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Improvement in dysphagia outcomes following clinical target volume reduction in the De-ESCALaTE study

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Author declarations

Introduction The De-ESCALaTE study showed an overall survival advantage for the administration of synchronous cisplatin chemotherapy with radiotherapy in low risk oropharyngeal cancer when compared with synchronous cetuximab. During the trial, a radiotherapy quality assurance (RTQA) protocol amendment permitted centres to swap from the original radiotherapy contouring protocol (incorporating the whole oropharynx into the high dose clinical target volume (CTV) (anatomical protocol)), to a protocol which incorporated the gross tumour volume with a 10mm margin into the CTV (volumetric protocol). The purpose of this study was to examine both toxicity and tumour control related to this protocol amendment.

Methods Overall survival and recurrence at 2 years were used to compare tumour control in the two contouring cohorts. For toxicity, the cohorts were compared by both the number of severe (grades 3-5) and all grades acute and late toxicities. In addition, quality of life and swallowing were compared using EORTC-C30 and MD Anderson Dysphagia Inventory (MDADI) respectively.

Results Of 327 patients included in this study, 185 were contoured according to the anatomical protocol and 142 by the volumetric protocol. The two cohorts were well balanced with the exception of significantly more patients in the anatomical cohort undergoing prophylactic feeding tube insertion ($p < 0.001$). With a minimum of two years follow up there was no significant difference in overall survival or recurrence between the two contouring protocols. Similarly, there was no significant difference in the rate of reported severe or all grades acute or late toxicity and no sustained significant difference in quality of life. However, there was a significant difference in favour of volumetric contouring in several domains of the MDADI questionnaire at 1 year which persisted to 2 years in the dysphagia functional ($p = 0.002$), dysphagia physical ($p = 0.009$) and dysphagia overall function ($p = 0.008$) domains.

Conclusion In the context of the unplanned post-hoc analysis of a randomised trial, measureable improvement in long term dysphagia has been demonstrated following a reduction in CTV. Further reduction in CTV should be subject to similar scrutiny within the confines of a prospective study.

Introduction

Between November 2012 and October 2016, the De-ESCALaTE study randomised 334 patients with low risk oropharyngeal cancer (T3N0-T4N0 or T1N1-T4N3, p16+, <10 pack year history of smoking) to either synchronous cisplatin or synchronous cetuximab with radiotherapy [1]. There was an overall survival advantage at 2 years in favour of synchronous cisplatin. (98% v. 89%, p=0.001).

In 2011, the phase 3 PARSPORT trial reported 2 year results on 94 patients with squamous cell carcinoma of the head and neck who had been randomised to 3D conformal radiotherapy or parotid sparing Intensity Modulated Radiotherapy (IMRT). A reduction of grade 2 or worse xerostomia from 83% to 29% was observed with IMRT (p<0.0001) [2]. This trial used an anatomical approach to clinical target volume (CTV) definition where the whole oropharynx was incorporated into the high dose CTV. In 2011, 25% of surveyed UK clinical oncologists treating head and neck cancer were using a geometrical expansion of the gross tumour volume (GTV) to construct the high dose CTV [3]. However, to maintain continuity with the evidence base for IMRT in the UK it was initially decided to adopt an anatomical protocol for target volume definition in the De-ESCALaTE study.

Following presentation and publication of single centre UK series employing a geometric expansion, a radiotherapy quality assurance (RTQA) protocol amendment implemented in 2013 permitted centres to transition from the original radiotherapy contouring protocol (anatomical protocol), to a protocol which incorporated the gross tumour volume with a 10mm concentric margin in the CTV (volumetric protocol) [4, 5].

The purpose of this study was to examine acute and late toxicity, swallowing outcomes and tumour control related to the use of the two contouring protocols.

Methods

The methods for the conduct and statistical analysis of the De-ESCALaTE trial have been published previously [1].

For the purposes of this study the anatomical cohort and volumetric cohort were defined by the use of the original or modified contouring guidelines. Centres had to decide whether they were going to transition to the modified guidelines and contour all subsequent patients according to their decision.

In the original (anatomical) guidelines for the high dose CTV definition, the primary GTV was defined and then a 1cm margin was added (1.5 cm anteriorly if base of tongue tumour) and then edited off bone and air. The bilateral parapharyngeal spaces from the base of skull to the hyoid bone and oropharynx were then added to this volume in non-lateralised tumours. In lateralised tumours the ipsilateral parapharyngeal space and ipsilateral oropharynx was included. In cases of parapharyngeal involvement the volume was extended to include the medial pterygoid muscle.

