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Does FDG-PET/CT for incidentally found pulmonary lesions lead to a cascade of more incidental findings?

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ABSTRACT

Objective: To determine the frequency, nature, and downstream healthcare costs of new incidental findings that are found on whole-body FDG-PET/CT in patients with a non-FDG-avid pulmonary lesion ≥10 mm that was incidentally found on previous imaging.
Materials and methods: This retrospective study included a consecutive series of patients who underwent whole-body FDG-PET/CT because of an incidentally found pulmonary lesion ≥10 mm.
Results: Seventy patients were included, of whom 23 (32.9 %) had an incidentally found pulmonary lesion that proved to be non-FDG-avid. In 12 of these 23 cases (52.2 %) at least one new incidental finding was discovered on FDG-PET/CT. The total number of new incidental findings was 21, of which 7 turned out to be benign, 1 proved to be malignant (incurable metastasized cancer), and 13 whose nature remained unclear. One patient sustained permanent neurologic impairment of the left leg due to iatrogenic nerve damage during laparotomy for an incidental finding which turned out to be benign. The total costs of all additional investigations due to the detection of new incidental findings amounted to €9903.17, translating to an average of €141.47 per whole-body FDG-PET/CT scan performed for the evaluation of an incidentally found pulmonary lesion.
Conclusion: In many patients in whom whole-body FDG-PET/CT was performed to evaluate an incidentally found pulmonary lesion that turned out to be non-FDG-avid and therefore very likely benign, FDG-PET/CT detected new incidental findings in our preliminary study. Whether the detection of these new incidental findings is cost-effective or not, requires further research with larger sample sizes.

1. Introduction

Pulmonary lesions are common incidental findings on diagnostic tests such as radiography and CT, and their incidence is on the rise due to the increasing use of imaging.[1] FDG-PET/CT is considered an accurate method to diagnose or exclude cancer in pulmonary lesions ≥10 mm.[2,3] FDG-PET/CT is recommended by the Fleischner guidelines to evaluate all incidentally found single lesions >8 mm in adults, as an alternative to follow-up CT at 3 months or tissue sampling.[4]

If patients with an incidentally found pulmonary lesion are referred for FDG-PET/CT, a "whole-body" scan is generally done (i.e. imaging from midthighs to cranial vertex). This provides the opportunity to perform simultaneous whole-body staging in those patients who indeed have a pulmonary malignancy.[5] However, a proportion of patients has a benign pulmonary lesion according to FDG-PET/CT, obviating the need for whole-body staging.

Whole-body FDG-PET/CT in patients with a benign incidentally found pulmonary lesion may lead to more incidental findings. Additional diagnostic tests and treatments for new incidental findings that turn out to be clinically irrelevant unnecessarily increases healthcare costs and may cause patient anxiety and complications.[6] On the other hand, the early detection of a clinically relevant incidental finding (e.g. non-metastatic cancer that would turn into metastatic disease during a person's lifetime if untreated) may provide the opportunity to initiate a more timely treatment and improve outcome.[7–9]

It is currently unknown how often whole-body FDG-PET/CT leads to more incidental findings in patients with a non-FDG-avid pulmonary lesion ≥10 mm that was incidentally found on previous imaging. The nature and downstream healthcare costs of these new incidental findings are also unknown.

