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Performance of 18F-fluorodesoxyglucose positron-emission tomography/computed tomography for cancer screening in patients with unprovoked venous thromboembolism: Results from an individual patient data meta-analysis

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HAL Authorization

1 **TITLE PAGE**

2 **Article title:** Performance of 18F-Fluorodesoxyglucose Positron-Emission Tomography/Computed
3 Tomography for cancer screening in patients with unprovoked venous thromboembolism: results from
4 an individual patient data meta-analysis.

5

6 **Running title:** FDG PET/CT performance for occult cancer screening

7

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11

12

1 **ABSTRACT**

2 **Introduction**

3 Venous thromboembolism (VTE) may be the first manifestation of cancer. We aimed at evaluating the
4 performance of 18F-Fluorodesoxyglucose Positron-Emission Tomography/Computed Tomography
5 (FDG PET/CT) for occult cancer screening in patients with unprovoked VTE.

6

7 **Methods**

8 This was a pre-specified analysis of a systematic review and individual patient data meta-analysis
9 including prospective studies assessing cancer screening in patients with unprovoked VTE.
10 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FDG
11 PET/CT were calculated based on cancer diagnosis during a 1-year follow-up period.

12

13 **Results**

14 Four studies were identified as using FDG PET/CT as part of their extensive screening strategy. Out of
15 the 332 patients who underwent FDG PET/CT, the scan was interpreted as positive in 67 (20.2%), as
16 equivocal in 27 (8.1%), and as negative in 238 (71.7%). Seventeen (5.1%) patients were diagnosed
17 with cancer at inclusion or during the 12-month follow up period. All cancers were diagnosed at initial
18 screening. Pooled sensitivity, specificity, NPV, and PPV were 87.3% (95% CI, 55.3 to 97.4), 70.2%
19 (95% CI, 48.2 to 85.6), 98.9% (95% CI, 94.3 to 99.7), and 17.9% (95% CI, 8.5 to 33.6), respectively.

20

21 **Conclusion**

22 FDG PET/CT appears to have satisfactory accuracy indices for cancer diagnosis in patients with
23 unprovoked VTE. In particular, it exhibits a very high negative predictive value and could be used to
24 rule out the presence of an underlying occult malignancy in this setting.

25

1 **KEYWORDS**

2 Venous thromboembolism;
3 Neoplasms;
4 Screening;
5 Positron-Emission Tomography;
6 Fluorodeoxyglucose F18;

7

8 **ABBREVIATIONS**

- 9 - CT: Computed tomography
10 - DVT: Deep vein thrombosis
11 - FDG PET/CT: ¹⁸F-Fluorodeoxyglucose positron-emission tomography/computed tomography
12 - IPDMA: Individual participant data meta-analysis
13 - PE: Pulmonary embolism
14 - VTE: Venous thromboembolism

15

16 **HIGHLIGHTS**

- 17 - Venous thromboembolism can occur as the first manifestation of an occult malignancy.
18 - FDG PET/CT appears to have satisfactory accuracy indices in this setting.
19 - Occult cancer screening using FDG PET/CT seems to have a high Negative Predictive Value.
20 - A negative FDG PET/CT should be reassuring for patients and clinicians in this setting.

21

1 INTRODUCTION

2 Because acute venous thromboembolism (VTE) may be the first manifestation of an occult
3 malignancy, many efforts have been made to determine whether VTE patients benefit from cancer
4 screening, with the hope of being able to detect cancer earlier and consequently improve prognosis (1-
5 6). As all cancer types at various locations may be diagnosed in VTE patients, an extensive screening
6 may be required.

7 Extensive screening, however, remains controversial for several reasons. A recent individual
8 participant data meta-analysis (IPDMA) showed that extensive screening is able to double the
9 proportion of cancers diagnosed at the time of an acute VTE as compared with limited screening, but
10 that there was no significant difference after 1 year of follow-up (7). Several studies have used a
11 combination of multiple invasive and expensive tests (e.g. abdominal and pelvic imaging, upper and
12 lower gastrointestinal endoscopies, sputum cytology, tumor markers, mammography and Pap smear in
13 women, and prostate-specific antigen (PSA) and transabdominal prostate ultrasound in men), making
14 such screening strategies difficult to implement (3). A few years ago, a systematic review had
15 identified computed tomography (CT) as being the most promising test to improve the rate of cancer
16 detection in VTE patients (5). However, a large randomized controlled trial showed no benefit of
17 adding a comprehensive CT of the abdomen and pelvis to a limited screening strategy, with no
18 reduction in the rate of cancers that were missed by screening (6).

