



UNIVERSITY OF LEEDS

This is a repository copy of *Multi-observer concordance and accuracy of the British Thoracic Society scale and other visual assessment qualitative criteria for solid pulmonary nodule assessment using FDG PET-CT.*

White Rose Research Online URL for this paper:  
<https://eprints.whiterose.ac.uk/164102/>

Version: Accepted Version

---

**Article:**

Fatania, K, Brown, PJ, Xie, C et al. (6 more authors) (2020) Multi-observer concordance and accuracy of the British Thoracic Society scale and other visual assessment qualitative criteria for solid pulmonary nodule assessment using FDG PET-CT. *Clinical Radiology*. ISSN 0009-9260

<https://doi.org/10.1016/j.crad.2020.06.028>

---

© 2020 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

**Multi-observer concordance and accuracy of the BTS scale and other visual assessment qualitative criteria for solid pulmonary nodule (SPN) assessment with FDG PET-CT**

**Authors**

Fatania K<sup>1</sup>, Brown PJ<sup>1</sup>, Xie C<sup>2</sup>, McDermott G<sup>3</sup>, Callister MEJ<sup>4</sup>, Graham R<sup>5</sup>, Subesinghe M<sup>6,7</sup>, Gleeson FV<sup>2</sup>, Scarsbrook AF<sup>1,8</sup>

**Affiliations**

<sup>1</sup>Department of Radiology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, UK

<sup>2</sup>Department of Radiology, Oxford University Hospitals Foundation Trust, Oxford, UK

<sup>3</sup>Department of Medical Physics, Leeds Teaching Hospitals NHS Trust, Leeds, UK

<sup>4</sup>Department of Respiratory Medicine, Leeds Teaching Hospitals NHS Trust, Leeds, UK

<sup>5</sup>Department of Radiology, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK

<sup>6</sup>King's College London & Guy's and St. Thomas' PET Centre, St Thomas' Hospital, London, UK

<sup>7</sup>Department of Cancer Imaging, School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK

<sup>8</sup>Leeds Institute of Research at St James', University of Leeds, UK

**Corresponding Author**

Dr Kavi Fatania, Department of Radiology, Leeds General Infirmary, Leeds, LS1 3EX, UK

kavi.fatania@nhs.net

Tel: +44(0)1132068212

Fax: +44(0)112068228

### **Declaration of Interest Statement**

Fergus Gleeson is a share holder in Optellum

### **Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. However, the salaries of PB and KF, and part of the salary for AS were covered by a grant from Leeds Cares.

**Author Contributions**

1 guarantor of integrity of the entire study – Andrew Scarsbrook

2 study concepts and design – Andrew Scarsbrook

3 literature research – Kavi Fatania, Manil Subesinghe

4 clinical studies – Kavi Fatania, Peter Brown, Cheng Xie, Garry McDermott, Matthew

Callister, Richard Graham, Fergus Gleeson, Andrew Scarsbrook

5 experimental studies / data analysis – Kavi Fatania

6 statistical analysis – Kavi Fatania

7 manuscript preparation – Kavi Fatania

8 manuscript editing – Kavi, Fatania, Peter Brown, Manil Subesinghe, Andrew Scarsbrook

## **Abstract**

### Purpose

To compare the inter-observer reliability and diagnostic accuracy of the BTS scale and other visual assessment criteria in the context of FDG PET-CT evaluation of solid pulmonary nodules (SPNs).

### Method

50 patients who underwent FDG PET-CT for assessment of a SPN were identified. 7 reporters with varied experience at 4 centres graded FDG uptake visually using the British Thoracic Society (BTS) 4-point scale. 5 reporters also scored SPNs according to 3- and 5-point visual assessment scales and using semi-quantitative assessment (maximum standardised uptake value -  $SUV_{max}$ ). Inter-observer reliability was assessed with the intra-class correlation coefficient (ICC) and weighted Cohen's kappa ( $\kappa$ ). Diagnostic performance was evaluated by receiver operator characteristic (ROC) analysis.

### Results

Good inter-observer reliability was demonstrated with the BTS scale (ICC = 0.78, 95% CI 0.69-0.85) and 5-point scale (ICC = 0.78, 95 CI 0.68-0.86), whilst the 3-point scale demonstrated moderate reliability (ICC = 0.70, 95% CI 0.59-0.80). Almost perfect agreement was achieved between 2 consultants ( $\kappa$  = 0.85), and substantial agreement between 2 other consultants ( $\kappa$  = 0.78) using the BTS scale. ROC curves for the BTS and 5-point scales demonstrated equivalent accuracy (BTS AUC = 0.768; 5-point AUC = 0.768).  $SUV_{max}$  was no more accurate compared to the BTS scale ( $SUV_{max}$  AUC = 0.794; BTS AUC = 0.768,  $p$  = 0.43).

## Conclusions

The BTS scale can be applied reliably by reporters with varied levels of PET-CT reporting experience, across different centres and has a diagnostic performance that is not surpassed by alternative scales.

1 **Multi-observer concordance and accuracy of the BTS scale and other visual assessment**  
2 **qualitative criteria for solid pulmonary nodule (SPN) assessment with FDG PET-CT**

3

4 **Key Words**

5 Solitary pulmonary nodule; Fluorodeoxyglucose F18; PET-CT; Reproducibility of results;  
6 Observer variation

7

8

9 **Abbreviations**

10 ACCP – American College of Chest Physicians

11 AUC – Area under the curve

12 BTS – British Thoracic Society

13 CT – Computed tomography

14 FDG – 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose

15 ICC – Intraclass correlation coefficient

16 IQR – Interquartile range

17 MBP – Mediastinal blood pool

18 PET – Positron emission tomography

19 ROC – Receiver operator curve

20 SPN – Solid pulmonary nodule

21 SUV<sub>max</sub> - Maximum standardised uptake value

22

23

24 **Introduction**

25 Risk stratification of patients found to have a solid pulmonary nodule (SPN) on imaging helps  
26 guide optimal management, allowing improved identification and treatment for malignant  
27 lesions whilst reducing intervention and harm in patients with benign disease. 2-deoxy-2-  
28 [<sup>18</sup>F]fluoro-D-glucose (FDG) positron emission tomography-computed tomography (PET-CT) is  
29 widely used to non-invasively evaluate SPNs<sup>1,2</sup> and can improve the accuracy of risk  
30 prediction models when combined with clinical risk factors<sup>3</sup>.

