

World Journal of *Radiology*

World J Radiol 2017 July 28; 9(7): 295-320





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WJR covers topics concerning diagnostic radiology, radiation oncology, radiologic physics, neuroradiology, nuclear radiology, pediatric radiology, vascular/interventional radiology, medical imaging achieved by various modalities and related methods analysis. The current columns of *WJR* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (clinicopathological conference), and autobiography.

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World Journal of Radiology is now indexed in PubMed, PubMed Central, and Emerging Sources Citation Index (Web of Science).

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World Journal of Radiology

ISSN
ISSN 1949-8470 (online)

LAUNCH DATE
January 31, 2009

FREQUENCY
Monthly

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PUBLICATION DATE
July 28, 2017

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Interventional radiology treatment for pulmonary embolism

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Author contributions: All authors were involved in the planning the design and conduct of the review paper; each equally revises the manuscript and approve the final version; De Gregorio MA and Kuo WT conducted the initial research.

Conflict-of-interest statement: Miguel A De Gregorio, Jose A Guirola, Celia Lahuerta, Carolina Serrano, Ana L Figueredo and William T Kuo have no conflicts of interest or financial to disclose related to this review.

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Manuscript source: Invited manuscript

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Received: January 19, 2017

Peer-review started: January 19, 2017

First decision: March 27, 2017

Revised: April 29, 2017

Accepted: May 18, 2017

Article in press: May 18, 2017

Published online: July 28, 2017

Abstract

Venous thromboembolism (VTE) is an illness that has a potentially life-threatening condition that affects a large percentage of the global population. VTE with pulmonary embolism (PE) is the third leading cause of death after myocardial infarction and stroke. In the first three months after an acute PE, there is an estimated 15% mortality among submassive PE, and 68% mortality in massive PE. Current guidelines suggest fibrinolytic therapy regarding the clinical severity, however some studies suggest a more aggressive treatment approach. This review will summarize the available endovascular treatments and the different techniques with its indications and outcomes.

Key words: Pulmonary embolism; Massive pulmonary embolism; Venous thromboembolism; Pulmonary embolism treatment; Submassive pulmonary embolism; Catheter directed therapy; Interventional radiology

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Core tip: Venous thromboembolism (VTE) is an illness that is potentially life-threatening condition that affects a large percentage of the global population. VTE is the third leading cause of death related with cardiovascular pathology after myocardial infarction and stroke. This article summarizes the clinical management and emphasizes which interventional treatments that exist and the most effective ones to treat massive and submassive pulmonary embolism.

De Gregorio MA, Guirola JA, Lahuerta C, Serrano C, Figueredo

AL, Kuo WT. Interventional radiology treatment for pulmonary embolism. *World J Radiol* 2017; 9(7): 295-303 Available from: URL: <http://www.wjgnet.com/1949-8470/full/v9/i7/295.htm> DOI: <http://dx.doi.org/10.4329/wjrr.v9.i7.295>

INTRODUCTION

Venous thromboembolism (VTE) is a life-threatening condition that affects a large percentage of the global population; VTE includes the deep vein thrombosis (DVT) and pulmonary embolism (PE). The incidence rate of VTE is 100 cases per 100000 inhabitants in Europe^[1] and 160 per 100000 inhabitants in the United States^[2]. VTE is the third leading cause of death after myocardial infarction and stroke. In the first three months after an acute PE, there is an estimated of 15% mortality among submassive PE, and 68% mortality in massive PE^[3]. Acute PE is also the leading cause of pulmonary hypertension and right ventricular failure^[4].

From the clinical point of view, two different situations need to be considered, prognosis and therapeutic management. For a massive PE there are three different treatments options: (1) systemic thrombolysis; (2) Surgical pulmonary embolectomy; and (3) Endovascular techniques^[5]. Other authors also advocate to implant an inferior vena cava filter (IVCF) in massive PE to prevent further thrombus migration and avoid higher thrombotic load or avoid anticoagulation therapy. According to the clinical guidelines of the American College of Chest Physicians (ACCP) an interventional approach, in an acute massive PE, currently is only considered the treatment of choice when a systemic thrombolysis therapy fails or is contraindicated^[6]; however other authors advocate the use of the following procedures: Catheter directed therapy (CDT), mechanical fragmentation, thrombectomy procedures as a more aggressive therapeutic management that can provide excellent results in a massive PE^[7-10]. Since there are a variety of CDT and thrombectomy methods, more prospective studies are still needed to refine the interventional approach protocol and determine the safest techniques in larger cohorts. This review will outline the different clinical presentation of PE, and will summarize the available endovascular treatments and the different techniques with its indications and outcomes.

TYPES AND DEFINITIONS OF PE

The two main subtypes of PE that are necessary to address are the submassive (intermediate risk) and massive PE (high risk). The most frequent clinical symptoms are dyspnea (82%) and chest pain (49%), but it can also present: Cough (20%), syncope(14%) and Hemoptysis (7%)^[3].

Massive PE is defined as an hemodynamically unstable condition which has clinical presentation with

low blood pressure (systolic pressure < 90 mmHg or a decrease of more than 40 mmHg in baseline systolic pressure) and may develop a cardiac arrest. Other clinical manifestations related to hypotension may be present, such as tissue hypoperfusion and hypoxemia^[11].

Submassive PE (intermediate risk) is defined as a hemodynamically stable condition (normal blood pressure) with a right ventricular dysfunction or elevated cardiac biomarkers which can develop a reduced workload and an increased strain on the heart^[5].

It should not be confused with the radiological definitions of "massive" PE in which the criteria are related to the quantity of thrombus within the pulmonary trunk or the arterial pulmonary branches instead of the clinical presentation of the PE. A "massive" PE, from the radiological point of view, is described as a reduction of lung perfusion in one lung (> 90%) or total occlusion of a main pulmonary artery diagnosed with a pulmonary CT angiography^[12].

Mortality in massive PE patients with hemodynamic shock can reach a 68% in the first hours after diagnosis^[13]. However In submassive PE the mortality is lower compared to a massive PE.

The American College of Chest Physicians in their guidelines differentiates the considered treatment for both situations^[6]. While in the massive PE, thrombolysis (Class II a, Level of Evidence B) is recommended as the first option, in a submassive PE the thrombolysis is controversial. Thrombolysis may be indicated in submassive PE with a poor prognosis (RV dysfunction, severe respiratory failure, myocardial necrosis) and low risk of bleeding (Class II b level of evidence C). In the rest, thrombolysis is not recommended (Class III, level of evidence B).

PATHOPHYSIOLOGY OF MASSIVE PE

The severity of a massive PE is directly related to the amount of thrombus occluding the pulmonary arteries and the underlying cardiopulmonary status of the patient, which causes hemodynamic instability^[14]. A significant obstruction of the pulmonary vascular bed produces hypoxemia and results in the release of potent vasoconstricting substances that further aggravate the systemic hypoxia, with an increase in pulmonary arterial resistance that can cause an elevated right ventricular afterload^[15]. Right ventricular overload produces hypokinesia and ventricular dilatation with tricuspid regurgitation; in which can eventually lead to right ventricular failure. Increased pressure in the right ventricle (RV) may cause alteration in the cardiac wall with ischemia or myocardial infarction due to an increase in the demand for oxygen and a decrease in the supply. In addition, stress on the myocardial wall along with systemic arterial hypotension decreases the perfusion to the coronary arteries, which can also lead to RV ischemia with or without infarction^[16]. All of

Table 1 Predictive factors of severity and 30-d mortality

Predictors of 30-d mortality
Cardiac failure
COPD
Systolic pressure < 100 mmHg
Age over 70 yr
Heart rate > 100 bpm
ECG signs of RV dysfunction
Elevated cardiac biomarkers (Troponins, BNP, H-FABP)
CT findings: RV enlargement
Echocardiography findings:
RV hypokinesis and dilatation
Deviation of the interventricular septum
Tricuspid regurgitation > 2.6 m/s
Loss of inspiratory collapse of the inferior vena cava
Patent foramen ovale

Modified from Pizza *et al*^[16]. COPD: Chronic obstructive pulmonary disease; bpm: Beat per minute; ECG: Electrocardiogram; BNP: Brain-type natriuretic peptide; H-FABP: Heart-type fatty acid-binding protein; RV: Right ventricle; CT: Computed tomography.

these changes may lead to RV failure, diminished left ventricular output and life-threatening hemodynamic shock^[13].

