Interim 18F-FDG-PET based response-adaptive dose escalation of proton therapy for head and neck cancer: a treatment planning feasibility study

Guillermo Garrido-Hernandez

guillermo.g.hernandez@ntnu.no

Department of Physics, Norwegian University of Science and Technology

Helge Henjum
Department of Physics and Technology, University of Bergen

René Mario Winter
Department of Physics, Norwegian University of Science and Technology

Mirjam Delange Alsaker
Department of Radiotherapy, Cancer Clinic, St. Olav’s Hospital, Trondheim University Hospital

Signe Danielsen
Department of Oncology, St. Olav’s Hospital, Trondheim University Hospital

Camilla Grindeland Boer
Department of Oncology and Medical Physics, Haukeland University Hospital

Kristian Ytre-Hauge
Department of Physics and Technology, University of Bergen

Kathrine Røe Redalen
Department of Physics, Norwegian University of Science and Technology

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Abstract

Background

Image-driven dose escalation to tumor subvolumes has been proposed to improve treatment outcome in head and neck cancer (HNC). We used $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) acquired at baseline and two-three weeks into treatment (interim) to identify biologic target volumes (BTV). We assessed the feasibility of interim dose escalation to the BTV with proton therapy by simulating the effects to organs at risk (OARs).

Methods

We used the semiautomated just-enough-interaction (JEI) method to semi-automatically identify BTVs from $^{18}$F-FDG-PET images from nine HNC patients. Between baseline and interim FDG-PET all patients received photon radiotherapy. BTV was defined by assuming that lasting standardized uptake value (SUV) at interim reflects tumor radioresistance. Using Eclipse (Varian Medical Systems), we simulated the effects of a 10% (6.8 Gy(RBE$_{1.1}$)) dose escalation to the BTV with protons and compared results with proton plans without dose escalation.

Results

At interim $^{18}$F-FDG-PET, radiotherapy resulted in reduced SUV compared to baseline. However, there was a spatial overlap between high-SUV regions at baseline and interim that allowed definition of the BTV. Proton therapy planning demonstrated that dose escalation to the BTV was feasible while the increases in median and max dose to OARs remained below 2.0 Gy(RBE$_{1.1}$) and 1.0 Gy(RBE$_{1.1}$), respectively.

Conclusion

Our in silico analysis demonstrated the potential for response-adaptive dose escalation to the BTV with proton therapy based on interim $^{18}$F-FDG-PET. This approach may give more efficient treatment to HNC with radioresistant tumor subvolumes without increasing normal tissue toxicity. Further studies in larger cohorts are required to determine the full potential for interim $^{18}$F-FDG-PET-guided dose escalation of proton therapy in HNC.

Background

Head-and-neck cancer (HNC) patients often experience tumor recurrences within the gross tumor volume (GTV) (1). High-dose radiotherapy has been proven to improve local tumor control (2). As a consequence, image-driven dose escalation to sub-volumes within the GTV, often denoted as biologic
target volumes (BTV) (3), determined by factors such as tumor hypoxia or metabolism, has been proposed to improve treatment outcomes (4–8). While dose escalation studies in HNC to date has been performed using photons, proton therapy can potentially increase the dose to the tumor volume while reducing normal tissue toxicity, and thus result in improved treatment outcome compared to photon radiation (9–14). In HNC, dose escalation has been performed using dose painting by contours (DPBC) (11, 12) or dose painting by numbers (DPBN) (15, 16), requiring advanced imaging modalities like magnetic resonance imaging (MRI) and/or positron emission tomography (PET) to identify the BTV (6, 17).

Integrating PET into the radiotherapy workflow is attractive as PET gives insight into tumor metabolism and radiotherapy response (18, 19). HNC responses to radiotherapy are highly heterogeneous, and repeated imaging during the treatment course may be used for early identification of BTVs for dose escalation to improve treatment outcome. PET images acquired mid-treatment (interim) can be used to identify BTVs from persistent PET tracer avid regions. Dose escalation to interim BTVs may spare dose excesses to healthy tissue and tumor regions with good treatment response that may otherwise be targeted when using solely prior-to-treatment (baseline) PET images to define the BTV. While baseline PET imaging has been used for dose escalation with promising results (20), there is, to the extent of our knowledge, a lack of literature on response-adaptive dose escalation based on interim PET for proton therapy. Exploring this gap can contribute to more precise and effective proton therapy, our in silico analysis thus presents the first results of incorporating interim PET data into the proton therapy workflow.

