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FULL PAPER

Comparison of dose distribution for head and neck cancer patients with and without dose painting escalation during radiotherapy realized with tomotherapy unit

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Objective: To determine and quantify the percentage dose increase to organs at risk (OARs) with multiple-level dose painting (DP) for patients with head and neck cancer in comparison with standard regimen.

Methods: 12 patients who had undergone fluorine-18 fludeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)/CT scan were retrospectively enrolled. Two treatment plans—one using DP escalation and one without—were optimized for each patient base on PET/CT data. The following variables were assessed: dose to OARs and target volumes; execution time; equivalent uniform dose; and normal tissue complication probability.

Results: No statistically significant differences in beam-on time were observed between plans with and without DP. However, significantly higher doses were observed for all DP-escalated plans in the OARs, with only two exceptions: the brain stem and V_{60Gy} for the mandible. Multiple-level DP resulted in dose increases ranging from 3.0% to

12.9%, depending on the OAR. The largest increase was seen for the parotid glands and the smallest for the mandible. Significant differences in the equivalent uniform dose were observed only for the parotid glands and spinal column, where the dose without DP was lower. The normal tissue complication probability for most OARs was very small.

Conclusion: Importantly, even though DP escalation resulted in higher doses to OARs vs conventional treatment planning, these usually did not exceed the dose tolerance levels. However, clinical trials are necessary to confirm the benefits of DP and to guarantee no additional toxicity.

Advances in knowledge: Multiple-level DP by numbers resulted in 3.0–12.9% dose increase, depending on the OAR. Our findings may suggest that DP escalation to very high doses is feasible for about 83% of patients without higher toxicity; however, it still should be confirmed on a larger group of patients.

INTRODUCTION

In recent years, considerable technological advancements have been made in the field of radiotherapy, particularly in imaging modalities such as positron emission tomography (PET) and MRI.^{1,2} Another major advancement was the development of radiation delivery systems capable of delivering the radiation dose with submillimetre accuracy.^{3–5}

The combination of the two advancements has enabled the development of a novel technique known as dose painting by numbers (DPBN). The idea of DPBN is to sculpt and escalate the dose distribution individually for each patient based on biological processes captured during functional imaging. DPBN has potential advantages in comparison with uniform dose escalation to the whole macroscopic tumour volume—dose painting (DP) by contours. First of all, it was proven that dose delivery to certain tumour subsections is more effective with the DPBN method,

because with DP by contours, large volumes are irradiated to high dose levels.⁶ This may lead to an elevated risk of acute toxicity caused by increased dose in normal tissues.⁷ Moreover, DPBN provides a higher tumour control probability.⁷ The term “dose painting” was used for the first time in the year 2000 by Ling et al.⁸

Like every new treatment planning method, DPBN requires clinical validation. It is necessary to understand all aspects of dose escalation based on molecular images and to ensure that this approach provides a significant clinical gain before implementing it into routine clinical practice. Previous publications have demonstrated that commercially available systems such as TomoTherapy® Hi-ART® (Accuray®, Madison, WI) or RapidArc® (Varian Medical Systems, Inc.),^{9–11} as well as systems developed in-house,^{6,12} can both be used for DPBN treatment planning.

Figure 1. Examples of target volumes: (a) oral cavity, (b) oropharynx and (c) hypopharynx. The planning target volume (PTV_{56.00Gy}) and seven dose painting by number (DPBN) subcontours are drawn on each CT scan.

A randomized Phase II clinical trial to evaluate DPBN is currently under way at the Ghent University Hospital in Belgium, and the results of that study are expected to answer the question of the clinical value of this technique. This study is based on glucose analogue fluorine-18 fludeoxyglucose (^{18}F -FDG) PET. This tracer is widely available and well understood with standardized imaging protocols. High ^{18}F -FDG uptake is associated with worse survival and corresponds to the relapse-prone subvolumes in head and neck cancer which may require higher doses.¹³ However, many questions about DPBN remain unanswered, primarily the dose levels to which it should be escalated and the effect of the technique on dose distribution in organs at risk (OARs) among other questions.^{6,8–12,14}

Given this context, we carried out the present study to quantify the percentage increase in dose to the OARs when DPBN is used. The main variables assessed were beam-on time, dose to OARs, equivalent uniform dose (EUD) and normal tissue complication probability (NTCP). To our knowledge, this is one of the first studies to compare treatment plans with and without DPBN.

