Dose-escalated intensity-modulated radiotherapy in patients with locally advanced laryngeal and hypopharyngeal cancers

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Dose-Escalated Intensity Modulated Radiotherapy in Patients with Locally-Advanced Laryngeal and Hypopharyngeal Cancers: ART DECO, a Phase 3 Randomised Controlled Trial.

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Abstract

Background

Radical (chemo)radiotherapy offers potentially curative treatment for patients with locally-advanced laryngeal or hypopharyngeal cancer. We aimed to show that dose-escalated intensity-modulated radiotherapy (IMRT) improved locoregional control.

Methods

We performed a phase 3 open-label randomised controlled trial in patients with laryngeal or hypopharyngeal cancer (AJCC III-IVa/b, TNM 7). Patients were randomised (1:1) to dose-escalated (DE-IMRT) or standard dose (ST-IMRT) using a minimisation algorithm, balancing for centre, tumour site, nodal status and chemotherapy use. DE-IMRT was 67.2 gray (Gy) in 28 fractions (f) to the primary tumour and 56Gy/28f to at-risk nodes; ST-IMRT was 65Gy/30f to primary tumour and 54Gy/30f to at-risk nodes. Suitable patients received 2 cycles of concomitant cisplatin and up to 3 cycles of platinum-based induction chemotherapy. The primary endpoint was time to locoregional failure analysed by intention-to-treat using competing risks methodology.

Findings

Between Feb 2011 and Oct 2015, 276 patients (138 ST-IMRT; 138 DE-IMRT) were randomised. A pre-planned interim futility analysis met the criterion for early closure. After a median follow-up of 47.9 months (IQR 37.5-60.52) there were locoregional failures in 38/138 (27.5%) ST-IMRT patients and 42/138 (30.4%) DE-IMRT patients; an adjusted subhazard ratio of 1.16 (95% CI: 0.74–1.83, p=0.519) indicated no evidence of benefit with DE-IMRT. Acute grade 2 pharyngeal mucositis was reported more frequently with DE-IMRT than ST-IMRT (42% vs 32%). No differences in grade ≥3 acute or late toxicity rates were seen.

Conclusion

Dose-escalated IMRT did not improve locoregional control in patients with laryngeal or hypopharyngeal cancer.

The trial is registered: ISRCTN01483375.

KEYWORDS: head and neck cancer, IMRT, dose escalation, clinical outcomes, toxicity, phase III, randomised controlled trial, larynx cancer, hypopharynx cancer

Introduction

Radical chemoradiation or surgery ((pharyngo-)laryngectomy) with post-operative (chemo)radiation are the treatment options for locally-advanced squamous cell cancer of the larynx and hypopharynx. Radical chemoradiation offers potentially curative treatment with larynx preservation, thus avoiding tracheostomy and maintaining optimal quality of life in terms of speech, swallowing function and cosmesis. However, current chemoradiation treatment for locally-advanced laryngeal and hypopharyngeal cancers gives poor results with two-year locoregional failure-free rates (LRFFR) of 60-65% and laryngeal preservation rates of 35-65%.[1-4]

Previous research from our group showed that intensity modulated radiotherapy (IMRT) reduced the volume of normal tissue receiving high dose radiation.[5] Our early phase trials of dose-escalation[6, 7] confirmed the radiobiological modelling that a 10% escalation of radiation dose may significantly improve locoregional control.[8] Accelerated radiotherapy schedules have also shown improved locoregional tumour control,[9] but increased toxicity when using conventional radiotherapy techniques.[10] In this phase 3 randomised controlled trial we aimed to evaluate the therapeutic benefit of dose-escalated accelerated IMRT to improve outcomes for patients with locally-advanced laryngeal or hypopharyngeal cancer.

Materials and methods

Participants

Participants were aged >16 years with biopsy confirmed locally-advanced (stage III-IV) squamous cell carcinoma of the larynx or hyopharynx with no metastatic disease and no previous malignancy (except non-melanoma skin cancer and early-stage cancer in remission for at least five years). They were suitable for radical chemoradiation, had WHO performance status 0-1 and creatinine clearance >50 mL/min. Previous radiotherapy to the head and neck region was not permitted. Patients with pre-existing speech or swallowing problems unrelated to cancer diagnosis and those with large primary tumours where organ preservation was unrealistic were not eligible. All participants provided written informed consent.

Randomisation

Participants were centrally allocated (1:1) to standard dose IMRT (ST-IMRT) or accelerated dose-escalated IMRT (DE-IMRT). A minimisation algorithm incorporating a random element with balancing factors of treatment centre, tumour site (larynx vs. hypopharynx), nodal status (N0-2 vs. N3) and chemotherapy use (induction and concomitant vs. concomitant only) was used. An additional balancing factor strata of no chemotherapy was added with an amendment to eligibility criteria

(protocol v4.0, 07/02/2013). After nine patients had been randomised, a protocol amendment (v2.0 24/05/2011) mandated target volume delineation be performed prior to randomisation to avoid the potential for clinician knowledge of treatment allocation to bias their contouring. Treatment was not masked.

Treatment

Radiotherapy planning followed trial-specific Quality Assurance guidelines (Supplementary Appendix 1). In brief, patients were immobilised using an immobilisation shell and had a radiotherapy CT planning scan of the neck in the treatment position. Using clinical and radiological staging information, gross tumour volumes (GTVs) of the primary tumour and any lymph node metastases were localised. A high-dose clinical target volume (CTV1) was constructed to include the entire larynx and hypopharynx, involved nodal levels and retropharyngeal nodes. Pre-chemotherapy tumour volumes were used where appropriate. Elective lymph nodal regions at risk of harbouring occult microscopic disease in levels Ib-V bilaterally were delineated as CTV2. Additional 3–5 mm margins were added to CTV1 and CTV2 to form planning target volumes (PTV1 and PTV2).Participants allocated ST-IMRT received a median dose of 65 gray (Gy) in 30 fractions (f) of 2.17Gy to PTV1, and 54Gy in 30f of 1.8Gy to PTV2, once daily Monday to Friday over 6 weeks. Participants allocated DE-IMRT received 67.2Gy in 28f of 2.4Gy to PTV1 and 56Gy in 28f of 2.0Gy to PTV2, once daily Monday to Friday over 5.5 weeks. A simultaneous integrated boost IMRT technique was used.

