planned treatment and dose-volume histogram contouring

Participants were treated with AFRT-CB of 66Gy in 35 fractions over 5 weeks using 3D conformal planning techniques as per our institutional head and neck cancer treatment protocol. In the final two weeks of treatment, participants were given a second daily dose of 1.6Gy with at least 6 hours interfraction interval. Planning target volumes (PTV) were as follows: PTV1 to cover the primary and involved nodal regions and potential areas of local extension or lymphatic spread, (gross target volume [GTV] + 1.5cm plus potential areas of spread to nodes), and PTV2 to primary and involved node regions (GTV + 1.0cm). Contralateral nodes were included in the treatment field in patients with supraglottic and base of tongue disease or where there were pathological nodes in the ipsilateral neck [(28)]. Unilateral treatment was given in patients with oropharyngeal disease where the ipsilateral neck was N0 [(28)].

On completion of treatment, dose-volume histograms were generated for each participant to capture eight structures critical for swallowing in each participant. Two specialist radiation oncologists (SP and MP) supervised two junior medical staff (CB and RMR) in the accurate delineation of the target structures using CT imaging. From this information, DVHs of the BOT, PC, SPC, MPC, IPC, GSL, UES, and ES were generated using the Eclipse Treatment Planning System version 8.6 (Varian Medical Systems, Palo Alto, CA). The procedure for DVH generation was that described by the Trans-Tasman Radiation Oncology Group (TROG) in the 07.04 protocol (TROG registered number: A0031029V), and abided by anatomic boundaries described

previously [4, 12, 13, 16]. Copies of the pictorial DVHs, as well as descriptive data regarding mean and maximum doses to each structure were provided to the principal investigator for analysis. DVHs were analysed for the following end points to determine: the percent volume to the BOT, PC, SPC, MPC, IPC, GSL, UES, and ES receiving partial doses of 40Gy (V_{40}), 50Gy (V_{50}), 60Gy (V_{60}), the mean dose (M_D), and the maximum dose (Max_D). The dosimetric data of each individual were then compared to the parameters in Figure 2 and coded as either 0 (structure received mean dose of less than that verified by the literature) or 1 (structure received mean dose of greater than that verified by the literature) for all eight swallowing structures. This identified which patients received doses to specific structures that met or exceeded suggested dose constraints to each swallowing structure.

Outcome Measures

The coded dose constraints (did or did not meet the criteria outlined in Figure 2) were then analysed against eleven end points measured at 6 months post-treatment in the AFRT-CB cohort to explain whether adherence to specific dosimetric parameters accurately identified who would be impaired/unimpaired post-treatment. These twelve endpoints included: 1) xerostomia and dysphagia toxicity grades 0-4 as per the Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE v.3.0, [29]; 2) full diet versus modified diet following following clinical swallow evaluation (CSE); 3) functional swallowing status using the Royal Brisbane Hospital Outcome Measure for Swallowing score (scores of 1-7 = impaired vs scores 8-10 = not impaired) (RBHOMS, [30] following CSE; 4) physiological swallowing impairment in pharyngeal contraction/bolus propulsion, laryngeal excursion, and clearance of pyriform sinus residue (0 = not impaired, 1 = impaired) using Subscale One of the

New Zealand Index for Multidisciplinary Evaluation of Swallowing (NZIMES, [31] following videofluoroscopy (VFS); 5) presence of penetration or aspiration using the validated Penetration-Aspiration Scale (PAS, [32] using VFS; 6) general patient-rated function using the Functional Assessment of Cancer Therapy Additional Concerns for Head and Neck version 4 (FACT-H&N, [33], Head and Neck Specific score (score <36 = impaired); 7) response FACT-H&N to question 7 " I can swallow naturally and easily"(scores 3-4 = not impaired, scores 0-2 = impaired); 8) patient-rated swallowing function using the M. D. Anderson Dysphagia Inventory (MDADI, [34] global score (score <100 = impaired); 9) response to MDADI physical question 6 "swallowing takes me great effort" (scores 3-5 = not impaired, scored 1,2 = impaired); 10) global nutrition using the Patient-Generated Subjective Global Assessment (PG-SGA, [35] global score of A (not impaired) vs B or C (impaired); 11) loss of weight (LOW) of > 10% between pre-treatment and 6 months post-treatment; and 12) requirement of alternative feeding at any time during or post-treatment.