In the modified (volumetric) guidelines for the high dose CTV definition, the primary GTV was defined and then a 1cm margin was added (1.5 cm anteriorly if base of tongue tumour) and then edited off bone and air. The parapharyngeal spaces and oropharyngeal mucosa were not included if not incorporated in the 1-1.5 cm margin around GTV. At the clinician's discretion, it was possible to include these structures in the low dose CTV. An example non-lateralised case to illustrate the difference between the high dose CTV for the two different guidelines is given in figure 1.

In both the anatomical and geometric protocols the whole involved lymph node levels were included in the high dose CTV. The inclusion of lymph node levels at risk in the low dose CTV was modified during the recruitment period in both protocols to reflect the updated consensus guidelines for delineation of neck node levels published in October 2013 [6]. PTV margins (3-5mm) were added according to local departmental protocol.

All centres entering the trial before the introduction of the volumetric guidelines were required to complete a benchmark contouring and planning exercise using the anatomical guidelines. Centres that chose to adopt the volumetric contouring guidelines were required to perform a further benchmark contouring and planning exercise using these guidelines. The first lateralised and non-lateralised cases performed using either set of guidelines were subject to live central review of contours and volumes.

Statistical Methods

Analyses were performed on an intention-to-treat basis. Baseline patient characteristics by RTQA protocol were compared using the Mann-Whitney test for continuous data and Pearson's chi-squared for categorical data (with continuity adjustment as required). Overall survival (using all-cause mortality) was calculated from the date of randomisation to the date of death with surviving patients being censored at the date of their last follow-up. Time to any recurrence, time to locoregional recurrence and time to distant recurrence were calculated from the date of randomisation to the date of recurrence or censored at last follow-up for recurrence free patients. Overall survival and time to recurrence compared data across RTQA protocol using the log-rank test and Kaplan-Meier curves. Mean numbers of acute, late and overall toxicity are presented with 95% confidence intervals for severe (grades 3-5) and all grades and compared by RTQA protocol using two sample t-tests. In addition, quality of life and swallowing were compared using EORTC-C30 and MD Anderson Dysphagia Inventory (MDADI) respectively [7]. Wilcoxon two sample tests were used to assess

differences in MDADI by RTQA protocol using a 5% significance threshold with no adjustment for multiple tests.

Results

Of 33 centres randomising patients into the trial, 21 were approved for contouring using the anatomical protocol. Eight of these centres subsequently switched to the volumetric protocol. Twelve centres joining the trial after the protocol amendment were only approved for volumetric contouring. Of 327 patients included in this study, 185 were contoured according to the anatomical protocol and 142 by the volumetric protocol. Table 1 illustrates the baseline characteristics of the two cohorts. The two cohorts were well balanced apart from a statistically significantly higher rate of planned feeding tube insertion before treatment in the anatomical contouring cohort 139 (75%) v. 77 (54%) ($p < 0.001$).

With a minimum follow up of two years there was no significant difference in 2 year overall survival between the protocols 95% (anatomical) v. 93% (volumetric) ($p = 0.10$) (Figure 2). Similarly, no significant difference was detected in time to any recurrence (locoregional or distant) (2 year recurrence rate 12% (anatomical) v. 17% (volumetric) ($p = 0.09$)). Separate analyses of recurrence type confirmed no difference in time to locoregional recurrence (2 year rate 5% (anatomical) v. 9% (volumetric) ($p = 0.25$)) and no difference in time to distant recurrence (2 year rate 5% (anatomical) v. 7% (volumetric) ($p = 0.07$)).

There was no significant difference in the rate of reported severe or all grades acute or late toxicity and no sustained significant difference in quality of life (Table 2). However, there was a significant difference between the cohorts in several domains of the MDADI questionnaire. In dysphagia global there was a statistically significant difference favouring volumetric contouring at 3 ($p = 0.027$), 6 months ($p = 0.013$) and 12 months ($p = 0.015$) post treatment (Table 3 and Figure 3). In dysphagia emotional there was a statistically significant difference favouring volumetric contouring at 3

($p=0.003$) and 12 months ($p<0.001$) post treatment (Table 3). In dysphagia functional there was a statistically significant difference favouring volumetric contouring at 3 ($p=0.003$) persisting to 24 months ($p=0.002$) post treatment (Table 3). In dysphagia physical there was also a statistically significant difference favouring volumetric contouring at 3 months ($p=0.007$) and 1 year (<0.001) which persisted to 2 years ($p=0.009$) (table 3 and figure 3) Finally, in the dysphagia overall function domain there was a statistically significant difference in favour of volumetric contouring at 3 months ($p=0.002$) persisting to 2 years ($p=0.008$) (table 3)..

