First-in human simultaneous [18F]FDG PET-MRI voxel-wise correlation analysis

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Declarations

**Ethical approval and consent to participate**

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments. The local institutional review board (SHFJ Research Steering Committee, DRF/JOLIOT/SHFJ/2020/10) approved this study and all patients signed a written informed consent.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets generated and analyzed during the current study are not publicly available, in accordance with the General Data Protection Regulation (GDPR) of the European Union, but are available from the corresponding author on request, after justification that meets the GDPR principles.

**Competing interests**

Brice Fernandez (second author) is a PET/MR lead scientist employed by GE Healthcare

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Author’s contributions (ICMJE recommendations)

All authors:

- Design, acquisition analysis
- Revising for intellectual content
- Final approval
- Agreement to be accountable for all aspects of this work (accuracy and integrity of any part of the work)

In addition:

- Kinetic parameter programming: Florent L. Besson, Sylvain Faure
- MRI sequence optimization: Florent L. Besson, Brice Fernandez
- Patient recruitment and / or surgical procedure: Olaf Mercier, Andrei Seferian, Xavier Mignard, Sacha Mussot, Cécile le Pêchoux, Caroline Caramella, Angela Botticella, Antonin Levy, Florence Parent, Sophie Bulifon, David Montani, Delphine Mitilian, Elie Fadel, David Planchard, Benjamin Besse
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Abstract

Objectives:
To decipher the interlinks between PET and DCE kinetic parameters in non-small-cell lung cancer (NSCLC), by using voxel-wise analysis of full dynamic simultaneous [18F]FDG PET-MRI.

Material and methods:
Fourteen treatment-naïve patients with biopsy proven NSCLC prospectively underwent a one-hour dynamic [18F]FDG thoracic PET-MRI scan including DCE. The PET and DCE data were normalized to their corresponding T1-weighted MR morphological space, and tumors were masked semi-automatically. Voxel-wise parametric maps of PET and DCE kinetic parameters were computed by fitting the dynamic PET and DCE tumor data to the Sokoloff and Extended Tofts models respectively, by using in-house developed procedures. Curve fitting errors were assessed by computing the relative root mean square error (rRMSE) of the estimated PET and DCE signals at the voxel level. For each tumor, Spearman correlation coefficients ($r_s$) between all the pairs of PET and DCE kinetic parameters were estimated on a voxel-wise basis, along with their respective bootstrapped 95% confidence intervals (n = 1000 iterations).

Results:
Curve fitting metrics provided fit errors under 20% for almost 90% of the PET voxels (median rRMSE = 10.3, interquartile ranges IQR = 8.1; 14.3), whereas 73.3% of the DCE voxels showed fit errors under 45% (median rRMSE = 31.8%, IQR = 22.4; 46.6). The PET-PET, DCE-DCE and PET-DCE voxel-wise interlinks were heterogeneous, with variations related to individual tumor behaviors. Beyond this wide variability, the PET-PET and DCE-DCE interlinks were mainly high (absolute $r_s$ values > 0.7), whereas the PET-DCE interlinks were mainly low to moderate (absolute $r_s$ values < 0.7). Half the tumors showed an hypometabolic with low perfused/vascularized profile, a hallmark of hypoxia and tumor aggressiveness.

Conclusion:
The interlinks between dynamic PET and DCE kinetic parameters assessed simultaneously with [18F]FDG PET-MRI are heterogeneous among NSCLC tumors. In the era of precision medicine, PET-MRI has unique capability to go further insight the individual tumor behavior in NSCLC.
**Introduction**

Positron emission tomography (PET) combined with magnetic resonance imaging (MRI) emerged a decade ago [1,2]. Since the beginning, substantial efforts have been made to promote its clinical use, but disappointing results compared to more cost-effective and former imaging modalities still make the positioning of PET-MRI challenging in clinical practice [3]. In the era of precision medicine, multiparametric imaging offers many opportunities to better characterize the biological processes of tumors [4–6]. Compared to visual or semi quantitative methods, the more sophisticated dynamic kinetic analyses go further insight the quantification of biological pathways in tissues. In integrated PET-MRI, combining kinetic models of glucose metabolism and angiogenesis simultaneously may be of particular interest to revisit the complex relationship between these two fundamental tumor hallmarks [7,8] at the intra-tumor level. In lung cancer, previous [18F]FDG PET/MRI imaging studies have been performed mainly for clinical disease staging evaluation [9–13], SUV-ADC correlation analyses [14–17] and prognostic value [18]. Metabolism and vascularization are two fundamental hallmarks of cancer [8]. To date, only few multimodal imaging studies compared tumor metabolism assessed with PET and angiogenesis assessed with dynamic contrast enhanced (DCE) MRI or CT in primary non-small-cell lung cancer (NSCLC) [19–23], of which only two combined dedicated [18F]FDG PET and DCE-MRI imaging data [19,23]. So far, full dynamic [18F]FDG PET and DCE-MRI analyses have never been performed simultaneously at the individual voxel-wise tumor level.

In this study, we deciphered the interlinks between [18F]FDG PET and DCE kinetic parameters at the intra-tumor level in newly diagnosed, biopsy proven NSCLC, by using full dynamic simultaneous [18F]FDG PET-MRI voxel-wise analysis.
Material and Methods

Patients

Between January 2018 and April 2019, a total of 14 treatment-naive patients with biopsy proven NSCLC prospectively underwent a dynamic [18F]FDG PET-MRI for thoracic oncology purpose. The exclusion criteria were claustrophobia, metal implants, renal failure (clearance < 30 mL/min), and uncontrolled diabetes mellitus. Patient’s characteristics are summarized in Table 1. The local institutional review board approved this study (SHFJ Research Steering Committee, DRF/JOLIOT/SHFJ/2020/10) and all patients signed a written informed consent.

