European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:1596–1604
https://doi.org/10.1007/s00259-019-04338-z

ORIGINAL ARTICLE

Independent and incremental value of ventilation/perfusion PET/CT and CT pulmonary angiography for pulmonary embolism diagnosis: results of the PECAN pilot study

Pierre-Yves Le Roux[1,2] · Amir Iravani[1] · Jason Callahan[1] · Kate Burbury[3,4] · Peter Eu[1] · Daniel P. Steinfort[5] · Eddie Lau[1] · Beverly Woon[1] · Pierre-Yves Salaun[2] · Rodney J. Hicks[1,4] · Michael S. Hofman[1,4]

Received: 28 February 2019 / Accepted: 15 April 2019 / Published online: 1 May 2019

Abstract

Purpose This pilot study assessed the independent and incremental value of ^{68}Ga-V/Q PET/CT as compared with CT pulmonary angiography (CTPA) for the management of cancer patients with suspected acute pulmonary embolism (PE).

Methods All 24 cancer patients with suspected acute PE prospectively recruited underwent both ^{68}Ga-V/Q PET/CT and CTPA within 24 h. PET/CT was acquired after inhalation of Galligas prepared using a Technegas generator and administration of ^{68}Ga-macroaggregated albumin. Initially, PET/CT and CTPA scans were read independently with the reader blinded to the results of the other imaging study. CTPA and PET/CT were then coregistered and reviewed by consensus between a radiologist and nuclear medicine physician. The therapeutic management was established by the managing physician based on all available data.

Results The diagnostic conclusion was concordantly negative in 18 patients (75%). Of the six discordant diagnoses on independent reading, combined interpretation of V/Q PET/CTPA enabled a consensus conclusion in two patients, excluding PE in one and confirming PE in the other, similar to the initial diagnostic conclusion of the V/Q PET/CT. Of the remaining four patients, three had a single subsegmental thrombus on CTPA but a negative V/Q PET/CT scan, and two of these did not receive long-term anticoagulation and did not have a venous thromboembolic event during a 3-year follow-up period. The third patient, along with a patient with a positive V/Q PET/CT scan but a negative CTPA scan, presented with acute complications preventing any conclusions with regard to the appropriateness of the V/Q PET/CT results in the management of PE. Overall, V/Q PET had an impact on management in four patients (17%).

Conclusion In this pilot study, we demonstrated the feasibility and potential utility of V/Q PET/CT for the management of patients with suspected PE. V/Q PET/CT may be of particular relevance in patients with equivocal findings or isolated subsegmental findings on CTPA, adding further discriminatory information to allow important decision-making regarding the use or withholding of anticoagulation. Given the other advantages of V/Q PET/CT (reduced acquisition time, low radiation dose), and with the increasing availability of ^{68}Ga generators, PET/CT is a potential replacement for V/Q SPECT/CT imaging.

Keywords Pulmonary embolism · V/Q PET/CT · Gallium-68 · CT pulmonary angiography

✉ Pierre-Yves Le Roux
pierre-yves.leroux@chu-brest.fr

✉ Michael S. Hofman
Michael.hofman@petermac.org

[1] Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Australia

[2] Nuclear Medicine, Brest University Hospital, EA3878 (GETBO) IFR 148, Brest, France

[3] Department of Haematology and Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia

[4] Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia

[5] Respiratory Medicine, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia

Introduction

Pulmonary embolism (PE) is a potentially life-threatening condition and remains a diagnostic and therapeutic challenge [1]. An accurate diagnosis is required in all patients with suspected PE since, while anticoagulant therapy is effective, it is also expensive and is associated with the risk of bleeding [2]. Since venous thromboembolism (VTE) occurs in up to 20% of cancer patients and is both a predictor of poor survival and a significant cause of death [3, 4], robust diagnostic paradigms are vital in this population. This is particularly important since these patients have an incidence of major bleeding ranging from 6.5% to 18% [5, 6].

Computed tomography pulmonary angiography (CTPA) and ventilation-perfusion (V/Q) lung scan are the two noninvasive procedures validated for the diagnosis of PE. CTPA enables direct visualization of clot, and V/Q scintigraphy demonstrates the functional consequences of PE. In cancer patients, the interpretation of both techniques can be confounded, to variable degrees, by the presence of coexistent lung conditions. These can include pleural effusions, infection, metastases, extrinsic compression of pulmonary vessels, parenchymal lung disease and the effects of prior radiotherapy or surgical intervention.

CTPA has become the initial imaging modality for suspected PE in most institutions for a variety of reasons including assessment of other differential diagnoses, a reported lower rate of nondiagnostic scans and 24-h availability. However, CTPA has some limitations, particularly related to the use of intravenous contrast agent (e.g. anaphylaxis, renal failure, thyroid dysfunction). Nondiagnostic results can occur because of technical failure in up to 10% of patients. A major current concern is that CTPA may lead to overdiagnosis and overtreatment of PE [7–10], especially given a trend towards prolonged duration of anticoagulation [11]. This has significant implications in cancer patients given the incidence and consequences of bleeding in this population.

V/Q lung scintigraphy is also a widely validated procedure for the diagnosis of PE. A normal scan essentially excludes the diagnosis of PE (1% VTE rate on follow-up) [7, 12]. The most important limitation of planar V/Q scan is the higher proportion of nondiagnostic tests [13], although the introduction of single photon emission computed tomography (SPECT) [14–16], and more recently SPECT/CT [17], has been reported to improve the diagnostic performance of V/Q imaging, allow binary reporting and reduce the proportion of non diagnostic scans [17, 18].

