Volumetric-modulated arc therapy (RapidArc) vs. conventional fixed-field intensity-modulated radiotherapy for ^{18}F -FDG-PET-guided dose escalation in oropharyngeal cancer: A planning study

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ABSTRACT

Fluorine-18-fluorodeoxyglucose-positron emission tomography (^{18}F -FDG-PET)-guided focal dose escalation in oropharyngeal cancer may potentially improve local control. We evaluated the feasibility of this approach using volumetric-modulated arc therapy (RapidArc) and compared these plans with fixed-field intensity-modulated radiotherapy (IMRT) focal dose escalation plans. Materials and methods: An initial study of 20 patients compared RapidArc with fixed-field IMRT using standard dose prescriptions. From this cohort, 10 were included in a dose escalation planning study. Dose escalation was applied to ^{18}F -FDG-PET-positive regions in the primary tumor at dose levels of 5% (DL1), 10% (DL2), and 15% (DL3) above standard radical dose (65 Gy in 30 fractions). Fixed-field IMRT and double-arc RapidArc plans were generated for each dataset. Dose-volume histograms were used for plan evaluation and comparison. The Paddick conformity index ($\text{CI}_{\text{Paddick}}$) and monitor units (MU) for each plan were recorded and compared. Both IMRT and RapidArc produced clinically acceptable plans and achieved planning objectives for target volumes. Dose conformity was significantly better in the RapidArc plans, with lower $\text{CI}_{\text{Paddick}}$ scores in both primary (PTV1) and elective (PTV2) planning target volumes (largest difference in PTV1 at DL3; 0.81 ± 0.03 [RapidArc] vs. 0.77 ± 0.07 [IMRT], $p = 0.04$). Maximum dose constraints for spinal cord and brainstem were not exceeded in both RapidArc and IMRT plans, but mean doses were higher with RapidArc (by 2.7 ± 1 Gy for spinal cord and 1.9 ± 1 Gy for brainstem). Contralateral parotid mean dose was lower with RapidArc, which was statistically significant at DL1 (29.0 vs. 29.9 Gy, $p = 0.01$) and DL2 (29.3 vs. 30.3 Gy, $p = 0.03$). MU were reduced by 39.8–49.2% with RapidArc (largest difference at DL3, 641 ± 94 vs. 1261 ± 118 , $p < 0.01$). ^{18}F -FDG-PET-guided focal dose escalation in oropharyngeal cancer is feasible with RapidArc. Compared with conventional fixed-field IMRT, RapidArc can achieve better dose conformity, improve contralateral parotid sparing, and uses fewer MU.

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Introduction

The rate of locoregional relapse for squamous cell carcinoma (SCC) of the oropharynx is high, with up to 50% of locally advanced tumors relapsing within 5 years.^{1,2} This is despite significant improvements in treatment with concurrent chemoradiotherapy, biologic agents, and altered fractionation.^{1–3} These tumors often display features associated with an aggressive disease phenotype and intrinsic radioresistance, which could account for this high rate of local treatment

failure.⁴ Because there is an established dose–response relationship in these tumors, escalating the radiation dose may improve tumor control and treatment outcomes. This has previously been difficult to implement with conventional radiotherapy techniques because of the increased risk of radiation-induced toxicity. However, with advances in radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), highly conformal dose distributions and improved sparing of organs at risk (OARs) can be achieved, which could potentially allow for dose escalation strategies.

A phase I/II trial conducted at the Royal Marsden Hospital (UK) has reported high rates of locoregional control with dose escalation using IMRT in locally advanced laryngeal and hypopharyngeal tumors.⁵ In

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this study, dose escalation was applied to a large planning target volume (PTV) that included the entire primary tumor subsite and involved neck lymph node levels. Although toxicity was reported to be acceptable, significant acute and late side effects were still observed. An alternative approach would be to target specific regions within the tumor that are at the highest risk of local relapse for dose escalation. This approach is supported by the observation that most local relapses (53–97%) occur within the high-dose radiotherapy volume.⁶ The anticipated toxicity would be reduced because the volumes receiving very high radiation doses would be significantly smaller.⁷