31

32 In UK practice, the investigation and management of patients with pulmonary nodules is  
33 based upon the 2015 British Thoracic Society (BTS) guidelines, which recommend a clinico-  
34 radiological approach to risk stratification<sup>4,5</sup>. Following the detection of a SPN on initial CT,  
35 the estimated likelihood of malignancy is determined using the Brock model<sup>6</sup>, stratifying  
36 patients into either < or > 10% risk of malignancy based upon CT findings (nodule size, count,  
37 type, location, spiculation, emphysema) and patient risk factors (age, gender, history of lung  
38 cancer). Those with >10% risk of malignancy undergo further assessment with FDG PET-CT,  
39 and risk stratification using the Herder model. The combination of SPN FDG uptake  
40 assessment and other clinico-radiological risk factors in the Herder model has been shown to  
41 improve diagnostic accuracy <sup>3</sup>, which has been validated and confirmed in a UK population<sup>7</sup>.

42

43 The Herder model requires SPN FDG uptake to be classified according to a 4-point ordinal  
44 scale (none, faint, moderate and intense); the BTS guideline development group adapted the  
45 Herder model 4-point visual assessment scale by providing definitions for the categories of  
46 FDG uptake with reference to background uptake in the lungs and mediastinal blood pool  
47 (MBP)<sup>4,8,9</sup>. The BTS scale is the recommended method for assessment of FDG uptake in SPNs



48 in UK practice<sup>10,11</sup>, and has been shown recently to have very good inter-observer  
49 agreement within single UK institutions <sup>12,13</sup>. However, in order to demonstrate that this  
50 high agreement within institutions isn't due to common training methods or similar reporting  
51 techniques, it would be reassuring to reproduce these results across different institutions.  
52 Given that the BTS scale is widely used across centres in the UK, it is necessary to establish  
53 whether inter-observer agreement is of a sufficiently high standard across different UK  
54 institutions and between reporters with varying levels of PET-CT reporting experience, to  
55 confirm that the BTS scale is likely to be consistently applied nationwide. In addition, other  
56 visual assessment scales have been proposed to assess FDG uptake in SPN<sup>8</sup>, which have not  
57 been compared to the BTS scale, between reporters working across different UK institutions.

58

59 To the best of our knowledge, the BTS scale has not been assessed with regard to its inter-  
60 observer agreement between reporters working in different UK institutions, nor compared  
61 against other visual assessment scales. The aims of this study were to evaluate the inter-  
62 observer agreement across multiple reporters at 4 different UK centres and assess the relative  
63 diagnostic accuracy of 3 visual assessment scales of FDG uptake: i) BTS scale, ii) a 5-point scale  
64 modified from Fletcher et al.<sup>8</sup>, and iii) a novel 3-point visual assessment scale.

65

66

67 **Methods**

68 **Patient selection**

69 The reporting data set comprised initial pre-treatment FDG PET-CT scans performed in 50  
70 patients with SPNs, who were randomly selected from an institutional database of patients  
71 at a single tertiary referral centre and who were subsequently assessed in nodule follow-up  
72 clinics between 2008 and 2013. Patients were included in this study if they had a SPN, and  
73 the diameter of their dominant SPN was between 8 and 30mm; 8mm is the minimum  
74 threshold size for resolving FDG uptake with a SPN<sup>4</sup>, and this range of nodule size reflects the  
75 standard practice of nodule assessment for UK departments<sup>7</sup>. Patients with part-solid or  
76 ground glass nodules were not included. Patients with a history of extra-pulmonary sites of  
77 malignancy and a new SPN were included as the Herder model accounts for a history of extra-  
78 pulmonary malignancy in the assessment of a SPN, and this also reflects the reality of SPN  
79 evaluation practice.

80

81 Final diagnosis was considered benign when histopathology demonstrated a benign  
82 condition, the SPN remained stable over 2 years of radiological follow-up, or the SPN  
83 spontaneously decreased or resolved without treatment. A SPN was considered malignant  
84 when histopathology confirmed primary lung cancer, there was serial interval growth of the  
85 SPN on imaging and treatment for malignancy was instigated, or the patient was known to  
86 have a histologically confirmed extra-pulmonary malignancy and new lung nodules were  
87 consistent with metastases radiologically. If patients had multiple nodules, only the largest  
88 SPN was considered for the study.

89

90 Prospective consent was obtained from all patients at the time of imaging for use of their  
91 anonymised FDG PET-CT imaging data in research and service development projects. All  
92 patients were prospectively entered into a departmental database used for retrospective  
93 identification and audit. Formal ethics committee approval was waived for this study which  
94 was considered by the institutional review board to represent evaluation of a routine clinical  
95 service.

96

### 97 **Imaging acquisition and reconstruction**

98 A standard protocol was used for FDG PET-CT examinations with half-body acquisition from  
99 the skull base to upper thighs. Scans prior to June 2010 were performed on a 16-slice  
100 Discovery STE PET-CT scanner (GE Healthcare, Chicago, IL, USA) and from June 2010 to  
101 December 2013 on a 64-slice Philips Gemini TF64 scanner (Philips Healthcare, Best,  
102 Netherlands). The CT component was acquired with the following settings: 140kV; 80mAs;  
103 tube rotation time 0.5 seconds per rotation; 3.75mm section thickness. Patients were asked  
104 to maintain normal shallow respiration during the CT acquisition. No iodinated contrast  
105 material was administered. Serum blood glucose was routinely checked and if blood glucose  
106 was > 10 mmol/L scanning was not performed. Patients fasted for 6 hours prior to intravenous  
107 FDG injection (dose varied according to patient body weight). All scans used iterative  
108 reconstruction (details are outlined in **Table 1**), CT for attenuation correction, applied scatter  
109 and randoms correction. Each scanner used consistent reconstruction settings, matrix and  
110 voxel size.

111

112

113

## 114 **Image Analysis**

115 PET-CT images for each patient were anonymised and distributed to each participating centre.  
116 Each reporter scored the FDG uptake within the dominant SPN independently, using the 3  
117 visual assessment scales, blinded to all clinical information about the patient including  
118 eventual diagnosis. SPNs were scored using the scales outlined in **Table 2**. Each nodule was  
119 scored by visually comparing the uptake of FDG within the nodule to background tissues,  
120 including the lung parenchyma, the mediastinal blood pool (lumen of the aortic arch) and the  
121 liver, and its score assigned according to the definitions provided in **Table 2**. Examples of  
122 pulmonary nodules from each of the categories using the 5-point scale are illustrated in  
123 **Figure 1**. Mediastinal blood pool FDG uptake was determined by visually assessing uptake  
124 within the aortic arch lumen, taking care to ignore uptake in the vessel wall. Liver FDG uptake  
125 was determined by assessing the uptake within right lobe hepatic parenchyma, ignoring  
126 uptake clearly within a focal lesion (e.g. cyst), or within the vasculature.