MASSIVE PE DIAGNOSIS

Clinical manifestations play an important role in the differential diagnosis between massive PE and non-massive PE. Hemodynamic instability with suspected PE (blood pressure < 90 mmHg) establishes the diagnosis of massive PE, while to diagnose a submassive PE it is essential to rule out right ventricular dysfunction by echocardiography and/or elevated cardiac biomarkers. Computed tomography pulmonary angiography (CTPA) should report the size of the thrombus and percentage of occlusion of the pulmonary arteries. The amount and size of the thrombus should not be used to differentiate between clinical massive and submassive PE. If the patient has a good pulmonary reserve, a massive embolism (high thrombotic load) does not always have an hemodynamic repercussion. CTPA also provides information on pulmonary vascular perfusion as well as other chest findings such as pleural effusion, pneumonic foci, neoplasia, *etc.* Finally CTPA can also describe RV failure by comparison of the diameter of the RV with the left ventricle (LV) and determine RV dilatation (RV/LV ratio > 1)^[17]. The main echocardiographic signs of submassive PE are RV dilation and septum deviation to the LV^[16,18]. Clinical history and physical examination are the key to establish the prognostic signs of severity. The International Cooperative Pulmonary Embolism Registry (ICOPER) identifies many clinical factors that can predict an increased mortality at 30 d (Table 1)^[3]. Ventilation/perfusion (V/Q) scanning is reserve as a diagnostic tool only in patients in whom CTPA is contraindicated or inconclusive and V/Q scanning should only be performed in patients with normal chest radiograph^[19].

Other supportive diagnostic tools include elevated

d-dimer, cardiac biomarkers, DVT diagnosed with lower limb duplex, and RV dysfunction and elevated pulmonary pressure with echocardiography^[20].

MEDICAL TREATMENT AND SUPPORT IN MASSIVE AND SUBMASSIVE PE

It is important from the outset to establish if the PE has hemodynamic stability, and to choose the appropriate therapeutic guideline. The ACCP^[6] in its guidelines for the treatment and management of pulmonary PE recommends systemic fibrinolytic agent for massive PE with hemodynamic instability and low bleeding risk (Grade 1B). While a patient with a low risk PE it is only recommended anticoagulation therapy. However, the treatment of submassive PE is controversial. For submassive PE, the ACCP currently recommends, in selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet not develop a hypotension and who have a low bleeding risk, they suggest systemically administered fibrinolytic therapy. In patients who have a higher risk of bleeding with systemic fibrinolytic therapy, the physicians with access to CDT are likely to choose this treatment over systemic fibrinolytic therapy^[6].

Massive and submassive PE has an important mortality in the first few hours, therefore urgent diagnosis and therapeutic approach is required^[13]. It has been established that more than 25% of patients diagnosed with massive PE with hemodynamic instability die within the first two weeks^[3,7]. The first therapeutic measures with fluid therapy and vasoactive drugs (dopamine, noradrenaline, *etc.*) should be directed to correct the hypotension and the RV failure. It is important to maintain patent airway with good oxygen supply, if necessary with tracheal intubation and mechanical ventilation, to improve oxygenation and prevent respiratory failure.

Anticoagulation treatment, if there is no contraindication, should be administered immediately. Low-molecular-weight heparin (LMWH) or unfractionated heparin can be used in therapeutic range. ACCP recommends systemic thrombolysis in the case of massive PE with haemodynamic instability, and low bleeding risk. Urokinase (UK) and recombinant tissue plasminogen activator (r-TPA) are used as fibrinolytic substances. For massive PE, standard doses are: UK 4400 IU/kg per hour in 12-24 h, streptokinase 250000 IU bolus and then 100000 U/h for 12-24 h, or 1500000 U over 2 h, and 100 mg r-TPA over 2 h. The UKEP study did not demonstrate significant differences between 12 and 24-h therapeutic regimens in terms of safety and efficacy^[21]. Other studies have used higher doses of UK (3 million IU) and streptokinase (1.5 million IU) in two hours with similar efficacy and safety results (Table 2)^[22,23].

Currently the ACCP guidelines^[6] recommend short treatments of 2 h of fibrinolytic agents for massive PE

Table 2 Fibrinolytic treatments used in massive pulmonary embolism

Fibrinolytic agent	Infusion treatment 12-24 h	Short infusion treatment
Urokinase	4400 IU/kg (bolus/30 min) +	3 million IU/2 h
Streptokinase	4400 IU/kg per hour 12-24 h 250000 IU (bolus/15 min) +	1.5 million IU/2 h
r-tPA	100000 IU/h 12-24 h N/A	100 mg/2 h

N/A: Not applicable.

(Recommendation Grade 2C). In submassive PE, the ACCP^[6] recommends the use of fibrinolytics only in cases of clinical deterioration despite anticoagulation. In this case the doses to be used will be the same as for the massive PE, however some advocate for half-dose of r-TPA to decrease the bleeding risk.

Regarding the route of administration, the systemic effect is recommended in severe PE. However, when the patient has a high risk of bleeding or the systemic therapy hasn't been effective, a lower-dose fibrinolytic therapy can be administered *via* catheter placed within the pulmonary artery or directly in the thrombus; this procedure may be performed with or without thrombectomy and/or clot fragmentation. Regarding massive PE, Kuo *et al.*^[9] in their recent multicenter study, showed that a catheter-directed therapy (CDT) improves pulmonary hypertension and RV function effectively without more complications.

When pharmacological treatment (anticoagulant or thrombolysis) fails or is contraindicated, an IVCf can be implanted to prevent the migration of thrombi to the lung from a previous DVT (Recommendation Grade 1B). There are many types of filters on the market with similar efficacy and safety, although there are few comparative studies^[7]. The development of the retrievable filters has expanded its use since it is possible to recover the IVCf once as filtration is no longer necessary or the risk of embolism has been resolved^[24,25]. In the long term, The IVCf may become a thrombogenic device as and therefore may require long-term anticoagulant treatment to mitigate the risk of filter-related thrombosis^[26]. The FDA in 2010 issued a recommendation advising the recovery of every IVCf as soon as possible, once they had fulfilled their clinical mission^[27]. Only temporary IVCf should be implanted based on the available evidence and routinely removed within 25-54 d according to the guidelines of the USFDA^[28].

ENDOVASCULAR TECHNIQUES FOR THE TREATMENT OF MASSIVE PE

The first objective in a massive PE is to remove the artery obstruction in order to reduce pulmonary hy-

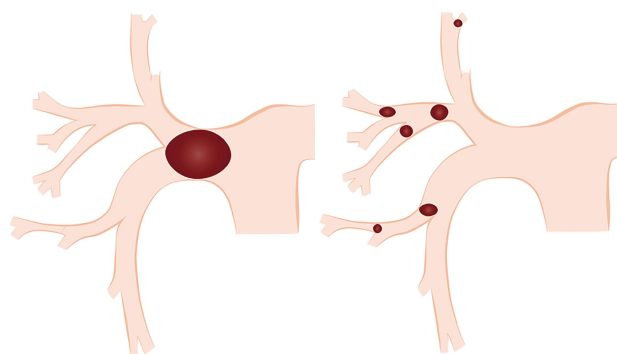


Figure 1 Schematic representation of thrombus fragmentation by a mechanical thrombolysis resulting a distal embolization of smaller thrombi, creating a larger surface area of the clot improving the efficacy of the thrombolytic agent therapy.

pertension and RV failure. Endovascular treatment by different devices of fragmentation or thrombectomy can help reduce the thrombotic load and improve the reperfusion of the vascular system. At the same time, thrombus fragmentation exposes a larger surface area of clot, producing a superior efficacy of the fibrinolytic therapy (Figure 1)^[29].

Systemic fibrinolytic therapy has demonstrated to flow in other continuous patent vessels without acting directly into the clogged vessel. Some studies have shown a more precise action of these drugs when it was administered directly within the thrombus with excellent results^[30]. Several devices have been used to perform a CDT with different levels of efficacy^[12,29,31-41].

