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Identification of residual metabolic-active areas within NSCLC tumours using a pre-radiotherapy FDG-PET-CT scan: A prospective validation

Hugo J.W.L. Aerts[a,*], Johan Bussink[b], Wim J.G. Oyen[c], Wouter van Elmpt[a], Annemieke M. Folgering[b], Daisy Emans[a], Marije Velders[a], Philippe Lambin[a], Dirk De Ruysscher[a]

[a] Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands
[b] Department of Radiation Oncology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
[c] Department of Nuclear Medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

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ABSTRACT

It was recently described that high FDG-uptake areas pre-radiotherapy largely correspond with residual metabolic-active areas post-radiotherapy. Here, an independent prospective validation of these results was performed using an overlap-fraction (OF) calculation of various FDG-uptake based thresholds. Data from twelve patients treated at Radboud University Nijmegen Medical Center with lung cancer were analyzed. All patients underwent two FDG-PET-CT scans, one pre-radiotherapy (pre-RT) and one approximately three months after treatment (post-RT). Of the twelve analyzed patients, eight patients showed residual FDG uptake on the post-RT scan and were included for analysis. One of these patients had a residue that was not clearly distinguishable from the surrounding tissue due to FDG avid inflammation. Therefore, seven patients remained for further analysis. The mean volume of the residual metabolic-active areas post-RT was 14.6 ± 10.0% (mean ± SD) of the mean volume of the gross tumour volume (GTV) pre-RT. The residual metabolic-active areas largely corresponded with the pre-RT GTV (OF = 93.7 ± 7.2%). The pre-RT-scan threshold delineations of 34%, 40% and 50% of the SUV_{max} had a large OF with the residual region, 86.9 ± 8.3%, 77.4 ± 8.1% and 67.9 ± 6.8%, respectively. In this independent dataset, we confirmed that the location of residual FDG-uptake areas after radiotherapy corresponds with the high FDG-uptake areas pre-radiotherapy. Therefore, a pre-radiotherapy FDG-PET-CT scan can potentially be used for radiotherapy dose redistribution.

1. Introduction

Lung cancer is one of the most frequent and lethal solid tumours [1]. Although the prognosis has improved, the 5-year survival is about 20% in locally advanced non-small cell lung cancer (NSCLC) [2,3]. While concurrent chemo-radiation improved local control and long-term survival compared to traditional sequential (chemo-) radiotherapy, local tumour failure is still observed in the majority of patients [4]. Improvements in local tumour control can be achieved by escalating the radiation dose, where local control rates over 90% can be reached for tumour doses of 120 Gy [5,6]. However, the problem is that tumour dose escalation is limited by the radiation toxicity of normal tissues such as the lungs and the spinal cord.

A solution to this problem may be found in the intra-tumour heterogeneity. It has become increasingly clear that tumour tissue is often not homogeneous, but can have large spatial variations with different biological characteristics, like perfusion, hypoxia, cell density, proliferation and subsequent radio-resistance [7–12]. Therefore, a strategy to increase the dose to more radio-resistant areas within the tumour, while reducing the dose to more susceptible zones, can result in better local control rates with the same healthy tissue toxicity [13].

A strategy to determine the location of the radio-resistant areas within the tumour is the use of non-invasive imaging. Since high pre-treatment ^{18}F-deoxyglucose (FDG) uptake levels in the primary tumour result in lower survival in patients with NSCLC [14–16], we hypothesized that the regions with high FDG uptake before treatment identify more radio-resistant areas within the tumour. If true, an increased survival could be expected from radiation dose redistribution according to FDG uptake pre-radiotherapy. In an earlier study, we demonstrated that this hypothesis holds true for a group

* Corresponding author at: Maastricht University, Department of Radiation Oncology (MAASTRO), 6201 BN Maastricht, The Netherlands. Tel.: +31 88 44 55 666; fax: +31 88 44 55 667.
E-mail addresses: Hugo.Aerts@maastro.nl, Hugo.Aerts@Maastrichtuniversity.nl (H.J.W.L. Aerts).

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of NSCLC patients in MAASTRO Clinic (Maastricht, The Netherlands) [17]. Here, we report on an independent prospective dataset to validate that the high FDG uptake areas pre-radiotherapy identify the residual metabolic active areas post-radiotherapy.

