



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Can dynamic imaging, using 18F-1 FDG PET/CT and CT perfusion differentiate between benign and malignant pulmonary nodules?

Citation for published version:

Marin, A, Murchison, JT, Skwarski, KM, Tavares, AAS, Patel, D, Fetcher, A, Walker, W, Wallace, W, Salapura, V, van Beek, EJR & Mirsarraee, S 2021, 'Can dynamic imaging, using 18F-1 FDG PET/CT and CT perfusion differentiate between benign and malignant pulmonary nodules?', *Radiology and Oncology*.
<https://doi.org/10.2478/raon-2021-0024>

Digital Object Identifier (DOI):

[10.2478/raon-2021-0024](https://doi.org/10.2478/raon-2021-0024)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Radiology and Oncology

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



1 **Can dynamic imaging, using 18F-FDG PET/CT and CT perfusion**
2 **differentiate between benign and malignant pulmonary nodules?**

3 Aleksander Marin ^{a,c}, John T Murchison ^b, Kristopher Skwarski ^b, Adriana A. S.
4 Tavares ^a, Dilip Patel ^c, Alison Fetcher ^a, William Walker ^d, William Wallace ^e,
5 Vladka Salapura ^f, Edwin J.R. van Beek ^a, Saeed Mirsardraee ^{a,g}

6 a Edinburgh Imaging facility Queens Medical Research Institute, University of
7 Edinburgh, Edinburgh, United Kingdom, b Departments of Respiratory
8 Medicine, c Radiology, d Thoracic Surgery, and e Pathology Royal Infirmary
9 of Edinburgh, Edinburgh, United Kingdom, f Faculty of Medicine, University of
10 Ljubljana, Ljubljana, Slovenia, g National Lung and Heart Institute, Imperial
11 College London, United Kingdom

12

13 **Introduction**

14 Pulmonary nodules are detected with increasing frequency due to widespread
15 use of computed tomography (CT).^{1,2} The prevalence of incidental pulmonary
16 nodules on standard CT studies is around 13%, while lung cancer screening
17 will detect lung nodules in up to 53% of subjects, leading to a lung cancer
18 prevalence of around 1.4% (0.5–2.7%).³ The optimal diagnostic approach for
19 the management of indeterminate pulmonary nodules has been the subject of
20 much discussion.⁴

21

22 The widely accepted guidelines published by the British Thoracic Society
23 (BTS) and the Fleischner Society recommend the minimum nodule diameter

24 thresholds and CT follow-up time intervals for surveillance of solitary nodules
25 smaller than 8 mm.^{3,5} For nodules of ≥ 8 mm (300 mm³), the BTS guidelines
26 recommend risk assessment using the Brock model. The above guidelines
27 recommend either 3-month CT follow-up, work-up with positron emission
28 tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (¹⁸F-FDG),
29 tissue sampling, or resection for nodules of ≥ 8 mm. CT characterisation using
30 only morphological features is imprecise,^{6,7} leading to an increased interest in
31 computer-based radiomics assessment.⁸⁻¹⁵ Serial CT imaging to monitor
32 nodule size can be problematic as nodule growth varies with different cancers
33 and causes patient anxiety.¹⁶⁻¹⁸ ¹⁸F-FDG PET has high sensitivity but lower
34 specificity of 82% for detecting malignant pulmonary nodules, particularly in
35 those smaller than 10 mm.¹⁹ Imaging guided sampling of small nodules is also
36 difficult, is associated with complications, and its diagnostic yield decreases
37 further as nodule size decreases.^{3,20,21}

38

39 Neovascularisation is a complex process known to be central to
40 carcinogenesis.²² Advances in the imaging technology in the last two decades
41 have enabled the study of perfusion characteristics within pulmonary
42 nodules.²³⁻²⁷ As benign and malignant lesions have different vascularity,
43 different perfusion parameters and dynamic ¹⁸F-FDG uptake properties can
44 be expected.²⁷⁻³²

45

46 The purpose of this pilot study was to evaluate the feasibility and accuracy of
47 CT perfusion and dynamic ¹⁸F-FDG PET imaging in differentiating proven
48 benign and malignant pulmonary nodules.

49 **Materials and methods**

50 This single-centre prospective study was approved by the local Research
51 Ethics Committee (13/SS/0153) and written informed consent was obtained
52 from all participants.

53

54 Between December 2014 and December 2015, 20 consecutive patients who
55 were referred to our respiratory outpatient clinic for an indeterminate
56 incidental pulmonary nodule were recruited. The inclusion criteria were: a)
57 incidentally detected soft tissue (solid) pulmonary nodules measuring ≥ 8 mm
58 and < 30 mm on CT, b) either surgical excision, imaging guided biopsy or
59 imaging follow up of the nodule planned. The exclusion criteria were: a)
60 abnormal renal function, b) previous adverse reaction to iodinated contrast
61 agent, c) known history of malignancy, d) pregnancy or breast feeding, e)
62 patients who refused or were unable to provide informed consent.

63

64 The patients underwent a dynamic ^{18}F -FDG PET/CT and dynamic perfusion
65 CT imaging within a 3 week time frame (mean, 6.4 days: range 1–18 days).
66 Due to technical reasons, the dynamic PET data could not be used in 4
67 patients for the analysis, one of these patients had two synchronous nodules.
68 CT perfusion analysis was performed in 17 of the nodules. One patient
69 declined the CT perfusion scan and 3 patients had significant breathing
70 artefact on the scans, rendering analysis non-feasible. All nodules were
71 classified into either benign or malignant on the basis of a histopathological
72 diagnosis (n=16), or stability during 2 years follow up CT imaging (n=5).

73

74 *Dynamic PET/CT image acquisition:*

75 All patients were fasted for at least six hours before the imaging. Following a
76 low dose CT scan for attenuation correction and localisation (120 kV, 50 mAs,
77 5/3 mm), patients were administered 400 MBq of ¹⁸F-FDG intravenously, and
78 a dynamic 60 minute image acquisition was performed using a Siemens
79 Biograph PET/CT scanner (Siemens Healthcare, Erlangen, Germany).
80 Respiratory-gated PET data were reconstructed using a 15-frame protocol (7
81 frames×180 s, 7×300 s, 1×240 s), a matrix size of 256×256×53 with a voxel
82 size of 2.65×2.65×3.00 mm³, and subsets expectation maximization (OSEM)
83 method. A conventional PET/CT scan was performed on completion of the
84 dynamic phase of the scan at 1 hour after injection of the tracer.

85

86 *Perfusion volume CT acquisition:*

87 Dynamic perfusion CT scans were performed as previously described^{25,28,33,34}
88 on a 320-detector row CT scanner (Aquilion ONE; Toshiba Medical Systems,
89 Tokyo, Japan) with 16 cm field of view coverage. Imaging was performed at 0,
90 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 40, 50, 60, 90, 120 seconds, 3
91 minutes, 4 minutes, and 10 minutes following the intravenous injection of 70
92 ml of iodinated contrast (Iomeron 400 mg/ml, Bracco, Milan, Italy) followed by
93 a 30 ml bolus of saline both at 9 ml/s through a 16 G cannula sited in the ante
94 cubital fossa. Acquisition parameters were 100 kV, 100 mA, 0.5 seconds
95 rotation time, 320 x 0.5 mm collimation, 512 x 512 matrix.

96

97 *Image Analysis:*

98 Dynamic PET/CT:

99 Reconstructed images were imported into PMOD 3.409 software (PMOD
100 Technologies, Zurich, Switzerland) and the input function was determined by
101 placing a spherical volume of interest (VOI) with diameter of 1 cm in the
102 ascending aorta. VOIs were drawn around the pulmonary nodules semi-
103 automatically with a threshold of 50% of the maximum voxel value within the
104 nodule, and then the VOIs were copied to the dynamic imaging sequence to
105 obtain the time activity curves (TACs) (Figure 1). The influx constant K_i (min^{-1}
106 or $(\text{ml plasma}) \cdot (\text{ml tissue})^{-1} \cdot \text{min}^{-1}$) was determined by Patlak analysis.³⁵ The
107 Patlak plot model is a graphical analysis technique based on a 2-tissue
108 compartment model with irreversibly trapped tracer. A mathematical
109 transformation of the tissue compartment and plasma TACs produces a
110 straight line plot which provides information about the blood volume (BV) of
111 the tissue compartment and the exchange rate (K_i) (Figure 2).