127

128 Reporters received no additional training in the use of these visual assessment scales; the BTS  
129 scale is commonly used assessment scale in the reporting of PET-CT at each of the 4  
130 participating centres. Reporters varied in their prior PET-CT interpretation experience: 3  
131 'novice' reporters with less than 6 months' experience, 1 consultant radiologist who is a  
132 nuclear medicine expert with under 10 years' experience, and 3 consultant radiologists who  
133 are nuclear medicine experts each with over 10 years' experience. All 7 reporters assessed  
134 SPNs using the BTS scale. Due to logistical constraints, 5 out of initial 7 reporters, including 3  
135 consultants and 2 novice reporters, also scored SPNs using the 3 and 5-point visual  
136 assessment scales and by semi-quantitative assessment ( $SUV_{max}$ ) at the same time as using  
137 the BTS scale. Semi-quantitative assessment consisted of drawing a region of interest (ROI)

138 around the SPN, and the maximum FDG uptake within this was calculated by the reporting  
139 software.

140

#### 141 **Statistical Analysis**

142 Agreement between observers was measured using two-way random effects intraclass  
143 correlation coefficient (ICC) for multi-rater agreement and weighted Cohen's kappa ( $\kappa$ ) for  
144 pair-wise agreement. ICC values below 0.5 indicate poor reliability, between 0.5 and 0.75  
145 indicate moderate reliability, between 0.75 and 0.9 indicate good reliability and above 0.9  
146 indicate excellent reliability<sup>14</sup>. Kappa values between 0.81 and 1 indicate almost perfect  
147 agreement, between 0.61 and 0.8 substantial agreement, and between 0.41 and 0.6  
148 moderate agreement<sup>15</sup>. Diagnostic performance (i.e. discrimination of malignant from  
149 benign SPNs) of each visual assessment scale and semi-quantitative assessment with  $SUV_{max}$ ,  
150 was assessed using the total area under the curve (AUC) from receiver operator characteristic  
151 (ROC) curves separately averaged across all reporters and across expert reporters only.  
152 Derivation of the averaged AUC was based on multi-rater multi-case (MRMC) statistical  
153 analysis developed by Gallas et al. and described elsewhere<sup>16</sup>, and AUCs for each assessment  
154 scale were compared using a t-test as outlined by Hillis et al.<sup>17</sup> – this analysis was performed  
155 with the freely available software package (iMRMC: Multi-Reader, Multi-Case Analysis  
156 Methods; Version 1.2.0). Other statistical analyses were performed using SPSS (Version<sup>25</sup>;  
157 IBM, Armonk, New York, USA).

158

159

## 160 **Results**

### 161 **Demographic data and nodule characteristics**

162 50 patients were included in the study. Demographic information and SPN characteristics are  
163 provided in **Table 3**. The median age was 67 years (IQR 62-75 years) and 21 of the 50 patients  
164 were male (42%). 40 patients (80%) were current or former smokers and there were 37  
165 patients (74%) with an eventual diagnosis of malignancy – 30 patients with primary lung  
166 malignancy and 7 with pulmonary metastases from an extra-pulmonary primary malignancy  
167 – the majority of patients with pulmonary metastases had metastatic colorectal carcinoma (5  
168 patients, 10%). Median SPN diameter was 16mm (IQR 11.5-23.5mm). The mean SUV<sub>max</sub> for  
169 benign SPNs was 2.5 (range 0.6-5.8), and for malignant SPNs 5.4 (range 1.2-12.4).

170

### 171 **Interobserver agreement**

172 **Table 4** summarises the results of inter-observer agreement analysis. Inter-observer  
173 reliability for the BTS scale, for all 7 reporters including consultants and novices (ICC = 0.78,  
174 95% CI 0.69-0.85), and between all 4 consultants (ICC = 0.77, 95% CI 0.67-0.85) was good. 5  
175 out of 7 reporters, including 3 consultants and 2 novice reporters, also scored SPNs using the  
176 3 and 5-point visual assessment scales and by semi-quantitative assessment (SUV<sub>max</sub>). For the  
177 5-point scale, agreement between all 5 reporters (ICC = 0.78, 95 CI 0.68-0.86), and between  
178 3 consultants (ICC = 0.75, 95% CI 0.63-0.84) was good. For the 3-point scale, agreement  
179 between all 5 reporters (ICC = 0.70, 95% CI 0.59-0.80), and between 3 consultants (ICC = 0.64,  
180 95% CI 0.49 0.76) was moderate.

181

182 Pair-wise analysis of agreement was performed for the BTS scale. Weighted  $\kappa$  demonstrated  
183 almost perfect agreement between 2 consultants, one with under (expert 1), and the other

184 with over 10 years' experience (expert 2) ( $\kappa = 0.85$ ), and substantial agreement between 2  
185 consultants both with over 10 years' experience (expert 3 vs expert 4) ( $\kappa = 0.78$ ) all working  
186 across different centres. Comparison of agreement between one consultant with over 10  
187 years' experience with reporters of reduced experience also demonstrated substantial  
188 agreement (expert 4 vs novice 1  $\kappa = 0.71$ , expert 4 vs expert 2  $\kappa = 0.75$ ).

189

### 190 **Diagnostic accuracy**

191 **Table 5** summarises the AUCs from ROC analysis for visual assessment scales and semi-  
192 quantitative assessment ( $SUV_{max}$ ), and **Figure 2** illustrates ROC curves for each assessment  
193 method. ROCs for the BTS and 5-point scales demonstrated equivalent overall accuracy (BTS  
194 = 0.768; 5-point AUC = 0.768). The BTS scale demonstrated improved accuracy compared to  
195 the 3-point scale, although did not reach statistical significance (BTS AUC = 0.768; 3-point AUC  
196 = 0.715,  $p = 0.08$  (Hillis, t-test)).  $SUV_{max}$  did not demonstrate statistically significant higher  
197 accuracy compared to the BTS scale ( $SUV_{max}$  AUC = 0.794; BTS AUC = 0.768,  $p = 0.43$ ).