PET/MRI

All the examinations were performed in supine position on the same integrated 3T PET-MRI scanner (Signa PET/MR, GE Healthcare, Waukesha, WI, USA). All patients fulfilled the international procedure guideline for [18F]FDG PET tumor imaging [24], verifying fasting of 6 hours and blood glucose level under 1.8g/L at the time of the imaging procedure. A one-hour dynamic thoracic PET acquisition started immediately after the intravenous injection of 3-4 MBq/kg of [18F]FDG. The dynamic PET data were histogrammed into multiframe sinograms (41 frames of 12 x 10s, 12 x 20s, 4 x 60s, 5 x 120s, 8 x 300s respectively) to be reconstructed using an iterative algorithm (3D TOF-OSEM, 6 iterations and 28 subsets with time of flight and point spread function modeling, and with random, dead time, scatter, decay, and attenuation corrections, matrix size = 256x256; voxel size = 2 × 2 × 2.78 mm). Simultaneously, the following MR thoracic acquisitions were performed using a thoracic phased array radiofrequency (RF) coil (GEM Coil Suite, GE Healthcare, Waukesha, WI, USA):

- A two-point (fat, water) axial 3D-Dixon pulse sequence (TR/TE1/TE2 = 4/1.1/2.2ms, Field-Of-View (FOV): 500/500/332.8 mm, Number of excitations (NEX) = 0.7, voxel size 1.95x1.95x2.6 mm) for MR-based attenuation correction.
- A PROPELLER fast recovery Fast Spin Echo sequence with respiratory triggering for T2-weighted morphology (TR/TE = 8000/117ms, FOV: 400/400/90 mm, NEX = 2; voxel size 1.0x1.0x6.0 mm, Acceleration factor = 3).
• a 2D saturation recovery pulse sequence for pre-contrast T₁-mapping (heartbeats triggering, inversion times in ms = [136/136/136/136/818/1583/2109/2808/20000], TR/TE = 2.9 / 1.1ms; FOV: 420/420/30 mm, NEX = 1; voxel size 1.64×1.64×5.0 mm) [25];

• DCE acquisitions performed before, during, and after the automated injection of Gadolinium contrast agent (Gd, 0.2 mmol/kg body weight, Dotarem, Guerbet GmbH, Germany; injecting rate of 2.0 ml/s by power injector) using 3D T1-Fast Spoiled Gradient Recalled (Fast SPGR) pulse sequences under free breathing (120 frames of 3.03 second each for a total acquisition time of 6 minutes, TR/TE = 3.46 / 1.10ms; FOV: 400/320/120 mm, NEX = 0.69, voxel size 1.56×1.25×2.5 mm);

• A post-contrast 3D T1-Fast SPGR sequence in breath-hold position (TR/TE = 4.48/2.41ms, FOV: 440/352/179.2 mm, NEX = 0.7, voxel size 1.72×1.72×0.8 mm).

Image processing

All the data processing was performed off-line using Python (version 3.6; Python Software Foundation, www.python.org; libraries numpy, pandas, nibabel, nilearn, nipype, scipy, math). The general study workflow is provided in the Figure 1. For each patient, the same image processing was performed:

a) Data normalization: [18F]FDG-PET and DCE-MRI data were first normalized to the 3D-T₁ reference isotropic space (i.e the post-contrast 3D T₁-weighted MRI resampled to 2mm³). For this purpose, the dynamic PET data and the MR pre-contrast T₁-mapping data were resampled to the 3D-T₁ space, whereas the DCE data were motion-compensated (warping to the 3D-T₁ space) using the SyNQuicK procedure implemented in Advanced Normalization Tools (ANTs) [26,27].

b) Tumor mask: the last frame of [18F]FDG-PET and DCE data, the pre-contrast T₁-mapping data and the post-contrast 3D-T₁ data were masked semi-automatically with ITK-SNAP, an active contour-based algorithm [28,29]. The resulting PET, DCE, T₁-mapping and 3D-T₁ tumor masks were intersected into one multimodal tumor mask.

c) Arterial mask for image-based derived input function (IDIF): IDIF is non-invasive and has been validated against arterial sampling (the gold standard) in oncological patients [30]. For this
purpose, the following procedure was performed with the graphical user interface ITK-SNAP: a small volume of interest (VOI) was carefully positioned on the center of the thoracic aorta to avoid spill-in and spill-over effects. The position was carefully chosen to fit with the FOVs of all the PET, T₁-mapping and DCE fused data.

d) Signal processing: the 4D-PET data were smoothed with an 8 mm Gaussian filter, and the DCE imaging data were converted to Gadolinium plasma concentration C(t) using the following equation [31]:

\[
C(t) = \frac{1}{(1 - \text{Hct})} \times \frac{-1}{r_{\text{Gd}} \times T_R} \times \left[ T_R \times T_{10} + L \ln \left( \frac{S(t)}{S_0} \times \frac{1 - E - 1}{1 - \cos(\alpha) - 1} \right) \right],
\]

with \( S_0 \) and \( S(t) \) the signals measured before contrast-enhancement and at time \( t \) after contrast injection, \( \text{Hct} \) the hematocrit level fixed at 0.45 [32], \( r_{\text{Gd}} = 3.4 \text{ s}^{-1} \text{mM}^{-1} \) the relaxivity of Dotarem at 3T [33], \( E = e^{-T_R/T_{10}} \) with \( T_{10} \) the estimated pre-contrast T₁ value in the voxel of interest, and \( \alpha \) the flip angle of the 3D fast-SPGR pulse sequence, set to 15° in our imaging protocol.

e) Voxel-wise parametric maps computation: tumor and IDIF data were extracted from the masked 4D PET and DCE data, and the [18F]FDG PET (\( K_1, k_2, k_3, v_p, \text{MRGlu} \)) and DCE-MRI (\( K_{\text{trans}}, v_e, K_{\text{ep}}, v_b \)) kinetic parameters were finally computed by fitting the extracted data to the reference Sokoloff’s ([18F]FDG PET) [34] and extended Tofts (DCE) [35] compartmental models on a voxel-wise basis, using “in-house” second order Runge-Kutta procedures combined with Levenberg-Marquardt non-linear least-square fitting optimization.

