

Imaging in lung cancer

Characterization of tumor heterogeneity using dynamic contrast enhanced CT and FDG-PET in non-small cell lung cancer



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ABSTRACT

Purpose: Dynamic contrast-enhanced CT (DCE-CT) quantifies vasculature properties of tumors, whereas static FDG-PET/CT defines metabolic activity. Both imaging modalities are capable of showing intra-tumor heterogeneity. We investigated differences in vasculature properties within primary non-small cell lung cancer (NSCLC) tumors measured by DCE-CT and metabolic activity from FDG-PET/CT.

Methods: Thirty three NSCLC patients were analyzed prior to treatment. FDG-PET/CT and DCE-CT were co-registered. The tumor was delineated and metabolic activity was segmented on the FDG-PET/CT in two regions: low (<50% maximum SUV) and high (\geq 50% maximum SUV) metabolic uptake. Blood flow, blood volume and permeability were calculated using a maximum slope, deconvolution algorithm and a Patlak model. Correlations were assessed between perfusion parameters for the regions of interest.

Results: DCE-CT provided additional information on vasculature and tumor heterogeneity that was not correlated to metabolic tumor activity. There was no significant difference between low and high metabolic active regions for any of the DCE-CT parameters. Furthermore, only moderate correlations between maximum SUV and DCE-CT parameters were observed.

Conclusions: No direct correlation was observed between FDG-uptake and parameters extracted from DCE-CT. DCE-CT may provide complementary information to the characterization of primary NSCLC tumors over FDG-PET/CT imaging.

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One of the hallmarks of cancer is angiogenesis [1]. As a result of the abundant and non-structured production of angiogenic proteins, blood vessels in tumors become abnormal. Paradoxically, tumor angiogenesis therefore leads to hypoxia, one of the most important triggers for tumor progression, metastasis formation and treatment resistance [2]. As angiogenesis can indirectly be quantified by perfusion, techniques to determine blood flow have gained increasing interest. ¹⁸F-deoxyglucose (FDG) uptake by means of PET scans is used to stage non-small cell lung cancer (NSCLC) and has prognostic value as well [3,4]. FDG uptake is related to many biological processes, including glucose metabolism and hypoxia [5]. Angiogenesis and FDG uptake thus define distinct, though relevant biological processes.

With the introduction of the latest state-of-the-art CT scanners, volumetric imaging using dynamic contrast-enhanced CT imaging (DCE-CT) of primary lung cancer is now possible [6–8]. Parameters derived from DCE-CT in NSCLC were previously shown to correlate with tumor characteristics such as micro vessel density (MVD) [9–11] and negative correlations between blood vessel permeability and the glucose transporter (Glut-1) receptor [12] were observed. Li et al. demonstrated a direct strong correlation between blood volume and MVD in a heterogeneous group of peripheral lung cancers, proposing DCE-CT for the *in vivo* evaluation of necrosis and neoangiogenesis [11].

Furthermore, DCE-CT was found to correlate with the gold standard of perfusion, [(15)O]H₂O-PET [13]. Although dynamic FDG acquisitions may also give insight of tumor perfusion, in routine clinical practice, static PET scans are used. Static high FDG-uptake patterns prior to treatment have been shown to identify resistance areas within a tumor indicated by residual metabolic tumor activity in follow-up imaging after radiotherapy [14–16]. It is therefore of interest to investigate the correlations between vasculature parameters derived from DCE-CT and metabolic imaging parameters from FDG-PET/CT [17]. However, previous studies found mixed

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results, i.e., some studies showing positive [18], others inverse [19,20] or no correlation [20–22] between FDG-PET and DCE-CT parameters. Furthermore, typically these studies report only modest correlation coefficients around 0.5. This suggests possible complementary information of DCE-CT compared to FDG-PET imaging, the first one being more specific for quantification of vasculature properties and the second identifying metabolic status of the tumor. Quantification of tumor heterogeneity by combining vasculature and metabolic properties of the tumor could in future be important factors to use for treatment individualization [23–25].

In the context of radiotherapy of non-small cell lung cancer, few DCE-CT imaging studies are being performed. Permeability derived from DCE-CT was hypothesized to relate to tumor response or outcome after (chemo-)radiotherapy [21,26]. During radiotherapy, different spatial uptake patterns between the core and the rim of the tumor were described, with the latter being more vascularized [27]. However, the authors did not investigate and compare the results with the FDG-uptake pattern.