Statistical Analysis

Receiver operating characteristic (ROC) analysis was used to determine which dose constraints accurately identified impairment in toxicity, dysphagia, patient-rated functional impact or nutrition endpoints at 6 months post-treatment in the AFRT-CB cohort. The data meeting the following two criteria were considered clinically important if: 1) the area under the curve (AUC) was > 0.75, and 2) the ROC curve assessed > 75% of the participants correctly (ie. met dose constraints and not impaired, plus exceeded dose constraints and impaired).

RESULTS

Thirty-eight radiation dosimetric parameters were identified in the literature, and 25 of those (66%) accurately identified the presence / absence of impairment in the AFRT-CB cohort at 6 months post-treatment. Table 4 and 5 report the ROC analyses meeting both clinically important criteria outlined above for toxicity/swallowing, and patient-rated functional impact/ nutritional end points, respectively.

Analysis revealed specific partial doses to the BOT, SPC, and GSL correctly identified ongoing salivary or dysphagia toxicity at 6 months post-treatment. Additionally, a mean dose of greater than 51Gy to the SPC also identified ongoing salivary toxicity post-treatment. There were 13 dose constraints verified in the literature that correctly identified penetration and aspiration events (for fluids) in the current cohort (Table 4). Partial doses to the PC (V_{65}), MPC (V_{65}), IPC (V_{45}-V_{60}), GSL (V_{65}), UES (V_{60}, V_{65}), and ES (V_{40}) all correctly identified penetration and aspiration of fluids at 6 months post-treatment. Mean dose to the GSL of greater than 48Gy, maximum dose to the UES of greater than 60Gy, and mean dose to the ES of greater than 17Gy also correctly identified penetration and aspiration of fluids at 6 months. Other measures of physiological swallowing impairment (laryngeal excursion or clearance of pharyngeal residue) were correctly identified by partial doses to the BOT, PC, SPC, and IPC (Table 4). Additionally, partial doses to the BOT, SPC, and GSL correctly identified impairment in functional swallowing (RBHOMS) or the need for a modified diet at 6 months post-treatment (Table 4).

A number of verified dose constraints also correctly identified some patient-rated functional impact and nutrition outcomes at 6 months post-treatment (Table 5). Only the mean (> 51Gy) and V_{40} partial (< 95%) doses to the SPC correctly identified

patient-rated functional impact for head and neck specific concerns on the FACT-H&N, and responses to the statement "I can swallow naturally and easily". All other dose constraints did not correctly identify any other patient-rated functional impact outcomes. Mean doses to the IPC (< 32Gy) and UES (<23Gy), as well as partial doses to the PC (V_{50}), IPC (V_{40}), and GSL (V_{35}, V_{70}) correctly identified the presence or absence of global nutritional impairment at 6 months post-treatment. A 10% loss of weight was correctly identified by partial doses to the BOT (V_{50}) and SPC (V_{50}) (Table 5).

DISCUSSION

The emerging evidence identifying radiation dosimetric factors which impact on swallowing and nutritional outcomes post-treatment is novel and innovative. The purpose of the current study was to highlight the accuracy of previously reported dose constraints in detailing a range of swallowing and nutritional outcomes at 6 months post-treatment, and has added to the emerging evidence in this area in two ways. Firstly, this study provides evidence that 66% of radiation dosimetric parameters verified by the literature accurately identify swallowing and nutritional outcomes at 6 months post-treatment in a cohort of patients with oropharyngeal SCC treated with AFRT-CB, despite the methodological limitations of previous research. Secondly, this study presents seminal evidence for the impact of radiation dosimetric parameters on global nutritional status and percentage weight loss at 6 months post-treatment.

The Current Evidence for Dosimetric Constraints and Swallowing Outcomes

The current evidence base is small, generally retrospective in design, and has commonly utilised heterogenous head and neck cohorts, thus limiting the