Statistical analysis

All the statistical analyses were performed with Python (version 3.6; Python Software Foundation, www.python.org) and R studio (version 3.4.0; R Project for Statistical Computing, www.r-project.org). Curve fitting errors of our in-house PET and DCE kinetic modeling implementation were assessed voxel-wise by computing the relative Root Mean Square Errors, defined by \( rRMSE = \frac{\| \text{signal} - \text{signal} \|}{\| \text{signal} \|} \)

where \( \text{signal} \) is the measured signal and \( \text{signal} \) is the estimated signal after fitting procedure. The PET and DCE kinetic microparameters values are expressed as median ± IQR. After data transformation into
z-score (zero mean and unit variance) and cleaning-up from outliers (z-score > 3), the PET-PET, DCE-DCE and PET-DCE voxel-wise interlinks were assessed for each tumor by estimating the related spearman coefficients (r_s), along with their respective bootstrapped 95% confidence intervals (n = 1000 iterations). The absolute r_s estimated values (|r_s|) were considered low under 0.4, moderate between 0.4 and 0.7, and high above 0.7 [36].
**Results**

The general characteristics of the 14 patients are summarized in Table 1. Briefly, 9 were male and 5 were female (sex ratio M/F = 1.8), aged 65.5±10.6 years. The tumor localization was the right upper lobe for the majority of the patients (7 patients), followed by the left upper lobe (5 patients). The two remaining patients had tumor in the right lower lobe and the right medium lobe respectively.

The voxel-wise curve fitting metrics (fit errors) of the PET and DCE kinetic measurements are provided in Tables 2, 3 and Figure 2. Among the 14 tumors (21 555 estimated voxels), the overall PET rRMSE was 10.3% (8.1; 14.3), corresponding to 89.3% of voxels with error under 20%. The overall DCE rRMSE was 31.8% (22.4; 46.6), corresponding to 73.3% of voxels with error under 45%. The estimated \[^{18}F\]FDG PET and DCE kinetic parameters are summarized in Table 2. The correlation analyses showed wide variability in the PET-PET, DCE-DCE and PET-DCE interlinks (Figures 3 and 4 and supplementary material). The PET-PET and DCE-DCE interlinks were mainly moderate to strong for all the tumors, but with high individual variabilities (Figure 3 and supplementary material). When considering the PET-DCE interlinks exclusively, the 14 tumors showed weak (|r| <0.4) to moderate (0.4 ≤ |r| < 0.7) interlinks exclusively (Figure 4 and supplementary material). MRGlu was positively correlated to k3 in all tumors; and inversely correlated with K\text{trans}, v_p or v_b in the majority of tumors. The 3D parametric maps clearly showed regional decoupling patterns of hypoperfused (K\text{trans} or K_1) and poor vascularized areas (v_h or v_p) with high metabolic enzymatic activity (k_3) in five tumors, as illustrates Figure 5 (tumors 1, 5, 12, 13 and 14).
**Discussion**

This simultaneous dynamic PET-DCE MRI study shows that dynamic PET and DCE monotonic interlinks, measured in exactly the same conditions, are highly variable at the tumor level in treatment-naïve NSCLC. [18F]FDG dynamic PET-DCE MRI has unique capability to capture the individual tumor biological behavior of NSCLC. Vascularity and perfusion properties are spatially heterogeneous in NSCLC [37,38]. This wide variability has been recently highlighted in [18F]FDG PET compartmental analyses [39], and was qualitatively illustrated in our full dynamic PET-DCE MRI study.

As expected, MRGlu and k3 PET microparameters were positively correlated in all the tumors, emphasizing the expected close interlinks between the regional metabolic and phosphorylated rates of glucose. In more than half the tumors, both MRGlu and k3 were inversely correlated to Ktrans, vp and vb, suggesting high metabolic but low perfused / vascularized cells, a well-known hallmark of tumor hypoxia or aggressiveness [7]. Recent Head and Neck 18F-FMISO [40] and preclinical VX-2 13N-NH3 [41] PET/DCE MRI studies showed weak correlation between K1 and Ktrans perfusion parameters. In our NSCLC [18F]FDG PET/DCE-MRI clinical study, the K1-Ktrans interlinks were also mainly weak. This general trend is not surprising considering the three following key concepts: First, Perfusion reflects a weighted mixture of blood flow and Permeability-Surface area product [42–44] that depends, in the case of fixed flow and microvascular characteristics, on the tracers exchange properties ([18F]FDG is actively transported across the cellular membrane, whereas Gd is a purely extra cellular diffusive contrast agent). Second, DCE Tofts models [35,45] do not consider the intra-cellular space (ICS), whereas standard compartmental PET models [34] do not distinguish the extravascular extracellular space (EES) from the ICS, assuming steady state between EES and ICS at the injection time. Consequently, K1 depends on a mixed perfusion-extraction weighting of [18F]FDG that may, in the case of high metabolic rate conditions, overestimate the perfusion component [43]. Our study has several limitations. Our data sample was limited to 14 biopsy proven NSCLC. Also, because pre-contrast T1-mapping was limited to 6 slices per tumor for practical considerations, we could not capture the multimodal interlinks of the entire tumor volumes. Compared to PET, DCE kinetic modeling showed higher voxel-wise fit errors. It is well-known that many factors hamper the accuracy of DCE pharmacokinetic modeling, making this approach highly challenging in clinical practice [46–48]. For
illustration, considering the same patients and imaging data, using multiple commercially available software was reported to lead to within-patient variabilities up to 74% in DCE-MRI measurements [49]. In our study, motion corruption was probably the major explanation of the measurement errors. The high-resolution time of DCE frames emphasized the motion corruptions effects, only slightly compensated by our standard motion correction method. Anyway, the mean fraction of outliers used for the correlation analyses was under 10% among all the 14 tumors (7.8% ± 2.8%). A better availability of research advanced motion compensation techniques [50] would be of particular interest. We did not include the $K_i$ PET parameter, but directly the MRGlu parameter, which is the $K_i$-glycaemia product normalized by the lumped constant (LC). We justified this choice because LC is arbitrarily set to 1 in oncology studies (the unknown true LC precludes from any other value) [51,52] making MRGlu a basic multiple of $K_i$. Also, dual arterial input implementation has been recently proposed in few CT or MR-based perfusion studies [53–57], based on the fact that lung tumors may have a dual blood supply [58]. The selection of the right model for the right tumor is limited by what is named the “mixed tissue conundrum” [59], and remains mainly driven by both its bias-variance tradeoff and clinical relevance. In this way, DCE Tofts models have become standards in oncology [60,61], and have shown preclinical and clinical relevance in lung cancer specifically [62–64]. Also, the dual AIF has never been validated on dynamic PET analyses, and therefore cannot be considered as a reference. Finally, despite the fact that the majority of the included tumors were in the upper lobes, our results are prone to potential uncertainties related to respiratory motion artefacts, despite our motion compensation procedure. Despite these limitations, this study show that simultaneous dynamic PET-MRI is feasible in NSCLC patients, and has provided evidence of the unique capability of simultaneous PET/MRI imaging to further characterize the individual biological tumor behavior in NSCLC. We hope our results will stimulate future research in this field.