Discussion

Dysphagia is a common toxicity of radiotherapy for head and neck cancer [8-10]. Many studies have shown a clinically significant decrease in MDADI scores (>10 points) at 3 months post treatment with improvement in a majority of patients over the two years following treatment [11-13]. A longitudinal study of patients over 65 years found MDADI scores continued to be persistently lower at 24 months when compared with baseline, suggesting the prolonged impact of radiotherapy on swallowing [14-15]. Worse long term swallowing outcomes are associated with higher total doses of radiotherapy and multiple modality treatments emphasising the importance of de-intensifying treatment where this can be done without compromising tumour control and survival outcomes [13,15].

There are very few randomised trials designed primarily to evaluate the impact of changing the radiotherapy technique and/or target volume. The PARSPORT study confirmed the benefits of IMRT with regards to salivary sparing [2]. An improvement in overall quality of life was observed in favour of IMRT but this did not reach statistical significance.. In view of the benefits seen with salivary sparing IMRT and the imperative to improve post radiotherapy swallowing function, numerous studies have tried to identify the organs at risk for swallowing and develop normal tissue complication probability (NTCP) models based on dose to these structures [16-19]. A recent systematic review of a number of NTCP models concluded that the pharyngeal constrictor muscles, in addition to the glottic and the supraglottic larynx, were the organs at risk with greatest association with severe dysphagia [20]. Subsequent to the PARSPORT study, the same group undertook the DARS study which randomised 111 patients between dysphagia optimised IMRT (where sparing the pharyngeal constrictor muscles were prioritised over the low dose CTV) or standard IMRT (s-IMRT). Dysphagia optimised IMRT resulted in significantly higher mean MDADI score at 12 months post RT (78 vs. 70) ($p= 0.02$) with no apparent detriment to local control [21-22].

Studies such as PARSPORT and DARS constitute a structured, evidence based approach to the introduction of new radiotherapy technology and contouring guidelines. However, such studies can be difficult to undertake due to lack of clinical equipoise. The general consensus in recent years has been to reduce the high dose target volume in order to lower dose to organs at risk and improve quality of life. The international consensus 5+5 contouring guidelines were proposed on this basis [23]. Microscopic tumour infiltration in surgical samples is most commonly between 0 and 10mm from macroscopic tumour margin, therefore a 5mm expansion to the GTV was proposed for the high dose CTV with a further 5mm for an intermediate or low dose CTV[24-26] . Sparing of anatomical structures with strong barriers to tumour cell diffusion was permitted based on the T stage and anatomical sub-site of the tumour. Despite international calls for such a study, it is uncertain whether this shift in technique will now ever be the subject of a randomised clinical trial [27]. Careful evaluation of outcomes and analysis of data from clinical trials asking other clinical questions may prove helpful to explore the risk benefit ratio from this and other radiotherapy technique changes [28]. The findings within the current unplanned analysis of the De-ESCALaTE trial do support the hypothesis that reducing the high dose volume, without specifically sparing swallowing OARs, may improve dysphagia outcomes.

Following the identification of potential dysphagia related organs at risk, other approaches to improving dysphagia in addition to dysphagia optimised IMRT and clinical target volume reduction have included the use of protons and surgical strategies to avoid radiotherapy or to permit dose de-intensification. Several non-randomised studies have reported reduced gastrostomy dependence and dysphagia outcomes when head and neck cancer patients treated with intensity modulated proton therapy (IMPT) were compared with patients treated with standard IMRT [29-32]. The TORPEdO study is a prospective phase 3 trial randomising patients with oropharyngeal cancer between IMRT and IMPT to assess if IMPT results in better long-term swallowing function and improved patient

