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Hypoxia-targeted radiotherapy dose painting for head and neck cancer using ^{18}F-FMISO PET: a biological modeling study

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Running title: Hypoxia-targeted dose painting for head and neck cancer

Abstract

Background

This study investigates the use of ^{18}F-fluoromisonidazole (FMISO) PET-guided radiotherapy dose painting for potentially overcoming the radioresistant effects of hypoxia in head and neck squamous cell carcinoma (HNSCC).

Material and Methods

The study cohort consisted of eight patients with HNSCC who were planned for definitive radiotherapy. Hypoxic subvolumes were automatically generated on pre-radiotherapy FMISO PET scans. Three radiotherapy plans were generated for each patient: a standard (STD) radiotherapy plan to a dose of 70 Gy, a uniform dose escalation (UDE) plan to the standard target volumes to a dose of 84 Gy, and a hypoxia dose-painted (HDP) plan with dose escalation only to the hypoxic subvolume to 84 Gy. Plans were compared based on tumor control probability (TCP), normal tissue complication probability (NTCP), and uncomplicated tumor control probability (UTCP).

Results

The mean TCP increased from 73% with STD plans to 95% with the use of UDE plans ($p < 0.001$) and to 93% with HDP plans ($p < 0.001$). The mean parotid NTCP increased from 26% to 44% with the use of UDE plans ($p = 0.003$), and the mean mandible NTCP increased from 2% to 27% with the use of UDE plans ($p = 0.001$). There were no statistically significant

differences between any of the NTCPs between the STD plans and HDP plans. The mean UTCP increased from 48% with STD plans to 66% with HDP plans ($p = 0.016$) and dropped to 37% with UDE plans ($p = 0.138$).

Conclusion

Hypoxia-targeted radiotherapy dose painting for head and neck cancer using FMISO PET is technically feasible, increases the TCP without increasing the NTCP, and increases the UTCP. This approach is superior to uniform dose escalation.

Keywords:
Head and Neck Neoplasms
Positron-Emission Tomography
Radiotherapy, Intensity-Modulated
FMISO

Introduction

Tumor hypoxia is associated with a poor response to radiotherapy. Experiments in malignant cell cultures have shown that under hypoxic conditions, approximately three times the radiotherapy dose is required to produce equivalent biological effect [1]. Clinical studies have also confirmed in head and neck cancer patients that hypoxia is correlated with poorer outcomes in terms of locoregional control, disease-free survival, and overall survival [2].

Several strategies have been developed and tested in large prospective trials to overcome the negative effects of hypoxia, including hyperbaric oxygen, carbogen and nicotinamide, hemoglobin modification, hypoxic radiosensitizers, and hypoxic cell cytotoxins [1]. A metaanalysis has shown that overall, hypoxic modification can improve outcomes in terms of locoregional control, disease specific survival and overall survival [3].

One emerging strategy to overcome hypoxia is the use of functional imaging to identify the hypoxic subvolume within tumors for the purposes of radiotherapy dose escalation. This strategy emerged partly due to the observation that following radiotherapy for head and neck cancers, locoregional recurrences tend to occur "in-field", in volumes that received the highest radiotherapy doses, possibly due to the presence of hypoxic cells [4, 5]. If the hypoxic - and therefore more radioresistant - subvolume can be identified, delivering a higher dose of radiation to this subvolume may overcome the radioresistance.

Past studies have demonstrated the ability of functional imaging such as ^{18}F-fluoromisonidazole (FMISO) PET to identify subvolumes of increased hypoxia within tumors [6, 7]. FMISO PET has been shown to correlate better with hypoxia [6] than the more

widely available ^{18}F-fluorodeoxyglucose (FDG) PET, therefore this was chosen as the imaging modality for identifying hypoxia in this study.

A Monte Carlo modeling study of the effects of transient and chronic hypoxia has shown that a modest radiotherapy boost dose (120 – 150% of the primary dose) to the hypoxic subvolume increases tumor control probability (TCP) back to that found in the absence of hypoxia [8].

