Adaptive Dose Escalated Radiotherapy in Oropharyngeal Cancers: A Treatment Planning Feasibility Study

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Research Article

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Abstract

**Background:** A significant proportion of patients with poor prognosis squamous cell cancer of the oropharynx relapse loco-regionally despite radical (chemo)radiotherapy. If a predictive biomarker for disease control can be identified during treatment then individualised and adaptive treatment strategies may be employed. The aim of this study is to assess the feasibility of adaptive and dose-escalated RT to the gross tumour volume without increasing surrounding planning target volume doses and maintaining clinically acceptable organs at risk doses.

**Materials and methods:** Twenty representative patients with poor prognosis locally advanced OPSCC who were known to have relapsed post RT, were re-planned retrospectively using Eclipse TPS v15.5, RapidPlan™ and multi-criteria optimisation. In our centre, areas of gross disease (PTV65) are treated with 65Gy in 30# while areas at risk of containing microscopic disease (PTV54) are treated synchronously to 54Gy in 30#. The original clinical plans were re-optimised to act as controls (Group I). These plans were split into two plans of 15# each, with the latter 15# used to escalate the dose to the GTV to 73Gy (Group II) and 82Gy (Group III). Plan sums were created for the total 30# to record plan evaluation parameters along with assessments of plan deliverability.

**Results:** For all groups, the dose coverage at D98% and D50% for the PTVs were comparable. As expected, the D2% dose levels for PTV65 increased. All dose levels associated with PTV54 remained largely unaffected by the dose escalation regimens. Conformity indices for PTV65 and PTVAll reveal comparable conformity across all three groups. Despite the GTV being escalated by 12.3% and 26.2% in groups II and III, the volume of GTV receiving > 84 Gy was considerably less than 1.75 cc. While OAR doses increased for the escalated groups, these increases were not clinically significant.

**Conclusion:** This planning feasibility study exploring RapidPlan™ combined with multi-criteria optimisation has demonstrated that doses to the GTV may be escalated without increasing PTV or OAR doses considerably, suggesting an interventional clinical trial using this approach would be feasible. Given loco-regional control remains an unmet need, response-adaptive dose-escalated RT has the potential to improve outcomes for poor-prognosis patients.

Introduction

Head and neck (H&N) cancers are the 6th most common cancer worldwide [1]. 95% are squamous cell carcinomas (HNSCC), originating from the epithelial mucosal lining of the upper aerodigestive tract. Around 60% of HNSCCs present with locally advanced but non-metastatic disease and are associated with poor survival outcomes [2]. The pattern of treatment failure is loco-regional; many patients go on to die from this disease without developing distant metastases [3-5]. Radical (chemo)radiotherapy ((C)RT) involving 6-7 weeks of daily RT with concurrent platinum-based chemotherapy is widely accepted as standard of care in locally advanced HNSCC.
In oropharyngeal squamous cell cancer (OPSCC) there are several ongoing international trials in treatment de-intensification for Human Papillomavirus (HPV)-positive cancers given their very good prognosis [6]. In contrast, Ang et al.’s pivotal study showed patients with high risk features including heavy smoking history and HPV-negative disease had a 3 year overall survival of only 46.2% [7]. The analysis by Ang et al. also showed that the differences in survival between the good and poor prognosis groups were largely due to differences in loco-regional control (LRC), indicating treatment intensification to improve LRC may improve outcomes significantly.

Increasing the dose of RT is an appropriate avenue to explore; there is an established dose–response relationship in HNSCC, therefore escalating the radiation dose may improve tumour control and treatment outcomes [8]. Higher rates of LRC have been demonstrated in early stage clinical trials of uniform dose-escalation with acceptable toxicity profiles [9-11]. This is yet to translate into improved disease outcomes in larger phase 3 trials e.g. the ART-DECO study in larynx and hypopharynx SCC showed no improvement in LRC with dose-escalated intensity modulated radiotherapy (IMRT) [12]. It must be noted that this uniform approach to dose-escalation has only been applied to entire poor prognostic groups as described above. An individualised dose-escalation strategy using a predictive biomarker of response during treatment could be used to select the sub-group of patients for whom intensified treatment is most beneficial. This may allow us to realise the full potential of RT dose-escalation.

Adaptive radiotherapy can be divided into two distinct categories; anatomy adapted and response adapted [13]. In this study we have focused on the latter scenario. Response adapted radiotherapy consists of changing the target volumes and/or the doses depending on the response to treatment. Functional imaging techniques such as PET-CT and fMRI are under development as imaging biomarkers of response in H&N cancer and are conducive to response adapted radiotherapy becoming a feasible paradigm [14].

Dose escalation was previously difficult to implement in HNSCC with conventional radiotherapy techniques because of the proximity of organs at risk (OARs) to target volumes and increased risk of radiation-induced toxicity. However, with advances in radiotherapy technologies, such as IMRT, highly conformal dose distributions and improved sparing of OARs can be achieved. Eclipse™ v15.5 has advanced features that give the user more control and speed during the planning process. RapidPlan™ (RP) and the Multi-Criteria Optimisation (MCO) features can offer the user additional solutions during the plan optimisation stage. RP is a knowledge based algorithm, which estimates dose volume histogram curves and suggests optimisation objectives with priorities for OARs for the current plan by extracting pertinent information from previously optimised plans. During MCO, a library of “Pareto optimal” plans is generated, automatically highlighting different trade-off objectives. The user can vary the clinical criteria, navigating across the Pareto surface, exploring the variations between optimal OAR sparing and tumour target volume coverage to create a final deliverable treatment plan.

The aim of this study was to investigate the feasibility of adaptive, dose-escalated radiotherapy in patients with poor prognosis OPSCC, increasing dose to gross tumour volume (GTV) while maintaining
dose to surrounding planning target volume (PTV) and nearby OARs.