reported QOL [33]. DAHANCA 35 is examining late dysphagia and xerostomia in laryngeal and oropharyngeal carcinoma patients randomised either to IMPT vs IMRT. [34]. Similarly, the M D Anderson Cancer Centre Group trial NCT01893307 is prospectively comparing IMPT to IMRT in patients with oropharyngeal carcinoma with a particular emphasis on swallowing outcomes [35]. Surgical studies, such as the PATHOS phase 3 randomised trial, seek to avoid radiotherapy altogether, to reduce the dose to or volume of CTVs or to avoid delivery of concurrent chemotherapy, by surgically staging patients and assigning risk categories [36]. The PATHOS study will determine whether de-intensifying adjuvant treatment after transoral laser microsurgery or transoral robotic surgery in low to intermediate risk HPV-positive oropharyngeal cancer reduces the extent of dysphagia post treatment, whilst maintaining overall survival. A sub-study focuses on the correlation between dose to swallowing organs at risk and both patient reported and objective measures of swallowing outcomes. The ORATOR study compared patients with oropharyngeal cancer treated with either transoral robotic surgery (and neck dissection with adjuvant radiotherapy or chemoradiotherapy where indicated) versus patients treated with definitive radiotherapy or chemoradiation finding statistically significant superior MDADI scores at 1 year post treatment in the non-surgical arm ($p=0.04$) [9]. Further studies are ongoing to determine the true comparative impact of transoral surgery versus definitive radiotherapy/chemoradiotherapy on swallowing outcomes, including the EORTC 1420 phase 3 randomised trial (NCT02984410) which is comparing the ‘best-of’ surgery compared to the ‘best-of’ radiotherapy for early stage oropharyngeal cancer [37].

In the current study volumetric contouring was associated with statistically significantly higher MDADI scores at several time points within several domains without a statistically significant increase in local recurrence. However, there are limitations to this analysis. The anatomical protocol was initially adopted to maintain continuity with the PARSPORT study but several large centres were not using this protocol in routine practice [2,3]. However, despite attempts made to reflect current clinical practice, both methods have become outdated, as the contralateral uninvolved oropharynx

would not be routinely included in a low dose volume. In addition, this study reports an unplanned analysis within the context of a randomised trial. Patients in this study were randomised to synchronous cisplatin chemotherapy versus synchronous cetuximab rather than radiotherapy technique. The baseline characteristics in this study were equally balanced between the two radiotherapy protocol groups, except for an increased percentage of prophylactic gastrostomies in the anatomical group ($p < 0.001$). Prophylactic gastrostomy insertion prior to commencing radiotherapy may improve nutritional outcomes of the patient by aiding maintenance of calorific input, but has been associated with more persistent dysphagia and increased enteral feeding dependence compared to reactive nasogastric tube insertion [38-40]. Therefore, the excess of patients with prophylactic gastrostomy in the anatomical cohort may be a significant confounding factor in this analysis and could potentially account for the long term differences seen in swallowing between the cohorts.

In summary, despite limitations, this analysis adds to the existing data suggesting improved swallowing outcomes following a reduction in CTV volumes. Further target volume reduction, if not carried out within the setting of a randomised trial, should be the subject of careful audit to ensure that such a reduction is not associated with a decrease in local control.

References

1. Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet*. 2019 Jan 5;393(10166):51-60. doi: 10.1016/S0140-6736(18)32752-1. Epub 2018 Nov 15. PMID: 30449623; PMCID: PMC6319250.
2. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol*. 2011 Feb;12(2):127-36. doi: 10.1016/S1470-2045(10)70290-4. Epub 2011 Jan 12. PMID: 21236730; PMCID: PMC3033533.
3. Pettit L, Hartley A, Bowden SJ, Mehanna H, Glaholm J, Cashmore J, et al. Variation in volume definition between UK head and neck oncologists treating oropharyngeal carcinoma. *Clin Oncol (R Coll Radiol)*. 2011 Nov;23(9):654-5. doi: 10.1016/j.clon.2011.07.006. Epub 2011 Aug 4. PMID: 21820293.
4. Loo SW, Geropantas K, Wilson P, Martin WM, Roques TW. Target volume definition for intensity-modulated radiotherapy after induction chemotherapy and patterns of treatment failure after sequential chemoradiotherapy in locoregionally advanced oropharyngeal squamous cell carcinoma. *Clin Oncol (R Coll Radiol)*. 2013;25(3):162-170. doi:10.1016/j.clon.2012.07.015
5. Benghiat H, Sanghera P, Cashmore J, et. al. Four Week Hypofractionated Accelerated Intensity Modulated Radiotherapy and Synchronous Carboplatin or Cetuximab in Biologically Staged Oropharyngeal Carcinoma *Cancer and Clin Onc*; 2014 3(2)
6. Gregoire, V., et al., Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiotherapy and Oncology* 2013 <http://dx.doi.org/10.1016/j.radonc.2013.10.010>

7. Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J, Goepfert H. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg.* 2001 Jul;127(7):870-6. PMID: 11448365.
8. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol.* 2008 Aug 1;26(22):3770-6. doi: 10.1200/JCO.2007.14.6647. PMID: 18669465.
9. Nichols AC, Theurer J, Prisman E, Read N, Berthelet E, Tran E et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. *Lancet Oncol.* 2019 Oct;20(10):1349-1359. doi: 10.1016/S1470-2045(19)30410-3. Epub 2019 Aug 12. Erratum in: *Lancet Oncol.* 2019 Dec;20(12):e663. PMID: 31416685.
10. Salama JK, Stenson KM, List MA, Mell LK, Maccracken E, Cohen EE, et al. Characteristics associated with swallowing changes after concurrent chemotherapy and radiotherapy in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2008 Oct;134(10):1060-5. doi: 10.1001/archotol.134.10.1060. PMID: 18936351.
11. Goepfert R, Lewin J, Barrow M, Gunn B, Fuller D, Beadle B et al. Long-Term, Prospective Performance of the MD Anderson Dysphagia Inventory in “Low-Intermediate Risk” Oropharyngeal Carcinoma After Intensity Modulated Radiation Therapy. *International Journal of Radiation Oncology Biology Physics.* 2017. Vol. 97, No. 4, pp. 700e708. <http://dx.doi.org/10.1016/j.ijrobp.2016.06.010>
12. Roe JW, Drinnan MJ, Carding PN, Harrington KJ, Nutting CM. Patient-reported outcomes following parotid-sparing intensity-modulated radiotherapy for head and neck cancer. How important is dysphagia? *Oral Oncol.* 2014 Dec;50(12):1182-7. doi: 10.1016/j.oraloncology.2014.09.009. Epub 2014 Oct 14. PMID: 25448227.

13. Wilson JA, Carding PN, Patterson JM. Dysphagia after nonsurgical head and neck cancer treatment: patients' perspectives. *Otolaryngol Head Neck Surg.* 2011 Nov;145(5):767-71. doi: 10.1177/0194599811414506. Epub 2011 Jul 11. PMID: 21746839.
14. Hutcheson KA, Barrow MP, Lisec A, Barringer D, Gries K, Lewin J. What is a clinically relevant difference in MDADI scores between groups of head and neck cancer patients? *Laryngoscope* 2016;126:1108-1113. <https://doi.org/10.1002/lary.25778>.
15. Hutcheson KA, Nurgalieva Z, Zhao H, Gunn GB, Giordano SH, Bhayani MK, et al. Two-year prevalence of dysphagia and related outcomes in head and neck cancer survivors: An updated SEER-Medicare analysis. *Head Neck.* 2019 Feb;41(2):479-487. doi: 10.1002/hed.25412. Epub 2018 Dec 7. PMID: 30536748; PMCID: PMC6355350.
16. Christianen ME, Schilstra C, Beetz I, Muijs CT, Chouvalova O, Burlage FR et al. Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study. *Radiother Oncol.* 2012 Oct;105(1):107-14. doi: 10.1016/j.radonc.2011.08.009. Epub 2011 Sep 8. PMID: 21907437.
17. Levendag PC, Teguh DN, Voet P, van der Est H, Noever I, de Kruijf WJ, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology.* 2007; 85:64–73. [PubMed: 17714815]
18. MD Anderson Head and Neck Cancer Symptom Working Group. Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: Dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. *Radiother Oncol.* 2016 Feb;118(2):304-14. doi: 10.1016/j.radonc.2016.01.019. Epub 2016 Feb 17. PMID: 26897515; PMCID: PMC4794433.
19. Vlacich G, Spratt DE, Diaz R, Phillips JG, Crass J, Li CI, et al. Dose to the inferior pharyngeal constrictor predicts prolonged gastrostomy tube dependence with concurrent intensity-modulated radiation therapy and chemotherapy for locally-advanced head and neck