Our aim was to simulate the effects of using \(^{18}\)F-fluorodexogycglucose (\(^{18}\)F-FDG)-PET data from HNC patients acquired at baseline and at interim for dose escalation to the BTV with proton therapy. Nine patients treated with photon radiotherapy were re-planned with protons. The BTVs were defined assuming that persistently high standardized uptake value (SUV) regions, detected both at baseline and interim PET, reflect resistant tumor regions. The feasibility of dose escalation was evaluated considering the resulting increase in dose to organs at risk (OARs).

**Methods**

**Patients**

HNC patients with locally advanced biopsy-proven squamous cell carcinoma (TNM8 T3/T4 and/or N+) scheduled for radical intensity modulated (chemo) radiotherapy were enrolled in the ongoing prospective EMINENCE study (NCT04612075). The study was approved by the Regional Committee for Medical Research Ethics in Central Norway (approval number 2019/64744) and all patients gave their written informed consent. This observational imaging study includes positive and negative human papilloma virus (HPV) patients. In this analysis, data from eleven patients (7 male, 4 female) with median age 62 (range; 51–74) years were included. Primary tumors were completely or partially removed before
radiotherapy, hence our study focused on lymph node lesions as a rationale for dose escalation. Four patients had a cystic/necrotic lymph node.

### 2.2 Imaging

PET/MRI was conducted before (baseline) and two-three weeks (range; 11–26 days) into radiotherapy (interim). For accurate image alignment with the radiotherapy planning CT, PET/MRI was performed in treatment position using a flat tabletop and dedicated coil set up with a custom-made rigid mask (21, 22). PET data was corrected for the attenuation of the radiotherapy setup using CT-based attenuation maps of the hardware in image reconstruction. One patient had a PET/CT at baseline, and one patient did not have the interim. PET data from these patients were used to evaluate the lesion segmentation algorithm but not for proton therapy planning. Planning CT was acquired on average 5 days (range; 0–11) before PET/MRI, MRI data was not used in this analysis. PET was acquired using a matrix size of 344 x 344 mm$^2$ and 2.03 mm slice thickness (voxel size of 2.09 x 2.09 x 2.03 mm$^3$). Median injected activity of $^{18}$F-FDG was 323 MBq (range; 273–386) at baseline and 321 MBq (range; 247–383) at interim. SUV was calculated as tracer uptake in a region of interest (ROI) / (injected activity / patient weight). Planning CT was acquired on a PET/CT scanner (Biograph 64 mCT Siemens Healthineers, Erlangen, Germany) and PET/MRI on a 3T PET/MR scanner (Biograph mMR Siemens Healthineers). See Supplementary Table 1 for a summary of patient and imaging specifics.

### Radiotherapy

Patients, as part of the EMINENCE B study, received photon radiotherapy using the volumetric modulated arc therapy (VMAT) technique with a prescribed dose of 68 Gy to high-risk planning target volume (PTV$_{68}$) and clinical target volume (CTV$_{68}$), 60 Gy to intermediate-risk PTV$_{60}$ and CTV$_{60}$, and 50 Gy to low-risk PTV$_{50}$ and CTV$_{50}$ in 34 fractions as 6 fractions/week. Primary tumor, lymph nodes and organs at risk (OARs) were manually delineated on the CT-images by an experienced oncologist.

### Proton therapy plan simulations

Two proton plans were made for each patient; one standard plan and one dose escalation plan where dose escalation, performed as DPBC and based on the interim PET, was added to the standard plan for the remaining treatment by weighting with respect to the number of fractions (12 fractions from the original standard plan plus 22 fractions from the plan with dose escalation). Targets for dose escalation were defined assuming that persistently high-SUV regions at interim PET correspond to aggressive/radioresistant tumor tissue (23). When identified at interim, we refer to the potentially radioresistant volumes as BTV. Three semi-automatic methods to define the BTV were investigated using 3D Slicer software (version 4.10, slicer.org): the just-enough-interaction (JEI) method from Beichel $et$ $al$ (24), 2) isocontouring SUV = 2.5 around lesions (SUV$_{2.5}$), and 3) isocontouring a 40% of the local SUV$_{\text{max}}$ around lesions (SUV$_{40\%}$). These methods have previously been used for lesion segmentation before treatment (24–26), but there is no consensus and only limited data to support an optimal method to be employed on interim images (27, 28).
Proton therapy plans were made in head-first supine position with Eclipse version 15.6.6 (Varian Medical Systems, Palo Alto, CA, USA) using the non-linear universal proton optimizer (NUPO, Varian Medical Systems, Palo Alto, CA, USA) and proton convolution superposition (PCS, Varian Medical Systems, Palo Alto, CA, USA). Multifield optimization was performed with a constant 1.1 relative biological effectiveness (RBE\text{1.1}). Robust optimization was performed with 14 uncertainty scenarios (4mm/3.5% and 0.0mm/3.5%). Prescribed doses from the VMAT plans were used as reference for proton plans. Dose escalation plans simulated a 10% dose increase to the BTV following Håkansson et al. (13). Planning constrains to OARs and target volumes followed the Danish Head and Neck Cancer (DAHANCA) 2020 guidelines (29), except the constraints on the mucosa, obtained from (30).