Materials And Methods

Patient selection

Eligible patients were those with locally advanced poor prognosis oropharyngeal SCC [7] who had received radical primary RT or CRT. Patients had participated in the MeRInO study (study of diffusion weighted MRI as a predictive biomarker of response during radiotherapy for high and intermediate risk squamous cell cancer of the oropharynx) [5] and those selected for this sub-study were participants who were known to have loco-regional relapse. Research ethics committee approval was gained for the primary study (reference 15/WS/0159) and written informed consent was obtained for each patient with specific permission requested to use their imaging dataset for additional research beyond the primary study.

Target volume and OAR delineation

GTV was delineated for primary tumour and involved lymph nodes. A 10–15 mm margin was added, then the outline further edited to exclude natural barriers to spread e.g. bone and air cavities, and extended to include the whole involved nodal level(s) to create the clinical target volume (CTV65). CTV54 included nodal areas considered at risk of containing microscopic disease as per international guidelines [15]. A 3 mm geometric expansion created planning target volumes (PTV65 and PTV54). A dose of 65 Gy in 30 fractions over 6 weeks was prescribed to gross disease (PTV65) and 54 Gy to elective areas (PTV54). Pertinent OAR outlining consisted of the larynx (from hyoid to cricoid), ipsi and contra-lateral parotids, spinal cord and brainstem. Planning organ at risk volumes (PRVs) of 3mm were added to the spinal cord and brainstem.

Treatment planning

Planning objectives

Table 1 details the planning constraints set for PTV coverage and OAR sparing. While OAR constraints for this study were in line with the Phase 3 PARSPORT trial [16], PTV constraints were slightly stricter by ensuring 98% of the prescribed dose to 95% of the PTV volumes as per ICRU 83 [17].

PTV65 was used as a surrogate of mucosa and as such a mandatory constraint of no more than 1.75 cc of GTV/PTV65 was allowed to receive > 84 Gy, this having previously been shown to be the dosimetric threshold above which late grade 4 mucosal ulcers will develop. [18] Remaining OAR and target volume dosimetry was considered along with clinical context by an experienced head and neck clinical oncologist to determine acceptability. Table 2 shows the 3 dose/fractionation schedules investigated. Plan 1 represents the dose per fraction for the first 15 fractions, while Plan 2 signifies the dose per fraction for the remaining 15 fractions. PTV65 and PTV54 received 2.17 Gy per # and 1.80 Gy per #, respectively in all plans and all dose cohorts, the change in dose per fraction was applied only to GTV. Group I received
standard dose and fractionation, 2.17 Gy per # for plan 1 and 2. Group II received 2.17 Gy per # in Plan 1 and 2.70 Gy per # in Plan 2. Group III received 2.17 Gy per # in Plan 1 and 3.30 Gy per # in Plan 2.

Planning technique

The Eclipse™ treatment planning system (TPS) Varian Medical Systems, Palo Alto, Ca, v15.5 was used to create the treatment plans. An interactive dose-volume optimiser is used to define and fine-tune the desired doses to the PTVs and close lying structures and compute an optimal plan for the patients which best achieves the stated dose while minimising the dose to the OARs. Eclipse™ uses photon optimiser (PO) for plan optimisation and Acuros® XB advanced dose calculation algorithm v15.5.7 for dose calculation. All radiotherapy plans were generated using a grid size of 2.5mm. A 6 MV photon energy and 600 MU/min dose rate was used for all Volumetric Arc Therapy (VMAT) plans utilising two full coplanar arcs with the collimator rotated to 30 degrees for clockwise rotation and 330 degrees for counter clockwise rotation. Collimator jaw tracking was applied to each plan. For each plan re-optimisation, our previously published Head & Neck RP model was used in conjunction with MCO [19].

Plan optimisation

Group I plans were re-optimised first; the RP model was used to generate DVH estimates which then translated into optimisation objective parameters, which were applied during the optimisation process. An experienced planner modified the parameters as necessary to achieve an optimal plan. Once an optimal plan solution was achieved, the planner then selected MCO for objective trade-off exploration. Each dose objective associated with PRV spinal cord, PRV brainstem, ipsi- and contra- lateral parotids and larynx was selected individually for trade-off exploration. Upper and lower point dose objectives were chosen for PTV65 and PTV54. The dose distribution was evaluated according to the clinical planning objectives (Table 1). Once acceptable, plan re-optimisation for group II and group III then commenced; the group I plans were subsequently split into Plan 1 and Plan 2 plans consisting of 15 fractions each. As described above, the Plan 1 plans are identical (e.g., 32.5 Gy in 15 fractions) across the three groups but additional optimisation objectives were added to the GTV for the Plan 2 plans in group II and III. For example, the group II plans had GTV escalated to 73 Gy in the Plan 2 plan while using the Plan 1 plan as a base dose plan in the optimiser. Once the GTV was escalated with an acceptable solution, MCO was selected and the additional upper and lower point dose objectives were chosen for the GTV. Trade-off exploration was launched once again in an effort to further reduce OAR doses. The plans for each group were added together into a plan sum following final dose calculation and the clinical objectives were assessed. The dose was prescribed to the median dose as recommended by the ICRU 83; in other words, all plans were normalised so that the prescription dose to PTV65 was 65 Gy ± 1 Gy. Furthermore, the GTV was escalated to 73 Gy ± 1 Gy and 82 Gy ± 1 Gy for the group II and III plans, respectively. One experienced planner was responsible for undertaking all of the treatment planning tasks while another experienced planner assumed the role of checking all plans.

Analysis of plans
Dose volume histogram parameters

The plans in each group were quantitatively compared by DVH analysis. To evaluate the irradiated dose to the OARs, PTVs and the GTV, the analysis involved comparisons to the constraints presented in Table 1. The dose to 1 cc of the target volumes (D 1cc) was also recorded.

