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Citation for published version (APA):

Lazzeroni, M., Uhrdin, J., Carvalho, S., van Elmpt, W., Lambin, P., Dasu, A., Wersall, P., & Toma-Dasu, I. (2018). Evaluation of third treatment week as temporal window for assessing responsiveness on repeated FDG-PET-CT scans in Non-Small Cell Lung Cancer patients. *Physica Medica: European journal of medical physics*, 46, 45-51. <https://doi.org/10.1016/j.ejmp.2018.01.012>

Document status and date:

Published: 01/02/2018

DOI:

[10.1016/j.ejmp.2018.01.012](https://doi.org/10.1016/j.ejmp.2018.01.012)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

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Original paper

Evaluation of third treatment week as temporal window for assessing responsiveness on repeated FDG-PET-CT scans in Non-Small Cell Lung Cancer patients

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ARTICLE INFO

Keywords:

FDG-PET-CT

NSCLC

Treatment adaptation

ABSTRACT

Purpose: Early assessment of tumour response to treatment with repeated FDG-PET-CT imaging has potential for treatment adaptation but it is unclear what the optimal time window for this evaluation is. Previous studies indicate that changes in SUV_{mean} and the effective radiosensitivity (α_{eff} , accounting for uptake variations and accumulated dose until the second FDG-PET-CT scan) are predictive of 2-year overall survival (OS) when imaging is performed before radiotherapy and during the second week. This study aims to investigate if multiple FDG-PET-derived quantities determined during the third treatment week have stronger predictive power.

Methods: Twenty-eight lung cancer patients were imaged with FDG-PET-CT before radiotherapy (PET1) and during the third week (PET2). SUV_{mean} , SUV_{max} , SUV_{peak} , $MTV_{41\%–50\%}$ (Metabolic Tumour Volume), $TLG_{41\%–50\%}$ (Total Lesion Glycolysis) in PET1 and PET2 and their change (Δ), as well as average α_{eff} ($\bar{\alpha}_{eff}$) and the negative fraction of α_{eff} values ($f_{\alpha_{eff} < 0}$) were determined. Correlations were sought between FDG-PET-derived quantities and OS with ROC analysis.

Results: Neither SUV_{mean} , SUV_{max} , SUV_{peak} in PET1 and PET2 (AUC = 0.5–0.6), nor their changes (AUC = 0.5–0.6) were significant for outcome prediction purposes. Lack of correlation with OS was also found for $\bar{\alpha}_{eff}$ (AUC = 0.5) and $f_{\alpha_{eff} < 0}$ (AUC = 0.5). Threshold-based quantities ($MTV_{41\%–50\%}$, $TLG_{41\%–50\%}$) and their changes had AUC = 0.5–0.7.

P-values were in all cases $\gg 0.05$.

Conclusions: The poor OS predictive power of the quantities determined from repeated FDG-PET-CT images indicates that the third week of treatment might not be suitable for treatment response assessment. Comparatively, the second week during the treatment appears to be a better time window.

1. Introduction

The development and the clinical implementation of functional and molecular imaging during the last decades, together with sustained research work and innovations in imaging segmentation, registration and fusion, have imposed repeated imaging as one of the most promising tools for treatment response assessment [1]. The identification of predictive factors for tumour responsiveness at an early stage is fundamental for cancer treatment adaptation and individualisation. A

patient-specific treatment adaptation, possibly through a dose escalation in the most radioresistant regions for the poor responders at risk of local recurrence, could improve treatment results [2–5]. ^{18}F -fluorodeoxy-D-glucose Positron Emission Tomography and Computed Tomography (FDG-PET-CT) have a great impact on cancer detection, staging, and treatment outcome assessment in a broad range of tumour types [6–8]. For lung cancer, several studies have already explored the possibility of identifying universal criteria for tumour responsiveness to chemoradiotherapy or radiotherapy alone from FDG-PET imaging

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Table 1

Characteristics of the Non-Small Cell Lung Cancer (NSCLC) patients in the study. Information on the age, gender, and sex of the patients are reported together with the histology of the tumour, number of days between the first PET scan (PET1) and the second PET scan (PET2), number of days between the start of radiotherapy (RT) and PET2, number of fractions (fx) delivered by the time of PET2, dose delivered until PET2, and overall survival (OS) at 2 years (2Y) follow-up (1 = survivor, 0 = non-survivor).