112

113 Conventional PET/CT scan:

114 The maximum standardised uptake value (SUV_{max}) was measured for each
115 nodule on conventional FDG PET/CT images. For the semi-quantitative
116 analysis, the mean standardised uptake values (SUV_{mean}) were measured of
117 the ascending aorta at the level of the arch, and within the right lobe of the
118 liver. SUV ratios (SUR) were calculated between the nodule SUV_{max} , and the
119 SUV_{mean} of the mediastinal blood pool ($\text{SUR}_{\text{BLOOD}}$) and liver
120 ($\text{SUR}_{\text{LIVER}}$). Criteria for malignancy were specified as $\text{SUV}_{\text{max}} \geq 2.5$; $\text{SUR}_{\text{BLOOD}}$
121 ≥ 1.56 ; $\text{SUR}_{\text{LIVER}} \geq 1.12$. Qualitative assessment PET features were specified
122 as following: 0 = no visible uptake; 1 = uptake less than mediastinal blood
123 pool; 2 = uptake comparable to mediastinal blood pool; 3 = uptake greater

124 than mediastinal blood pool; 4 = distant metastases. Qualitative specified
125 criteria for malignancy was PET grade ≥ 3 .^{36,37} Volumes of interest (VOIs)
126 were placed over the nodules, the ascending aorta at the level of the arch,
127 and within the right lobe of the liver for determination of the SUV_{mean} and
128 SUV_{max} values using OsiriX software (OsiriX, version 8.0.1 64 bit; OsiriX
129 Imaging Software, Geneva, Switzerland).

130

131 Perfusion CT:

132 Perfusion analysis was performed using Body Perfusion Application on a
133 Vitrea Workstation (Vitrea fX 6.0; Vital Images, Minnetonka, MN, USA).
134 Regions of interest (ROIs) were placed over the pulmonary nodules and
135 contralateral lung parenchyma (diameter range, 7–29 mm) on all perfusion CT
136 images. Arterial input was determined by placing 1 cm ROI over the main
137 pulmonary artery. Time-density graphs were then reviewed and adjustments
138 to start point and end point of the maximum slope were made if needed to
139 define the optimal slope range. Arterial flow perfusion maps overlaying CT
140 images were visually analysed and ROIs were placed over the nodules to
141 obtain the equivalent blood volume parameter calculated by Patlak plot model
142 (BV, expressed in ml per 100 ml) and Arterial Flow (AF, expressed in ml per
143 100g per minute) using single-input maximum slope model for calculation.

144

145 *Statistical Analysis:*

146 All results were expressed as mean \pm standard deviation (SD) unless
147 indicated. K_i and perfusion indices BV and AF of benign and malignant
148 nodules were statistically compared using the nonparametric Mann-Whitney U

149 test. The accuracy of the different techniques and parameters was tested with
150 area under the curve (AUC) in receiver operating characteristic (ROC)
151 analysis with 95% confidence interval (CI). Comparison between the ROCs
152 was performed using DeLong's test. Youdin index analysis was used to derive
153 the optimised cut-point values. Mann-Whitney U test and ROC curve analyses
154 were performed on GraphPad Prism version 8.2.1 for Windows (GraphPad
155 Software, San Diego, CA, USA). Youdin index analysis and nonparametric
156 DeLong's test were performed on MedCalc Statistical Software version 19.8
157 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2021). A
158 p value < 0.05 was considered statistically significant.

159 **Results**

160 The demographic data, average nodule size, SUV_{max} , metabolic parameter
161 relating to the pulmonary nodules through dynamic ^{18}F -FDG PET/CT, and
162 perfusion parameters through perfusion CT for the benign and malignant
163 nodules are summarised in Table 1 and Fig 3. We analysed 21 soft tissue
164 nodules in 20 patients (male/female=11/9; mean age \pm SD: 65.3 \pm 7.4; age
165 range: 50–76 years) with mean nodule diameter \pm SD of 20.1 \pm 7.5 mm (9–29
166 mm); mean nodule volume \pm SD: 2849 \pm 2338.7 mm³ (247–9348 mm³). 52% of
167 the nodules were located in the upper lung lobes (right upper lobe 7/21, left
168 upper lobe 4/21), 48% were in middle and lower lung lobes (right middle lobe
169 2/21, right lower lobe 6/21 and left lower lobe 2/21). Final diagnosis was
170 determined after surgical resection in 10 patients, core CT guided biopsy or
171 bronchoscopy in 6 patients, and over 2 years stability on follow up CT imaging
172 in 5 patients.

173 As shown in Table 1 and Fig 3, SUV_{max} derived from the conventional ^{18}F -
174 FDG PET/CT and K_i derived from dynamic ^{18}F -FDG PET/CT were
175 significantly higher in malignant nodules than in benign nodules. Also, the
176 Patlak model derived BV on perfusion CT was significantly higher in malignant
177 nodules. The difference in AF between the benign nodules and malignant
178 nodules was not statistically significant.

179 The benign outlier on ^{18}F -FDG PET/CT (SUV_{max} =6.3) and dynamic ^{18}F -FDG
180 PET/CT (K_i =0.0179 min⁻¹) was an 18 mm nodule of inflammation and fibrosis
181 (Fig 3 (a) and (b)). The perfusion CT indices BV and AF in this nodule were
182 relatively low, 3.8 ml/100ml and 51.5 ml/100g/min, respectively (Fig 3 (c) and

183 (d)). The two malignant outliers on conventional ^{18}F -FDG PET/CT and
184 dynamic ^{18}F -FDG PET/CT were 12 mm and 16 mm mucinous
185 adenocarcinomas *in situ* (12 mm nodule with $\text{SUV}_{\text{max}}=0.7$ and $K_i=0.0015 \text{ min}^{-1}$
186 (BV and AF analysis non-feasible due to respiratory motion artefact); 16 mm
187 nodule with $\text{SUV}_{\text{max}}=1.0$, $K_i=0.0033 \text{ min}^{-1}$, $\text{BV}=48.8 \text{ ml}/100\text{ml}$ and $\text{AF}=154.1$
188 $\text{ml}/100\text{g}/\text{min}$) (Fig 3 (a) and (b)). The mean CT densities of these two nodules
189 on unenhanced CT images were 16.3HU and 15.9HU, while the mean density
190 \pm SD of all benign and malignant nodules analysed was 24.55 ± 12.01 HU. The
191 benign outlier in AF on perfusion CT was a 10 mm perivascular epithelioid cell
192 tumour (PEComa), $\text{AF}=272.7 \text{ ml}/100\text{g}/\text{min}$ (Fig 3 (d)). The BV in this nodule
193 was $20.5 \text{ ml}/100\text{ml}$, the ^{18}F -FDG PET/CT indices were low, $\text{SUV}_{\text{max}}=0.7$ and
194 the $K_i=0.001 \text{ min}^{-1}$.

195 Table 2 and Figure 4(a) show diagnostic accuracy of conventional PET/CT
196 derived parameters with pre-specified and derived cut-point values though
197 ROC analysis.^{36,37} $\text{SUR}_{\text{BLOOD}}$ parameter had overall highest accuracy,
198 however, pairwise comparison of AUCs showed no significant difference ($p =$
199 0.5308 vs SUV_{max} ; $p = 1.0000$ vs $\text{SUR}_{\text{LIVER}}$; $p = 0.1083$ vs PET grade). ROC
200 analysis and diagnostic accuracy for the diagnosis of malignancy by dynamic
201 ^{18}F -FDG PET/CT parameter K_i , and perfusion CT indices BV and AF
202 compared to $\text{SUR}_{\text{BLOOD}}$ are further detailed in Table 2 and Figure 4(b).
203 Pairwise comparison of AUCs of $\text{SUR}_{\text{BLOOD}}$, K_i , BV and AF showed no
204 significant difference in their diagnostic performances ($p > 0.1$ for all
205 comparisons).

