Evaluation of radiotherapy techniques for radical treatment of lateralised oropharyngeal cancers: Dosimetry and NTCP

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Zusammenfassung:

Ziel:

Das Ziel dieser Studie ist die Untersuchung potenzieller Vor- und Nachteile verschiedener moderner Bestrahlungstechniken für die ipsilaterale Bestrahlung von Oropharynx-Tumoren hinsichtlich der resultierenden Dosisverteilung im Planungszielvolumen (PTV), den Risikoorganen (OARs) und der Komplikationswahrscheinlichkeit in Normalgeweben (NTCP). Im Rahmen dieser Analyse wird die dreidimensionale, konformale Strahlentherapie (3DCRT), die intensitätsmodulierte Strahlentherapie (IMRT) in Step-and-Shoot Technik und die intensitätsmodulierten Rotationstherapie (volumetric arc, VMAT) verglichen.

Materialen und Methoden:

Im Rahmen einer Planungsstudie für die Primärtherapie unterschiedlicher Fälle von streng unilateralen Oropharynx-Tumoren wurden Dosisverteilungen von 3DCRT, IMRT und VMAT anhand verschiedener Parameter miteinander verglichen. Hierfür wurden Konformitätsindex (CI), Homogenitätsindex (HI), Dosis-Volumen- Histogramme (DVHs) des PTVs und der OARs, NTCP, Risiko von strahleninduzierten Zweittumoren und die aufsummierte applizierte Gesamtdosis untersucht.

Ergebnisse:

Die Bestrahlungspläne von IMRT und VMAT waren im Bezug auf den CI, HI, die Dosisverteilung im Zielvolumen und im Unterkiefer sowie in der tatsächlich applizierten Dosis der 3DCRT überlegen. Bezüglich der Dosisverteilung, der NTCP der kontralateralen Mundhöhle und des Unterkiefers bei Anwendung einer dedizierten Dosisvolumen-Beschränkung der Mundhöhle konnten keine Unterschiede zwischen den Bestrahlungstechniken festgestellt werden. Obwohl das Niedrigdosis-Volumen bei IMRT und VMAT signifikant höher war als bei 3DCRT, ist das erwartete Risiko strahleninduzierter Zweittumoren abhängig vom verwendeten mathematischen Modell.

Schlussfolgerung:

Die untersuchten IMRT/VMAT Techniken sind der 3DCRT bei der Bestrahlung streng unilateraler oropharyngealer Tumore in Bezug auf die Dosishomogenität, Konformität und konsistenten Bestrahlung des PTV während der gesamten Behandlungsdauer überlegen. Dosimetrie und NTCP Berechnungen zeigen, dass diese Techniken in Bezug auf das Risiko einer akuten Mukositis bei Anwendung einer spezifischen Dosisbeschränkung auf die kontralateralen Mundhöhle äquivalent zu 3DCRT sind.

Abstract

Aim:

The aim of this study was to investigate potential advantages and disadvantages of three-dimensional (3D)-conformal technique (3DCRT), multiple fixed-field intensity-modulated

radiotherapy (referred to as IMRT hereafter) and volumetric modulated arc therapy (VMAT) in terms of dose to the planning target volume (PTV), organs at risk (OARs), and normal tissue complication probability (NTCP) for delivering ipsilateral radiotherapy.

Materials and methods:

We compared 3DCRT, IMRT and VMAT in patients with well-lateralised primary tonsillar cancers who underwent primary radical ipsilateral radiotherapy. The following parameters were compared: conformity index (CI), homogeneity index (HI), dose volumes histograms (DVHs) of PTVs and OARs, normal tissue complication probability (NTCP), risk of radiation induced cancer and dose accumulation during treatment.

Results:

IMRT and VMAT were superior to 3DCRT in terms of CI, HI, dose to the target volumes and mandible and dose accumulation robustness. The techniques were equivalent in terms of dose and NTCP for contralateral oral cavity, contralateral submandibular gland and mandible when specific dose constraint objectives were used on the oral cavity volume. Although the volume of normal tissue exposed to low dose radiation was significantly higher with IMRT and VMAT, the risk of radiation induced second malignancy was dependant on the mathematical model used.

Conclusion:

This study demonstrates the superiority of IMRT/VMAT techniques over 3DCRT in terms of dose homogeneity, conformity and consistent dose delivery to the PTV throughout the course of treatment for patients with lateralised oropharyngeal cancers. Dosimetry and NTCP calculations show that these techniques are equivalent to 3DCRT in regard to the risk of acute mucositis when specific dose constraint objectives were used on a contralateral oral cavity OAR.

Introduction

Radiotherapy to the ipsilateral oropharynx and neck is a well-established treatment technique for patients with well-lateralised tonsillar squamous cell carcinomas [1-6]. An acceptable rate (2-8%) of contralateral nodal recurrence in a carefully selected population is supported by published evidence in the form of single centre retrospective case series [1-6]. The rationale behind using an ipsilateral technique is to achieve sparing of contralateral normal structures; the parotid salivary gland, in particular, reducing the rates of long-term xerostomia and its associated morbidities. This improves quality of life in survivors [5]. In addition, it is presumed that the lower dose is delivered to the contralateral oral cavity and mandible, reduces the rates of acute oral mucositis and mandibular osteoradionecrosis (ORN) [1,2,4].