198

199

200 **Discussion**

201 Our study demonstrates good interobserver agreement of BTS scale, which is not improved  
202 by using a 3- or 5-point scale. The BTS scale has similar diagnostic performance across a range  
203 of reporters and sites of practice compared with other assessment methods including semi-  
204 quantitative FDG uptake measurement. The 2015 BTS guidelines for SPN evaluation advocate  
205 the use of an ordinal visual assessment scale to assess FDG uptake in SPNs on PET-CT, with  
206 the 4-point BTS scale the standard assessment scale in UK reporting practice 4,5. Murphy et  
207 al. demonstrated that the BTS scale has good inter-observer agreement within a single UK  
208 institution, using 2 different PET-CT reconstruction techniques 12 and our study further  
209 corroborates this by demonstrating good inter-observer agreement when using the BTS scale  
210 across multiple reporters from different institutions. Although the BTS scale has been  
211 advocated in national guidance, drawn together by collaborators across many institutions,  
212 this study confirms that multi-centre application of the BTS scale is reliable and extends the  
213 results of single-centre studies sharing similar conclusions 12,13. Furthermore, the study  
214 confirms that a 4-point BTS scale is not improved, with respect to its inter-observer  
215 agreement, by using a 3- or 5-point visual assessment scale. In addition, reporters of varying  
216 levels of experience showed good agreement in our study, and these results suggest that SPN  
217 risk stratification using the Herder model is likely being consistently applied across different  
218 UK centres.

219

220 Our study used visual assessment of FDG uptake within the SPN and reference background  
221 tissues to classify SPNs according to the different assessment scales (**Table 2**). In the  
222 assessment of FDG PET-CT for response assessment in Hodgkin's and diffuse large B cell  
223 lymphoma, the 5-point scale, i.e. Deauville criteria, has demonstrated high inter-observer



224 agreement<sup>18–20</sup>, utilising both visual assessment of FDG uptake with comparison to  
225 reference background tissues, and semi-quantitative assessment in order to confirm the  
226 results of visual assessment<sup>21</sup>. This may overcome some of the difficulties that arise from a  
227 inhomogeneous background tissue used for comparison that may lead to interobserver  
228 disagreement in visual analysis. The study by Murphy et al. demonstrated good inter-  
229 observer agreement using a similar method of visual assessment with confirmatory semi-  
230 quantitative assessment of reference background FDG uptake in the liver and blood pool. Our  
231 study shows similar results using a visual assessment of SPN FDG uptake and reference  
232 background tissue uptake, and importantly, this was observed in reporters with varying levels  
233 of experience in PET-CT reporting and across different institutions, suggesting that the BTS  
234 scale is reproducible and not due to common training in one centre alone.

235

236 The 3-point visual scale had the lowest inter-observer concordance. This could be explained  
237 by a small proportion of cases being classified on opposite ends of the 3-point scale (i.e. one  
238 reporter scored a SPN as “1” and the other as “3”), whereas they were categorized into  
239 adjacent categories for the 4-point scale (scored “2” vs “3”) or only 2 categories apart in the  
240 5-point scale (a score of “2” vs “4”). This disagreement could not be attributed to lack of  
241 reporter experience as, even when novice reporters were excluded from analysis, 5 cases  
242 (10%) were categorised in this manner. Hence reliability was likely lower for the 3-point scale  
243 because of these cases being classified at opposite ends of the scale. It should also be noted  
244 that the reduced agreement of the 3-point scale could reflect the small sample size in our  
245 study, and that over a larger population, a difference might not have been observed.  
246 Nevertheless, the simplified 3-point scale did not perform better than the standard BTS scale  
247 recommended in the 2015 BTS guidelines.

248

249 Overall accuracy of FDG PET-CT to discriminate malignant and benign SPNs, as measured by  
250 ROC analysis, did not vary with the visual assessment scale used, and although semi-  
251 quantitative assessment of FDG uptake performed equally to visual assessment, it did not  
252 improve diagnostic accuracy to a statistically significant degree. This concurs with previous  
253 data reporting that use of semi-quantitative measurement does not improve the sensitivity  
254 of PET-CT<sup>22</sup>, but can improve its specificity<sup>23,24</sup>. Although they may not have played a  
255 significant role in our study, in general there are several factors that can limit the use of a  
256 semi-quantitative measure for distinguishing malignant and benign SPNs. First, technical  
257 factors can limit the standardisation of SUV values across different scanner and sites where  
258 scan technique, for example reconstruction algorithms, may vary and therefore so too will  
259 the SUV measurements<sup>25</sup>. All the images used in this study were acquired in a single  
260 institution. Using an alternative reconstruction algorithm has recently been shown to increase  
261 the Herder score for SPNs, although not the overall diagnostic performance of the Herder  
262 scale, for example 12. Second, studies utilising semi-quantitative measures typically use a  
263 single cut-off value to distinguish benign and malignant nodules<sup>26</sup>, and typically do not  
264 include a validation cohort to test their cut-off values<sup>9,27</sup>, whereas the use of visual ordinal  
265 scales can reflect increasing likelihood that a nodule is malignant and overcome the  
266 difficulties of semiquantitative measurement<sup>8</sup>. Lastly, the calculated SUV can be erroneous  
267 due to tracer extravasation or inaccurate patient weight.

268

269 The diagnostic accuracy of both visual assessment scales and semi-quantitative  
270 measurements were lower in this study than previously reported by others<sup>2,9,28</sup>. This may  
271 be explained by the high proportion of malignant SPNs included in this patient cohort, which

272 might have influenced test sensitivity and specificity<sup>29</sup>. Our results are similar to those of  
273 Lopez et al. who also had a high prevalence of malignant nodules in their study sample<sup>23</sup> and  
274 to Murphy et al. whose prevalence of malignancy was 77%<sup>12</sup>. The high proportion of current  
275 or former smokers in our patient cohort is also likely to have influenced the AUC, as it is known  
276 that in higher risk patients, FDG PET-CT has reduced specificity<sup>9</sup>. Finally, the mean SUV<sub>max</sub> for  
277 benign SPNs in the study was 2.5, which in other studies<sup>27,30</sup> is taken as the threshold for  
278 assigning a nodule as malignant on PET-CT, suggesting that our sample may have over-  
279 represented benign SPNs (i.e. inflammatory or infective SPNs) with ‘false’ positive FDG  
280 uptake<sup>31</sup> compared with other studies. This will have further reduced the specificity of  
281 assessment. The accuracy of visual assessment might have been improved by using semi-  
282 quantitative assessment of uptake in reference tissues to confirm the results of visual  
283 assessment, as used in Deauville criteria<sup>21</sup> and by Murphy et al<sup>12</sup>.