19 ¹⁸F-Fluorodeoxyglucose (FDG) positron emission tomography combined with computed
20 tomography (PET/CT) is a non-invasive whole-body imaging test that is widely used for diagnosing,
21 staging, and therapeutic monitoring of many cancers (8-10). FDG PET/CT could thus be an ideal test
22 for cancer screening in patients with unprovoked VTE (11-14). A randomized trial failed to show a
23 higher rate of cancer diagnosis at initial screening when adding an FDG PET/CT to limited screening.
24 On the other hand, the risk of subsequent cancer diagnosis during follow-up was significantly lower in
25 patients in the FDG PET/CT group as compared with patients in the limited screening group (11). The
26 trial had limited statistical power, due to the lower than expected cancer incidence rate. Other cohorts
27 of more limited sample size also used FDG PET/CT for screening in VTE patients (12-14).

1 To gain further knowledge on the performance of FDG PET/CT for cancer screening in
2 patients with unprovoked VTE, we sought to analyze all available data on the use of FDG PET/CT as
3 an extensive screening tool in patients included in the aforementioned IPDMA.

4

5

1 **METHODS**

2 *Study population*

3 This was a pre-specified analysis of a recently published individual patient data meta-analysis
4 (IPDMA) that included prospective studies assessing cancer screening in patients with unprovoked
5 VTE (PROSPERO: CRD42016033371). Methods, including literature search, study selection process,
6 and data extraction, have been previously described (15). For this analysis, we only included studies
7 that assessed a whole-body FDG PET/CT for the detection of occult cancer in patients with
8 unprovoked VTE.

9 Three cohort studies and one randomized controlled trial were identified to address the
10 question (11-14). In these studies, adult patients with unprovoked and objectively confirmed deep vein
11 thrombosis (DVT) or pulmonary embolism (PE), in the absence of major risk factors such as recent
12 surgery, immobilization, known cancer, or ongoing pregnancy, were prospectively included. All
13 studies were approved by the institutional review boards of participating centers.

14

15 *Types of interventions*

16 One study enrolled patients before any screening procedure was performed (11). Patients were
17 randomly assigned to a limited screening strategy (i.e medical history taking, physical examination,
18 basic blood tests, chest radiography, and age- and sex-specific tests such as mammography or
19 prostate-specific antigen testing), or an extensive screening strategy consisting of the limited strategy
20 plus an FDG PET/CT (11). The other three studies enrolled patients after negative results on limited
21 screening (12-14). Patients were followed up for 2 years in the four studies for cancer occurrence.

22

23

1 *FDG-PET/CT acquisition*

2 FDG-PET/CT were performed using Gemini GXLi, Philips; Discovery ST, General Electric;
3 Biograph 6 LSO Pico 3D HI-REZ, Siemens Medical; Gemini GXL, Philips and Discovery 690,
4 General Electric (11); Biograph Duo LSO, Siemens Medical (14); Biograph 4 tomograph , Siemens
5 Medical (12); Allegro, Philips (13).

6 Patients fasted for at least 6 hours before PET acquisitions, and blood glucose had to be less
7 than 7 mmol/l (11), 7.8 mmol/l (14), 10 mmol/l (13), and 11.1 mmol/l (12) before injection of 370-555
8 MBq of ¹⁸F-FDG. Intravenous injection was followed by a period of approximately 60 minutes when
9 the patients remained in a quiet room. Computed tomography was performed from mid-forehead to the
10 feet in normal shallow respiration using a low-dose setting. Intravenous iodinated contrast was not
11 administered. Data obtained from the CT-scan (11, 12, 14) or from single acquisition mode using a
12 ¹³⁷Cs point source (13) were used for attenuation correction of PET data and for fusion with
13 attenuation-corrected PET images.

14

15 *FDG-PET/CT interpretation*

16 FDG PET/CT was interpreted as positive for possible malignancy based on the following
17 criteria: foci of non-physiological FDG uptake, not attributable to the acute venous thromboembolism
18 (i.e. areas of vascular thrombosis or lung infarcts were excluded), with no predetermined cut-off
19 maximum standard uptake values. In the MVTEP trial and in Beckers' study, FDG PET/CT could also
20 be classified as equivocal when doubt existed (11, 13).

21

22

1 *Outcome and statistical analysis*

2 The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV),
3 and negative and positive likelihood ratio of FDG PET/CT were calculated. To compute these
4 accuracy indices, patients were considered as having cancer if they were diagnosed with histologically
5 confirmed cancer following the initial screening strategy results, or based on any diagnostic test
6 performed during the first 12 months of follow-up.