Plan evaluation parameters

For PTV65, PTV54 and GTV, the conformity index (CI) and homogeneity index (HI) were recorded for each group. Furthermore, we introduce a new conformity index; high dose fall-off index (HDFI). The CI is an indicator that is used to assess target volume coverage together with the extent of normal tissue sparing. In this study, we have defined the CI as outlined by Equation 1, which is a modified version of the prescription dose spillage equation defined in the most recent SABR consortium guidelines [20]. Unlike SABR, which uses a 100% reference isodose volume, we recorded a more study appropriate 98% reference isodose volume for the PTVs (CI) and 107% reference isodose volume for the GTV (HDFI).

\[
CI_{(x_n)} = \frac{\text{Body} \left( V_{98\%} \right)_{(y_n)}}{TV_{x_n} \left( V_{98\%} \right)_{(y_n)}}; \quad \text{Equation 1}
\]

where

- \( x_1 = \text{PTV65} \) and \( y_1 = 65 \text{ Gy prescription dose} \)
- \( x_2 = \text{PTVAll} \) and \( y_2 = 54 \text{ Gy prescription dose} \)

Body = volume of patient receiving at least 98% of the prescription dose

TV = target volume receiving at least 98% of the prescription dose

The HDFI quantitatively describes the dose fall-off from a boost region (e.g., GTV) fully encompassed by a larger PTV. HDFI's were calculated for group II and group III plans by recording the V107% of the 65 Gy prescription dose inside and surrounding the GTV with specific ring structures/growth margins applied. V107% was chosen given its importance as an upper planning objective for H&N VMAT plans.

\[
HDFI_{(GTV \times)} = \frac{\text{Body} \left( V_{107\% (65Gy)} \right)_{(65Gy)}}{GTV_{x} \left( V_{107\% (65Gy)} \right)_{(65Gy)}}; \quad \text{Equation 2}
\]

where

- \( x = 0 \text{ mm}, 5 \text{ mm or } 10 \text{ mm margin surrounding the GTV} \)

Body = volume of patient receiving at least 107% of the prescription dose, 65 Gy

GTV = volume of GTV receiving at least 107% of the prescription dose, 65 Gy

For CI and HDFI; 1 is the ideal value representing better conformal coverage.

The HI is a metric ratio used to analyse the uniformity of the dose distribution in the target volume. In this study, we have defined the HI as

\[
HI_{(x)} = \frac{D_{5\% (x)}}{D_{95\% (x)}}, \quad \text{Equation 3}
\]
where \( x \) = target volume of GTV, PTV65 or PTV54

For HI; 1 is the ideal value representing better dose homogeneity.

Furthermore, the volume of the body receiving 6 Gy \( (V_{6\text{ Gy}}) \), 12 Gy \( (V_{12\text{ Gy}}) \), 24 Gy \( (V_{24\text{ Gy}}) \) and 48 Gy \( (V_{48\text{ Gy}}) \) were recorded as a measure for scatter dose. The low dose fall-off (LDF) beyond the GTV regions was sampled for each group. The gradient of LDF beyond the GTV was calculated using regression analysis. Finally, the high dose fall-off (HDF) outside the GTV was plotted as a function of distance, i.e., GTV + 5 mm and GTV + 10 mm, in an effort to quantify the volume of 107% of 65 Gy that surrounded the GTV.

Plan deliverability

To examine plan deliverability, quality assurance (QA) measurements were performed on a Varian TrueBeam™ linear accelerator equipped with millennium Multi Leaf collimator (MLC) (60 leaf pairs, maximum leaf speed of 2.5 cm/s, maximum gantry speed of 6 degrees/s and variable dose rate up to 600 MU/min). A comparison between the planned dose and delivered dose was performed using the Mapcheck2 phantom device; a 3D global gamma evaluation together with an acceptance of 95% points passing the criteria of 3 mm for the distance to agreement (DTA) and a dose difference tolerance level of 3% was employed. In addition to the machine QA performed, RadCalc v6.3 was used to re-calculate each plan offering an independent MU check along with other complexity parameters such as the modulation factor (MF) (defined as the ratio of MU required at a reference point with dynamic MLC to the MU required at a reference point in an open field) and average leaf pair opening (ALPO) (defined as the average leaf pair opening at each control point with a weight assignment proportional to the number of MUs).

Radiobiological calculation

As there is an abundance of clinical radiotherapy studies where treatments have been delivered at 2 Gy per fraction, comparisons made between this reference schedule and treatments with alternative schedules are deemed appropriate and widely accepted within the clinic. Consequently, equivalent doses in 2 Gy per fraction (EQD2) were calculated for each of the study groups using an \( \alpha/\beta \) ratio for early and late responding tissues. EQD2 Gy values were calculated individually for the plan 1 and plan 2 plans, which were then subsequently combined for each group using the equation below:

\[
EQD2\text{ Gy} \left[ 1 + \frac{2}{\alpha/\beta} \right] = nd \left[ 1 + \frac{d}{\alpha/\beta} \right]
\]

Equation 4

where \( \alpha/\beta = 10 \) for early responding tissues or

3 for late responding tissues

\( n \) = number of fractions
d = dose per fraction

where d = 2.17 Gy; 2.70 Gy; or 3.30 Gy

Statistical analysis

All statistical analyses between the three groups were performed using the ANOVA test followed by the Bonferroni post-hoc test. The threshold for statistical significance was, therefore, set to \( p < 0.0167 \); a \( p \)-value less than 0.02 was considered significant.