Conclusion

Dynamic PET and DCE interlinks based on reference compartmental PET and MRI kinetic modeling are highly heterogeneous in NSCLC. In the era of personalized medicine, this study has provided evidence of the unique capability of simultaneous PET-MRI imaging to further characterize individual tumor biological behavior in NSCLC.
Compliance with ethical standards

Funding The imaging facility (SHFJ) where acquisitions were performed has received funding from the French programs “Investissements d’avenir” run by the “Agence Nationale de la Recherche” and “Infrastructure d’avenir en Biologie Santé” France Life Imaging (grant ANR-11-INBS-0006).

Conflicts of interest None

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee (SHFJ Research Steering Committee, DRF/JOLIOT/SHFJ/2020/10) and with the principles of the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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References

1. Zaidi H, Ojha N, Morich M, Griesmer J, Hu Z, Maniawski P, et al. Design and performance evaluation of a whole-body Ingenuity TF PET–MRI system. Phys Med Biol. 2011;56:3091–106.
2. Delso G, Furst S, Jakoby B, Ladebeck R, Ganter C, Nekolla SG, et al. Performance Measurements of the Siemens mMR Integrated Whole-Body PET/MR Scanner. Journal of Nuclear Medicine. 2011;52:1914–22.
3. Czernin J, Ta L, Herrmann K. Does PET/MR Imaging Improve Cancer Assessments? Literature Evidence from More Than 900 Patients. Journal of Nuclear Medicine. 2014;55:598-625.
4. Padhani AR, Miles KA. Multiparametric Imaging of Tumor Response to Therapy. Radiology. 2010;256:348–64.
5. Tunariu N, Kaye SB, deSouza NM. Functional imaging: what evidence is there for its utility in clinical trials of targeted therapies? Br J Cancer. 2012;106:619–28.
6. Lin G, Chung Y-L. Current Opportunities and Challenges of Magnetic Resonance Spectroscopy, Positron Emission Tomography, and Mass Spectrometry Imaging for Mapping Cancer Metabolism In Vivo. BioMed Research International. 2014;2014:1–13.
7. Miles KA. Warburg revisited: imaging tumour blood flow and metabolism. Cancer Imaging. 2008;8:81–6.
8. Fouad YA, Aanei C. Revisiting the hallmarks of cancer. Am J Cancer Res. 2017;7:1016–36.
9. Heusch P, Buchbender C, Kohler J, Nensa F, Gauer T, Gomez B, et al. Thoracic Staging in Lung Cancer: Prospective Comparison of 18F-FDG PET/MR Imaging and 18F-FDG PET/CT. Journal of Nuclear Medicine. 2014;55:373–8.
10. Schaarschmidt B, Buchbender C, Gomez B, Rubbert C, Hild F, Köhler J, et al. Thoracic staging of non-small-cell lung cancer using integrated 18F-FDG PET/MR imaging: diagnostic value of different MR sequences. Eur J Nucl Med Mol Imaging. 2015;42:1257–67.
11. Ohno Y, Koyama H, Yoshikawa T, Takenaka D, Seki S, Yui M, et al. Three-way Comparison of Whole-Body MR, Coregistered Whole-Body FDG PET/MR, and Integrated Whole-Body FDG PET/CT Imaging: TNM and Stage Assessment Capability for Non–Small Cell Lung Cancer Patients. Radiology. 2015;275:849–61.
12. Schaarschmidt BM, Grueneisen J, Metzenmacher M, Gomez B, Gauer T, Roesel C, et al. Thoracic staging with 18F-FDG PET/MR in non-small cell lung cancer – does it change therapeutic decisions in comparison to 18F-FDG PET/CT? Eur Radiol. 2017;27:681–8.
13. Kirchner J, Sawicki LM, Nensa F, Schaarschmidt BM, Reis H, Ingenwerth M, et al. Prospective comparison of 18F-FDG PET/MRI and 18F-FDG PET/CT for thoracic staging of non-small cell lung cancer. Eur J Nucl Med Mol Imaging. 2019;46:437–45.
14. Regier M, Derlin T, Schwarz D, Laqmani A, Henes FO, Groth M, et al. Diffusion weighted MRI and 18F-FDG PET/CT in non-small cell lung cancer (NSCLC): Does the apparent diffusion coefficient (ADC) correlate with tracer uptake (SUV)? European Journal of Radiology. 2012;81:2913–8.
15. Heusch P, Köhler J, Wittsack H-J, Heusner TA, Buchbender C, Poeppe1 TD, et al. Hybrid [18F]-FDG PET/MRI including non-Gaussian diffusion-weighted imaging (DWI): Preliminary results in non-small cell lung cancer (NSCLC). European Journal of Radiology. 2013;82:2055–60.
16. Schaarschmidt BM, Buchbender C, Nensa F, Grueneien J, Gomez B, Köhler J, et al. Correlation of the Apparent Diffusion Coefficient (ADC) with the Standardized Uptake Value (SUV) in Lymph Node Metastases of Non-Small Cell Lung Cancer (NSCLC) Patients Using Hybrid 18F-FDG PET/MRI. Byrnes KR, editor. PLOS ONE. 2015;10:e0116277.
17. Metz S, Ganter C, Lorenzen S, van Marwick S, Holzapfel K, Herrmann K, et al. Multiparametric MR and PET Imaging of Intratumoral Biological Heterogeneity in Patients with Metastatic Lung Cancer Using Voxel-by-Voxel Analysis. Muñoz-Barrutia A, editor. PLOS ONE. 2015;10:e0132386.
18. Iizuka Y, Matsuo Y, Umeoka S, Nakamoto Y, Ueki N, Mizowaki T, et al. Prediction of clinical outcome after stereotactic body radiotherapy for non-small cell lung cancer using diffusion-weighted MRI and 18F-FDG PET. European Journal of Radiology. 2014;83:2087–92.
19. Hunter GJ, Hamberg LM, Choi N, Jain RK, McCloud T, Fischman AJ. Dynamic T1-weighted magnetic resonance imaging and positron emission tomography in patients with lung cancer: correlating vascular physiology with glucose metabolism. Clin Cancer Res. 1998;4:949–55.
20. Tateishi U, Nishihara H, Tsukamoto E, Morikawa T, Tamaki N, Miyasaka K. Lung tumors evaluated with FDG-PET and dynamic CT: the relationship between vascular density and glucose metabolism. J Comput Assist Tomogr. 2002;26:185–90.
21. Hoekstra CJ, Stroobants SG, Hoekstra OS, Smit EF, Vansteenkiste JF, Lammertsma AA. Measurement of perfusion in stage IIIA-N2 non-small cell lung cancer using H(2)(15)O and positron emission tomography. Clin Cancer Res. 2002;8:2109–15.
22. Miles KA, Griffiths MR, Keith CJ. Blood flow-metabolic relationships are dependent on tumour size in non-small cell lung cancer: a study using quantitative contrast-enhanced computer tomography and positron emission tomography. Eur J Nucl Med Mol Imaging. 2006;33:22–8.
23. Zhang J, Chen L, Chen Y, Wang W, Cheng L, Zhou X, et al. Tumor Vascularity and Glucose Metabolism Correlated in Adenocarcinoma, but Not in Squamous Cell Carcinoma of the Lung. Zhang Z, editor. PLoS ONE. 2014;9:e91649.
24. Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. European Journal of Nuclear Medicine and Molecular Imaging. 2015;42:328–54.
25. Slavin GS, Stainsby JA. True T1 mapping with SMART1Map (saturation method using adaptive recovery times for cardiac T1 mapping): a comparison with MOLLI. J Cardiovasc Magn Reson. 2013;15:P3, 1532–1534.
26. Avants B, Epstein C, Grossman M, Gee J. Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. Medical Image Analysis. 2008;12:26–41.
27. Avants BB, Tustison NJ, Stauffer M, Song G, Wu B, Gee JC. The Insight ToolKit image registration framework. Frontiers in Neuroinformatics [Internet]. 2014 [cited 2019 May 28]:8. Available from: http://journal.frontiersin.org/article/10.3389/fninf.2014.00044/abstract.
28. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage. 2006;31:1116–28.
29. Besson FL, Henry T, Meyer C, Chevance V, Roblot V, Blanchet E, et al. Rapid Contour-based Segmentation for 18F-FDG PET Imaging of Lung Tumors by Using ITK-SNAP: Comparison to Expert-based Segmentation. Radiology. 2018;288:277–84.