Up to three (21-day) cycles of platinum-based induction chemotherapy was permitted based on TNM staging as per predefined protocols at each centre. All participants with adequate haematological and renal function and no other contraindications received concomitant cisplatin 100mg/m^2 on days 1 and 29 of radiotherapy. Following implementation of protocol v4.0 (07/02/2013) participants could receive radiotherapy alone if chemotherapy was contra-indicated.

Assessments

Prior to trial entry, patients had a diagnostic CT or MRI of head and neck region, chest X-ray or CT of thorax, full blood count, renal function, electrolytes, liver function tests, histology report, dental assessment and baseline toxicity assessment.

Acute toxicity was assessed weekly during radiotherapy using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Specific events of interest included dermatitis, mucositis, dysphagia, hoarse voice, weight loss, fatigue and xerostomia.

Late toxicities were recorded 3, 6, 12, 18 and 24 months after end of radiotherapy using the CTCAE v4.0, and Late Effects on Normal Tissues: Subjective/Objective/Management (LENT SOM) scoring systems. Late toxicities of interest included dysphagia, dermatitis, mucositis, voice alteration, auditory toxicity, nephropathy, oesophageal stricture, aspiration and skin changes.

All participants were clinically assessed 6-8 weeks after completing radiotherapy to determine treatment response. Radiological evaluation was performed with CT/MRI at 3 months. Examination under anaesthesia +/- biopsy and fine needle aspiration of lymph node was undertaken where there was suspicion of residual/recurrent disease. Subsequent clinical assessments were six monthly to 2 years and then annually to 5 years.

In an optional sub-study EORTC QLQC30 v.3.0 and H&N35 quality of life questionnaires were administered on paper in clinic (baseline and end of treatment) or mailed directly to the participant (6 months onwards).

Outcomes

The primary outcome was locoregional failure analysed as time from randomisation to (i) relapse at the primary site or neck more than 3 months after radiotherapy, or (ii) completion of radiotherapy in patients with persistent disease or locoregional disease which became apparent within 3 months of completion of radiotherapy. Persistent disease had to be confirmed at 3 month follow-up. All potential primary outcome events were reviewed by the Chief Investigator blind to treatment allocation to confirm event status. Secondary outcomes included laryngo-oesophageal dysfunction-free rate (LODFR) defined as time from randomisation to the first event which compromised laryngo-oesophageal function (local relapse, total or partial laryngectomy, tracheostomy, feeding tube insertion >3 months after radiotherapy or disease-specific death); overall survival, acute (up to 8 weeks after radiotherapy) and late toxicity and patient-reported quality of life (with key items being overall quality of life and H&N35 dry mouth, swallowing and speech subscales).

Statistical considerations

The target sample size was 354 participants (100 events), sufficient to detect a hazard ratio (HR) of 0.5 in favour of DE-IMRT (90% power, 5% two-sided significance, estimated 2-year locoregional failure-free rate (LRFFR) of 60% with ST-IMRT). Target effect size was based on radiobiological modelling for a 10% dose escalation.[8]

An interim analysis was pre-planned after half the required events with early stopping recommended for futility (HR>1; Whitehead stopping rule) or toxicity (high rate of grade≥3 dysphagia at 12 months). In September 2015, the Independent Data Monitoring Committee reviewed the interim results and recommended that recruitment was stopped because the pre-defined futility criterion had been met.

Time to locoregional failure was analysed using competing risks methodology with death as the competing event, comparisons by Gray's test and treatment effect estimated using Fine and Gray's regression models. For other time-to-event endpoints Cox regression was used to estimate treatment effects. HRs are presented unadjusted and adjusted for tumour site, nodal status, chemotherapy use, tumour stage, age and gender. All time-to-event endpoints were analysed by

intention-to-treat. Safety analysis included all participants who had at least one fraction of radiotherapy. Proportions experiencing any grade and grade≥3 toxicity were compared using Chi-squared or Fisher's exact test. Change from baseline in quality of life scores was compared by t-test at end of radiotherapy and 24 months. A 1% significance level was used for toxicity and patient-reported outcomes to make some allowance for multiple testing. Further details are provided in supplementary appendix 2.

Analyses were conducted using STATA v15.1 on a data snapshot taken on 11th July 2019. This snapshot supersedes that used for the interim analysis that led to closure of the trial to enable reporting of all endpoints with minimum 2 years follow-up.

Governance

The trial was approved by Central London Research Ethics Committee 4 (10/H0715/48), sponsored by The Royal Marsden NHS Foundation Trust and conducted in accordance with principles of good clinical practice. The Clinical Trials and Statistics Unit at The Institute of Cancer Research coordinated the study and conducted all analyses. The Trial Management Group was overseen by Independent Data Monitoring and Trial Steering Committees (supplementary appendix 3). The study is registered (ISRCTN01483375). The full protocol is available (supplementary appendix 4).

Role of the funder

The funder reviewed and approved the trial design but had no role in collection, analysis or interpretation of data, writing the report or in the decision to submit for publication.

Results

Between 11th February 2011 and 9th October 2015, 276 patients were randomised (138 ST-IMRT; 138 DE-IMRT) from 32 UK centres. Patients' characteristics were balanced between treatment groups (Table 1); 66% had cancer of the larynx and 34% of the hypopharynx; 52% had AJCC stage III disease and 48% had stage IVA/B.

133/138 participants allocated ST-IMRT received 65Gy to PTV1 and 54Gy to PTV2 and 133/138 participants allocated DE-IMRT received 67.2Gy to PTV1 and 56.1Gy to PTV2 according to protocol (Figure 1). Median (min,max) dose to PTV1 was 65.0Gy (34,7,66,1) for ST-IMRT and 67.2Gy (65.0, 74.4) for DE-IMRT and for PTV2 was 54.0Gy (28.8,70.4) for ST-IMRT and 56.1Gy (54.0,63.0) for DE-IMRT. Median time from randomisation to starting radiotherapy was 13 days in both groups. Median duration of radiotherapy was 39 days for ST-IMRT and 37 days for DE-IMRT.

Induction chemotherapy was received by 38% participants (50/137 ST-IMRT; 54/137 DE-IMRT) with six, 73 and 25 patients receiving one, two or three cycles respectively. Taxotere, cisplatin and 5-Fluorouracil (TPF) was the most common schedule (27 ST-IMRT; 26 DE-IMRT), followed by PF (20 ST-IMRT; 21 DE-IMRT). Concomitant chemotherapy was received by 85% participants (116/137 ST-IMRT; 118/138 DE-IMRT) and 88% (206/234) of those completed two cycles of treatment. Chemotherapy was completed with no reductions, no delays and no substitution with carboplatin by 127/234 (54%). . Dose reductions were reported in 24/234 (10%) and chemotherapy delays in 29/234 (12%); 47/234 (20%) had carboplatin substituted for cisplatin on at least one occasion due to renal or auditory toxicity.