The aim of this study was twofold, first to investigate the heterogeneity of vasculature within primary NSCLC for various frequently used kinetic algorithms and secondly to compare the extracted perfusion parameters from DCE-CT with different metabolically active regions defined on FDG-PET.

Materials and methods

Patient characteristics

We analyzed advanced stage NSCLC patients (stage II and III) from two different hospitals. Images were acquired at the Maastricht University Medical Centre (MUMC, Maastricht, The Netherlands) (dataset A, NCT01024829 and NCT01210378) and the Cantonal Hospital Luzern (Switzerland) (dataset B, Cantonal Ethics Trial Nr.1000) prior to intended (chemo-)radiotherapy treatment.

DCE-CT image acquisition

DCE-CT imaging was performed on a second generation dual source CT scanner (Definition Flash; Siemens Healthcare, Forchheim, Germany) in both centers. Image acquisition was performed using either 80 kVp/120 mAs (dataset A) or 100 kVp/100 mAs setting (dataset B) using a cranial caudal field of view of 13 cm (dataset A) and 7 cm (dataset B) centered on the primary tumor at a slice thickness of 5 mm. The first 50 s (dataset A) or 60 s (dataset B) were scanned at a cycle time of 1.5 and 1.0 s per image, for dataset A and B, respectively, and captured with a delay of two (dataset A) or three (dataset B) seconds after start of the contrast injection. The contrast agent was iodine based, either using 60 ml iopromide (Ultravist 300, Bayer Healthcare, Berlin, Germany) injected at 7.0 ml/s for dataset A or 40 ml (Ultravist 370) injected at 4.5 ml/s for dataset B. Patients were advised to do a breath-hold at expiration or resume shallow breathing for the entire duration of the scan. Image reconstruction encompassing the entire thorax was performed with a 512×512 pixel matrix and (medium) smooth B20f (dataset A) or B30f (dataset B) kernel.

FDG-PET/CT acquisition

On the same day of the DCE-CT, patients underwent an FDG-PET/CT acquisition on an integrated PET/CT scanner according to institutional protocols. Image acquisition started 1 h after injection of approximately 250 MBq FDG (depending on patient weight) on a Siemens Biograph 40 PET/CT (Siemens Healthcare, Erlangen, Germany) for dataset A or on a GE Discovery 600 PET/CT scanner (GE Healthcare, Waekesha (WI), USA) for dataset B. Images were

converted into standardized uptake values (SUV) correcting for injected activity and body weight.

DCE-CT and SUV analysis

Tumor volumes of the primary tumor were manually delineated on the PET/CT scan by experienced radiation oncologists. Tumor volumes were also classified as small or large tumors using a cut-off of 30 cm^3 [19]. Metabolic uptake regions within this primary tumor were automatically segmented using the FDG-PET images and divided into a low (0–50% of the maximum SUV) and high metabolic uptake ($\geq 50\%$ of the maximum SUV). The 50% SUV-max cut-off has been hypothesized to contain residual disease after treatment [15] and is used as target in on-going dose-boosting trials [28]. Additionally, the maximum SUV inside the region of interest was extracted. Furthermore, an analysis according to histological subtype was performed.

Subsequently, the CT scan of the PET/CT acquisition and the first frame (time point) of the DCE-CT scan were non-rigidly registered using previous validated in-house developed software [29]. The contours of the primary tumor, low and high uptake regions on the PET/CT scan were copied to the DCE-CT. In order to assure correct calculation, the deformation fields were visually assessed. By transferring the contour of the region of interest from one image set to the other, we prevent interpolation issues from down and up scaling that might distort the original image (e.g., SUV) values that could occur if the images themselves are deformed. Parameters from the DCE-CT were calculated using commercial software (Siemens VPCT body (VE36A), Siemens Healthcare, Forchheim, Germany). Both motion correction and noise reduction algorithms implemented in the software were applied. For the arterial input function a region of interest was chosen inside the aortic arch. Three kinetic analysis algorithms were calculated: maximum slope model (S), a deconvolution algorithm (A) and a Patlak (P) analysis. From these algorithms various parameters for the primary tumor were extracted. Blood flow (BF) was extracted for the maximum slope and deconvolution algorithm, blood volume (BV) for all three algorithms, and a measure of permeability (PMB) was calculated for the deconvolution and Patlak model. For the primary tumor, low and high uptake regions, the average blood flow, blood volume and permeability were calculated. Voxel-by-voxel parameter maps were exported and combined with the volume of interest defined on the PET/CT images. Average blood flow, volume and permeability parameters were then calculated for the specific parameter under investigation. Also, correlations between the extracted parameters within the algorithms and between different kinetic models were assessed.