30. de Geus-Oei L-F, Visser EP, Krabbe PFM, van Hoorn BA, Koenders EB, Willemsen AT, et al. Comparison of image-derived and arterial input functions for estimating the rate of glucose metabolism in therapy-monitoring 18F-FDG PET studies. J Nucl Med. 2006;47:945–9.
31. Chao S-L, Metens T, Lemort M. TumourMetrics: a comprehensive clinical solution for the standardization of DCE-MRI analysis in research and routine use. Quant Imaging Med Surg. 2017;7:496–510.
32. Billett HH. Hemoglobin and Hematocrit. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations [Internet]. 3rd ed. Boston: Butterworths; 1990 [cited 2020 Feb 23]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK259/
33. Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, et al. The [14C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem. 1977;28:897–916.
34. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. J Magn Reson Imaging. 1997;7:91–101.
35. Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. Anesth Analg. 2018;126:1763–8.
36. Ushijima C, Tsukamoto S, Yamazaki K, Yoshino I, Sugio K, Sugimachi K. High vascularity in the peripheral region of non-small cell lung cancer tissue is associated with tumor progression. Lung Cancer. 2001;34:233–41.
37. Birau A, Ceausu RA, Cimpean AM, Gaje P, Raica M, Olariu T.Assessement of angiogenesis
reveals blood vessel heterogeneity in lung carcinoma. Oncol Lett. 2012;4:1183–6.
39. Silvestri E, Scolozzi V, Rizzo G, Indovina L, Castellaro M, Mattoli MV, et al. The kinetics of 18F-FDG in lung cancer: compartmental models and voxel analysis. EJNMMI Res. 2018;8:88.
40. Simonic U, Leibfarth S, Welz S, Schwenzer N, Schmidt H, Reischl G, et al. Comparison of DCE-MRI kinetic parameters and FMISO-PET uptake parameters in head and neck cancer patients. Med Phys. 2017;44:2358–68.
41. Lee KH, Kang SK, Goo JM, Lee JS, Cheon GJ, Seo S, et al. Relationship Between Ktrans and K1 with Simultaneous Versus Separate MR/PET in Rabbits with VX2 Tumors. Anticancer Res. 2017;37:1139–48.
42. Cuenod CA, Balvay D. Perfusion and vascular permeability: Basic concepts and measurement in DCE-CT and DCE-MRI. Diagnostic and Interventional Imaging. 2013;94:1187–204.
43. Mullani NA, Herbst RS, O’Neil RG, Gould KL, Barron BJ, Abbruzzese JL. Tumor blood flow measured by PET dynamic imaging of first-pass 18F-FDG uptake: a comparison with 15O-labeled water-measured blood flow. J Nucl Med. 2008;49:517–23.
44. Sourbron SP, Buckley DL. On the scope and interpretation of the Tofts models for DCE-MRI. Magn Reson Med. 2011;66:735–45.
45. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusible tracer: standardized quantities and symbols. J Magn Reson Imaging. 1999;10:223–32.
46. Lavini C. Simulating the effect of input errors on the accuracy of Tofts’ pharmacokinetic model parameters. Magnetic Resonance Imaging. 2015;33:222–35.
47. Kim H. Variability in Quantitative DCE-MRI: Sources and Solutions. J Nat Sci. 2018;4.
48. Shukla-Dave A, Obuchowski NA, Chenevert TL, Jambawalikar S, Schwartz LH, Malyarenko D, et al. Quantitative imaging biomarkers alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials: QIBA Recommendations. Journal of Magnetic Resonance Imaging [Internet]. 2018 [cited 2019 May 28]; Available from: http://doi.wiley.com/10.1002/jmri.26518
49. Heye T, Davenport MS, Horvath JJ, Feuerlein S, Breault SR, Bashir MR, et al. Reproducibility of dynamic contrast-enhanced MR imaging. Part I. Perfusion characteristics in the female pelvis by using multiple computer-aided diagnosis perfusion analysis solutions. Radiology. 2013;266:801–11.
50. Filipovic M, Vuissoz P-A, Codreanu A, Claudon M, Felmblinger J. Motion compensated generalized reconstruction for free-breathing dynamic contrast-enhanced MRI. Magn Reson Med. 2011;65:812–22.
51. Spence AM, Muzi M, Graham MM, O’Sullivan F, Krohn KA, Link JM, et al. Glucose metabolism in human malignant gliomas measured quantitatively with PET, 1-[C-11]glucose and FDG: analysis of the FDG lumped constant. J Nucl Med. 1998;39:440–8.
52. Doot RK, Dunnwald LK, Schubert EK, Muzi M, Peterson LM, Kinahan PE, et al. Dynamic and static approaches to quantifying 18F-FDG uptake for measuring cancer response to therapy, including the effect of granulocyte CSF. J Nucl Med. 2007;48:920–5.
53. Yuan X, Zhang J, Quan C, Cao J, Ao G, Tian Y, et al. Differentiation of malignant and benign pulmonary nodules with first-pass dual-input perfusion CT. Eur Radiol. 2013;23:2469–74.
54. Li XS, Fan HX, Fang H, Huang H, Song YL, Zhou CW. Value of Whole-Tumor Dual-Input Perfusion CT in Predicting the Effect of Multiarterial Infusion Chemotherapy on Advanced Non–Small Cell Lung Cancer. American Journal of Roentgenology. 2014;203:W497–505.
55. Nguyen-Kim TDL, Frauenfelder T, Strobel K, Veit-Haibach P, Huellner MW. Assessment of Bronchial and Pulmonary Blood Supply in Non-Small Cell Lung Cancer Subtypes Using Computed Tomography Perfusion: Investigative Radiology. 2015;50:179–86.
56. Ohno Y, Koyama H, Fujisawa Y, Yoshikawa T, Seki S, Sugihara N, et al. Dynamic contrast-enhanced perfusion area detector CT for non-small cell lung cancer patients: Influence of mathematical models on early prediction capabilities for treatment response and recurrence after chemoradiotherapy. European Journal of Radiology. 2016;85:176–86.
57. Lee SH, Rimner A, Deasy JO, Hunt MA, Tyagi N. Dual-input tracer kinetic modeling of dynamic contrast-enhanced MRI in thoracic malignancies. J Appl Clin Med Phys. 2019;20:169–88.
58. Milne EN. Circulation of primary and metastatic pulmonary neoplasms. A postmortem microarteriographic study. Am J Roentgenol Radium Ther Nucl Med. 1967;100:603–19.
59. Duan C, Kallehauge JF, Bretthorst GL, Tanderup K, Ackerman JJH, Garbow JR. Are complex DCE-MRI models supported by clinical data? Magn Reson Med. 2017;77:1329–39.
60. Leach MO, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A, et al. The assessment of antiangiogenic and antivasular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations. Br J Cancer. 2005;92:1599–610.
61. O’Connor JP, Jackson A, Asselin M-C, Buckley DL, Parker GJ, Jayson GC. Quantitative imaging biomarkers in the clinical development of targeted therapeutics: current and future perspectives. The Lancet Oncology. 2008;9:766–76.
62. Kelly RJ, Rajan A, Force J, Lopez-Chavez A, Keen C, Cao L, et al. Evaluation of KRAS Mutations, Angiogenic Biomarkers, and DCE-MRI in Patients with Advanced Non-Small-Cell Lung Cancer Receiving Sorafenib. Clinical Cancer Research. 2011;17:1190–9.
63. Cheng JC-H, Yuan A, Chen J-H, Lu Y-C, Cho K-H, Wu J-K, et al. Early Detection of Lewis Lung Carcinoma Tumor Control by Irradiation Using Diffusion-Weighted and Dynamic Contrast-Enhanced MRI. Lin C-P, editor. PLoS ONE. 2013;8:e62762.
64. Tao X, Wang L, Hui Z, Liu L, Ye F, Song Y, et al. DCE-MRI Perfusion and Permeability Parameters as predictors of tumor response to CCRT in Patients with locally advanced NSCLC. Sci Rep. 2016;6:35569.
Table 1. Patients characteristics.