206

207 **Discussion**

208 Our results demonstrate that the metabolic parameter K_i of dynamic ^{18}F -FDG
209 PET/CT and the BV parameter of perfusion CT are significantly lower in
210 benign nodules.

211 Our study showed that the diagnostic accuracy of the conventional ^{18}F -FDG
212 PET/CT was best when semi-quantitative assessment and measuring the
213 uptake ratio of the lung nodule to the mediastinal blood pool with cut-point
214 criteria for malignancy $\text{SUR}_{\text{BLOOD}} \geq 1.56$ was used. This has been confirmed in
215 a larger multicenter trial by Evangelista *et al.*³⁶ Different to the SPUTNIK trial
216 which has shown SUV_{max} to be the most accurate and reproducible technique
217 with a caveat of introducing additional cut-point values altered according to
218 the nodule size, we did not see significant improvement in diagnostic
219 accuracy when replicating the multiple cut-points in our group of nodules (see
220 * in Table 2).³⁷

221 The accuracies of the new metabolic parameter K_i and perfusion parameter
222 BV were not significantly different to the conventional ^{18}F -FDG PET/CT. The
223 derived K_i cut-point for malignancy was $\geq 0.01 \text{ min}^{-1}$ resulting in
224 sensitivity/specificity/accuracy of 77.8%/85.7%/81.3%, respectively. This is in
225 good agreement with K_i cut-point $\geq 0.014 \text{ min}^{-1}$ reported in the study by Huang
226 *et al.* (n=35).²⁶ The derived BV cut-point value of $\geq 21 \text{ ml}/100\text{ml}$ for malignancy
227 showed comparable diagnostic accuracy to conventional and dynamic ^{18}F -
228 FDG PET/CT parameters. The high specificity of BV demonstrated in our
229 nodules would need to be confirmed in larger studies.

230 The benign outlier on dynamic ^{18}F -FDG PET/CT with a high K_i parameter
231 histopathologically represented inflammation (Fig 3 (b)). Higher metabolic
232 activity is not only a feature of malignant cells, it can be observed in
233 inflammatory nodules due to increased glucose metabolism in granulocytes
234 and macrophages in a range of diseases, including fungal and necrobiotic
235 rheumatoid nodules, sarcoidosis, tuberculosis, and other granulomas.^{38,39}
236 Dual time PET/CT did not prove to be useful for differentiating benign and
237 malignant pulmonary nodules with an SUV_{max} less than 2.5 in regions with
238 high prevalence of granulomatous disease.^{40,41} Huang *et al.* showed that
239 dynamic ^{18}F -FDG PET/CT is valuable in differentiating benign from malignant
240 pulmonary nodules with the potential to differentiate malignant from
241 granulomatous disease.²⁶ Our study showed limited diagnostic accuracy of
242 the dynamic ^{18}F -FDG PET/CT in assessing inflammatory nodules.

243 The malignant outliers on dynamic ^{18}F -FDG PET/CT with low K_i parameters
244 were histopathologically mucinous adenocarcinoma *in situ*. Other malignant
245 nodules in which low metabolic activity can be measured on ^{18}F -FDG PET/CT
246 are minimally invasive adenocarcinoma, carcinoid, and lung lymphoma.^{38,42}
247 Another important finding was that both malignant nodules with low metabolic
248 activity were of lower CT density analysed on the initial perfusion CT images
249 but also appreciable on low-dose CT scan of PET/CT examination. Further
250 studies on low density lung nodules are needed for evaluation of using lower
251 cut-point values for malignancy in conventional and dynamic PET/CT.
252 Malignant lung nodules with low CT density and measuring less than 1 cm are
253 known to have low metabolic activity on conventional ^{18}F -FDG PET/CT.^{43,44}
254 Berger *et al.* have reported up to 41% of lung lesions to be false-negative on

255 conventional ^{18}F -FDG PET/CT in analysis of 25 mucinous, hypocellular lung
256 lesions (3/9 false negative lesions were ≤ 2 cm, range, 1–5 cm).⁴⁵ Our study
257 showed a limited diagnostic accuracy of the dynamic ^{18}F -FDG PET/CT in
258 assessing low density malignant pulmonary nodules with K_i cut-point set at
259 0.01 min^{-1} .

260 Dynamic enhancement CT studies help identify false positive results in both
261 inflammatory and infective conditions, and sometimes in benign vascular
262 tumours.^{46,47} The perfusion CT parameters for the inflammatory nodule in our
263 study were low and indicative of a benign lesion despite high metabolic
264 activity on ^{18}F -FDG PET/CT. We have shown that the parameters of perfusion
265 CT of both malignant nodules with low metabolic activity were higher than the
266 BV and AF in benign nodules. Therefore, our findings indicate parameters of
267 perfusion CT may aid in the identification of benign nodules with high glucose
268 metabolic activity and in the identification of malignant nodules with low
269 glucose metabolic activity. Ohno *et al.* have shown that perfusion CT is more
270 specific and accurate than conventional ^{18}F -FDG PET/CT.^{24,29} Our study on a
271 small sample of cases suggests that perfusion CT also performs better than
272 dynamic ^{18}F -FDG PET/CT.

273 The AF parameter of the perfusion CT obtained by the maximum slope
274 method was not significantly different between benign and malignant nodules.
275 Benign nodules had a lower AF parameter value than malignant nodules
276 overall with one significant benign outlier with markedly high AF.
277 Histopathologically, this represented an extremely rare 'light cell' or 'sugar
278 type' PEComa. There are only about 50 cases of this neoplasm described in

279 the literature.^{48,49} PEComas are more commonly found as angiomyolipomas
280 in the kidneys, or as lesions in the retroperitoneal space, gastrointestinal tract,
281 or uterus. Only 7 cases of malignant pulmonary PEComa have been reported
282 ⁵⁰. A case report of a benign pulmonary PEComa showing early wash-in
283 enhancement with an early washout pattern of a malignant lesion on perfusion
284 CT has been reported by Kim *et al.*⁵¹ Despite a markedly high AF, the
285 PEComa had a BV just under the cut-point value for malignancy and a low
286 metabolic parameter K_i of dynamic ¹⁸F-FDG PET/CT. The BV parameter in
287 combination with low K_i parameter proved to be more reliable for defining this
288 extremely rare histological type of a pulmonary nodule.

289 Our study has limitations. This pilot study was performed in a small sample of
290 patients and appropriately powered studies will be required for further
291 validation. The mean nodule size was 18 mm for benign and 22 mm for
292 malignant nodules, which would not normally be referred for imaging follow-
293 up. The BTS and Fleischner Society recommended lower thresholds for
294 nodule follow up (5mm and 6mm, respectively). More novel reconstruction
295 methods in PET/CT such as specific point spread function (PSF) are enabling
296 better spatial resolution and enable its use in 6 mm pulmonary nodules.⁵²

297 Perfusion CT is quite demanding on patients with a prolonged breath-hold,
298 which limits the availability of reliable data in some patients. All 3 nodules in
299 which analysis was non-feasible due to the significant breathing artefact were
300 near the diaphragm (2 in the right lower lobe and 1 in the right middle lobe).
301 Segmentation of the pulmonary nodules on image analysis is restricted when
302 the images were affected by respiratory motion artefact, especially in small