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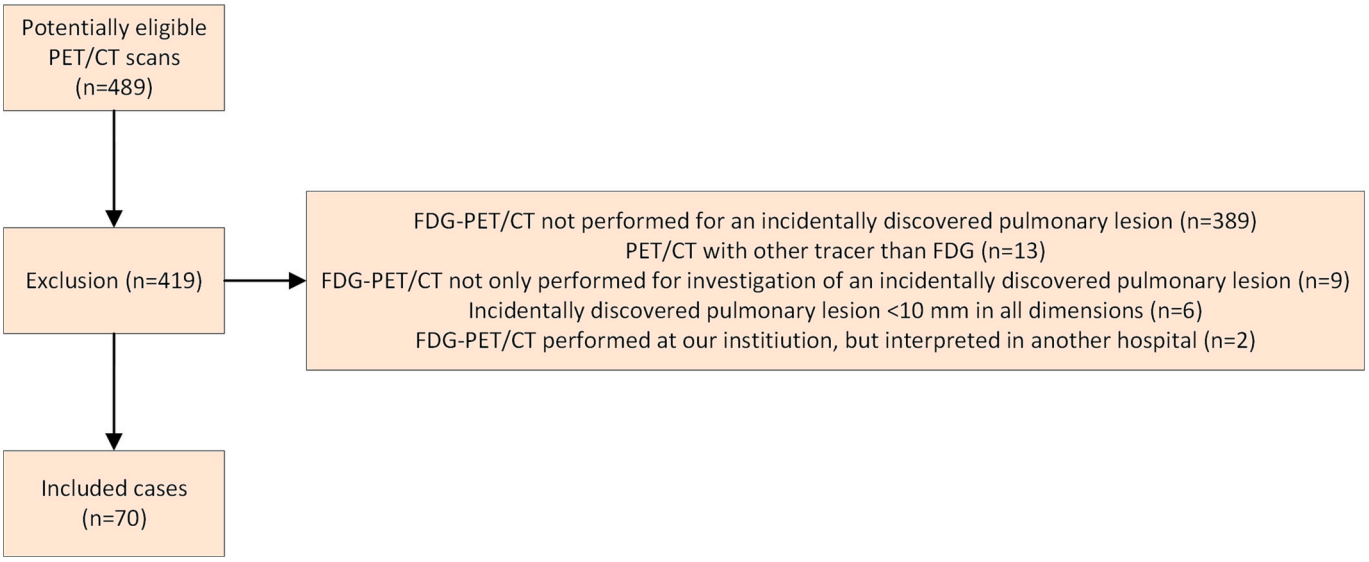

Fig. 1. Patient inclusion flowchart.

Table 1
Characteristics of all included cases.

Gender (%)	Male	43 (61.4 %)
	Female	27 (38.6 %)
	Other	0 (0 %)
Age at time of discovery of incidental pulmonary lesion	41–50 years	6 (8.6 %)
	51–60 years	13 (18.6 %)
	61–70 years	26 (37.1 %)
	71–80 years	21 (30.0 %)
	80+ years	4 (5.7 %)
Imaging modality on which the pulmonary lesion was incidentally found	Chest radiography	10 (14.3 %)
	Chest CT	24 (34.3 %)
	CT part of the lungs[a]	30 (42.9 %)
	MRI part of the lungs[b]	4 (5.7 %)
	Other[c]	1 (1.4 %)
	Unknown	1 (1.4 %)
Size incidentally found pulmonary lesion	Median	19 mm
	Range	10–92 mm
	Interquartile range	11 mm
Appearance incidentally found pulmonary lesion	Solid	65 (92.9 %)
	Ground glass	4 (5.7 %)
	Mixed	1 (1.4 %)
Anatomical position incidentally found pulmonary lesion	Free from pleura	65 (92.9 %)
	(Sub)pleural	5 (7.1 %)
Availability of concomitantly performed diagnostic CT[d] along with low-dose FDG-PET/CT	Yes	43 (61.4 %)
	No	27 (38.6 %)

Abbreviations: SPECT: single photon emission computed tomography.
[a] CT cardio ($n = 14$), CT head neck ($n = 8$), CT abdomen (n = 5), CT neck (n = 2), CT shoulder ($n = 1$).
[b] MRI cervical spine (n = 2), MRI cardio (n = 1), MRI abdomen (n = 1).
[c] SPECT/CT cardio (n = 1).
[d] Contrast-enhanced portal venous phase CT (100–120 kV and automatic tube current modulation) of the chest and abdomen.

The purpose of this study was therefore to determine the frequency, nature, and downstream healthcare costs of new incidental findings that are found on whole-body FDG-PET/CT in patients with a non-FDG-avid pulmonary lesion ≥10 mm that was incidentally found on previous imaging.

2. Materials and methods

2.1. Study design and patients

This retrospective study was approved by the local ethical review board and the need for informed consent was waived. All patients who were referred for whole-body FDG-PET/CT at our tertiary care institution between February 2006 and February 2023 because of an incidentally found pulmonary lesion on any other imaging modality than FDG-PET/CT were potentially eligible for inclusion. All PET/CT scans in the aforementioned period with the Dutch synonym for "incidental finding" in the report were retrieved from the Picture Archiving and Communications System (PACS, IDS7, Sectra AB, Linköping, Sweden). Retrieved PET/CT scans and reports were reviewed by a research fellow (T.E.S.) and excluded if PET/CT was not performed for an incidentally found pulmonary lesion, if PET/CT was performed with another radiotracer than FDG, if PET/CT was performed for both an incidentally found pulmonary lesion and another clinical reason, if the pulmonary lesion was smaller than 10 mm, or if PET/CT was performed at our institution but for interpretation in another hospital.