| Patient | Age | Gender | NSCLC localization       | Histology                                | Voxels (2mm$^3$) |
|---------|-----|--------|--------------------------|------------------------------------------|------------------|
| 1       | 82  | M      | Right upper lobe         | Poorly differentiated NSCLC              | 540              |
| 2       | 47  | M      | Right upper lobe         | NSCLC                                    | 1271             |
| 3       | 71  | F      | Right lower lobe         | NSCLC (undifferentiated carcinoma)       | 799              |
| 4       | 67  | F      | Left upper lobe          | NSCLC (ADK)                              | 211              |
| 5       | 80  | F      | Left upper lobe          | NSCLC (SCC)                              | 1207             |
| 6       | 53  | M      | Right medium lobe        | NSCLC (ADK)                              | 88               |
| 7       | 78  | F      | Left upper lobe          | NSCLC (ADK)                              | 629              |
| 8       | 55  | M      | Right upper lobe         | NSCLC (ADK)                              | 318              |
| 9       | 63  | M      | Left upper lobe          | NSCLC (poorly differentiated SCC)        | 2409             |
| 10      | 57  | M      | Left upper lobe          | NSCLC (ADK)                              | 2338             |
| 11      | 62  | M      | Right upper lobe         | NSCLC (ADK)                              | 1151             |
| 12      | 61  | M      | Right upper lobe         | NSCLC (SCC)                              | 5340             |
| 13      | 71  | F      | Right upper lobe         | NSCLC (ADK)                              | 3845             |
| 14      | 71  | M      | Right upper lobe         | NSCLC (ADK)                              | 1409             |