284

285 The study had a number of important limitations. First, 50 patients is a relatively small sample  
286 size, and it is possible that a larger cohort may have revealed differences in accuracy and/or  
287 reliability between the BTS and 5-point scales. Second, not all diagnoses were confirmed  
288 histologically, and therefore it is possible that this introduced inaccuracy in the classification  
289 of a SPN being definitely malignant or benign, again which would affect the overall diagnostic  
290 accuracy. However, each scale would be similarly affected, and this should not limit the  
291 comparison between them. Furthermore, these criteria reflect the reality of clinical practice,  
292 when treatment decisions are not always based on histological diagnosis. The images used in  
293 assessment were acquired on different scanners, using different imaging conditions which  
294 introduces a potential source of variation in the image quality, however this should not have  
295 a strong effect on the comparative assessment of different assessment methods. Lastly, this

296 was a retrospective analysis on non-consecutive patients which is potentially a source of bias,  
297 however this would have affected each assessment scale equally and is unlikely to affect our  
298 conclusions.

299

### 300 **Conclusion**

301 Our study confirms recent single-centre experiences and extends this to demonstrate that  
302 the BTS scale can be applied consistently in the assessment of SPNs by observers working at  
303 different centres and by individuals with limited prior PET-CT interpretation experience. The  
304 BTS scale is advocated in national guidance for evaluation of SPN's and although it would be  
305 expected that the scale is easily reproducible across multiple institutions, our study confirms  
306 that this is the case. The BTS scale, which is being increasingly used as part of risk stratification  
307 of SPNs has an accuracy which is not surpassed by alternative visual or semi-quantitative  
308 assessment scales.

309

### 310 **Ethical approval**

311 All procedures performed in studies involving human participants were in accordance with  
312 the ethical standards of the institutional and/or national research committee and with the  
313 1964 Helsinki declaration and its later amendments or comparable ethical standards. This  
314 article does not contain any studies with animals performed by any of the authors.

315

### 316 **Informed consent**

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

318

319

320

321 References

- 322 1. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of Positron  
323 Emission Tomography for Diagnosis of Pulmonary Nodules and Mass Lesions. *JAMA*  
324 2001;**285**(7):914. <https://doi.org/10.1001/jama.285.7.914>.
- 325 2. Ruilong Z, Daohai X, Li G, Xiaohong W, Chunjie W, Lei T. Diagnostic value of 18F-FDG-  
326 PET/CT for the evaluation of solitary pulmonary nodules. *Nucl Med Commun*  
327 2017;**38**(1):67–75. <https://doi.org/10.1097/MNM.0000000000000605>.
- 328 3. Herder GJ, van Tinteren H, Golding RP, *et al*. Clinical Prediction Model To Characterize  
329 Pulmonary Nodules. *Chest* 2005;**128**(4):2490–6.  
330 <https://doi.org/10.1378/chest.128.4.2490>.
- 331 4. Callister MEJ, Baldwin DR, Akram AR, *et al*. British Thoracic Society guidelines for the  
332 investigation and management of pulmonary nodules: accredited by NICE. *Thorax*  
333 2015;**70**(Suppl 2):ii1–54. <https://doi.org/10.1136/thoraxjnl-2015-207168>.
- 334 5. Graham RNJ, Baldwin DR, Callister MEJ, Gleeson F V. Return of the pulmonary nodule:  
335 the radiologist’s key role in implementing the 2015 BTS guidelines on the  
336 investigation and management of pulmonary nodules. *Br J Radiol*  
337 2016;**89**(1059):20150776. <https://doi.org/10.1259/bjr.20150776>.
- 338 6. McWilliams A, Tammemagi MC, Mayo JR, *et al*. Probability of Cancer in Pulmonary  
339 Nodules Detected on First Screening CT. *N Engl J Med* 2013;**369**(10):910–9.  
340 <https://doi.org/10.1056/NEJMoa1214726>.
- 341 7. Al-Ameri A, Malhotra P, Thygesen H, *et al*. Risk of malignancy in pulmonary nodules:  
342 A validation study of four prediction models. *Lung Cancer* 2015;**89**(1):27–30.  
343 <https://doi.org/10.1016/j.lungcan.2015.03.018>.

- 344 8. Fletcher JW, Kymes SM, Gould M, *et al.* A Comparison of the Diagnostic Accuracy of  
345 18F-FDG PET and CT in the Characterization of Solitary Pulmonary Nodules. *J Nucl*  
346 *Med* 2008;**49**(2):179–85. <https://doi.org/10.2967/jnumed.107.044990>.
- 347 9. Evangelista L, Cuocolo A, Pace L, *et al.* Performance of FDG-PET/CT in solitary  
348 pulmonary nodule based on pre-test likelihood of malignancy: results from the  
349 ITALIAN retrospective multicenter trial. *Eur J Nucl Med Mol Imaging*  
350 2018;**45**(11):1898–907. <https://doi.org/10.1007/s00259-018-4016-1>.
- 351 10. Callister MEJ, Baldwin DR. How should pulmonary nodules be optimally investigated  
352 and managed? *Lung Cancer* 2016;**91**:48–55.  
353 <https://doi.org/10.1016/j.lungcan.2015.10.018>.
- 354 11. Baldwin D, Callister M, Akram A, *et al.* British Thoracic Society quality standards for  
355 the investigation and management of pulmonary nodules. *BMJ Open Respir Res*  
356 2018;**5**(1):e000273. <https://doi.org/10.1136/bmjresp-2017-000273>.
- 357 12. Murphy D, Royle L, Chalampalakis Z, *et al.* The effect of a novel Bayesian penalised  
358 likelihood PET reconstruction algorithm on the assessment of malignancy risk in  
359 solitary pulmonary nodules according to the British Thoracic Society guidelines. *Eur J*  
360 *Radiol* 2019;**117**:149–55. <https://doi.org/10.1016/j.ejrad.2019.06.005>.
- 361 13. Ordidge KL, Gandy N, Arshad MA, *et al.* Interobserver agreement of the visual Herder  
362 scale for the assessment of solitary pulmonary nodules on 18F Fluorodeoxyglucose  
363 PET/computed tomography. *Nucl Med Commun* 2020;**41**(3):235–40.  
364 <https://doi.org/10.1097/mnm.0000000000001146>.
- 365 14. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation  
366 Coefficients for Reliability Research. *J Chiropr Med* 2016;**15**(2):155–63.  
367 <https://doi.org/10.1016/j.jcm.2016.02.012>.