Results

20 patients were included in the study. On average the plans had a mean (± standard deviation) PTV65 volume of 367.9 cc (± 101.4 cc), PTV54 volume of 272.4 cc (± 84.8 cc) and GTV volume of 19.8 cc (± 11.6 cc). Figure 1 presents the mean absolute doses for the pertinent OARs as a function of study group. As the dose is escalated to group II and group III plans, OAR doses increase accordingly. Although there was a 12.3% and 26.2% prescription dose increase to the GTV between group I & group II, and group I & group III, respectively, the percentage dose increases to the pertinent OARs were considerably less, ranging from 1.4–6% in group II and 4.1% and 13.7% in group III as shown in Table 3. Figure 2 illustrates the mean absolute doses for PTV65-GTV and PTV54 for all study groups. All radiotherapy plans achieved the lower planning objectives (D98%) for the target volumes. Furthermore, the median dose, D50% equivalent to 65 Gy ± 1 Gy was accomplished for PTV65 among the three groups. The median dose to the GTV in the escalated groups was within ± 1 Gy of their respective prescriptions. As expected D2% for PTV65-GTV, PTV65 and GTV saw a notable percentage increase in the escalated groups (group II; 3.8% (PTV65-GTV), 7.4% (PTV65), 10.8% (GTV), and group III; 14.9% (PTV65-GTV), 20.3% (PTV65), 24.1% (GTV)) compared to the standard group. The dose to 1cc of the PTV65-GTV volume was recorded and found to increase by 3.0% and 14.5% for group II and group III, respectively when compared to group I. Furthermore, we found the volume of GTV/PTV65 receiving > 84 Gy to be considerably less than 1.75 cc (group I; V84 Gy = 0.0 ± 0.0: group II; V84 Gy = 0.0 ± 0.0: and group III; V84 Gy = 0.3 ± 0.5). All PTV54 constraints, i.e., D98%, D50%, D5 and D2% were achieved for each of the three groups and found to be within a 1% variation.

Dose metrics

Similar CI\textsubscript{(PTV65)} and CI\textsubscript{(PTVAll)} where found between the three groups. Superior GTV dose homogeneity, HI\textsubscript{(GTV)} was attained for group II; 1.03 ± 0.01 followed by group III; 1.04 ± 0.01 and group I; 1.05 ± 0.01. The volume of the total body receiving specified low dose levels were recorded. Comparing the range of dose volumes as depicted in Figure 3, it can be shown that the dose splash or scatter dose in the body at each selected dose level is comparable between the three groups (6 Gy, \( p > 0.02 \); 12 Gy, \( p > 0.02 \); 24 Gy, \( p > 0.02 \); 48 Gy, \( p > 0.02 \)). By subtracting the volume of the GTV structures from the total body structure, the LDF beyond these targets was assessed for the 6 Gy, 12 Gy, 24 Gy and 48 Gy dose levels. As illustrated in
Figure 4 (a) we found that the fall-off profile could be best fitted by logarithmic curves using the following equation

\[ y = -a \ln(x) + b \]

where \( a \) and \( b \) are constant values.

Converting the dose data in Figure 4 (a) to a logarithmic scale, Figure 4 (b) subsequently highlights the gradient or slope \((m)\) of LDF beyond the GTV by plotting the normalised volume, i.e., Body-GTV as a function of \( \ln(Dose) \). Assessing the LDF from the GTV, we found the similar gradients for all three groups (group I; \( m = 0.3896 \), group II; \( m = 0.3859 \) and group III; 0.3829. An average \( R^2 \) coefficient of determination of 0.997 indicates that the data is close to the fitted regression line.

For comparison of the high dose fall-off outside the GTV boost volume, HDFI's were calculated for the escalated plans. We found the Body/GTVx ratio to increase from 2.05 ± 0.54 for group II to 4.79 ± 2.00 for group III. Considering GTV plus a 5 mm margin, the ratio between the body receiving 107% of 65 Gy and this structure also increased from 1.06 ± 0.09 for group II to 1.50 ± 0.30 for group III. Applying a 10 mm margin around the GTV for comparison with the body, we found the V107% to be comparable and close to 1 for both groups (group II; 1.06 ± 0.09 and group III; 1.04 ± 0.06), indicating that the dose has fallen off significantly 10 mm beyond the GTV. In fact for group II, the dose fall-off was equally close to 1, 5 mm beyond the GTV emphasising an initial sharper fall-off associated with the lower escalated dose of 73 Gy (Table 4).

The HDF beyond the GTV was calculated by plotting the normalised volume as a function of distance (mm) (Fig. 5). Dose fall-off outside the GTV was ascertained by recording the V107% (cc) from the body structure minus the specific ring structures. While we found a similar fall-off with the 65 Gy group plans, the V107% decreased by 86.6% (73 Gy) and 60.2% (82 Gy) at a distance of 5 mm from the GTV. At a distance of 10 mm outside the GTV, the V107% decreased by 87.6% (73 Gy) and 93.9% (82 Gy).

The escalated dose to the GTV boost volume is clearly displayed in groups II and III emphasising the fact that the dose increase is concentrated in the vicinity of the GTV while lower dose levels remain largely unaffected beyond the GTV plus 10 mm structure. Beyond the GTV plus 10 mm margin, all plans qualitatively display similar dose coverage at the 51.30 Gy and 61.75 Gy dose levels (Fig. 6).

**Machine delivery parameters**

Complexity assessments were carried out using metrics as shown in Table 5. We found that the MF and ALPO increased as the dose was escalated to the GTV, indicating a lower level of modulation. An increase in the number of MUs associated with the standard group I plans corroborates a higher plan complexity compared to the group II and III plans. Furthermore, QA measurements were performed on each plan with results again suggesting that group II and group III plans were comparable to group I plans in terms of plan calculation accuracy.