METHODS AND MATERIALS

Patients

12 retrospective patients with locally advanced head and neck tumours (hypopharynx, oropharynx and oral cavity) were selected. All patients underwent planning ^{18}F -FDG PET/CT (Philips Medical Systems, Amsterdam, Netherlands) scans in the treatment position. All were immobilized in the supine position with an individualized thermoplastic mask (CIVCO Medical Solutions, Kalona, IA). Next, the clinical target volume, gross tumour volumes and OARs were contoured on the planning CT using Eclipse™ v. 10.0 (Varian Medical Systems, Palo Alto, CA). The OARs included the following: the parotid glands, spinal cord (SC), planning organ-at-risk volume (PRV) SC, brain stem (BS) and mandible. A limited number of OARs was used during the optimization process. The reason for that was to reduce a user bias during treatment planning. The optic nerves, chiasm, eyes and lenses were contoured but were not included into the optimization process, and because they were far away from the radiation field, the dose to those OARs was very low in all plans. The clinical target volumes and SC were expanded with an isotropic 3-mm margin to create the planning target volume (PTV) and PRV SC, respectively. The elective lymph node regions (PTV_{56.00Gy}), high-risk lymph node regions (PTV_{62.08Gy}) and the primary PTV (PTV_{67.20Gy}) were contoured for each patient. Figure 1 shows three locations of the target volumes used in this study. In the Supplementary material, the minimal distance from the DPBN region to different OARs was stated for each patient to provide more information about geometrical location of the DPBN region. Detailed information about images and contouring are available in a previous publication.¹⁰

The study was approved by the ethics committee of the Pozan University of Medical Sciences and registered under the number 364/15.

Treatment plans

Two separate treatment plans were optimized for each patient using a simultaneous integrated boost technique with and

without DPBN. Treatment planning was performed using the TomoTherapy Hi-ART treatment planning system (v. 4.2) using a 6-MV photon beam. A superposition/convolution algorithm with fine calculation grid size (0.2×0.2 cm) was used. Field width (FW), pitch factor and modulation factor (MF) parameters (1.05, 0.287 and 3 cm, respectively) were selected based on the relevant literature.^{9,10,14} The dose prescription (Table 1) for both plan types was scheduled for 32 fractions. An extensive description of the methodology applied to create DPBN plans was published previously.¹⁰ Briefly, however, treatment planning with DPBN was performed using a structure-based method with seven subcontours.^{6,9} PET voxel intensities selected for dose escalation ranged from 0.25 $I_{95\%}$ to $I_{95\%}$, where $I_{95\%}$ is 95% of the maximum PET voxel intensity within the dose-painted region. Because the radiobiological meaning of the PET voxel intensity values is not known, we assumed that the relationship between the voxel intensity and dose was linear.^{6,9,15}

Since user bias can influence plan comparisons, we decided that all plans would be optimized by the same planner with the same goal. Therefore, the optimization process was divided into two parts. First, 100 iterations were performed to reduce doses to the OARs. The maximum dose limits to the SC, PRV SC, BS and mandible were set at <45, 50, 54 and 70 Gy, respectively. The mean dose to the parotid glands was limited to <25 Gy. Next, during the subsequent (and final) 100 iterations, we focused on achieving dose distribution conformity and homogeneity within the target volumes, based on the International Commission on Radiation Units and Measurements report no. 83.¹⁶

Analysis

Dose-volume histograms (DVHs) were used to collect the data. The mean dose for the parotid glands and $D_{1\%}$ (where $D_{x\%}$ is a dose in $x\%$ of the volume) for the SC, PRV SC, BS and mandible were investigated. We also analyzed $V_{50\text{Gy}}$ (where $V_{x\text{Gy}}$ is the volume covered by the $x\text{Gy}$ isodose) and $V_{60\text{Gy}}$ for PRV SC and mandible, respectively. For the PTVs, we assessed $D_{99\%}$, $D_{95\%}$ and $V_{95\%}$.

All treatment plans were also analyzed for beam-on time, NTCP and EUD. The formula developed by Niemierko^{17,18} and Niemierko and Gay¹⁹ was used to calculate EUD and NTCP as follows:

$$\text{EUD} = \left[\sum_{i=1}^n (v_i D_i^a) \right]^{\frac{1}{a}} \quad (1)$$

$$\text{NTCP} = \frac{1}{1 + \left(\frac{\text{TD}_{50}}{\text{EUD}} \right)^{4\gamma_{50}}} \quad (2)$$

where a and γ_{50} are unitless characteristic parameters for tissue type, v_i is the i th part of the volume that received D_i dose, and TD_{50} is the tolerance dose for 50% complication probability during a specific time period. For all OARs, γ_{50} was set to 4, except for BS, for which $\gamma_{50} = 3$ was used. Parameter a was as follows: 13, 7, 1 and 14 for the SC, BS, parotid gland and mandible, respectively. TD_{50} was 66.5, 65, 31.4 and 72 for the SC, BS, parotid gland and mandible, respectively. All parameters were based on published data.^{19–24} An in-house software program was developed using the MATLAB® v. R2009b environment (MathWorks® Inc., Natick, MA) to calculate EUD and NTCP.