Two or three ipsilateral wedged fields with (3DCRT) or inverse planning tecniques (IMRT/VMAT) can be used to deliver ipsilateral radiotherapy. In the published studies of ipsilateral radiotherapy, some centres have used 3DCRT [1,4,6], some centres have used (IMRT/VMAT) [2] and some centres historically used 3DCRT and converted to IMRT/VMAT [3]. When treating non-lateralised tumours of the oropharynx, the advantages of IMRT techniques (multiple-field and arc therapy) in sparing parotid gland and constrictor muscles are well proven [7,8]. Such techniques represent the standard of care in the majority of radiotherapy departments. In contrast, there is a lack of evidence to support the use of IMRT/VMAT techniques over 3DCRT when treating well-lateralised oropharyngeal tumours. They use two to three times more monitor units, which results in increased total body dose due to increased radiation leakage. Optimal organ sparing using inverse techniques necessitates the use of more treatment fields, which results in a larger volume of normal tissue exposed to a low radiation dose. These factors can potentially increase the risk of acute radiation toxicity and of radiation-induced malignancies by two-fold compared to

3DCRT [9]. Quantification of predicted NTCP for 3DCRT and IMRT/VMAT will aid the choice of optimal treatment technique in the setting of ipsilateral irradiation.

The specific aim of this study was to demonstrate the potential dosimetric advantages (or at least equivalence) of the IMRT techniques (using precise well defined optimisation) compared to 3DCRT in terms of dose to the PTV, OARs, and NTCP (including risk of second malignancy) for treatment of well-lateralised oropharyngeal SCC, before implementation into clinical practice. The secondary aim was to study the dosimetric effect of volumetric changes during treatment for each of these three techniques.

Materials and Methods

This was a non-interventional retrospective planning study in ten patients with well-lateralised primary tonsillar cancers who underwent primary radical ipsilateral radiotherapy at our institute. The cases selected for this study had well-lateralised SCC of the tonsil (T1/T2, N0-N2b). Tonsillar cancer without involvement of soft palate or base of tongue is defined as "well-lateralised" according to our institutional protocol. All patients had a high risk of metastases or involvement of ipsilateral cervical lymph nodes and therefore required ipsilateral neck irradiation. All patients underwent a diagnostic tonsillectomy prior to radiotherapy, which is standard practice across the majority of centres. Five of the patients were treated with 3DCRT and the remaining cases were treated with VMAT. The variation in treatment technique was as a result of patients being treated at two different locations at our institute. All patients were treated with doses of 65 Gy in 30 fractions (2.17 Gy/fraction) over 6 weeks to the primary target (PTV1). Doses to the elective target (PTV2) were 54 Gy in 30 fractions (1.8 Gy/fraction) over six weeks for VMAT and 50 Gy in 25 fractions (2

Gy/fraction) over five weeks for 3DCRT. Patients with node positive disease and under the age of seventy-one years received platin-based concomitant chemoradiotherapy.

Target volume delineation

All patients were treated in a standard thermoplastic shell. Planning CT scans at 2 mm intervals were obtained. Clinical target volume (CTV) 1 included gross tumour volume (GTV) plus a 1 cm isotropic margin plus ipsilateral level Ib, IIa and any involved lymph nodes. Uninvolved barriers to tumour spread, such as bone and fasciae, were excluded. The elective nodal volume (CTV2) included uninvolved levels III–V and supraclavicular fossa (SCF) nodes ipsilaterally. Delineation was performed according to the consensus guidelines [10,11]. A 3 mm isotropic margin was added to the CTVs to obtain the planning target volumes PTVs [12]. Organ-at-risk (OAR) volumes for spinal cord, brainstem, parotid salivary glands, lenses, optic nerves, and optic chiasm were routinely delineated. In addition, contralateral and ipsilateral mandible, contralateral oral cavity, contralateral sub-mandibular gland (SMG) and posterior fossa were delineated on the CT by an experienced clinical oncologist (SB). The sections of the mandible ipsilateral and contralateral to the side of the tumour, with the mid-line as the medial border were delineated as ipsilateral and contralateral mandible, respectively. The surfaces of the inner table of mandible, tongue, floor of mouth and hard palate with the medial border at mid-line at a distance of 1cm from the PTV were outlined as the contralateral oral cavity. The remaining volume at risk (RVR) was defined as the remaining non-contoured normal tissue. Hippocampal structures were delineated using atlas-based methods [13].

Treatment planning methods

Radiotherapy plans were generated using the Philips Pinnacle3 v9.6 (Philips, Fitchburg, WI) treatment planning system (TPS). IMRT and VMAT plans were retrospectively generated for cases that were initially treated using 3DCRT, and IMRT and 3DCRT plans were produced for patients treated using VMAT.

3DCRT was planned using a single isocentre anterior-oblique and posterior-oblique wedged pair to encompass the CTV1. The Ipsilateral lower neck was treated with a matched anterior and posterior parallel opposed fields. A low weighted lateral beam was typically used together with the wedged-pair in order to ensure the dose within the target remained below 107% of that prescribed. Both IMRT and VMAT plans were optimised by the Pinnacle3 TPS to ensure that the clinical dose objectives were satisfied (Table 1). VMAT plans consisted of partial arcs varying from 90 to 105 control points with 2^{o} control point spacing, optimised using Pinnacle's SmartArc algorithm. The fixed-field IMRT plans consisted of five co-planar beams with a maximum of 50 control points in total. Pinnacle's Direct Machine Parameter Optimisation (DMPO) was used to generate the individual control point shapes and weights of the IMRT plans. PTV ring structures and other 'optimisation' regions of interest (ROIs) (in otherwise non-contoured tissue) were used in VMAT and IMRT inverse planning in order to generate conformal plans with reduced RVR integral dose. VMAT and IMRT plans were further optimised with a constraint of maximum mean dose of 36 Gy (based on average mean dose from the 3DCRT plans, Table 2) on the contralateral oral cavity volume.