**Radiobiological calculation**
EQD2 comparisons were carried out for the three groups according to Equation 4. For group I plans; 65 Gy in 30 fractions resulted in a total dose of 65.92 Gy$_{10}$ (EQD2 Gy) for early responding and 67.18 Gy$_{3}$ (EQD2 Gy) for late responding tissue. For group II plans; 73 Gy in 30 fractions resulted in total dose of 75.82 Gy$_{10}$ (EQD2 Gy) and 79.75 Gy$_{3}$ (EQD2 Gy). Finally for group III plans; 82 Gy in 30 fractions resulted in total dose of 87.82 Gy$_{10}$ (EQD2 Gy) and 95.95 Gy$_{3}$ (EQD2 Gy).

**Discussion**

Functional imaging during radiotherapy has the potential to identify the sub-group of patients who are not responding adequately to treatment, during treatment. The delivery of response adaptive and dose-escalated radiotherapy for those predicted to ‘fail’ treatment is crucial to the paradigm of biologically adaptive radiotherapy and this in-silico study has demonstrated the feasibility of adaptive dose-escalated radiotherapy for poor prognosis OPSCC.

Despite relatively small GTV volumes, clinically acceptable PTV and OAR doses that adhered to accepted constraints were maintained. Our main findings were that for a 12.5% (Group II) and 25.9% (Group III) increase in median dose to the GTV the associated OAR doses increased by 1.4 – 6.0% and 4.1 – 13.7%, respectively. As reported in Table 3, we found no significant increase in OAR (PRV Brainstem, Ipsi-lateral and Contra-lateral Parotids, and Larynx) doses across the three groups (p < 0.02), suggesting that the dose-escalation proposed is likely to be acceptable clinically.

A variety of plan quality parameters were calculated all target volumes. Dose metrics, such as, dose conformity, homogeneity and coverage were analysed. For each of the three groups, the dose coverage at D98% and D50% for the PTVs were comparable. As expected, the D2% dose levels for the PTV65 and PTV65-GTV (Fig. 2(a)) increased. All dose levels associated with PTV54 remained largely unaffected by the dose escalation regimens (Fig. 2 (b)). The conformity indices for PTV65 and PTVAll reveal comparable coverage for all three groups (Table 4).

Merlotti et al., [21] recommended that no more than 20% of PTV65 and no more than 1 cc of the tissue outside PTV65 should receive > 110% of the prescription dose. In keeping with this, we found that on average no more than 13.5% of PTV65-GTV received > 110% of 65 Gy and 0.2 cc of the Body–PTV65 structure received 71.5 Gy for the higher escalated group III. Furthermore, the volume of the body exposed to low dose levels as depicted in Figure 3 are similar across the three groups. In addition to this, the LDF quantified by subtracting the GTV from the body structure demonstrated that the low dose gradient, specified by m, was largely independent of escalated doses to the GTV indicating that intensifying the dose to the GTV has a negligible effect on normal tissues at low dose levels (Fig. 4(b)).

Olteanu et al., [18] compiled their excellent body of work on dose escalation for H&N cancer and attempted to identify certain risk factors that influence late grade 4 mucosal ulcers. The most pertinent risk factor that can be applied directly to this study is a dosimetric threshold above which, one can assume, the occurrence of late grade 4 mucosal ulcers will most likely occur. Adopting the previously
mentioned threshold of no more than 1.75 cc should receive > 84 Gy, we ensured agreement with this constraint. Every plan met this dosimetric threshold, which served as a valuable planning clinical goal. Turning our attention to GTV volumes, our manually delineated GTVs were also of comparable size (19.8 cc ± 11.6 cc) to those reported by the Belgian group with a range of 10.7 – 73.1 cc.

While only pertinent OARs were focused on in this study given their proximity to the PTVs, the LDF and HDF outside the GTV boost volume along with PTV65 doses were used as a surrogate of mucosal doses. By evaluating the ratios, Body/GTVx and doses to structures such as Body-GTV, Body-(GTV+0.5mm) and Body-(GTV+10mm), we found that the 107% volume of the conventional prescribed dose, 65 Gy, increased albeit to clinically acceptable levels inside the PTV65 volumes as described by the HDFI's in Table 4 and the 107% HDF in Figure 5. These margins could be reasonably interpreted as safety margins ensuring that escalated dose levels to the PTV65-GTV and the OAR volumes were not excessively high. At a distance of 10 mm outside the GTV, the V107% had decreased by 87.6% (2.1 cc) for the 73 Gy group and 93.9% (3.4 cc) for the 82 Gy group plans. These values can be reassuringly compared to 3.5 cc at a 10 mm distance for the 65 Gy group. Although there may be an increased volume of 107% up to 10 mm outside the GTV, De Felice et al., reported that the majority of recurrences occur within the GTV-CTV 10 mm margin [22].

We found the escalated plans to be less modulated than the standard, control plans. This may be attributed to how the optimisation objective priorities were modified during planning. As we allowed the dose to escalate for the group II and group III plans, our cost functions weren’t penalised to the same extent resulting in fewer objective priorities driving the optimiser. Nevertheless, the recorded modulation values for all plans were within the range accepted in standard clinical plans.

IMRT planning techniques, such as VMAT when compared to conventional planning can offer greater protection of normal tissue adjacent to tumours while still delivering targeted therapeutic radiotherapy doses. VMAT when conflated with advanced treatment planning solutions, such as RapidPlan™ and MCO can result in highly conformal dose distributions in areas specifically defined by the radiation oncologist and targeted by the treatment planner. The simultaneous integrated boost (SIB) technique is a strategy that enables simultaneous planning and irradiation of multiple target volumes to varying dose levels [23, 24]. Our approach intended to intensify the dose of radiation to the GTV, while maintaining dosimetrically acceptable PTV coverage, OAR doses and overall clinically acceptable treatment plans. The radiobiological calculations determined for this treatment planning feasibility study lie within a range previously published from a collection of dose escalation studies [25].