At median follow up of 47.9 (IQR 37.5-60.5) months, locoregional failure events were observed in 80/276 (29.0%) patients (38 (27.5%) ST-IMRT; 42 (30.4%) DE-IMRT). There was no evidence of a difference in time to locoregional failure between treatment groups with an adjusted sub-HR of 1.16 (95%CI: 0.74-1.83, p=0.519). The unadjusted sub-HR was 1.18 (95%CI: 0.76-1.82, p=0.464). Cox regression gave similar results (Figure 2A). Two-year LRFFR was 73.4 (95%CI: 65.0-80.2) in the ST-IMRT group and 71.4 (95%CI: 62.8-78.3) in the DE-IMRT group.

There was no evidence of a difference in LODFR with an adjusted HR of 0.75 (95%CI: 0.50-1.11, p=0.154) (unadjusted HR=0.86 (95%CI: 0.58-1.26), p=0.436). Two year LODFR was 64.6% (95%CI: 55.8-72.1) for ST-IMRT and 70.3% (95%CI: 61.7-77.4) for DE-IMRT (Figure 2B).

One hundred and two participants died (55 ST-IMRT; 47 DE-IMRT). There was no evidence of a difference in overall survival: adjusted HR=0.83 (95%CI: 0.55-1.23; p=0.350) (unadjusted HR=0.83, 95%CI: 0.56-1.22, p=0.340). Two-year survival rates were 74.7% (95%CI: 66.4-81.2) for ST-IMRT and 79.1% (95%CI: 71.2-85.1) for DE-IMRT (Figure 2C). Most deaths were due to laryngeal/hypopharyngeal cancer (36 ST-IMRT; 29 DE-IMRT; Supplementary Table 1).

Following treatment 191/261 (73%) participants had a complete response at the primary site (98/131 (75%) ST-IMRT; 93/130 (72%) DE-IMRT). Tumour recurrence at the primary site only was observed in 25/276 (9.1%) participants (16/138 (11.6%) ST-IMRT; 9/138 (6.5%) DE-IMRT); in the neck only in 15/276 (5.4%) participants (4/138 (2.9%) ST-IMRT; 11/138 (8.0%) DE-IMRT) and in the primary site and neck in 10/276 (3.6%) (7/138 (5.1%) ST-IMRT; 3/138 (2.2%) DE-IMRT). Distant recurrences were reported in 29/276 (10.5%) participants (17 ST-IMRT; 12 DE-IMRT) with 24 (14 ST-IMRT; 10 DE-IMRT) of these in the lung.

Forty-three participants (18 ST-IMRT; 25 DE-IMRT) had 47 (20 ST-IMRT; 27 DE-IMRT) surgical procedures for recurrence or known/suspected residual disease and 12 participants (7 ST-IMRT; 5 DE-IMRT) had 15 surgical procedures for other reasons (supplementary table 2). The larynx was preserved in 124 (89.9%) and 125 (90.6%) of ST-IMRT and DE-IMRT patients, respectively.

There were no statistically significant differences in worst acute any grade or grade ≥3 toxicity (Table 2). Grade 4 acute events were rare: one dermatitis (DE-IMRT), one pharyngeal dysphagia (DE-IMRT) and one oesophageal dysphagia (ST-IMRT). Pharyngeal dysphagia was the most common grade≥3 acute toxicity reported in 64.9% ST-IMRT and 71.1% DE-IMRT patients. Grade≥3 acute pharyngeal mucositis was reported in 53.7% ST-IMRT and 54.1% DE-IMRT patients although grade 2 events were reported in a further 32.1% ST-IMRT and 41.5% DE-IMRT patients.

Two years after radiotherapy, there were no differences in late radiation toxicity between treatment groups (Tables 3-4, Supplementary figures 1-2). Pharyngeal dysphagia was common with 43.1% ST-IMRT and 39.5% DE-IMRT patients reporting grade≥1 events; grade≥3 events were infrequent: 8.3% ST-IMRT and 4.0% DE-IMRT. Grade≥1 oesophageal dysphagia occurred in 27.8% ST-IMRT and 29.0% DE-IMRT patients. A higher proportion of DE-IMRT patients had grade≥3 voice alteration 8.6% versus 1.5% ST-IMRT, although this was not statistically significant.

The lowest overall quality of life scores were reported at the end of radiotherapy and were similar in both groups (Supplementary Table 3). This deterioration in overall quality of life had improved by 6 months and remained stable to 2 years but scores did not return to baseline levels (Figure 3A). There was no clinically or statistically significant difference in change scores between groups at end of radiotherapy (p=0.543) or 2 years (p=0.995). Patient reported swallowing function was also at its worst at the end of radiotherapy (Supplementary Table 4). Consistently worse problems with swallowing, dry mouth and speech problems were reported in the DE-IMRT group (Figure 3 B-D), although there was no evidence of statistically significant differences between treatment groups. In both treatment groups, dry mouth scores never recovered to baseline levels.

Discussion

Prior to this trial we had performed a non-randomised pilot study which suggested that a ~10% increase in radiation dose (based on log cell kill) increased local control by 16% (HR 0.5 95%CI: 0.2-1.3) without significant effect on late radiation toxicities[6,7]. However, when this approach was tested in our current randomised trial, we found no benefit in local control or survival outcomes with DE-IMRT. In our trial, absolute difference in dose between the two randomised arms was 4.12 Gy and the reduction in treatment time was 3 days. We had thought that this increase in total dose and shortening of the treatment duration (acceleration) would be sufficient to improve outcome, but this was not observed in our trial. Instead, we have demonstrated that the modest increase in total dose by acceleration did not improve tumour related outcomes. Whilst there was no evidence of a difference in severe (grade ≥3) acute or late toxicity, acute grade ≥2 pharyngeal mucositis was reported more frequently with DE-IMRT than ST-IMRT suggesting that the experimental arm was more active in fast responding tissues..

Since the 1990s, chemo-radiotherapy has been offered to patients as an alternative to laryngectomy and tracheostomy in the treatment of locally-advanced laryngeal and hypopharyngeal cancers. Laryngeal preservation rates >60% have been demonstrated with induction chemotherapy followed by radiotherapy[1,11] or concurrent chemoradiotherapy,[1-3,12,13] however there has been no improvement in overall survival.