generalizability of dose constraint recommendations into clinical populations with head and neck cancer. Furthermore, there is a very high degree of methodological variability between the tools used to determine dysphagia presence with assessment procedures varying from crude rating scales performed by medical staff [11, 13, 16, 17, 36] to detailed videofluroscopic assessments performed by speech pathologists [12, 22, 37]. Similarly the variability between the outcome time points scored also varies dramatically. The majority of papers have compared the dosimetric parameters to swallowing outcomes at only one time point post-treatment, and this ranges from 4-8 weeks [11] to more than seven years post-treatment [18]. Some of the relationships have been established on outcomes seen as early as 3 months post-treatment [16, 20] [21] while most of the work has explored relationships to long term outcomes at either 6 months [20, 22, 36], or beyond [10, 12-14, 18-23, 25]. Very few papers routinely scored outcomes at multiple time points post-treatment [20-22, 36]. Furthermore the specific types of outcomes vary between studies with authors commenting on dose constraints to reduce dysphagia toxicity, aspiration, physiological impairment, stricture formation, patient-reported dysphagia, quality of life (QoL), and the need for alternative feeding. Hence it becomes obvious by examining this variability in methodology between studies that consistency in the recording and reporting of a core set of specific dysphagia and nutritional outcomes needs to be established.

Application of Verified Dosimetric Parameters to an AFRT-CB Cohort

The current study has found two thirds of published dose constraints accurately identified toxicity, swallowing, nutrition, and patient-rated function impairment at 6 months post-treatment in the current AFRT-CB cohort. Those dose constraints included partial doses to the BOT, PC, SPC, MPS, IPC, GSL, UES, and ES, as well

as mean doses to the SPC, IPC, GSL, UES, and ES, and maximum dose to the UES. Conversely, several of the dose constraints previously reported did not accurately identify impairment in the AFRT-CB cohort at 6 months post-treatment, indicating further detailed and systematic study is required.

Previously, a partial dose to the BOT of 50% receiving greater than 50Gy had been associated with aspiration [18], however the current study revealed this dose constraint also accurately identified impairment in salivary toxicity, laryngeal excursion, the need for a modified diet, and weight loss at 6 months post-treatment. It is not an unexpected result that the dose to the BOT, closely aligned with the parotid glands, is associated with long-term xerostomia. The impact of xerostomia on dietary modifications and subsequent weight loss has also been reported previously [38, 39], and it is not unanticipated that these impairments have co-occurred in the current cohort. The finding of impaired laryngeal excursion associated with BOT partial dose may reflect airway protection impairment. Adequate laryngeal excursion is necessary for epiglottic deflection and airway protection, and if impaired may result in penetration and aspiration as found by Jensen et al. (2007)[18]. Similarly, the co-occurrence of the need for a modified diet and weight loss both identified with a partial dose to the SPC of 90% receiving 50Gy. Feng et al. (2007)[16] suggested partial V_{50} dose to the SPC be reduced to 90% to avoid aspiration, however in the current cohort neither aspiration or penetration of fluids or solids was correctly identified with this dose constraint.

Mean, maximum, and partial doses to the MPC, IPC, GSL, UES, and ES verified by the literature showed strong identification of penetration and aspiration events in the

current cohort. It appears that larger doses to these structures are a potential contributing factor to aspiration risk at 6 months post-treatment. With significant aspiration, often alternative feeding is recommended. Very few of the current cohort required short term NGT feeding, however Caudell et al. [12] found conservative partial doses to the IPC from V_{45}-V_{60} were not associated with the need for alternative feeding. Thus, our results may confirm that the partial doses suggested by Caudell et al. [12] do accurately identify those at risk for alternative feeding as a result of penetration or aspiration. Only three of the suggested dose constraints to the GSL to reduce aspiration (MD <48Gy)[11] and alternative feeding (V65<23% and V70<4%)[12] correctly identified those who penetrated/aspirated at 6 months post-treatment in the current cohort. UES partial doses receiving 60 and 65Gy did however accurately identify penetration and aspiration, whereas the literature has previously reported an association with stricture formation and patient-reported dysphagia not found in this study [20]. The UES dose parameter previously associated with aspiration (V_{40}<50%)[18], did not correctly identify it in the current cohort. Both esophageal (ES) doses previously associated with aspiration correctly identified penetration and aspiration in the current cohort (mean dose <17Gy, [23]; V40<88%, [16]).

Global nutritional outcome was correctly identified by mean and partial doses to the IPC, GSL, and UES. Global nutritional outcome has not previously been assessed in relation to dosimetric parameters, so this study provides the first evidence that parameters which have previously been associated with dysphagia toxicity (IPC mean dose <32Gy)[19], alternative feeding (IPC V40<65% and GSL V35<79%)[12], and aspiration (UES mean dose <23Gy)[23] also correctly identify those patients who will be at risk of malnutrition at 6 months post-treatment. In the general HNC population,

it could be hypothesised that dysphagia toxicity (grade 4 toxicity requiring alternative feeding), the need for alternative feeding, and aspiration would result in poor global nutritional status, so this finding confirms the clinical relevance of these dosimetric parameters.