In recent years, nuclear medicine and molecular imaging have undergone a technological revolution with the development of new radioisotopes for positron emission tomography (PET). The technical advantages of PET over conventional single-photon techniques include higher sensitivity, spatial and temporal resolution, speed of acquisition and quantitative capability [19–21]. The transition from SPECT to PET imaging have already rendered some SPECT applications obsolete, e.g. for imaging somatostatin receptor expression on neuroendocrine tumours [22]. Similarly, it is now possible to perform V/Q imaging with PET technology using the same carrier molecule as conventional V/Q scans substituting ^{99m}Tc with ^{68}Ga [23, 24]. Ventilation imaging can be performed with a ^{68}Ga-labelled equivalent of Technegas. Perfusion imaging can be acquired after injection ^{68}Ga-macroaggregated albumin (^{68}Ga-MAA). Similar physiological processes are therefore evaluated, but V/Q PET/CT is inherently a superior technology for image acquisition.

Previous studies from our group have yielded promising results in various clinical conditions. These have included assessment of regional lung function [25, 26], radiotherapy planning [27–29], presurgical evaluation of patients undergoing bronchoscopic lung volume reduction surgery [30], and assessment of pulmonary reserve prior to pulmonary resection surgery [31]. Similarly, V/Q PET/CT imaging offers an opportunity to improve the accuracy of V/Q imaging in patients with suspected PE, while decreasing the acquisition time and maintaining the advantages of V/Q imaging over CTPA. This includes a low radiation dose and no contraindications or acute side effects related to the injection of iodinated contrast agents. To our knowledge, no study has so far assessed the performance of V/Q PET/CT imaging for PE diagnosis as compared with CTPA. Furthermore, no study has combined the two modalities in a single test and has analysed the incremental value of the coregistration for PE diagnosis.

The aim of this pilot study was to assess, in a prospective design, the independent and incremental value of V/Q PET/CT as compared with CTPA for the management of cancer patients with suspected acute PE.

Materials and methods

Study population and enrolment

The eligible study population consisted of patients aged 18 years or older with a diagnosis of malignancy who were referred for CTPA or V/Q scan for suspected acute PE at the Peter MacCallum Cancer Center, Melbourne, Australia, between October 2014 and September 2017. Exclusion criteria were contraindication to the administration of contrast agent, inability to tolerate a supine position, inability to perform CTPA and V/Q PET/CT during the 24 h following the suspicion of PE, deep vein thrombosis (DVT) or PE diagnosed within the previous 3 months, use of therapeutic doses of parenteral anticoagulants for more than 48 h, pregnancy and breastfeeding. The protocol was approved by the Ethics Committee of our institution (14/117) and was sponsored by the Peter MacCallum Cancer Centre. The study was registered

with the Australian New Zealand Clinical Trial Registry (ACTRN12614001170617). Written informed consent was obtained from all patients.

Image acquisition

All patients underwent both ^{68}Ga V/Q PET/CT and CTPA within 24 h following referral for suspected PE. The V/Q PET/CT scan was acquired on a Discovery 690 PET/CT scanner (GE Healthcare, WI, USA) using a procedure that we have previously described [32]. Ventilation images were acquired after inhalation of Galligas prepared using a Technegas generator (Cyclopharm, Sydney, Australia). Approximately 200 MBq of ^{68}Ga was added to the carbon crucible. The patients were placed in a supine position and inhaled Galligas using the standard ventilation technique. Ventilation images were then acquired over two bed positions. Each bed position was acquired for 5 min. Without the patient moving, approximately 50 MBq of ^{68}Ga-MAA was then injected [23]. Perfusion PET images were acquired with two bed positions. Each bed position was acquired for 3 min. CTPA images were acquired on a Siemens SOMATOM Definition AS+ (Siemens Healthcare, Erlangen, Germany) from 2014 until June 2016 and a Siemens SOMATOM Force (Siemens Healthcare, Erlangen, Germany) from July 2016. Acquisition was performed during the pulmonary arterial enhancement phase following intravenous injection of contrast agent.

Scheduling and clinical management

Initially, CTPA and ^{68}Ga V/Q PET/CT scans were read independently with the reader blinded to the results of the other imaging study. ^{68}Ga V/Q PET/CT images were interpreted by a nuclear medicine physician. Studies were read as positive if there was at least one segmental or two subsegmental mismatched defects without anomaly on CT. These criteria have been widely used and validated for V/Q SPECT interpretation [14, 33, 34]. CTPA scans were read by a radiologist. Scans were interpreted as positive if there was a constant intraluminal filling defect with a configuration consistent with thrombus. No communication between the two physicians occurred before they had provided their final diagnostic conclusions. The CTPA and ^{68}Ga V/Q PET/CT scans were then coregistered using CT–CT registration (MIM Software, OH, USA). Images were reviewed by a radiologist and a nuclear medicine physician in a side-by-side consensus reading of all lesions detected on CTPA and V/Q PET. In the event of a discordant diagnostic conclusion between CTPA and ^{68}Ga V/Q PET/CT, the physician in charge of patient care was contacted to discuss patient management. The final diagnostic conclusion and the therapeutic management were established by the physician in charge of patient care based on clinical symptoms, laboratory test results, CTPA, ^{68}Ga V/Q PET/CT and other imaging procedures performed. The follow-up period to determine if the patients did have VTE was at least 3 months. The impact of ^{68}Ga V/Q PET/CT imaging on patient management was assessed by monitoring the change in anticoagulation therapy in terms of duration or dose of treatment, as compared with management based only on CTPA. This information was obtained from the clinician and/or medical records.

Data analysis and sample size

The study aimed to recruit up to 50 patients, with the sample size being pragmatic based on logistical considerations including PET scanner, radiopharmaceutical availability and departmental funding. After 24 patients had been recruited, the study was ceased as the principal investigator (PYLR) had left the institution resulting in difficulty in resourcing the study; furthermore, it was felt that the aim of the pilot study had been met and would not be enhanced by increasing the number of patients.