Statistics

Differences between two groups were compared using a Student's *t*-test or a one-way ANOVA testing for multiple groups, whereas paired statistics were calculated using the paired *t*-test. Correlations were assessed using linear regression and Pearson's coefficient *r* with $r < 0.3$ indicating small or no correlation, $0.3 < r < 0.5$ for moderate and $r > 0.5$ for strong correlations. Values of $p < 0.05$ were considered as statistically significant.

Results

In total 33 patients were included in the analysis, 11 patients from dataset A and 22 patients from dataset B. There were no significant differences between dataset A and B in distribution of the maximum SUV ($p = 0.45$) or extracted perfusion parameters (range *p*-values: 0.15–0.86), therefore we pooled both datasets for subsequent analysis. An example of a patient is shown in Fig. 1.

Two types of correlations were assessed for the parameters extracted within the primary tumor. First, correlation between the average extracted parameters between different models was assessed. Blood flow correlated strongly between the maximum slope and deconvolution model, $r = 0.91$ ($p < 0.001$), however, the slope between both models was 2.08 indicating an almost double parameter estimation for the deconvolution model compared to the maximum slope model. For blood volume, correlations were also strong: maximum slope versus deconvolution algorithm: $r = 0.94$ ($p = 0.001$, slope: 1.01); maximum slope versus Patlak: $r = 0.70$ ($p < 0.001$, slope: 0.76); and deconvolution algorithm versus Patlak: $r = 0.72$ ($p < 0.001$, slope: 0.74). For permeability the correlation parameters were $r = 0.68$ ($p < 0.001$), slope: 0.69 between the deconvolution and Patlak model.

Second, we investigated the correlation between the various perfusion parameters within one algorithm; see [Supplemental Fig. S1](#) for the results of the deconvolution algorithm. For the maximum slope algorithm (2 kinetic parameters extracted), blood flow was highly correlated with blood volume ($r = 0.91$, $p < 0.001$). For the deconvolution algorithm (3 parameters estimated), blood flow and blood volume were also highly correlated ($r = 0.77$, $p < 0.001$) as well as permeability and blood volume ($r = 0.71$, $p < 0.001$), and to a lesser extent also blood flow and permeability ($r = 0.59$, $p < 0.001$; [Supplemental Fig. S1](#)). For the Patlak model (2 parameters estimated) blood volume and permeability were not correlated ($r = 0.26$, $p = 0.15$).

There was no statistical difference between perfusion parameters extracted for small or large tumors ($p > 0.2$ for all parameters; [Table 1](#)). Maximum SUV showed a difference between small and large tumors: 4.5 ± 2.3 (1 SD) and 6.5 ± 2.8 ($p = 0.008$), respectively.

In [Fig. 2](#), the (non-) correlation between maximum SUV and perfusion parameters derived for the deconvolution algorithm

are shown. These correlations were non-significant for PMB ($p = 0.13$) and only moderately correlated for BF ($r = 0.45$, $p = 0.008$) and BV ($r = 0.35$, $p = 0.04$). Similar results, were found for the maximum slope method (BF: $r = 0.35$, $p = 0.04$, BV: $r = 0.41$, $p = 0.02$) and Patlak model (BV: $p = 0.07$, PMB: $r = 0.41$, $p = 0.02$) showing moderate correlation with the maximum FDG-uptake.

There was no significant difference between the high and low-uptake FDG regions ([Fig. 3](#) and [Table 2](#)). Although permeability extracted using the deconvolution algorithm showed higher values for the high metabolic uptake region, this did not reach significance ($p = 0.08$).

Also for histological subtypes, grouped between adenocarcinoma ($N = 15$), squamous cell carcinoma ($N = 8$), large cell carcinoma ($N = 9$) and one neuroendocrine tumor, results did not show statistical differences, see [Supplemental Table S1](#).