Bilateral CTV cases required five fields (see Fig. 1): one frontal field targeting the CTV below the chin, two oblique anterior fields targeting the right- and left-side of the CTV above the shoulders, and two oblique posterior fields targeting the right- and left-side of the CTV above the skull base. Unilateral CTV cases required three fields being oblique fields at the side without lesions removed. Proton fields required range shifters and a 10 cm air gap between snout and patient skin. No field directly traverses through dental artifacts, which were accounted for with HU = 0 (water). In case of large overlap between CTV and OARs, tumor dose coverage was prioritized.

Results

Figure 2 shows an example of the PET/MR scans at baseline and interim with the corresponding high-SUV volumes delineated. It also shows the planning CT with the BTV for dose escalation segmented. The BTV corresponds to the high-SUV volume at interim. Data on the volumetric similarity and position differences between high-SUV regions at baseline and interim is shown in the Supplementary Table 2. Volume similarity for the JEI method, given by the Dice coefficient, results in the highest mean value and lowest standard deviation (0.60 ± 0.18). The position differences, given by the overlapping fraction, was similar for the JEI and SUV\textsubscript{2.5} methods, with the lowest standard deviation for the JEI method (0.65 ± 0.20).

Variations between baseline and interim maximum and median SUV for all high-SUV regions, as well as on their volume for the JEI segmentation method are shown in Fig. 3. Maximum and median SUV showed a reduction from baseline to interim PET scans. Volume changes of the high-SUV structures from baseline to interim are seen in the top panel, showing a general volume reduction except for lesions 4, 8, 9 and 10 where the interim volume was larger than at baseline. Compared to the SUV\textsubscript{2.5} and SUV\textsubscript{40%}, the JEI method showed the highest overlap between baseline and interim high-SUV regions, and the most consistent results with lowest variability with respect to the expected treatment response (Fig. 3, Supplementary Figs. 1 and 2).

Proton dose escalation plans were therefore made using BTVs from JEI at interim. The 10% dose escalation (6.8 Gy(RBE\text{1.1})) to BTV was achieved while OAR doses, measured by the near-maximum (D\textsubscript{2%}) and median dose, showed minor changes between dose escalation and standard plans, see
In cases with an overlap between OARs and the BTV a small volume of the OARs experienced a dose increase. The largest $D_{2\%}$ increase was found for the right parotid in four cases where $D_{2\%}$ was increased to between 3.8 and 6.4 Gy(RBE$_{1.1}$). For the oral cavity, one patient presented an increase in $D_{2\%}$ of 3.2 Gy(RBE$_{1.1}$). For $D_{\text{median}}$ the largest increases were found for the oral cavity, larynx, and parotids, although always below 2.0 Gy(RBE$_{1.1}$).

Figure 5 shows the dose volume histograms (DVHs) from the OARs, BTV, and the CTV$_{68}$ for the standard and dose escalation proton therapy plans. The results show that standard proton therapy plans gave a homogeneous dose distribution of 68 Gy(RBE$_{1.1}$) to all target volumes with no substantial differences between CTV$_{68}$ and BTV. For the dose escalation plans, the CTV$_{68}$ curves showed a dose increase and reduction in dose homogeneity, while the BTV curves show the intended homogeneous dose distribution of 75 Gy(RBE$_{1.1}$) after dose escalation. The DVHs for the OARs show minor differences between standard and dose escalation proton plans. The individual patient DVHs are shown in Supplementary Fig. 3.

**Discussion**

We used $^{18}$F-FDG-PET of HNC to identify the BTV at interim assuming that lasting high-SUV tumor regions represent radioresistance. We then simulated response-adaptive dose escalation to the BTV for the remaining fractions from the interim onwards with proton therapy, using a constant 1.1 RBE according to current clinical practice. Our simulations showed that a 10% dose escalation to the BTV can be achieved with protons, with no significant increase in OAR dose.