The simplest and most widespread technique is the use of pigtail catheters to fragment the thrombus by continuous rotation of the catheter^[42]. The proximal fragmentation of the thrombus leads to distal embolization of smaller thrombi (Figure 1), however some authors have reported pulmonary hypertension with the use of this technique^[43]; other authors or many years had shown the contrary^[8,34,44,45]. Other devices like balloon catheters of different sizes are inflated and deflated successively for the fragmentation of the thrombi. The aspiration of thrombi located in the pulmonary arteries can also be attempted with aspiration of large caliber catheters (8 French or more)^[14]. All of them are used in combination with locally administered fibrinolytic agents through an intra-thrombus catheter. The great advantage of these devices although of dubious effectiveness, is that they are simple to use and available at a low price (Figure 2).

The mechanical devices of thrombectomy or endovascular aspiration can be classified by their mechanism of action in: Rheolytic, rotational, aspiration and fragmentation (Table 3)^[39].

The AngioJet (Boston Scientific Voisins-le-Bretonneux, France) rheolytic system is a thrombectomy designed to aspirate the thrombus using the Venturi-Bernoulli effect. With high-pressure jets and velocity in the distal holes of the system, it creates a zone of low pressure and a suction effect. The system

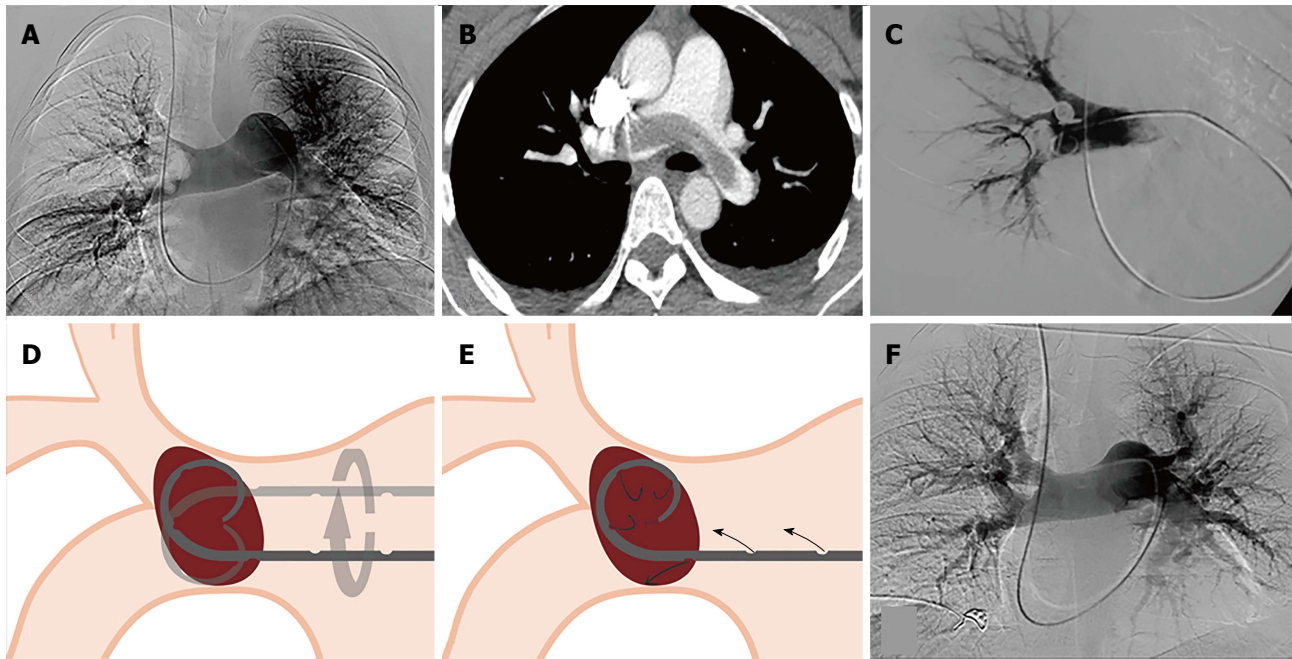


Figure 2 The great advantage of these devices although of dubious effectiveness, is that they are simple to use and available at a low price. A, B: Pulmonary angiography and CT angiography, of a 37-year-old male patient diagnosed with a massive pulmonary embolism; C: Catheter drug therapy, and mechanical thrombolysis; D, E: Schematic representation of mechanical thrombolysis and the infusion of fibrinolytic agents through the pigtail catheter; F: Pulmonary angiography after 24 h of perfusion with 100000.00 UI/h of urokinase, showing no residual occlusion.

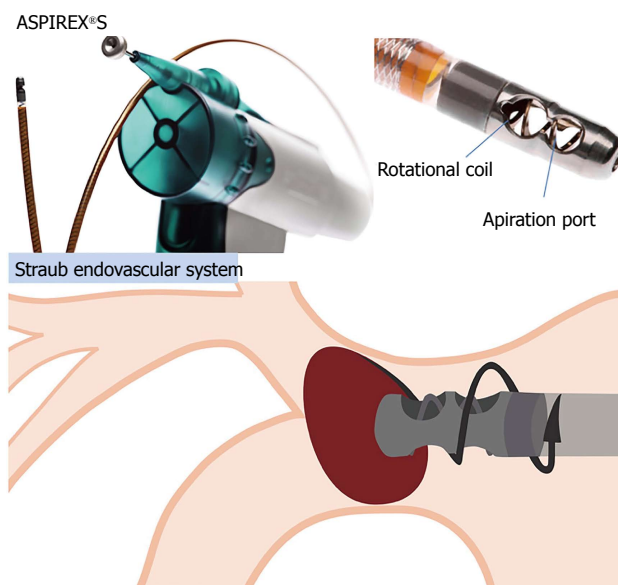


Figure 3 Aspirex®S by Straub Endovascular System. Mechanism of thrombectomy in which has a screw that rotates inside the catheter lumen, and this spiral movement is generated by an active motor that produces a thrombus aspiration.

has been associated with multiple complications including bradycardia, blockage, hemoglobinuria, renal insufficiency, severe hemoptysis, even procedural death^[29], which the FDA advises against its use as the first therapeutic option in PE^[32,46].

The Helix Clot Buster (Medtronic Minneapolis, United States), formerly known as the Amplatz thrombectomy

device, is an FDA-approved device for the endovascular treatment to treat dialysis grafts and AV fistulas, but hasn't been used for thrombectomy in PE. It is a reinforced polyurethane catheter of 7 Fr with lengths from 75 to 120 cm. At its distal end it has a metal impeller that is connected to a motor that rotates more than 140000 rpm, which generates a pressure of 30-35 psi that allows the suction of the thrombus^[33].

Two relatively new devices are Aspirex and Rotarex (Straub, Wangs, Switzerland). The Aspirex catheter acts as the archimedean screw, that rotates inside the catheter lumen; this spiral mechanism is connected to an active motor producing a thrombus aspiration. A catheter system transports the aspirated material to a manifold. Its clinical results are promising but there are no controlled studies that can support it (Figure 3)^[18].

The Indigo mechanical aspiration system (Penumbra Alameda, United States) is an aspiration thrombectomy catheter system. A large caliber (8 Fr) catheter with dirigible and soft tip, allows easy aspiration of the thrombi housed in the pulmonary arteries due to the great suction power of the suction pump. Several studies are being performed to evaluate safety and efficacy of this device (Figure 4).