The main difficulty in delivering boost doses however, is the possibility of increasing normal tissue toxicity due to the proximity of multiple sensitive organs at risk (OAR) to the target volumes. This difficulty can potentially be overcome through the use of "dose painting", which employs IMRT to deliver heterogeneous dose distributions to specific subvolumes within the tumor, while sparing surrounding organs at risk.

This study investigates the use of FMISO PET scans in identifying hypoxic subvolumes for the purposes of designing dose-painted radiotherapy plans. Hypoxia dose painted (HDP) radiotherapy plans are compared with standard radiotherapy plans and uniform dose escalation (UDE) plans. UDE plans illustrate what kind of results can be expected if dose escalation is given to the entire high dose planning target volume (PTV) without using FMISO PET guidance. Plans are compared based on their ability to achieve target objectives and normal tissue dose constraints, and calculations of TCP, normal tissue complication probability (NTCP), and uncomplicated tumor control probability (UTCP).

Material and Methods

Patient characteristics

The study cohort consisted of eight patients with primary head and neck squamous cell carcinoma (HNSCC) who had FMISO PET scans prior to definitive radiotherapy. All patients recruited into this study had previously untreated HNSCC and had good performance status (ECOG < 2). No patient was entered into the study who had received prior surgery or radiotherapy for their HNSCC, had symptomatic or radiological evidence of distant metastatic disease, was being treated with other anti-cancer therapy, or had a medical condition that would compromise the safe delivery of radiotherapy. This prospective study was approved by the Austin Health Human Research Ethics Committee. The patient characteristics are listed in Table 1.

All patients underwent standard diagnostic and staging investigations including physical examination, endoscopic examination, endoscopically-guided biopsy, CT, and FDG PET/CT. Pre-radiotherapy FMISO PET scans and radiotherapy planning CT scans were done within 2 weeks of starting radiotherapy. Following these investigations, the patients underwent radiotherapy with or without concurrent chemotherapy according to standard departmental protocols.

FMISO PET protocol

The FMISO was prepared in-house using a cyclotron, as previously described [7, 9]. FMISO PET studies were acquired on an Allegro GSO-based full-ring PET scanner (Philips Healthcare, Cleveland, OH, USA). These were performed in three-dimensional (3D) detection mode with a transaxial spatial resolution of 5 mm full width at half maximum

(FWHM). Patients were scanned two hours after intravenous injection of approximately 370 MBq of FMISO. Patient positioning was identical to that of the radiotherapy planning CT scan with immobilization using a neck support and a thermoplastic mask extending to the shoulders. For each patient a short transmission scan covering the patient's head and neck region was acquired using a single rotating ^{137}Cs point source (740 MBq) for attenuation correction. Following this, a PET emission scan of the same region was acquired in three bed positions of 6 mins each and reconstructed using a 3D row action maximum likelihood iterative algorithm (3D-RAMLA). The image voxel size after reconstruction is 4mm × 4mm × 4mm. The FMISO PET scan was co-registered with the radiotherapy planning CT scan using rigid body transformation.

Radiotherapy planning

Standard target volumes were manually contoured. The Gross Tumor Volume (GTV) was defined as gross demonstrable tumor using all available diagnostic and staging examinations and investigations excluding the FMISO PET scan. The Clinical Target Volume (CTV) was defined as the volume of tissue containing the GTV and subclinical malignant disease extension. Depending on the clinical scenario the CTV was split into high risk and low risk CTVs. Three Planning Target Volumes (PTVs) were generated: PTV1, PTV2 and PTV3. These were generated by 5 mm isotropic expansions around the low risk CTV, high risk CTV and GTV, respectively.