#	Age	Gender	Weight	Histology	Days between PET1 and PET2	Days between start of RT and PET2	Fx at PET2	Dose at PET2 (Gy)	OS at 2Y
1	53	F	64	Adeno	22	12	24	36	0
2	48	F	65	Adeno	24	13	26	39	1
3	58	F	48.5	Adeno	24	12	24	36	0
4	59	F	60	Squam	22	12	24	36	1
5	63	M	84	Squam	21	12	24	36	0
6	49	M	70	Squam	21	12	24	36	1
7	67	F	78	Adeno	31	14	28	42	0
8	59	F	54	Other	23	13	26	39	1
9	66	M	66	Squam	21	12	24	36	1
10	70	M	93	Other	23	13	26	39	0
11	68	M	84	Adeno	25	12	24	36	0
12	56	M	80	Other	27	15	30	45	1
13	71	M	83	Other	21	12	24	36	1
14	78	F	63	Other	22	12	24	36	1
15	60	M	79	Squam	21	12	24	36	1
16	55	F	91	Adeno	26	14	28	42	0
17	66	M	78	Squam	20	12	24	36	1
18	66	F	50	Other	21	12	24	36	1
19	64	M	103	Squam	22	12	24	36	0
20	59	F	61	Other	23	13	26	39	0
21	67	F	65	Adeno	25	12	24	36	1
22	64	M	81	Other	21	12	24	36	1
23	71	F	64	Other	23	14	28	42	0
24	58	F	68	Squam	28	15	30	45	1
25	38	F	47	Adeno	21	9	18	27	1
26	86	M	59	Squam	23	12	24	36	1
27	52	M	78	Adeno	25	12	24	36	1
28	69	F	74	Adeno	22	12	24	36	0

acquired after the completion of the treatment [9–12]. However, a limited number of investigations have so far accounted for changes in specific parameters at an early stage of chemoradiotherapy [13–17]. Recently, two independent studies on the same Non-Small Cell Lung Cancer (NSCLC) patient cohort have shown that different quantities can be calculated and were predictive of 2-year overall survival (OS) when imaging was performed before radiotherapy and during the second week [18,19]. Van Elmpt et al. [18] studied the change in the metabolic activity of the tumour based on the difference between the mean Standard Uptake Value (SUV), while Toma-Dasu et al. [19] adopted a volumetric approach and stratified the patients in good and poor responders based on calculations of an operational parameter, the effective radiosensitivity (α_{eff}).

In the assessment of the tumour response to treatment with repeated FDG-PET-CT imaging, the identification of the optimal window to performing the FDG-PET-CT scan during treatment is still unclear and few studies exist on the topic [20,21]. The time lapse between the first and the second FDG-PET-CT scan should be compatible with individualized treatment adaptation and should be carefully selected so that clonogenic cells are still detectable but the FDG-PET response is not affected to a large extent by the inflammatory reactions following chemoradiotherapy [22]. It could be hypothesised that the third week during the treatment might have a stronger predictive power on treatment outcome as compared to the second week since a larger portion of clonogenic cells has been depleted and therefore larger variations in the radiotracer uptake with respect to the initial FDG-PET image might be expected. At the same time, however, radiation induced inflammation might introduce a bias in the assessment of the uptake variation.

The present study therefore aims at assessing whether the third week of treatment could be a suitable time window for the assessment of tumour responsiveness as a predictor for the treatment outcome. In particular, parameters related to the distributions of α_{eff} values were for the first time tested for robustness of outcome prediction with respect to time window.

2. Materials and methods

2.1. Treatment protocol and PET-CT acquisition

Twenty-eight patients with advanced stage (stage III and IV) of NSCLC (10 adenocarcinoma cases, 9 squamous cell carcinoma cases, and 9 non-otherwise specified cases) were treated with concomitant chemoradiotherapy at the Maastricht University Medical Center (The Netherlands) between 2011 and 2012 and were analysed in this study. Patients enrolled in the clinical trial (NCT00522639 at clinicaltrials.gov) had no surgery and no previous cancer within five years prior to diagnosis. The administered chemotherapy agent was carboplatin-gemcitabine. The radiotherapy treatment consisted of two consecutive regimens of photon IMRT (Intensity Modulated Radiotherapy): a dose of 45 Gy was delivered in 1.5 Gy fractions twice per day followed by a dose-escalation up to 69 Gy in 2 Gy daily fractions.

The Xio/Focal System (Computerized Medical Systems, St. Louis, MO, USA) was used for radiotherapy planning. The software makes use of a convolution-superposition algorithm with inhomogeneity corrections. ICRU 50 [23] guidelines were adopted for treatment planning.

The primary Gross Tumour Volume (GTV_{prim}) was delineated on fused FDG-PET-CT images by experienced radiation oncologists.