2. Materials and methods

2.1. Patient characteristics

Twelve patients of Radboud University Nijmegen Medical Center (Nijmegen, The Netherlands) with inoperable non-small cell lung cancer (NSCLC), UICC stage II–III, eleven treated with sequential chemo-radiotherapy and one with radical radiotherapy (RT) alone. The sequential chemo-radiotherapy schedule consisted of 1–3 cycles of cisplatin and gemcitabine before the start of RT. Patients were included from June 2007 until August 2008. Mean age was 66.2 ± 9.5 years (range: 52–83 years). Two FDG-PET-CT scans were available for each patient. The first scan was performed before start of RT while the second scan was performed approximately three months after the end of RT. Both scans were performed under similar conditions. For the patients receiving sequential chemo-radiotherapy the pre-RT scan was performed after the chemotherapy. No treatment was given to any of the patients between the end of RT and the post-RT scan.

2.2. Radiotherapy simulation and planning

Patients were simulated in radiotherapy position on a CT-simulator, multislice spiral CT scanner (Philips AcQsim, Philips, Cleveland, USA) with both arms above the head. For the FDG-PET-CT scans (Siemens/CTI, Knoxville, Tennessee, USA) was used. An intravenous injection of 250 MBq FDG (Covidien, Petten, The Netherlands) was followed by 10 ml normal saline. After a 60 min uptake period, during which the patient was encouraged to rest, PET-CT images were acquired.

Radiotherapy planning was performed on a Pinnacle (version 8.0d; Philips Radiation Oncology System, Madison, WI, USA), the radiotherapy planning system routinely used which is based on a convolution algorithm using inhomogeneity corrections. The Gross Tumour Volume (GTV) and the Planning Target Volume (PTV) were defined for all patients, based on PET and CT data. The Clinical Target Volume (CTV) was defined as the GTV with a 5 mm margin incorporating microscopic disease. Subsequently, this CTV was expanded with 1 cm to draw the PTV to incorporate the internal respiratory motion and setup errors. A 3D conformal treatment plan was calculated on the PTV for all patients according to ICRU 50 guidelines. Dosimetric values were calculated on the basis of dose-volume histograms and dose distributions on each axial CT plan.

2.3. Image analysis

The pre- and post-RT scans were analyzed and delineated using the Siemens TrueD system (Version VC-30, Siemens A.G., Darmstad, Germany). On the pre-RT scan, the location and volume of the FDG uptake within the GTV were quantified using the threshold 34, 40, 50, 60 and 70% of the maximal SUV (SUV_{max}). On the post-RT scan, residual metabolic areas were defined as FDG uptake higher than in the aortic arch ($SUV > SUV_{aorta}$) [18]. Within the residual FDG-positive areas, the high FDG uptake areas were defined using the thresholds 70, 80, and 90% of the tumour SUV_{max}. Using an automatic rigid-registration algorithm, based on mutual information of the CT scans, the images of pre-RT scan were fused to the post-RT scan on the Siemens TrueD system. If the automatic registration showed a large deviation between the two CT scans, the images were manually registered on the anatomy surrounding the tumour, e.g. the bony anatomy or large vessels. The contours of the FDG-based thresholds on the post-RT scan were then transformed to the pre-RT scan using the derived registration matrices. The contours of the pre- and post-RT scan were exported from TrueD as DICOM-RT structure sets. Using MATLAB (R2008b, The MathWorks Inc, Natick, MA, USA) the overlap fractions (OF) and volumes of these contours were calculated. The overlap fraction was defined as the volume of overlap divided by the smallest volume [17,19]. By using this methodology it is possible to assess which threshold on the pre-RT scan matches the residual disease on the post-RT scan. All data are expressed as mean ± standard deviation (SD) and range.

3. Results

3.1. Patient characteristics

To assess whether the location of the residual metabolic active areas are located within the initial FDG-high uptake areas of the primary tumour, two ^{18}Fluorodeoxyglucose (FDG) PET-CT scans were analyzed for all patients, one before radiotherapy (pre-RT) and one after radiotherapy (post-RT). Of the twelve analyzed patients, four patients showed no residual FDG uptake on the post-RT scan and had a complete metabolic response. The other eight patients showed residual FDG uptake within the primary tumour ($SUV_{max} > SUV_{aorta}$). One of these patients had a residue that was not clearly distinguishable from the surrounding tissue due to FDG avid inflammation. Therefore, seven patients remained for further analysis.

3.2. Overlap of FDG-uptake before RT with residual areas

In Fig. 1, pre- and post-RT CT-PET images are shown of a representative patient. The high FDG uptake areas (50% SUV_{max}) on the pre-RT scan and the location of the residual areas on the post-RT scan are shown. The residual areas are transposed to the pre-RT scan, to show the overlap with 50% SUV_{max} high uptake area pre-RT. Visual evaluation shows that the location of the residual areas largely corresponds with the high FDG uptake areas pre-RT.