Although the evidence base is as yet small, current research has proposed a number of dosimetric constraints to key swallowing structures which may be influential in minimising the negative impact on swallowing, and potentially nutritional outcomes, following radiotherapy. Unfortunately, the number of significant methodological weaknesses in the current available literature must be acknowledged when interpreting the data at this time. Despite this, the application of the existing dosimetric parameters identified in the literature to our current cohort revealed that over two-thirds were consistent with the patient outcomes achieved. Future studies examining the predictive power of dosimetric factors need to include pre-treatment data, agreement on which swallowing OAR are contoured and how, and include outcome measure assessment which addresses the multifactorial nature of dysphagia and nutritional impairment, and uses validated measures. It is the hope that future rigorous, multidisciplinary studies will guide radiation oncologists and radiation therapists to optimize treatment plans and dose gradients to structures identified as associated with poor functional outcomes, allowing speech pathologists, dietitians and nurses involved in the rehabilitation of this population to better identify those patients at risk of developing dysphagia and/or nutritional compromise at 6 months post-treatment. Accordingly, this knowledge may guide alternative service delivery in the post-treatment phase to prevent functional impairment for those at risk.

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TABLES

Table 1. Consensus ratings given for each study reviewed using the TREND checklist

Numbered TREND checklist items		Alphabetical identifier of reviewed article															
		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1.	Title and abstract	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Introduction																
2.	Background	✓	✓	✓	×	✓	✓	✓	×	✓	×	✓	✓	✓	✓	✓	✓
	Methods																
3.	Participants	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.	Interventions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5.	Objectives	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
6.	Outcomes	×	✓	✓	×	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓
7.	Sample size	×	×	✓	×	×	×	×	×	×	×	✓	✓	✓	✓	×	×
8.	Assignment method	×	×	✓	×	×	×	×	×	×	×	×	×	✓	×	×	×
9.	Blinding (masking)	×	✓	×	×	×	×	×	×	×	×	×	×	×	✓	×	×
10.	Unit of analysis	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×

11.	Statistical methods	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×
	Results																
12.	Participant flow	✓	✓	×	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓
13.	Recruitment	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	×	✓	✓	✓	✓
14.	Baseline data	×	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
15.	Baseline equivalence	×	×	×	×	×	×	×	×	✓	×	×	✓	×	×	×	×
16.	Numbers analysed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
17.	Outcomes and Estimation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
18.	Ancillary analyses	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×	×
19.	Adverse events	✓	×	×	×	×	×	×	✓	×	×	×	×	✓	×	×	×
	Discussion																
20.	Interpretation	×	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
21.	Generalizability	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
22.	Overall evidence	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TOTAL QUALITY SCORE	/22	11	16	15	12	15	13	13	14	16	14	16	16	17	17	14	14

A = Anand et al., 2008, B = Bhide et al., 2009, C = Calgar et al., 2008, D = Caudell et al. 2010, E = Dirix, Abbeel, Vanstraelen, Hermans, & Nuyts, 2009, F = Dornfeld et al., 2007, G = Feng et al., 2007, H = Fua et al., 2007, I = Jensen, Lambertsen, & Grau, 2007, J = Levendag et al., 2007, K = Li et al., 2009, L = Mittal et al., 2001, M = Sanguineti et al., 2011, N = Schwartz et al., 2010, O = Teguh, Levendag, Noever, et al., 2008, P = Teguh, Levendag, Sewnaik, et al., 2008

Table 2. Demographics of AFRT-CB participants for whom DVHs were generated

Participant	Age	Sex*	TNM† Classification	Stage	Smoking	Alcohol	Weight (kgs)
AF01	82	M	T1N0 left pharyngeal wall	I	Ex	Current	70.3
AF02	63	M	T2N0 supraglottic	II	Current	Current	77.8
AF06	69	F	T2N2b left tonsil	IV	Ex	N/A	73
AF07	73	M	T2N0 left tonsil	II	Ex	Ex	61
AF08	70	M	T1N0 left tonsil	I	Ex	Current	106.7
AF09	69	M	T2N1 right tonsil	III	Ex	Current	65.8
AF10	69	M	T3N0 right supraglottic	III	Current	Current	81
AF12	59	M	T2N0 right supraglottic	II	Ex	Current	81
AF13	59	M	T1N2a right tonsil	IV	Never	Current	83.4
AF14	58	F	T3N0 right tonsil	III	Current	Current	59.5
AF15	53	M	T2N1 right tonsil	III	Never	Current	142
AF16	54	M	T1N2a right tonsil	IV	Never	Current	113

*M = male, F = female. †T = T stage, N = N stage.