The EKOSonic system (Ekosonic endovascular System BTG Riverside Way, Watchmoor Park, United Kingdom) is the only device approved by the FDA to treat PE. This system generates an acoustic pulse fibrinolytic agent, which have shown satisfactory results to treat massive and submassive PE. The catheter lodges in its interior a sophisticated catheter with an

Table 3 Fragmentation and aspiration devices used in the endovascular treatment of pulmonary embolism

Endovascular mechanisms of thrombectomy and thrombolysis	Rheolytic	Rotational	Aspiration	Fragmentation	Ultrasound
Devices	Angio Jet Boston Scientific Hydrolyzer Cordis	Rotarex Aspirex Straub Medical	Indigo Penumbra	Fogarty arterial balloon embolectomy catheter Edwards Pig-tail Catheter Cook Medical	Ekos Sonic BTG
Mechanism	Pressurized saline or fibrinolytic agent injection through the catheter in the distal tip, and the remaining fragmented thrombus is aspirated	High-speed rotation coil within the catheter, creating a negative pressure and aspiration of the thrombus	Aspiration pump that provides a high negative pressure of suction with a guide-wire (separator) to create fragmentation of the thrombus	Performing balloon sweeps or manually rotation of the standard Pig-tail to fragment the thrombus	Ultrasound emitting catheter localized within the thrombus to generate an acoustic field creating a more lytic dispersion of the drug infused

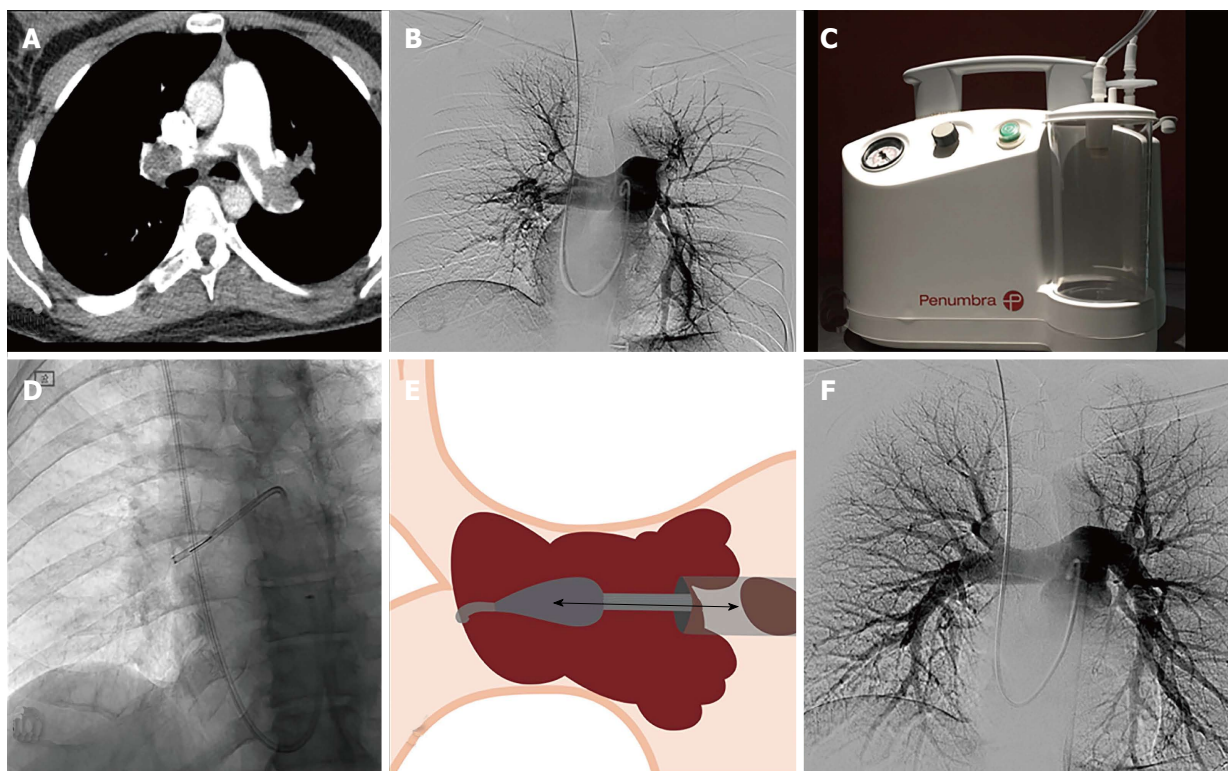
Modified from Barjaktarevic *et al*^[39].

Figure 4 The Indigo mechanical aspiration system (Penumbra Alameda, United States) is an aspiration thrombectomy catheter system. A, B: Pulmonary angiography and CT angiography, of a 37-year-old male patient diagnosed with a massive pulmonary embolism, 24-year-old female patient diagnosed with massive pulmonary embolism; C-F: Treated with CAT8 and SEP8 Indigo System® by PENUMBRA and catheter directed therapy with Pig-tail catheter with an infusion of 1200000.00 UI urokinase administered in 12 h. CT: Computed tomography.

ultrasonic core to effectively target an entire clot. This catheter uses two systems, the ultrasound and the infusion of the fibrinolytic agent. It consists of a 5.4 Fr catheter and has a functional distal tip ranging from 6 to 50 cm in length^[41]. However, acoustic field catheters may accelerate dispersion, clinical advantage vs standard infusion catheters is unclear and unproven (Figure 5).

RESULTS OF ENDOVASCULAR TECHNIQUES FOR THE TREATMENT OF PE

There are few randomized studies comparing both types of fibrinolytic administration (systemic vs CDT)^[47]. The first study on which the ACCP recommendations

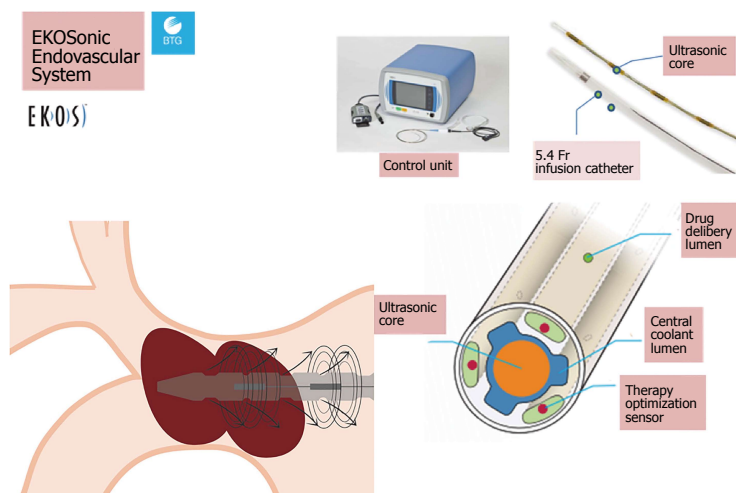


Figure 5 EKOSonic Endovascular System by BTG. Specialized catheter that lodges in its interior a sophisticated mechanism that has an ultrasonic core to effectively target an entire clot producing thrombolysis effect, and also helps the infusion of the fibrinolytic agent work faster and more efficient.

are based, was published by Verstraete *et al.*^[48]. In this study, 34 patients were treated with local or systemic thrombolysis and did not observe significant differences between the two groups in terms of efficacy and complications. It should be noted that in the CDT group, the fibrinolytic agent was administered from the catheter located in a non intra-thrombus approach within the pulmonary artery. The meta-analysis published in 2008 about 35 studies, indicates that 594 patients with PE were treated with CDT and of them 67% received intra-thrombotic thrombolysis during CDT^[31]. Treatment with CDT with or without thrombolysis produced a clinical success of 86.5% (356/535). Similar results have now been obtained by combining local fibrinolytic agent with thrombus fragmentation or aspiration^[8,49]. PERFECT, a multicenter trial with a total of 101 patients were treated with CDT and achieved a clinical success of 85.7% of the patients diagnosed with massive PE and 97.3% in submassive PE^[9]. The use of new devices for fragmentation and/or aspiration of the thrombi can improve these results. The use of ultrasound through a 5.4 Fr catheter with infusion of fibrinolytic leads to rapid lysis of the thrombi located in the pulmonary artery^[40,50,51]. Seattle II, a prospective study of 150 patients diagnosed with massive or submassive PE using EKO-sonic and a low dose of r-TPA through CDT, reduced the RV/LV ratio measured with CT by 25% in 48 h, showed a 30% improvement of the systolic pressure and another 30% in the pulmonary artery obstruction^[41]. These results, however, according to several authors, do not represent significant differences with those obtained by the standard CDT^[49,52].

COMPLICATION

In a randomized study of 1006 patients with submassive PE the risk of intracranial hemorrhage also with systemic thrombolysis is 3%-5% in the various studies^[3,53]. Other complications have been described such as: Bradyarrhythmia, cardiac tamponade, rupture or dissection of the pulmonary arteries, severe

hemoptysis, renal failure and hemoglobinuria. Major complications (major bleeding and death) ranged from 0%-3%^[9,45,49]. A meta-analysis of PE treated with CDT had a 2.4% of major complications and 7.9% of minor complications^[29].