3.3. Overlap fractions of the FDG based thresholds

Fig. 2A depicts the overlap fractions and volumes of the FDG uptake based thresholds within the primary tumour pre-RT and post-RT. Here it is shown that the residual areas were mainly located within the original GTV (OF = 93.7 ± 7.2% [range: 82.8–100]). Also, the 70%, 80% and 90% SUV_{max} high-uptake areas within the residual areas showed a high overlap with the GTV volume (OF = 93.5 ± 10.6% [range: 71.6–100%], 94.2 ± 11.5% [range: 69.6–100.0%], and 96.1 ± 10.2% [range: 73.0–100%] respectively).

Also, the pre-RT FDG uptake thresholds had a large overlap with the residual areas. The 34% threshold pre-RT had an OF with the residual areas of 86.9 ± 8.3% [range: 77.2–98.2%] and with the high-uptake areas within the residue. Moreover, the same is true for the pre-RT 40% and 50% SUV_{max} high FDG uptake area (OF = 77.4 ± 8.1% [range: 67.7–89.9%] and OF = 67.9 ± 6.8% [range: 61.5–82.6%]). This pre-RT 50% SUV_{max} area also largely corresponded with the 70–90% SUV_{max} high-uptake areas within the residue.

3.4. Volumes of the FDG based thresholds

The volumes of the FDG based thresholds within the primary tumour pre-RT and the post-RT thresholds are shown in Fig. 2B. The FDG uptake areas (40–70% SUV_{max}) within the tumour on the pre-RT scan were small compared to the GTV. The 40% SUV_{max} encompassed 46.4 ± 14.4% [range: 23.0–66.5%] of the original GTV, whereas this was 35.8 ± 11.8% [range: 19.6–54.7%] for the 50%

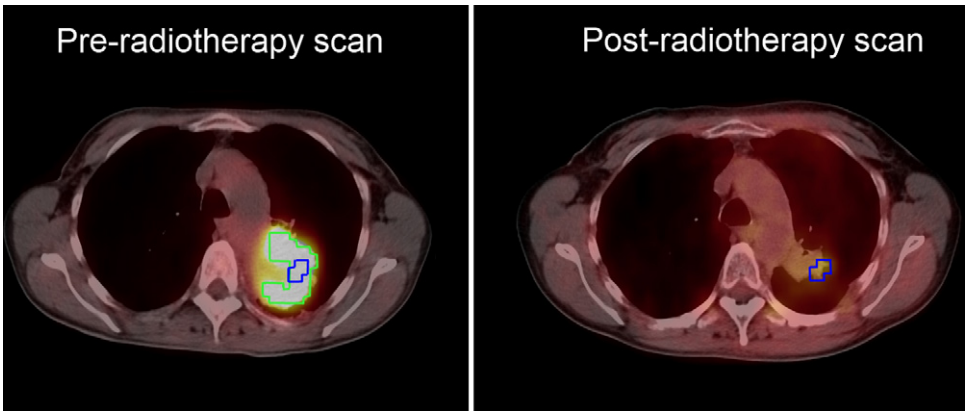

Fig. 1. Representative FDG-PET-CT images of a patient pre- and post-radiotherapy. The green lines indicate the 50% SUV_{max} FDG high uptake area pre-radiotherapy. The blue lines indicate the residual metabolic active areas post-radiotherapy, also transposed on the pre-radiotherapy scan. Visual evaluation shows a large correspondence between the residual areas post-radiotherapy with the high FDG uptake areas pre-radiotherapy.

SUV_{max}, 23.9 ± 7.8% [range: 13.2–37.5%] for the 60% SUV_{max}, and 12.9 ± 5.1% [range: 8.2–23.3%] for the 70% SUV_{max} threshold.

The volume of the residual metabolic active areas on the post-RT scan was 14.6 ± 10.0% [range: 4.3–31.2%] of the pre-RT GTV (Fig. 2B). The relative volumes of the high uptake areas within the residual areas were very small: 11.9 ± 7.7% [range: 2.9–15.8%] for the 70% SUV_{max}, 5.8 ± 4.9% [range: 0.8–15.6%] for the 80% SUV_{max}, and 1.9 ± 2.0% [range: 0.3–6.1%] for the 90% SUV_{max} threshold.