Table 3. Mean (Gy), maximum (Gy) and partial doses (%) to eight swallowing structures in the AFRT-CB cohort

Site[*]	M_D[†] (SD)	Max_D[‡] (SD)	% V_{40}[§] (range)	% V_{50}[‖] (range)	% V_{60}[¶](range)
BOT	57.2 (11.3)	68.9 (2.63)	88 (34-100)	77 (5-100)	56 (2-100)
PC	47.6 (9.9)	68.7 (1.69)	72 (42-100)	60 (33-98)	43 (13-77)
SPC	59.9 (6.2)	67.7 (2.8)	97 (65-100)	91 (53-100)	63 (0-100)
MPC	55.5 (9.5)	65.7 (5.6)	88 (38-100)	73 (15-100)	50 (0-100)
IPC	35.5 (19.1)	63.5 (7.7)	49 (6-100)	35 (0-100)	24 (0-100)
GSL	41.3 (18.1)	64.6 (6.6)	60 (12-100)	47 (5-98)	31 (0-83)
UES	19.2 (19.8)	36.4 (16.5)	19 (38.4)	15 (36.2)	7 (22.8)
ES	11.5 (12.3)	31.5 (13.4)	8.3 (27.9)	3 (9.2)	0 (0)

[*]BOT = base of tongue, PC = pharyngeal constrictors, SPC = superior pharyngeal constrictor, MPC = middle pharyngeal constrictor, IPC = inferior pharyngeal constrictor, GSL = glottic/supraglottic larynx, UES = upper esophageal sphincter, ES = esophagus. [†]M_D = mean dose to structure. [‡]Max_D = maximum dose to structure. [§, ‖, ¶] Percentage of structure receiving partial dose of 40Gy, 50Gy, and 60Gy, respectively.

Table 4. Clinically relevant ROC analysis of dose-constraints regarding toxicity and swallowing end points at 6 months post-AFRT-CB