303 nodules which were also abutting the chest wall or mediastinal structures.
304 Some authors recommend quiet breathing during the perfusion CT scans but
305 this is only acceptable in larger lung masses.⁵³ There is a need for further
306 optimisation of nodule segmentation and advanced image registration
307 techniques that allow accurate assessment of pulmonary nodules without
308 need for long breath-hold.^{23,54} The effective radiation dose for dynamic ¹⁸F-
309 FDG PET/CT was around 8 mSv and for perfusion CT around 20 mSv. The
310 radiation dose for perfusion CT can be improved by reducing the field of view
311 from 16 cm to the nodule only and reducing tube voltage in smaller size
312 patients.⁵⁵

313 Potential increase in the demand for these not widely available novel dynamic
314 imaging studies would consequently put additional strain on the imaging
315 departments with increased demand for scanner time, funding and training of
316 the staff. Limited capacity for a wider use of the dynamic imaging in lung
317 nodules could be overcome by developing systems of identification of nodules
318 with highest diagnostic benefit from dynamic imaging. A multicentre
319 prospective cohort observational study initiated in 2016 is set to assess the
320 performance and the cost-effectiveness of the dynamic CT and PET/CT in the
321 characterisation of solitary pulmonary nodules.⁵⁶

322 The small sample size limits the assessments of accuracy in our study.
323 However, on this small sample we showed increase diagnostic improvement
324 in the accuracy of diagnosis in both dynamic studies when compared to the
325 conventional ¹⁸F-FDG PET/CT. Specificity in K_i and BV on our small sample

326 size were higher at the estimated threshold values of 0.01 min^{-1} and 21
327 ml/100ml, respectively. This would need to be confirmed in larger studies.

328 Early identification of a lung nodule as benign or malignant by analysing its
329 metabolic and perfusion parameters could reduce the need for CT to monitor
330 lung nodule size, thereby reducing the number of CT scans required. It could
331 also reduce the need for CT guided biopsy or other invasive procedures.
332 Patients with malignant lung nodules could thus be identified more quickly and
333 referred for radical treatment. With our study, we have demonstrated the
334 potential of perfusion CT. The BV parameter assessed by perfusion CT was
335 not only significantly lower in benign nodules, it also aided in correctly
336 characterising the metabolically active inflammation, hypervascular benign
337 PEComa and low density malignancy.

338 In conclusion, this study demonstrated the feasibility of dynamic ^{18}F -FDG
339 PET/CT and CT perfusion studies in differentiating benign and malignant
340 pulmonary nodules. The dynamic ^{18}F -FDG PET/CT and perfusion CT derived
341 blood volume can assist to differentiate benign and malignant lung nodules
342 and in indeterminate cases, a combined approach can be helpful.

343 **References**

- 344 1. Furtado CD, Aguirre DA, Sirlin CB, Dang D, Stamato SK, Lee P, et al. Whole-
345 body CT screening: Spectrum of findings and recommendations in 1192
346 patients. *Radiology*. 2005;237(2):385–94.
- 347 2. Brenner DJ, Hall EJ. Computed Tomography — An Increasing Source of
348 Radiation Exposure. *N Engl J Med*. 2007 Nov 29;357(22):2277–84.
- 349 3. Callister MEJ, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al.
350 British thoracic society guidelines for the investigation and management of
351 pulmonary nodules. *Thorax*. 2015;70:ii1–54.
- 352 4. Shinohara S, Hanagiri T, Takenaka M, Chikaishi Y, Oka S, Shimokawa H, et
353 al. Evaluation of undiagnosed solitary lung nodules according to the probability
354 of malignancy in the American College of Chest Physicians (ACCP) evidence-
355 based clinical practice guidelines. *Radiol Oncol*. 2014;48(1):50–5.
- 356 5. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al.
357 Guidelines for management of incidental pulmonary nodules detected on CT
358 images: From the Fleischner Society 2017. *Radiology*. 2017;284(1):228–43.
- 359 6. Li F, Sone S, Abe H, MacMahon H, Armato SG, Doi K. Lung cancers missed
360 at low-dose helical CT screening in a general population: Comparison of
361 clinical, histopathologic, and imaging findings. *Radiology*. 2002;225(3):673–83.
- 362 7. Joo HO, Je RY, Sung HK, Hyung SS, Soo KC. Clinical significance of small
363 pulmonary nodules with little or no 18F-FDG uptake on PET/CT images of
364 patients with nonthoracic malignancies. *J Nucl Med*. 2007;48(1):15–21.
- 365 8. Chen S, Harmon S, Perk T, Li X, Chen M, Li Y, et al. Diagnostic classification
366 of solitary pulmonary nodules using dual time 18F-FDG PET/CT image texture

- 367 features in granuloma-endemic regions. *Sci Rep.* 2017;7(1).
- 368 9. Wilson R, Devaraj A. Radiomics of pulmonary nodules and lung cancer. Vol. 6,
369 *Translational Lung Cancer Research.* 2017. p. 86–91.
- 370 10. Hawkins S, Wang H, Liu Y, Garcia A, Stringfield O, Krewer H, et al. Predicting
371 Malignant Nodules from Screening CT Scans. *J Thorac Oncol.*
372 2016;11(12):2120–8.
- 373 11. Xu Y, Lu L, Lin-Ning E, Lian W, Yang H, Schwartz LH, et al. Application of
374 radiomics in predicting the malignancy of pulmonary nodules in different sizes.
375 *Am J Roentgenol.* 2019;213(6):1213–20.
- 376 12. Ather S, Kadir T, Gleeson F. Artificial intelligence and radiomics in pulmonary
377 nodule management: current status and future applications. Vol. 75, *Clinical*
378 *Radiology.* 2020. p. 13–9.
- 379 13. Khawaja A, Bartholmai BJ, Rajagopalan S, Karwoski RA, Varghese C,
380 Maldonado F, et al. Do we need to see to believe?—radiomics for lung nodule
381 classification and lung cancer risk stratification. Vol. 12, *Journal of Thoracic*
382 *Disease.* 2020. p. 3303–16.
- 383 14. Feng B, Chen X, Chen Y, Liu K, Li K, Liu X, et al. Radiomics nomogram for
384 preoperative differentiation of lung tuberculoma from adenocarcinoma in
385 solitary pulmonary solid nodule. *Eur J Radiol.* 2020;128.
- 386 15. Palumbo B, Bianconi F, Palumbo I, Fravolini ML, Minestrini M, Nuvoli S, et al.
387 Value of Shape and Texture Features from 18F-FDG PET/CT to Discriminate
388 between Benign and Malignant Solitary Pulmonary Nodules: An Experimental
389 Evaluation. *Diagnostics.* 2020;10(9).
- 390 16. Henschke CI, Yankelevitz DF, Yip R, Reeves AP, Farooqi A, Xu D, et al. Lung

- 391 cancers diagnosed at annual CT screening: Volume doubling times.
392 Radiology. 2012;263(2):578–83.
- 393 17. Koroscil MT, Bowman MH, Morris MJ, Skabelund AJ, Hersh AM. Effect of a
394 pulmonary nodule fact sheet on patient anxiety and knowledge: A quality
395 improvement initiative. *BMJ Open Qual.* 2018;7(3).
- 396 18. Slatore CG, Wiener RS, Golden SE, Au DH, Ganzini L. Longitudinal
397 assessment of distress among veterans with incidental pulmonary nodules.
398 *Ann Am Thorac Soc.* 2016;13(11):1983–91.
- 399 19. Cronin P, Dwamena BA, Kelly AM, Carlos RC. Solitary pulmonary nodules:
400 Meta-analytic comparison of cross-sectional imaging modalities for diagnosis
401 of malignancy. *Radiology.* 2008 Mar;246(3):772–82.
- 402 20. Wu CC, Maher MM, Shepard JAO. Complications of CT-guided percutaneous
403 needle biopsy of the chest: Prevention and management. Vol. 196, *American*
404 *Journal of Roentgenology.* 2011.
- 405 21. Huang M De, Weng HH, Hsu SL, Hsu LS, Lin WM, Chen CW, et al. Accuracy
406 and complications of CT-guided pulmonary core biopsy in small nodules: A
407 single-center experience. *Cancer Imaging.* 2019;19(1).
- 408 22. Folkman J. How is blood vessel growth regulated in normal and neoplastic
409 tissue?—G. H. A. clowes memorial award lecture. *Cancer Res.*
410 1986;46(2):467–73.
- 411 23. Cavalcanti PG, Shirani S, Scharcanski J, Fong C, Meng J, Castelli J, et al.
412 Lung nodule segmentation in chest computed tomography using a novel
413 background estimation method. *Quant Imaging Med Surg.* 2016;6(1):16–24.
- 414 24. Ohno Y, Nishio M, Koyama H, Seki S, Tsubakimoto M, Fujisawa Y, et al.