Identification of the BTV was based on semi-automatic segmentation of high-SUV regions (Fig. 3, Supplementary Figs. 1 and 2). Comparison of baseline and interim high-SUV regions revealed typically a large volume similarity and overlap, but considerable variability of these parameters hinders the accuracy of targeting potential radioresistant tumor tissue (Fig. 3, Supplementary Table 2), thus using interim PET could be valuable to maintain treatment accuracy. We identified the JEI algorithm as the preferred segmentation method. The SUV$_{40\%}$ method resulted in volume increases from baseline to interim, inconsistent with therapeutic responses, and was found to be unreliable. The JEI and SUV$_{2.5}$ methods performed similarly, but, however, the JEI semiautomatic segmentation approach turns the segmentation problem into a graph-based optimization problem employing a cost function that takes into account local image statistics. Because of this, JEI required fewer manual corrections. Our results are in line with a recent study which found that gradient-based and SUV$_{2.5}$-based methods were preferable over the SUV$_{40\%}$ method to assess volumetric tumor response (27, 28). Before clinical implementation of $^{18}$F-FDG-PET-based dose escalation with proton therapy becomes a reality, a reliable BTV definition would be needed. Further studies in larger patient cohorts and with a ground truth (expert segmentation) will be needed for reliable BTV detection. To make response-based adaptation a reality, semi- or fully automatic methods are required to enable fast and potentially real-time treatment adaptation.
Regarding the target volumes, Fig. 4 shows that the 10% dose increase (6.8 Gy\((\text{RBE}_{1.1})\)) to the BTV was achieved for all patients. As for the OARs, Fig. 4 shows how some patients exhibited a \(D_{2\%}\) increase to some OARs (Supplementary Fig. 3: Patient C, right parotid; Patient F, right parotid; Patient G, right parotid; Patient H, right parotid). These increases were not so high for the \(D_{\text{median}}\) meaning that the results can be explained by an overlap between the corresponding OAR and the BTV. For some patients, dose escalation even resulted in reduced doses to OARs (Supplementary Fig. 3: Patient D). This could be due to decreased proton dose uniformity in target volumes. When performing proton treatment planning, Eclipse covers the target volume in spots and assigns a pencil beam to each spot. Each pencil beam is transported through the medium, calculating the dose to each voxel analytically. Total dose distributions are obtained after summing all doses to the voxels (31). Dose escalation to the BTV is achieved by increasing the weight on pencil beams assigned to spots in the BTV and reducing the weight on spots near target volume edges. In doing so, target volume edges and nearby OARs would absorb most dose from the pencil beam plateaus instead of from the Bragg peaks, lowering the dose placed in this area. As seen in our results, when OARs overlap with the BTV this behavior was not exhibited, in such cases dose escalation may not be recommended.

Figure 5 shows that the 10% dose increase (6.8 Gy\((\text{RBE}_{1.1})\)) was performed homogeneously to the BTVs. According to the CTV\(_{68}\), a loss of homogeneity after dose escalation was seen on the appearance of a second shoulder on the DVHs. Even though such effect was expected (BTV is contained by the CTV\(_{68}\)), neither BTV size nor BTV-CTV\(_{68}\) overlap clearly correlate with this effect (Supplementary Fig. 3: Patient A, lesion 1; Patient E, lesion 8; Patient F, lesion 9; Patient I, lesion 12). At the same time, minor differences were seen between the shoulder at the standard plan to the CTV\(_{68}\) and the first shoulder at the dose escalation plan to the CTV\(_{68}\) in terms of position and shape. This means that the dose escalation to the BTV was performed accurately and homogenously without changing the dose to the surrounding target tissue that was not eligible for dose escalation. The small differences between the OAR-DVHs at standard proton plans and dose escalation proton plans (Fig. 5) confirmed that dose escalation in proton therapy can also be performed without drastically increasing the dose to the healthy tissue surrounding the targets.

We performed our simulations using \(\text{RBE}_{1.1}\). Published variable RBE models show a lower plateau region in the spread-out Bragg peak (SOBP) and higher dose at the distal edge compared to a \(\text{RBE}_{1.1}\) SOBP (32). This could be exploited to reach dose escalation targets using lower physical doses, resulting in lower dose on the SOBP plateau and reduced dose to the OARs when compared with \(\text{RBE}_{1.1}\) dose distributions. This hypothesis has not yet been tested and will be explored together with linear energy transfer (LET)-based dose escalation in a future study.

Limitations of our dose escalation approach arise from keeping the proton beam angle configuration identical as in the standard proton plans. Changing the beam angles when creating dose escalation proton plans could potentially have resulted in superior BTV coverage and even lower OAR irradiation.
However, the potential benefits of doing so are unknown, and allowing for new beam configurations would also increase the planning time, hindering the optimization of a future automated workflow.