CONCLUSION

CDT is an accepted therapeutic technique for the treatment of acute massive PE and cases of submassive PE with RV dysfunction or failure. However it requires a well-trained medical and interventional team to achieve best results. Further clinical studies are needed to analyze the CDT protocol for massive and submassive PE, define which submassive PE patients should be treated with early CDT, and determine if early CDT treatment can decrease the long-term risk of developing chronic thromboembolic pulmonary hypertension.

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P- Reviewer: Gao BL, Pereira-Vega A, Schoenhagen P, Tawfik MM

S- Editor: Song XX **L- Editor:** A **E- Editor:** Lu YJ



Retrospective Study

Incidental extravascular findings in computed tomographic angiography for planning or monitoring endovascular aortic aneurysm repair: Smoker patients, increased lung cancer prevalence?

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Institutional review board statement: The study was reviewed and approved by the University of Siena Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: None.

Data sharing statement: No additional data are available.

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Manuscript source: Invited manuscript

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Received: December 27, 2016

Peer-review started: December 31, 2016

First decision: March 28, 2017

Revised: April 16, 2017

Accepted: May 30, 2017

Article in press: June 1, 2017

Published online: July 28, 2017

Abstract

AIM

To validate the feasibility of high resolution computed tomography (HRCT) of the lung prior to computed tomography angiography (CTA) in assessing incidental thoracic findings during endovascular aortic aneurysm repair (EVAR) planning or follow-up.

METHODS

We conducted a retrospective study among 181 patients (143 men, mean age 71 years, range 50-94) referred to our centre for CTA EVAR planning or follow-up. HRCT and CTA were performed before or after 1 or 12 mo respectively to EVAR in all patients. All HRCT examinations were reviewed by two radiologists with 15 and 8 years experience in thoracic imaging. The results were compared with histology, bronchoscopy or follow-up HRCT in 12, 8 and 82 nodules respectively.

RESULTS

There were a total of 102 suspected nodules in 92 HRCT examinations, with a mean of 1.79 nodules per patient and an average diameter of 9.2 mm (range 4-56 mm). Eighty-nine out of 181 HRCTs resulted negative for the presence of suspected nodules with a mean smoking history of 10 pack-years (p-y, range 5-18 p-y). Eighty-two out of 102 (76.4%) of the nodules met criteria for computed tomography follow-up, to exclude the malignant evolution. Of the remaining 20 nodules, 10 out of 20 (50%) nodules, suspected for malignancy, underwent biopsy and then surgical intervention that confirmed the neoplastic nature: 4 (20%) adenocarcinomas, 4 (20%) squamous cell carcinomas, 1 (5%) small cell lung cancer and 1 (5%) breast cancer metastasis; 8 out of 20 (40%) underwent bronchoscopy (8 pneumonia) and 2 out of 20 (10%) underwent biopsy with the diagnosis of sarcoidosis.

CONCLUSION

HRCT in EVAR planning and follow-up allows to correctly identify patients requiring additional treatments, especially in case of lung cancer.

Key words: Computed tomography angiography; Aorta; Endovascular aortic aneurysm repair; Cigarette smoking; Lung cancer

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Core tip: Nowadays the use of high resolution computed tomography in endovascular aortic aneurysm repair (EVAR) patients planning and follow up is not yet recommended. Our study demonstrates the possibility to early diagnose lung cancer during EVAR follow-up or planning in smoker patients, overcoming the concept of dose radiation induced neoplasms, especially in over 65 years old patients.

Mazzei MA, Guerrini S, Gentili F, Galzerano G, Setacci F, Benevento D, Mazzei FG, Volterrani L, Setacci C. Incidental extravascular findings in computed tomographic angiography for planning or monitoring endovascular aortic aneurysm repair: Smoker patients, increased lung cancer prevalence? *World J Radiol* 2017; 9(7): 304-311 Available from: URL: <http://www.wjgnet.com/1949-8470/full/v9/i7/304.htm> DOI: <http://dx.doi.org/10.4329/wjr.v9.i7.304>

INTRODUCTION

Vascular diseases cover an extended selection of pathologies comprising cardiovascular, thoracoabdominal, peripheral vascular and cerebrovascular disease^[1]. Smoking is considered one of the main risk factors for the development of atherosclerosis and, in particular, oxidative stress and inflammation that constitute the physiological connection between smoking and vascular diseases. Polycyclic aromatic hydrocarbons (PAH) represent the main carcinogenic compound found in cigarettes, produced during the incomplete combustion of organic matter. Many articles demonstrate the double activity of PAH, both carcinogenic (lung and other tissues) and inflammatory, provoking endothelial dysfunction and several studies demonstrate that oxidants directly impair endothelial function, increasing nitric oxide scavenging by oxygen free radicals^[2-6]. In the literature it is well known that cardiovascular diseases are often diagnosed on the basis of imaging findings, such as suspected atherosclerotic plaques of the chest in computed tomography (CT), also incidentally^[7-9]. A similar approach should be used to identify extravascular findings, when the CT examination is required to explore vascular diseases. In particular, since cigarette smoking is the main risk factor for both vascular and neoplastic lung diseases, radiologists should examine the chest in evaluation of vascular patients with many risk factors suggesting possible synchronous pathologies. It has been reported that CTs requested for the exclusion of pulmonary embolism give a high yield of chest abnormalities, such as mediastinal adenopathy, paratracheal adenopathy, atelectasis, emphysema and pulmonary nodules or masses^[10,11]. Although not the target of the investigation, lung abnormalities, especially lung cancer, could become the main finding with prognostic relevance in terms of life-long survivor risk in vascular patients. Furthermore, even if many articles over the last decade have reported the problem of unsuspected thoracic findings in CTs, performed for suspected pulmonary embolism or thoracic aortic pathology, the possibility of finding chest pathology, and in particular lung cancer, in smoker patients suffering from vascular disease has been underestimated^[12,13]. Moreover, several articles have reported a high cumulative radiation dose in patients treated with endovascular aneurysm repair (EVAR), both during the interventional procedure and CT follow-up, suggesting a possible role of radiation exposure in developing cancer in these patients^[14-16]. On the contrary, there have been no articles to date about the discovery of lung cancer during EVAR planning or surveillance in smokers suggesting that smoking rather than the exposure of patients to radiation is the main risk factor for lung cancer. Considering the previous statements, the purpose of this study is to assess the prevalence of lung cancer in patients with a smoking

attitude, who underwent computed tomography angiography (CTA) for planning or monitoring EVAR in our department.

MATERIALS AND METHODS

Patient characteristics

Institutional review board approval was obtained for this retrospective study, as well as informed consent from all subjects. We reviewed the report results of 250 CTs of patients referred to our department for EVAR planning or follow-up between June 2014 and May 2016, searching for lung abnormalities in the patients who underwent high resolution computed tomography (HRCT) of the lung before contrast agent administration. Patients were identified throughout a digital radiological database (Picture Archive and Communication System, PACS) which registers all radiological studies performed by the Department of Radiology. The mean age of patients at the time of CT was 71 years, in a range from 50 to 94, and 38 (21%) were female. Sixty-nine (26.6%) patients were excluded for the following reasons: 30 (43.5%) because of the absence of synchronous chest HRCT, 21 (30.4%) because of lack of proven histological findings of lung cancer or HRCT follow-up examinations, and 18 (26.1%) because of non-smoking attitude. The CTA and HRCT were performed simultaneously in all selected cases to avoid interpretation bias. Seventy-four (40.8%) CTs were performed for EVAR planning and 107 for EVAR surveillance (67 at 1 mo and 40 at 12 mo after EVAR). All the selected patients had a documented history of smoking [number of pack-years (p-y)]^[17-19].