The success of a focal dose escalation strategy would depend on the accurate detection of these biologically radioresistant regions. This could be achieved with functional imaging techniques, such as fluorine-18-fluorodeoxyglucose-positron emission tomography (¹⁸F-FDG-PET).⁸ Head and neck squamous cell carcinoma (SCC) is commonly ¹⁸F-FDG-avid, with up to 90–100% of these tumors identifiable on ¹⁸F-FDG-PET.⁸ Furthermore, there is evidence that the degree of ¹⁸F-FDG uptake is correlated with inferior locoregional control and survival.⁹ This could imply a more aggressive biologic phenotype in ¹⁸F-FDG-positive tumors, which may require higher radiation doses to achieve tumor control. There have been few planning studies that have evaluated focal dose escalation to ¹⁸F-FDG-PET-positive regions in head and neck cancer using conventional fixed-field IMRT.¹⁰ The phase I trials conducted by Madani *et al.*^{11,12} are the only published studies that have reported on clinical outcomes, with early results showing excellent response and local control rates. Although more studies evaluating IMRT are in progress, further developments in treatment delivery techniques may offer alternative solutions to allow clinical implementation of ¹⁸F-FDG-PET-guided focal dose escalation.

One such recent advancement is the development of volumetric-modulated arc therapy (VMAT) technology.¹³ Very few studies have evaluated VMAT in the context of focal dose escalation in head and neck cancer.^{14,15} An early planning study by Korreman *et al.*¹⁴ evaluated the feasibility of targeting copper-61-diacyetyl-bis(N⁴-methylthiosemicarbazone) (⁶¹Cu-ATSM)-avid regions of hypoxia using RapidArc in a single head and neck case. The study concluded that RapidArc was able to produce deliverable plans with good dose conformity. The results of a planning study conducted by the Ghent group,¹⁵ which compared VMAT with fixed-field IMRT to dose-escalate ¹⁸F-FDG-positive regions in head and neck cancer, were presented at a recent international conference. Preliminary results indicated improved biologic conformality and organs at risk (OAR) sparing with VMAT.

The aims of our planning study were to:

1. Evaluate RapidArc compared with conventional fixed-field IMRT in locally advanced oropharyngeal SCC using standard dose prescriptions.
2. Evaluate the feasibility of focal dose escalation to ¹⁸F-FDG-positive regions within the primary tumor using RapidArc.
3. Evaluate the RapidArc dose escalation plans compared with fixed-field IMRT dose escalation plans to assess the difference in dose distributions between these 2 techniques.

Methods and Materials

Patients, volumes, and planning objectives

Twenty patients with locally advanced oropharyngeal SCC receiving radical radiotherapy at the Royal Surrey County Hospital between August 2008 and July 2011 were evaluated in the initial planning study (standard dose). All patients had routine imaging (magnetic resonance imaging [MRI] of head and neck, computed tomography [CT] of the head and neck/thorax/upper abdomen) for staging of their disease before treatment. Ten patients from this initial cohort had additional ¹⁸F-FDG-PET/CT scans as part of their staging procedure and were selected for the dose escalation (boost) planning study. A customized thermoplastic mask was used for immobilization, and radiotherapy planning CT scans were taken with contrast (Niopam, Bracco, Milan, Italy) enhanced acquisition at 1- to 3-mm slice thickness.

Target volumes were defined according to ICRU 50, 62, and 83 guidelines.^{16–18} Gross tumor volume (GTV) was defined as the visible tumor, seen as the area of en-

hancement on the planning CT and delineated taking into consideration the findings from clinical examination and diagnostic imaging. The primary clinical target volume (CTV1) included the GTV with a 1- to 1.5-cm margin, expanded to include neighboring and nodal areas requiring irradiation to a radical dose and edited away from anatomical barriers. The elective CTV (CTV2) included the neck nodal regions that are considered at risk of microscopic involvement and delineated according to the Consensus guidelines.^{19,20} A 3D margin of 3 mm was added to CTV1 and CTV2 to produce the primary planning target volume (PTV1) and elective PTV (PTV2), respectively. OAR including the spinal cord, brainstem, and parotid glands were also contoured.

For the boost study, a biologic GTV (GTV_B) was defined as the ¹⁸F-FDG-positive region within the primary tumor as seen on the ¹⁸F-FDG-PET/CT scan. ¹⁸F-FDG-positive regions in the neck lymph nodes were not included in the dose-escalated volume. This was because in our clinical setting, patients with residual nodal disease after radiotherapy can undergo a neck dissection. A freehand delineation method based on visual interpretation of the PET images was used to define the PET-positive regions, which were then contoured on the radiotherapy planning CT scan. Rigid coregistration of the PET and planning CT images was not performed because patients were not in identical positions for both scans.