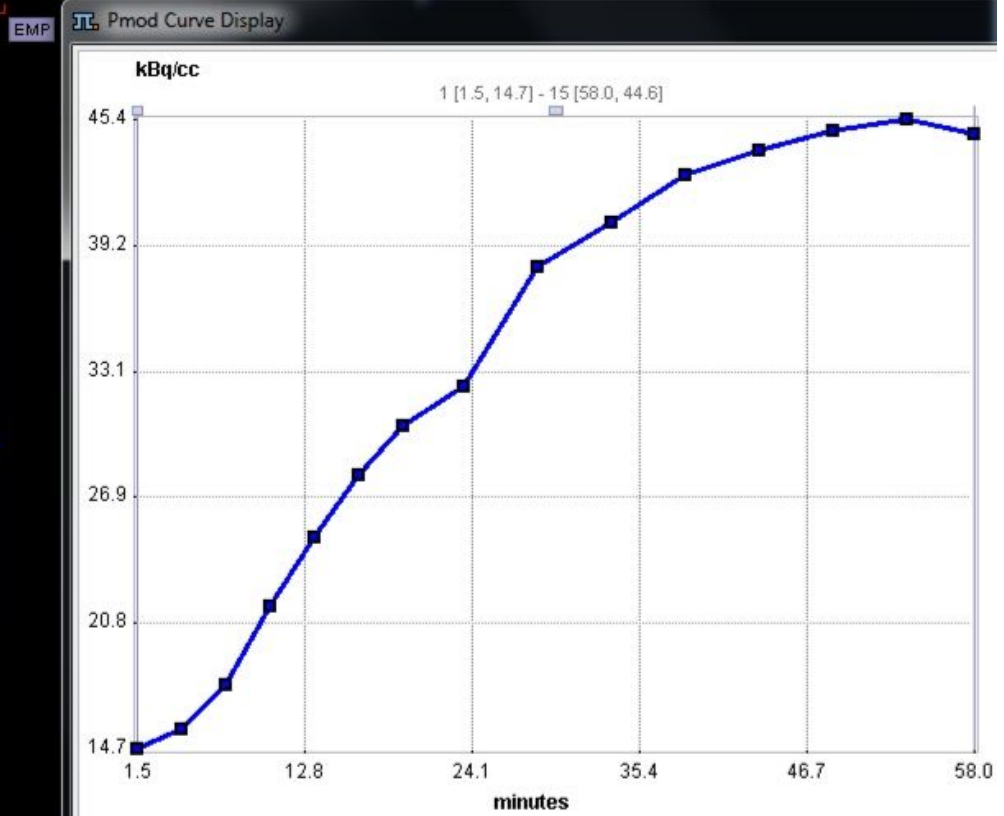
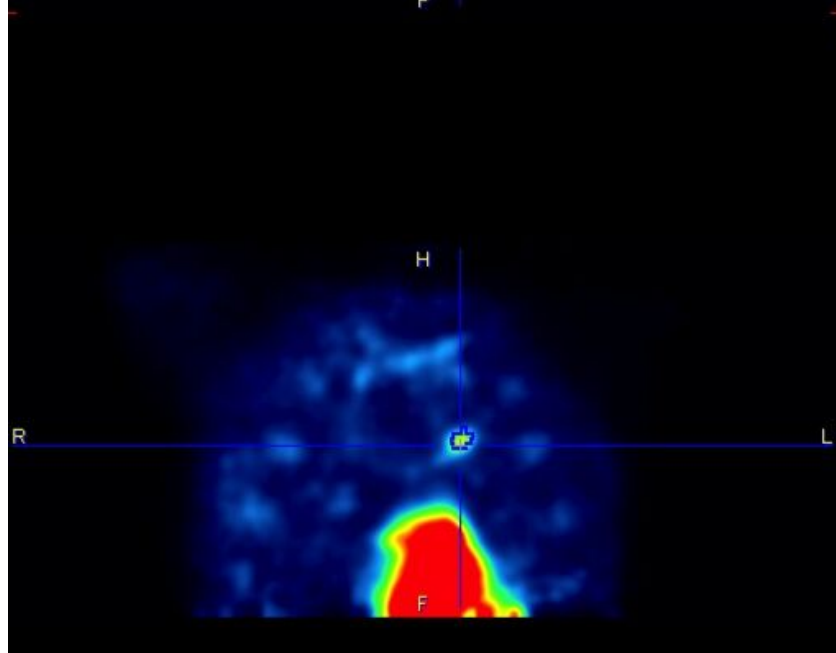
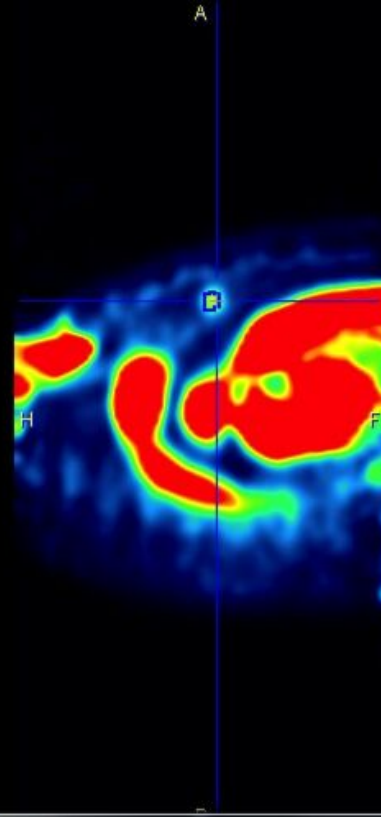
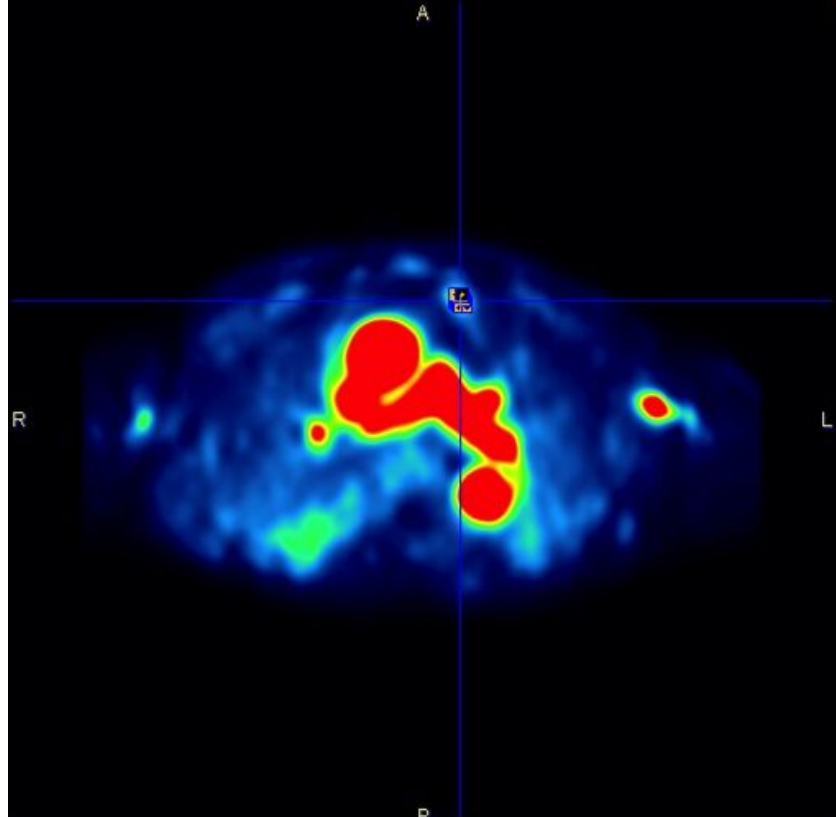
- 415 Solitary pulmonary nodules: Comparison of dynamic first-pass contrast-
416 enhanced perfusion area-detector CT, dynamic first-pass contrast-enhanced
417 MR imaging, and FDG PET/CT. *Radiology*. 2015;274(2):563–75.
- 418 25. Ohno Y, Nishio M, Koyama H, Miura S, Yoshikawa T, Matsumoto S, et al.
419 Dynamic contrast-enhanced CT and MRI for pulmonary nodule assessment.
420 *Am J Roentgenol*. 2014;202(3):515–29.
- 421 26. Huang YE, Lu HI, Liu FY, Huang YJ, Lin MC, Chen CF, et al. Solitary
422 pulmonary nodules differentiated by Dynamic F-18 FDG PET in a region with
423 high prevalence of granulomatous disease. *J Radiat Res*. 2012
424 Jan;53(2):306–12.
- 425 27. Yuan X, Zhang J, Quan C, Cao J, Ao G, Tian Y, et al. Differentiation of
426 malignant and benign pulmonary nodules with first-pass dual-input perfusion
427 CT. *Eur Radiol*. 2013;23(9):2469–74.
- 428 28. Ohno Y, Koyama H, Fujisawa Y, Yoshikawa T, Seki S, Sugihara N, et al.
429 Dynamic contrast-enhanced perfusion area detector CT for non-small cell lung
430 cancer patients: Influence of mathematical models on early prediction
431 capabilities for treatment response and recurrence after chemoradiotherapy.
432 *Eur J Radiol*. 2016 Jan;85(1):176–86.
- 433 29. Ohno Y, Nishio M, Koyama H, Fujisawa Y, Yoshikawa T, Matsumoto S, et al.
434 Comparison of quantitatively analyzed dynamic area-detector CT using
435 various mathematic methods with FDG PET/CT in management of solitary
436 pulmonary nodules. *Am J Roentgenol*. 2013;200(6).
- 437 30. Karakatsanis NA, Lodge MA, Tahari AK, Zhou Y, Wahl RL, Rahmim A.
438 Dynamic whole-body PET parametric imaging: I. Concept, acquisition protocol
439 optimization and clinical application. *Phys Med Biol*. 2013 Oct 21;58(20):7391–