7 For the purpose of this analysis, we considered patients with equivocal FDG PET/CT results
8 as positive for possible malignancy. Indeed, in the setting of cancer screening, it appears important not
9 to miss a cancer in patients with dubious images, who should be further explored. In a second analysis,
10 we considered patients with equivocal FDG PET/CT results as negative for possible malignancy.

11 FDG PET/CT was considered true-positive if a cancer was diagnosed during follow-up in a
12 patient with FDG PET/CT interpreted as positive or equivocal for possible malignancy. FDG PET/CT
13 was considered false positive in patients with an FDG PET/CT interpreted as positive or equivocal for
14 possible malignancy but who were not diagnosed with malignant disease during follow-up. FDG
15 PET/CT was considered true-negative in patients with an FDG PET/CT interpreted as negative for
16 malignancy who were not diagnosed with malignancy during follow-up. FDG PET/CT was considered
17 false-negative in patients with an FDG PET/CT interpreted as negative for possible malignancy who
18 were diagnosed with malignant disease during follow-up.

19 Due to the low number of studies included as well as the absence of events in one study, we
20 first considered the four studies as one cohort and present the estimates as proportions. In a second
21 analysis, pooled estimates were obtained in random-effects meta-analysis using the bivariate model of
22 Reitsma and colleagues (16) in which a continuity correction of 0.5 was used for studies with zero
23 events. Statistical analysis was performed using R, version 3.5.1 (www.R-project.org), in particular
24 using the *mada* package version 0.5.8.

25

1 **RESULTS**

2 *Included studies*

3 Four studies from France, The Netherlands, Spain, and United States were identified in the
4 systematic review as using FDG PET/CT as part of their extensive screening strategy. A summary of
5 each individual study (e.g. inclusion period, inclusion criteria, and number of included patients) is
6 available in Table 1.

7

8 *Patient Population*

9 Altogether, 364 patients were included in the four identified studies. Of the 364 patients, 32
10 (8.8%) were excluded from the dataset, because they withdrew consent and refused the use of their
11 data (n=3), did not present for their FDG PET/CT or refused to undergo the examination (n=23), were
12 enrolled more than 90 days after their VTE diagnosis (n=4), or had their index VTE not confirmed
13 (n=2). Characteristics of the remaining 332 patients are summarized in Table 2. Mean age was 63
14 years (77% were older than 50 years), 56% of the patients were men, and 66% had PE with or without
15 DVT.

16

17 *Occult cancer diagnosis*

18 Out of the 332 analyzed patients, 67 FDG PET/CT were interpreted as positive (20.2%), 27
19 were interpreted as equivocal (8.1%), and 238 were interpreted as negative (71.7%). Seventeen (5.1%)
20 patients were diagnosed with cancer at inclusion or during the 12-month follow up period. All occult
21 cancers were detected at initial screening. Location of the 17 diagnosed cancers was as follows:
22 prostate (n=3), pancreas (n=3), lung (n=3), colorectal (n=2), thyroid (n=2), head and neck (n=1),
23 uterus/ovary (n=1), stomach (n=1), and testicle (n=1). After a negative FDG PET/CT, no cancer was
24 diagnosed during the first year of follow-up. The 12-month period prevalence of occult cancer after
25 VTE diagnosis was 5.1% (95% CI, 3.2% to 8.1%) in all analysed patients, and 6.6% (95% CI, 4.1% to
26 10.4%) in patients \geq 50 years.

27

28

1 *Accuracy of FDG PET/CT (positive + equivocal vs. negative FDG PET/CT)*

2 The FDG PET/CT was deemed positive or equivocal for possible malignancy in 94 of 332
3 patients (28.3%). Of these 94 patients, 17 were diagnosed with cancer at 1 year, corresponding to a
4 PPV of 18.1% (pooled PPV, 17.9%; 95% CI, 8.5 to 33.6). None of the 238 patients (71.7%) with a
5 negative FDG PET/CT were diagnosed with cancer during the following year corresponding to an
6 NPV of 100% (pooled NPV, 98.9%; 95% CI, 94.3 to 99.7). All cancers were diagnosed by PET/CT
7 (either positive or equivocal) corresponding to a sensitivity of 100% (pooled sensitivity, 87.3%; 95%
8 CI, 55.3 to 97.4). Specificity was 75.6% (pooled specificity, 70.2%; 95% CI, 48.2 to 85.6). The
9 positive likelihood ratio was 4.1 and the negative likelihood ratio could not be calculated since no
10 patients with a negative FDG PET/CT result were diagnosed with cancer.