Baseline statistics including primary malignancy, respiratory diseases, signs and symptoms, clinical probability of PE using the revised Geneva score [35] are summarized using descriptive statistics. The time between V/Q PET/CT and CTPA was recorded. Patients were divided into two groups, those with concordant and those with discordant V/Q PET/CT and CTPA findings. Patients of the later group were then divided into two groups, those with consensual and discordant V/Q PET/CTPA.

Results

Populations

We recruited 24 patients with a median age of 58 years (range 21–79 years). The general characteristics of the included patients are shown in Table 1. The primary malignancies were lung (five), lymphoma (four), head and neck (three), melanoma (three), leukaemia (two), breast (two), and sarcoma, multiple myeloma, neuroendocrine tumour, mesothelioma and rectum (one each). The clinical probabilities for PE as assessed by the revised Geneva score were low, intermediate and high in 6 patients (25%), 16 patients (67%) and 2 patients (8%), respectively. All included patients underwent both CTPA and V/Q PET/CT scans within 24 h as planned. The median time between the two acquisitions was 1 h 45 min (30 min to 24 h). All patients tolerated V/Q PET/CT and CTPA without complications.

Table 1 Patient characteristics

Characteristic	Value
Age (years)	55 ± 16
Female sex	10 (40)
Malignancy	
Metastatic	16 (67)
Surgery <3 months	5 (21)
Chemotherapy <3 months	16 (67)
Radiotherapy <3 months	11 (46)
Respiratory	
Lung malignancy	11 (46)
Prior lung surgery	4 (17)
Prior chest radiation therapy	9 (38)
Prior venous thromboembolism (PE and/or DVT)	7 (29)
Chronic respiratory insufficiency	3 (13)
Chronic obstructive pulmonary disease	6 (25)
Signs and symptoms	
Shortness of breath	21 (88)
Chest pain	13 (54)
Haemoptysis	2 (8)
Cough	8 (33)
Pretest clinical probability	
Low	6 (25)
Intermediate	16 (67)
High	2 (8)

The values presented are number (%) of patients, except age as mean ± SD

Lung imaging results and management

The diagnostic conclusions of the independent V/Q PET/CT scan interpretations were negative in 22 and positive in 2 patients. The diagnostic conclusions of the CTPA scan interpretations were negative in 20, positive in 3 and equivocal in 1 patient. The diagnostic conclusions were concordant in 18 of the 24 patients (75%; Fig. 1). All these patients had both a negative CTPA scan and a negative V/Q PET/CT scan. During the 3-month follow-up period, none of these patients received anticoagulant therapy or developed a confirmed VTE event. Three patients died as a consequence of advanced cancer.

Six patients (25%) had a discordant diagnostic conclusion (Fig. 1). In two patients, the combined interpretation of coregistered V/Q PET/CTPA images led to consensus conclusions excluding PE in one patient and confirming PE in the other. The first patient had an equivocal CTPA scan and a negative V/Q PET/CT scan (Fig. 2), and was deemed not to have PE and thereafter did not receive anticoagulant therapy or have a VTE event. The second patient, with no documented history of VTE, had a negative CTPA scan but the V/Q PET/CT scan was positive for PE (Fig. 3). After consensus reading, the patient received anticoagulant therapy for a likely subacute/chronic rather than acute PE. A follow-up V/Q PET/CT scan was performed 2 months later and again demonstrated multiple unmatched wedge-shaped perfusion defects, unchanged in size. The patient had chronic shortness of breath associated with pulmonary and pleural metastases and bilateral pleural effusions. After a 2-year follow up, the patient was still on long-term thromboprophylaxis due to her risk profile (hormonal therapy for metastatic breast cancer).

In the remaining four patients with a discordant diagnostic conclusion, consensus was not reached in the combined interpretation of coregistered V/Q PET/CTPA images. Three patients had a negative V/Q PET/CT scan but a positive CTPA scan with one isolated subsegmental thrombus in each patient (Fig. 4). Coregistered V/Q PET/CTPA images confirmed normal perfusion beyond the thrombus and also the presence of iodinated contrast agent beyond the clot, consistent with an isolated non-occlusive subsegmental thrombus. One of these patients who had a low pretest clinical probability of PE and no DVT on lower limb compression ultrasonography was not treated. After a 3-year follow-up period, the patient had not developed any VTE event. The second patient with an intermediate pretest clinical probability and no DVT on lower limb compression ultrasonography was treated with enoxaparin for 3 months. The patient was then reviewed by the haematologist and a decision was made to cease enoxaparin. After a 3-year follow-up period, the patient remained free of VTE events. The final patient, with a history of rectal carcinoma and two episodes of provoked VTE, had suspicion of acute PE recurrence 3 days after abdominal surgery (closure of ileostomy). A V/Q PET/CTPA scan showed an isolated 4 mm non-occlusive subsegmental thrombus along with an anastomotic leak with intraperitoneal bleeding on a contemporaneous CT scan of the abdomen. V/Q PET/CT was negative for PE. The patient was taken back to theatre without thromboprophylaxis for 24 h because of the bleeding risk. Six days later, a further CTPA scan showed a new segmental thrombus. At the time of this report, the patient had been anticoagulated since that time.

One patient had a negative CTPA scan but a positive V/Q PET/CT scan, with one segmental and one subsegmental unmatched defect. This patient was admitted for shortness of breath in the setting of metastatic lung cancer and anaemia. On the coregistered V/Q PET/CTPA image there was no definite filling defect corresponding to the unmatched V/Q PET defects. Given the concern of possible bleeding in the setting of anaemia, anticoagulation was maintained at a preventive dose. The following day, the patient presented with respiratory distress and intraperitoneal bleeding on CT and died the next day.