- cancer. *Radiotherapy and Oncology*. 2014 Mar;110(3):435-40. doi: 10.1016/j.radonc.2013.12.007. Epub 2014 Jan 16. PMID: 24440043.
20. Brodin NP, Kabarriti R, Garg MK, Guha C, Tomé WA. Systematic Review of Normal Tissue Complication Models Relevant to Standard Fractionation Radiation Therapy of the Head and Neck Region Published After the QUANTEC Reports. *Int J Radiat Oncol Biol Phys*. 2018 Feb 1;100(2):391-407. doi: 10.1016/j.ijrobp.2017.09.041. Epub 2017 Sep 29. PMID: 29353656; PMCID: PMC5915347.
21. Nutting et al. 2020. Results of a randomised phase 3 study of dysphagia-optimised intensity modulated radiotherapy (Do-IMRT) versus standard IMRT (S-IMRT) in head and neck cancer. DOI: 10.1200/JCO.2020.38.15_suppl.6508 *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 6508-6508.
22. Petkar I, Rooney K, Roe JW, Patterson JM, Bernstein D, Tyler JM, et al. DARS: a phase III randomised multicentre study of dysphagia- optimised intensity- modulated radiotherapy (Do-IMRT) versus standard intensity- modulated radiotherapy (S-IMRT) in head and neck cancer. *BMC Cancer*. 2016 Oct 6;16(1):770. doi: 10.1186/s12885-016-2813-0. PMID: 27716125; PMCID: PMC5052945.
23. Gregoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. *Radiother Oncol*, 2018. 126(1): p. 3-24. <https://doi.org/10.1016/j.radonc.2017.10.016>.
24. Campbell S, Poon I, Markel D, Vena D, Higgins K, Enepekides D, et al. Evaluation of microscopic disease in oral tongue cancer using whole-mount histopathologic techniques: implications for the management of head-and-neck cancers. *Int J Radiat Oncol Biol Phys* 2012;82:574–81.

25. Fleury B, Thariat J, Barnoud R, Buiret G, Lebreton F, Bancel B, et al. Microscopic extensions of head and neck squamous cell carcinomas: impact for clinical target volume definition. *Cancer Radiother* 2014;18:666–71.
26. Yuen PW, Lam KY, Chan AC, Wei WI, Lam LK. Clinicopathological analysis of local spread of carcinoma of the tongue. *Am J Surg* 1998;175:242–4.
27. Corkum MT, Mitchell S, Venkatesan V, Read N, Warner A, Palma D. Does 5+5 equal better radiation treatment plans in head and neck cancers? *Advances in Radiation Oncology* (2019) 4, 683-688
28. Vreugdenhil M, Fong C, Sanghera P, Hartley A, Dunn J, Mehanna H. Hypofractionated chemoradiation for head and cancer: Data from the PET NECK trial. *Oral Oncol.* 2020 Dec 13;113:105112. doi: 10.1016/j.oraloncology.2020.105112. Epub ahead of print. PMID: 33321287; PMCID: PMC7733600.
29. Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez Met al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer - A case matched analysis. *Radiother Oncol.* 2016 Jul;120(1):48-55. doi: 10.1016/j.radonc.2016.05.022. Epub 2016 Jun 21. PMID: 27342249; PMCID: PMC5474304.
30. Gunn GB, Blanchard P, Garden AS, Zhu XR, Fuller CD, Mohamed AS, et al. Clinical Outcomes and Patterns of Disease Recurrence After Intensity Modulated Proton Therapy for Oropharyngeal Squamous Carcinoma. *Int J Radiat Oncol Biol Phys.* 2016 May 1;95(1):360-367. doi: 10.1016/j.ijrobp.2016.02.021. Epub 2016 Feb 12. PMID: 27084653; PMCID: PMC5474303.
31. McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. *Radiat Oncol.* 2016 Feb 27;11:32. doi: 10.1186/s13014-016-0600-3. PMID: 26922239; PMCID: PMC4769827.

