Dose painting in lung cancer

PET-based dose painting in non-small cell lung cancer: Comparing uniform dose escalation with boosting hypoxic and metabolically active sub-volumes

Aniek J.G. Even a,*, Judith van der Stoep a, Catharina M.L. Zegers a, Bart Reymen a, Esther G.C. Troost a,b, Philippe Lambin a, Wouter van Elmpt a

a Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands; and b Institute of Radiooncology, Helmholtz-Zentrum Dresden-Rossendorf, Germany

ABSTRACT

Background and purpose: We compared two imaging biomarkers for dose-escalation in patients with advanced non-small cell lung cancer (NSCLC). Treatment plans boosting metabolically active sub-volumes defined by FDG-PET or hypoxic sub-volumes defined by HX4-PET were compared with boosting the entire tumour.

Materials and methods: Ten NSCLC patients underwent FDG- and HX4-PET/CT scans prior to radiotherapy. Three isotopic dose-escalation plans were compared per patient: plan A, boosting the primary tumour (PTVprim); plan B, boosting sub-volume with FDG >50% SUVmax (PTVFDG); plan C, boosting hypoxic volume with HX4 tumour-to-background >1.4 (PTVHX4).

Results: Average boost volumes were 507 ± 466 cm³ for PTVprim, 173 ± 127 cm³ for PTVFDG, and 114 ± 73 cm³ for PTVHX4. The smaller PTVHX4 overlapped on average 87 ± 16% with PTVFDG. Prescribed dose was escalated to 87 ± 10 Gy for PTVprim, 107 ± 20 Gy for PTVFDG, and 117 ± 15 Gy for PTVHX4, with comparable doses to the relevant organs-at-risk (OAR). Treatment plans are available online (https://www.cancerdata.org/10.1016/j.radonc.2015.07.013).

Conclusions: Dose escalation based on metabolic sub-volumes, hypoxic sub-volumes and the entire tumour is feasible. Highest dose was achieved for hypoxia plans, without increasing dose to OAR. For most patients, boosting the metabolic sub-volume also resulted in boosting the hypoxic volume, although to a lower dose, but not vice versa.

© 2015 The Authors. Published by Elsevier Ireland Ltd. Radiotherapy and Oncology 116 (2015) 281–286

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
aggressiveness and radioresistance \cite{10,11}. The 2-nitroimidazole tracer $^{18}$F-fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol (HX4) is an example of a PET tracer whose ability to assess tumour hypoxia non-invasively has been validated \cite{12–15}. Another biological process that can be assessed is tumour glucose metabolism, which is imaged with the commonly used tracer $^{18}$F-fluorodeoxyglucose (FDG). For FDG-PET, it has been shown that volumes of local relapse are correlated with high uptake regions on pre-treatment images and are stable over time \cite{16–19}.

The question of which imaging surrogate should be used for dose painting is still under debate, but several surrogates have been and are being used in clinical trials \cite{8,9,20,21}. FDG is commonly used and widely available; its high pre-treatment uptake is related to local relapses. However, spatial correlation between uptake and local recurrences is not perfect. Aerts et al. \cite{18} found that 30% of relapses were outside the high FDG region. On the other hand, hypoxia is known to be an important factor in chemotherapy and radiotherapy resistance. Although hypoxia imaging has only been used in clinical trials so far, these tracers are receiving more attention for dose painting purposes.

Zegers et al. \cite{22} compared metabolic and hypoxic uptake patterns and found a good correlation between high uptake volumes of both tracers for most patients. For frequently used thresholds, the hypoxic volumes were generally smaller than the high metabolic uptake volumes. Consequently, creating a boost plan based on hypoxia imaging may reduce the boost volume and increase dose-escalation levels even further. However, since margins have to be added in dose painting by contours to account for treatment delivery uncertainties, smaller high uptake sub-volumes on PET do not automatically result in smaller planning boost volumes. Furthermore, Zegers et al. \cite{22} described a partial mismatch between hypoxic and metabolic volumes in some patients. For those patients, it is an a priori unknown what effect the selected boost volume with appropriate margins will have on the dose distributions of different dose painting plans.