Patients were imaged in radiotherapy position with FDG-PET-CT before the treatment and during the third week of radiotherapy. The mean and median time interval between the first FDG-PET-CT acquisition and the start of radiotherapy were equal to 11 and 10 days, respectively; while the mean and median time interval between the first and second FDG-PET-CT scan were both equal to 23 days.

Second FDG-PET-CT acquisitions were performed with a Siemens Truepoint 40 camera (Siemens AG, Munich, Germany) in radiotherapy position. Patients fasted for at least 6 h before scanning and the NEDPAS [24] protocol was used with a FDG activity in MBq equal to 2.5 times the body weight in kg injected intravenously. FDG-PET image reconstruction was performed using an Ordered Subset Expectation

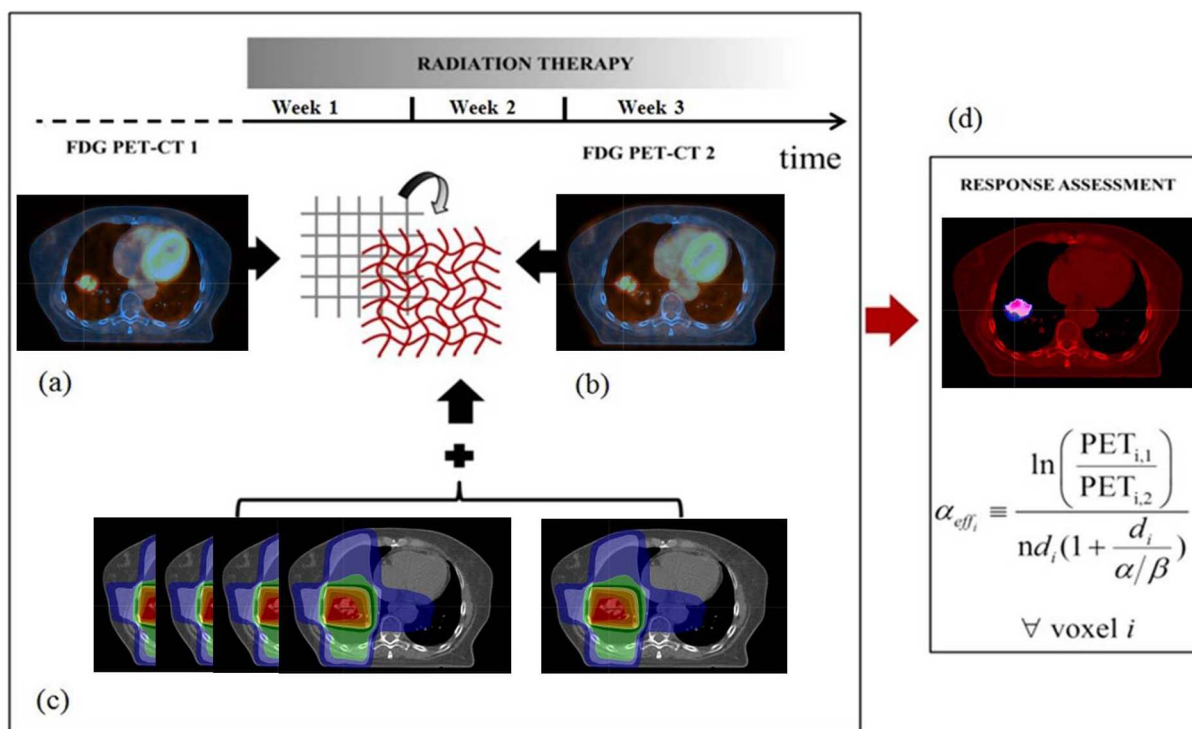


Fig. 1. Schematic illustration of the tumour response assessment method. Two [18F]-fluorodeoxy-D-glucose positron emission tomography images taken before (a) and during the third week of treatment (b), and the accumulated dose distribution calculated by summing up the planned doses for each fraction delivered up to the second scan (c) are used to calculate a voxel-based effective radiosensitivity (d) and, thus, assess the responsiveness of the tumour to radiotherapy.

Maximization 2D four iterations eight subsets (OSEM2D 4i8s) algorithm. Corrections for random events and decay were applied, as well as scattering corrections using model-based methods. FDG-PET scans were also corrected for attenuation either using the mid-ventilation phase of the 4D-CT or a 3D-CT thorax. FDG-PET-CT scans were performed as static studies. No special breathing instructions were given to the patients, but normal breathing was recommended. CT and FDG-PET image voxel sizes were respectively equal to $(0.098 \times 0.098 \times 0.3) \text{ cm}^3$ and $(0.407 \times 0.407 \times 0.3) \text{ cm}^3$. Additional information on patient data, treatment protocol, and image data acquisition are described in Ref. [25].