The hypoxic GTV (GTVH) was defined as the hypoxic subvolume within the GTV containing a significant number of hypoxic clonogens. A previous study showed that hypoxic tumors ($pO2 < 5$ - 10 mmHg) corresponded to a tumor to muscle standardized uptake value

(SUV) ratio of approximately 1.5 [6]. The GTVH was therefore automatically generated using Mim Maestro (MIM Software Inc., Cleveland, OH, USA) by applying a sub-thresholding algorithm within the GTV with a tumor to muscle SUV ratio of greater than 1.5 on the FMISO PET scan (see Figure. 1A). The ipsilateral nuchal muscles were used as the reference muscle tissue. A hypoxic PTV (PTVH) was generated by applying a 3 mm isotropic expansion margin around the GTVH.

Step-and-shoot IMRT plans were created using 7 or 9 equally spaced fields using the Monaco 3.0 (Elekta CMS Software, St Louis, MO, USA) treatment planning system. Biologically-based optimization was employed, and X-ray Voxel Monte Carlo algorithms were used to calculate dose. Three radiotherapy plans were created for each patient: a standard (STD) plan, a hypoxia dose-painted (HDP) plan, and a uniform dose escalation (UDE) plan. The STD plan consisted of a simultaneous integrated boost with 3 dose levels: 56 Gy, 63 Gy and 70 Gy, prescribed to the PTV1, PTV2 and PTV3, respectively. The HDP plan consisted of the same dose levels as the standard plan, as well as a dose of 84 Gy prescribed to the PTVH. The UDE plan consisted of a simultaneous integrated boost with 3 dose levels: 56 Gy, 63 Gy and 84 Gy, prescribed to the PTV1, PTV2 and PTV3, respectively. The treatment was planned to be given over 35 fractions for all plans. The highest dose level of 84 Gy was chosen based on a Monte Carlo modeling study which showed that 120 – 150% of the primary dose is required to negate the detrimental effects of hypoxia on the TCP [8]. Target volume objectives and OAR constraints were derived from the Radiation Therapy and Oncology Group (RTOG) 0615 protocol [10] (see Table 2). If significant portions of the PTV extended outside of the patient contour, the evaluation of target coverage was made based on contours clipped at the patient surface. Planning organ at risk volumes (PRVs) were created for the spinal cord and brainstem by generating 5 mm isotropic expansion margins.

Biological modeling

The tumor control probability (TCP) was calculated according to the Poisson TCP model [11] with modifications for additional radiobiological parameters [12] (see equations 1 – 5 in Appendix A). The following parameters were used : $\alpha/\beta = 10$, $\alpha = 0.396$, $\sigma_\alpha = 0.07$, clonogenic cell density (ρ)= 10^7 clonogens/cm^3, kickoff time (T_k) = 28 days, potential doubling time (T_{pot}) = 3 days [12], sensitiser enhancement ratio (SER) = 1.1 [13]. Within the GTVH volume, the oxygen enhancement ratio (OER) was defined as 1.5 [14]; and within the GTV (excluding the GTVH), no OER adjustment was made. The OER was then used to calculate the hypoxic α value as described in equations 4 and 5 in Appendix A. This dichotomous grouping of clonogens into hypoxic and non-hypoxic follows the methodology used in previous hypoxia modeling studies [12, 14].

The normal tissue complication probability (NTCP) was calculated using the Lyman-Kutcher-Burman model [15] with corrections for dose-per-fraction. The following parameters were used: n = 1.0, m = 0.53, TD50 = 31.4 Gy, α/β = 3 Gy for the parotid glands [16], n = 0.07, m = 0.10, TD50 = 72 Gy, α/β = 2 Gy for the mandible, n = 0.05, m = 0.17, TD50 = 66.5 Gy, α/β = 2 Gy for the spinal cord, and n = 0.16, m = 0.14, TD50 = 65 Gy, α/β = 2.5 Gy for the brainstem [1, 15].

The uncomplicated tumor control probability (UTCP) was calculated using the formula as defined by Agren et al. [17] (see Appendix B) with $\delta = 0.2$.

Biological modelling indices (TCP, NTCP and UTCP) were compared using two-way analysis of variance (ANOVA) with patient and plan as blocking factors. Pairs of means were compared with least significant difference. Statistical tests were performed using SPSS Statistics 17.0 (IBM, Armonk, NY, USA).

