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A secondary analysis of FDG spatio-temporal consistency in the randomized phase II PET-boost trial in stage II–III NSCLC

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ABSTRACT

Purpose: FDG-PET scans have shown spatial consistency in NSCLC patients before and following chemoradiotherapy, implying radioresistance. We hypothesized that patients, who received FDG-PET redistributed dose painting, would demonstrate reduced spatial consistency when compared to registered patients or to escalated dose treatment.

Methods: Stage II–IIIB, inoperable NSCLC patients were randomized in a phase II trial (NCT01024829) to (chemo)radiotherapy of either homogeneous boosting to the primary tumor, or redistributed inhomogeneous boosting to the GTV subvolume (FDG-SUV > 50% SUV_{max}). Patients who could not be boosted ($\geq$72 Gy) received 66 Gy in 24 fractions. Spatial consistency of pre-treatment and post-treatment (3 months) FDG-PET scans was measured by various overlap fraction thresholds.

Results: 66/82 patients analyzed received randomized treatment in the trial. Thresholds of 50% SUV_{max} pre-treatment and 70% SUV_{max} post-treatment yielded a median overlap fraction of 0.63 [interquartile range: 0.15–0.93], with similar results for other thresholds. No significant differences were found among overlap fractions of the treatment groups. A high incidence of FDG-uptake in normal lung (grade-1 pneumonitis: 73%) was found post-treatment.

Conclusion: FDG redistributed boosting did not reduce FDG spatial consistency from pre-treatment to post-treatment, which was highly variable among patients. The study found high numbers of patients with lung inflammation after treatment.

 Radiotherapy and Oncology xxx (2018) xxx–xxx

Patients with non-small cell lung cancer (NSCLC) have shown poor local–regional progression free and overall survival, where an improvement of local control has been associated with an increase in overall survival [1–3]. As the primary tumor is the dominant location of failure, boosting strategies might be favorable [4]. While dose escalation has shown promise in phase I-II trials, it was detrimental in a randomized phase III trial [5,6]. Although homogeneous dose escalation may be limited by nearby organs at risk, dose painting may be a solution to higher local control rates with limited increase in normal tissue toxicity [7–10]. Imaging and treatment for dose painting, where higher dose levels are delivered to radio-resistant subvolumes of the tumor, have been a focus in several studies of NSCLC patients [11–15].

Of available imaging biomarkers, ^{18}F-Fluorodeoxsyglucose (FDG), a surrogate for metabolic activity, is a prime target for dose escalation in NSCLC patients [14,15]. FDG has been a widely available tracer with an established imaging and analysis protocol [16]. Pre-treatment FDG-PET imaging metrics (e.g. SUV_{max}) have shown to be prognostic for both survival and local control [17–19]. Pre- and 3-months post-treatment FDG-PET imaging have demonstrated spatially consistent high uptake regions in non-responders, implying treatment resistance in high uptake areas, and providing potential dose redistribution regions within the tumor [15]. In addition, the pre-treatment FDG avid areas (surrogate for radioresistance) may be spatially consistent throughout the course of treatment; therefore, potentially not causing with an increase in adaptive replanning requirements in a dose painting trial targeting the high uptake regions [20].

From the conclusions of these studies, a multi-institutional trial (PET-boost trial; ClinicalTrial.gov identifier: NCT01024829) was initiated to improve local control of NSCLC patients. The trial was

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an international, randomized phase II trial, where patients received concomitant or sequential chemoradiotherapy or radiotherapy alone with either a homogenous boost to the primary tumor (Arm A) or an inhomogeneous boost (Arm B) to the FDG avid areas (>50% SUV_{max}) [14]. The remaining part of the tumor in Arm B and the involved lymph nodes were planned to receive 66 Gy in 24 fractions. Patients, who signed informed consent, where the primary tumor could not be escalated (≥72 Gy), were designated as registered patients (REG) and received 66 Gy in 24 fractions. The primary endpoint of this trial was local progression free survival at 1 year. The secondary endpoints were acute and late toxicity, overall survival, and quality of life.

In the present work, we followed the analysis methodology of Aerts et al. [15] in the PET-boost trial. We hypothesized that the non-randomized group of patients (no boost) maintains a high consistency between pre- and post-treatment FDG-PET as seen in Aerts et al. [15]. In addition, the patients who received a homogeneous boost would have higher spatial consistency than patients who received an inhomogeneous boost. Furthermore, we hypothesized that fewer randomized patients would have residual FDG-PET uptake when compared to the non-randomized group (REG).

Thus, the purpose of this planned secondary analysis was to investigate if inhomogeneous dose boosting reduced post-treatment FDG uptake and the spatial stability of the high FDG uptake tumor regions 3-month post-treatment.