Treatment outcome in terms of OS at 2 years was available for all the patients in the *ensemble*. Seventeen patients were alive at two years.

The patient characteristics most relevant for the presented analysis are listed in Table 1.

2.2. Image registration and image analysis

FDG-PET-CT scans acquired at the two successive time points were imported and co-registered in a research version of the treatment planning system RayStation version 4.6.100.4 (RaySearch Laboratories AB). Specifically, the two CT images, inherently registered to the FDG-PET scans, were co-registered to achieve a voxel-to-voxel correlation between the two corresponding FDG-PET images. The registration consisted of a rigid registration based on bony anatomy followed by a hybrid deformable registration. The latter combines image information with anatomical information as provided by contoured image sets and uses as controlling region the external patient contour aiming at anatomical structure integrity [26].

Co-registered FDG-PET images were exported from the RayStation and analysed with an in-house MatLab code (The MathWorks Inc., Natick, MA, version R2011b) able to handle FDG-PET-CT images, dose distribution and delineated structures outside RayStation as well as to calculate the quantities of interest to perform the rest of the analysis.

2.3. Calculation of FDG-PET-related quantities of interest

To assess tumour early responsiveness to the treatment, a systematic voxel-based analysis using the co-registered FDG-PET images taken before radiotherapy and during the third week in the primary gross tumour volume (GTV_{prim}) was performed. The method, developed by Toma-Dasu et al. [19], takes into account the local uptake changes in the target volume of the paired FDG-PET images and the planned accumulated dose distribution at the second FDG-PET acquisition. The algorithm assumes that the uptake variation at voxel level in the images is proportional to the variation of functional clonogenic cell density and it is based on the Linear Quadratic (LQ) [27] formalism for cell killing. The same radiosensitivity to fractionation (i.e. $\alpha/\beta = 10 \text{ Gy}$ for the tumour) is assumed for all the patients and an operational parameter, the effective radiosensitivity α_{eff} , is calculated:

$$\alpha_{\text{eff},i} = \frac{\ln\left(\frac{PET_{i,1}}{PET_{i,2}}\right)}{nd_i\left[1 + \frac{d_i}{\alpha/\beta}\right]}, \quad (1)$$

where $PET_{i,1}$ and $PET_{i,2}$ are the SUV values in the FDG-PET images for the voxel of interest i acquired before and during radiotherapy, respectively; d_i and n are the planned dose per fraction and the number of fractions delivered until the second FDG-PET image, respectively.

A positive value of the effective radiosensitivity parameter indicates a decrease in the tracer uptake of the FDG-PET scan acquired during the treatment with respect to the initial FDG-PET scan for a certain voxel under consideration and a negative value indicates an increase, respectively.

The distribution of the effective radiosensitivity, α_{eff} , in each voxel in a volume of interest is therefore obtained. The average value of the effective radiosensitivity, $\bar{\alpha}_{\text{eff}}$, and the fraction of negative values of α_{eff} , $f_{\alpha_{\text{eff}} < 0}$, are also calculated. The volume of interest in this study in which the distribution of the effective radiosensitivity was assessed was GTV_{prim} .

A schematic illustration of the method for assessing the early tumour responsiveness to treatment is presented in Fig. 1.

Additionally, other FDG-PET-derived quantities were also scored in the first and second FDG-PET scan. The mean and the maximum SUV values (SUV_{mean} , SUV_{max}) in the first and second FDG-PET scan were scored in the volume corresponding to GTV_{prim} . Following the European Association of Nuclear Medicine (EANM) guidelines for tumour imaging with FDG-PET-CT (version 2.0, [28]), SUV_{peak} was scored in a 1.2 cm diameter spherical volume of interest (VOI) positioned such that the average value across all positions within the lesion is maximised. Threshold-based quantities such as the Metabolic Tumour Volume (MTV) and the corresponding Total Lesion Glycolysis (TLG) were also considered in the study. The MTV41% and MTV50% corresponded, respectively, to a 3D isocontour at 41% of the maximum pixel value and to a 3D isocontour at 50% of the maximum pixel value [28]. The TLG values (TLG41% and TLG50%, respectively) were obtained as the product of the mean SUV value in the MTV VOI and the MTV volume (MTV41% and MTV50%, respectively) [28].