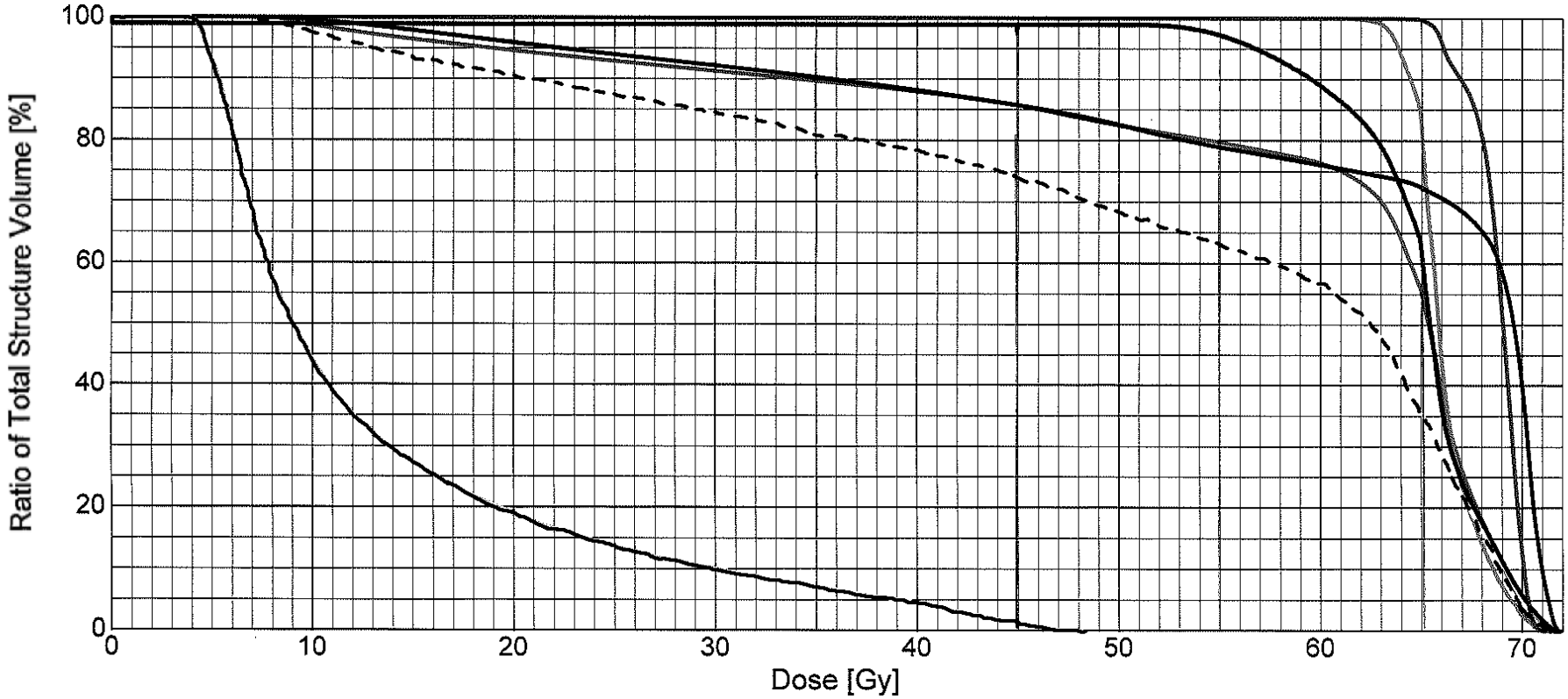
Site	DVH parameter	CTCAE Xerostomia		CTCAE Dysphagia		Pen/Asp Fluids		Pen/Asp Solids		Bolus Propulsion		Larynx Excursion		Clearance Residue*		RBHOMS		Modified Diet	
		AUC	%	AUC	%	AUC	%	AUC	%	AUC	%	AUC	%	AUC	%	AUC	%	AUC	%
BOT	V50<50%	**1.0**	**100**	0.7	50	0.6	33	0.75	58	0.65	75	**0.85**	**75**	0.8	67	0.7	50	**0.85**	**75**
PC	V65<50%	0.61	42	0.5	58	**0.83**	**92**	0.67	67	0.67	50	0.78	67	**0.83**	**75**	0.72	75	0.56	50
SPC	Mean<51Gy	**0.95**	**92**	0.68	42	0.59	25	0.73	50	0.36	67	0.82	67	0.78	58	0.68	42	0.82	67
	V40<95%	**0.95**	**92**	0.68	42	0.59	25	0.73	50	0.36	67	0.82	67	0.77	58	0.68	42	0.82	67
	V50<90%	0.7	83	0.7	50	0.3	16	0.45	42	0.35	58	0.55	42	0.5	50	0.7	50	**0.85**	**75**
	V55<80%	0.67	67	0.5	50	0.5	50	0.42	42	0.58	58	**0.75**	**75**	0.67	67	0.5	50	0.58	58
	V65<33%	0.63	50	0.44	50	0.56	67	0.56	58	0.69	58	**0.81**	**75**	0.69	67	0.63	67	0.63	58
MPC	V65<75%	0.59	25	0.32	58	**0.95**	**92**	0.82	67	0.64	33	0.73	50	0.77	58	0.32	58	0.18	33
IPC	V45<58%	0.44	33	0.44	60	**0.75**	**83**	0.56	58	0.5	42	0.63	58	0.69	67	0.63	67	0.44	42
	V50<48%	0.44	33	0.44	50	**0.75**	**83**	0.56	58	0.5	42	0.63	58	0.69	67	0.63	67	0.44	42
	V55<21%	0.44	33	0.44	50	**0.75**	**83**	0.56	58	0.5	42	0.63	58	0.69	67	0.63	67	0.44	42
	V60<12%	0.44	33	0.44	50	**0.75**	**83**	0.56	58	0.5	42	0.63	58	0.69	67	0.63	67	0.44	42
	V65<2%	0.47	42	0.56	58	0.7	75	0.49	50	0.54	50	0.69	67	**0.76**	**75**	0.56	58	0.34	33
GSL	Mean<48Gy	0.44	33	0.44	50	**0.75**	**83**	0.56	42	0.5	42	0.63	58	0.69	67	0.63	67	0.44	42
	V65<23%	0.44	33	0.44	50	**0.75**	**83**	0.56	58	0.5	42	0.63	58	0.69	67	0.63	67	0.44	42
	V70<4%	0.59	25	**0.86**	**75**	0.41	75	0.27	50	0.64	33	0.73	50	0.77	58	**0.86**	**75**	0.73	50
UES	Max<60Gy	0.59	25	0.32	58	**0.95**	**92**	0.82	67	0.64	33	0.73	50	0.77	58	0.32	58	0.18	33
	V60<78%	0.59	25	0.32	58	**0.95**	**92**	0.82	67	0.64	33	0.73	50	0.78	58	0.32	58	0.18	33
	V65=0%	0.59	25	0.32	58	**0.95**	**92**	0.82	67	0.64	33	0.73	50	0.77	58	0.32	58	0.18	33
ES	Mean<17Gy	0.59	25	0.32	58	**0.95**	**92**	0.82	67	0.73	50	0.64	33	0.77	58	0.32	58	0.18	33
	V40<88%	0.59	33	0.32	58	**0.95**	**92**	0.82	67	0.64	33	0.73	50	0.77	58	0.32	58	0.18	33