Imaging technique

All the CTs were performed with a 64-detector row CT scanner (Discovery HD 750, General Electric Healthcare, and Milwaukee, United States). HRCTs were acquired at end of inspiration using volumetric technique in the caudocranial direction from the basis to the apex of the lung; patients were in supine position. The following technical parameters were used: Effective slice thickness 3.75 mm, collimation 40 mm, beam pitch 0.969, reconstruction interval 1 mm, tube voltage 140 kVp and reference mAs 250/400. Automatic tube current modulation was used to minimise radiation exposure. Chest CTs were acquired using a standard algorithm, then data were reconstructed by using a high spatial-frequency algorithm (bone plus), with 1.25 mm slice thickness. Abdominal CT angiography (CTA) was performed with a spiral technique in the caudocranial direction (from the pelvic brim to the lung bases) with the patients supine. Patients were instructed to hold their breath during helical imaging to avoid motion artefacts. After a scout-view scan, intravenous injection of 1.5 mL/kg non-ionic contrast material (Iomeprol 400 mg iodine/mL; Iomeron 400, Bracco Diagnostics, Milan, Italy) followed by 40 mL saline solution was administered with an 18-gauge needle in the antecubital

vein, using a dual-barrel injector (4 mL/s flow rate, CT Motion, Ulrich Medical, Ulm, Germany). Arterial phase images were obtained 4 seconds after bolus detection in the suprarenal aorta. The following technical parameters were used: Effective slice thickness 1.25 mm, collimation 40 mm, beam pitch 0.969, reconstruction interval 0.8 mm, tube voltage 140 kVp and reference mAs 250/700. A standard reconstruction algorithm was used. In 24 out of 181 patients (13.2%), the contrast CT was extended to the thorax using the same technical parameters. Automatic tube current modulation was also used to minimise radiation exposure in the post-contrast examination^[16].

Image analysis

All images were analysed independently and blindly by two readers with 15 and 8 years' experience in chest-imaging respectively. HRCT scans were analysed on a reconstruction and image interpretation console (Advantage Workstation 4.4, GE Healthcare, Milwaukee, Wis, United States), adjusting the image level, window and enlargement values each time, and routinely using a 2D multiplanar reconstruction technique (coronal, sagittal and oblique planes). Pulmonary HRCT findings included: Pleural effusion, atelectasis/pneumonia, pericardial effusion, cardiomegaly, coronary artery calcifications, bone findings, hiatal hernia, emphysema, mediastinal or hilar adenopathy, pulmonary micronodule (< 4 mm), pulmonary nodule (> 4 mm and < 30 mm) and pulmonary mass (> 30 mm). The readers recorded any incidental finding, with particular attention to pulmonary nodules or masses and differences were resolved by consensus. All nodules were characterised by number, size (measured in their greatest diameter) and CT characteristic appearance (solid, ground-glass or partially solid, edge characteristics, speculated or smooth, presence or absence of pleural-tag, bronchus sign, calcifications, intralesional fat or intralesional air) and reviewed with the smoking history of the patient. According to Fleischner Society guidelines, all suspected nodules were addressed to CT biopsy or surgical intervention, whereas nodules with a CT low risk appearance for lung cancer were addressed to CT follow-up^[20] (Table 1). All previous medical reports, clinical notes, discharges summaries and medical histories of patients were examined to potentially define every mass or nodule as a new incidental finding.

Statistical analysis

The lung findings detected by the readers were collected, and the results expressed as mean \pm SD. A descriptive statistical analysis was performed; the quantitative variables were expressed as means and range whereas the qualitative values as percentages. The statistical review of the study was performed by a biomedical statistician. The analysis was performed using Stata version 8.0 (Stata Corp, College Station, Texas).

Table 1 Recommendations for follow-up and management of nodules and micronodules^[20]

Nodule size (mm)	Low risk patient ¹	High risk patient ²
≤ 4	No FU needed	Follow-up CT at 12 mo; if unchanged, no further follow-up
> 4-6	FU CT at 12 mo; if unchanged, no further FU	Initial follow-up CT at 6-12 mo then at 18-24 mo if no change
> 6-8	Initial FU CT at 6-12 mo then at 18-24 mo if no change	Initial follow-up CT at 3-6 mo then at 9-12 and 24 mo if no change
> 8	FU CT at around 3, 9, and 24 mo, dynamic contrast-enhanced CT, PET, and or biopsy	Same as for low-risk patient

¹Minimal or absent history of smoking and of other known risk factors; ²History of smoking or of other known risk factors. CT: Computed tomography; FU: Follow-up; PET: Positron emission tomography.

Table 2 Incidental findings

Patients (n)	Findings
31	Pleural effusion
5	Atelectasis
8	Pneumonia
16	Pericardial effusion
48	Cardiomegaly
57	Coronary artery calcifications
0	Bone findings
23	Hiatal hernia
94	Emphysema
39	Mediastinal or hilar adenopathy

Table 3 Computed tomography nodules characteristics

Nodules size	n (tot 102)
Pulmonary micronodule (< 4 mm)	43
Pulmonary nodule (> 4 mm and < 30 mm)	51
Pulmonary mass (> 30 mm)	8
Nodules characteristics	n
Solid	73
Ground-glass	21
Partially solid	8
Spiculated	9
Smooth	4
Pleural tag	3
Bronchus sign	6
Calcifications	7
Intralesion fat	4
Intralesional air	2

RESULTS

A total of 181 HRCTs were reviewed. The incidental lung findings reported on chest CT are shown in Table 2. There were a total of 102 (56%) nodules in 92 out of 181 (50.8%) HRCTs, with a mean of 1.79 nodules per patient and an average diameter of 9.2 mm, ranging from 4 to 56 mm. All the CT nodules characteristics are reported in Table 3. After radiologists' review, 82 (76.4%) of the nodules met criteria for CT follow-up and were submitted to a second HRCT examination (performed between 6-12 mo), to exclude the possibility of malignant evolution. Of the remaining 20 nodules, 10 out of the 20 (50%) suspected for malignancy underwent biopsy and then surgical intervention which confirmed the following neoplastic nature: 4 (20%) adenocarcinomas (Figure 1), 4 (20%) squamous cell carcinomas, 1 (5%) small cell lung cancer and 1 (5%) breast cancer metastasis (Figure 2); 8 out of 20 (40%) underwent bronchoscopy (8 pneumonia) and 2 out of 20 (10%) underwent biopsy with the diagnosis of sarcoidosis. All the patients diagnosed with lung cancer (1 female and 8 males) had a smoking history with a mean quantity of 60 p-y (range 45-83 p-y). The remaining patients with non-neoplastic nodules had a smoking history with a mean quantity of 35 p-y (range 20-46 p-y) per patient. Eighty-nine out of 181 HRCTs resulted negative for the presence of suspected nodules with a mean smoking history of 10 p-y (range 5-18 p-y).

DISCUSSION

EVAR currently represents a safe and effective treat-

ment for abdominal aortic aneurysms exclusion with an increase in the choice of this treatment over traditional open repair, especially in elderly patients^[21,22]. In particular, EVAR is also becoming the method of choice for aneurysmal sac exclusion in vascular patients with difficult vascular anatomies due to its favourable outcomes, customised approach and easy technical execution^[23-25]. Despite these advantages some articles debate the risk of long-term lifelong EVAR CT follow-up, with a remarkable amount of radiation exposure carrying the risk of developing cancers; moreover they report the need of dose optimisations using new targeted CT protocols, considering that the absorbed dose by the patient differs on the basis different scanners, patient body size and age^[26-28]. However to our knowledge there are no articles discussing the prevalence of lung cancer, prior to EVAR treatment, in patients with a smoking attitude. Furthermore, lung cancer represents the most important cause of death in the world, and the majority of patients suffering from lung cancer present mild or no symptoms, with nodular lesions being the most common presentation of peripheral lung adenocarcinoma^[12]. Moreover, a large number of patients with vascular disease have a smoking history and, in particular, smoking is one of the major risk factors for developing vascular diseases. At the same time, smoking also represents the main risk factor for lung cancer due to the activation of the same inflammatory pathway with continuous endothelial damage. In our study we assess the prevalence of