Therefore, we compared different dose-escalation strategies to determine the influence of the used imaging biomarker on achieved tumour dose levels. For each patient, we created an iso-toxic dose-painting plan boosting the FDG high uptake volume and a plan boosting the hypoxic volume. For comparison, a plan with a boost to the whole tumour was created. We evaluated the feasibility of these treatment plans together with dosimetrically achieved parameters for organs-at-risk dose and target volume. Furthermore, we evaluated the accuracy of a particular imaging surrogate for dose boosting on the coverage of the other biological sub-volumes.

**Materials and methods**

**Patients**

NSCLC patients who were inoperable or had irresectable disease (cT2–T4, stage IB–III) were included in an ongoing phase II randomised clinical trial (NCT01024829). To be eligible, the primary tumour had to have a minimum diameter of 4 cm and maximum standardised uptake value (SUV$_{\text{max}}$) $\geq 5$ on pre-treatment FDG-PET \cite{8}. The study was approved by the Medical Ethics Review Committee and all patients gave written informed consent.

A dummy treatment plan was generated and a minimal dose of 72 Gy in 24 fractions (i.e. 3 Gy/fraction) to the planning target of the primary tumour (PTV$_{\text{prim}}$) ought to be feasible before randomisation was performed. We selected patients with hypoxic sub-volumes as detected on HX4-PET for this study.

**Image acquisition**

Patients were scheduled for FDG-PET/CT and hypoxia HX4-PET/CT scans on different days, within the same week before radiotherapy. A pre-treatment respiratory gated 4D FDG-PET/CT was acquired using a Siemens Biograph 40 PET/CT scanner (Siemens Healthcare, Erlangen, Germany), according to the NEDAP protocol \cite{23}. HX4-PET/CT acquisition was performed four hours after injection of the hypoxia tracer on a Philips Gemini TF 64 scanner (Philips Healthcare, Best, the Netherlands) \cite{13}. Patients were scanned in treatment position on a flat table top using the same fixation devices.

**Boost volumes**

Gross tumour volumes of the primary tumour (GTV$_{\text{prim}}$) and involved lymph nodes (GTV$_{\text{LN}}$) were delineated on the mid-ventilation phase of the 4D FDG-PET/CT scan by an experienced radiation oncologist. A 5-mm margin was added to the GTV$_{\text{prim}}$ to include microscopic disease extension and create the clinical target volume (CTV$_{\text{prim}}$). An individualised margin, depending on the movement of the tumour on the 4D planning CT, was added to the CTV$_{\text{prim}}$ to create the planning target volume (PTV$_{\text{prim}}$) \cite{24}. For the lymph nodes, we used a 5-mm CTV and 5-mm PTV margin irrespective of the motion of the nodes. The PTV$_{\text{prim}}$ was used as uniform boost planning target for plan A; additional structures were created to boost the metabolic and hypoxic sub-volumes. Boosting the metabolic target (GTV$_{\text{FDG}}$) was based on FDG-PET/CT and defined as the region within GTV$_{\text{prim}}$ with an SUV above 50% of SUV$_{\text{max}}$ (Plan B). Since the FDG-PET/CT scan was used as planning CT, no additional registration of the PET to the CT had to be performed. Boosting the hypoxic volumes (GTV$_{\text{HX4}}$) was based on HX4-PET/CT (plan C). The HX4-PET/CT scan was registered rigidly to the planning FDG-PET/CT scan using the treatment planning system (Eclipse version 11.0, Varian Medical Systems, Palo Alto, CA). We applied a bony anatomy match, followed by a soft tissue match with the primary tumour as region of interest. Background was defined as mean uptake in the aortic arch. Voxels with a tumour-to-background ratio (TBR) $> 1.4$ within the GTV$_{\text{prim}}$ were classified as GTV$_{\text{HX4}}$. The TBR $> 1.4$ cut-off value was chosen based on published research \cite{12,25–27}. For GTV$_{\text{FDG}}$ and GTV$_{\text{HX4}}$, we used the same individualised GTV-PTV margins to create PTV$_{\text{FDG}}$ and PTV$_{\text{HX4}}$ \cite{8}.