Materials and methods

Trial and treatment

From April 2010 through November 2016, 136 NSCLC patients gave informed consent to participate in an IRB approved study. These patients were imaged and treated in the multicenter, randomized phase II PET-boost trial (closed November 2017) with the primary aim of improving local control. The trial required a minimum tumor diameter (≥4 cm) and a minimum SUV_{max} (≥5) to allow tumor dose escalation. Patients were excluded if they had prior radiotherapy to the thorax, distant metastases or tumor growth into large vessels. All patients received daily radiotherapy for 24 fractions. Treatment allowed for a combination with either concurrent or sequential chemotherapy in the presence of stage III disease. The chemotherapy regimen varied according to site. The concurrent chemo-radiotherapy regimen consisted of Cisplatin-Etoposide, Cisplatin-Vinorelbin, or daily dose Cisplatin. Carboplatin instead of Cisplatin was incidentally applied. Patients may have received one course of chemotherapy followed by concurrent chemo-radiotherapy or two cycles of induction chemotherapy (any type) followed by radiation. Dose escalation was pursued until either normal tissue tolerances were met, or until a dose of up to 5.4 Gy per fraction was reached (129.6 Gy in 24 fractions). The gross tumor volume of the primary tumor (GTV) was delineated on a mid-ventilation planning CT. Planned tumor volume (PTV) margins varied according to institutional policies. In the case of nearby organs at risk for the PTV, a 15% reduction of volume of the PTV was allowed. For each randomized patient, a treatment plan (IMRT or VMAT) for both arms was made with the Mean Lung Dose (MLD) being within 0.5 Gy of one another, effectively normalizing the mean PTV dose [14]. This led to the homogeneously escalated dose in Arm A to be redistributed in Arm B from the FDG cold to the FDG hot spots of the primary tumor GTV. Treatment consisted of step-and-shoot IMRT with an integrated boost, where 5–7 co-planar beams of 10 MV were applied. Previously published work provides details on the specifics of the trial, target and tissue volume definitions, treatment planning, prescribed dose, and constraints for the organs at risk [14].

Imaging analysis

Patients received a pre-treatment FDG-PET scan according to the NEDPAS protocol or EANM guidelines within 4 weeks of the beginning of treatment, and a follow-up FDG-PET/CT scan scheduled 3-months post-treatment [16]. Patients undergoing sequential chemoradiotherapy were required to have a new pre-treatment PET scan after chemotherapy, which was used in this analysis. Patients received a PET/CT scan after approximately 60 min of uptake time. All patient data were sent to a central location for analysis (NKI). For FDG PET analysis, the standardized uptake value (SUV) was defined as the measured activity (MBq/mL) normalized by the ratio of the injected activity (MBq) over the bodyweight (kg). The corresponding CT scans of the pre-treatment and post-treatment FDG-PET scans were rigidly registered to the planning CT using in-house software (WorldMatch). In the case of the planning CT being also the pre-treatment CT scan of the FDG-PET scan, only the post-treatment CT scan was registered to the planning CT. Tumors connected to the rib cage were registered according to a bony anatomy match, while tumors connected to the mediastinum were registered to the carina. Tumors not attached to either, were registered without rotations using a mask of the tumor. Registrations were visually verified by an independent observer (radiation oncologist), where discrepancies were resolved with a consensus between observers. The same procedure was used even for post-treatment scans demonstrating tumor regression as the rigid registration attempted to mimic the work of Aerts et al. [15].

We applied the analysis as presented by Aerts et al. [15], using the aorta SUV_{max} to threshold background activity in the tumor post-treatment FDG PET scan, which was used to identify metabolic responders [15,21]. Due to the escalated treatment doses, there was a possibility of normal tissue uptake in the GTV as well as non-disease related inflammation at the 3 month post-treatment FDG-PET scan in the lung. For each patient, a nuclear medicine physician (W. Vogel) contoured out non-disease related tissue uptake in the lung (normal tissue, inflammation) using a visual inspection of differences found from pre-treatment to post-treatment HU on the CT scans and their corresponding FDG PET scans. Found differences in normal tissue uptake that extended within the GTV contour were excluded from analysis, where physician uncertainty in a tissue between normal tissue and tumor inside the GTV resulted in tissue classification as tumor. Patients with marked post-treatment FDG PET uptake (above aorta SUV_{max}) and changes in HU from pre-treatment to post-treatment CT scans were noted as having grade 1 radiation induced pneumonitis.

The overlap fraction of high uptake FDG regions from pre-treatment to post-treatment scans was used to evaluate spatial consistency of FDG-uptake [15,22]. The overlap fraction was defined as the intersecting volume divided by the smallest volume. The intersecting volume was determined by comparing a post-treatment tumor volume of a specific PET threshold (SUV_{max}: 70%, 80%, and 90%, SUV: 2.5, 5.0) to 50% of SUV_{max} of the pre-treatment tumor volume. The intersecting volume was then normalized by the smaller of the two intersecting volumes, coinciding with the post-treatment volume for all, but five patients analyzed. The PET threshold used for pre-treatment (50% SUV_{max}) was determined by the boosted volume of the primary tumor in Arm B, as well as the recommended choice as determined by a sensitivity study of various overlap fractions of Aerts et al. [15].

Statistical analysis

The overlap fraction was calculated for each treatment group. Mann–Whitney U tests were used to determine if there was a difference in overlap fractions, tumor SUV, and tumor volume

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