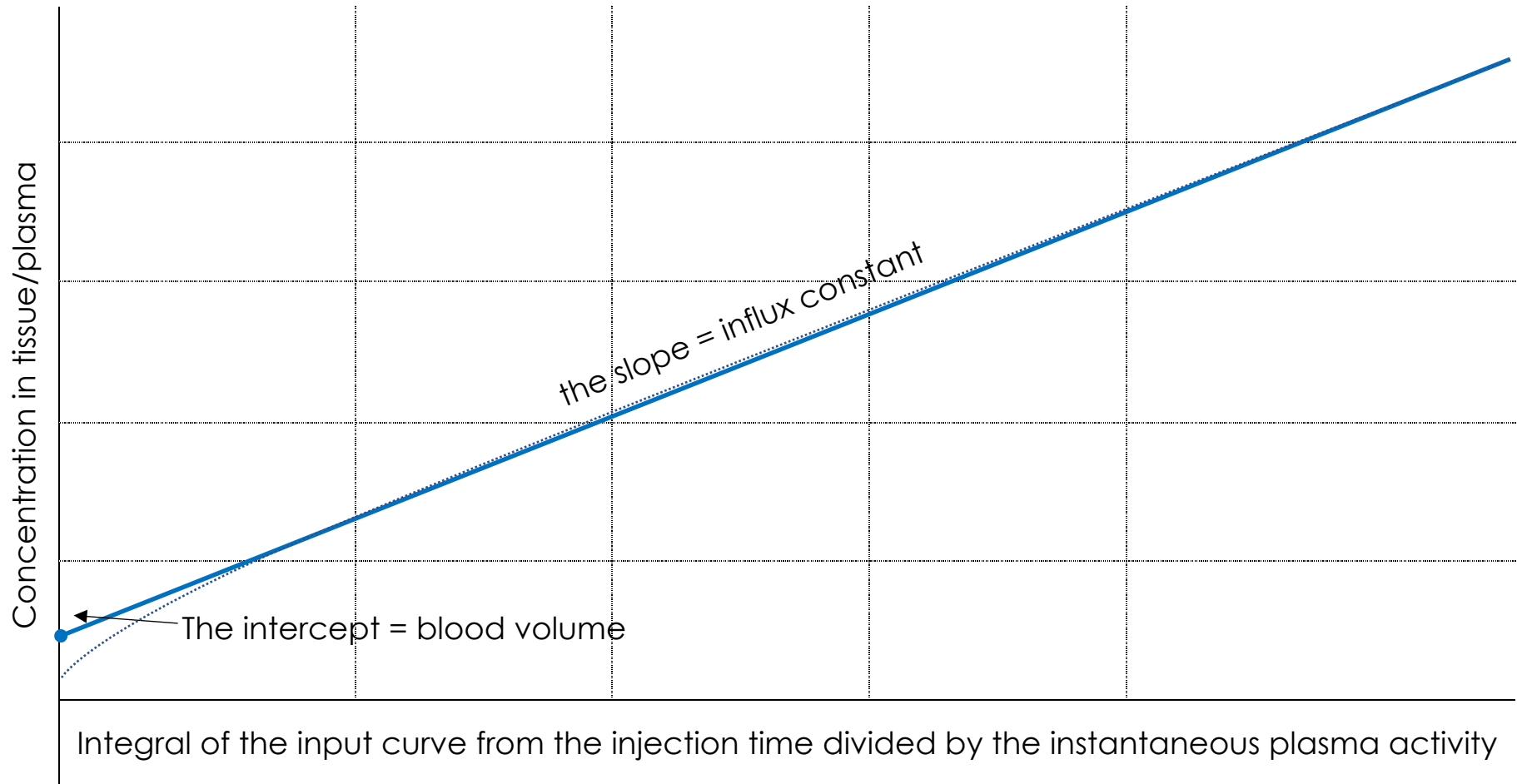
- 440 418.
- 441 31. Dimitrakopoulou-Strauss A, Pan L, Strauss LG. Quantitative approaches of
442 dynamic FDG-PET and PET/CT studies (dPET/CT) for the evaluation of
443 oncological patients. *Cancer Imaging*. 2012 Jan;12:283–9.
- 444 32. Yi CA, Kyung SL, Kim BT, Joon YC, Kwon OJ, Kim H, et al. Tissue
445 characterization of solitary pulmonary nodule: Comparative study between
446 helical dynamic CT and integrated PET/CT. *J Nucl Med*. 2006;47(3):443–50.
- 447 33. Ohno Y, Koyama H, Matsumoto K, Onishi Y, Takenaka D, Fujisawa Y, et al.
448 Differentiation of malignant and benign pulmonary nodules with quantitative
449 first-pass 320-detector row perfusion CT versus FDG PET/CT. *Radiology*.
450 2011 Feb 1;258(2):599–609.
- 451 34. Mirsadraee S, Reid JH, Connell M, MacNee W, Hirani N, Murchison JT, et al.
452 Dynamic (4D) CT perfusion offers simultaneous functional and anatomical
453 insights into pulmonary embolism resolution. *Eur J Radiol*. 2016;85(10):1883–
454 90.
- 455 35. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-
456 brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow
457 Metab*. 1983;3(1):1–7.
- 458 36. Evangelista L, Cuocolo A, Pace L, Mansi L, Del Vecchio S, Miletto P, et al.
459 Performance of FDG-PET/CT in solitary pulmonary nodule based on pre-test
460 likelihood of malignancy: results from the ITALIAN retrospective multicenter
461 trial. *Eur J Nucl Med Mol Imaging*. 2018;45(11):1898–907.
- 462 37. Weir-McCall JR, Harris S, Miles KA, Qureshi NR, Rintoul RC, Dizdarevic S, et
463 al. Impact of solitary pulmonary nodule size on qualitative and quantitative
464 assessment using 18F-fluorodeoxyglucose PET/CT: the SPUTNIK trial. *Eur J*