The percent change in the maximum SUV (ΔSUV_{max}) within GTV_{prim} between the FDG-PET scans before the treatment ($SUV_{max,1}$) and during the third week ($SUV_{max,2}$) was calculated as $\Delta SUV_{max} = 100 (SUV_{max,1} - SUV_{max,2}) / SUV_{max,1}$. Similarly, the percent changes in the other FDG-PET-derived quantities mentioned above (ΔSUV_{mean} , ΔSUV_{peak} , $\Delta MTV41\%$, $\Delta MTV50\%$, $\Delta TLG41\%$, and $\Delta TLG50\%$) were calculated.

2.4. Statistical analysis

The statistical analysis was performed by using the Receiver Operating Characteristic (ROC) method to seek for correlations between the treatment outcome of NSCLC patients, expressed as 2-year OS, and the quantities of interest mentioned above ($\bar{\alpha}_{eff}$, $f_{\alpha_{eff} < 0}$, SUV_{max} , SUV_{mean} , SUV_{peak} , MTV41%, MTV50%, TLG41% and TLG50% in PET1 and PET2, the percentage change of SUV_{mean} , SUV_{max} , SUV_{peak} , MTV41%, MTV50%, TLG 41% and TLG50%). The Area Under the ROC curve (AUC) and corresponding p-values were scored. A p-value below 0.05 was considered statistically significant.

The commercial software, MedCalc, version 13.1.0.0 (MedCalc Software, Ostend, Belgium) was used for the calculations.

3. Results

Fig. 2 shows the distribution of the percent change in the FDG-PET-derived quantities analysed in the study (SUV_{mean} , SUV_{max} , SUV_{peak} , MTV41%, MTV50%, TLG 41% and TLG50%), together with the distributions of $\bar{\alpha}_{eff}$ and $f_{\alpha_{eff} < 0}$ for the NSCLC cohort under investigation. Patients were divided based on the 2-year OS as survivors and non-survivors. As seen, the distribution of the data is similar for survivors (black) and non-survivors (red) in all cases, as evidenced also by the similar median and mean values of the distributions (empty square and horizontal line, respectively, in the box plot).

Fig. 3 shows the ROC curves investigating the correlation between all the FDG-PET-derived quantities under analysis in this study and the treatment outcome. As reasonably expected from the results shown in Fig. 2, the ROC analysis indicates that none of the considered quantities has a statistically significant discriminant power. AUC values for $\bar{\alpha}_{eff}$ and $f_{\alpha_{eff} < 0}$ were, respectively, AUC = 0.5 with p = 0.7 and AUC = 0.5 with p = 0.8. The change between the FDG-PET uptake in PET1 and PET2 did not correlate with the outcome either and resulted in an AUC = 0.6 with p = 0.3 for ΔSUV_{max} , AUC = 0.5 with p = 0.7 for ΔSUV_{mean} , and AUC = 0.6 with p = 0.4 for ΔSUV_{peak} . Similar results are also found for the SUV_{max} , SUV_{mean} , and SUV_{peak} values in PET1 or PET2 having all AUC values in the range 0.5–0.6 with p-values between 0.5 and 0.9.

Threshold-based methods (MTV41%, MTV50%, TLG41%, and

TLG50%) calculated in PET1 and PET2 did not result in better predictive power either with an AUC value range equal to 0.5–0.7 and p-values in the range 0.2–0.7. Percentage difference of the mentioned threshold-based quantities, i.e. $\Delta MTV41\%$, $\Delta MTV50\%$, $\Delta TLG41\%$, and $\Delta TLG50\%$, had AUC values respectively equal to 0.7 (p = 0.1), 0.6 (p = 0.2), 0.6 (p = 0.5), and 0.6 (p = 0.3).