While very promising, this dose escalation study using the SIB technique has some limitations. All treatment plans were carried out on a single pre-treatment CT scan for each patient. Patients with OPSCC can undergo significant weight loss and changes in anatomy over their several weeks of treatment. Further work will examine the impact these changes may have on the feasibility of dose-escalation to GTV in the 2nd half of treatment, in particular the doses to OARs and surrounding PTVs.
Conclusions

This planning study in OPSCC showed the feasibility of significant dose-escalation to the GTV while maintaining clinically acceptable PTV and OAR doses. Analysis of the plan quality metrics indicate that this can be achieved without a compromise to plan quality. This work lays the foundations for the clinical investigation of response adaptive dose-escalated radiotherapy in poor prognosis OPSCC.

Abbreviations

ALPO: Average leaf pair opening; CI: Conformity Index; C(RT): Chemoradiotherapy; CTV: Clinical Target Volume; DTA: Distance to agreement; DVH: Dose Volume Histogram; EQD2: Equivalent dose in 2Gy per fraction; GTV: Gross Tumour Volume; H&N: Head and Neck; HDF: High-dose falloff; HDFI: High-dose falloff index; HI: Homogeneity Index; HPV: Human Papillomavirus; HNSCC: Head and Neck Squamous Cell Carcinoma; LDF: Low-dose falloff; IMRT: Intensity Modulated Radiotherapy; LRC: Loco-regional Control; MCO: Multi-Criteria Optimisation; MF: Modulation Factor; OAR: MLC: multi-leaf collimator; MU: Monitor units; Organs at risk; OPSCC: Oropharangeal Squamous cell Carcinoma; PTV: Planning Target Volume; PO: Photon optimiser; PRV: Planning risk volume; PTV65: Main planning target volume; PTV54: Low-risk planning target volume; PTVAI: PTV65 plus PTV54; QA: Quality Assurance; RP: RapidPlan; SIB: Simultaneous integrated boost; TPS: Treatment planning system; VMAT: Volumetric Arc Therapy

Declarations

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Authors’ Contributions

All authors wrote, read, and approved the final manuscript.

Availability of Data and Materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Consent for the use of patients’ data for retrospective and scientific investigation.

Consent for Publication

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Competing Interests

The authors declare that they have no competing interests.

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Table 1. Dose-volume planning objectives for target volumes and OARs.

| Structure                  | Dose-volume planning objective                                                                 |
|----------------------------|------------------------------------------------------------------------------------------------|
| PTV65 (65 Gy prescribed in 30 fractions); | 99% volume more than 90% of the dose                                                                |
|                            | 98% volume more than 95% of the dose                                                                |
|                            | 50% volume equal to 100% of the dose                                                                |
|                            | 5% volume less than 105% of the dose                                                                |
|                            | 2% volume less than 107% of the dose                                                                |
| PTV54 (54 Gy prescribed in 30 fractions); | 99% volume more than 90% of the dose                                                                |
|                            | 98% volume more than 95% of the dose                                                                |
|                            | 50% volume equal to 100% of the dose                                                                |
|                            | 5% volume less than 117% of the dose                                                                |
|                            | 2% volume less than 122% of the dose                                                                |
| PRV Spinal Cord           | 1% of volume less than 44 Gy;                                                                       |
|                            | Dmax less than 48Gy                                                                                 |
| PRV Brainstem             | 1% of volume less than 48 Gy                                                                       |
| Ipsi-lateral Parotid      | As low as reasonably practicable                                                                   |
| Contra-lateral Parotid    | Dmean less than 24 Gy                                                                               |
| Larynx                    | Dmean less than 40 Gy                                                                               |

Note: GTV; dose-volume planning objectives similar to as described for PTV65 but for an overall escalated prescribed dose of 73 Gy in 30 fractions or 82 Gy in 30 fractions.

Table 2. Three groups each with alternative dose and fractionation regimens employed in this study.
| Target Volume | Dose/ Fraction (Gy) | Fractions | Dose/ Fraction (Gy) | Fractions | Dose/ Fraction (Gy) | Fractions |
|---------------|---------------------|-----------|---------------------|-----------|---------------------|-----------|
| PTV65, Plan 1 | 2.17                | 1 – 15    | 2.17                | 1 – 15    | 2.17                | 1 – 15    |
| GTV           | 2.17                | 1 – 15    | 2.17                | 1 – 15    | 2.17                | 1 – 15    |
| Total Dose    | 32.5 Gy / 15 Fractions |         | 32.5 Gy / 15 Fractions |         | 32.5 Gy / 15 Fractions |         |
| PTV65, Plan 2 | 2.17                | 16 – 30   | 2.17                | 16 – 30   | 2.17                | 16 – 30   |
| GTV           | 2.17                | 16 – 30   | **2.70**            | **16 – 30** | **3.30**           | **16 – 30** |
| Total Dose    | 65 Gy / 30 Fractions |         | **73 Gy / 30 Fractions** |         | **82 Gy / 30 Fractions** |         |