11 In patients aged 50 or older (257 patients, 77%), the FDG PET/CT was deemed positive or
12 equivocal for possible malignancy in 79 (30.7%). Of these 79 patients, 17 were diagnosed with cancer
13 at 1 year, corresponding to a PPV of 21.5% (pooled PPV, 20.6%; 95% CI, 10.0 to 37.8). The
14 diagnostic accuracy indices of FDG PET/CT (*positive and equivocal vs. negative FDG PET/CT*) in all
15 patients, and in patients aged 50 or older are shown in Table 3.

16

17 *Accuracy of FDG PET/CT (positive vs. negative + equivocal FDG PET/CT)*

18 The FDG PET/CT was deemed positive for possible malignancy in 67/332 patients (20.2 %),
19 of them 15 were diagnosed with cancer at one year, corresponding to a PPV of 22.4% (pooled PPV,
20 26.3%; 95% CI, 7.0 to 62.9). Two of the 265 patients (0.8%) with a negative or equivocal FDG
21 PET/CT were diagnosed with cancer during the following year corresponding to a NPV of 99.2%
22 (pooled NPV, 98.3%; 95% CI, 95.4 to 99.4). Sensitivity for the 1-year follow-up period was 88.2%
23 (pooled sensitivity, 80.5%; 95% CI, 55.9 to 93.1) and specificity 83.5% (pooled specificity, 84.6%;
24 95% CI, 45.9 to 97.3). The positive likelihood ratio was 5.3 and the negative likelihood ratio was 0.14.

25 In patients aged 50 or older (257 patients, 77%), the FDG PET/CT was deemed positive for
26 possible malignancy in 57 (22.4%). Of these 57 patients, 15 were diagnosed with cancer at 1 year,
27 corresponding to a PPV of 26.3% (pooled PPV, 29.8%; 95% CI, 8.0 to 67.4). The diagnostic accuracy

1 indices of FDG PET/CT (*positive vs. negative and equivocal FDG PET/CT*) in all patients, and in
2 patients aged 50 or older are shown in Table 4.

3

4

1 **DISCUSSION**

2 In this analysis of individual patient data from four prospective management studies, we found
3 FDG PET/CT to have satisfactory accuracy for cancer diagnosis in patients with unprovoked VTE
4 after a 1-year follow-up period: pooled sensitivity, specificity, NPV and PPV were 87.3% (95% CI,
5 55.3 to 97.4), 70.2% (95% CI, 48.2 to 85.6), 98.9% (95% CI, 94.3 to 99.7), and 17.9% (95% CI, 8.5 to
6 33.6), respectively.

7 Identifying occult cancers at the time of VTE diagnosis is an important issue for patients, who
8 want to ensure that they have no underlying cancer that might have triggered the VTE. Our analysis
9 shows that FDG PET/CT has a very high NPV, with no patients being diagnosed with cancer during
10 follow up after a negative screening strategy. On the other hand, one could argue that the observed
11 PPV of 18% is relatively modest, meaning that approximately 80% of patients with a positive or
12 equivocal FDG PET/CT will likely undergo additional testing while they do not have cancer.
13 However, we believe that an eighteen percent risk of cancer is substantial and justifies further
14 investigations. Moreover, in a post-hoc analysis of the MVTEP trial, we did not find any significant
15 increase in unnecessary invasive diagnostic procedure following the extensive screening compared
16 with the more limited screening (17).

17 What are the clinical implications of our findings? There is equipoise around the use of
18 screening for cancer among patients with unprovoked VTE. Following the publication of two recent
19 clinical trials and of an IPDMA (6, 7, 11) on occult cancer screening, the most recent guidance from
20 the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and
21 Haemostasis does not currently recommend to go beyond a limited screening comprising medical
22 history and physical examination, basic laboratory tests, chest X-ray, and age and gender-specific
23 recommended cancer screening in all patients with unprovoked VTE. However, the SSC
24 acknowledges that further clinical trials are required to assess the risks and benefits of an extensive
25 occult cancer screening program in high-risk patients with unprovoked VTE (18). An IPDMA tested
26 several predictors of occult malignancy and reported that the 1-year period prevalence of occult cancer
27 was 7-fold higher in patients aged 50 years or older (6.8%; 95% CI, 5.6 to 8.3) as compared with those
28 younger than 50 years (1.0%; 95% CI, 0.5 to 2.3). Given the high prevalence of occult cancer in