Treatment plan evaluation

Coverage of PTVs was evaluated using volume receiving 95% of the prescribed dose (V_{95}); and dose distribution to PTV1 was further evaluated using the Paddick conformity index (CI) and the homogeneity index (HI). CI was defined as, $CI = ([TV(PIV)]^2)/[TV*V(RI)]$, where

TV(PIV), TV, and V(RI) are the volumes of the target covered by the 95% isodose, the target volume, and the total volume covered by the 95% isodose [11]. Perfectly conformal plans have CI = 1, whilst smaller CI values correspond to less conformal dose distributions. HI was defined as, HI = $(D_2 - D_{98})$/Dmedian, where D_2 and D_{98} are the maximum and minimum doses, respectively [14]. Smaller HI values correspond to more homogeneous plans with HI = 0 corresponding to absolute homogeneity within the target volume. Dose to OARs were evaluated using the following dosimetric criteria: clinical dose objectives (Table 1), mean and maximum dose (D_2-dose to 2% volume) to the ipsilateral and contralateral mandible, mean dose contralateral oral cavity, contralateral SMG and posterior fossa. The volume of RVR receiving 10 Gy was also assessed. Dose cubes were exported from Pinnacle to the RayStation TPS (RaySearch Laboratories, Stockholm, Sweden) in order to generate dose difference maps.

NTCP calculations:

The doses to bilateral hippocampi and contra-lateral oral cavity were converted to the equivalent dose in 2 Gy fractions (EQD2) using the Withers formula and $\alpha/\beta = 2$ [15] and 10, respectively [16]. The probability of neurocognitive function (NCF) impairment was evaluated using the NTCP model described by Gondi et al[15], where the probability of a decline in short-term memory function, as measured by the Wechsler Memory Scale-III Word Lists delayed recall at 18 months post-RT, is related to the bilateral hippocampal EQD2 D_{40}. The NTCPs of grade 3 dysphagia and grade 3 oral mucositis were predicted according to the models derived by Bhide et al [17].

Probability of secondary cancers

The probability of secondary cancers was estimated using the dose to all normal tissue (whole body – PTV). To capture the range of possible estimates of second cancer risk the probability was assessed using a model with reducing risk for higher doses where the risk is assumed to fall off for increasing dose with D_0=10 and a dose plateau model, where the risk of radiation induced cancer is postulated to plateau beyond a threshold dose of 4 Gy [7].

Dose accumulation

Cone Beam CT (CBCT) images, acquired on day 1-3 and at weekly intervals thereafter, were used to calculate dose accumulation for each of the plans. CBCT images lack sufficient quality for use in dose calculation so the images were post processed to remove scatter, using data from the patients' planning CTs [11]. In addition, to correct for, when, the patient's shoulders and top of head were outside the field of view (FOV) of the CBCT, the FOV was increased and these structures were mapped to the CBCT from the planning CT and the Hounsfield units were set to values for soft tissue. In addition, the patient's shoulders and top of head, which were outside the imaged field of view (FoV) on treatment, were outlined on the planning CT and mapped across to the on-treatment images with density overrides applied to the body tissue outside of the CBCT FoV. 3DCRT, IMRT, and VMAT plans were then calculated in each of the manifested patient geometries observed during treatment. The CBCT images were deformably registered with the planning CT using the ANACONDA [18] algorithm available within the RayStation® TPS. The deformations were then applied to the dose cube calculated on the CBCT to enable dose summation and therefore allowing us to calculate an estimate of the delivered accumulated dose. Estimates for the changes in the dose to target volumes and OARs, from planning to treatment were then quantified.

Data analysis

Statistical data analysis was performed using R (R Foundation of Statistical Computing, Vienna, Austria) and Microsoft Excel (Redmond, WA, US). Wilcoxon signed-rank tests were used to compare differences between 3DCRT, IMRT, and VMAT plans, with a statistical significance level of alpha=0.05.

Results

A statistically significant (p-values Table 2), higher percentage volume of PTV 1 and 2, respectively, received 95% of the prescribed dose (V_{95}) when using IMRT (97% and 98%) and VMAT (97% and 97%) as opposed to 3DCRT (92% and 89%) (Table 2). In addition, the IMRT (0.8 and 0.1) and VMAT (0.8 and 0.1) plans were more conformal and homogenous compared to 3DCRT (0.6 and 0.2), based on the superior CI and HI, respectively. The differences between the doses to PTV's, CI and HI were statistically significant (Table 2). The There was no statistical difference in the V_{95}, HI and CI between IMRT and VMAT plan (p-values Table 2).