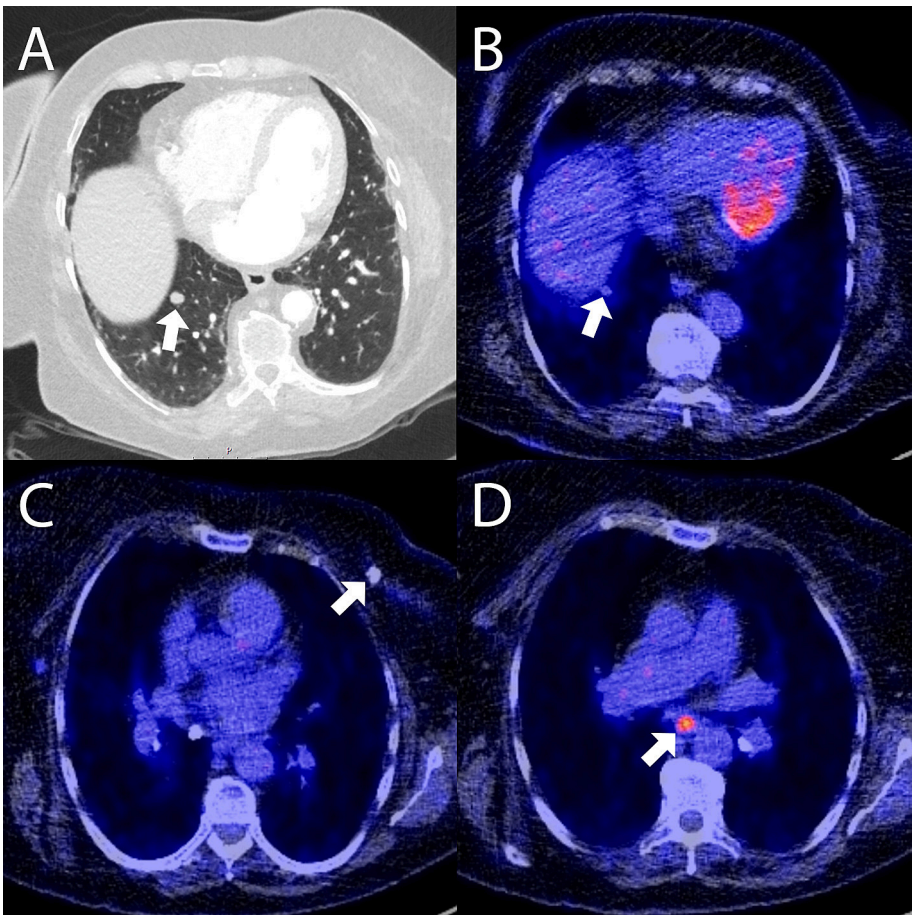

Fig. 2. A 76-year-old female in whom cardiac CT was performed to assess for coronary atherosclerosis prior to pulmonary vein isolation, with an incidentally discovered 10x9x8 mm pulmonary lesion (A, arrow). This pulmonary lesion turned out to be metabolically inactive on FDG-PET/CT (B, arrow). However, FDG-PET/CT showed a calcified lesion in the left breast (C, arrow) and an FDG-avid mediastinal lymph node (D, arrow) as new incidental findings. Mammography of the left breast diagnosed a (benign) BI-RADS lesion. No further investigation was performed for the mediastinal lymph node.

2.2. FDG-PET/CT acquisition

FDG-PET/CT imaging and reconstruction were carried out in accordance with the European Association of Nuclear Medicine guidelines.[10] Patients fasted for a minimum of 6 h before intravenous administration of 3 MBq of FDG per kg of body weight, and blood glucose levels were verified to be <11 mmol/L. PET/CT images were acquired using different systems (Biograph mCT, Biograph Vision, or Biograph Vision Quadra; Siemens Healthineers, Erlangen, Germany), from midthighs to cranial vertex, 60 min after FDG injection. Low-dose CT (100 kV and automatic tube current modulation) was performed for attenuation correction and anatomic mapping. Concomitant contrast-enhanced portal venous phase CT (100–120 kV and automatic tube current modulation) of the chest and abdomen was performed in a subset of patients.