XLstat software (Addinsoft SARL, New York, NY) was used for the statistical analysis. To compare plans (with and without DPBN) for each patient, a Wilcoxon (double-sided) test was used. All statistics were performed for $\alpha = 0.05$.

RESULTS

Table 2 shows the data from 24 treatment plans (12 plans with and 12 without DP), including DVH-based parameters, beam-on time, EUD and NTCP.

Beam-on time

Overall, no statistically significant differences were seen in beam-on time between plans with and without DP. In three patients, the treatment time was shorter without DP, but this difference was small (around 5%).

Target volume coverage

No significant differences between plans were observed in the maximum dose to the PTVs (PTV_{56.00Gy}, PTV_{62.08Gy} and PTV_{67.20Gy}). However, for $D_{99\%}$ and $V_{95\%}$, a statistically significant difference was found; for both of these parameters, the target coverage was better for plans without DP. Table 2

Table 1. Dose prescription for plans with and without dose painting

Description	Plans with dose painting	Plans without dose painting	D_{total} (Gy)	NID _{2Gy} (Gy)
	D_{fx} (Gy)	D_{fx} (Gy)		
Elective LNRs—PTV _{56.00Gy}	1.75		56.00	51.57
High risk LNRs—PTV _{62.08Gy}	1.94		62.08	61.33
Primary CTV—PTV _{67.20Gy}	2.10		67.20	70.00
PET primary (only for plans with dose painting)	2.16–3.00	–	69.12–96.00	73.00–120.71

CTV, clinical target volume; D_{total} , total dose; LNRs, lymph node regions; NID_{2Gy}, normalized isoeffective dose; PET, positron emission tomography; D_{fx} , dose per fraction; PTV, planning target volume.

Table 2. Dose–volume statistics (median dose with range) for all patients comparing treatment plans with and without dose painting (DP)

Parameter X		With DP	Without DP	p-value	Mean difference (%) $\frac{X_{\text{with DP}} - X_{\text{without DP}}}{X_{\text{with DP}}} \cdot 100\%$
Beam-on time (s)		1007.2 (907.7–1255.0)	1001.2 (907.7–1255.0)	0.174	1.4
$D_{1\%}$ (Gy)	PTV _{56.00Gy}	58.1 (57.2–60.0)	58.0 (57.3–58.7)	0.065	0.3
	PTV _{62.08Gy}	63.9 (63.1–66.0)	63.9 (63.1–65.3)	0.498	–3.5
	PTV _{67.20Gy}	69.4 (67.5–70.3)	69.1 (67.6–70.0)	0.237	0.2
$D_{99\%}$ (Gy)	PTV _{56.00Gy}	53.2 (51.8–54.3)	54.2 (53.1–54.8)	0.003	–1.8
	PTV _{62.08Gy}	59.0 (57.6–60.7)	60.3 (58.9–61.8)	0.003	–1.8
	PTV _{67.20Gy}	64.3 (61.0–65.2)	65.0 (63.5–65.8)	0.014	–1.6
$V_{95\%}$ (%)	PTV _{56.00Gy}	99.0 (98.3–99.5)	99.5 (98.9–99.9)	0.004	–0.5
	PTV _{62.08Gy}	99.0 (98.4–100.0)	99.6 (99.0–99.9)	0.025	–0.4
	PTV _{67.20Gy}	99.5 (96.0–100.0)	99.7 (99.1–100.0)	0.025	–0.7
Brain stem	$D_{1\%}$ (Gy)	36.2 (29.3–44.8)	36.9 (28.3–42.6)	0.656	–0.5
	EUD (Gy)	18.4 (14.1–24.2)	18.8 (13.5–23.0)	0.656	–0.7
Spinal cord	$D_{1\%}$ (Gy)	39.7 (38.8–41.3)	36.6 (34.6–40.0)	0.003	7.5
	EUD (Gy)	27.0 (26.2–28.6)	23.9 (22.4–27.7)	0.003	10.6
PRV spinal cord	$D_{1\%}$ (Gy)	43.8 (42.9–45.0)	42.2 (40.3–43.8)	0.007	3.4
Mandible	$D_{1\%}$ (Gy)	67.8 (55.8–75.2)	66.6 (55.9–68.9)	0.041	3.0
	$V_{60\text{Gy}}$ (%)	26.8 (0.2–40.9)	26.6 (0.1–38.5)	0.056	5.2
	EUD (Gy)	60.5 (42.7–66.0)	59.4 (42.5–62.7)	0.092	1.8
	NTCP (%)	6.0 (0.0–19.8)	4.5 (0.0–9.8)	0.065	17.0
Contralateral parotid	EUD = D_{mean} (Gy)	24.0 (18.8–28.1)	21.9 (17.3–26.4)	0.003	10.2
	NTCP (%)	20.5 (15.3–24.9)	18.5 (14.0–23.3)	0.003	10.5
Ipsilateral parotid	EUD = D_{mean} (Gy)	28.8 (25.1–35.1)	25.4 (22.3–31.7)	0.004	12.9
	NTCP (%)	25.2 (21.5–32.9)	22.0 (18.7–29.2)	0.004	13.3