Discussion

DCE-CT is a suitable technique for visualization and quantification of heterogeneity in vasculature of NSCLC tumors. Blood flow and volume are both indirect measures of tumor angiogenesis, which have shown to be measurable with perfusion studies [30,31]. Perfusion parameters extracted using the frequently used kinetic models in DCE-CT did not show strong correlations with static FDG-uptake in primary non-small cell lung cancer tumors indicating additional quantitative characteristics of the primary tumor. Perfusion parameters within the high and low metabolically active regions did not show large differences which may suggest that there is no difference in vasculature between metabolically active and non-active regions. DCE-CT thus gives additional information on vasculature that is not directly related to metabolic tu-

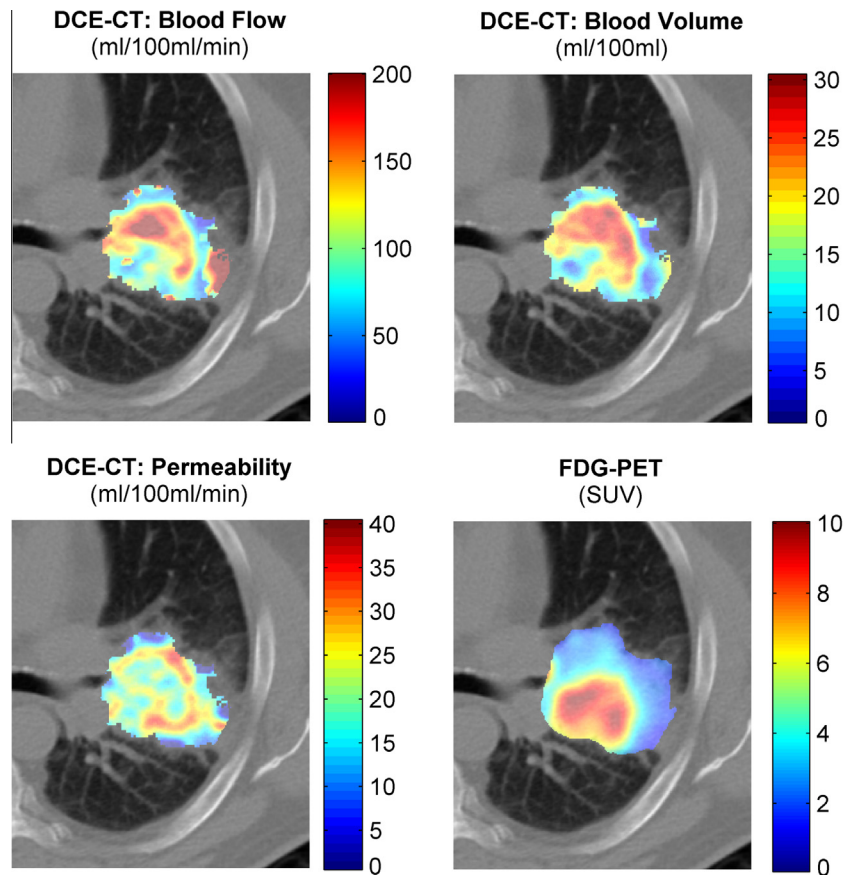


Fig. 1. DCE-CT and FDG-PET example of a patient.

Table 1
Overview of the extracted perfusion parameters for the entire primary tumor, small and large tumors. *p*-Values are calculated using a *t*-test between small and large tumors.

| | | All tumors (N = 33) Mean ± SD | Small tumors (<30 cm ³) (N = 8) Mean ± SD | Large tumors (>30 cm ³) (N = 25) Mean ± SD | Small versus large tumors <i>p</i> -Value |
|----------------------------------|-----------------------|-------------------------------------|---|--|---|
| Blood flow [ml/100 ml/min] | Maximum slope | 36.5 ± 20.8 | 39.2 ± 34.6 | 35.7 ± 14.9 | 0.996 |
| | Deconvolution alg. | 74.7 ± 47.7 | 92.7 ± 87.0 | 68.9 ± 26.1 | 0.250 |
| Blood volume [ml/100 ml] | Maximum slope | 7.4 ± 4.0 | 9.1 ± 6.4 | 6.9 ± 2.9 | 0.374 |
| | Deconvolution alg. | 8.9 ± 4.3 | 10.7 ± 5.9 | 8.4 ± 3.6 | 0.434 |
| | Patlak | 7.9 ± 4.4 | 8.3 ± 4.8 | 7.8 ± 4.4 | 0.969 |
| Permeability [ml/100 ml/ min] | Deconvolution alg. | 16.1 ± 10.0 | 17.9 ± 13.4 | 15.5 ± 8.9 | 0.885 |
| | Patlak | 21.6 ± 9.7 | 26.4 ± 9.8 | 20.0 ± 9.3 | 0.222 |
| FDG-PET [SUV] | Mean SUV | 6.1 ± 2.8 | 4.5 ± 2.3 | 6.5 ± 2.8 | <0.001 |
| | Maximum SUV | 13.8 ± 6.1 | 9.0 ± 4.8 | 15.3 ± 5.7 | 0.008 |