More recently, strategies for dose-intensification of radiotherapy have been investigated, by delivering: (i) a higher total dose over the same period of time (hyperfractionation) (ii) the same total dose in a shorter period of time (acceleration) or (iii) a smaller total dose over a very short period (acceleration with reduced dose). Two meta-analyses have demonstrated an improvement in survival with these strategies, particularly hyperfractionation.[12, 13] Hyperfractionated treatments have not been implemented into routine clinical practice in the UK (or elsewhere) because of resource limitations and development of altered hypofractionated accelerated schedules has been limited by concerns about the volumes of normal tissues irradiated to a high dose, resulting in late side effects.

IMRT delivers radiation in a much more conformal way, thus reducing the volumes of normal tissues receiving high radiation dose.[5]

Overall survival and local control rates in ART DECO compared favourably to outcomes reported in seven phase 3 trials of hyperfractionation with chemotherapy published to date (Table 5)[14-21], with 2-year overall survival rates of 79.1% for DE-IMRT and 74.7% for ST-IMRT. This may be due to greater use of concomitant chemoradiation (86.6% participants in ART DECO), and/or technical improvements in target volume coverage by the high radiation dose delivered by IMRT. ARTDECO therefore provides a contemporaneous benchmark for the outcomes of patient treated with state of the art chemo-radiotherapy using IMRT.

A limitation of our study is the heterogeneous group of patients included with 38% receiving induction chemotherapy and 13% radiotherapy alone, however this was balanced by treatment group and therefore was unlikely to impact on results. Although 85% of our participants received concurrent chemotherapy there was a substitution of cisplatin for carboplatin in 20%, and either delay in chemotherapy or dose reduction in others. This reflects real world practice and is unlikely to have affected the main conclusions of the trial.

The results from the RTOG 91-11 trial [22] highlighted the possibility that non-cancer deaths may be caused by swallowing dysfunction and subsequent complications such as aspiration pneumonia. This has led to a better appreciation of the importance of dysphagia aspiration-related structures (DARS).[23-25] In oropharyngeal cancer, prospective data have shown promising results with the use of dose constraints to these structures [26] and this approach is being evaluated in a UK randomised phase III trial.[27] However, this technique may be more difficult to apply to laryngeal cancers as the organs at risk that ensure a safe swallow (e.g. supraglottic and glottic larynx) are included in the

treatment target volume. In both arms of our trial, the entire larynx/hypopharynx was irradiated using an anatomical CTV. In the future, volumetrically designed smaller target volumes may result in further toxicity reduction.

In the past, patients with stage III/IV disease might progress and succumb to their disease before the development of late toxicity. However, our study suggests that state of the art chemoradiotherapy has a high local tumour control rate, and the proportion of patients developing metastatic disease is low. Furthermore, that this moderately hypofractionated dose with IMRT is feasible and may achieve similar outcomes to hyperfractionated regimens, without unacceptable late toxicities. In addition, we would argue that this approach is deliverable in clinical practice without added time and economic pressure. The updated American Society of Clinical Oncology (ASCO) guidelines [28] reflect the understanding that, for some patients with extensive T3 or large T4a lesions and/or poor pre-treatment laryngeal function, better survival rates and quality of life may be achieved with total laryngectomy rather than with organ-preservation approaches and may be the preferred approach. Our study stipulated that patients where the local investigator determined organ preservation was not feasible should not be enrolled and this may partly explain the higher survival outcomes compared to other phase III trials.In patients where organ-preservation is appropriate, the question remains as to the preferred approach to treatment intensification: acceleration, hyperfractionation, hypofractionation or acceleration and hypofractionation, with or without chemotherapy. The added advantage of a shorter treatment time, which is beneficial for both patients in terms of time and cost and for reducing pressure on radiotherapy services, should not be underestimated. The use of geometric target volume delineation with dose constraints for dysphagia aspiration related structures may reduce the toxicity profile. The incorporation of novel targeted therapies to standard chemoradiation and the stringent use of dose constraints to swallowing structures may offer potential for improvement in survival and morbidity outcomes.

Conclusion

Rates of severe (grade ≥3) acute and late toxicities were similar for DE-IMRT and ST-IMRT. Dose-escalated IMRT did not improve locoregional control.

[3226 words]

Contributors

CN is the ART DECO trial Chief Investigator and EH is the methodological lead. Both led study design and acquired funding for the trial. CN, PS, BF, MB, AS, NP, TGU, MS, MR, KW, SR, EJ, AC, TR, CS, DB, VC, ME, SF, DG, KH, HM, AM, JM, DGa, CW and EH are members of the ART DECO

Trial Management Group which contributed to study design, was responsible for oversight throughout the trial and contributed to data interpretation and manuscript preparation. DB and DG responsible for the RTTQA and collecting the Plan Assessment Forms with details of radiotherapy dose planned and delivered. CN, PS, BF, MB, AS, NP, TGU, MS, WS, MR, KW, SR, EJ, AC, TR, CS, SB were involved in recruitment and treatment of participants and contributed to data collection and manuscript preparation. EH oversaw statistical analyses and was responsible for central management of the trial at ICR-CTSU, with ME's support. DGa conducted central study management at ICR-CTSU and contributed to data acquisition, interpretation and manuscript writing. JM and CG conducted statistical analyses at ICR-CTSU and contributed to data interpretation. CG responsible for manuscript preparation. All authors reviewed and approved the manuscript.

Declaration of interests

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Data sharing statement

The ICR-CTSU supports the wider dissemination of information from the research it conducts, and increased cooperation between investigators. Trial data is collected, managed, stored, shared and archived according to ICR-CTSU Standard Operating Procedures in order to ensure the enduring quality, integrity and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements.

Data recipients are required to enter a formal data sharing agreement which describes the conditions for release and requirements for data transfer, storage, archiving, publication and Intellectual Property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations including patient consent. Data sharing is undertaken if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee as required. Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymizing identifiable patient data.