**Organs-at-risk**

Organs-at-risk (OAR) were delineated on the planning FDG-PET/CT. Dose constraints were chosen according to the ongoing clinical trial protocol \cite{8,28}: lungs $D_{\text{mean}} < 20$ Gy (corrected to EQD2); spinal cord $D_{0.1} < 51$ Gy (EQD2 $< 52$ Gy); oesophagus $V_{30} < 80\%$ \cite{29}; brachial plexus $D_{0.1} < 66$ Gy (EQD2 $< 66$ Gy); whole heart $D_{\text{mean}} < 46$ Gy (EQD2 $< 46$ Gy); planning organ-at-risk volume mediastinal structures (OAR + 5-mm margin) $D_{0.1} < 76$ Gy (EQD2 $< 94$ Gy), where $D_{\text{mean}}$ is the mean dose, $D_{0.1}$ the dose delivered to 0.1% of the OAR, $V_{30}$ the volume receiving 36 Gy and EQD2 the equivalent 2 Gy dose. For the biological dose calculation, we used an $\alpha/\beta$ value of 3 Gy for the lungs, heart and mediastinal structures, 2 Gy for the spinal cord and 10 Gy for the oesophagus.

**Treatment planning**

Experienced radiation technicians created three volumetric modulated arc therapy plans (VMAT; typically two half arcs for lateral tumours and two full arcs for medial tumours) for each patient using RapidArc (Eclipse version 11.0). Plans were created using a
simultaneous integrated boost in 24 fractions. Doses were calculated with a type B dose calculation algorithm (AcurosXB-10.0). The prescribed dose was escalated until one or more of the OAR constraints was reached, or when a maximum dose of 129.6 Gy in 24 fractions in the PTVboost volume (PTVprim for plan A; PTVFDG for plan B; PTVHX4 for plan C) was achieved. An isotropic planning strategy was applied to ensure equal lung toxicity. The target maximum mean lung dose difference between plans was 0.5 Gy. Plans with a higher mean lung dose were downscaled and reoptimised. This normalisation strategy has been shown to lead to similar mean doses in the PTVprim [8].

The PTVboost was planned to have 99% of the volume covered by 90–115% of the prescribed dose. If there was overlap of less than 15% between PTVboost and OAR, a partial underdosage was accepted: 85% of PTVboost was required to receive at least 90% of the prescribed dose where the dose in the overlap volume was escalated to 90% of the allowed OAR dose constraint. If this overlap was more than 15%, no underdosaging was accepted and 90% of the prescribed dose should cover 99% of the target, equal to the non-overlapping scenario. Lymph nodes were planned to receive 90–115% of 66 Gy. If PTVn overlapped with PTVprim, the PTVprim was prioritised. Created treatment plans are available online at https://www.cancerdata.org/10.1016/j.radonc.2015.07.013.

Analysis of the plans

We calculated dose distributions and generated dose-volume histograms for the three treatment strategies. We compared prescribed and mean doses in the PTVprim, between plans and calculated appropriate dose metrics for the OAR. We used a Wilcoxon signed rank test in SPSS (IBM Corp., Version 22.0, Armonk, NY) to compare prescribed doses and OAR doses between plan A, B and C. The significance level was adjusted for multiple comparisons (Bonferroni correction): a p-value < 0.017 was assumed to be statistically significant. Finally, we calculated the overlap between PTVFDG and PTVHX4 to evaluate how boosting one of the two sub-volumes affected the other sub-volume.

Results

Between September 2011 and August 2014, 35 NSCLC patients were included in the PBT-blended clinical trial at our institute. 14 patients were not eligible because they did not receive a HX4-PET/CT which was part of the translational research of the trial and not mandatory for inclusion in the study, 8 patients did not have a hypoxic tumour and in 3 patients dose-escalation up to more than 72 Gy was not feasible. In total, 10 patients were selected for this study. Patient and tumour characteristics are listed in Table 1.