N, number; SD, standard deviation; alg., algorithm; SUV, standardized uptake value.

mor activity. Some authors already suggested such a decoupling between perfusion characteristics and metabolic activity for larger tumor volumes [19,20]. This is in line with our dataset where even though the majority of primary tumors were fairly large in size, we did not observe a correlation between any of the perfusion parameters and metabolic activity. Furthermore, this study shows that besides for tumor size this decoupling might also hold true within the primary tumor, where no differences were found between metabolic (non-) active regions.

There was a high correlation between similar extracted parameters on DCE-CT that were calculated using different models, e.g., the blood flow extracted using the maximum slope model and the deconvolution algorithm had a strong correlation. Furthermore, it is worthwhile to note that the deconvolution algorithm had typically a twice as high value for blood flow. Smaller discrepancies between the various algorithms were found for blood volume and permeability. This discrepancy has previously been shown for other software packages and models [32].

There are several restrictions and limitations that have to be taken into account for the interpretation of DCE-CT studies. First, for this study we used data from two centers having slightly different acquisition procedures (e.g., acquisition length, iodine delivery rates and temporal resolution). However, for the current study we could not identify a difference in extracted parameters for both centers. Furthermore, fast CT acquisition techniques can be performed in breath hold or provide a snapshot of the tumor during the breathing cycle. Compared to a PET technique one has to realize that PET imaging is typically performed using a 3D acquisition over multiple breathing cycles causing blurring due to breathing motion and possible patient movement. Hence, registration between (DCE-)CT and PET/CT images has to be evaluated carefully especially in transferring regions of interest from one dataset to the other.

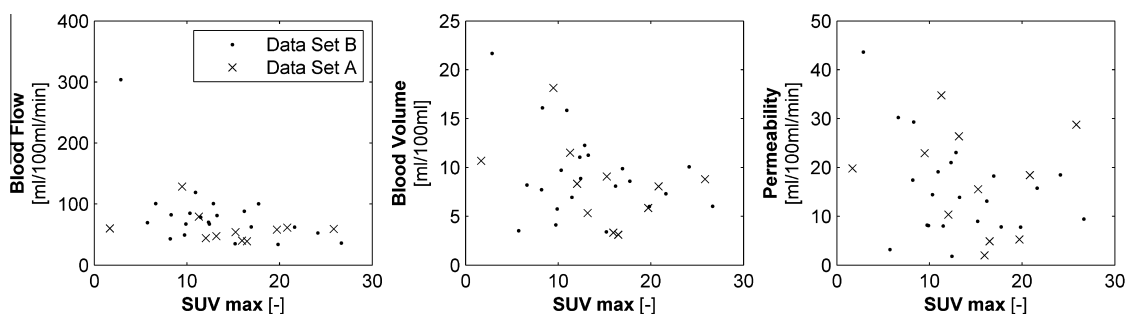


Fig. 2. Scatter plot of the extracted kinetic parameters (blood flow (left), blood volume (middle) and permeability (right panel) calculated using the deconvolution algorithm and maximum SUV inside the primary lung tumor.