Note. AUC = area under the curve where >0.75 considered significant, % refers to percent correctly identified (met dose constraint + not impaired plus exceeded dose constraint + impaired), **bold** refers to results which met both clinically important criteria (AUC>0.75 + % correctly identified >75%). *Refers to clearance of pyriform sinus residue

Table 5. Clinically relevant ROC analysis of dose-constraints regarding patient-rated function and nutrition end points at 6 months post-AFRT-CB

Site*	DVH parameter	MDADI Global		MDADI Physical Q6		FACT H&N		FACT H&N Q7		NGT		PG-SGA Global		>10% loss of weight	
		AUC	%	AUC	%	ACU	%	AUC	%	AUC	%	AUC	%	AUC	%
BOT	V50<50%	0.5	83	0.7	50	0.7	83	0.65	75	0.6	33	0.35	25	**0.85**	**75**
PC	V50<80%	0.5	25	0.28	42	0.61	42	0.67	50	0.39	58	**0.78**	**83**	0.33	33
SPC	Mean<51Gy	0.5	92	0.68	42	**0.95**	**92**	**0.91**	**83**	0.59	25	0.64	33	0.82	67
	V40<95%	0.5	92	0.68	42	**0.95**	**92**	**0.91**	**83**	0.59	25	0.64	33	0.82	67
	V50<90%	0.5	83	0.7	50	0.7	83	0.65	75	0.6	33	0.65	42	**0.85**	**75**
IPC	Mean<32Gy	0.5	50	0.33	33	0.67	67	0.42	42	0.67	67	**0.75**	**75**	0.58	58
	V40<65%	0.5	42	0.21	25	0.64	58	0.37	33	0.53	58	**0.80**	**83**	0.51	50
GSL	V35<79%	0.5	42	0.21	25	0.64	58	0.37	33	0.53	58	**0.80**	**83**	0.51	50
	V70<4%	0.5	8	0.32	58	0.59	25	0.64	33	0.41	75	**0.91**	**83**	0.73	50
UES	Mean<23Gy	0.5	25	0.28	42	0.61	42	0.44	33	0.61	75	**0.78**	**83**	0.33	33

Note. AUC = area under the curve where >0.75 considered significant, % refers to percent correctly identified (met dose constraint + not impaired plus exceeded dose constraint + impaired), **bold** refers to results which met both clinically important criteria (AUC>0.75 + % correctly identified >75%). *Structures where no clinically relevant ROC analyses were found have not been included



Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
Constrictors	Unapproved	100.0 / 99.8	18.7 [cm³]	6.9 Gy	72.0 Gy	59.1 Gy	65.8 Gy	65.3 Gy	15.1 Gy
INFER PC	Unapproved	100.0 / 99.8	10.9 [cm³]	7.0 Gy	71.5 Gy	53.4 Gy	65.8 Gy	62.5 Gy	18.1 Gy
BASE OF TONGUE	Unapproved	100.0 / 99.7	15.5 [cm³]	0.0 Gy	71.2 Gy	68.8 Gy	69.4 Gy	69.1 Gy	1.2 Gy
MIDDLE PC	Unapproved	100.0 / 99.6	4.4 [cm³]	0.0 Gy	71.8 Gy	64.4 Gy	0.0 Gy	65.4 Gy	7.4 Gy
GLOTTIC LARYNX	Unapproved	100.0 / 100.0	61.7 [cm³]	7.6 Gy	72.0 Gy	61.9 Gy	70.4 Gy	69.6 Gy	15.4 Gy
OESOPHAGUS	Unapproved	100.0 / 99.7	6.9 [cm³]	0.0 Gy	48.4 Gy	13.4 Gy	5.8 Gy	9.0 Gy	10.3 Gy
SUPER PC	Unapproved	100.0 / 99.7	4.8 [cm³]	61.3 Gy	71.6 Gy	66.2 Gy	65.0 Gy	65.8 Gy	1.6 Gy