2.3. FDG-PET/CT interpretation and definition of new incidental findings

All FDG-PET/CT scans (including low-dose CT) were interpreted by nuclear medicine physicians or radiologists certified to interpret FDG-PET/CT. Concomitant contrast-enhanced CT scans, if performed, were interpreted by radiologists or nuclear medicine physicians certified to interpret CT. Pulmonary lesions were considered non-FDG-avid (and therefore benign) if their uptake was not higher than that of mediastinal blood pool activity.[2,3] Semi-quantitative analyses were not performed because they do not improve the accuracy of FDG-PET/CT over that obtained with a visual method for pulmonary lesion characterization.[2,3] In all cases with a non-FDG-avid pulmonary lesion, all new incidental findings were noted. Incidental findings were defined as newly detected asymptomatic findings that may require treatment to prevent morbidity or death, and are not related to the finding for which the scan was performed.[11] Clearly benign lesions such as a simple cyst in the liver or kidney were not considered incidental findings. We did not assess for incidental findings in cases in which the incidentally found pulmonary lesion proved to be FDG-avid, because it is virtually impossible to reliably classify other pathology that is visible on FDG-PET/CT as either related to the FDG-avid pulmonary lesion or as a new incidental finding.

2.4. Nature of new incidental findings

An attempt was made to determine the nature of all new incidental findings on FDG-PET/CT in those patients in whom the initially found pulmonary lesion was non-FDG-avid. Histopathology was used as reference standard if this could yield a specific benign or malignant diagnosis. If histopathology was not available or inconclusive, additional diagnostic tests and/or a minimum of one year of follow-up imaging were used to determine the nature of the new incidental finding, when available.

2.5. Downstream healthcare costs

The types and costs of additional imaging, other investigations, and interventions directed towards all new incidental findings on FDG-PET/CT in those patients in whom the initially found pulmonary lesion was