**Conclusion**

We used $^{18}$F-FDG-PET to identify the BTV at interim in HNC and simulated response-adaptive dose escalation to the BTV with proton therapy, assuming that high-SUV tumor regions at interim represent the radioresistant BTV. Differences between high-SUV regions at baseline and interim suggest that using interim $^{18}$F-FDG-PET data could increase the accuracy of targeting radioresistant tumor tissue throughout the treatment course. Simulations using planning tools widely available in the clinic showed that an accurate and homogeneous 10% (6.8 Gy(RBE$_{1.1}$)) dose escalation to the BTV could be achieved with protons with no significant increase in OAR dose. Our response-adaptive approach provides an example on how $^{18}$F-FDG-PET can be used to potentially improve treatment outcomes in HNC patients. Since this study was conducted with a constant RBE$_{1.1}$, future studies may be extended to investigate possible improvements or pitfalls when accounting for RBE variability.

**Abbreviations**

- **BTV**: Biological Target Volume
- **CT**: Computerized Tomography
- **CTV**: Clinical Target Volume
- **DE**: Dose Escalation
- **DPBC**: Dose Painting By Contours
- **DPBN**: Dose Painting By Numbers
- **DVH**: Dose Volume Histogram
- **FDG**: Fluorodeoxyglucose
- **GTV**: Gross Tumor Volume
- **HNC**: Head and Neck Cancer
- **JEI**: Just Enough Interaction
- **LET**: Linear Energy Transfer
- **MRI**: Magnetic Resonance Imaging
Declartions

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None.

Author contributions

All authors were involved in the study design with main responsibilities laying on GGH, KYH and KRR. RMW, MDA and SD assisted with patient data management and data acquisition. RMW carried out $^{18}$F-FDG-PET image processing, assisted with image registration and provided support on the choice of segmentation methodology. MDA was responsible for OAR delineation. HH and CBG assisted on proton therapy planning using Eclipse TPS. GGH, KYH and KRR prepared the manuscript, while all authors contributed to manuscript review and discussion. All authors read and approved the final manuscript.

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Availability of data and materials

Data can be made available based on a reasonable request to the authors.

Ethics approval and consent to participate

The study was approved by the Regional Committee for Medical Research Ethics in Central Norway (approval number 2019/64744) and all patients gave their written informed consent. The study is available in ClinicalTrials.gov with identifier NCT04612075.
Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References


**Figures**

![Figure 1](image-url)
Proton plan field arrangement for a bilateral clinical target volume (CTV) head and neck cancer (HNC) case. Organs at risk (OARs): Right parotid (blue), left parotid (cyan), spinal cord (yellow) and oral cavity (salmon). Optimization structures: high-risk CTV\textsubscript{68} (pink), high-risk planning target volume (PTV\textsubscript{68}) (green) and low-risk PTV\textsubscript{50} (white).

**Figure 2**

Example of PET/MR scan at baseline (A) and interim (B) for the same patient. The high standardized uptake value (SUV) at the interim image (B) shows the biological target volume (BTV) for dose escalation semi-automatically contoured using the just-enough-interaction (JEI) method. Panel C shows the BTV and clinical target volume (CTV) on the planning CT for the same patient.
Figure 3

Structure statistics from the just-enough-interaction (JEI) method (structure volume, maximum and median SUV within structure) applied to all studied lesions from patients eligible for preliminary assessment and study of $^{18}$F-fluorodexogyc glucose ($^{18}$F-FDG)-PET scans. Results shown for baseline and interim $^{18}$F-FDG-PET.

![Figure 3](image)

Figure 4

Organs at risk (OARs) and target volumes differences in near-maximum dose ($D_{2\%}$) (panel A) and median dose (panel B). Dose differences were calculated between standard proton plans and dose escalation (DE) proton plans with 10% (6.8 Gy(RBE$_{1.1}$)) dose escalation to the positron emission tomography (PET)-based biological tumor volume (BTV) at the interim timepoint.

![Figure 4](image)
Figure 5

Organs at risk (OARs) and targets (CTV₆₈ and BTV) dose volume histogram (DVH) plots for all head and neck cancer (HNC) patients eligible for the proton therapy planning part of the study. Gray shaded areas mark the dose objective for the standard plan (light: 68 Gy(RBE₁.₁)) and for the dose escalation plan (dark: 75 Gy(RBE₁.₁)).
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile.pdf