32. Sio TT, Lin HK, Shi Q, Gunn GB, Cleeland CS, Lee JJ, et al. Intensity Modulated Proton Therapy Versus Intensity Modulated Photon Radiation Therapy for Oropharyngeal Cancer: First Comparative Results of Patient-Reported Outcomes. *Int J Radiat Oncol Biol Phys*. 2016 Jul 15;95(4):1107-14. doi: 10.1016/j.ijrobp.2016.02.044. Epub 2016 Feb 18. PMID: 27354125; PMCID: PMC5409532.
33. Price J, Hall E, West C, Thomson D. TORPEdO - A Phase III Trial of Intensity-modulated Proton Beam Therapy Versus Intensity-modulated Radiotherapy for Multi-toxicity Reduction in Oropharyngeal Cancer. *Clin Oncol (R Coll Radiol)*. 2020 Feb;32(2):84-88. doi: 10.1016/j.clon.2019.09.052. Epub 2019 Oct 8. PMID: 31604604.
34. Jensen K, Friberg J. DAHANCA 35. Proton versus photon radiotherapy for pharynx and larynx cancer. A randomized trial using a model based enriched population. Presented at PTCOG58 June 2019. <https://doi.org/10.26226/morressier.5cb7218dae0a09001583057e>
35. MD Anderson Cancer Centre. 2020. Randomised Trial of Intensity-Modulate Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck. *ClinicalTrials.gov*. [online] Available at: <https://clinicaltrials.gov/ct2/show/NCT01893307> [Accessed 31 January 2021].
36. Owadally W, Hurt C, Timmins H, Parsons E, Townsend S, Patterson J, et al. PATHOS: a phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for Human papillomavirus (HPV) positive oropharyngeal cancer. *BMC Cancer*. 2015 Aug 27;15:602. doi: 10.1186/s12885-015-1598-x. PMID: 26311526; PMCID: PMC4549836.
37. Stelmes JJ, Gregoire V, Poorten VV, Golusiński W, Szewczyk M, Jones T et al. Organ Preservation and Late Functional Outcome in Oropharyngeal Carcinoma: Rationale of EORTC 1420, the "Best of" Trial. *Front Oncol*. 2019 Oct 22;9:999. doi: 10.3389/fonc.2019.00999. PMID: 31696052; PMCID: PMC6817682.

38. Fietkau R, Thiel HJ, Iro H, Richter B, Senft M, Rössler C, et al. Vergleich von oraler und enteraler Ernährung mittels perkutaner endoskopisch kontrollierter Gastrostomie (PEG) bei Strahlentherapie-Patienten mit Kopf-Hals-Tumoren [Comparison between oral nutrition and enteral nutrition using a percutaneous endoscopically guided gastrostomy (PEG) in patients undergoing radiotherapy for head and neck tumors]. *Strahlenther Onkol.* 1989 Dec;165(12):844-51. German. PMID: 2513655.
39. 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 May 1;91(9):1785-90. PMID: 11335904.
40. Morton RP, Crowder VL, Mawdsley R, Ong E, Izzard M. Elective gastrostomy, nutritional status and quality of life in advanced head and neck cancer patients receiving chemoradiotherapy. *ANZ J Surg.* 2009 Oct;79(10):713-8. doi: 10.1111/j.1445-2197.2009.05056.x. PMID: 19878166.

Table 1

Baseline characteristics of the anatomical and volumetric planning guideline cohorts

	Anatomical	Volumetric	Total
	N=185	N=142	N=327
Treatment			
Cisplatin+RT	92 (49.7%)	70 (49.6%)	162 (49.7%)
Cetuximab+RT	93 (50.3%)	71 (50.4%)	164 (50.3%)
Age			
Mean (SD)	57.0 (7.9)	57.1 (8.3)	57.0 (8.0)
Median (IQR)	57.0 (51.0-63.0)	57.0 (52.0-63.0)	57.0 (52.0-63.0)
Sex			
Men	149 (80.5%)	112 (78.9%)	261 (79.8%)
Women	36 (19.5%)	30 (21.1%)	66 (20.2%)
HPV testing results			
p16-positive, HPV-ISH positive	172 (94.5%)	125 (92.6%)	297 (93.7%)
p16-positive, HPV-ISH negative	10 (5.5%)	10 (7.4%)	20 (6.3%)
Tumour stage			
T1-T2	120 (64.9%)	91 (64.1%)	211 (64.5%)
T3-T4	65 (35.1%)	51 (35.9%)	116 (35.5%)
T4 only	34 (100.0%)	21 (100.0%)	55 (100.0%)
Nodal Stage			
N0-N1	44 (23.8%)	35 (24.6%)	79 (24.2%)
N1-N2	141 (76.2%)	107 (75.4%)	248 (75.8%)
N3 only	1 (100.0%)	1 (100.0%)	2 (100.0%)
Primary subsite			
Base of Tongue	64 (34.6%)	47 (33.1%)	111 (33.9%)
Tonsil	119 (64.3%)	91 (64.1%)	210 (64.2%)
Other	2 (1.1%)	4 (2.8%)	6 (1.8%)