REFERENCES

1. Department of Veterans Affairs Laryngeal Cancer Study G, Wolf GT, Fisher SG, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med. 1991;324(24):1685-90.
2. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349(22):2091-8.
3. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet. 2000;355(9208):949-55.
4. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst. 1996;88(13):890-9.
5. Clark CH, Bidmead AM, Mubata CD, Harrington KJ, Nutting CM. Intensity-modulated radiotherapy improves target coverage, spinal cord sparing and allows dose escalation in patients with locally advanced cancer of the larynx. Radiother Oncol. 2004;70(2):189-98.
6. Guerrero Urbano T, Clark CH, Hansen VN, et al. A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer. Radiother Oncol. 2007;85(1):36-41.
7. Gujral DM, Miah AB, Bodla S, et al. Final long-term results of a phase I/II study of dose-escalated intensity-modulated radiotherapy for locally advanced laryngo-hypopharyngeal cancers. Oral Oncol. 2014;50(11):1089-97.
8. Bentzen SM. Radiobiological considerations in the design of clinical trials. Radiother Oncol. 1994;32(1):1-11.
9. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys. 2000;48(1):7-16.
10. Maciejewski B, Skladowski K, Pilecki B, et al. Randomized clinical trial on accelerated 7 days per week fractionation in radiotherapy for head and neck cancer. Preliminary report on acute toxicity. Radiother Oncol. 1996;40(2):137-45.
11. Janoray G, Pointreau Y, Garaud P, et al. Long-term Results of a Multicenter Randomized Phase III Trial of Induction Chemotherapy With Cisplatin, 5-fluorouracil, +/- Docetaxel for Larynx Preservation. J Natl Cancer Inst. 2016;108(4).
12. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet. 2006;368(9538):843-54.
13. Lacas B, Bourhis J, Overgaard J, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. Lancet Oncol. 2017;18(9):1221-37.
14. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med. 1998;338(25):1798-804.
15. Dobrowsky W, Naude J. Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. Radiother Oncol. 2000;57(2):119-24.
16. Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol. 2000;18(7):1458-64.
17. Budach V, Stuschke M, Budach W, et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 Prospective Randomized Trial. J Clin Oncol. 2005;23(6):1125-35.
18. Budach V, Stromberger C, Poettgen C, et al. Hyperfractionated accelerated radiation therapy (HART) of 70.6 Gy with concurrent 5-FU/Mitomycin C is superior to HART of 77.6 Gy alone in locally advanced head and neck cancer: long-term results of the ARO 95-06 randomized phase III trial. Int J Radiat Oncol Biol Phys. 2015;91(5):916-24.

19. Bensadoun RJ, Benezery K, Dassonville O, et al. French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: Results at 2 years (FNCLCC-GORTEC). Int J Radiat Oncol Biol Phys. 2006;64(4):983-94.
20. Ghadjar P, Simcock M, Studer G, et al. Concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer: 10-year follow-up of a randomized phase III trial (SAKK 10/94). Int J Radiat Oncol Biol Phys. 2012;82(2):524-31.
21. Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol. 2012;13(2):145-53.
22. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol. 2013;31(7):845-52.
23. Eisbruch A, Schwartz M, Rasch C, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys. 2004;60(5):1425-39.
24. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys. 2007;68(5):1289-98.
25. Levendag PC, Teguh DN, Voet P, 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. Radiother Oncol. 2007;85(1):64-73.
26. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol. 2010;28(16):2732-8.
27. Petkar I, Rooney K, Roe JW, 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;16(1):770.
28. Forastiere AA, Ismaila N, Lewin JS, et al. Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2018;36(11):1143-69.

Table 1 Patient and tumour characteristics at baseline

	ST-IMRT (N = 138)		DE-IMRT (N = 138)		Total (N = 276)	
	n	%	n	%	n	%
Site of tumour*						
Larynx	91	65.9	92	66.7	183	66.3
Hypopharynx	47	34.1	46	33.3	93	33.7
Nodal status*						
N0-2	135	97.8	135	97.8	270	97.8
N3	3	2.2	3	2.2	6	2.2
Intended chemotherapy*						
Induction and concomitant chemotherapy	52	37.7	54	39.1	106	38.4
Concomitant chemotherapy only	67	48.6	66	47.8	133	48.2
No chemotherapy	19	13.8	18	13.0	37	13.4
Sex						
Male	119	86.2	114	82.6	233	84.4
Female	19	13.8	24	17.4	43	15.6
Age at randomisation						
<50	10	7.2	18	13.0	28	10.1
50-59	36	26.1	46	33.3	82	29.7
60-69	68	49.3	58	42.0	126	45.7
≥70	24	17.4	16	11.6	40	14.5
Median	63.1		61.1		62.4	
IQR	57.1-68.1		55.2-66.9		56.3-67.3	
Range	40.1-82.8		39.0-85.3		39.0-85.3	
Side of tumour						
Left	71	51.8	68	49.3	139	50.6
Right	58	42.3	64	46.4	122	44.4
Bilateral	8	5.8	6	4.4	14	5.0
Data not available	*1*		*0*		*1*	
T-stage						
T1	5	3.7	3	2.2	8	2.9
T2	19	13.9	23	16.7	42	15.3
T3	83	60.6	82	59.4	165	60.0
T4a	27	19.7	24	17.4	51	18.6
T4b	3	2.2	6	4.4	9	3.3
Data not available	*1*		*0*		*1*	
N-Stage						
N0	69	50.4	60	4.5	129	46.9
N1	17	12.4	19	13.8	36	13.1
N2X	2	1.5	1	0.7	3	1.1
N2a	1	0.7	0	0	1	0.4
N2b	31	22.6	41	29.7	72	26.2
N2c	14	10.2	14	10.1	28	10.2
N3	3	2.2	3	2.2	6	2.2
Data not available	*1*		*0*		*1*	
AJCC stage						
III	70	51.1	72	52.2	142	51.6
IVA	62	45.3	57	41.3	119	43.3
IVB	5	3.7	9	6.5	14	5.1
Data not available	*1*		*0*		*1*	

* Used as balancing factors for minimisation. TNM 7th Edition

Table 2 Maximum grade of acute CTCAE toxicity reported during and up to 8 weeks after radiotherapy