Overall, V/Q PET correctly excluded PE in 18 patients (75%) and had a further incremental impact on management in four patients (17%), including three patients in whom anticoagulant therapy was avoided or reduced in duration despite equivocal findings or small thrombi on CTPA. In these three

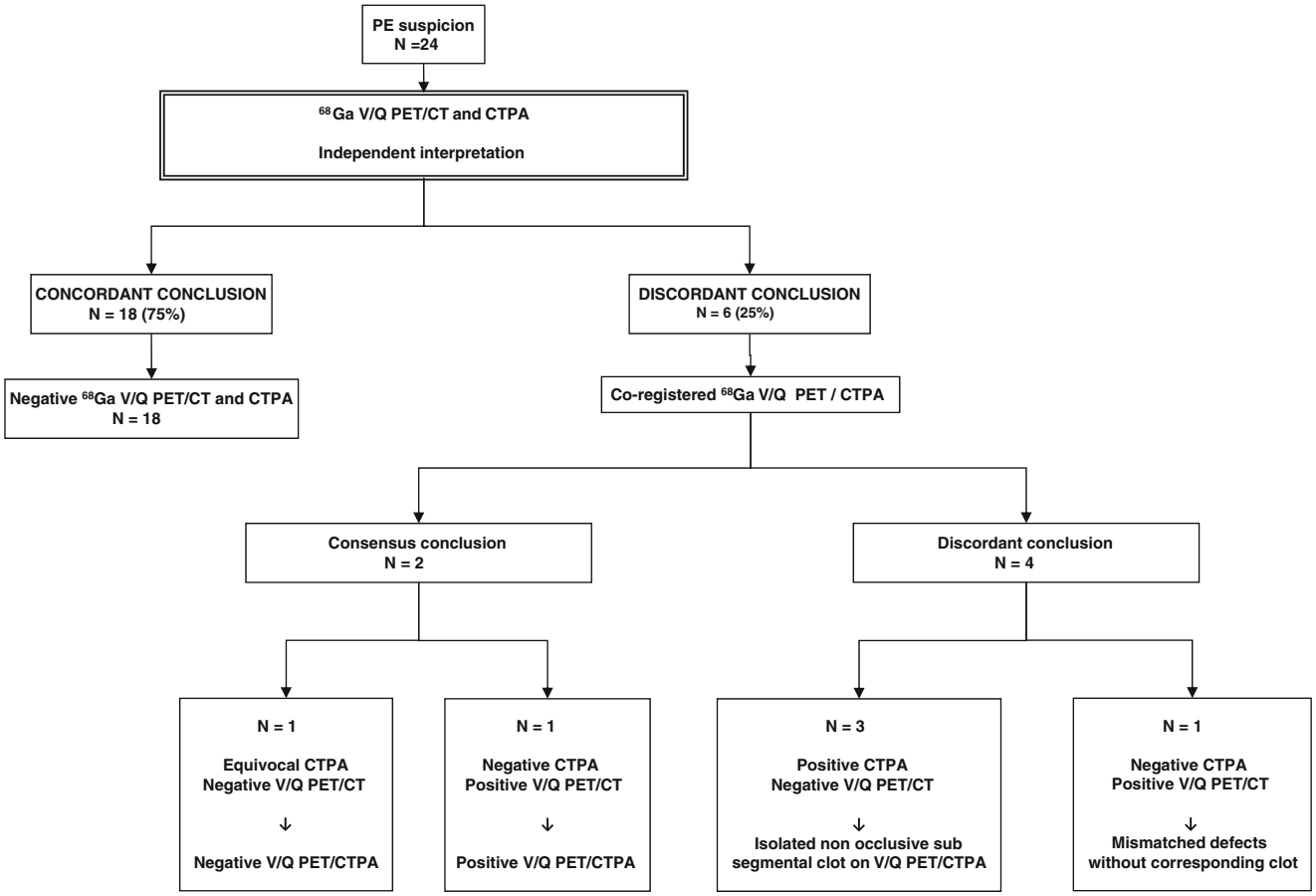

Fig. 1 Study flow chart

patients, long-term follow-up confirmed the appropriateness of withholding long-term anticoagulant therapy with no VTE event recorded. The fourth patient received long-term anticoagulant therapy despite a negative CTPA scan because of multiple mismatched defects on V/Q PET images consistent with chronic PE.

Discussion

In this prospective pilot study, we assessed the potential utility of V/Q PET/CT imaging as compared with CTPA for the management of cancer patients with suspected acute PE. To the best of our knowledge, this is the first study to directly compare V/Q PET/CT imaging and CTPA for PE diagnosis, and to combine the two modalities in a single imaging study. The diagnostic conclusion was concordantly negative in 18 of 24 patients (75%), while V/Q PET/CT would have appropriately directed management in four additional patients if used as a stand-alone investigation. These included two patients in whom a consensus diagnosis could be reached in favour of the V/Q PET/CT findings and two patients in whom the results were clearly discordant but management was eventually directed by the V/Q PET/CT result.