The mean GTVprim was 199 cm³ (range 32–853), mean GTVFDG 48 cm³ (range 15–85) and mean GTVHX4 30 cm³ (range 5–58); see Supplementary Table 1. The respective mean planning target volumes were 507 cm³ (range 149–1749), 173 cm³ (range 53–484) and 114 cm³ (range 32–273). Table 1 presents the boost volumes and overlap between those volumes. The volume encompassing both PTVFDG and PTVHX4 overlapped for 61% with PTVFDG and for 87% with PTVHX4. As shown in Table 1, PTVHX4 was smaller than PTVFDG for nine of the ten patients; PTVHX4 was almost completely within PTVFDG for eight patients. Patient 3 is an example of such a patient: Fig. 1 shows both PET scans and the delineated planning target volumes. Patient 7 (also shown in Fig. 1) is the only patient with a spatial mismatch between FDG and HX4 high uptake volumes.

It was feasible to generate plans with a boost to PTVprim, PTVFDG and PTVHX4 for all patients. The dose distributions of two patients, patient 3 and 7, are shown in Fig. 1. The corresponding dose-volume histograms are displayed in Fig. 2. For both patients, the histograms show that boosting the FDG volume also resulted in a boost to almost the entire hypoxic volume, while boosting hypoxia only increased the dose in part of the FDG high uptake volume.

For nine patients the highest dose was prescribed for plan C (see Supplementary Fig. 1); the tenth patient had a larger PTVHX4 than PTVFDG. The average prescribed doses to the boost volume were 87.1 ± 10.1 Gy (plan A), 107.3 ± 20.6 Gy (plan B) and 117.6 ± 15.2 Gy (plan C). The prescribed doses for plans B (p = 0.005) and C (p = 0.005) were statistically significantly higher than for plan A. Prescribed doses and boost volumes per patient are listed in Table 2. Comparing prescribed doses with respect to boost volumes, Fig. 3, shows that it is generally more difficult to prescribe a high dose to large boost volumes.

The isotropic planning approach resulted in no significant differences in OAR doses (see Supplementary Table 2). Two examples of OAR dose-volume histograms are shown in Fig. 2. Prescribed dose was limited either by the mediastinal structures (seven patients), or mean lung dose (three patients).

Discussion

We performed a dosimetric comparison of three clinically feasible dose-escalation plans for ten NSCLC patients: boosting FDG and HX4 high uptake volumes was compared with boosting the entire tumour. The size of the boost volume appears to be an important factor for the height of the dose level that can be prescribed. Hypoxia planning volumes were generally smaller than FDG boost volumes, resulting in less overlap between target and surrounding

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient and tumour characteristics. Volumes of boost planning target for plan A (PTVprim), plan B (PTVFDG) and plan C (PTVHX4), and the overlap between the planning volumes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Gender</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PTVprim = planning target volume of the primary tumour; PTVFDG = planning target volume of the high FDG sub-volume; PTVHX4 = PTv of the hypoxic sub-volume.
In two cases, underdosage of the boost volumes was allowed in the hypoxia plan because overlap with the OAR was less than the predefined threshold (i.e. 15% of the volume), but it was not tolerated for the other two plans. This facilitated further dose-escalation in the hypoxia boost plan.

To our knowledge, this is the first study showing the feasibility of boosting hypoxia in NSCLC. This approach was already proven feasible in head and neck cancer [30–33]. It is important to note that not all patients were eligible for hypoxia boosting; 50% of the patients had hypoxic tumours. We do not expect that this approach is suitable for all patients; patient selection is essential and treatment should be adapted for every patient. Patients with non-hypoxic tumours have generally a better prognosis [34–38] and probably do not need an aggressive treatment as presented.

OAR. In two cases, underdosage of the boost volumes was allowed in the hypoxia plan because overlap with the OAR was less than the predefined threshold (i.e. 15% of the volume), but it was not tolerated for the other two plans. This facilitated further dose-escalation in the hypoxia boost plan.