Toxicity	N	Grade 1		Grade 2		Grade 3		Grade 4		Any grade		Grade ≥3	
		n	%	n	%	n	%	n	%	n	%	n	%
Inner ear/hearing													
ST-IMRT	129	44	*34.1*	12	*9.3*	6	*4.7*	0	*0.0*	62	*48.1*	6	*4.7*
DE-IMRT	126	46	*36.5*	20	*15.9*	1	*0.8*	0	*0.0*	67	*53.2*	1	*0.8*
Total	255	90	*35.3*	32	*12.6*	7	*2.8*	0	*0.0*	129	*50.6*	7	*2.8*
P-value											*0.414*		*0.120**
Radiation dermatitis													
ST-IMRT	134	19	*14.2*	67	*50.0*	46	*34.3*	0	*0.0*	132	*98.5*	46	*34.3*
DE-IMRT	135	11	*8.2*	64	*47.4*	59	*43.7*	1	*0.7*	135	*100.0*	60	*44.4*
Total	269	30	*11.2*	131	*48.7*	105	*39.0*	1	*0.4*	267	*99.3*	106	*39.4*
P-value											*0.154*		*0.090*
Alopecia													
ST-IMRT	134	52	*38.8*	42	*31.3*	0	*0.0*	0	*0.0*	94	*70.2*	0	*0*
DE-IMRT	135	56	*41.5*	34	*25.2*	0	*0.0*	0	*0.0*	90	*66.7*	0	*0*
Total	269	108	*40.2*	76	*28.3*	0	*0.0*	0	*0.0*	184	*68.4*	0	*0*
P-value											*0.539*		*-*
Oral mucositis													
ST-IMRT	134	21	*15.7*	49	*36.6*	47	*35.1*	0	*0.0*	117	*87.3*	47	*35.1*
DE-IMRT	135	17	*12.6*	48	*35.6*	55	*40.7*	0	*0.0*	120	*88.9*	55	*40.7*
Total	269	38	*14.1*	97	*36.1*	102	*37.9*	0	*0.0*	237	*88.1*	102	*37.9*
P-value											*0.690*		*0.338*
Pharyngeal mucositis													
ST-IMRT	134	13	*9.7*	43	*32.1*	72	*53.7*	0	*0.0*	128	*95.5*	72	*53.7*
DE-IMRT	135	6	*4.4*	56	*41.5*	73	*54.1*	0	*0.0*	135	*100.0*	73	*54.1*
Total	269	19	*7.1*	99	*36.8*	145	*53.9*	0	*0.0*	263	*97.7*	145	*53.9*
P-value											*0.013*		*0.955*
Oesophageal dysphagia													
ST-IMRT	134	12	*9.0*	33	*24.6*	73	*54.5*	1	*0.8*	119	*88.8*	74	*55.2*
DE-IMRT	135	7	*5.2*	29	*21.5*	83	*61.5*	0	*0.0*	119	*88.8*	83	*61.5*
Total	269	19	*7.1*	62	*23.1*	156	*58.0*	1	*0.4*	238	*88.5*	157	*58.4*
P-value											*0.866*		*0.298*
Pharyngeal dysphagia													
ST-IMRT	134	8	*6.0*	36	*26.9*	87	*64.9*	0	*0.0*	131	*97.8*	87	*64.9*
DE-IMRT	135	8	*5.9*	29	*21.5*	95	*70.4*	1	*0.7*	133	*98.5*	96	*71.1*
Total	269	16	*6.0*	65	*24.2*	182	*67.7*	1	*0.4*	264	*98.1*	183	*68.0*
P-value											*0.646*		*0.277*
Laryngeal inflammation													
ST-IMRT	133	23	*17.3*	78	*58.7*	23	*17.3*	0	*0.0*	124	*93.2*	23	*17.3*
DE-IMRT	133	23	*17.3*	78	*58.7*	26	*19.6*	0	*0.0*	127	*95.5*	26	*19.6*
Total	266	46	*17.3*	156	*58.7*	49	*18.4*	0	*0.0*	251	*94.4*	49	*18.4*
P-value											*0.425*		*0.635*
Mouth dryness													
ST-IMRT	134	31	*23.1*	79	*59.0*	18	*13.4*	0	*0.0*	128	*95.5*	18	*13.4*
DE-IMRT	135	31	*23.0*	73	*54.1*	26	*19.3*	0	*0.0*	130	*96.3*	26	*19.3*
Total	269	62	*23.1*	152	*56.5*	44	*16.4*	0	*0.0*	258	*95.9*	44	*16.4*
P-value											*0.749*		*0.196*
Salivary gland inflammation													
ST-IMRT	134	30	*22.4*	77	*57.5*	7	*5.2*	0	*0.0*	114	*85.1*	7	*5.2*
DE-IMRT	135	23	*17.0*	79	*58.5*	16	*11.9*	0	*0.0*	118	*87.4*	16	*11.9*

Toxicity	N	Grade 1		Grade 2		Grade 3		Grade 4		Any grade		Grade ≥3	
		n	%	n	%	n	%	n	%	n	%	n	%
Total	269	53	*19.7*	156	*58.0*	23	*8.6*	0	*0.0*	232	*86.3*	23	*8.6*
P-value											*0.579*		*0.052*
Fatigue													
ST-IMRT	134	33	*24.5*	77	*57.5*	22	*16.4*	0	*0.0*	132	*98.5*	22	*16.4*
DE-IMRT	135	24	*17.8*	87	*64.4*	22	*16.3*	0	*0.0*	133	*98.5*	22	*16.3*
Total	269	57	*21.2*	164	*61.0*	44	*16.4*	0	*0.0*	265	*98.5*	44	*16.4*
P-value											*0.994*		*0.978*
Pain due to radiation													
ST-IMRT	134	10	*7.5*	74	*55.2*	48	*35.8*	0	*0.0*	132	*98.5*	48	*35.8*
DE-IMRT	135	12	*8.9*	67	*49.6*	55	*40.7*	0	*0.0*	134	*99.3*	55	*40.7*
Total	269	22	*8.2*	141	*52.4*	103	*38.3*	0	*0.0*	266	*98.9*	10	*38.3*
P-value											*0.557*		*0.407*
Weight													
ST-IMRT	134	47	*35.1*	65	*48.5*	6	*4.5*	0	*0.0*	118	*88.1*	6	*4.5*
DE-IMRT	135	54	*40.0*	66	*48.9*	7	*5.2*	0	*0.0*	127	*94.1*	7	*5.2*
Total	269	101	*37.6*	131	*48.7*	13	*4.8*	0	*0.0*	245	*91.1*	13	*4.8*
P-value											*0.084*		*0.787*

The proportion of patients experiencing any grade and the proportion experiencing grade 3 or 4 toxicity is compared using a Chi-square test (or Fisher's Exact test if fewer than 5 patients in either treatment group experienced the toxicity of interest, indicated with an asterisk)