4. Discussion

One of the most quoted reasons of concern when assessing the response to treatment of patients receiving chemoradiotherapy based on repeated FDG-PET-CT imaging at different time points during the course of the treatment is related to the possibility of quantifying the metrics used in the comparison in an artefact-free manner [20,22]. Thus, the potentially radiation-induced image misrepresentations due to, for example, tissue inflammations and the way they might affect the results should be taken into account. The feasibility of designing metrics based on significant changes in the SUV values at different time points during the course of chemoradiotherapy for NSCLC patients has been shown in the study by Edet-Sanson et al. [20]. The authors aimed at verifying whether significant changes in the uptake of FDG or in the volumes defined based on the tracer uptake could be determined at different points during the course of a conventionally fractionated radiotherapy treatment, early enough to allow treatment adaptation. They performed 5–6 FDG-PET-CT scans, one every 7 fractions of 2 Gy, during the course of the treatment for 10 NSCLC patients. Their results lead to the conclusion that although the normalised SUV_{max} determined at different time points within the treatment could be determined in a radiation-induced misrepresentation-free manner, other parameters, depending on the size of the volume delineated using FDG-PET-based thresholds, were not reliable after about one to two weeks. However, this study did not include in the analysis the correlation between the tracer uptake and the treatment outcome. A prospective subsequent study by the same group, investigated the potential of using FDG-PET-based metrics and their changes during chemoradiotherapy as predictive factors for the treatment outcome at 1 year, expressed as OS or tumour progression [21]. The first FDG-PET image was acquired right before the start of the radiotherapy and the second image five weeks within the treatment after the delivery of 40–45 Gy. They concluded that the only parameter that was actually able to predict the outcome at 1 year was SUV_{max} in the second FDG-PET image taken at 5 weeks after the start of the treatment. Furthermore, Vera et al. [21] showed that the fixed threshold methods, based on FDG uptake, such as 40% SUV_{max} , tend to delineate larger volumes even when the lesions were obviously decreasing at visual examination. It seems plausible to hypothesize that radiation-induced inflammation or similar processes is the reason for this increase in size. To some extent, the present and the above described studies point to the similar conclusion that beyond 1–2 weeks within the treatment the delineation of volumes based on FDG-PET becomes problematic. Consequently, the derivation of related parameters, such as SUV_{mean} and its changes, becomes unreliable and leads to poor correlation with the treatment outcome with the exception just mentioned (i.e. SUV_{max} at 5 weeks during the treatment). Nonetheless, a direct comparison between the findings of our study and the one by Vera et al. [21] is not entirely relevant because of the non-identical manner in which the analysed parameters were derived. The predictive value of repeated FDG-PET-CT for the treatment outcome for NSCLC patients was also investigated in a recent study by Mattoli et al. [29] concluding that early metabolic response was predictive for local control, progression free survival and overall survival after low-dose fractionated radiotherapy with concurrent chemotherapy. However, a direct comparison of the findings of the study by Mattoli et al. and the present one is not possible due to the different treatment regimens employed for the patient cohorts in the two studies.

The analysis of the tumour responsiveness performed in this study based on the effective radiation sensitivity, α_{eff} , did not lead to better