D_{mean} , mean dose; $D_{x\%}$, dose in x% volume; EUD, equivalent uniform dose; NTCP, normal tissue complication probability; PRV, planning organ-at-risk volume; PTV_{yGy} excludes PTV_{xGy} for $x > y$; $V_{x\text{Gy}}$, volume of the structure that is covered by the isodose x Gy.

Statistically significant results (confidence level $\alpha = 0.05$) are marked in bold.

shows that the mean difference between plans with and without DP was usually small and always $\leq 2\%$, a finding that indicates that no clinically relevant differences in PTV doses were observed.

Normal tissue sparing

Doses to the PRV SC were < 50 Gy in all cases; for this reason, no statistical analysis was performed for this parameter. The dose was significantly higher for DP-based plans (Table 2) for all OARs with two (non-significant) exceptions: the BS and $V_{60\text{Gy}}$ for the mandible.

The largest differences were observed for the parotid glands and SC. For the parotid glands, the median dose was 2.1 Gy higher (contralateral gland) and 3.4 Gy higher (ipsilateral) with DP. The median doses to the SC and PRV SC were lower by 3.1 and

1.6 Gy, respectively, without DP escalation. A statistically significant difference in the maximum dose was also seen in the mandible. However, clinical relevance was less important, as the 1.2-Gy increase for DP escalation is unlikely to substantially increase the risk of osteoradionecrosis.

It was also verified that the lower dose to OARs in plans without DP was not due to lower doses to target volumes.

Equivalent uniform dose and normal tissue complication probability

Significant differences in EUD were observed in the parotid glands and SC (Table 2), but not in other sites. The mean dose difference (absolute dose comparison) between plans with and without DP was clinically relevant for EUD and these differed by $> 10\%$.

The NTCP values were very small for both plans with and without DP (NTCP <0.001); as a result, no statistical analysis was performed for this parameter, except for the mandible and parotid glands. For $D_{1\%}$ in the mandible, the median dose was 1.5 Gy higher with DP, although no statistically significant difference was found. In case of the parotid glands, an increase of >10% in the EUD was observed.

DISCUSSION

To the best of our knowledge, this is the second article to compare dose distribution with DP *vs* a conventional scheme. The first article was published by Thorwarth et al;⁷ however, a different approach to the problem was carried out. In our study, we compared plans with and without DP to determine the extent to which the dose in the OARs increases when dose escalation was used. Whereas, in the article by Thorwarth et al,⁷ comparison of normal tissue doses was not performed because the study was designed to keep the same isototoxicity for all plans. This means that the target volume would be always compromised for more challenging tumours. In this study, if the target goal was hard to achieve, the dose to OARs could be compromised. Nevertheless, Thorwarth et al⁷ showed that with DPBN, doses up to 82 Gy may be applied without increase of toxicity. However, no constraints for normal tissue were stated in that article. Hence, comparison with our study is cumbersome.

Our main finding was that doses in OARs increased by 3.0–12.9% depending on the OAR. The largest dose increase occurred in the parotid glands (12.9% and 10.2% to the ipsilateral and contralateral glands, respectively), followed by the SC (7.5%), PRV SC (3.4%) and mandible (3.0%). Figure 2 presents the DVH for one patient, where the above-mentioned dose increase may be noticed. These findings may be of use for decision making about whether to treat the patient with DP or not.