- 465 Nucl Med Mol Imaging. 2020;
- 466 38. Sim YT, Poon FW. Imaging of solitary pulmonary nodule-a clinical review.
467 Quant Imaging Med Surg. 2013;3(6):316–26.
- 468 39. Ambrosini V, Nicolini S, Caroli P, Nanni C, Massaro A, Marzola MC, et al.
469 PET/CT imaging in different types of lung cancer: An overview. Vol. 81,
470 European Journal of Radiology. 2012. p. 988–1001.
- 471 40. Chen CJ, Lee BF, Yao WJ, Cheng L, Wu PS, Ching LC, et al. Dual-phase
472 18F-FDG PET in the diagnosis of pulmonary nodules with an initial standard
473 uptake value less than 2.5. Am J Roentgenol. 2008 Aug 23;191(2):475–9.
- 474 41. Cloran FJ, Banks KP, Song WS, Kim Y, Bradley YC. Limitations of dual time
475 point PET in the assessment of lung nodules with low FDG avidity. Lung
476 Cancer. 2010 Apr 1;68(1):66–71.
- 477 42. Chiu CH, Yeh YC, Lin KH, Wu YC, Lee YC, Chou TY, et al. Histological
478 subtypes of lung adenocarcinoma have differential 18F-fluorodeoxyglucose
479 uptakes on the positron emission tomography/computed tomography scan. J
480 Thorac Oncol. 2011;6(10):1697–703.
- 481 43. Veronesi G, Bellomi M, Veronesi U, Paganelli G, Maisonneuve P, Scanagatta
482 P, et al. Role of Positron Emission Tomography Scanning in the Management
483 of Lung Nodules Detected at Baseline Computed Tomography Screening. Ann
484 Thorac Surg. 2007;84(3):959–66.
- 485 44. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K. Evaluation
486 of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less
487 than 3 cm in diameter, with special reference to the CT images. Lung Cancer.
488 2004;45(1):19–27.

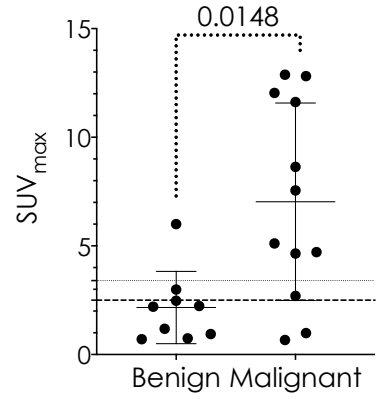
- 489 45. Berger KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET evaluation of
490 mucinous neoplasms: Correlation of FDG uptake with histopathologic features.
491 Am J Roentgenol. 2000;174(4):1005–8.
- 492 46. Yi CA, Lee KS, Kim EA, Han J, Kim H, Kwon OJ, et al. Solitary pulmonary
493 nodules: Dynamic enhanced multi-detector row CT study and comparison with
494 vascular endothelial growth factor and microvessel density. Radiology. 2004
495 Oct;233(1):191–9.
- 496 47. Zhang M, Kono M. Solitary pulmonary nodules: Evaluation of blood flow
497 patterns with dynamic CT. Radiology. 1997 Nov;205(2):471–8.
- 498 48. Hornick JL, Fletcher CDM. PEComa: What do we know so far? Vol. 48,
499 Histopathology. 2006. p. 75–82.
- 500 49. Stallmann S, Fisseler-Eckhoff A. Mesenchymale Tumoren der Lunge.
501 Pneumologie. 2014;12(1):34–43.
- 502 50. Chakrabarti A, Bandyopadhyay M, Purkayastha B. Malignant perivascular
503 epitheloid cell tumour (PEComa) of the lung-A rare entity. Innov Surg Sci.
504 2020;2(1):39–42.
- 505 51. Kim WJ, Kim SR, Choe YH, Lee KY, Park SJ, Lee HB, et al. Clear cell
506 “sugar” tumor of the lung: A well-enhanced mass with an early washout pattern
507 on dynamic contrast-enhanced computed tomography. J Korean Med Sci.
508 2008;23(6):1121–4.
- 509 52. Suljic A, Tomse P, Jensterle L, Skrk D. The impact of reconstruction
510 algorithms and time of flight information on PET/CT image quality. Radiol
511 Oncol. 2015;49(3):227–33.
- 512 53. Bhalla A, Das A, Naranje P, Irodi A, Raj V, Goyal A. Imaging protocols for CT

- 513 chest: A recommendation. *Indian J Radiol Imaging*. 2019;29(3):236.
- 514 54. Dolde K, Naumann P, Dávid C, Kachelriess M, Lomax AJ, Weber DC, et al.
515 Comparing the effectiveness and efficiency of various gating approaches for
516 PBS proton therapy of pancreatic cancer using 4D-MRI datasets. *Phys Med
517 Biol*. 2019;64(8).
- 518 55. McCollough CH, Primak AN, Braun N, Kofler J, Yu L, Christner J. Strategies
519 for Reducing Radiation Dose in CT. Vol. 47, *Radiologic Clinics of North
520 America*. 2009. p. 27–40.
- 521 56. Qureshi NR, Rintoul RC, Miles KA, George S, Harris S, Madden J, et al.
522 Accuracy and cost-effectiveness of dynamic contrast-enhanced CT in the
523 characterisation of solitary pulmonary nodules — The SPUtNIk study. *BMJ
524 Open Respir Res*. 2016;3(1).
- 525



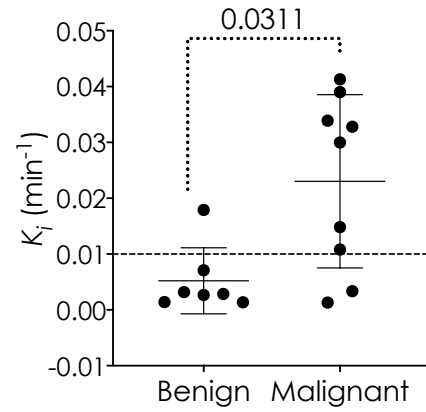


^{18}F -FDG PET/CT
 SUV_{max}



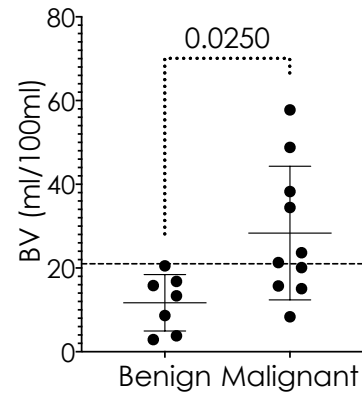
(a)

Dynamic ^{18}F -FDG PET/CT
 K_i



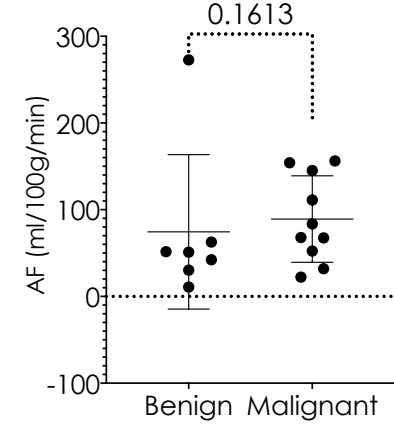
(b)