Maximum doses to the spinal cord and brainstem, respectively, were significantly higher with IMRT (43 Gy, p = 0.008 and 46 Gy, p = 0.002) and VMAT (42 Gy, p = 0.004 and 44 Gy, p = 0.002) compared to 3DCRT (36 Gy and 35 Gy) (Table 2). However, these were within published tolerance values [19,20]. The mean dose and percentage volume receiving 60 Gy (V_{60}) to the ipsilateral mandible was significantly lower with IMRT and VMAT versus 3DCRT (Table

2 for p-values). The posterior fossa D_{50} dose was significantly higher with 3DCRT (17 Gy) versus IMRT (12 Gy, p = 0.01) and VMAT (10 Gy, p = 0.01).

3DCRT resulted in lower mean doses to the contralateral OARs, when using standard optimisation ROIs However, when the IMRT and VMAT plans were re-optimised with a constraint on the contralateral oral cavity volume, the differences between the mean doses to the contralateral oral cavity were non-significant, without dose compromise for PTV1 and PTV2 (Table 2 for dose statistics and p-values). The 3DCRT and IMRT plans were significantly superior to the VMAT plans for dose to the contralateral mandible (Table 2). 3DCRT plans remained significantly superior for contralateral parotid sparing. However, dose to the contralateral SMG was not significantly lower with 3DCRT when plans were re-optimised with the specific oral cavity constraint.

3DCRT (2011cm^3) delivered the lowest, statistically significant volume of RVR receiving 10 Gy compared to IMRT (3042cm^3, p = 0.002) and VMAT (2767cm^3, p = 0.002). VMAT was superior to IMRT (p=0.01), Table 2.

NTCP calculations (Table 3)

There was no significant difference between the three techniques for probability of NCF impairment based on NTCP calculations (Table 3). The probability of grade 3 oral mucositis and grade 3 dysphagia were significantly lower for 3DCRT for plans without a specific oral cavity constraint. When a specific oral cavity constraint was used, the apparent advantage of 3DCRT disappeared. However, the IMRT technique maintained its significant advantage over VMAT.

Radiation-induced cancers (table 3)

The predicted probabilities of radiation-induced cancers depend on the applied model and are always higher for IMRT and VMAT than 3DCRT. always resulting in higher risk values than that for 3DCRT. However, differences between the planning techniques were not statistically significant (Table 3).

Dose accumulation (table 4)

Data on estimates of change in dose from planned to treatment were available for eight of the ten patients. Image quality of the CBCT in two patients was deemed unsatisfactory in spite of the scatter corrections and these were excluded from the analyses. Statistically significant reduction in the D_{95} for CTV1 was observed for all 3DCRT (3.5 Gy), IMRT (1.9 Gy) and VMAT (1.9 Gy) plans with the largest reduction observed for 3DCRT. A statistically significant increase of approximately 1 Gy in both, the brain stem ($D_{0.1cm3}$) and posterior fossa (mean dose), was measured for IMRT and VMAT as compared to the original treatment plan. Additionally, 3DCRT resulted in a significant ($p = 0.014$) reduction in elective target (CTV2) coverage.

Discussion

This study demonstrates that IMRT and VMAT resulted in improved dose conformity (CI) and homogeneity to both primary and elective targets. However, this was at the expense of a higher dose to the contralateral oral cavity, when using standard 'optmisation' ROIs for inverse planning. IMRT and VMAT were equivalent to 3DCRT for contralateral oral cavity sparing when optimised using a specific dose constraint of <36 Gy to the contralateral oral

cavity, without affecting PTV. This is reflected in the NTCP calculations with equivalent probabilities of acute mucositis for the re-optimised plans.

The mean dose and V_{60} to the ipsilateral mandible were significantly lower for IMRT and VMAT, Table 2. A study of 30 patients with ORN (out of total of 402 patients with oropharyngeal cancer) demonstrated V_{50} and V_{60} as a significant factor for development of ORN [21]. Grade 4 ORN in that study manifested on the side ipsilateral to disease with a mean dose to the ipsilateral mandible of 66 Gy in patients who developed ORN. Lee et al. have shown that a mean dose of >54 Gy (1.8 Gy per fraction) predicts for ORN [22]. Therefore, lower mean dose and V_{60} achieved with IMRT and VMAT should reduce the incidence of ORN compared to 3DCRT in the ipsilateral mandible. Indeed, results from retrospective series reviews (bilateral irradiation) with historical controls for comparison suggest that the incidence of ORN is lower with IMRT techniques [23,24].

The mean dose to the contralateral parotid gland was significantly lower with 3DCRT (5.6 Gy) compared to VMAT (11.8 Gy) and IMRT (15.9 Gy). The mean dose with all three techniques was lower than the 26 Gy threshold for <25% reduction in parotid function, reported in the landmark Eisbruch study [25]. The predicted risk of late grade 2 xerostomia is less than 5% with 3DCRT and VMAT based on the dose response curves reported by Houweling et. al. using larger patient dataset (including the one used in the Eisbruch study). In addition, there was no significant difference in the dose to the contralateral SMG, when IMRT/VMAT plans were re-optimised using specific dose constraints. The SMG contributes majority of the mucin rich saliva in unstimulated state and determines patient reported xerostomia following radiotherapy [26]. Therefore, 3DCRT and IMRT/VMAT are likely to be equivalent in terms of the late patient reported xerostomia scores.