Results

In all 24 radiotherapy plans generated, the target volume objectives were met. All STD and HDP plans were within all OAR constraints, however only one out of eight UDE plans (Patient 1) were within all OAR constraints. For UDE plans, five out of eight patients exceeded mandible constraints, and seven out of eight patients exceeded parotid constraints. Dose distributions for a STD plan, a HDP plan and a UDE plan for a representative patient are shown in Figure 1 and the dose volume histograms (DVH) for that patient are shown in Figure 2.

The mean TCPs were 73%, 93%, and 94% for STD plans, HDP plans and UDE plans, respectively. HDP plans had a 27% higher TCP than STD plans and the two plans were statistically significantly different ($p < 0.001$). UDE plans had a 29% higher TCP than standard plans and the two plans were statistically significantly different ($p < 0.001$). There was no statistically significant difference between HDP plans and UDE plans ($p = 0.166$). The TCPs and UTCPs for each patient are listed in Table 3.

The mean parotid NTCPs were 26%, 26%, and 44% for STD plans, HDP plans and UDE plans, respectively. UDE plans had a 71% higher ($p = 0.03$) parotid NTCP than STD plans,

and a 68% higher (p = 0.03) parotid NTCP than HDP plans. There was no statistically significant difference in parotid NTCPs between STD and HDP plans (p = 0.938).

The mean mandible NTCPs were 1%, 2%, and 27% for STD plans, HDP plans and UDE plans, respectively. UDE plans had a 15 times higher (p = 0.001) mandible NTCP than STD plans, and a 13 times higher (p = 0.001) mandible NTCP than HDP plans. There was no statistically significant difference in mandible NTCPs between STD and HDP plans (p = 0.969).

There were no statistically significant differences in NTCP between standard plans, HDP plans, and UDE plans for the spinal cord (p = 0.174) and brainstem (p = 0.529). The NTCPs for each patient are listed in Table 4.

The mean UTCPs were 48%, 66% and 37% for STD plans, HDP plans and UDE plans, respectively. HDP plans had a 38% higher UTCP than STD plans, and the two plans were statistically significantly different (p = 0.016). HDP plans had a 75% higher UTCP than UDE plans, and the two plans were statistically significantly different (p = 0.001). There were no statistically significant differences in UTCP between UDE plans and STD plans (p = 0.138).

Discussion

All STD and HDP plans were within all normal tissue constraints, however not all UDE plans were within all normal tissue constraints. Compared with STD plans, HDP plans had higher TCP, comparable NTCP, and overall higher UTCP. Compared with STD plans, UDE plans also had higher TCP, but had worse NTCP, and therefore tended towards having a worse

UTCP. Overall, these results show that HDP plans may improve the therapeutic ratio, whereas UDE plans may actually worsen the therapeutic ratio, as they are limited by increased toxicity. These results support the strategy of using FMISO PET-guided dose painting over undirected dose escalation.

Similar to our study, previous planning studies have shown that boosts to hypoxic subvolumes are technically feasible and improve biological modeling indices. Thorwarth et al. [18] performed a planning study with biological modeling on 13 patients with HNSCC, comparing three different treatment plans: standard plans to a dose of 70 Gy in 35 fractions, uniform dose escalation plans to a dose of 77 Gy in 35 fractions, and hypoxia "dose painting by numbers" plans with variable dose prescriptions, up to a maximum of 2.4 Gy per fraction. TCPs increased from 55.9% with standard plans to 57.7% with uniform dose escalation plans, to 70.2% with hypoxia "dose painting by numbers" plans. The same equivalent uniform dose constraints for OARs were used for all the plans, however the exact constraints were not described and NTCPs were not calculated. This makes it difficult to assess the level of toxicity that would have been associated with these plans. Hendrickson et al. [19] performed a planning study on 10 patients with HNSCC, comparing standard radiotherapy to 70 Gy in 35 fractions with HDP plans to 80 – 90 Gy. HDP plans were associated with a mean 17% increase in TCP. Mean NTCPs were also increased with HDP plans; however this was described as "clinically acceptable". A UTCP metric was not used; therefore the overall benefit was not fully evaluated.