1 patients with unprovoked VTE older than 50 years old (~7%), this group may represent the optimal
2 population for cancer screening (7). Our results indicate that FDG PET/CT is a promising option in
3 this setting. Therefore, we are currently planning a multinational randomized controlled trial of an
4 extensive screening strategy including an FDG PET/CT versus standard of care in 1276 patients older
5 than 50 years with an unprovoked VTE. The primary outcome will be the rate of cancer diagnosis
6 during follow-up among patients with an initial negative screening. We aim to show that the risk of
7 subsequent cancer is significantly lower among those patients who tested negative on FDG PET/CT at
8 the time of their acute thromboembolic event (NCT04304651).

9 Our study has strengths and limitations. This work was conducted by a multidisciplinary team
10 of investigators with expertise in nuclear medicine and thrombosis from different institutions. The
11 study included all currently available data on extensive screening based on FDG PET/CT for occult
12 cancer in patients with unprovoked VTE. All cases of cancer were adjudicated. Among the limitations
13 is that defining standardized criteria (e.g. standardized uptake value (SUV) cut-off) for FDG PET/CT
14 interpretation in the specific setting of occult cancer screening may not be possible, given that patients
15 with unprovoked VTE may develop any cancer type, location or stage. However, all studies used
16 similar interpretation criteria based on assessment of foci of non-physiological FDG uptake. Secondly,
17 our total sample size was relatively small despite the inclusion of all available data. The sensitivity and
18 NPV obtained in the pooled analysis are likely conservative since a 0.5 continuity correction was used
19 for studies with no events. Finally, PET/CT is a fast-evolving technology and data included in our
20 analysis were obtained on devices that are now outdated. Access to imaging and cost are other
21 challenges in an era of scarce health care resources and admittedly, further medico-economic
22 evaluations are necessary to balance screening cost with cost savings potentially resulting from earlier
23 cancer detection.

24

25

1 **CONCLUSION**

2 In summary, FDG PET/CT appears to have satisfactory accuracy for cancer diagnosis in
3 patients with unprovoked VTE. In particular, it exhibits a very high negative predictive value and could
4 be used to rule out the presence of an underlying occult malignancy in this setting. Two ongoing
5 randomized controlled trials will aim to test this hypothesis (NCT04304651, NCT03937583).

6

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2 **Conflict of interest:**

3 Dr. Le Gal holds an Early Researcher Award from the Province of Ontario; a Heart and Stroke
4 Foundation of Canada (HSFC) Ontario Mid-Career Investigator Award; and the Chair on Diagnosis of
5 Venous Thromboembolism from the Department of Medicine at the University of Ottawa. Dr. Salaun
6 reports a grant from the French Health Ministry (PHRC Cancer 2008) during the conduct of the
7 MVTEP study. Authors not named here have disclosed no conflicts of interest.

8
9 **Author's contribution:**

10 Drs Robin, Salaun, van Es had full access to all of the data in the study and take responsibility for the
11 integrity of the data and the accuracy of the data analysis.

12 Study concept and design: Le Gal, Salaun.

13 Acquisition, analysis or interpretation of data: All the authors.

14 Drafting of the manuscript: Le Gal, Salaun, Robin, van Es.

15 Critical revision of the manuscript: All the authors.

16 Statistical analysis: van Es.

17 Study supervision: Le Gal, Salaun.

18

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25

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Authors	Inclusion period	Study design	Inclusion criteria	Number of included patients
Alfonso et al. (14)	2007/01-2010/06	Prospective cohort study.	Patients \geq 50 years old with a first objectively confirmed episode of unprovoked VTE. FDG PET/CT performed if negative limited screening (clinical history, complete physical examination and blood count).	99 patients included (Spain), 98 patients analyzed (one patient was excluded because enrolled more than 90 days after VTE diagnosis)
Beckers et al. (13)	2003/04-2006/01	Cohort study (pilot study).	Patients with a first unprovoked VTE. FDG PET/CT performed if negative limited screening (Chest X-ray, Abdomen ultrasound).	25 patients included (The Netherland), 22 patients analyzed (three patients were excluded because enrolled more than 90 days after VTE diagnosis)
Robin et al. (11)	2009/03-2012/08	Randomized clinical trial.	Patients with a first unprovoked VTE were randomly assigned in a 1:1 ratio to a limited screening strategy (physical examination, usual laboratory tests, and basic radiographs) or a the limited strategy + FDG PET/CT	200 patients allocated to the extensive screening group (France), 172 patients with FDG PET/CT were analyzed.
Rondina et al. (12)	2008/11-2010/01	Prospective cohort study (pilot study).	Patients with a first unprovoked VTE. FDG-PET/CT performed if negative limited screening (comprehensive history, physical examination, usual laboratory tests).	40 patients included (USA)