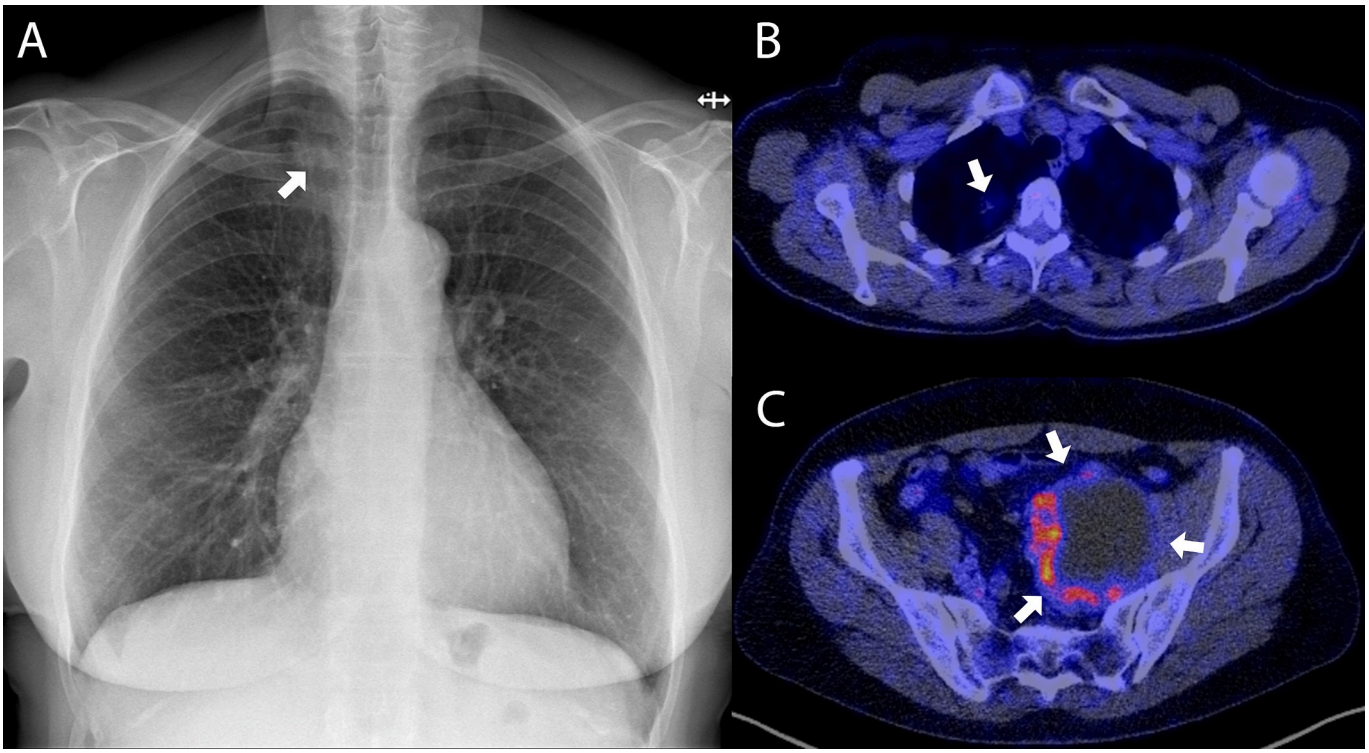

Fig. 3. A 74-year old female in whom a 22x19x15 mm pulmonary lesion was incidentally found on routine chest radiography before aortic valve replacement (A, arrow). This pulmonary lesion turned out to be metabolically inactive on FDG-PET/CT (B, arrow). However, FDG-PET/CT showed a cystic, partly FDG avid tumor in the pelvis (C, arrows) as a new incidental finding. Abdominal CT and MRI were performed, followed by explorative laparotomy with radical excision and unilateral ovariectomy. Pathological examination demonstrated a schwannoma without malignant characteristics. The surgery led to damage of the sciatic nerve (confirmed with electromyography) with permanently decreased strength and sensibility in the left leg.

Table 2
Locations of new incidental findings on FDG-PET/CT in the 23 cases with a non-FDG-avid pulmonary lesion that was incidentally found on previous imaging. The number of new incidental findings visible on FDG-PET only, on CT only (either low-dose of diagnostic CT), and on both FDG-PET and CT, is also indicated.

Location	Only visible on FDG-PET[a] (no.)	Only visible on CT[b] (no.)	Visible on both[c] (no.)	Total (no.)
Lymph node (s)	3	1	1	5
Lungs	0	1	1	2
Uterus and/or ovaries	0	1	1	2
Upper urinary tract	0	0	2	2
Brain	1	0	0	1
Heart	0	1	0	1
Liver	0	0	1	1
Breast	0	0	1	1
Mandible	1	0	0	1
Ribs	0	0	1	1
Sigmoid	1	0	0	1
Soft tissue of the arm	0	0	1	1
Thyroid	0	1	0	1
Tongue	1	0	0	1

[a] FDG uptake above background in a location incompatible with normal physiologic conditions, but without any structural abnormality on CT.
[b] Structural abnormality on CT, but without FDG uptake above background.
[c] FDG uptake above background in a location incompatible with normal physiologic conditions, and with corresponding structural abnormality on CT.

FDG-avid, were recorded. Complications and costs due to these additional investigations and interventions and their costs were also recorded. Other related costs such as those for hospitalization, outpatient visits, sick leave from work and immaterial damage and its consequences were not analyzed. Costs were determined according to the average reimbursement rates as agreed upon by Dutch health insurance providers and health care providers for the year 2023.[12]

2.6. Data analysis

The frequency of patients with a non-FDG-avid pulmonary lesion was calculated as a proportion of all patients with an incidentally found pulmonary lesion who were referred for FDG-PET/CT, along with 95 % confidence intervals (CIs). The frequency of new incidental findings on FDG-PET/CT in this group of patients was also calculated. The average downstream healthcare costs per FDG-PET/CT scan were calculated. All other analyses were descriptive.

3. Results

3.1. Case characteristics

489 potentially eligible cases were found, of which 419 cases were excluded and 70 cases were included (Fig. 1). Our study population included 43 males (61.4 %) and 27 females (38.6 %), most patients were aged 61–70 years (37.1 %), the majority of incidental pulmonary lesions for which FDG-PET/CT was performed were detected on CT (77.2 %), and the pulmonary lesions had a median size of 19 mm. Most FDG-PET/CT scans (61.4 %) were accompanied by a diagnostic CT of the chest and abdomen. Detailed case characteristics are shown in Table 1.

3.2. Non-FDG-avid pulmonary lesions and new incidental findings on FDG-PET/CT

In 23 out of 70 patients (32.9 %; 95 % CI: 23.0 %–44.5 %) the

Table 3
Description of the 8 new incidental findings on FDG-PET/CT for which further diagnostic work-up was performed, description of all additional investigations and costs of these additional investigations, final diagnosis and reference standard.