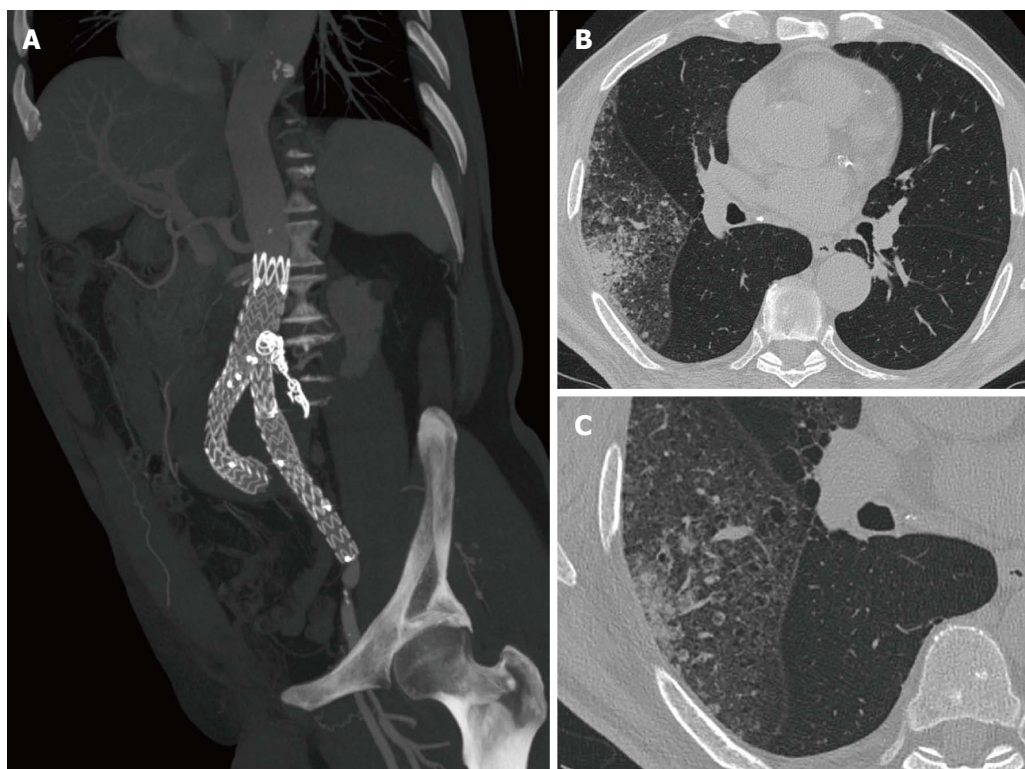


Figure 1 Lepidic predominant adenocarcinoma diagnosed during endovascular aortic aneurysm repair follow-up. A-C: A 80-year-old male with a LPA of the right upper lobe diagnosed during endovascular aortic aneurysm repair follow-up for a type II endoleak treated with glue and coils (A). HRCT images (B and C) demonstrate the lepidic growth of the tumor and aerogenous metastases in the same lobe. LPA: Lepidic predominant adenocarcinoma; HRCT: High resolution computed tomography.

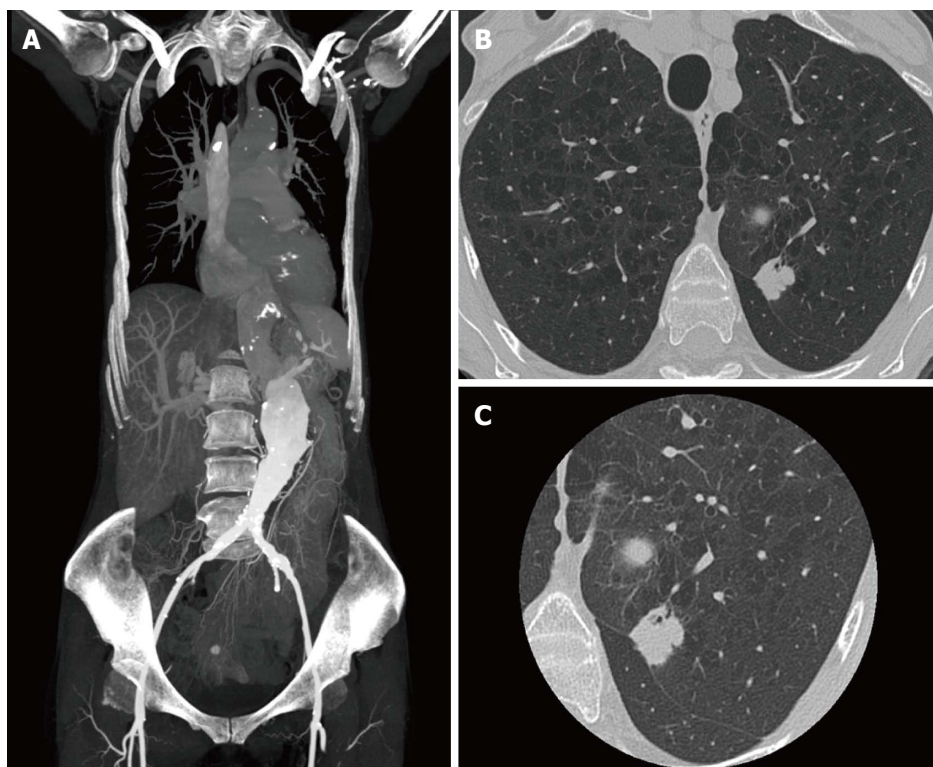


Figure 2 Breast cancer lung metastasis diagnosed during endovascular aortic aneurysm repair planning. A-C: A-63-year-old woman, with a history of breast cancer (10 year before, pT1c, N0, M), addressed to our institution for vascular planning due to an abdominal aortic aneurysm (A). HRCT image (B) performed before the contrast media administration showed diffuse emphysema in upper lobes and the presence in the left upper lobe of a solid nodule (18 mm) with spiculated margins and bronchus sign, confirmed at small FOV reconstruction (C). Histological evaluation, after surgical intervention, demonstrated a breast cancer lung metastasis. HRCT: High resolution computed tomography.

lung nodules through HRCT in a cohort of smoker patients who underwent abdominal CTA for planning or follow-up EVAR; considering the mean advanced age of patients (71 years), stochastic radiation damage deriving from the extra dose of HRCT (respectively mean CTDI 12.6 mGy (range 9.4-15.2) for HRCT vs 22.3 mGy (19.8-24.3) for abdominal CTA) can be considered negligible, comparing to the benefit of early tumor detection; in fact 9 out of 102 nodules (8.8%) in 9 out of 181 (4.9%) patients were finally diagnosed as lung cancer with consequent surgery (6 patients), chemotherapeutic treatment (1 patient) or both (2 patients), with a free survivor rate of 100% at one years. All the other patients were correctly addressed to the appropriate treatment or follow-up. In this context, performing HRCT of the lung to optimise morphological evaluation of lung nodules and/or adding advanced imaging procedure such as CT perfusion or CT volumetric assessment of lung nodules during CTA for the evaluation of vascular aneurysm, offers radiologists the possibility of performing a differential diagnosis between benign or malignant nodules, choosing the correct management for each patient^[29-33]. Moreover, CTA can be performed in the emergency setting to exclude or confirm the presence of aneurysmal sac or EVAR complications or to investigate an abdominal pain after a doubtful ultrasound examination; incidental findings can also occur in that setting^[34-37].

In fact several articles in the literature have reported the possibility of discovering coexistent neoplasms such as gastrointestinal and gall bladder cancers during CT examination of vascular patients^[38-40].

Our study had some limitations. First of all, it is a retrospective study with some possible bias in patient selection, although the database used to find the patients was complete in medical records. Secondly, not all the patients underwent a prior chest radiography that could exclude patients with negative reports from the study. Additionally, a prospective study is mandatory to test the real impact of incidental findings in smoker patients who underwent EVAR planning or follow-up, in order to support the introduction of HRCT of the lung in the CT protocol for smoker patients.

In conclusion, this study actually demonstrates the possibility of early diagnosis of lung cancers during CTA EVAR planning or follow-up, overcoming the concept of dose radiation induced neoplasms, especially in patients over the age of 65.

COMMENTS

Background

Vascular diseases include an extended selection of pathologies (cardiovascular disease, thoraco-abdominal, peripheral vascular disease and brain vascular disease) and smoking is considered one of the main risk factor for the development of atherosclerosis and in particular oxidative stress and inflammation that provide the physiological connection between smoking and vascular diseases. Even if many articles reported the problem of unsuspected thoracic findings at computed tomographies, performed for suspected pulmonary

embolism or thoracic aortic pathology, the possibility to find chest pathology, and in particular lung cancer, in smoker patients suffering from vascular disease is underestimated.

Research frontiers

Nowadays the use of high resolution computed tomography (HRCT) in endovascular aortic aneurysm repair (EVAR) patients planning and follow up is not yet recommended but this study demonstrates the possibility to early diagnose lung cancers during EVAR planning or follow-up, overcoming the concept of dose radiation induced neoplasms, especially in over 65 years old patients.