Table 3 lists plan evaluation parameters and % difference/statistical results.
| Parameters                  | Group I (65 Gy) | Group II (73 Gy) | Group III (82 Gy) | (I vs II) | (I vs III) | (I vs II) | (I vs III) | (II vs III) |
|-----------------------------|-----------------|------------------|-------------------|----------|-----------|----------|-----------|------------|
| Dose-volume values (Gy)     | Mean ± SD (95% CI) | Mean ± SD (95% CI) | Mean ± SD (95% CI) | % Diff  | % Diff    | p-value  | p-value   | p-value    |
| Targets                     |                 |                  |                   |          |           |          |           |            |
| PTV65 (D98%)                | 62.8 ± 0.4 (62.6 - 62.9) | 62.6 ± 0.3 (62.5 - 62.7) | 62.2 ± 1.2 (61.6 - 62.8) | -0.3%   | -1.0%     | p=0.19   | p<0.02    | p<0.02     |
| PTV65 (D50%)                | 65.8 ± 0.2 (65.7 - 65.8) | 65.7 ± 0.2 (65.6 - 65.8) | 65.6 ± 0.2 (65.5 - 65.7) | -0.3%   | -0.3%     | p=0.28   | p<0.02    | p=0.12     |
| PTV65 (D2%)                 | 68.5 ± 0.4 (68.3 - 68.7) | 73.6 ± 0.9 (73.2 - 74.0) | 82.4 ± 1.1 (81.9 - 82.9) | +7.4%   | +20.3%    | p<0.02   | p<0.02    | p<0.02     |
| PTV65 (D1cc)                | 70.4 ± 0.9 (70.2 - 70.9) | 74.6 ± 0.3 (74.1 - 74.8) | 83.5 ± 0.3 (83.2 - 83.9) | +6.0%   | +18.6%    | p<0.02   | p<0.02    | p<0.02     |
| PTV65-GTV (D98%)            | 62.6 ± 0.3 (62.5 - 62.8) | 62.5 ± 0.3 (62.3 - 62.6) | 62.1 ± 0.3 (62.0 - 62.3) | -0.2%   | -0.8%     | p=0.02   | p<0.02    | p<0.02     |
| PTV65-GTV (D50%)            | 65.8 ± 0.3 (65.5 - 65.8) | 65.6 ± 0.2 (65.5 - 65.7) | 65.4 ± 0.3 (65.3 - 65.5) | -0.2%   | -0.2%     | p=0.02   | p<0.02    | p=0.03     |
| PTV65-GTV (D2%)             | 68.3 ± 0.4 (68.1 - 62.5) | 70.9 ± 0.4 (70.6 - 71.1) | 78.5 ± 0.7 (78.2 - 78.8) | +3.8%   | +14.9%    | p<0.02   | p<0.02    | p<0.02     |
| PTV65-GTV (D1cc)            | 70.4 ± 0.9 (70.0 - 70.8) | 72.5 ± 0.6 (72.2 - 72.8) | 80.6 ± 0.5 (80.3 - 80.8) | +3.0%   | +14.5%    | p<0.02   | p<0.02    | p<0.02     |
| GTV (D98%)                  | 64.0 ± 0.4 (63.8 - 64.2) | 71.9 ± 0.4 (71.7 - 72.0) | 80.0 ± 0.8 (79.6 - 80.3) | +12.3%  | +25.0%    | p<0.02   | p<0.02    | p<0.02     |
|                   |       |       |       |       |       |       |       |       |       |       |       |       |
|-------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| **GTV (D50%)**    | 65.6 ± | 0.5   | 65.4 – | 65.8 |       |       |       |       | +12.5% | +25.9% | p<0.02 | p<0.02 | p<0.02 |
|                   | (65.4 – | 65.8) | 73.8 ± | 0.3   | (73.7 – | 73.9) | 82.6 ± | 0.2   | (82.5 – | 82.7) |       |       |       |
| **GTV (D2%)**     | 67.5 ± | 0.5   | 67.3 – | 67.8 |       |       |       |       | +10.8% | +24.1% | p<0.02 | p<0.02 | p<0.02 |
|                   | (67.3 – | 67.8) | 74.8 ± | 0.2   | (74.7 – | 74.9) | 83.8 ± | 0.4   | (83.6 – | 83.9) |       |       |       |
| **PTV54 (D98%)**  | 51.5 ± | 0.4   | 51.3 – | 51.7 |       |       |       |       | +0.6%  | +1.0%  | p<0.02 | p<0.02 | p=0.21 |
|                   | (51.3 – | 51.7) | 51.8 ± | 0.3   | (51.7 – | 52.0) | 52.0 ± | 0.5   | (51.8 – | 52.3) |       |       |       |
| **PTV54 (D50%)**  | 54.9 ± | 0.5   | 54.7 – | 55.1 |       |       |       |       | +0.5%  | +1.0%  | p=0.05 | p<0.02 | p<0.02 |
|                   | (54.7 – | 55.1) | 55.2 ± | 0.5   | (55.0 – | 55.5) | 55.4 ± | 0.6   | (55.2 – | 55.8) |       |       |       |
| **PTV54 (D2%)**   | 60.4 ± | 0.8   | 60.1 – | 60.8 |       |       |       |       | 0.0%   | +0.1%  | p=0.81 | p=0.80 | p=0.61 |
|                   | (60.1 – | 60.8) | 60.4 ± | 0.7   | (60.0 – | 60.7) | 60.5 ± | 0.7   | (60.2 – | 60.8) |       |       |       |