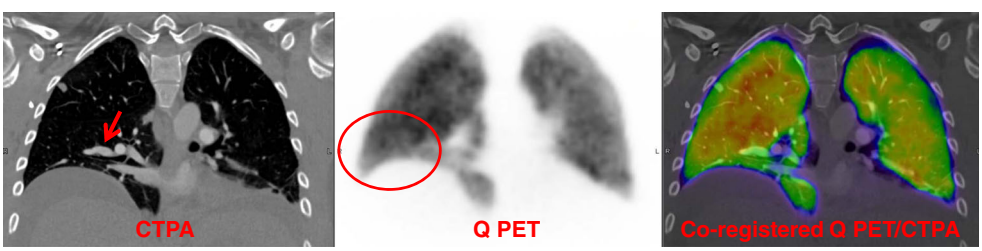

Fig. 2 Patient with a focus of low attenuation within a segmental artery in the middle lobe of the right lung (*arrow*) on CTPA interpreted as suspicious but not diagnostic of a pulmonary embolus. The V/Q PET/CT image is negative. The co-registered V/Q PET/CTPA coregistered image shows normal perfusion distal to the equivocal CT abnormality. In light of this finding, the CT appearance was not considered to represent thrombus and the V/Q PET/CTPA was considered negative for PE

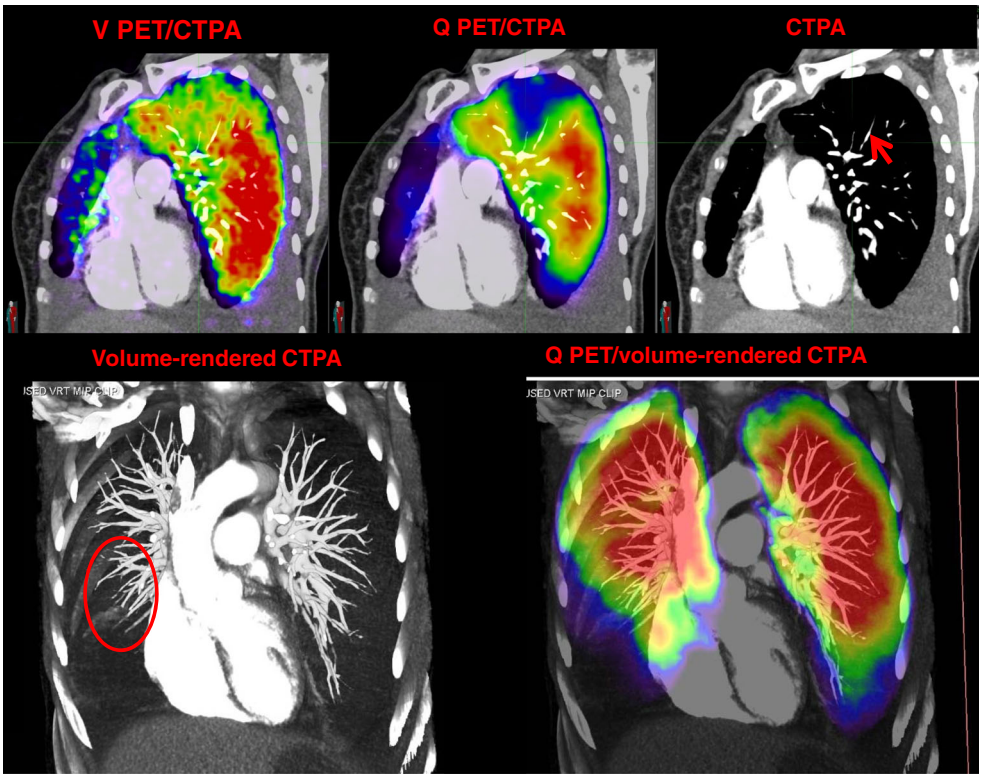

Fig. 3 Patient with a normal CTPA scan and positive V/Q PET/CT scan. PET/CT demonstrated normal ventilation and multiple unmatched, wedge-shaped perfusion defects. The coregistered V/Q PET/CTPA images show tapering of subsegmental pulmonary arteries with distal oligaemia in the regions of segmental unmatched perfusion defects, supporting a diagnosis of PE. The lack of overt filling defects suggests subacute rather than acute PE

Six patients (25%) had discordant findings. This group included three patients in whom CTPA showed a single subsegmental clot but no corresponding perfusion abnormality on PET imaging leading to conservative management. This