The dose prescriptions to PTV1 and PTV2 were 65 and 54 Gy in 30 daily fractions, respectively. For the boost study, dose escalation to GTV_B was applied in dose levels of 5% (dose level 1, DL1); 10% (dose level 2, DL2); and 15% (dose level 3, DL3) above the PTV1 prescription dose. The equivalent dose in 2-Gy fractions (EQD2) for each dose level was calculated using:

$$EQD2 = D \left[\frac{d + \left(\frac{\alpha}{\beta} \right)}{2 + \left(\frac{\alpha}{\beta} \right)} \right],$$

where D = total dose, d = dose per fraction, and α/β of 2 and 3 for late toxicity used for calculation.²¹ The total dose to GTV_B was 68.1 Gy (EQD2 71.8–72.7 Gy) for DL1, 71.5 Gy (EQD2 77.0–78.4 Gy) for DL2, and 74.8 Gy (EQD2 82.2–84.0 Gy) for DL3. A simultaneous integrated boost technique was used to deliver the dose to the PTVs.

The planning objectives were to achieve:

1. Dose to 99% of volume (D₉₉) of >90% of the prescription dose to PTV1 and PTV2.
2. Dose to 95% of volume (D₉₅) of >95% of the prescription dose to PTV1 and PTV2.
3. Dose to 2% of volume (D₂) of <107% of the prescription dose to PTV1.
4. For the boost study, dose to GTV_B of >95% and <107% of the prescription dose to GTV_B.
5. For spinal cord, maximum dose (D_{max}) = 46 Gy.
6. For brainstem, maximum dose (D_{max}) = 54 Gy.
7. For parotids, mean dose (D_{mean}) = 20 Gy for unilateral sparing and 25 Gy for bilateral sparing.

Planning techniques

All 20 patients had 2 plans generated (1 fixed-field IMRT and 1 double-arc RapidArc) for the standard dose study. The 10 patients in the boost study also had these plans generated at each dose escalation level. All plans were generated using the Varian Eclipse treatment planning system (Eclipse version 8.9.08, Varian Medical Systems, Palo Alto, CA) and designed to be delivered using 6-MV photons from a Varian Clinac iX linear accelerator.

The fixed-field IMRT plans were optimized using 5–7 coplanar fields and delivered using the sliding window technique. RapidArc plans were optimized using 2 360° coplanar arcs, with collimator angles of 20–45° to minimize the tongue-and-groove effect. Double arcs have previously been shown to be superior to single arcs in improving target volume coverage and dose homogeneity.²² Both arcs were simultaneously optimized using the Progressive Resolution Optimizer (PRO, version 8.9.08, Varian Medical Systems, Palo Alto, CA, USA).¹³ Similar dose objectives and the “normal tissue objective” function were used in the optimization process for both fixed-field IMRT and RapidArc plans.

The final dose calculation was performed using the Anisotropic Analytic Algorithm (AAA, version 8.9.08) with a calculation grid of 2.5 mm.²³ Couch attenuation using the Exact image-guided radiation therapy couch top (thin) model in Eclipse was corrected for 360° arc delivery in the RapidArc plans. All plans were performed by a single planner.

Plan evaluation

Quantitative analysis of the plans was performed using dose-volume histograms (DVHs). For the PTVs and GTV_B, the values recorded were D₉₉, D₉₅, D₅₀, D₅, and D₂. Dose conformity was expressed as the Paddick Conformity Index (CI_{Paddick}), which is defined as:

$$CI_{\text{Paddick}} = \left[\frac{TV_{95}}{TV} \right] \times \left[\frac{TV_{95}}{V_{95}} \right]$$

where TV is the total target volume and TV₉₅ is the target volume within the volume receiving at least 95% of the prescribed dose to the PTVs (V₉₅). The CI_{Paddick} score would be expected to decrease with reduced plan conformity.²⁴ For the spinal cord and brainstem, the DVH values recorded were D_{max}, D_{mean}, D₂, and volume receiving at least 35