**Organs at risk**

|                   |       |       |       |       |       |       |       |       |       |       |       |       |
|-------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| **PRV Spinal Cord** | 36.4 ± | 2.5   | 35.2 – | 37.6 |       |       |       |       | +6.0%  | +13.7% | p<0.02 | p<0.02 | p<0.02 |
|                   | (35.2 – | 37.6) | 38.6 ± | 2.6   | (37.3 – | 39.8) | 41.4 ± | 3.4   | (39.8 – | 43.0) |       |       |       |
| **PRV Brainstem**  | 36.6 ± | 5.5   | 34.0 – | 39.2 |       |       |       |       | +1.4%  | +4.1%  | p=0.69 | p=0.71 | p=0.65 |
|                   | (34.0 – | 39.2) | 37.1 ± | 5.6   | (34.5 – | 39.8) | 38.1 ± | 5.6   | (35.5 – | 40.8) |       |       |       |
| **Ipsi-lateral Parotid** | 30.2 ± | 8.2   | 26.3 – | 34.0 |       |       |       |       | +5.0%  | +9.6%  | p=0.54 | p=0.61 | p=0.59 |
|                   | (26.3 – | 34.0) | 31.7 ± | 8.2   | (27.9 – | 35.6) | 33.1 ± | 8.4   | (29.2 – | 37.0) |       |       |       |
| **Contra-lateral Parotid** | 21.5 ± | 6.1   | 18.6 – | 24.3 |       |       |       |       | +5.0%  | +9.5%  | p=0.49 | p=0.51 | p=0.54 |
|                   | (18.6 – | 24.3) | 22.6 ± | 6.3   | (19.7 – | 25.6) | 23.8 ± | 6.5   | (20.8 – | 26.9) |       |       |       |
| **Larynx**        | 43.3 ± | 8.1   | 39.5 – | 47.1 |       |       |       |       | +3.0%  | +6.0%  | p=0.61 | p=0.65 | p=0.62 |
|                   | (39.5 – | 47.1) | 44.6 ± | 8.2   | (40.7 – | 48.4) | 45.9 ± | 8.8   | (41.8 – | 50.0) |       |       |       |

**Table 4 outlines the conformity and homogeneity indices for the plan**
| Parameters | Group I (65 Gy) | Group II (73 Gy) | Group III (82 Gy) | (I vs II) | (I vs III) | (II vs III) |
|------------|----------------|-----------------|------------------|----------|-----------|------------|
| Dose metric values | Mean ± SD | Mean ± SD | Mean ± SD | % Diff | % Diff | p-value | p-value | p-value |
| CI\(_{PTV65}\) | 1.07 ± 0.03 | 1.06 ± 0.03 | 1.05 ± 0.03 | -0.9% | -1.9% | p=0.17 | p=0.15 | p=0.20 |
| CI\(_{PTVAll}\) | 1.38 ± 0.09 | 1.41 ± 0.08 | 1.42 ± 0.08 | +2.2% | +2.9% | p=0.33 | p=0.37 | p=0.34 |
| HI\(_{PTV65}\) | 1.07 ± 0.01 | 1.14 ± 0.03 | 1.27 ± 0.05 | +6.5% | +18.7% | p<0.02 | p<0.02 | p<0.02 |
| HI\(_{PTV54}\) | 1.07 ± 0.01 | 1.10 ± 0.01 | 1.20 ± 0.02 | +2.8% | +12.1% | p<0.02 | p<0.02 | p<0.02 |
| HI\(_{GTV}\) | 1.05 ± 0.01 | 1.03 ± 0.01 | 1.04 ± 0.01 | -1.9% | -1.0% | p<0.02 | p<0.02 | p=0.02 |
| HI\(_{PTV54}\) | 1.12 ± 0.02 | 1.11 ± 0.01 | 1.12 ± 0.01 | -0.9% | 0.0% | p=0.60 | p=0.62 | p=0.59 |
| HDFI\(_{GTV}\) | -- | 2.05 ± 0.54 | 4.79 ± 2.00 | -- | -- | -- | -- | -- |
| HDFI\(_{GTV 5mm}\) | -- | 1.06 ± 0.09 | 1.50 ± 0.30 | -- | -- | -- | -- | -- |
| HDFI\(_{GTV 10mm}\) | -- | 1.06 ± 0.09 | 1.04 ± 0.06 | -- | -- | -- | -- | -- |

Table 5. Plan deliverability parameters for each group of plans (mean ± standard deviation)
# Deliverability Metrics

| Deliverability Metrics | Group I (65 Gy) | Group II (73 Gy) | Group III (82 Gy) | (I vs II) | (I vs III) | (I vs II) | (I vs III) |
|------------------------|-----------------|-----------------|------------------|-----------|-----------|-----------|-----------|
|                        | Mean ± SD       | Mean ± SD       | Mean ± SD        | % Diff    | % Diff    | p-value   | p-value   |
| MUs                    | 752 ± 9         | 710 ± 7         | 709 ± 7          | -5.6%     | -5.7%     | p=0.14    | p=0.12    | p=0.10    |
| ALPO                   | 2.61 ± 0.31     | 2.87 ± 0.24     | 2.90 ± 0.28      | +10.0%    | +11.1%    | p<0.02    | p<0.02    | p=0.75    |
| MF                     | 0.31 ± 0.05     | 0.35 ± 0.05     | 0.38 ± 0.07      | +12.9%    | +22.6%    | p<0.02    | p<0.02    | p=0.23    |
| Pass Rate (%) Global   | 99.7% ± 0.3     | 99.9% ± 0.2     | 100% ± 0.1       | + 0.2%    | +0.3%     | –         | –         | –         |

## Figures

**Figure 1**

Mean absolute doses for all pertinent OARs in each of the study groups.
Figure 2

Mean absolute doses (Gy) for (a) PTV65-GTV and PTV54 in each of the study groups.
Figure 3

Volume of body encompassed by low dose levels for each study group.
Figure 4

(a) LDF and (b) Gradient of LDF beyond the GTV for all plans across all three groups for 6 Gy, 12 Gy, 24 Gy and 48 Gy dose levels.
**Figure 5**

107% HDF as a function of varying distances from the GTV.
Figure 6

Examples of colour wash dose distributions on CT axial slices (a) 51.30 Gy (95% of 54 Gy, PTV54); (b) 61.75 Gy (95% of 65 Gy, PTV65); and (c) 69.55 Gy (107% of 65 Gy, PTV65) for a representative case in groups I (left), II (middle) and III (right). Structure colours: PTV54 – blue; PTV65 – red; GTV – black; GTV plus 5 mm margin – magenta; GTV plus 10 mm margin – green.