Our study builds on top of the previously performed studies in a number of ways. We have included a third comparison plan with a UDE to the same dose as the HDP plan, which proves that any improvements in biological modeling indices are not purely a function of

using higher doses. We have also performed GTVH contouring using automatic contouring with validated and clearly defined parameters, which ensures that our methodology is reproducible. Finally, we have provided a quantitative way to assess the therapeutic ratio in the form of the UTCP metric.

There are a few caveats to modeling hypoxia that should be considered when interpreting our results. Firstly, hypoxia within tumors has been shown to be dynamic, reflecting its acute and chronic components, and also reoxygenation following treatment [1]. The dynamic nature of hypoxia can be both an advantage and a disadvantage for HDP strategies. The main disadvantage is that if hypoxia is defined based on a single pre-treatment FMISO scan (as in this study), it may not be completely reflective of the actual hypoxia present in the tumor at each fraction of radiotherapy. If the hypoxia changes significantly during the treatment, our study may overestimate the benefits of a HDP plan. Reassuringly, Lin et al. showed that a dose painted radiotherapy plan prescribed to the initial hypoxic subvolume still results in significantly increased EUDs when applied to a scan done at a separate time point [20] and, Eschmann et al. showed that hypoxic volumes tend to shrink as defined on serial FMISO scans during radiotherapy, reflecting reoxygenation [21]. A possible advantage to the dynamic nature of hypoxia that can be exploited in future studies would be that the changing hypoxic volumes can be tracked with multiple FMISO PET scans during treatment, and the radiotherapy plan can be adapted to reflect these changes. Potentially, the high dose volumes may change locations during a course of treatment, and thus ensure that adjacent sensitive normal tissues such as mucosa do not become overdosed. This would be an interesting avenue for future research.

Secondly, hypoxia has substantial spatial variation, with steep oxygen gradients demonstrated over distances of only a few cell diameters, which is beyond the resolution of any non-invasive imaging modality [1]. This means that our study (or any imaging-based study) will be unable to detect every single hypoxic clonogen. However, it should still allow the identification of significant concentrations of hypoxic clonogens, which still has the greatest impact on TCP.

Thirdly, hypoxia has been shown to cause many more deleterious effects than just increased radioresistance. For instance, tumors often adapt to hypoxic environments by upregulation of hypoxia-inducible factor 1 (HIF-1), which regulates the transcriptional induction of more than 100 different known genes [1]. These target genes regulate multiple tumor characteristics that confer not only increased radioresistance but also increased angiogenesis, metabolism, invasion, and metastasis. The HDP strategy and the biological modeling used in this study only address the increased radioresistance, and do not address these other aggressive characteristics of hypoxic tumors. As such, this study probably oversimplifies the effects of hypoxia. However, even such a simplification provides important insights for future research.

Fourthly, uncertainties related to the delivery of the HDP plan must be considered. There are the random and systematic errors associated with patient positioning and patient movement that are present with any delivery of radiotherapy, and these are adequately dealt with using the PTV margins. There are errors in defining the hypoxic volume as described above which may lessen the advantages of dose painting. There are also errors associated with the co-registration of FMISO PET with the planning CT. Because of the high clinical workload on the combined PET/CT scanner in our department, only the single modality PET scanner was available for use in this research protocol. The FMISO PET scans were co-registered to the

planning CT scans using manual rigid body transformation which introduces additional error. If a combined PET/CT scan was performed instead, the manual registration step could potentially be eliminated, and the uncertainty would be considerably reduced. This is something which needs to be considered for future clinical studies. For the purposes of this biological modeling study which is designed to prove the feasibility of HDP, the registration error should not change the final results.