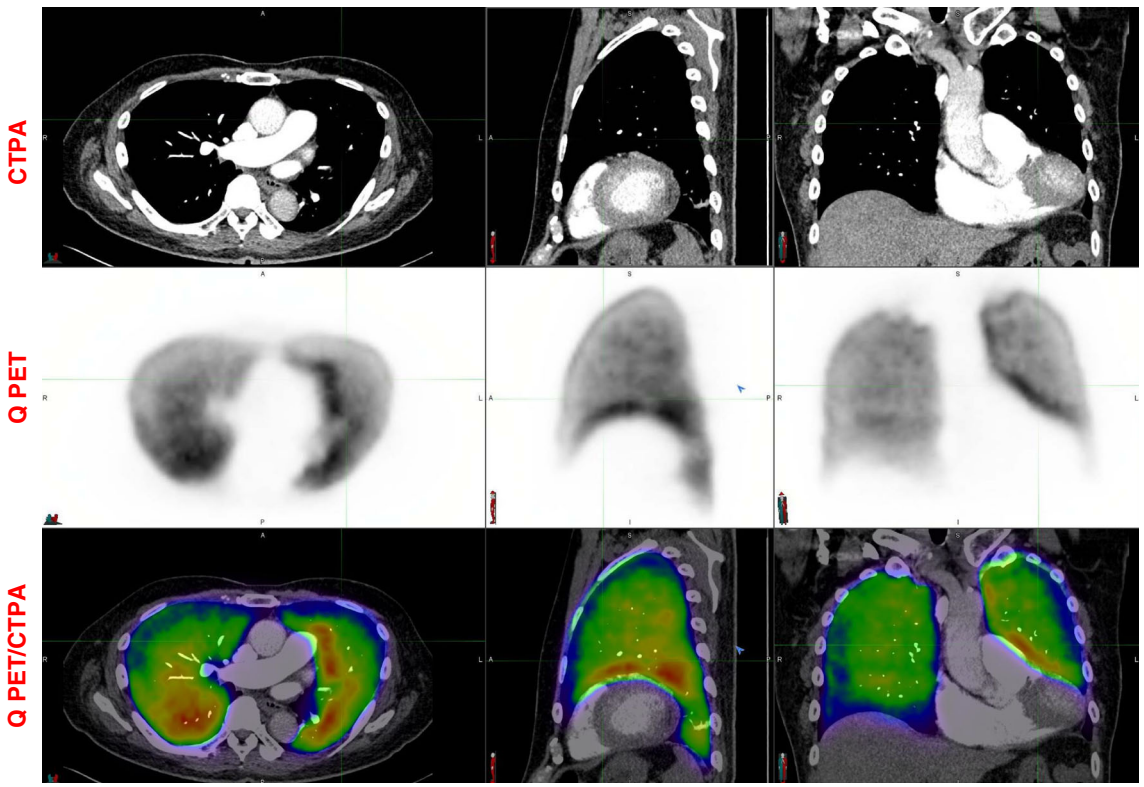

Fig. 4 The CTPA images show one isolated subsegmental thrombus in the lingula. The V/Q PET/CT and coregistered Q PET/CT images are negative for PE with no perfusion abnormality beyond the clot

is, however, a controversial issue since the clinical significance and therapeutic implications (i.e. the need for anticoagulation treatment) of isolated subsegmental PE on CTPA remains uncertain. There is growing evidence that CTPA may lead to overdiagnosis and/or overtreatment of PE. In a randomized clinical trial that directly compared a CTPA-based strategy and a planar V/Q-based strategy, Anderson et al. did not find a significant difference in terms of the safety of diagnostic exclusion of PE despite CTPA detecting PE in 30% more patients than V/Q imaging [7]. This suggests that, in a significant proportion of patients, PE diagnosed using CTPA may not be clinically relevant or may represent false-positive results. Several recent cohort studies strengthen this idea [8, 10, 36]. A recent time trend analysis on the impact of CTPA on the diagnosis of PE in the USA concluded that the introduction of CTPA had been associated with changes consistent with overdiagnosis: rising incidence but minimal change in mortality leading to an apparently lower case fatality rate [9]. Moreover, a low interobserver agreement between radiologists has been reported for the diagnosis of subsegmental PE ($\kappa = 0.38$, 95% CI 0.0–0.89) [37]. As a consequence, in patients with subsegmental PE, clinical guidelines do not provide clear recommendations [11, 38, 39] and management is often made on an individual basis, taking into account the clinical probability and the bleeding risk, as well as the results of correlative imaging tests, especially lower limb ultrasonography. In all three patients in our series with one isolated subsegmental clot, V/Q PET/CT was negative for PE. Many studies have shown the safety of not treating patients with anticoagulant in the context of a normal planar V/Q scan [7, 40, 41] or a negative SPECT V/Q scan [16, 42, 43]. As PET/CT is likely to be a more sensitive technique, an even stronger argument for not treating these patients can be made.

Besides improving the diagnostic performance of V/Q imaging, transitioning from conventional scintigraphy to PET is appealing for several reasons [24]. PET allows a reduction in the acquisition time (approximately 10–15 min with current PET/CT scans and probably less than 5 min with new digital PET/CT scans, as compared with 30–40 min for SPECT imaging). Respiratory-gated acquisition is now possible with PET technology, which may further improve the accuracy of images and enable improved the coregistration with CTPA images. PET remains a simple and noninvasive test, with no contraindications or side effects related to the injection of contrast agent. The radiation dose from V/Q PET/CT is similar to the dose from conventional V/Q SPECT/CT (approximately 2–3 mSv for the PET acquisition plus an additional 1–2 mSv for the low-dose CT component), and lower than the dose from CTPA. In departments that routinely perform V/Q scans with Technegas, and equipped with a ^{68}Ga generator, performing V/Q PET/CT does not require significant expenditure and additional resources. While V/Q PET requires a ^{68}Ga generator, these are becoming increasingly available in nuclear medicine departments owing to growing use for neuroendocrine [22] and prostate cancer imaging [44]. Whereas radiolabelling of MAA with ^{99m}Tc is a well established in nuclear medicine practice, an automated kit or synthesis device for radiolabelling of MAA with ^{68}Ga is not yet routinely available. The lead shielding in the Technegas generator is designed for ^{99m}Tc (140 keV). Additional radiation precautions (increased distance and decreased time) should be used by the technical staff operating the device because of the higher energy of the annihilation photons. Pressure on PET/CT imaging resources may, in some institutions, limit the ability to respond to requests for the diagnosis of suspected acute PE.

A unique characteristic of this study was the inclusion of patients with active malignancy. The integration of both anatomical and functional imaging may be an important method to improve the diagnosis of PE in this challenging population. As previously detailed, in this population there are many causes of perfusion abnormalities that may act as diagnostic confounders increasing the risk of misdiagnosis. In our series, 46% of the patients had malignancy in the lungs, 17% had prior lung surgery and 38% had previously undergone chest radiation therapy. Furthermore, patient management with regard to anticoagulation therapy is challenging given the increased risk and consequences of both VTE [3, 4, 45] and bleeding [5, 6]. An accurate diagnosis is therefore required as both missed diagnosis and overdiagnosis may have major consequences.

Our study had some limitations. Firstly, the study was not designed as a formal study of diagnostic accuracy with an independent reference standard used to assess the diagnostic performance of the new test. Both CTPA and V/Q PET/CT were used for patient management. Accordingly, it was not possible to compute accuracy indices (sensitivity, specificity) as there would have been a major incorporation bias [46]. As a consequence, even though this pilot study showed promising results for the management of patients with suspected PE, firm conclusions cannot be drawn. A formal study of diagnostic accuracy using an independent reference standard is now required. In this study, V/Q PET/CT and CTPA scans were interpreted by senior imaging specialists in a routine clinical setting in order to mimic daily clinical practice. It would be of value to assess and compare interobserver and intraobserver variability in the interpretation of both V/Q PET/CT and CTPA scans in a larger series of patients.