Figure 1. Example of cumulative dose volume histogram where each line represents the DVH of a specific structure (highlighted is the base of tongue [dashed line]. X axis refers to the Gray (Gy) dose delivered, and Y axis refers to the percentage (%) of the organ receiving the dose (Gy).

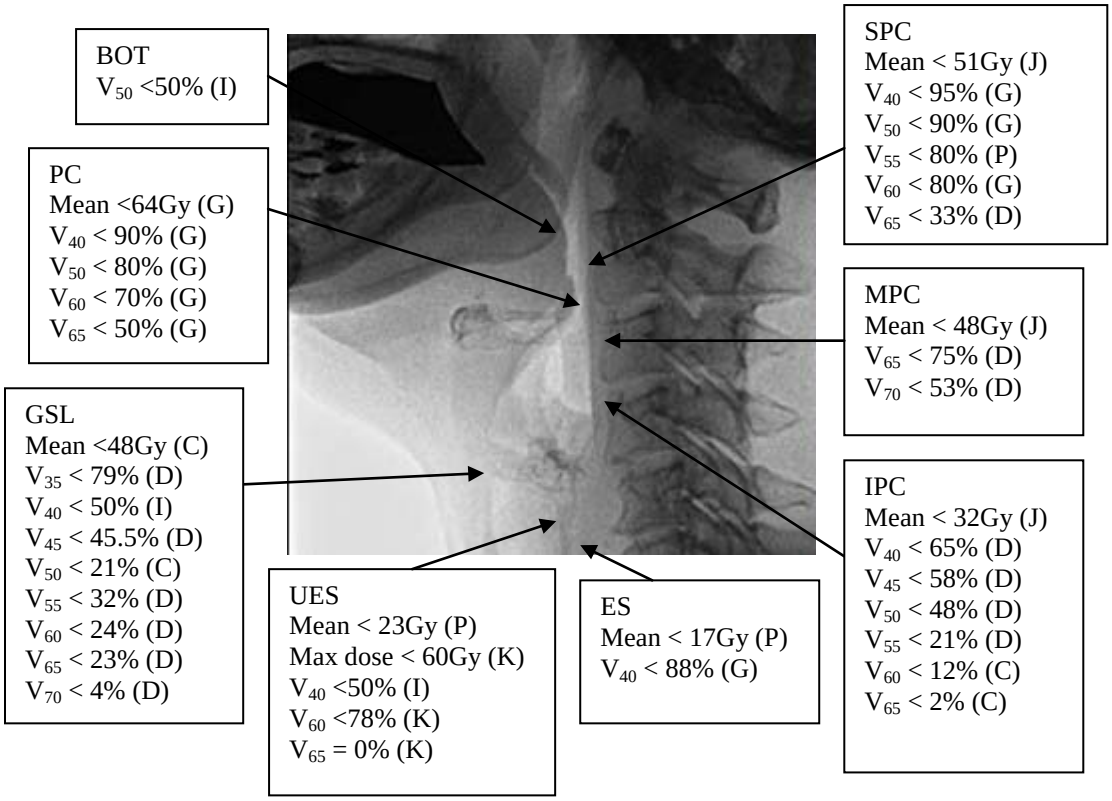


Figure 2. Dose parameters recorded for swallowing structures reported in the literature (study identified with alphabetical identifier as in Table 1) as relevant for swallowing outcomes, where BOT = base of tongue, PC = pharyngeal constrictors, GSL = glottic/supraglottic larynx, UES = upper esophageal sphincter, ES = esophagus, IPC = inferior pharyngeal constrictor, MPC = middle pharyngeal constrictor, and SPC = superior pharyngeal constrictor.