New incidental finding	Additional investigations and costs	Final diagnosis	Reference standard
Cystic, partly FDG-avid tumor in the pelvis	1 × CT (€213,51) 1 × MRI (€349.17) 1 × Explorative laparotomy (€2326.07) 1 × Electromyography (€181.34) 1× Histopathology (€955.44)	Schwannoma	Histopathology
FDG-avid hilar lymph node	1 × EBUS with biopsy (€756.49) 1× Histopathology (€69.12)	Benign lymph node[b]	Histopathology
Multiple FDG-avid pulmonary lesions	1 × [^{68}Ga]Ga-DOTA-TOC PET/CT (€1181.41) 2 × CT (€404.82)	Benign pulmonary lesions[b]	Additional imaging and follow-up
Multiple non-FDG-avid subpleural lesions	1× follow-up FDG-PET/CT (€1181.41) 1 × CT-guided transthoracic biopsy (€660.01) 1 × CT-guided vertebral biopsy[a] (€660.01) 2× Histopathology (€244.55)	Metastasized mucinous adenocarcinoma	Histopathology
Multiple enlarged non-FDG-avid hilar and axillary lymph nodes	2 × CT (€404.82)	Benign lymph nodes[b]	Follow-up
Non-FDG-avid breast calcification	1 × mammography (€104.57)	Calcified fibroadenoma	Additional imaging
FDG-avid axillary lymph node	1 × ultrasonography (€96.74)	Benign lymph node[b]	Additional imaging
Multiple non-FDG-avid liver lesions, not evidently benign cysts	1 × ultrasonography (€113.69)	Multiple simple liver cysts	Additional imaging

Abbreviations:
EBUS: Endobronchial ultrasound.
[^{68}Ga]Ga-DOTA-TOC: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-*d*-Phe1-Tyr3-octreotide.
[a] Follow-up FDG-PET/CT detected a vertebral lesion.
[b] Benign, but without a specific diagnosis.

incidentally found pulmonary lesion was non-FDG-avid. In 12 out of these 23 cases (52.2 %; 95 % CI: 33.0 %–70.8 %) at least one new incidental finding was discovered on FDG-PET/CT (Figs. 2 and 3). The total number of new incidental findings on FDG-PET/CT was 21, with 1, 2, and 4 new incidental finding(s) in 5, 6, and 1 case(s), respectively. The locations of the new incidental findings on FDG-PET/CT are shown in Table 2. The most frequent new incidental findings concerned lymph nodes ($n = 5$). 8 out of 21 new incidental findings were visible only on FDG-PET, 4 out of 21 were visible only on CT, and 9 out of 21 were visible on both FDG-PET and CT (Table 2). None of these 21 new incidental findings was detectable on previous imaging studies.

3.3. Nature of new incidental findings on FDG-PET/CT

According to the American College of Radiology white papers[13] and the article by Pencharz et al.[14] on the evidence-based management of incidental focal FDG uptake on PET/CT, follow-up of recommendations of 18 of the 21 incidental findings would be justified. Only for 3 out of 21 incidental findings (brain, heart, and soft tissue of the arm) no guidelines exist, to the best of our knowledge. The nature of 8 out of 21 new incidental findings on FDG-PET/CT could be determined because of additional investigations. Seven lesions turned out to be benign and 1 lesion proved to be malignant (incurable metastasized cancer), based on histopathology ($n = 3$), follow-up imaging ($n = 2$), or a single additional imaging test (n = 3), as shown in Table 3. The nature of the other 13 newly found incidental findings could not be determined because no additional investigations were initiated ($n = 12$) or because additional investigations were performed in another hospital and their outcome was unknown (n = 1).

3.4. Downstream healthcare costs

The additional investigations for the above-mentioned 8 new incidental findings on FDG-PET/CT consisted of additional imaging ($n = 11$), image-guided biopsies ($n = 3$), and explorative laparotomy (n = 1), as shown in Table 3. One complication occurred due to these additional investigations, in a 74-year-old female in whom a cystic, partially FDG-avid mass in the pelvis was incidentally discovered. Laparotomy and radical resection revealed a schwannoma, but the surgery also caused damage to the sciatic nerve (confirmed with electromyography) with permanently decreased strength and sensibility in the left leg (Fig. 3). The total costs of all additional investigations due to the detection of new incidental findings on FDG-PET/CT amounted to €9903.17, which translated to an average of €141.47 per whole-body FDG-PET/CT scan performed for the evaluation of an incidentally found pulmonary lesion (Table 3).