Perfusion CT
BV

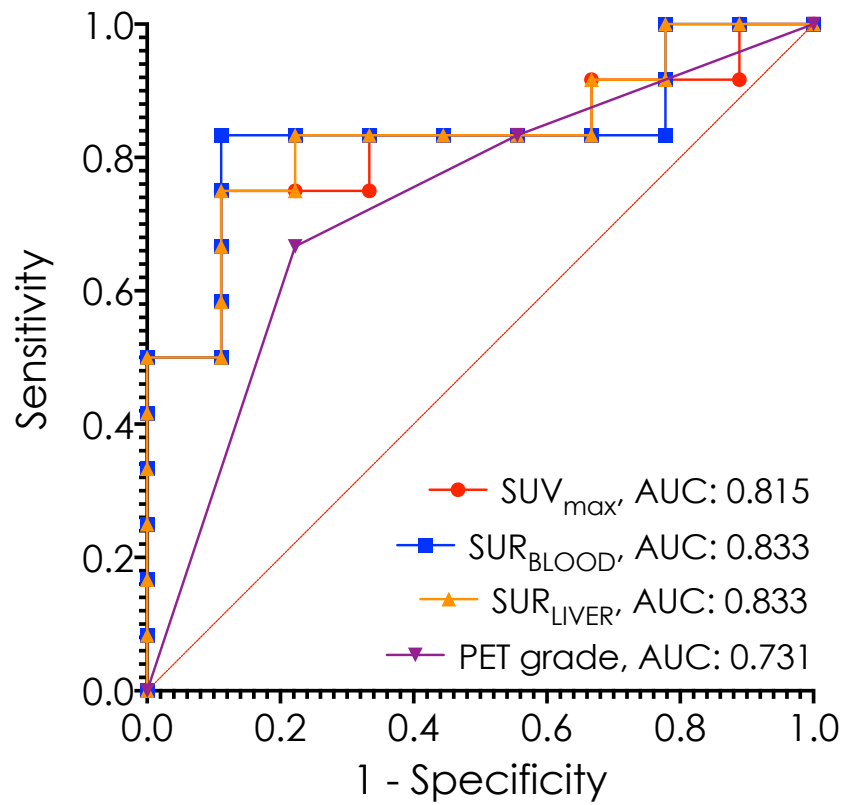


(c)

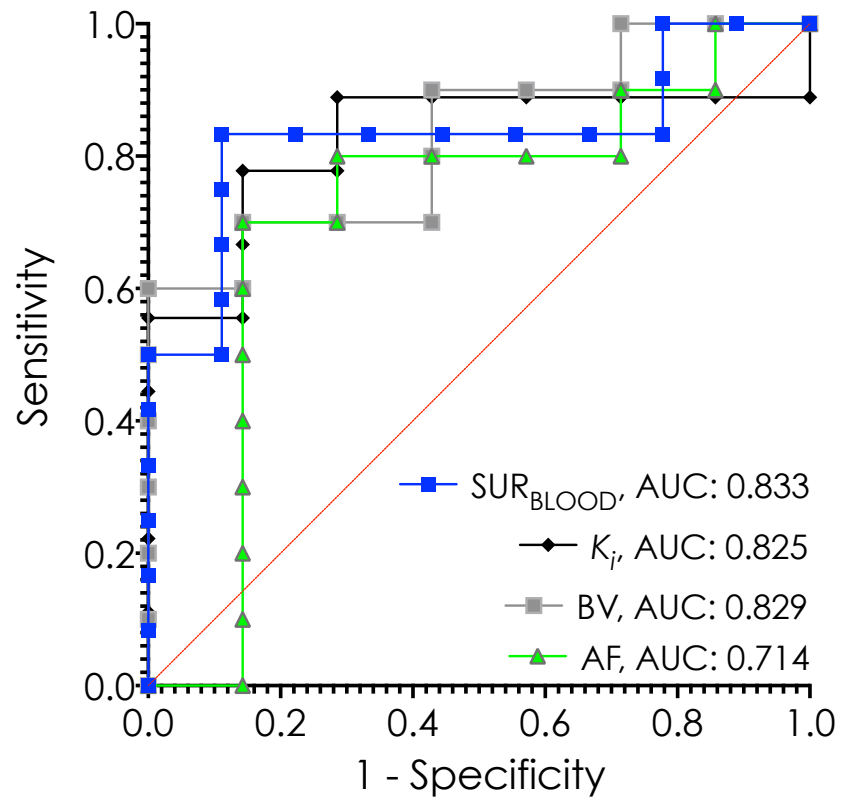
Perfusion CT
AF



(d)



(a)



(b)

TABLE 1. The demographic data, average nodule size, SUV_{max} , metabolic parameter relating to the pulmonary nodules through dynamic ^{18}F -FDG PET/CT, and perfusion parameters through perfusion CT for the benign and malignant nodules.

| | Benign Nodules | Malignant Nodules | p value |
|---|-----------------------|-----------------------|---------|
| Total Number of nodules | 9 | 12 | |
| Number of male patients (%) | 5/9 (55 %) | 6/12 (50 %) | |
| Average patient age (years \pm SD) | 63 \pm 7.5 | 68 \pm 6.7 | |
| Average nodule size, Range (mm) | 18, 9–29 | 22, 12–30 | |
| Average SUV_{max} ^{18}F -FDG PET/CT \pm SD | 2.2 \pm 1.7 | 7.0 \pm 4.5 | 0.0148 |
| Number of nodules analysed for dynamic ^{18}F -FDG PET/CT | 7 | 9 | |
| Average $K_i \pm$ SD (min^{-1}) | 0.0057 \pm 0.0071 | 0.0230 \pm 0.0155 | 0.0311 |
| Number of nodules analysed for perfusion CT parameters | 7 | 10 | |
| Average BV \pm SD (Patlak, ml/100ml) | 11.6857 \pm 6.7347 | 28.3400 \pm 15.9672 | 0.0250 |
| Average AF \pm SD (ml/100g/min) | 74.4571 \pm 89.0321 | 89.2000 \pm 49.8883 | 0.1613 |

TABLE 2. Comparison of the diagnostic accuracy of different techniques and parameters with pre-specified and derived cut-point values for malignancy.

| Parameter | Cut-point value/grade | | Sensitivity (95% CI) | Specificity (95% CI) | Accuracy |
|----------------------|-------------------------|-------------------------|-----------------------|------------------------|----------|
| SUV _{max} | Pre-specified | ≥2.5* | 75.0% (46.8 to 91.1%) | 66.7% (35.4 to 87.9%) | 71.4% |
| | Derived | ≥3.4 | 75.0% (46.8 to 91.1%) | 88.9% (56.5 to 99.43%) | 81.0% |
| SUR _{BLOOD} | Pre-specified | ≥1.56 | 83.3% (55.2 to 97.0%) | 88.9% (56.5 to 99.4%) | 85.7% |
| | Derived | | | | |
| SUR _{LIVER} | Pre-specified | ≥1.12 | 83.3% (55.2 to 97.0%) | 66.7% (35.4 to 87.9%) | 76.2% |
| | Derived | ≥1.65 | 75% (46.8 to 91.1%) | 88.9% (56.5 to 99.4%) | 81.0% |
| SUV grade | Pre-specified & Derived | ≥3 | 66.7% (39.0 to 86.2%) | 77.8% (45.3 to 96.0%) | 71.4% |
| K _i | Derived | ≥0.01 min ⁻¹ | 77.8% (45.2 to 96.0%) | 85.7% (48.7 to 99.3%) | 81.3% |
| BV | Derived | ≥21 ml/100ml | 70% (39.7 to 89.2%) | 100% (64.6 to 100%) | 82.4% |
| AF | Derived | ≥65 ml/100g/min | 70% (39.7 to 89.2%) | 85.7% (48.7 to 99.3%) | 76.5% |

* adding cut-points SUV_{max} ≥1.75 and ≥3.6 for nodules <12 mm and >16 mm, respectively,³⁷ resulted in sensitivity, specificity and accuracy of 72.7%, 70.0% and 71.4%, respectively.