IMRT techniques resulted in a statistically significant increase in the volume of normal tissue receiving low dose radiation (table 2). There are two reasons why the change from 3DCRT to IMRT may result in an increase in second malignancies. First, IMRT involves the use of more fields, and as a consequence, a bigger volume of normal tissue is exposed to lower doses. Second, this risk may be higher due to the increased scatter associated with use of IMRT. This scattered radiation is made up of three components, internal patient scatter, collimator scatter, and head leakage. The first two of these are probably lower with IMRT due to the reduced high dose field sizes and reduced intensity of the individual beam. The head leakage is responsible only for scatter radiation >15-30 cm from the treatment area [27]. The radiation dose to distant tissues from head leakage is very low and data from clinical and experimental studies suggest that risk from doses <0.15 Gy is negligible [28]. Nevertheless, IMRT delivery requires increased number of monitor units, resulting in increased head scatter and the potential risks from this cannot be ignored. Rubens et al. modeled the risk of radiation-induced cancer with IMRT from increased head scatter and predicted for a negligible risk in IMRT treatment plans requiring 2-4 times higher monitor units. The head leakage is hardware- and software-dependent with variation among treatment centres [29].

The probability of developing second malignancy as a result of low dose irradiation to a greater volume in proximity of treatment fields depends on the model applied. It is higher when using “the plateau model of risk” as opposed to the “reducing risk at higher doses” model. We have used radiocarcinogenesis models of Hall et al [9]. Equivalent risks observed in our study with “reducing risk at higher doses” contradict the findings of the Hall study. The study by Rubens et al. who also modelled the risk using measurements of dose in phantom to tissues within the proposed target volumes for various possible treatment sites, which included tonsillar and nasopharyngeal cancer failed to demonstrate increased risk with either of these models [29]. Given the uncertainties in the model of second cancer risk, more research in this area is required prior to drawing definite conclusions [28].

Dose accumulation calculations demonstrate that the mean D_{95} to CTV1 throughout the 6 weeks of treatment was, on average, 1.6 Gy lower for 3DCRT plans compared to both IMRT and VMAT. The IMRT techniques resulted in 1 Gy higher dose to the brain stem, which did not exceed the dose constraints. The radiobiological and clinical significance of these findings is unclear. It should be noted, however, that in spite of the absence of statistically significant differences between treatment techniques, the difference for an individual patient might still be clinically significant.

Conclusion:

This study demonstrates that VMAT, that is highly optimised to minimise dose deposition in areas outside the PTV, is the best technique in terms of dose homogeneity, conformity, risk of ORN and consistent dose delivery to the PTV throughout the course of treatment for patients with lateralised oropharyngeal cancers. Dosimetric and NTCP calculations show that VMAT is equivalent to 3DCRT in regard to the risk of acute mucositis and late xerostomia with specific dose constraints on a contralateral oral cavity OAR.

The likelihood of late ORN is lower with IMRT/VMAT techniques. A higher volume of normal tissue outside the PTV is exposed to a low radiation dose with these techniques, which may translate into a higher a risk of radiation-induced malignancies depending on the applied radiobiological model.

References

1. O'Sullivan, B. *et al.* The benefits and pitfalls of ipsilateral radiotherapy in carcinoma of the tonsillar region. *Int J Radiat Oncol Biol Phys* **51**, 332-43 (2001).
2. Al-Mamgani, A., van Rooij, P., Fransen, D. & Levendag, P. Unilateral neck irradiation for well-lateralized oropharyngeal cancer. *Radiother Oncol* **106**, 69-73 (2013).
3. Chronowski, G.M. *et al.* Unilateral radiotherapy for the treatment of tonsil cancer. *Int J Radiat Oncol Biol Phys* **83**, 204-9 (2012).
4. Jackson, S.M. *et al.* Cancer of the tonsil: the results of ipsilateral radiation treatment. *Radiother Oncol* **51**, 123-8 (1999).
5. Jensen, K., Overgaard, M. & Grau, C. Morbidity after ipsilateral radiotherapy for oropharyngeal cancer. *Radiother Oncol* **85**, 90-7 (2007).
6. Lynch, J. *et al.* Multiple cervical lymph node involvement and extra-capsular extension predict for contralateral nodal recurrence after ipsilateral radiotherapy for squamous cell carcinoma of the tonsil. *Oral Oncol* **50**, 901-6 (2014).
7. Feng, F.Y. *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* **68**, 1289-98 (2007).
8. Nutting, C.M. *et al.* Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* **12**, 127-36 (2011).
9. Hall, E.J. & Wuu, C.S. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* **56**, 83-8 (2003).
10. Gregoire, V., Eisbruch, A., Hamoir, M. & Levendag, P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. *Radiother Oncol* **79**, 15-20 (2006).
11. Gregoire, V. *et al.* CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. *Radiother Oncol* **69**, 227-36 (2003).
12. Humphreys, M. *et al.* Assessment of a customised immobilisation system for head and neck IMRT using electronic portal imaging. *Radiother Oncol* **77**, 39-44 (2005).
13. Desikan, R.S. *et al.* An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968-80 (2006).
14. 83, I. Prescribing, recording, and reporting Intensity-Modulated Photon-Beam Therapy (IMRT). *Journal of ICRU* **10**, 55-59 (2010).
15. Gondi, V., Hermann, B.P., Mehta, M.P. & Tome, W.A. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys* **85**, 348-54 (2013).
16. Withers, H.R., Thames, H.D., Jr. & Peters, L.J. A new isoeffect curve for change in dose per fraction. *Radiother Oncol* **1**, 187-91 (1983).
17. Bhide, S.A. *et al.* Characteristics of response of oral and pharyngeal mucosa in patients receiving chemo-IMRT for head and neck cancer using hypofractionated accelerated radiotherapy. *Radiother Oncol* **97**, 86-91 (2010).
18. Weistrand, O. & Svensson, S. The ANACONDA algorithm for deformable image registration in radiotherapy. *Med Phys* **42**, 40-53 (2015).