Lastly, the findings in this study are based on biological modeling only, which is known to have many limitations. The UTCP model is highly controversial because it assumes that increases in TCP are equivalent to decreases in NTCP and vice versa. This is an overly simplistic model that does not take the relative importance of the different kinds of tumor control and normal tissue toxicity endpoints into account. Moreover, very different results can potentially be obtained by using different models or different model parameters. As such, these results need to be proven in a prospective clinical trial before any firm conclusions can be drawn.

Evidence is now accumulating to justify a clinical trial on HDP in HNSCC. As outlined previously, there is ample evidence for hypoxia being associated with poorer outcomes after radiotherapy [2], and there is now also level 1a evidence for a benefit with hypoxic modification in patients with HNSCC [3]. Studies of conventional radiotherapy have shown that locoregional recurrences tend to occur “in-field”, in volumes that received the highest radiotherapy doses, possibly due to the presence of hypoxic cells [4]. Our study shows that dose-painted radiotherapy based on FMISO PET scans are technically feasible, have clear benefits in terms of increasing the TCP without increasing the NTCP, and therefore should be tested in clinical trials. An FMISO PET-based HDP plan as described in this study should be

safe to deliver as evidenced by our biological modeling, as well as by previous clinical trials of FDG PET scan-based dose painting, which have been safely delivered to more than 60 patients with HNSCC to doses as high as 85.9 Gy with acceptable toxicity at early followup [22, 23].

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Declaration of interest

The authors declare that there are no conflicts of interest.

Appendix A. Biological modeling equations

Readers are encouraged to read the original papers that described these equations in order to understand their derivation and limitations. The following is a brief summary of the equations used in this study.

The TCP was calculated according to the classically described equations for the Poisson TCP model [11] with modifications for SER as described by Avanzo et al. [12]:

$$TCP = \sum_i g_i(\sigma_\alpha) \cdot TCP(\alpha_i, \beta_i) \quad (1)$$

$$TCP(\alpha_i, \beta_i) = \prod_j TCP\left(\alpha_i, \beta_i, D_j, v_j\right)$$

$$= \prod_j exp\left[-\rho_c \cdot v_j \cdot \exp\left(-\alpha_i \cdot D_j \cdot SER\left(1 + \frac{\beta}{\alpha} d_j \cdot SER\right) + \frac{\ln(2)}{T_{pot}}(T - T_k)\right)\right] \quad (2)$$

$$g_i(\sigma_\alpha) \propto \left(\frac{1}{\sigma_\alpha} \cdot \sqrt{2\pi}\right) \cdot exp\left[\frac{-(\alpha_i - \bar{\alpha})^2}{2 \cdot \sigma_\alpha^2}\right] \quad (3)$$

where α and β are radiosensitivity parameters (where α has a Gaussian distribution with mean $\bar{\alpha}$ and standard deviation σ_α, representing the variation of α in the population), D_j is the dose delivered to a subvolume, v_j, ρ is the clonogenic cell density, SER is the sensitiser enhancement ratio, T is the overall treatment time, T_k is the kickoff time, and T_{pot} is the potential doubling time.

Linear quadratic radiosensitivity parameters for hypoxic (H) and aerobic (A) cells were determined through the following relations [14]:

$$\alpha_H = {}^{\alpha_A}/_{OER} \quad (4)$$

$$\left({}^{\alpha}/_{\beta}\right)_H = \left({}^{\alpha}/_{\beta}\right)_A \cdot OER \quad (5)$$

where OER is the oxygen enhancement ratio.

Appendix B

The UTCP was calculated according to the formula defined by Agren et al. [17]:

$$UTCP = TCP - P_I + \delta P_I(1 - TCP) \quad (6)$$

where δ is the statistically independent fraction and P_I is the probability of injury. The probability of injury is given by

$$P_I = 1 - \prod_{i=1}^{4}(1 - NTCP_i) \quad (7)$$

which takes account of the NTCPs for each of the four tissues, *i*.