There are two primary factors that could affect the decision to use DP. The first, and probably most important consideration, is the location of the DP volume. If this volume is located very close to an important OAR (e.g. the SC), then dose escalation may not be feasible. The second consideration is the upper limit of the DP dose prescription. In our study, we used an extreme situation (96 Gy), a dose that is unlikely to be used in a true clinical situation. However, we selected this high dose level to assess the worst-case scenario. Interestingly, despite the extremely high dose, the dose distribution quality was still within acceptable ranges. For 10 out of 12 plans with DP, the mean dose for at least one parotid gland was kept <25 Gy which correlates to a 20% risk of long-term salivary function of less than one-fourth of the pre-radiotherapy function. Contrarily, 11 out of 12 plans without DP met the above-mentioned constraint. These findings may suggest that escalation to very high doses is feasible for about 83% of patients without higher toxicity. However,

Figure 2. Dose–volume histogram for treatment plan with (solid line) and without (dotted line) dose painting for one of the patients. Planning target volumes (PTVs) from 69.12 to 96.00 Gy are positron emission tomography primary regions that were dose painted. PRV, planning organ-at-risk volume.

given a small cohort of patients, no generally applicable conclusions can be drawn.

In terms of beam-on time, we found no statistically significant differences between plans with and without DP escalation. Typically, patients with head and neck cancer are treated with the FW parameter set to 2.5 cm; consequently, beam-on time would be shorter than for FW = 1.05 cm. However, to compare the effect of dose escalation alone, we had to use the same treatment planning parameters (FW, pitch factor and MF) for both plans; otherwise, the comparison between plans would have been difficult or impossible since target volumes would be different, as would dose levels and field width.

Another aspect related to beam-on time is concerned with dynamic jaws, which could not be used in this study. The newest helical tomotherapy machines equipped with dynamic jaws reduce dose penumbra and thus the integral dose. However, the option of dynamic jaws is favourable only at the beginning and end of the PTV in the craniocaudal direction. None of the DP regions were at the edge of the PTV, thus even using the next generation helical tomotherapy would require the FW = 1.05 cm and hence no beam-on time improvement could be observed.

Although very promising, the DPBN method has some limitations. One of them is sensitivity to motion and geometric errors during radiotherapy. For conventional head and neck treatment, it is solved simply by adding the appropriate PTV margin to compensate for internal and setup errors. However, for DPBN subcontours such a margin does not exist. For this reason, the high dose may be deposited in the wrong region due to, for example, mispositioning. Moreover, one should keep in mind that high dose of the DP region may be deposited even inside or very close to the OAR. Sterpin et al¹⁴ proposed a method of modifying the dose prescription by dilation and deconvolution to compensate for geometric uncertainties.

Another limitation is concerned with PET imaging. It is well known that the spatial resolution of PET is limited and as a result partial volume effect occurs. This is even more important

for DPBN since the boosted volumes may be very small. Christian et al²⁵ proposed a solution for this by modifying the image reconstruction technique. One must remember that reconstruction algorithms also introduce signal noise which can deteriorate the tumour burden definition.²⁶ Moreover, stability of PET data is also an important factor, both spatial and temporal.^{26,27} Since PET imaging may take a lot of time (sometimes in uncomfortable position), patient motion may occur. Such situation will contribute to less accurate DP target delineation. Additionally, to maintain high quality of PET images, adequate protocols and procedures (depending on the tracer used) should be followed.²⁸ Furthermore, there is no consensus regarding the practice of standardized uptake value thresholds.^{29,30} However lately, Sher et al³¹ showed that for ¹⁸F-FDG tumours, the peak standardized uptake value may be the most robust parameter. Finally, different PET tracers may be used for DP (e.g. fluoromisonidazole, fluorothymidine and methylthiosemicarbazone). In our study, ¹⁸F-FDG was used which has high signal-to-background ratio, but hypoxia tracers have low signal-to-background ratio, and as a result, the delineation of functional areas is difficult and may contribute to higher uncertainties.²⁶ In the literature, some recommendations for implementation of PET images into treatment planning have been proposed.^{26,32} DP based on PET images should therefore be carefully considered and take all these limitations into account.

CONCLUSION

The present study shows that the TomoTherapy Hi-ART system is capable of generating discrete DP plans without a large dose increase to OARs. The highest dose increase occurred in the parotid glands, followed by the SC, PRV SC and mandible.

Although DPBN is a promising technique for dose escalation, treatment planning is highly challenging and appropriate patient selection is very important. The present study may be helpful in deciding whether a patient is suitable for DPBN treatment or not. However, before this technique can be introduced into routine practice, we must await the outcomes of clinical trials that are currently under way.

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