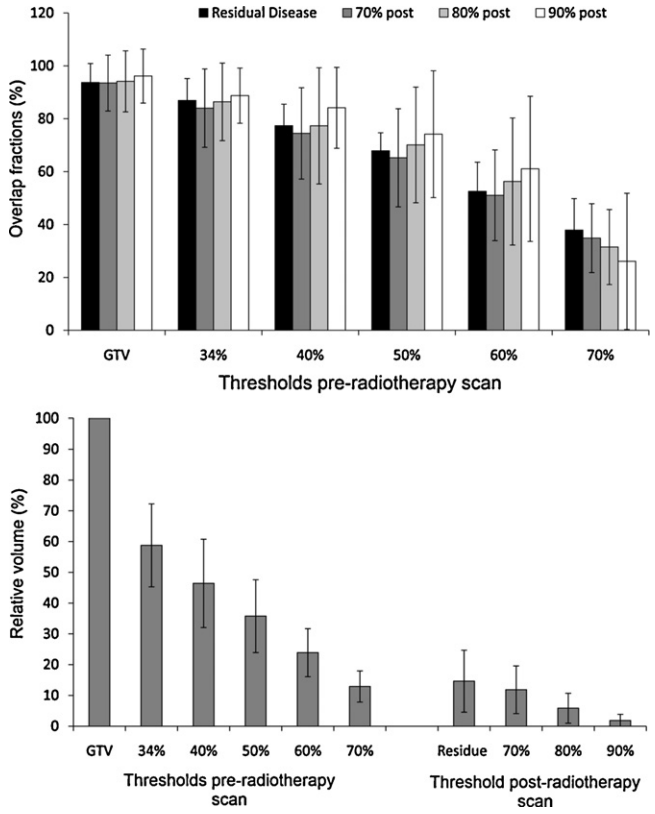

Fig. 2. (A) Overlap-fractions (OF) of the pre-radiotherapy thresholds with the post-radiotherapy relative thresholds. The OF of the post-radiotherapy residual-areas are indicated with the black-bars. The other bars indicate the OF with the high FDG-uptake (70–90%) areas within the residue. The data are expressed as mean ± standard deviation (error-bars). (B) Volumes of the SUV thresholds of the tumour pre- and post-radiotherapy. All volumes are relative to the pre-radiotherapy gross tumour volume (GTV). The data are expressed as mean ± standard deviation (error-bars).

4. Discussion

In radiation oncology there is an growing interest to increase the radiation dose towards more resistant tumour areas while reducing the dose to less resistant areas within the tumour [15]. In the present study, we confirmed in a prospective study the results that the areas of high FDG uptake within the tumour before treatment would allow identification of residual metabolic-areas after therapy [17]. Together with the results of the previous study, where it was demonstrated that the high-uptake areas of FDG within the tumour remained stable during a course of fractionated radiotherapy for NSCLC [19], radiation boosting of these zones might be beneficial.

Here, we have shown that the residual FDG uptake areas after treatment largely corresponded to the 50% SUV_{max} within the tumour before treatment, resulting in an overlap fraction of 68%. This was similar with the previous obtained results [17], where the overlap between these contours was 71%. The volume of the residual FDG-positive areas was on average 15% of the initial GTV volume. The hotspot within the residual area (90% SUV) was almost completely within the pre-RT GTV (OF = 96%), and had a high overlap with the pre-radiotherapy 50%SUV threshold (OF > 74%). Based on these results, we conclude that residual metabolic active areas within the tumour can be identified before treatment using an FDG-PET-CT scan.

The pre-radiotherapy 50% SUV_{max} threshold had a volume that encompassed 35% of pre-treatment GTV, similar with previous results (39%). This makes the 50% SUV_{max} threshold value a suitable threshold for future radiation boosting target to improve local control, not only because it yields good results, but also because it is a simple, reproducible, and robust method between institutions. A lower threshold would result in boosting the entire tumour and not only the most resistant areas, whereas a too high threshold would lead to only a few voxels to be treated, which is often impossible due to organ motion or dose delivery constraints. However, the most optimal threshold has to be determined in future studies.

A limitation of our study is that for the registration between the pre and post-scans a rigid registration was performed, not incorporating the non-rigid tissue changes possibly induced by radiotherapy. This could be improved by using deformable registration techniques. However, these are difficult to validate and the reproducibility, especially in different institutes, is limited. Another limitation of PET scanning is that due to partial volume effects small areas of residual tumour could be missed. Also, for a wide applicability of these results and before multi-center studies can be

initiated, a thorough standardisation and calibration of PET scanning and radiotherapy delivery has to be performed [20–22].

5. Conclusion

Our previous results were prospectively validated in an independent dataset in another institute, showing that the residual metabolic-active areas within the tumour after (sequential chemo-) radiotherapy are located in the high FDG uptake areas before therapy and can be delineated. This information is the basis for an ongoing randomized phase II trial to test the hypothesis that high FDG uptake areas reflect "radioresistance", by redistribution the dose according to pre-radiotherapy FDG uptake areas.

Conflict of interest statement

None declared.

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