- 368 15. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data.  
369 Biometrics 1977;**33**(1):159. <https://doi.org/10.2307/2529310>.
- 370 16. Gallas BD. One-Shot Estimate of MRMC Variance: AUC. Acad Radiol 2006;**13**(3):353–  
371 62. <https://doi.org/10.1016/j.acra.2005.11.030>.
- 372 17. Hillis SL, Berbaum KS, Metz CE. Recent Developments in the Dorfman-Berbaum-Metz  
373 Procedure for Multireader ROC Study Analysis. Acad Radiol 2008;**15**(5):647–61.  
374 <https://doi.org/10.1016/j.acra.2007.12.015>.
- 375 18. Barrington SF, Qian W, Somer EJ, *et al*. Concordance between four European centres  
376 of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma.  
377 Eur J Nucl Med Mol Imaging 2010;**37**(10):1824–33. [https://doi.org/10.1007/s00259-](https://doi.org/10.1007/s00259-010-1490-5)  
378 [010-1490-5](https://doi.org/10.1007/s00259-010-1490-5).
- 379 19. Biggi A, Gallamini A, Chauvie S, *et al*. International Validation Study for Interim PET in  
380 ABVD-Treated, Advanced-Stage Hodgkin Lymphoma: Interpretation Criteria and  
381 Concordance Rate Among Reviewers. J Nucl Med 2013;**54**(5):683–90.  
382 <https://doi.org/10.2967/jnumed.112.110890>.
- 383 20. Burggraaff CN, Cornelisse AC, Hoekstra OS, *et al*. Interobserver Agreement of Interim  
384 and End-of-Treatment 18 F-FDG PET/CT in Diffuse Large B-Cell Lymphoma: Impact on  
385 Clinical Practice and Trials. J Nucl Med 2018;**59**(12):1831–6.  
386 <https://doi.org/10.2967/jnumed.118.210807>.
- 387 21. Barrington SF, Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin  
388 lymphomas. Eur J Nucl Med Mol Imaging 2017;**44**:97–110.  
389 <https://doi.org/10.1007/s00259-017-3690-8>.
- 390 22. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K. Visual and  
391 Semiquantitative Analyses for F-18 Fluorodeoxyglucose PET Scanning in Pulmonary

- 392 Nodules 1 cm to 3 cm in Size. *Ann Thorac Surg* 2005;**79**(3):984–8.  
393 <https://doi.org/10.1016/j.athoracsur.2004.07.072>.
- 394 23. López OVG, María A, Vicente G, *et al*. F-FDG-PET/CT in the assessment of pulmonary  
395 solitary nodules: comparison of different analysis methods and risk variables in the  
396 prediction of malignancy. *Transl Lung Cancer Res* 2015;**4**(3):228–35.  
397 <https://doi.org/10.3978/j.issn.2218-6751.2015.05.07>.
- 398 24. Hashimoto Y, Tsujikawa T, Kondo C, *et al*. Accuracy of PET for diagnosis of solid  
399 pulmonary lesions with 18F-FDG uptake below the standardized uptake value of 2.5. *J*  
400 *Nucl Med* 2006;**47**(3):426–31.
- 401 25. Boellaard R. Standards for PET Image Acquisition and Quantitative Data Analysis. *J*  
402 *Nucl Med* 2009;**50**(Suppl\_1):11S-20S. <https://doi.org/10.2967/jnumed.108.057182>.
- 403 26. Gould MK, Donington J, Lynch WR, *et al*. Evaluation of Individuals With Pulmonary  
404 Nodules: When Is It Lung Cancer? *Chest* 2013;**143**(5):e93S-e120S.  
405 <https://doi.org/10.1378/chest.12-2351>.
- 406 27. Li S, Zhao B, Wang X, *et al*. Overestimated value of 18 F-FDG PET/CT to diagnose  
407 pulmonary nodules: Analysis of 298 patients. *Clin Radiol* 2014;**69**(8):352–7.  
408 <https://doi.org/10.1016/j.crad.2014.04.007>.
- 409 28. Cronin P, Dwamena BA, Kelly AM, Carlos RC. Solitary Pulmonary Nodules: Meta-  
410 analytic Comparison of Cross-sectional Imaging Modalities for Diagnosis of  
411 Malignancy. *Radiology* 2008;**246**(3):772–82.  
412 <https://doi.org/10.1148/radiol.2463062148>.
- 413 29. Leeflang MMG, Rutjes AWS, Reitsma JB, Hooft L, Bossuyt PMM. Variation of a test's  
414 sensitivity and specificity with disease prevalence. *Can Med Assoc J*  
415 2013;**185**(11):E537–44. <https://doi.org/10.1503/cmaj.121286>.



- 416 30. Orlacchio A, Schillaci O, Antonelli L, *et al.* Solitary pulmonary nodules: morphological  
417 and metabolic characterisation by FDG-PET-MDCT. *Radiol Med* 2007;**112**(2):157–73.  
418 <https://doi.org/10.1007/s11547-007-0132-x>.
- 419 31. Rosenbaum SJ, Lind T, Antoch G, Bockisch A. False-Positive FDG PET Uptake—the Role  
420 of PET/CT. *Eur Radiol* 2006;**16**(5):1054–65. [https://doi.org/10.1007/s00330-005-](https://doi.org/10.1007/s00330-005-0088-y)  
421 0088-y.

422

### 423 **Figures and tables**

424 **Table 1** - Reconstruction parameters for each scanner

425 **Table 2** - Visual assessment scale scoring criteria

426

427 **Table 3** – Demographic data and SPN characteristics (n=50)

428

429 **Table 4** – Inter-observer agreement for visual assessment scales

430

431 **Table 5** - Accuracy of visual assessment scales and semiquantitative assessment

432 **Figure 1** – Examples of pulmonary nodules demonstrating increasing FDG uptake

433

434 Caption for Figure 1:

435

436 Maximum intensity projection (MIP) image from 5 patients with SPN that demonstrate  
437 increasing FDG uptake (from right to left), and illustrate examples of each category using the  
438 5-point visual assessment scale. From the right-hand image, an example of no uptake,  
439 through to the left-hand image showing uptake above that of the liver. Black circles indicate  
440 the location of the SPN being assessed. MBP = mediastinal blood pool.

441

442 **Figure 2** – Receiver operator curves for visual assessment scales and semiquantitative  
443 assessment

444

445 Caption for Figure 2:

446 4 receiver-operator curves demonstrating similar diagnostic performance For visual uptake  
 447 scales and semiquantitative assessment compared to the BTS scale.