Table 1
Patient, tumor, and target volume characteristics

Patient no.	Age	Gender	TNM stage	UICC stage	PTV1 (cm ³)	PTV2 (cm ³)	GTV _B (cm ³)
1	53	M	T1N2b	IVa	337.7	397.8	11.8
2	45	F	T4aN1	IVa	225.5	225.6	2.7
3	50	M	T2N2a	IVa	392.7	602.1	14.1
4	47	F	T4aN2b	IVa	331.8	292.7	28.4
5	55	M	T2N2b	IVa	475.5	375.5	1.4
6	46	M	T1N2b	IVa	380.3	434.8	3.9
7	69	M	T3N2a	IVa	382.9	376.7	26.3
8	57	M	T4 N2c	IV	779.9	200.1	16.1
9	59	M	T3N1	III	392.4	257.9	12.6
10	53	M	T4aN2c	IVa	666.5	114.4	15.6
11	63	M	T1N2b	IVa	368.7	325.6	
12	60	M	T2N2b	IVa	573.5	440	
13	62	M	T4bN1	IVb	424.4	382.9	
14	66	M	T3N0	III	432.9	457.2	
15	59	M	T2N2b	IVa	409.8	242.4	
16	63	M	T4 N1	IV	658.3	156.4	
17	71	M	T4aN2b	IVa	435.1	392.8	
18	44	M	T1N2b	IVa	402.3	430.3	
19	67	M	T4aN2b	IVa	597.5	283.1	
20	52	M	T1N2b	IVa	469.1	335.7	

UICC = Union of International Cancer Control.

Gy ($V_{35\text{Gy}}$). For the parotid glands, D_{mean} and $V_{35\text{Gy}}$, and for healthy tissue (body), D_{mean} , $V_{5\text{Gy}}$, and $V_{35\text{Gy}}$ were recorded. MU for each plan were also recorded. The results of the fixed-field IMRT and RapidArc plans were compared using the paired Student *t*-test.

Results

The patient, tumor, and target volume characteristics are summarized in Table 1. The mean (± 1 SD) PTV1, PTV2, and GTV_B volumes were 456.8 ± 133.9 cm³, 335.7 ± 116.8 cm³, and 13.3 ± 9.2 cm³, respectively. An example of the dose distributions with fixed-field IMRT and RapidArc for a patient in the boost study is shown in Fig. 1.

Rapidarc vs. IMRT (standard dose study)

Both techniques produced clinically acceptable plans and achieved the planning objectives for PTVs. Target volume coverage was similar between RapidArc and IMRT plans. The mean values of the PTV dose parameters for RapidArc and IMRT are summarized in Table 2. Small but statistically significant differences were observed for D_5 and D_2 for PTV1, which were both 0.5% lower (on average) in the RapidArc plans. For PTV2, D_{99} and D_{95} were lower (on average) by 0.6% and 0.4%, respectively, in the RapidArc plans. Dose conformity was significantly improved with RapidArc, with lower $\text{CI}_{\text{Paddick}}$ scores for both PTVs (summarized in Table 3).

The mean values of the OAR dose parameters for RapidArc and IMRT are summarized in Table 4. Neither technique exceeded D_{max} constraints for spinal cord and brainstem. We observed statistically significant differences in D_{mean} for both of these OARs, with higher values in the RapidArc plans. No significant difference was seen in contralateral and ipsilateral parotid D_{mean} between the 2 techniques. $V_{35\text{Gy}}$ for the contralateral parotid was significantly lower with RapidArc, and $V_{5\text{Gy}}$ for healthy tissue was significantly higher in the RapidArc plans. RapidArc used fewer MU compared with IMRT (summarized in Table 5).

Rapidarc vs. IMRT (boost study)

Both techniques produced clinically acceptable plans at all 3 dose escalation levels. Table 2 shows the mean values of the PTV dose parameters for RapidArc and IMRT. Planning objectives for target volume coverage were achieved, with no significant differences for PTV1. However, D_{99} and D_{95} for PTV2 at all 3 dose levels were lower in the RapidArc plans. The largest difference was seen at DL3, where D_{99} and D_{95} were lower (on average) by 0.9% with RapidArc. For GTV_B, small

but statistically significant differences were observed for D_2 at DL2 and DL3 (0.4% and 0.5% higher with RapidArc, respectively), and D_5 at DL3 (0.5% higher with RapidArc).

Table 3 shows the $\text{CI}_{\text{Paddick}}$ scores of the PTVs calculated for each of the dose levels. Dose conformity for both PTV1 and PTV2 was significantly improved with RapidArc for all 3 dose escalation levels. The largest difference in the $\text{CI}_{\text{Paddick}}$ score for PTV1 was at DL3, whereas for PTV2, the largest difference was seen at DL1.