ECOG performance status			
0	168 (90.8%)	121 (85.8%)	289 (88.7%)
1	17 (9.2%)	20 (14.2%)	37 (11.3%)
Current Alcohol consumption			
No	43 (23.2%)	37 (26.1%)	80 (24.5%)
Yes	142 (76.8%)	105 (73.9%)	247 (75.5%)
Median reported units per week	11.0 (5.0-20.0)	10.0 (4.0-20.0)	10.0 (4.0-20.0)
Ever smoked?			
No	103 (55.7%)	72 (50.7%)	175 (53.5%)
Yes	82 (44.3%)	70 (49.3%)	152 (46.5%)
Median pack years	6.0 (2.0-11.0)	8.0 (4.0-16.0)	8.0 (3.0-14.0)
Radiotherapy			
Unilateral	34 (18.5%)	35 (24.8%)	69 (21.2%)
Bilateral	150 (81.5%)	106 (75.2%)	256 (78.8%)
Planned PEG use before treatment*			
No	46 (24.9%)	65 (45.8%)	111 (33.9%)
Yes	139 (75.1%)	77 (54.2%)	216 (66.1%)

* p<0.001

Table 2

Comparison of all grade and severe (grade 3-5) toxicities between the anatomical and volumetric planning protocol cohorts

	Anatomical	Volumetric	P-value
	N=185	N=142	
Overall			
Grade 3-5	4.78 (4.24-5.33)	4.91 (4.25-5.56)	0.773
All grades	30.69 (29.01-32.36)	28.65 (26.67-30.62)	0.119
Acute toxicities			
Grade 3-5	4.37 (3.88-4.85)	4.43 (3.85-5.01)	0.865
All grades	20.75 (19.69-21.80)	19.48 (18.19-20.76)	0.129
Late toxicities			
Grade 3-5	0.44 (0.31-0.58)	0.48 (0.29-0.68)	0.737
All grades	10.18 (9.33-11.04)	9.33 (8.43-10.24)	0.183

Table 3

Comparison of MD Anderson Dysphagia Questionnaire (MDADI) outcomes between the anatomical and volumetric planning protocol cohorts

Scales/measures	Number of patients		Mean Treatment difference from baseline		P-value (Wilcoxon)
	Anatomical	Volumetric	Anatomical	Volumetric	
MDADI dysphagia global					
End of treatment	120	94	-44.83	-45.32	0.988
3m after treatment	121	104	-27.11	-19.04	0.027
6 months	119	94	-20	-10.85	0.013
12 months	118	101	-16.44	-8.71	0.015
24 months	104	93	-16.92	-10.32	0.076
MDADI dysphagia emotional					
End of treatment	134	100	--23.26	-21.22	0.425
3m after treatment	129	110	-17.27	-11.11	0.003
6 months	126	100	-12.26	-8.19	0.062
12 months	126	104	-12.55	-5.27	<0.001
24 months	115	99	-9.26	-5.74	0.150
MDADI dysphagia functional					
End of treatment	133	100	-31.69	-28.68	0.199
3m after treatment	129	110	-22.61	-15.14	0.003
6 months	126	100	-17.02	-10.08	0.006
12 months	126	104	-13.37	-4.71	<0.001
24 months	115	99	-10.61	-1.98	0.002
MDADI dysphagia physical					
End of treatment	133	100	-33.85	-34.93	0.707
3m after treatment	129	110	-26.85	-19.51	0.007
6 months	126	100	-22.47	-17.38	0.062
12 months	126	104	-21.07	-11.07	<0.001
24 months	115	99	-18.81	-10.62	0.009
MDADI dysphagia overall function					
End of treatment	134	100	-29.91	-29.04	0.653
3m after treatment	129	110	-22.70	-15.65	0.002

6 months	126	100	-17.84	-12.58	0.014
12 months	126	104	-16.32	-7.55	<0.001
24 months	115	99	-13.60	-6.83	0.008

*Wilcoxon test used