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Table 1. Patient characteristics

Patient	Age	Sex	Site	Stage	GTV volume (cc)	BTV volume (cc)
1	68	M	Larynx	T3N2bM0	25.792	2.528
2	54	M	Oropharynx	T2N2bM0	52.344	5.352
3	59	M	Hypopharynx	T3N1M0	27.296	2.664
4	43	M	Oropharynx	T2N1M0	33.52	1.728
5	57	M	Nasopharynx	T1N0M0	14.48	1.496
6	57	M	Oropharynx	T3N2bM0	24.92	1.14
7	69	M	Oropharynx	T3N1M0	21.096	3.312
8	64	M	Oropharynx	T2N0M0	16.184	1.6

Table 2. Target objectives and OAR constraints

Target objectives	
PTV prescription dose (at each dose level)	D_{95} > prescription dose
	D_{99} > 93% of prescription dose
	D_{20} < 110% of prescription dose
	D_{5} < 115% of prescription dose
OAR constraint	
Brainstem	D_{max} < 54 Gy
Brainstem PRV	$D_{1\%}$ < 60 Gy
Spinal cord	D_{max} < 45 Gy
Spinal cord PRV	$D_{1\%}$ < 50 Gy
Bilat parotids or	D_{mean} < 26 Gy
L parotid or	D_{mean} < 20 Gy
R parotid	D_{mean} < 20 Gy
Mandible	D_{1cc} < 75 Gy

Table 3. TCPs and UTCPs

Patient	TCP (%)			UTCP (%)		
	STD	HDP	UDE	STD	HDP	UDE
1	71	93	95	57	73	78
2	70	92	93	49	71	32
3	70	92	92	49	67	62
4	75	93	95	50	69	28
5	72	94	95	25	50	22
6	74	95	97	50	77	48
7	71	91	92	39	49	23
8	83	94	96	63	71	8
Mean ± SD	73 ± 4	93 ± 1	95 ± 2	48 ± 12	66 ± 10	37 ± 23

The TCPs and UTCPs for each patient are shown. Abbreviations: STD, standard radiotherapy plan; HDP, hypoxia dose-painted plan; UDE, uniform dose escalation plan; SD, standard deviation

Table 4. NTCPs

	Parotid (%)			Mandible (%)			Spinal cord (%)			Brainstem (%)		
Patient	STD	HDP	UDE	STD	HDP	UDE	STD	HDP	UDE	STD	HDP	UDE
1	15	20	17	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1
2	21	22	49	1	< 1	26	< 1	< 1	< 1	< 1	< 1	< 1
3	238	26	31	< 1	< 1	1	< 1	< 1	< 1	< 1	< 1	< 1
4	22	19	32	5	7	52	< 1	< 1	< 1	< 1	< 1	< 1
5	50	43	71	1	1	12	< 1	< 1	< 1	< 1	< 1	< 1
6	24	18	22	2	1	35	< 1	< 1	< 1	< 1	< 1	< 1
7	32	41	60	4	2	26	< 1	< 1	< 1	< 1	< 1	< 1
8	20	20	70	2	4	64	< 1	< 1	< 1	< 1	< 1	< 1
Mean	26	26	44	2	2	27	< 1	< 1	< 1	< 1	< 1	< 1

The NTCPs for each patient are shown for each organ. Abbreviations: STD, standard radiotherapy plan; HDP, hypoxia dose-painted plan; UDE, uniform dose escalation plan

Figure 1

The FMISO PET/CT scan of a patient with a T3N2b oropharyngeal squamous cell carcinoma is shown (A). The GTVH, PTVH, PTV3 and PTV1 are outlined in yellow, green, blue and red, respectively. The dose distributions for the STD plan (B), the HDP plan (C) and the UDE plan (D) are demonstrated using “colorwash” with red indicating higher doses and blue indicating lower doses.

Figure 2

The DVHs are shown for the same patient shown in Figure 1. Solid lines represent the STD plan, dashed lines represent the HDP plan, and dotted lines represent the UDE plan.