Table 1: Summary of studies included in this analysis

Characteristics	
Mean age (SD), years	62.8 (16.0)
Older than 50 years	257 (77%)
Sex	
Male	187 (56%)
Female	145 (44%)
Index venous thromboembolism	
Deep vein thrombosis	113 (34%)
Pulmonary embolism ± deep vein thrombosis	219 (66%)
Smoking history, n (%)	
Current or former smoker	85 (26%)
Never smoked	127 (38%)
Missing	120 (6%)
Oral contraceptives, n (%)	12 (4%)
Missing	22 (7%)
Familial history of cancer, n (%)	75 (23%)
Missing	120 (36%)
Previous cancer, n (%)	17 (5%)
Missing	22 (7%)
Previous venous thromboembolism, n (%)	62 (19%)
Unprovoked	24 (7%)
Provoked	15 (5%)
Unknown	23 (7%)
Median time from index VTE to FDG PET/CT (IQR), days	30 (21 – 44)
Occult cancer diagnosis, n (%; 95%CI)	17 (5.1%; 95% CI, 3.2% to 8.1%)
Occult cancer diagnosis in patients ≥ 50 years, n (%; 95%CI)	17 (6.6%; 95% CI, 4.1% to 10.4%)

TABLE 2: General characteristics of the population

Accuracy indices	After a 1-year follow-up period (all patients)	After a 1-year follow-up period (patients ≥ 50 years)
Sensitivity, % (95% CI)	17/17 (100%; pooled sensitivity, 87.3%; 95% CI 55.3 to 97.4)	17/17 (100%; pooled sensitivity, 87.0%; 95% CI 53.8 to 97.5)
Specificity, % (95% CI)	238/315 (75.6%; pooled specificity, 70.2%; 95% CI 48.2 to 85.6)	178/240 (74.2%; pooled specificity, 66.3%; 95% CI 40.4 to 85.1)
Positive predictive value, % (95% CI)	17/94 (18.1%; pooled PPV, 17.9%; 95% CI 8.5 to 33.6)	17/79 (21.5%; pooled PPV, 20.6; 95% CI 10.0 to 37.8)
Negative predictive value, % (95% CI)	238/238 (100%; pooled NPV, 98.9%; 95% CI 94.3 to 99.9)	178/178 (100%; pooled NPV, 98.2; 95% CI 90.9 to 99.7)
Positive likelihood ratio (95% CI)	4.1	3.9
Negative likelihood ratio (95% CI)	-	-

TABLE 3: Accuracy of FDG PET/CT for the diagnosis of cancer after a 1-year follow-up period (positive or equivocal vs. negative FDG PET/CT) in all patients, and in patients aged 50 or older.

Accuracy indices	After a 1-year follow-up period (all patients)	After a 1-year follow-up period (patients \geq 50 years)
Sensitivity, % (95% CI)	15/17 (88.2%, pooled sensitivity, 80.5%; 95% CI 55.9 to 93.1)	15/17 (88.2%, pooled sensitivity, 80.0%; 95% CI 55.6 to 92.8)
Specificity, % (95% CI)	263/315 (83.5%, pooled specificity, 84.6%; 95% CI 45.9 to 97.3)	198/240 (82.5%, pooled specificity, 81.8%; 95% CI 38.6 to 97.0)
Positive predictive value, % (95% CI)	15/67 (22.4%, pooled PPV, 26.3%; 95% CI 7.0 to 62.9)	15/57 (26.3%, pooled PPV, 29.8%; 95% CI 8.0 to 67.4)
Negative predictive value, % (95% CI)	263/265 (99.2%, pooled NPV, 98.3%; 95% CI 95.4 to 99.4)	198/200 (99.0%, pooled NPV, 97.4%; 95% CI 93.2 to 99.1)
Positive likelihood ratio (95% CI)	5.3	5.0
Negative likelihood ratio (95% CI)	0.14	0.14

TABLE 4: Accuracy of FDG PET/CT for the diagnosis of cancer after a 1-year follow-up period (positive vs. negative or equivocal FDG PET/CT) in all patients, and in patients aged 50 or older.