Conclusion

In this pilot study, we demonstrated the feasibility and potential utility of V/Q PET/CT for the management of patients with suspected acute PE. V/Q PET/CT may be of particular relevance in patients with equivocal findings or subsegmental

clots on CTPA, and appears capable of accurately guiding the management of patients in whom CTPA is contraindicated.

Acknowledgments We acknowledge the doctors, radiopharmacists, technologists, nurses and medical physicists at the Peter MacCallum Cancer Team who enabled this research to occur.

Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol was approved by the Ethics Committee of our institution (14/117). The study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12614001170617).

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

References

1. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet. 1960;1(7138):1309–12.
2. Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med. 2010;152(9):578–89. https://doi.org/10.7326/0003-4819-152-9-201005040-00008.
3. Kuderer NM, Ortel TL, Francis CW. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. J Clin Oncol. 2009;27(29):4902–11. https://doi.org/10.1200/JCO.2009.22.4584.
4. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006;166(4):458–64. https://doi.org/10.1001/archinte.166.4.458.
5. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100(10):3484–8. https://doi.org/10.1182/blood-2002-01-0108.
6. Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? Am J Med. 2001;110(7):515–9.
7. Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA. 2007;298(23):2743–53. https://doi.org/10.1001/jama.298.23.2743.
8. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med. 2011;171(9):831–7. https://doi.org/10.1001/archinternmed.2011.178.
9. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. BMJ. 2013;347:f3368. https://doi.org/10.1136/bmj.f3368.
10. Sheh SH, Bellin E, Freeman KD, Haramati LB. Pulmonary embolism diagnosis and mortality with pulmonary CT angiography versus ventilation-perfusion scintigraphy: evidence of overdiagnosis with CT? AJR Am J Roentgenol. 2012;198(6):1340–5. https://doi.org/10.2214/AJR.11.6426.
11. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315–52. https://doi.org/10.1016/j.chest.2015.11.026.
12. Salaun PY, Couturaud F, Le Duc-Pennec A, Lacut K, Le Roux PY, Guillo P, et al. Noninvasive diagnosis of pulmonary embolism. Chest. 2011;139(6):1294–8. https://doi.org/10.1378/chest.10-1209.
13. Wells PS. Integrated strategies for the diagnosis of venous thromboembolism. J Thromb Haemost. 2007;5(Suppl 1):41–50. https://doi.org/10.1111/j.1538-7836.2007.02493.x.
14. Le Roux PY, Robin P, Delluc A, Abgral R, Le Duc-Pennec A, Nowak E, et al. V/Q SPECT interpretation for pulmonary embolism diagnosis: which criteria to use? J Nucl Med. 2013;54(7):1077–81. https://doi.org/10.2967/jnumed.112.113639.
15. Le Duc-Pennec A, Le Roux PY, Cornily JC, Jaffrelot M, Delluc A, de Saint-Martin L, et al. Diagnostic accuracy of single-photon emission tomography ventilation/perfusion lung scan in the diagnosis of pulmonary embolism. Chest. 2012;141(2):381–7. https://doi.org/10.1378/chest.11-0090.
16. Le Roux PY, Palard X, Robin P, Delluc A, Abgral R, Querellou S, et al. Safety of ventilation/perfusion single photon emission computed tomography for pulmonary embolism diagnosis. Eur J Nucl Med Mol Imaging. 2014;41(10):1957–64. https://doi.org/10.1007/s00259-014-2763-1.
17. Le Roux PY, Robin P, Delluc A, Abgral R, Palard X, Tissot V, et al. Additional value of combining low-dose computed tomography to V/Q SPECT on a hybrid SPECT-CT camera for pulmonary embolism diagnosis. Nucl Med Commun. 2015;36(9):922–30. https://doi.org/10.1097/MNM.0000000000000351.
18. Gutte H, Mortensen J, Jensen CV, Johnbeck CB, von der Recke P, Petersen CL, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. J Nucl Med. 2009;50(12):1987–92. https://doi.org/10.2967/jnumed.108.061606.
19. Hicks RJ, Hofman MS. Is there still a role for SPECT-CT in oncology in the PET-CT era? Nat Rev Clin Oncol. 2012;9(12):712–20. https://doi.org/10.1038/nrclinonc.2012.188.
20. Oehme L, Zophel K, Golgor E, Andreeff M, Wunderlich G, Brogsitter C, et al. Quantitative analysis of regional lung ventilation and perfusion PET with (68)Ga-labelled tracers. Nucl Med Commun. 2014;35(5):501–10. https://doi.org/10.1097/MNM.0000000000000084.
21. Le Roux PY, Robin P, Salaun PY. New developments and future challenges of nuclear medicine and molecular imaging for pulmonary embolism. Thromb Res. 2018;163:236–41. https://doi.org/10.1016/j.thromres.2017.06.031.
22. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. Radiographics. 2015;35(2):500–16. https://doi.org/10.1148/rg.352140164.
23. Hofman MS, Beauregard JM, Barber TW, Neels OC, Eu P, Hicks RJ. 68Ga PET/CT ventilation-perfusion imaging for pulmonary embolism: a pilot study with comparison to conventional scintigraphy. J Nucl Med. 2011;52(10):1513–9. https://doi.org/10.2967/jnumed.111.093344.
24. Le Roux PY, Hicks RJ, Siva S, Hofman MS. PET/CT lung ventilation and perfusion scanning using Galligas and gallium-68-MAA. Semin Nucl Med. 2019;49(1):71–81. https://doi.org/10.1053/j.semnuclmed.2018.10.013.