19. Mayo, C., Yorke, E. & Merchant, T.E. Radiation associated brainstem injury. *Int J Radiat Oncol Biol Phys* **76**, S36-41 (2010).
20. Kirkpatrick, J.P., van der Kogel, A.J. & Schultheiss, T.E. Radiation dose-volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys* **76**, S42-9 (2010).
21. Tsai, C.J. *et al.* Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys* **85**, 415-20 (2013).
22. Lee, I.J. *et al.* Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. *Int J Radiat Oncol Biol Phys* **75**, 1084-91 (2009).
23. Ben-David, M.A. *et al.* Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys* **68**, 396-402 (2007).
24. Gomez, D.R. *et al.* Correlation of osteoradionecrosis and dental events with dosimetric parameters in intensity-modulated radiation therapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* **81**, e207-13 (2011).
25. Eisbruch, A., Ten Haken, R.K., Kim, H.M., Marsh, L.H. & Ship, J.A. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* **45**, 577-87 (1999).
26. Murdoch-Kinch, C.A., Kim, H.M., Vineberg, K.A., Ship, J.A. & Eisbruch, A. Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* **72**, 373-82 (2008).
27. Lillicrap, S.C., Morgan, H.M. & Shakeshaft, J.T. X-ray leakage during radiotherapy. *Br J Radiol* **73**, 793-4 (2000).
28. Tubiana, M. Can we reduce the incidence of second primary malignancies occurring after radiotherapy? A critical review. *Radiother Oncol* **91**, 4-15; discussion 1-3 (2009).
29. Ruben, J.D. *et al.* The effect of intensity-modulated radiotherapy on radiation-induced second malignancies. *Int J Radiat Oncol Biol Phys* **70**, 1530-6 (2008).

Figure legends:

Figure 1: Isodose distributions for 3DCRT, IMRT and VMAT and the dose difference maps of 3DCRT versus IMRT and VMAT. Contours primary PTV (pink), contralateral oral cavity (green), contralateral parotid (orange) contralateral mandible (red), and spinal cord (white).

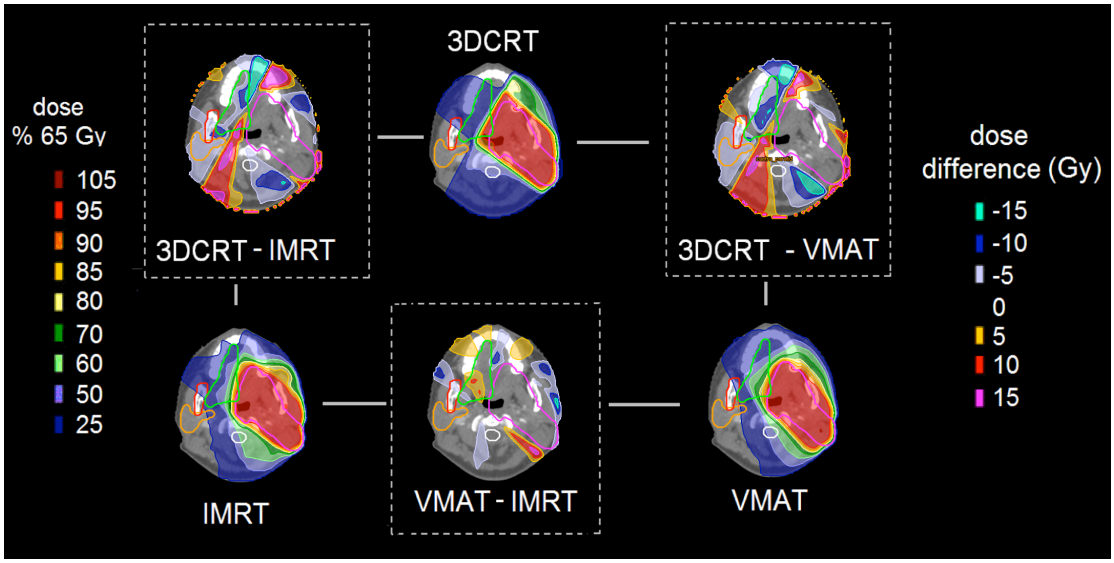

Figure 2: Dose volume histograms for the treatment plans of all patients without (A) and with (B) reoptimization of the treatment plan using 36 Gy as an additional constraint for the contralateral oral cavity