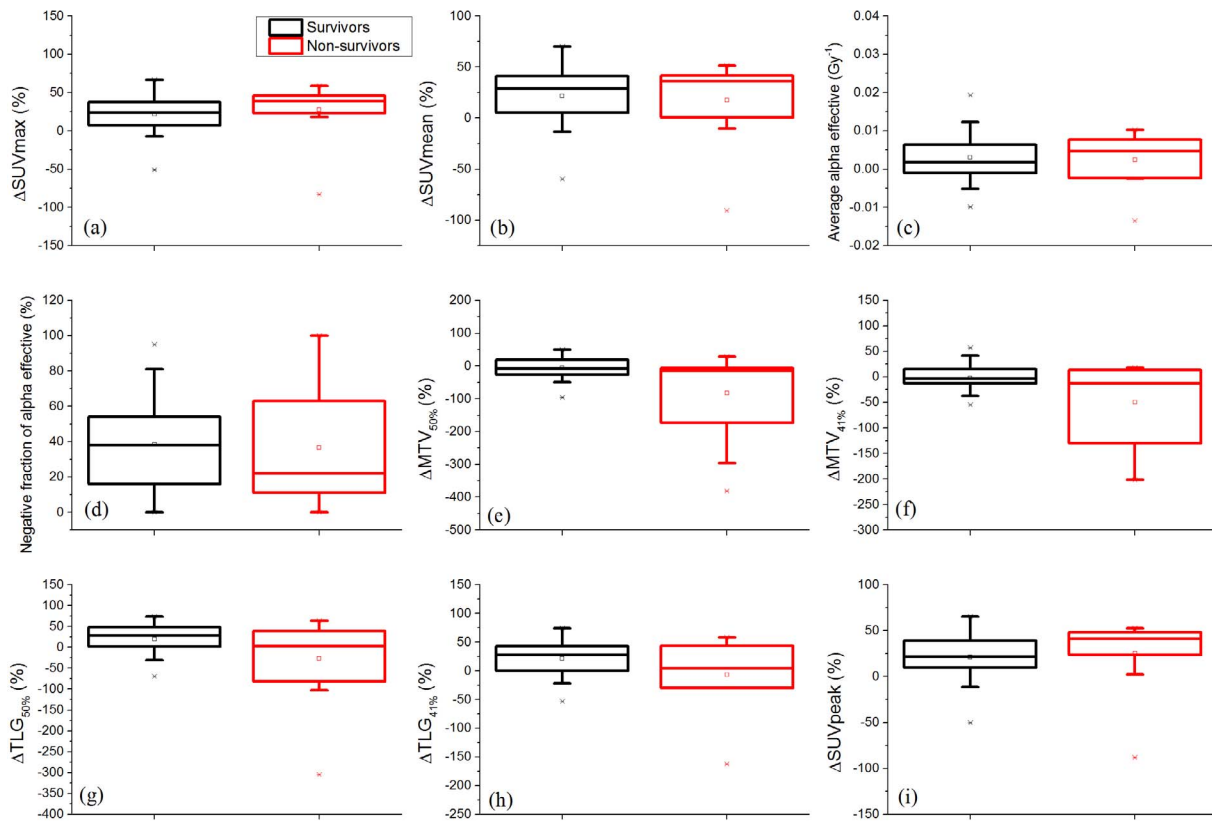


Fig. 2. Box plots of the distribution of PET-derived quantities of interest. Data are shown separately for survivors (black) and non-survivors (red). The horizontal line in the box indicates the median value of the data, and the small square indicates the mean value of the distribution. The box plot whiskers indicate scores outside the middle 50%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

predictions of the treatment outcome either, although it is not depending on a volume delineated based on FDG-PET uptake but strictly determined within the GTV_{prim} . Beyond the possible radiation-induced inflammation problem, one possible explanation for this result is the actual definition of the effective radiation sensitivity. In fact, α_{eff} implicitly assumes that the decrease in the FDG tracer uptake implies effective cell killing and an increase in the FDG uptake indicates that cell proliferation has a larger effect than treatment induced cell depletion. However, one has to keep in mind that the signal in the image is not given only by the surviving cells that metabolise the tracer but also by the damaged cells which are doomed to die but are still viable at the time of the scan and still capable of metabolising the tracer [22]. The proportion of the surviving clonogens in the entire cell population in the target, including the damaged clonogens doomed to die, varies at different moments during the treatment and therefore the discriminatory power of a metric for tumour response based on this is also expected not to be the same at different time points during the treatment.

The approach based on repeated examinations performed for the same patient in order to determine the effective radiation sensitivity, α_{eff} , provides however one strong advantage. By using each patient as its own reference, no specific assumptions regarding the radiosensitivity of the patient would be required. In addition, according to the assumed approach for calculation of the α_{eff} distributions, each voxel is its own reference and this avoids adding to the analysis unnecessary uncertainties associated with making specific assumptions regarding the initial cell density or proliferation rates in the voxels or possible causes for persistent uptake in the voxels. Uncertainties deriving from, for example, the limited resolution of the PET images and partial volume effects are also expected to be less pronounced. No specific strategy at the moment of the image acquisition was adopted to reduce the motion due breathing of the patient (except for normal

breathing recommendation) under the assumption that the possible blurring of the PET images would be overpassed by uncertainties related to the co-registration of images (FDG-PET-CT1 and FDG-PET-CT2).

The algorithm connected with the hybrid deformable registration was extensively tested and validated and found to perform well in comparisons to other algorithms, as discussed in Ref. [26]. The method for calculation of α_{eff} distributions was also tested for robustness by intentionally perturbing the registration between the FDG-PET images in Ref. [19]. Rigid 5 mm translations in anterior-posterior, left-right, and cranial-caudal directions were respectively introduced in the registration matrix. The classification of patients in responders and non-responders to treatment resulted to be robust against the performed perturbation [19].

A limitation of the present study is represented by the relatively low number of patients ($N = 28$). Unfortunately, this is a common problem in this kind of investigations (e.g. $N = 34$ in Van Elmpt et al. [18], $N = 26$ in Toma-Dasu et al. [19], and $N = 10$ in Edet-Sanson et al. [20]). Needless to say that the study would benefit from being repeated on a larger number of patients. In event of a positive correlation between the tumour responsiveness metrics and the treatment outcome, a cross-validation would have to be performed as in the previous study by Toma-Dasu et al. [19] on a similar number of patients imaged at 2 weeks from the start of the treatment but here it was not the case. So, one could only conclude from the current analysis that FDG-PET imaging at three weeks into treatment does not give any prognostic/predictive value for this dataset.