4. Discussion

In our study, about one-third of patients who were referred for FDG-PET/CT for the evaluation of a pulmonary lesion that was incidentally found on previous imaging had a metabolically inactive (and therefore highly likely benign) pulmonary lesion. However, approximately half of these cases were confronted with at least one new incidental finding on whole-body FDG-PET/CT. The phenomenon in which the diagnostic work-up of an incidental finding leads to a cascade of more incidental findings and further investigations is also referred to as "SPEW" (Scans Propagating Exponential Workload).[8] In our series, only a minority of these new incidental findings was subjected to additional investigations. Most of these new incidental findings for which further diagnostic work-up was done proved to be benign, except for one case with incurable metastasized cancer. Therefore, the detection of new incidental findings on whole-body FDG-PET/CT did not improve patient outcome in our study. In fact, one patient suffered from permanent iatrogenic nerve damage during laparotomy for a new incidental finding that turned out to be benign. Furthermore, the additional investigations for new incidental findings increased healthcare spending, at an average of €141.47 per whole-body FDG-PET/CT scan performed for the evaluation of an incidentally found pulmonary lesion.

Our results are still too preliminary to draw any definitive conclusions. However, if future research with larger sample sizes (similar to screening studies in breast cancer with mammography and low-dose CT in lung cancer) can show that it is not cost-effective to evaluate the remainder of the body in patients with a benign pulmonary lesion according to FDG-PET/CT, this practice should be reconsidered and also addressed in guidelines such as those of the Fleischner society. A potential solution may be the implementation of limited field of view (FOV) FDG-PET/CT. A limited FOV low-dose FDG-PET/CT scan at the

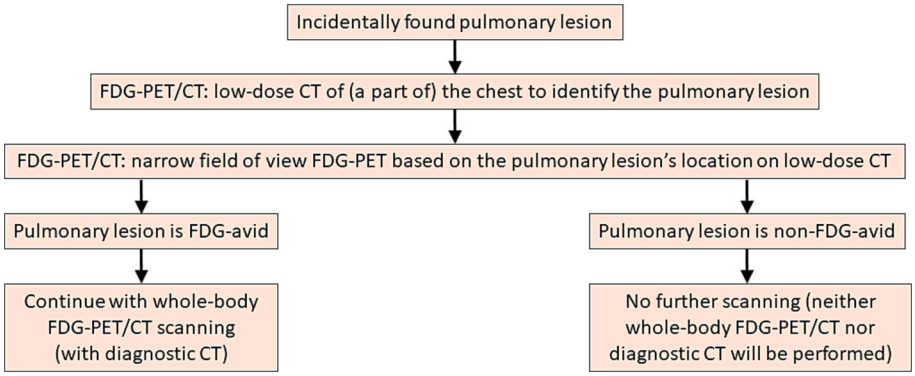

Fig. 4. Flowchart showing the theoretical approach of limited field of view FDG-PET/CT in patients with an incidentally found pulmonary lesion.

level of the pulmonary lesion may first be performed, after which the attending nuclear medicine physician or radiologist will determine if the pulmonary lesion is FDG-avid. If FDG-avid, subsequent whole-body FDG-PET/CT scanning (along with diagnostic CT) may be performed. If non-FDG-avid, no further scanning is done. A low-dose CT scan of (a part of) the chest may first be performed to identify the pulmonary lesion of interest. A narrow FOV FDG-PET scan (i.e. a very small FOV in the *z*-direction) may then be planned based on the pulmonary lesion's location on low-dose CT. The FOV of the FDG-PET scan at the level of the chest may be extended if there are multiple pulmonary lesions. If a pulmonary lesion is FDG-avid, subsequent whole-body FDG-PET/CT scanning (along with diagnostic CT) may be performed. If non-FDG-avid, no further scanning is done (i.e. neither whole-body FDG-PET/CT nor diagnostic CT will be performed) (Fig. 4). This approach may prevent low-value care due to the unrequested detection of new incidental findings. It also avoids unnecessary exposure of patients to ionizing radiation and contrast agents that are required for diagnostic CT. However, it should be noted that this theoretical approach would entail a workflow change for the attending nuclear medicine physician or radiologist since they will have to promptly assess the limited FOV scan, and it also requires a fast PET reconstruction because the patient is waiting in the scanner. The cost-effectiveness of such a practice change needs to be determined by future studies, which should also take into account the increasing workload of nuclear medicine physician and radiologists who would be burdened with an additional task in this setting. Alternatively, artificial intelligence techniques may potentially be used in the future for scanning and the automatic detection and characterization of incidentally found pulmonary lesions on FDG-PET/CT, and even obviate the need for any visual assessment by humans.[15] It should be noted that, conventional image reconstruction techniques that are used in clinical practice are relatively slow. However, new scanners with very fast time of flight are able to reconstruct images in very short time. If further acceleration of the reconstruction is needed one could increase the number of subsets (e.g. 20), make use of less iterations (e.g. 2) and a reconstruction at larger voxel size could be achieved with a 2-min scan and a 30-s reconstruction, sufficiently fast to assess the FDG uptake of a pulmonary lesion $\geq$10 mm while the patient remains in the scanner. One may also decide to scan an even smaller FOV, because this decreases the chance of detecting new incidental findings. Furthermore, with new deep learning techniques, the PET reconstruction speed may be further accelerated.[16]