**ADK:** adenocarcinoma

**SCC:** squamous cell carcinoma
| Tumors | PET parameters | DCE parameters |
|--------|----------------|----------------|
|        | $K_1$ (ml g⁻¹ min⁻¹) | $k_2$ (min⁻¹) | $k_3$ (min⁻¹) | MRGlu (µmol g⁻¹ min⁻¹) | $v_8$ | $K_{trans}$ (min⁻¹) | $v_e$ | $K_{app}$ (min⁻¹) | $v_e$ |
| 1      | 0.22 (0.18-0.26) | 0.71 (0.54-0.81) | 0.13 (0.1-0.14) | 0.15 (0.12-0.17) | 0.05 (0.03-0.07) | 0.30 (0.14-0.60) | 0.08 (0.42-1.0) | 0.60 (0.28-1.19) | 0.008 (0.0-0.05) |
| 2      | 0.26 (0.22-0.32) | 0.68 (0.45-1.03) | 0.15 (0.10-0.20) | 0.24 (0.19-0.26) | 0.05 (0.03-0.06) | 0.84 (0.67-1.17) | 1.0 (1-1.0) | 0.85 (0.68-1.18) | 0.40 (0.19-0.68) |
| 3      | 0.08 (0.06-0.11) | 0.31 (0.22-0.44) | 0.09 (0.05-0.14) | 0.09 (0.07-0.10) | 0.13 (0.09-0.18) | 0.17 (0.07-0.60) | 0.33 (0.09-1.0) | 0.56 (0.27-0.77) | 0.03 (0.0-0.12) |
| 4      | 0.15 (0.12-0.18) | 1.09 (0.85-1.40) | 0.033 (0.029-0.036) | 0.026 (0.022-0.032) | 0.084 (0.076-0.093) | 0.74 (0.25-1.36) | 0.63 (0.33-1.0) | 1.21 (0.57-2.66) | 0.15 (0.04-0.36) |
| 5      | 0.19 (0.15-0.24) | 0.57 (0.46-0.77) | 0.19 (0.15-0.24) | 0.35 (0.30-0.38) | 0.09 (0.08-0.10) | 0.07 (0.05-0.13) | 0.17 (0.13-0.21) | 0.47 (0.30-0.74) | 0.02 (0.009-0.024) |
| 6      | 0.38 (0.34-0.42) | 1.30 (1.14-1.47) | 0.089 (0.068-0.109) | 0.11 (0.09-0.14) | 0.066 (0.057-0.077) | 0.84 (0.36-1.75) | 1.0 (0.47-1.0) | 1.30 (0.66-2.25) | 0.05 (0.0-1.0) |
| 7      | 0.14 (0.12-0.16) | 0.41 (0.35-0.5) | 0.028 (0.022-0.034) | 0.053 (0.048-0.06) | 0.109 (0.084-0.13) | 0.06 (0.04-0.14) | 0.95 (0.32-1.0) | 0.12 (0.06-0.23) | 0.12 (0.06-0.23) |
| 8      | 0.11 (0.07-0.13) | 0.66 (0.44-0.72) | 0.08 (0.05-0.1) | 0.063 (0.045-0.084) | 0.18 (0.16-0.19) | 0.52 (0.15-1.06) | 0.19 (0.03-0.62) | 1.90 (1.20-3.78) | 1.0 (0.0-0.08) |
| 9      | 0.22 (0.17-0.26) | 0.55 (0.47-0.61) | 0.071 (0.059-0.088) | 0.14 (0.11-0.19) | 0.05 (0.03-0.07) | 0.32 (0.17-0.53) | 0.52 (0.29-0.77) | 0.63 (0.45-0.92) | 0.034 (0.0-0.09) |
| 10     | 0.26 (0.20-0.32) | 0.63 (0.45-0.83) | 0.08 (0.05-0.14) | 0.22 (0.14-0.34) | 0.11 (0.09-0.14) | 1.06 (0.64-1.47) | 1.0 (0.38-1.0) | 1.25 (0.91-2.67) | 0.25 (0.0003-0.81) |
| 11     | 0.15 (0.13-0.18) | 0.48 (0.34-0.65) | 0.11 (0.09-0.14) | 0.16 (0.13-0.19) | 0.09 (0.06-0.13) | 0.81 (0.34-1.28) | 0.74 (0.33-1.0) | 1.23 (0.90-1.65) | 0.08 (0.0001-0.27) |
| 12     | 0.29 (0.22-0.36) | 1.29 (0.80-1.96) | 0.32 (0.19-0.57) | 0.33 (0.22-0.43) | 0.05 (0.03-0.08) | 0.32 (0.12-0.77) | 0.29 (0.15-0.65) | 1.00 (0.54-1.69) | 0.04 (0.001-0.11) |
| 13     | 0.33 (0.23-0.44) | 0.77 (0.55-1.10) | 0.1 (0.06-0.14) | 0.21 (0.15-0.25) | 0.097 (0.077-0.14) | 1.02 (0.62-1.43) | 1.0 (0.85-1.0) | 1.17 (0.78-1.57) | 0.05 (0.0-0.22) |
| 14     | 0.31 (0.27-0.35) | 0.68 (0.57-0.77) | 0.07 (0.05-0.08) | 0.14 (0.11-0.17) | 0.052 (0.032-0.072) | 0.27 (0.14-0.57) | 0.53 (0.36-1.0) | 0.60 (0.35-0.80) | 0.008 (0.0-0.03) |
### Table 3. Curve fitting metrics for PET kinetic modeling