In summary, the lack of correlation of SUV_{max} , SUV_{mean} , SUV_{peak} , $MTV_{41\%}$, $MTV_{50\%}$, $TLG_{41\%}$, and $TLG_{50\%}$ and their percent changes between the FDG-PET scans before the treatment and during the third week with OS indicates that the third week of treatment might not be suitable for assessing the responsiveness to treatment and subsequent

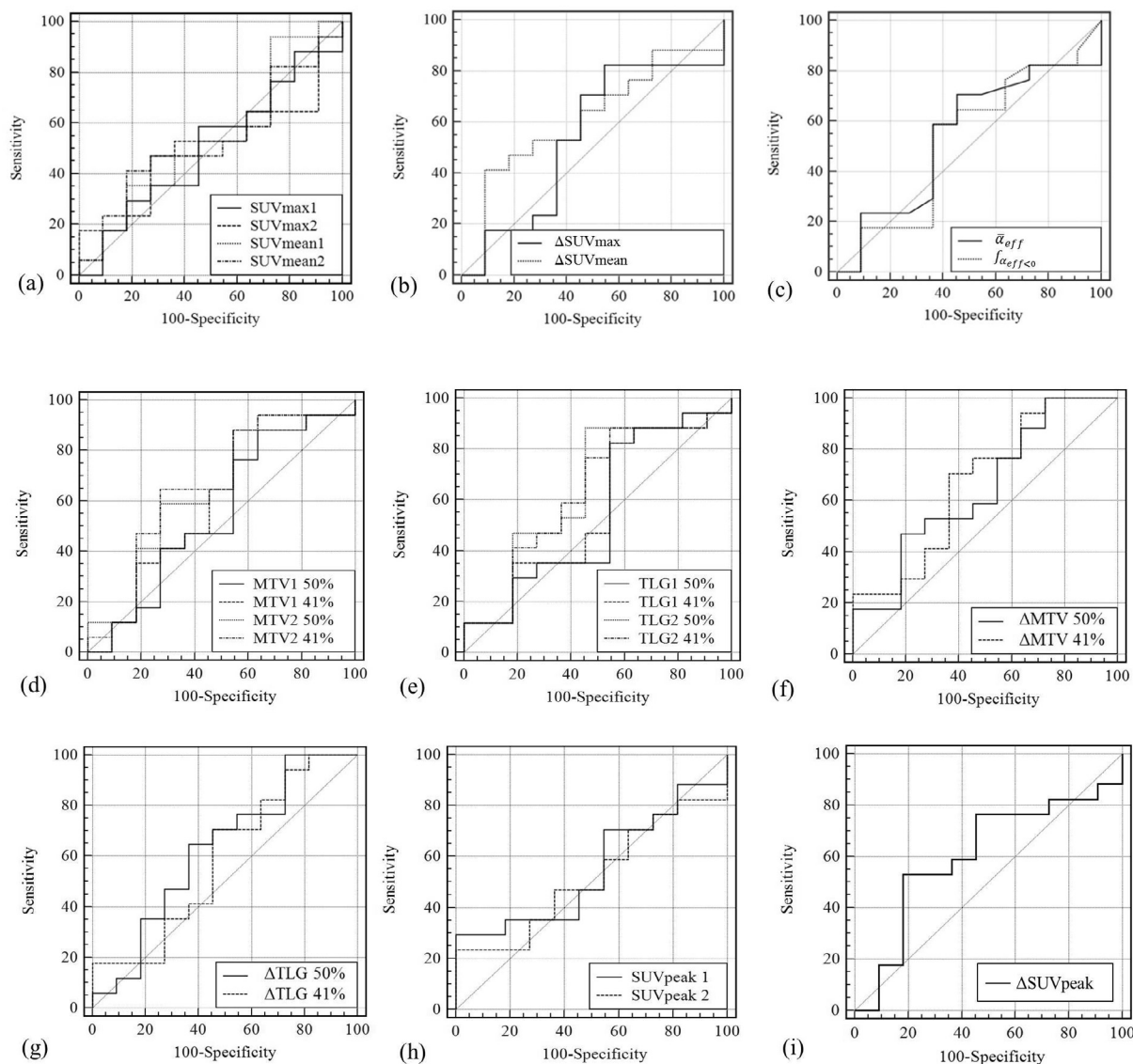


Fig. 3. ROC analysis. The correlation between PET-derived quantities of interest and the overall survival at 2 years is investigated.

treatment adaptation. In addition, the lack of correlation between the parameters derived from the distribution of the calculated effective radiosensitivity at three weeks from the start of the treatment with the treatment outcome points towards the same conclusion. Comparing with previous similar studies, the second week during the treatment appears to be a better time window for response assessment.

Conflict of interest declaration

Johan Uhrdin is employed by RaySearch Laboratories AB. The authors report no other conflicts of interest.

Acknowledgments

This research was supported by EU FP7 funding (ARTFORCE). Additional financial support from the Cancer Research Funds of Radiumhemmet is also acknowledged.

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