Table 4 shows the mean values for OAR dose parameters for RapidArc and IMRT. Neither technique exceeded D_{max} constraints for spinal cord and brainstem, as in the standard dose study. Higher spinal cord DVH values were observed in the RapidArc plans for all 3 dose levels. The largest difference in D_{max} was seen at DL1, which was 2.5% higher with RapidArc. For D_{mean} , the largest difference was seen at DL2, which was 7.9% higher with RapidArc. For the brainstem, there was no significant difference in D_{max} , but D_{mean} was higher in the RapidArc plans by up to 15.4%.

Contralateral parotid D_{mean} was lower with RapidArc, with statistically significant differences seen in 2 of the 3 dose levels. The D_{mean} was 0.9 and 1.0 Gy lower with RapidArc plans at DL1 and DL2, respectively. $V_{35\text{Gy}}$ for the contralateral parotid was also significantly lower with RapidArc at all 3 dose levels, with the largest difference seen at DL2 (26.3% lower with RapidArc). There were no significant differences in ipsilateral parotid doses.

For healthy tissue, the most pronounced finding was for $V_{5\text{Gy}}$, which was higher in the RapidArc plans. The largest difference was seen at DL1, which was 4.4% higher with RapidArc. RapidArc plans used significantly fewer MU compared with IMRT, with reductions of up to 49.2% (summarized in Table 5).

Discussion

The concept of focal dose escalation to biologically radioresistant regions in head and neck cancer has been of significant interest in recent years.⁷ To date, only one small planning study has reported on the feasibility of focal dose escalation using VMAT¹⁴ and to our knowledge, there have been no published papers comparing VMAT with conventional fixed-field IMRT in this context. First, our study has demonstrated that for focal dose escalation to ¹⁸F-FDG-positive regions in oropharyngeal cancer, RapidArc is able to achieve clinically acceptable plans without exceeding dose constraints to critical OAR (e.g., spinal cord, brainstem). Second, our results show that RapidArc can produce plans of comparable quality to conventional fixed-field

Fig. 1. Example of dose distributions in IMRT and RapidArc plans for a patient in the boost study. (A, B) Plans at DL1 (5% dose escalation); (C, D) plans at DL2 (10% dose escalation); and (E, F) plans at DL3 (15% dose escalation). PTV1 (red contour) and PTV2 (pink contour) are encompassed by the 95% isodose curves of 65 Gy (orange line) and 54 Gy (dark blue line), respectively. GTV_B (light green contour) is encompassed by the 105% (A, B); 110% (C, D); and 115% (E, F) isodose curves (bright pink line).

IMRT. Target volume coverage was similar between RapidArc and fixed-field IMRT plans at each dose escalation level. The absolute difference in statistically significant PTV DVH parameters was small and therefore unlikely to be clinically relevant. This is consistent with the results of other studies, which have performed similar comparisons using standard doses.^{22,25}

Several significant findings were demonstrated in our study. First, we observed significantly improved dose conformity with RapidArc compared with fixed-field IMRT. This is consistent with the preliminary results from the Ghent study,¹⁵ which reported improved biologic conformity with VMAT. However, other studies have reported conflicting results, with inferior dose conformity seen with RapidArc

Table 2
Mean values (± 1 SD) of PTV dose parameters between RapidArc and IMRT

	Standard		DL1		DL2		DL3	
	IMRT	RapidArc	IMRT	RapidArc	IMRT	RapidArc	IMRT	RapidArc
PTV1								
D95 (Gy)	62.7 (± 0.2)	62.8 (± 0.4)	62.8 (± 0.2)	62.8 (± 0.3)	62.8 (± 0.2)	62.7 (± 0.4)	62.7 (± 0.2)	62.7 (± 0.3)
D5 (Gy)	67.1 (± 0.3)	66.8 (± 0.3)	67.9 (± 0.8)	68.0 (± 0.8)	69.9 (± 1.8)	69.7 (± 1.8)	71.9 (± 2.8)	71.8 (± 3.0)
D2 (Gy)	67.6 (± 0.3)	67.3 (± 0.3)	68.8 (± 0.7)	68.9 (± 0.7)	71.5 (± 1.5)	71.6 (± 1.4)	74.3 (± 2.1)	74.4 (± 2.0)
PTV2								
D99 (Gy)	51.4 (± 0.5)	51.1 (± 0.4)	51.4 (± 0.4)	51.0 (± 0.5)	51.4 (± 0.5)	51.0 (± 0.4)	51.5 (± 0.5)	51.0 (± 0.4)
D95 (Gy)	52.5 (± 0.4)	52.3 (± 0.3)	52.5 (± 0.3)	52.1 (± 0.3)	52.5 (± 0.4)	52.1 (± 0.3)	52.5 (± 0.4)	52.0 (± 0.3)
D5 (Gy)	59.1 (± 1.7)	59.0 (± 1.7)	59.5 (± 2.0)	59.7 (± 2.0)	59.7 (± 1.8)	60.0 (± 1.7)	59.6 (± 1.9)	60.2 (± 1.8)
GTV _B								
D95 (Gy)	NA	NA	68.2 (± 0.4)	68.3 (± 0.2)	71.3 (± 0.4)	71.3 (± 0.3)	74.3 (± 0.4)	74.4 (± 0.4)
D5 (Gy)	NA	NA	69.8 (± 0.4)	70.0 (± 0.3)	73.0 (± 0.3)	73.2 (± 0.2)	76.1 (± 0.2)	76.4 (± 0.2)
D2 (Gy)	NA	NA	69.9 (± 0.4)	70.2 (± 0.3)	73.1 (± 0.3)	73.4 (± 0.2)	76.3 (± 0.3)	76.6 (± 0.2)