Table 3 CTCAE toxicity reported at 2 year follow-up

Toxicity	N	Grade 1		Grade 2		Grade 3		Grade 4		Any grade		Grade ≥3	
		n	%	n	%	n	%	n	%	n	%	n	%
Inner ear/hearing													
ST-IMRT	71	11	*15.5*	4	*5.6*	10	*14.3*	*0*	0.0	25	*35.2*	10	*14.1*
DE-IMRT	69	10	*14.5*	5	*7.3*	7	*10.1*	*0*	0.0	22	*31.9*	7	*10.1*
Total	140	21	*15.0*	9	*6.4*	17	*12.1*	*0*	0.0	47	*33.6*	17	*12.1*
P-value											*0.677*		*0.476*
Skin changes (telangiectasia)													
ST-IMRT	72	11	*15.3*	1	*1.4*	0	*0.0*	*0*	0.0	12	*16.7*	0	*0*
DE-IMRT	70	18	*25.7*	1	*1.4*	0	*0.0*	*0*	0.0	19	*27.1*	0	*0*
Total	142	29	*20.4*	2	*1.4*	0	*0.0*	*0*	0.0	31	*21.8*	0	*0*
P-value											*0.131*		*-*
Subcutaneous tissue (fibrosis)													
ST-IMRT	72	13	*18.1*	5	*6.9*	0	*0.0*	*0*	0.0	18	*25.0*	0	*0*
DE-IMRT	69	20	*29.0*	5	*7.3*	1	*1.5*	*0*	0.0	26	*37.7*	1	*1.5*
Total	141	33	*23.4*	10	*7.1*	1	*0.7*	*0*	0.0	44	*31.2*	1	*0.7*
P-value											*0.104*		*0.489**
Oesophageal dysphagia													
ST-IMRT	72	11	*15.3*	3	*4.2*	5	*6.9*	*1*	1.4	20	*27.8*	6	*8.3*
DE-IMRT	76	15	*19.7*	4	*5.3*	3	*4.0*	*0*	0.0	22	*29.0*	3	*4.0*
Total	148	26	*17.6*	7	*4.7*	8	*5.4*	*1*	0.7	42	*28.4*	9	*6.1*
P-value											*0.875*		*0.318**
Pharyngeal dysphagia													
ST-IMRT	72	20	*27.8*	5	*6.9*	5	*6.9*	*1*	1.4	31	*43.1*	6	*8.3*
DE-IMRT	76	20	*26.3*	7	*9.2*	2	*2.6*	*1*	1.3	30	*39.5*	3	*4.0*
Total	148	40	*27.0*	12	*8.1*	7	*4.7*	*2*	1.4	61	*41.8*	9	*6.1*
P-value											*0.658*		*0.318**
Voice alteration													
ST-IMRT	68	32	*47.1*	9	*13.2*	1	*1.5*	*0*	0.0	42	*61.8*	1	*1.5*
DE-IMRT	70	28	*40.0*	11	*15.7*	6	*8.6*	*0*	0.0	45	*64.3*	6	*8.6*
Total	138	60	*43.5*	20	*14.5*	7	*5.1*	*0*	0.0	87	*63.0*	7	*5.1*
P-value											*0.759*		*0.116**
Laryngeal oedema													
ST-IMRT	66	17	*25.8*	1	*1.5*	2	*3.0*	*0*	0.0	20	*30.3*	2	*3.0*
DE-IMRT	72	21	*29.2*	3	*4.2*	1	*1.4*	*1*	1.4	26	*36.1*	2	*2.8*
Total	138	38	*27.5*	4	*2.9*	3	*2.2*	*1*	0.7	46	*33.3*	4	*2.9*
P-value											*0.470*		*0.999**
Mouth dryness													
ST-IMRT	72	26	*36.1*	15	*20.8*	2	*2.8*	*0*	0.0	43	*59.7*	2	*2.8*
DE-IMRT	71	30	*42.3*	14	*19.7*	0	*0.0*	*0*	0.0	44	*62.0*	0	*0*
Total	143	56	*39.2*	29	*20.3*	2	*1.4*	*0*	0.0	87	*60.8*	2	*1.4*
P-value											*0.783*		*0.497**
Weight (grade loss)													
ST-IMRT	69	9	*13.0*	4	*5.8*	0	*0.0*	*0*	0.0	13	*18.8*	0	*0*
DE-IMRT	69	14	*20.3*	2	*2.9*	2	*2.9*	*0*	0.0	18	*26.1*	2	*2.9*
Total	138	23	*16.7*	6	*4.4*	2	*1.5*	*0*	0.0	31	*22.5*	2	*0.5*
P-value											*0.308*		*0.496**

Toxicity	N	Grade 1		Grade 2		Grade 3		Grade 4		Any grade		Grade ≥3	
		n	*%*	n	*%*	n	*%*	n	%	n	*%*	n	*%*
Mandible (osteonecrosis of the jaw)													
ST-IMRT	73	1	*1.4*	1	*1.4*	1	*1.4*	*0*	0.0	3	*4.1*	1	*1.4*
DE-IMRT	76	2	*2.6*	0	*0.0*	0	*0.0*	*0*	0.0	2	*2.6*	0	*0*
Total	149	3	*2.0*	1	*0.7*	1	*0.7*	*0*	0.0	5	*3.4*	1	*0.7*
P-value											*0.677**		*0.490**
Laryngo-pharyngeal pain													
ST-IMRT	72	5	*6.9*	2	*2.8*	1	*1.4*	*0*	0.0	8	*11.1*	1	*1.4*
DE-IMRT	73	6	*8.2*	0	*0.0*	0	*0.0*	*0*	0.0	6	*8.2*	0	*0.0*
Total	144	11	*7.6*	2	*1.4*	1	*0.7*	*0*	0.0	14	*9.7*	1	*0.7*
P-value											*0.556*		*0.497**

The proportion of patients experiencing any grade and the proportion experiencing grade 3 or 4 toxicity is compared using a Chi-square test (or Fisher's Exact test if fewer than 5 patients in either treatment group experienced the toxicity of interest, indicated with an asterisk)