25. Le Roux PY, Siva S, Steinfort DP, Callahan J, Eu P, Irving LB, et al. Correlation of 68Ga ventilation-perfusion PET/CT with pulmonary function test indices for assessing lung function. J Nucl Med. 2015;56(11):1718–23. https://doi.org/10.2967/jnumed.115.162586.
26. Le Roux PY, Siva S, Callahan J, Claudic Y, Bourhis D, Steinfort DP, et al. Automatic delineation of functional lung volumes with (68)Ga-ventilation/perfusion PET/CT. EJNMMI Res. 2017;7(1):82. https://doi.org/10.1186/s13550-017-0332-x.
27. Hardcastle N, Hofman MS, Hicks RJ, Callahan J, Kron T, MacManus MP, et al. Accuracy and utility of deformable image registration in (68)Ga 4D PET/CT assessment of pulmonary perfusion changes during and after lung radiation therapy. Int J Radiat Oncol Biol Phys. 2015;93(1):196–204. https://doi.org/10.1016/j.ijrobp.2015.05.011.
28. Siva S, Thomas R, Callahan J, Hardcastle N, Pham D, Kron T, et al. High-resolution pulmonary ventilation and perfusion PET/CT allows for functionally adapted intensity modulated radiotherapy in lung cancer. Radiother Oncol. 2015;115(2):157–62. https://doi.org/10.1016/j.radonc.2015.04.013.
29. Siva S, Hardcastle N, Kron T, Bressel M, Callahan J, MacManus MP, et al. Ventilation/perfusion positron emission tomography-based assessment of radiation injury to lung. Int J Radiat Oncol Biol Phys. 2015;93(2):408–17. https://doi.org/10.1016/j.ijrobp.2015.06.005.
30. Leong P, Le Roux PY, Callahan J, Siva S, Hofman MS, Steinfort DP. Reduced ventilation-perfusion (V/Q) mismatch following endobronchial valve insertion demonstrated by gallium-68 V/Q photon emission tomography/computed tomography. Respirol Case Rep. 2017;5(5):e00253. https://doi.org/10.1002/rcr2.253.
31. Le Roux PY, Leong TL, Barnett SA, Hicks RJ, Callahan J, Eu P, et al. Gallium-68 perfusion positron emission tomography/computed tomography to assess pulmonary function in lung cancer patients undergoing surgery. Cancer Imaging. 2016;16(1):24. https://doi.org/10.1186/s40644-016-0081-5.
32. Callahan J, Hofman MS, Siva S, Kron T, Schneider ME, Binns D, et al. High-resolution imaging of pulmonary ventilation and perfusion with 68Ga-VQ respiratory gated (4-D) PET/CT. Eur J Nucl Med Mol Imaging. 2014;41(2):343–9. https://doi.org/10.1007/s00259-013-2607-4.
33. Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan M, Jonson B. EANM guidelines for ventilation/perfusion scintigraphy: part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. Eur J Nucl Med Mol Imaging. 2009;36(8):1356–70. https://doi.org/10.1007/s00259-009-1170-5.
34. Le Roux PY, Pelletier-Galarneau M, De Laroche R, Hofman MS, Zuckier LS, Roach P, et al. Pulmonary scintigraphy for the diagnosis of acute pulmonary embolism: a survey of current practices in Australia, Canada, and France. J Nucl Med. 2015;56(8):1212–7. https://doi.org/10.2967/jnumed.115.157743.
35. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006;144(3):165–71.
36. Burge AJ, Freeman KD, Klapper PJ, Haramati LB. Increased diagnosis of pulmonary embolism without a corresponding decline in mortality during the CT era. Clin Radiol. 2008;63(4):381–6. https://doi.org/10.1016/j.crad.2007.10.004.
37. Ghanima W, Nielssen BE, Holmen LO, Witwit A, Al-Ashtari A, Sandset PM. Multidetector computed tomography (MDCT) in the diagnosis of pulmonary embolism: interobserver agreement among radiologists with varied levels of experience. Acta Radiol. 2007;48(2):165–70. https://doi.org/10.1080/02841850601100859.
38. Di Nisio M, Lee AY, Carrier M, Liebman HA, Khorana AA, Subcommittee on Haemostasis and Malignancy. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2015;13(5):880–3. https://doi.org/10.1111/jth.12883.
39. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033–80. https://doi.org/10.1093/eurheartj/ehu283.
40. Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet. 1999;353(9148):190–5. https://doi.org/10.1016/S0140-6736(98)05248-9.
41. Wells PS, Ginsberg JS, Anderson DR, Kearon C, Gent M, Turpie AG, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med. 1998;129(12):997–1005.
42. Leblanc M, Leveillee F, Turcotte E. Prospective evaluation of the negative predictive value of V/Q SPECT using 99mTc-Technegas. Nucl Med Commun. 2007;28(8):667–72. https://doi.org/10.1097/MNM.0b013e32827a8e99.
43. Truffault B, Robin P, Tromeur C, Le Duc Pennec A, Abgral R, Bourhis D, et al. Time trend analysis of pulmonary embolism diagnosis with single-photon emission computed tomography ventilation/perfusion imaging. Nucl Med Commun. 2019. https://doi.org/10.1097/MNM.0000000000000990.
44. Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific membrane antigen PET: clinical utility in prostate cancer, normal patterns, pearls, and pitfalls. Radiographics. 2018;38(1):200–17. https://doi.org/10.1148/rg.2018170108.
45. Sorensen HT, Mellemkjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med. 1998;338(17):1169–73. https://doi.org/10.1056/NEJM199804233381701.
46. Le Gal G, Le Roux PY. How to assess quality of primary research studies in the medical literature? Semin Nucl Med. 2019;49(2):115–20. https://doi.org/10.1053/j.semnuclmed.2018.11.007.