Statistically significant differences ($p < .05$) shaded in gray.

and VMAT.²² A possible reason for this discrepancy is that the fixed field IMRT technique in these studies used a larger number of fields (7–9) compared with our study, in which 5–7 fields were used, which could have led to improved conformity and quality of the IMRT plans. A 5- to 7-field technique is the current IMRT solution at our institution, because our experience suggests that clinically acceptable plans, which can be delivered in a shorter treatment time, are achievable with this technique. Our findings are consistent with the results of Bertelsen *et al.*'s study,²⁵ which also used 5–7 fields in their IMRT plans and demonstrated improved conformity with VMAT.

Another significant finding in our study was the lower mean dose received by the contralateral parotid gland with RapidArc compared with fixed-field IMRT. This is consistent with the results of other studies.^{22,25} The average mean dose in the plans was higher than our planning objectives, which are based on recent QUANTEC guidelines.²⁶ However, partial functional recovery can still occur with mean doses of 25–35 Gy, and therefore it is still worth sparing as much of the gland as possible even if planning objectives cannot be strictly met.²⁶ Our contralateral parotid mean doses were very similar to those found in Vanetti *et al.*'s study²² but was higher than those in Bertelsen *et al.*'s study.²⁵ A possible explanation for this discrepancy is that in Bertelsen *et al.*'s study, the patient cohort included patients with primary hypopharyngeal tumors that are likely to be situated further away from the parotid glands, which are therefore potentially easier to spare compared with the oropharyngeal cases in our study.

Neither RapidArc nor fixed-field IMRT exceeded the maximum dose constraints for spinal cord and brainstem, with minimal differences in absolute $D_{\max}$. However we observed higher mean doses with RapidArc, which were more prominent in the boost study. These results conflict with published data that report significantly lower doses with VMAT.²² This could again be explained by differences in planning and optimization techniques between studies. At our institution, the gantry angle positions for fixed-field IMRT are arranged to maximize avoidance of the central OARs, which could explain the

lower spinal cord and brainstem doses. Only the maximum dose was set as a dose constraint in our study and it is possible that different results would be obtained if additional constraints were used during optimization. It may also be possible to obtain lower doses to these OARs by application of avoidance sectors in the arcs and this will be further assessed in future planning studies.

The major advantages with RapidArc/VMAT are a reduction in treatment delivery time and MU,²² which could have a significant impact on clinical service efficiency. Our study confirmed a significant reduction in MUs with RapidArc, which was consistently seen at each dose level in the boost study and the standard dose study. The main benefit using fewer MU is the reduction in scattered and leakage radiation from the linear accelerator, and therefore a potential reduction in the risk of radiation-induced secondary malignancy. An interesting observation in our study was the higher volumes of normal tissue receiving very-low-dose radiation (higher V_{5Gy}) with RapidArc. It is uncertain whether this phenomenon, which is also reported in other studies,²⁷ will have a significant impact on the risk of secondary malignancy. Further investigation and longer follow-up of patients treated with RapidArc/VMAT are warranted to more accurately quantify this risk.