Table 4 LENTSOM toxicity reported at 2 year follow-up

Toxicity	N	Grade 1		Grade 2		Grade 3		Grade 4		Any grade		Grade ≥3	
		n	%	n	%	n	%	n	%	n	%	n	%
Mucosa-oral pharyngeal													
ST-IMRT	71	24	*33.8*	6	*8.5*	8	*11.3*	*3*	4.2	41	*57.8*	11	*15.5*
DE-IMRT	75	28	*37.3*	12	*16.0*	7	*9.3*	*5*	6.7	52	*69.3*	12	*16.0*
Total	146	52	*35.6*	18	*12.3*	15	*10.3*	*8*	5.5	93	*63.7*	23	*15.8*
P-value											*0.170*		*0.933*
Oesophagus													
ST-IMRT	71	12	*16.9*	9	*12.7*	3	*4.2*	*2*	2.8	26	*36.6*	5	*7.0*
DE-IMRT	76	17	*22.4*	10	*13.2*	3	*4.0*	*1*	1.3	31	*40.8*	4	*5.3*
Total	147	29	*19.7*	19	*12.9*	6	*4.1*	*3*	2.0	57	*38.8*	9	*6.1*
P-value											*0.604*		*0.739**
Larynx													
ST-IMRT	69	32	*46.4*	16	*23.2*	7	*10.1*	*0*	0	55	*79.7*	7	*10.1*
DE-IMRT	73	30	*41.1*	13	*17.8*	6	*8.2*	*4*	5.5	53	*72.6*	10	*13.7*
Total	142	62	*43.7*	29	*20.4*	13	*9.2*	*4*	2.8	108	*76.1*	17	*12.0*
P-value											*0.321*		*0.514*
Skin													
ST-IMRT	71	17	*23.9*	10	*14.1*	4	*5.6*	*0*	0.0	31	*43.7*	4	*5.6*
DE-IMRT	74	29	*39.2*	6	*8.1*	7	*9.5*	*0*	0.0	42	*56.8*	7	*9.5*
Total	145	46	*31.7*	16	*11.0*	11	*7.6*	*0*	0.0	73	*50.3*	11	*7.6*
P-value											*0.115*		*0.534**
Ear													
ST-IMRT	71	14	*19.7*	4	*5.6*	11	*15.5*	*1*	1.4	30	*42.3*	12	*16.9*
DE-IMRT	73	15	*20.6*	3	*4.1*	12	*16.4*	*0*	0.0	30	*41.1*	12	*16.4*
Total	144	29	*20.1*	7	*4.9*	23	*16.0*	*1*	0.7	60	*41.7*	24	*16.7*
P-value											*0.888*		*0.941*
Salivary gland													
ST-IMRT	70	18	25.7	12	*17.1*	11	*15.7*	*1*	1.4	42	*60.0*	12	*17.1*
DE-IMRT	73	25	34.3	21	*28.8*	4	*5.5*	*0*	0.0	50	*68.5*	4	*5.5*
Total	143	43	30.1	33	*23.1*	15	*10.5*	*1*	0.7	92	*64.3*	16	*11.2*
P-value											*0.289*		*0.034**
Spinal cord													
ST-IMRT	71	4	*5.6*	2	*2.8*	0	*0.0*	*0*	0.0	6	*8.5*	0	*0*
DE-IMRT	74	7	*9.5*	1	*1.4*	0	*0.0*	*0*	0.0	8	*10.8*	0	*0*
Total	145	11	*7.6*	3	*2.1*	0	*0.0*	*0*	0.0	14	*9.7*	0	*0*
P-value											*0.631*		*-*
Mandible													
ST-IMRT	71	5	*7.0*	2	*2.8*	2	*2.8*	*0*	0.0	9	*12.7*	2	*2.8*
DE-IMRT	74	1	*1.4*	6	*8.1*	1	*1.4*	*1*	1.4	9	*12.2*	2	*2.7*
Total	145	6	*4.1*	8	*5.5*	3	*2.1*	*1*	0.7	18	*12.4*	4	*2.8*
P-value											*0.925*		*0.999**
Teeth													
ST-IMRT	69	2	*2.9*	1	*1.5*	1	*1.5*	*1*	1.5	5	*7.3*	2	*2.9*
DE-IMRT	73	3	*4.1*	2	*2.7*	0	*0.0*	*0*	0.0	5	*6.9*	0	*0*
Total	142	5	*3.5*	3	*2.1*	1	*0.7*	*1*	0.7	10	*7.0*	2	*1.4*
P-value											*0.926*		*0.234**

The proportion of patients experiencing any grade and the proportion experiencing grade 3 or 4 toxicity is compared using a Chi-square test (or Fisher's Exact test if fewer than 5 patients in either treatment group experienced the toxicity of interest, indicated with an asterisk)

Table 5 Comparison of outcomes to randomised trials of chemotherapy and hyperfractionation

Study	Stage	Site	Locoregional control	Progression-free survival	Overall survival
Brizel 1998 [15] (N=56)	IV = 44% III = 56%	Oropharynx = 41% Larynx = 18% Hypopharynx = 23% *Other = 17%	10 yr = 40%	3 yr = 61%	3 yr = 55%
Dubrowsky 2000 [16] (N=80)	IV = 59% III = 26% II = 15%	Oropharynx = 38% Larynx = 14% Hypopharynx = 18% Other = 30%	4 yr = 48%	NR	2 yr = 40%
Jeremic 2000 [17] (N=65)	IV = 57% III = 43%	Oropharynx = 38% Larynx = 15% Hypopharynx = 15% Other = 32%	5 yr = 50%	5 yr = 46%	5 yr = 46%
Budach 2005, 2015 [18,19] (N=190)	IV = 93.7% III = 6.3%	Oropharynx = 57.4% Larynx = 32.6% Oral cavity = 10%	5 yr = 49.9% 10 yr = 38%	5 yr = 29.3% 10 yr = 25%	5 yr = 28.6% 10 yr = 10%
Bensadoun 2006 [20] (N=81)	IV = 65% III = 35%	Oropharynx = 75% Hypopharynx = 25%	2 yr = 59%	2 yr = 48.2%	2 yr = 37.8%
Ghadjar 2012 [21] (N=112)	IV = 71% III = 28%	Oropharynx = 53% Larynx = 16% Hypopharynx = 25% Oral cavity = 6%	10 yr = 40%	10 yr = 17%	10 yr = 28%
Bourhis 2012 [22] (N=280)	IV = 55% III = 45%	Oropharynx = 66% Larynx = 6% Hypopharynx = 17% Oral cavity = 11%	3 yr = 45.4%	3 yr = 34.1%	3 yr = 39.4%
ART DECO DE-IMRT (N=138)	IV = 48% III = 52%	Larynx = 66% Hypopharynx = 34%	2 yr = 74.7%	2 yr = NR	2 yr = 79.1%

*Other – paranasal sinus, nasopharynx, oral cavity