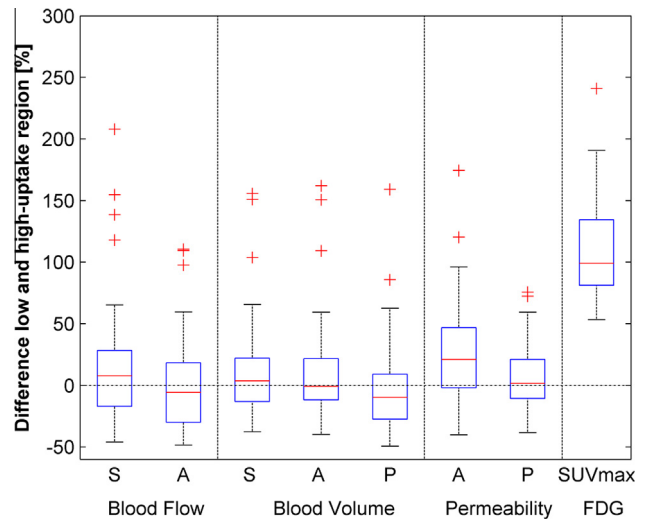


Fig. 3. Box-plot of the differences between the calculated perfusion parameters for the low and high uptake regions inside the primary tumor for the maximum slope (S), deconvolution algorithm (A) and Patlak model (P). Only maximum SUV showed a significant increase of 108% between both regions ($p < 0.001$) due to the definition of the two regions of interest.

Second, to assess permeability of vasculature typically longer acquisition times of up to 3 or 5 min have been used, whereas our perfusion protocols were (first-pass) perfusion of the tumor during the first minute after contrast administration. Extending acquisition time may give better estimations of the permeability and thus future studies need to be explored whether estimation

Table 2

Overview of the extracted perfusion parameters for the low and high uptake regions inside the primary tumor. *p*-Values are calculated using a paired *t*-test between low and high FDG-uptake values.

| | | Low FDG-uptake region (<50% maximum SUV) Mean ± SD | High FDG-uptake region (>50% maximum SUV) Mean ± SD | Low versus high uptake <i>p</i> -Value |
|------------------------------|--------------------|---|--|---|
| Blood flow [ml/100 ml/min] | Maximum slope | 39.0 ± 32.3 | 39.2 ± 20.8 | 0.961 |
| | Deconvolution alg. | 83.0 ± 62.1 | 74.6 ± 46.6 | 0.117 |
| Blood volume [ml/100 ml] | Maximum slope | 7.8 ± 5.7 | 8.0 ± 4.0 | 0.732 |
| | Deconvolution alg. | 9.2 ± 5.5 | 9.6 ± 4.3 | 0.472 |
| | Patlak | 8.6 ± 4.6 | 8.2 ± 5.1 | 0.547 |
| Permeability [ml/100 ml/min] | Deconvolution alg. | 15.7 ± 12.9 | 18.6 ± 13.0 | 0.080 |
| | Patlak | 21.4 ± 9.6 | 22.5 ± 10.2 | 0.181 |
| FDG-PET [SUV] | Mean SUV | 4.3 ± 1.8 | 9.0 ± 3.9 | <0.001 |
| | Maximum SUV | 7.6 ± 3.7 | 13.8 ± 6.1 | <0.001 |

SD, standard deviation; alg., algorithm; SUV, standardized uptake value.

of the permeability using longer acquisition durations is correlated with metabolic uptake [30].

Third, validation of kinetic analysis software is not trivial. The commercial software package we used in this study has been used by others to compare functional imaging parameters against histology [10]. However, in general, most commercial software solutions are black-box systems with build-in smoothing, noise reduction and automatic fitting procedures that are not directly interchangeable [32]. Thorough validation and benchmarking against other kinetic analysis models, e.g., an extended Tofts model or approximated adiabatic expansion model are necessary. Selecting a sound kinetic analysis model is topic of investigation for various groups and may need to be tailored to different tumor sites [33,34].

Lastly, in contradiction to some but not all literature [18,19], we did not find strong correlations between FDG-uptake measured on PET imaging and perfusion characteristics in non-small cell lung cancer. Several authors describe significant correlations, however, in our study these correlations appear to be weak or at maximum modest with moderate correlation coefficients, we therefore cannot conclude that metabolic and vasculature properties are linked using the current imaging and analysis methodology. Hence FDG uptake and perfusion derived parameters show distinct biological characteristics allowing further characterizing tumor heterogeneity that should be investigated in future as an independent factor for treatment outcome.

With the current frequently used first-pass perfusion protocols no correlation between metabolic uptake visualized on FDG-PET/CT imaging and extracted DCE-CT parameters was found. Further research in optimizing the acquisition settings and kinetic analysis models are necessary for exploration of the added value of DCE-CT for NSCLC.

Conflict of interest

J.E. Wildberger received grants and travel support from Siemens R&D.

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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.2013.08.032>.

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