In our study, ¹⁸F-FDG-PET was used to define the regions for focal dose escalation. ¹⁸F-FDG is the most widely available PET radiotracer and is a potential surrogate marker of hypoxia, which is strongly associated with radioresistance.⁸ However, some studies have shown that glucose metabolism and uptake do not always correlate to the level of hypoxia in tumors.²⁸ A further limitation of ¹⁸F-FDG is its relatively low specificity (e.g., false positives in areas of inflammation).²⁹ However, ¹⁸F-FDG uptake is also correlated with other features associated with radioresistance, such as increased tumor cell proliferation.³⁰ Most local recurrences tend to occur within ¹⁸F-FDG-positive regions and patients with ¹⁸F-FDG-positive disease have inferior treatment outcomes.⁹ It would therefore be reasonable to use ¹⁸F-FDG-PET for the identification of regions for dose escalation and selection of patients requiring intensification of treatment.

The optimal schedule for PET-guided focal dose escalation is still unknown. In our study, the escalated dose was planned to be delivered in daily fractions throughout the 6-week treatment course. In the phase I study by Madani *et al.*,¹¹ the escalated dose was delivered in the first 2 weeks of treatment. The rationale for this is to allow the boost to be delivered when there is the least anatomical and biologic discrepancy between the pretreatment PET and radiotherapy treatment. It has been shown that temporal variations in PET signal can occur during the course of radiotherapy, which can lead to uncertainties in defining regions for dose escalation as treatment progresses.³¹ An argument against this up-front boost strategy is that for head-and-neck SCC, accelerated repopulation of tumor cells is expected to occur

Table 3
Mean values (± 1 SD) of CI_{paddick} scores for PTVs*

	PTV1		PTV2	
	IMRT	RapidArc	IMRT	RapidArc
Standard dose study	0.79 (± 0.04)	0.83 (± 0.03)	0.61 (± 0.03)	0.65 (± 0.03)
Dose escalation study				
DL1	0.79 (± 0.04)	0.82 (± 0.04)	0.60 (± 0.04)	0.65 (± 0.03)
DL2	0.79 (± 0.04)	0.82 (± 0.04)	0.61 (± 0.04)	0.65 (± 0.04)
DL3	0.77 (± 0.07)	0.81 (± 0.03)	0.60 (± 0.04)	0.64 (± 0.03)

* All differences between IMRT and RapidArc were statistically significant ($p < 0.05$).

Table 4Mean values (± 1 SD) of OAR dose parameters between RapidArc and IMRT

	Standard		Dose level 1		Dose level 2		Dose level 3	
	IMRT	RapidArc	IMRT	RapidArc	IMRT	RapidArc	IMRT	RapidArc
Spinal cord								
D _{max} (Gy)	44.2 (± 0.8)	43.8 (± 1.1)	43.5 (± 0.7)	44.6 (± 0.6)	43.7 (± 0.7)	44.4 (± 0.4)	43.5 (± 0.6)	44.5 (± 0.9)
Dmean (Gy)	33.1 (± 2.3)	34.5 (± 1.7)	32.5 (± 2.5)	35.0 (± 2.3)	32.5 (± 2.6)	35.3 (± 1.8)	32.4 (± 2.6)	35.1 (± 1.7)
Brain stem								
D _{max} (Gy)	45.1 (± 6.4)	44.8 (± 5.5)	42.6 (± 7.7)	44.2 (± 7.2)	42.7 (± 7.5)	42.7 (± 6.9)	42.3 (± 7.9)	43.7 (± 7.0)
Dmean (Gy)	12.8 (± 5.6)	14.2 (± 5.6)	11.0 (± 6.0)	13.0 (± 6.3)	10.9 (± 5.9)	12.7 (± 6.1)	10.9 (± 5.9)	12.8 (± 6.1)
Contra-lateral parotid								
Dmean (Gy)	27.9 (± 6.6)	27.3 (± 6.3)	29.9 (± 5.4)	29.0 (± 5.1)	30.3 (± 5.0)	29.3 (± 5.2)	30.3 (± 5.1)	29.7 (± 5.4)
V35Gy (%)	34.1 (± 14.7)	26.6 (± 15.7)	40.1 (± 11.6)	29.4 (± 12.0)	41.0 (± 11.1)	29.5 (± 12.4)	40.9 (± 10.6)	30.6 (± 12.5)
Ipsilateral parotid								
Dmean (Gy)	52.6 (± 11.9)	52.3 (± 12.4)	50.6 (± 12.7)	47.6 (± 13.9)	50.4 (± 12.8)	50.5 (± 12.8)	50.4 (± 13.2)	50.1 (± 13.2)
V35Gy (%)	81.9 (± 21.2)	79.5 (± 26.9)	78.2 (± 23.7)	74.9 (± 31.5)	77.8 (± 24.1)	75.9 (± 30.9)	78.2 (± 25.4)	75.5 (± 31.7)
Healthy tissue								
Dmean (Gy)	14.0 (± 1.6)	14.2 (± 1.4)	14.0 (± 0.9)	14.1 (± 0.8)	14.0 (± 0.9)	14.2 (± 0.8)	14.0 (± 0.9)	14.3 (± 0.8)
V5Gy (%)	41.6 (± 5.7)	44.3 (± 5.2)	41.4 (± 3.2)	43.3 (± 3.3)	41.5 (± 3.1)	43.1 (± 3.5)	41.4 (± 3.1)	43.2 (± 3.4)