448

449 **Table 1** - Reconstruction parameters for each scanner

Scanner	Reconstruction	Scatter correction	Randoms correction	Matrix	Voxel size (x,y,z mm)
<b>GE Healthcare STE</b>	OSEM	Convolution subtraction	Singles	128	4.7 x 4.7 x 3.3
<b>Philips Gemini TF64</b>	BLOB-OS-TF	SS-Simul	DLYD	144 or 169	4.0 x 4.0 x 4.0

450

451 **Key:**

452 OSEM – Ordered subsets expectation maximisation

Uptake	3-point scale	BTS scale	5-point scale
Indiscernible from background lung	1	1	1
Greater than lung but less MBP		2	2
Equal to MBP	2		
Greater than MBP but less than liver	3	3	4
Greater than liver		4	5

MBP – mediastinal blood pool

453 BLOB-OS-TF – Spherically symmetric basis function ordered subset algorithm

454 DLYD – delayed event subtraction

455

456 **Table 2** - Visual assessment scale scoring criteria

457

458

459

460 **Table 3** – Demographic data and nodule characteristics (n=50)

461

Demographic	Value
Median age, years (IQR)	67 (62-75)
Male gender (%)	21 (42%)
Smoking status (%)	
Current or former smoker	40 (80%)
Never smoked	7 (14%)
Smoking status undocumented	3 (6%)
Diagnosis (%)	
Primary lung cancer	30 (60%)
Metastases from extra-pulmonary primary malignancy	7 (14%)
Colorectal adenocarcinoma	5 (10%)
Cervical squamous cell carcinoma	1 (2%)
Pancreatic large cell carcinoma	1 (2%)
Benign nodule	13 (26%)
Median nodule diameter, mm (IQR)	16 (11.5 – 23.5)

IQR = interquartile range

462

463

464 **Table 4** – Inter-observer agreement for visual assessment scales

465

Visual assessment scale	Agreement: All observers ICC (95% CI)	Agreement: Expert observers ICC (95% CI)
3-point scale	0.70 (0.59 - 0.80)	0.64 (0.49 - 0.76)
BTS scale	0.78 (0.69 - 0.85)	0.77 (0.67 - 0.85)
5-point scale	0.78 (0.68 - 0.86)	0.75 (0.63 - 0.84)

ICC = 2-way random effects intra-class correlation coefficient

466

467

468

469 **Table 5** - Accuracy of visual assessment scales and semiquantitative assessment  
470

Assessment method	Area under ROC	<i>p</i> value* (versus 4-point BTS scale)
3-point scale	0.715	0.08
BTS scale	0.768	NA
5-point scale	0.768	NA
SUV <sub>max</sub>	0.794	0.43

\* t-test – as outlined by Hillis et al.