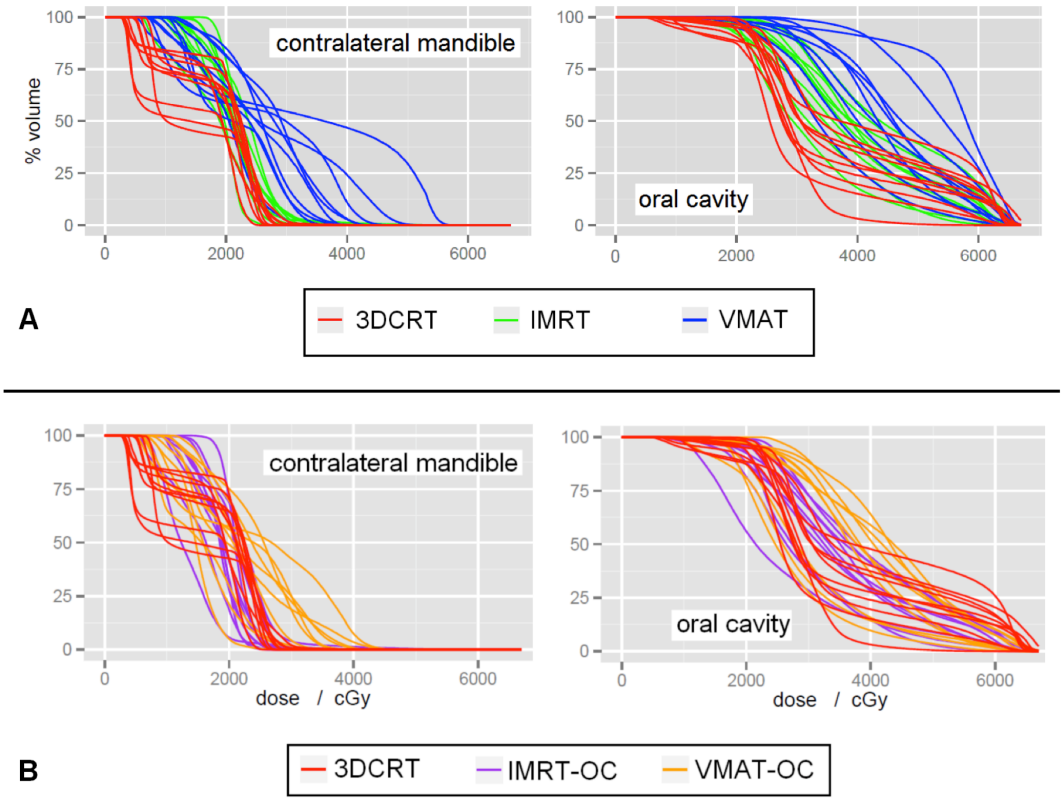

Table 1: Clinical dose objectives for IMRT and VMAT treatment plans

Structure	Dose statistic	Optimal	Required
PTV1	Dose to 99%		> 58.5 Gy (90%)
PTV1	Dose to 95%		> 61.8 Gy (95%)
PTV1	Dose to 50%		65 +/- 1 Gy
PTV1	Dose to 2 %		< 69.5 Gy (107%)
PTV2	Dose to 99%		> 48.6 Gy (90%)
PTV2	Dose to 95%		> 51.3 Gy (95%)
PTV2	Dose to 50%		54 +/- 1 Gy
Bilateral parotids	Mean dose	< 24 Gy	< 30 Gy
Superficial parotids	Mean dose	< 24 Gy	< 30 Gy
Spinal cord	Maximum point dose		< 46 Gy
Spinal cord PRV (+3mm)	Maximum point dose		< 48 Gy
Brain stem	Maximum point dose		< 50 Gy
Brain stem PRV (+3mm)	Maximum point dose		< 55 Gy
Optic chiasm	Maximum point dose		< 54 Gy
Bilateral optic nerves	Maximum point dose		< 55 Gy
Bilateral lens	Mean dose		< 6 Gy

Table 2: Dose statistics for 3DCRT, IMRT, and VMAT plans for all 10 cases with optimisation using standard generic optmisation ROIs and additionally with specific optimisation objectives for the oral cavity. Mean results with corresponding Standard Deviations (SDs) are shown along with p-values to test for statistical significance between the planning techniques.

		3DCRT	IMRT	VMAT	P-values, Wilcoxon signed-rank test		
Target Structure	**Dose Statistic**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**3DCRT Vs IMRT**	**3DCRT Vs VMAT**	**IMRT Vs VMAT**
PTV1	V_{95} (%)	92 (2.9)	97 (1.3)	97.0 (1.2)	0.009	0.002	0.721
PTV2	V_{95} (%)	89 (5.8)	98 (1.3)	97 (1.3)	0.015	0.015	0.204
Conformity Index (CI)	Paddick CI	0.64 (0.05)	0.77 (0.07)	0.78 (0.05)	0.022	0.014	0.353
Homogeneity Index (HI)	$(D_2 – D_{98}) / D_{50}$	0.2 (0.03)	0.1 (0.01)	0.1 (0.01)	0.002	0.002	0.919
OAR structure	**Dose Statistic**						
ipsi parotid	mean (Gy)	59 (6.2)	55 (7.2)	56 (6.8)	0.016	0.016	0.800
spinal cord	D_2 (Gy)	36 (3.3)	43 (1.4)	42 (2.1)	0.008	0.004	0.048
brain stem	D_2 (Gy)	35 (2.9)	46 (1.6)	44.0 (3.5)	0.002	0.002	0.202
post fossa	D_{50}(Gy)	17 (4.5)	12 (4.2)	10 (3.3)	0.010	0.010	0.010
ipsi mandible	mean (GY)	57 (2.9)	55 (3.9)	55 (3.2)	0.037	0.037	0.444
ipsi mandible	V_{60} (%)	71 (8.7)	53 (16.8)	51 (15.6)	0.002	0.002	0.322
Ipsi mandible	D_2 (Gy)	66 (0.7)	66 (1.0)	66 (1.0)	0.492	0.438	0.052
RVR	V_{10} (cm^3)	2011.0 (502)	3042.0 (1030)	2767.0 (879)	0.002	0.002	0.010
Generic Optimisation Volumes							
Contra oral cavity	mean (Gy)	35.1 (4.5)	39.3 (4.4)	45.2 (6.1)	0.010	0.020	0.020
contra mandible	mean (Gy)	17.4 (2.1)	21.0 (1.7)	25.5 (3.8)	0.004	0.004	0.002
Contra mandible	D2% (Gy)	27.2 (1.8)	30.3 (3.1)	40.1 (7.3)	0.014	0.002	0.002
contra parotid	mean (Gy)	5.6 (1.9)	15.9 (4.9)	11.8 (4.2)	0.002	0.009	0.006
Contra SMG	mean (Gy)	20.9 (7.7)	27.7 (5.8)	21.4 (6.5)	0.155	0.734	0.004