Statistically significant differences ($p < .05$) shaded in gray.

from around the third week of treatment, which may be a more appropriate time for dose escalation.³² However, a delayed boost strategy may not be feasible because dose escalation could be limited by radiation-induced mucositis, which typically increases in severity during the later stages of treatment.

In our study, a uniform dose escalation to the PET-positive regions was applied (dose-painting by contours). Other studies have investigated a dose-painting-by-numbers technique, in which the prescribed boost dose varies according to the signal intensity of the individual voxels within the target volume.¹⁰ Although this technique has the potential benefit of reducing the volume of tissues receiving very high radiation doses, it assumes that there is a linear relationship between radiotracer uptake and radiosensitivity, and could also be influenced by spatial and temporal variations of radiotracer uptake affecting voxel intensity. Furthermore, precise setup limits to maintain the high level of dose modulation and highly sophisticated planning software, which is not currently widely available, would be required.

The limited accuracy of PET-based delineation of tumor boundaries remains a problematic issue. To date, there is no general consensus on the best delineation method.³³ In our study, we delineated the boost volumes using a freehand method that is dependent on visual interpretation of the PET signal. This is the most commonly used method but is prone to intra- and interobserver variability. Operator-independent automatic segmentation tools may provide a more objective solution. Automatic segmentation requires a threshold of radiotracer uptake to be defined to identify the areas to be delineated.³³ However, the optimal threshold level remains unclear and these methods can also be affected by the partial volume effect, which can underestimate the actual tumor size.³⁴

One limitation to our study was that coregistration of the ¹⁸F-FDG-PET and radiotherapy planning CT images was not performed, because the immobilization shells could not be fitted onto the existing PET couch at our institution. Although this is an obvious problem for

clinical implementation, we were able to achieve the primary aims of our study, which were to evaluate the feasibility of focal dose escalation with RapidArc and to compare these plans with fixed-field IMRT. We have now developed an in-house PET headrest, which allows the patient to be scanned in their immobilization shells, thereby permitting rigid coregistration of PET and radiotherapy planning CT images. Comparative planning studies are prone to biases that have been discussed previously.²² We have attempted to reduce planner bias because all plans were generated by a single planner using the same optimization engine, dose objectives, and calculation algorithm. It is worth noting that the plans were generated with planning objectives and techniques that are used clinically and were not designed to push the optimizer to its maximum limit. It may be possible to achieve further improvements in dose distributions if more dose-volume constraints were used in the optimization process. Finally, the increasing complexity of radiotherapy plans and dose delivery would demand high levels of precision in geometrical verification procedures during treatment. Careful review of the current standard protocol at our institution (planar kilovoltage and/or cone-beam CT imaging on days 1–3 and weekly cone-beam CT) would be required to ensure adequate levels of accuracy for future practical implementation of this strategy.

Conclusions

Focal dose escalation to biologically radioresistant regions as defined by ¹⁸F-FDG-PET is feasible with RapidArc. In this setting, RapidArc is able to achieve clinically acceptable plans with superior dose conformity, improved sparing of parotid glands, and reduced MU compared with fixed-field IMRT. Larger clinical studies are required to assess the impact of focal dose escalation on treatment outcome parameters, such as local control and toxicity.

Table 5Mean MU/fraction values (± 1 SD)

Study	DL	Percentage escalation above standard prescription dose	IMRT	RapidArc	Percentage reduction (%)
Standard dose study	NA		1109 (± 124)	667 (± 95)	39.9
Dose escalation study	1	5%	1234 (± 111)	630 (± 108)	48.9
	2	10%	1220 (± 96)	632 (± 112)	48.2
	3	15%	1261 (± 118)	641 (± 94)	49.2

All differences between IMRT and RapidArc were statistically significant ($p < 0.05$).

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