NA – not applicable

471  
472  
473  
474

Figure 1

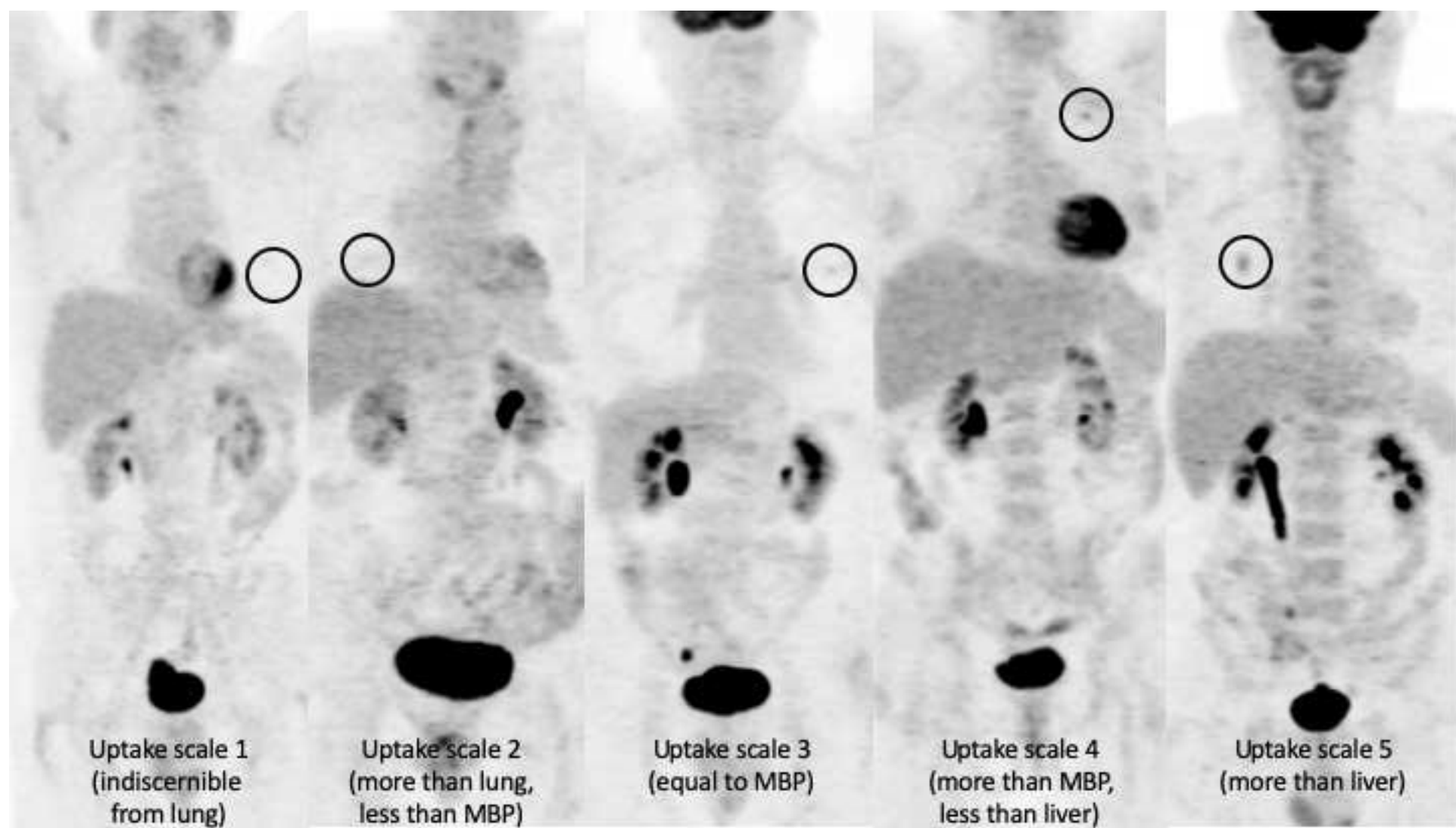
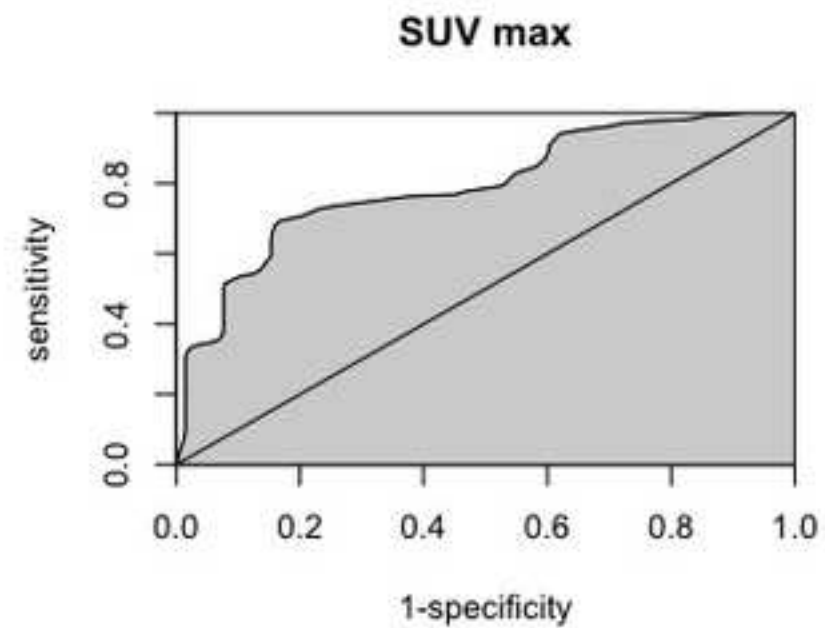
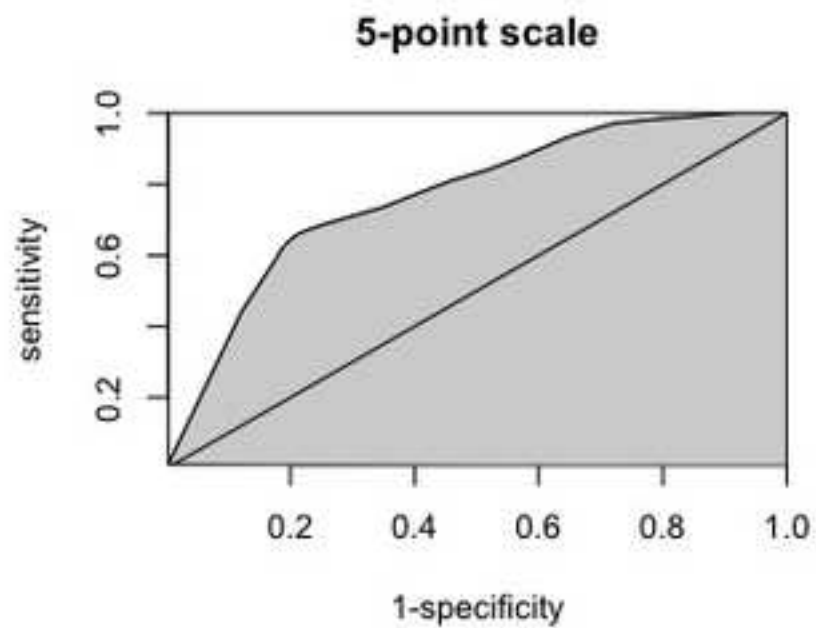
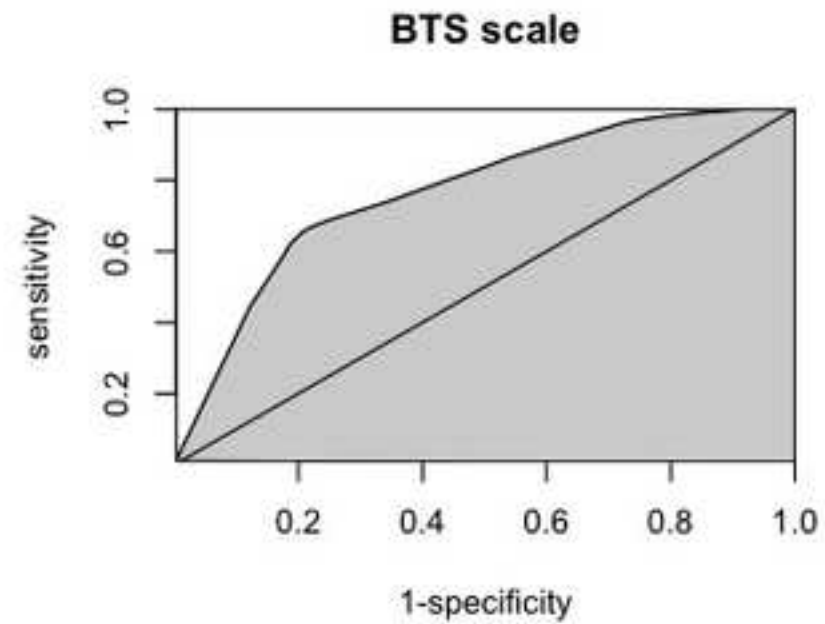
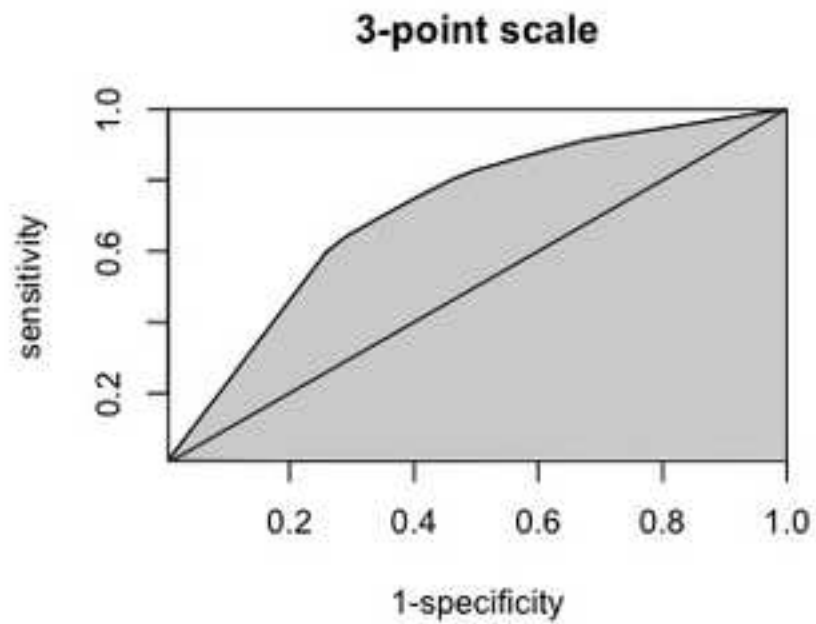


Figure 2



## **Highlights**

- British Thoracic Society scale of FDG uptake has good inter-observer agreement.
- British Thoracic Society scale is as reliable as 3 and 5 point visual scales.
- Visual assessment showed good agreement between reporters across institutions.
- Semi-quantitative assessment did not improve the diagnostic accuracy.