Contralaretal oral cavity sparing volume with 36Gy (mean dose) constraint							
Contra oral cavity	mean (Gy)	35.1 (4.5)	34.6 (4.7)	37.2 (6.3)	0.492	0.322	0.010
contra mandible	mean (Gy)	17.4 (2.1)	18.4 (2.7)	20.5 (3.8)	0.432	0.037	0.041
Contra mandible	D2% (Gy)	27.2 (1.8)	27.3 (3.4)	30 (6.2)	0.415	0.011	0.008
Contra parotid	mean (Gy)	5.6 (1.9)	14.7 (4.8)	10.3 (3.4)	0.002	0.014	0.004
Contra SMG	mean (Gy)	20.9 (7.7)	27.7 (7)	30.7 (5.7)	0.014	0.027	0.557

Table 3: Predicted NTCPs for 3DCRT, IMRT, and VMAT plans for all 10 cases.

		3DCRT	**IMRT**	**VMAT**	**P-values, Wilcoxon signed-rank test**		
NTCP model	**Dose Statistic**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**3DCRT Vs IMRT**	**3DCRT Vs VMAT**	**IMRT Vs VMAT**
NCF impairment [12]	EQD2 D_{40} bilateral hippocampi	0.058 (0.05)	0.050 (0.02)	0.052 (0.02)	0.297	0.051	0.834
Grade 3 dysphagia [13]	MD2Gy oral cavity	0.23 (0.08)	0.30 (0.08)	0.38 (0.09)	0.032	0.002	0.009
Grade 3 oral mucositis [13]	MD2Gy oral cavity	0.38 (0.10)	0.47 (0.10)	0.57 (0.10)	0.024	0.002	0.009
Grade 3 dysphagia [13]- **with constraint**	MD2Gy oral cavity	0.23 (0.08)	0.22 (0.10)	0.27 (0.09)	0.375	0.375	0.010
Grade 3 oral mucositis [13]- **with constraint**	MD2Gy oral cavity	0.38 (0.10)	0.37 (0.13)	0.43 (0.10)	0.375	0.412	0.010
Secondary cancers	Risk by Plateau Model	0.080 (0.008)	0.091 (0.015)	0.091 (0.016)	0.092	0.160	0.780
	Risk by D_0=10Gy Model	0.053 (0.004)	0.055 (0.006)	0.056 (0.008)	0.444	0.154	0.202

Table 4: Changes in dose metrics on estimated treatment dose. The mean change across patients is quoted with the range represented by the standard deviation. Statistically significant p-values (Wilcoxon signed-rank test) are shown in bold.

		Conventional		**IMRT**		**VMAT**	
		Mean (SD)	**p-value**	**Mean (SD)**	**p-value**	**Mean (SD)**	**p-value**
CTV Primary	D 95% [Gy]	-3.5 (2.0)	**0.008**	-1.9 (1.95)	**0.008**	-1.9 (1.7)	**0.008**
	D 2 % [Gy]	+0.2(0.5)	0.483	-0.1 (0.59)	0.547	0.17 (0.8)	0.844
CTV Nodes	D 95% [Gy]	-2.0 (2.4)	**0.014**	-1 (2.19)	0.383	-0.97 (2)	0.250
Contralateral Parotid	Mean Dose [Gy]	-0.2 (0.3)	0.091	-0.1 (0.62)	1.000	-0.02 (0.4)	1.000
Ipsilateral Mandible	Mean Dose [Gy]	-0.1 (1.1)	0.383	-0.3 (0.87)	0.250	-0.18 (1.4)	0.383
Contralateral Mandible	Mean Dose [Gy]	+0.1 (0.4)	0.461	-0.1 (0.53)	0.641	-0.05 (0.6)	0.944
Oral Cavity	Mean Dose [Gy]	+0.2 (0.6)	0.195	+0.1 (0.61)	0.945	0.10 (0.6)	0.844
Posterior Fossa	Mean Dose [Gy]	+0.7 (1.2)	0.052	+0.8 (1.15)	**0.008**	0.67 (0.9)	**0.008**
Spinal Cord	D 0.1cm^3 [Gy]	-0.5 (1)	0.250	-0.5 (1.15)	0.262	-0.59 (1.1)	0.109
Brain Stem	D 0.1cm^3 [Gy]	+1. (1.4)	0.055 (1)	+1 (1.4)	**0.016**	+0.8 (1.2)	**0.109**