To our knowledge, this is the first study showing the feasibility of boosting hypoxia in NSCLC. This approach was already proven feasible in head and neck cancer [30–33]. It is important to note that not all patients were eligible for hypoxia boosting; 50% of the patients had hypoxic tumours. We do not expect that this approach is suitable for all patients; patient selection is essential and treatment should be adapted for every patient. Patients with non-hypoxic tumours have generally a better prognosis [34–38] and probably do not need an aggressive treatment as presented. Based on pre-treatment hypoxia and FDG-PET/CT scans it can be decided to boost hypoxic or FDG sub-volumes, or a combination. For most patients the largest part of the hypoxic volume was located inside the high FDG volume. As a consequence, boosting FDG will also boost the hypoxia, but a boost to the hypoxic volume will not escalate the dose in the entire FDG volume. For patients without a hypoxia scan, FDG-PET imaging can be used as a surrogate for boosting hypoxia; however, less dose-escalation can be achieved.

We used commonly applied thresholds to determine FDG and HX4 high uptake sub-volumes, although these thresholds are arbitrarily defined. The FDG threshold is already used in a clinical trial...
whereas the HX4 threshold is based on the literature \[12,25–27\]. Zegers et al. \[22\] showed that the proportional overlap of the tracers is rather stable for varying thresholds. That suggests that the FDG plan will still boost the hypoxia volume with different thresholds, but not vice versa. The different thresholds are likely to have the greatest impact on the height of the prescribed dose levels, as these are linked to boost volume (Fig. 3).

An important aspect that has to be considered in hypoxia dose painting is stability of the target over time. Small studies testing temporal stability of hypoxia in NSCLC have so far found inconclusive results. Some studies have observed stable hypoxia \[39,40\], whereas others have reported a decrease in hypoxia \[26,41\], or a mix of stable and dynamic hypoxia \[42\]. Lin et al. \[43\] showed in head and neck cancer that when there is a spatial shift, dose painting of the initial sub-volume still results in improved equivalent uniform dose on a later scan. For pre-treatment FDG-PET/CT imaging, it is known that most local relapses are within the FDG high uptake region. However, it is still unknown whether pre-treatment hypoxic regions also correlate with the locations of local relapses. Because high correlations are observed between FDG high uptake areas and hypoxic areas on pre-treatment scans, we hypothesise that local recurrences will primarily occur in these hypoxic regions. It is essential to confirm this hypothesis before applying hypoxia boosting in clinical practice. This will in the future be assessed in the PET-boost clinical trial.

This study used a dose painting by contours approach. Compared to dose painting by numbers, this approach is easier to implement in clinical treatment planning software. Furthermore, it includes a safety PTV margin to tackle small deviations in target sub-volume definition.

Finally, there is still debate about the applicability and safety of dose escalation in NSCLC. Although multiple clinical trials suggest dose escalations could improve overall survival \[44–46\], a large randomised phase III trial showed an unexpected lower survival for the group that received a higher dose \[47\]. This unexpected outcome may result from various causes including longer overall treatment time, increased cardiac toxicity, or compromises in defining the PTV for the high dose group \[48\]. Alternatively, the results may suggest that standard dose escalation is not the way forward and more sophisticated dose redistribution techniques are necessary to improve local survival.

In conclusion, selective boosting of sub-volumes based on FDG or hypoxia is feasible and increases the prescribed dose compared to whole tumour boosting, without increasing the dose to the organs-at-risk.

**Conflict of interest statement**

The authors declare that there are no conflicts of interest.

**Acknowledgements**

Authors acknowledge financial support from EU 7th framework program (ARTFORCE), Kankeronderzoekfonds Limburg from the Health Foundation Limburg and the Dutch Cancer Society (KWF MAC 2011-5020 and KWF MAC 2011-4970). This research is also supported by the Dutch technology Foundation STW (Grant no. 10696 DuCAT), which is the applied science division of NWO, and the Technology Programme of the Ministry of Economic Affairs.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.07.013.
References