| PET | relative RMSE | Fraction of voxels in percent |  |  |  |
|-----|---------------|-------------------------------|---|---|---|
|     | relative RMSE ≤ 20% | 20% < relative RMSE ≤ 45% | 45% < Relative RMSE |
| 1   | 13.4 (10; 20.3) | 74% | 23% | 3% |
| 2   | 9.0 (6.9; 12.2) | 99.6% | 0.4% | 0% |
| 3   | 18.1 (12.9; 26.8) | 57% | 36% | 7% |
| 4   | 34.3 (29; 39) | 0% | 94.8% | 5.2% |
| 5   | 16.1 (14; 18.1) | 87.2% | 12.8% | 0% |
| 6   | 23.7 (19.6; 27.3) | 27% | 72% | 1% |
| 7   | 49.2 (44.1; 54) | 0% | 29% | 71% |
| 8   | 43.5 (39.7; 51.2) | 0% | 57.6% | 42.4% |
| 9   | 8.5 (7.4; 9.8) | 98.2% | 1.8% | 0% |
| 10  | 12.3 (9.8; 15.3) | 95.3% | 4.7% | 0% |
| 11  | 15.5 (11.5; 19.5) | 77.8% | 22.2% | 0% |
| 12  | 9.5 (7.6; 11.8) | 99.7% | 0.3% | 0% |
| 13  | 9.2 (7.7; 11.3) | 99.4% | 0.6% | 0% |
| 14  | 8.2 (7.4; 9.2) | 100% | 0% | 0% |
| All | 10.3 (8.1; 14.3) | 89.3% | 7.6% | 3.1% |

Relative RMSE data are expressed as median (IQR).
### Table 4. Curve fitting metrics for DCE kinetic modeling

| DCE | relative RMSE | Number of voxels in percent |   |   |
|-----|---------------|-----------------------------|---|---|
|     | relative RMSE ≤ 20% | 20% < relative RMSE ≤ 45% | 45% < Relative RMSE |
| 1   | 35 (26; 51.5) | 6.6% | 60% | 33.4% |
| 2   | 30.2 (25; 36) | 8.3% | 87.1% | 4.6% |
| 3   | 46.6 (32.4; 65.3) | 3.7% | 44% | 52.3% |
| 4   | 29.3 (22.1; 46.9) | 21.3% | 50% | 28.7% |
| 5   | 23.8 (20.5; 28.5) | 21.6% | 76% | 2.4% |
| 6   | 49.1 (39.5; 68.5) | 1.2% | 43% | 55.8% |
| 7   | 68.3 (63.4; 73.2) | 0% | 0% | 100% |
| 8   | 65.8 (54.9; 84.9) | 0% | 8.8% | 91.2% |
| 9   | 19.5 (14.2; 29.6) | 51.5% | 37% | 11.5% |
| 10  | 42.5 (35; 56) | 0.1% | 56% | 43.9% |
| 11  | 29.8 (23.1; 41.7) | 14.5% | 64.9% | 20.6% |
| 12  | 36.7 (28; 51.4) | 5% | 61.4% | 33.6% |
| 13  | 27 (19.7; 40.8) | 26.7% | 54.2% | 19.1% |
| 14  | 21.1 (15; 29.6) | 46.3% | 42.5% | 11.2% |
| All | 31.8 (22.4; 46.6) | 18.6% | 54.7% | 26.7% |

Relative RMSE data are expressed as median (IQR).
Supplementary material. Voxel-wise Spearman correlation coefficients ($r_s$) together with their respective bootstrap intervals ($n = 1000$ replications).

| ROI | Voxel 1 | Voxel 2 | Voxel 3 | Voxel 4 | Voxel 5 | Voxel 6 | Voxel 7 | Voxel 8 | Voxel 9 | Voxel 10 | Voxel 11 | Voxel 12 | Voxel 13 | Voxel 14 |
|-----|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| V1  | 0.12    | 0.02    | 0.04    | 0.06    | 0.08    | 0.10    | 0.12    | 0.14    | 0.16    | 0.18    | 0.20    | 0.22    | 0.24    | 0.26    |
| V2  | 0.03    | 0.01    | 0.02    | 0.03    | 0.04    | 0.05    | 0.06    | 0.07    | 0.08    | 0.09    | 0.10    | 0.11    | 0.12    | 0.13    |
| V3  | 0.04    | 0.02    | 0.03    | 0.04    | 0.05    | 0.06    | 0.07    | 0.08    | 0.09    | 0.10    | 0.11    | 0.12    | 0.13    | 0.14    |
| V4  | 0.05    | 0.03    | 0.04    | 0.05    | 0.06    | 0.07    | 0.08    | 0.09    | 0.10    | 0.11    | 0.12    | 0.13    | 0.14    | 0.15    |
| V5  | 0.06    | 0.04    | 0.05    | 0.06    | 0.07    | 0.08    | 0.09    | 0.10    | 0.11    | 0.12    | 0.13    | 0.14    | 0.15    | 0.16    |

Values in red correspond to statistically non-significant results.
**Figure 1. Study workflow.**

**ETM: extended Tofts model**
Figure 2. Curve fitting results for PET and DCE kinetic modeling. For each tumor (x-axis), voxel-wise relative root mean square errors (relative RMSE) are provided (y-axis). For each tumor, the vertical black lines are the standard deviations.
Figure 3. Illustration of the PET and DCE kinetic estimated parameter maps. Top: voxel-wise fitting results are provided for three voxels of interest. The PET signal is expressed in kBq/mL, and the DCE signal in mmol/L of Gd. For this latter, the blue curve corresponds to the measured $[\text{Gd}]_{\text{Plasma}}$, whereas the red one corresponds to the measured $[\text{Gd}]_{\text{Blood}}$ before plasma conversion. The voxel-wise rRMSE (PET in green, DCE in orange) are also provided at the tumor level. Bottom: the related PET and DCE 3D parametric maps after data fitting.
**Figure 4.** PET-PET and DCE-DCE correlation interlinks. For each tumor (1 to 14), all the PET-PET and DCE-DCE correlation pairs are provided.
**Figure 5.** PET-DCE correlation interlinks. For each tumor (1 to 14), all the PET-DCE correlation pairs are provided.
**Figure 6:** regional decoupling between perfusion/vascularization and metabolism. In all these tumors, whereas MRGlu appears relatively homogeneous, deep central hypoperfused/vascularized area of variable sizes are visible (low $K_{\text{trans}}$, $v_p$ or $v_b$), mirrored by high metabolic enzymatic activity ($k_3$). This pattern is highly suggestive of hypoxic tumor areas, a well-known hallmark of cancer aggressiveness.