The prevalence of incidental findings on FDG-PET/CT has been reported by several previous studies in other patient populations. In a study in 670 cancer patients, 11 % had an incidental finding on FDG-PET/CT.[17] In another study in 259 patients with psoriasis who underwent FDG-PET/CT, 12 % had an incidental finding.[18] In yet another study that analyzed 505 FDG-PET/CT scans performed because of proven or suspected vascular graft or endograft infections in 162 patients, 69 % of patients had at least one incidental finding.[19] Differences in the prevalence of incidental findings on FDG-PET/CT are likely related to the specific population characteristics, including the known positive correlation between advancing age and the presence of incidental findings.[18,19] In the present study in which the subjects were of relatively advanced age, 52.2 % had at least one new incidental finding on FDG-PET/CT. This information may be helpful to inform patients with an incidentally found pulmonary lesion beforehand about what can be expected from a whole-body FDG-PET/CT scan in terms of incidental findings. Several previous studies also calculated the downstream healthcare costs related to the investigation of incidental findings on FDG-PET/CT.[17,20] Although it is challenging to compare previously published downstream healthcare costs due to factors such as different reimbursement rates, currencies, and inflation, both previous studies and the present study showed that they cannot be ignored by healthcare policymakers.[17,20]

The present study had some limitations. First, the sample size was relatively small and our results should be regarded as hypothesis generating and as input for meta-analyses on this topic, rather than practice changing. Second, we included patients in whom clinicians decided to perform FDG-PET/CT for the evaluation of a pulmonary lesion, rather than follow-up CT which can also be performed for single lesions >8 mm according to the Fleischner guidelines.[4] The exact reasons why FDG-PET/CT was performed instead of follow-up CT remain unclear, but they are probably related to the clinician's degree of suspicion of malignancy. Third, this study was limited to pulmonary lesions that were incidentally found on previous imaging, in order to address the problem of SPEW in this setting. Whether or not our results are also applicable to pulmonary lesions that were not incidentally found, needs to be investigated by future studies. Fourth, our findings only apply to pulmonary lesions $\geq$10 mm. However, with newer PET/CT technology it may be possible to evaluate smaller pulmonary lesions, but this also requires further research. Fifth, 12/21 newly found incidental lesions on FDG-PET/CT did not receive any further diagnostic work-up, and the reasons why remain unclear. It can be speculated that the referring physicians deemed these incidental findings to be clinically irrelevant or ignored them because they were not related to the primary clinical purpose of the FDG-PET/CT scan.

In conclusion, in many patients in whom whole-body FDG-PET/CT was performed to evaluate an incidentally found pulmonary lesion that turned out to be non-FDG-avid and therefore very likely benign, FDG-PET/CT detected new incidental findings in our preliminary study. Whether the detection of these new incidental findings is cost-effective or not, requires further research with larger sample sizes.

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Guarantor

The scientific guarantor of this publication is Thomas C. Kwee, MD, PhD.

Informed consent

Written informed consent was waived by the Institutional Review Board.

Ethical approval

Institutional Review Board approval was obtained.

Credit authorship contribution statement

Tim E. Sluijter: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Derya Yakar:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Christian Roest:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Charalampos Tsoumpas:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Thomas C. Kwee:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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