Innovations and breakthroughs

To be known, this is the first study using HRCT for the evaluation of vascular patients during EVAR planning or follow-up.

Applications

HRCT could play a key role in the diagnosis of incidental lung findings during the evaluation of vascular patients (EVAR planning or follow-up) and surely in the management. In particular HRCT can discriminate patients with urgent lung surgical evaluation for the presence of malignancy, from patients in which a follow-up can be proposed, increasing lifelong patients expectancy.

Terminology

HRCT (high resolution computed tomography of the lung) before contrast agent administration, can lead a better evaluation of lung abnormalities enhancing nodule morphology and shape; CTA (computed tomography angiography) allow a better evaluation of vascular lumen during surgical planning and a correct assessment in cases of EVAR follow-up complications.

Peer-review

The manuscript is well written.

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P- Reviewer: Gao BL, Razek AAKA, Tarazov PG **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Lu YJ



Preoperative [18]fluorodeoxyglucose-positron emission tomography/computed tomography in early stage breast cancer: Rates of distant metastases

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authors reviewed and approved the final manuscript as submitted.

Conflict-of-interest statement: The authors declare no conflicts of interests for this article.

Data sharing statement: No additional data are available.

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Manuscript source: Invited manuscript

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Received: March 28, 2017

Peer-review started: March 29, 2017

First decision: April 18, 2017

Revised: May 20, 2017

Accepted: June 19, 2017

Article in press: June 20, 2017

Published online: July 28, 2017

Abstract

AIM

To investigate rates of distant metastases (DM) detected with [18]fluorodeoxyglucose-positron emission

tomography/computed tomography (¹⁸FDG-PET/CT) in early stage invasive breast cancer.

METHODS

We searched the English language literature databases of PubMed, EMBASE, ISI Web of Knowledge, Web of Science and Google Scholar, for publications on DM detected in patients who had ¹⁸FDG-PET/CT scans as part of the staging for early stages of breast cancer (stage I and II), prior to or immediately following surgery. Reports published between 2011 and 2017 were considered. The systematic review was conducted according to the PRISMA guidelines.

RESULTS

Among the 18 total studies included in the analysis, the risk of DM ranged from 0% to 8.3% and 0% to 12.9% for stage I and II invasive breast cancer, respectively. Among the patients with clinical stage II, the rate of occult metastases diagnosed by ¹⁸FDG-PET/CT was 7.2% (range, 0%-19.6%) for stage II A and 15.8% (range, 0%-40.8%) for stage II B. In young patients (< 40-year-old), ¹⁸FDG-PET/CT demonstrated a higher prevalence of DM at the time of diagnosis for those with aggressive histology (*i.e.*, triple-negative receptors and poorly differentiated grade).

CONCLUSION

Young patients with poorly differentiated tumors and stage II B triple-negative breast cancer may benefit from ¹⁸FDG-PET/CT at initial staging to detect occult DM prior to surgery.

Key words: Breast cancer; Early stage; Staging workup; Distant metastases; [18]fluorodeoxyglucose-positron emission tomography/computed tomography scan

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Core tip: This systematic review identifies groups of patients with early stage breast cancer who might benefit most from [18]fluorodeoxyglucose-positron emission tomography/computed tomography (commonly known as ¹⁸FDG-PET/CT) scan at initial staging, prior to surgery.

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INTRODUCTION

Breast cancer is the most common cancer in women

worldwide^[1]. Mortality of breast cancer has declined notably in the United States, with death rates in 2012 decreasing 36% from peak rates as a result of improvements in early detection and treatment^[2]. Yet, there remains considerable heterogeneity in the outcomes of early stage breast cancer^[3]. The rate of death at 7 year due to stage I breast cancer was 2.1% in women aged 40 years or younger (as compared to 1.6% in women aged over 50) and was 3.8% in women with negative estrogen receptor status (as compared to 1.1% in those with positive estrogen receptor status)^[3].

There is a large consensus that imaging should be limited to patients with apparent advanced disease or clinical suspicion of metastases^[4-7]. Accordingly, staging scans are seldom performed^[6,8]. The question arises, then, as to whether the excess mortality observed in "early stage" patients^[3] is due to unfavorable biological factors or instead to the initial misclassification as "early stage". We hypothesize that some clinically early stage breast cancer patients could benefit from a formal staging workup.

[18]fluorodeoxyglucose-positron emission tomography (¹⁸FDG-PET) scan is a valuable, well established tool for diagnostic staging in numerous cancer sites^[9-12], as well as for locally advanced breast cancer to detect distant metastases (DM)^[13-15]. Even though PET imaging is more sensitive for detection of loco-regional spread and metastatic disease in breast cancer compared to computed tomography (CT) scan alone, its high cost precludes the routine use of PET scan in clinical practice. Thus, a review of the literature is necessary for future guidelines about the benefit of PET scan in early stage breast cancer.

Standard-of-care for early stage breast cancer is surgery, either alone or followed by adjuvant radiotherapy and/or systemic therapy, depending on the pathologic stage and the type of surgery to be performed. The presence or absence of axillary lymph node metastases in patients with clinically non-palpable lymph nodes is routinely assessed through sentinel lymph node sampling or axillary lymph node dissection. Alternatively, PET scan could be most helpful in assessing the presence of DM in early stage breast cancer, which would preclude first-line surgery^[16]. The prevalence of occult DM diagnosed by PET scan in patients with early stage breast cancer has not been analyzed and was the topic of this literature review. In particular, we sought to identify subsets of early stage breast cancer patients who might benefit most from PET scan, prior to surgery.

MATERIALS AND METHODS

Literature search strategy

Electronic searches were performed in the following databases: PubMed, EMBASE, ISI Web of Knowledge (Web of Science), and Google Scholar. The following terms were explored and used in each database search: "Breast cancer", "surgery", "PET scan", "distant

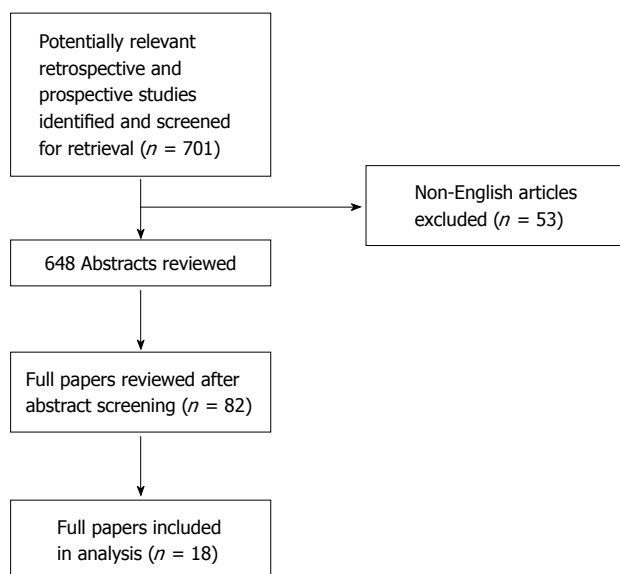


Figure 1 PRISMA flow diagram of the included studies.

metastases”, and “stage I (T1N0M0) and II (T0-2N1M0, T3N0M0)”. All relevant articles were accessed in full-text. The reference lists of relevant papers were then searched for additional publications.

Selection criteria

Eligible studies over the past 6 year (2011-2017) in the present review included those in which patients had ¹⁸FDG-PET/CT scan as part of their workup prior to or immediately after surgery for histologically-proven breast cancer, regardless of age or sex, and in which the rates of DM were reported by ¹⁸FDG-PET/CT scan. All patients had clinical stage I or stage II breast cancer. Only studies reported in English were considered. Duplicated studies were excluded.

Data extraction and critical appraisal

Prevalence of DM was extracted from each study and correlated to the disease stage. The influence of age, histology (e.g., lobular vs ductal), tumor grade (e.g., well differentiated vs poorly differentiated), and receptor status on the rate of DM (if reported) was also analyzed using descriptive summaries.

RESULTS

Number of reports analyzed

Figure 1 summarizes the search strategy. A total of 701 reports published between 2011 and 2017 were considered. Out of the 82 full papers that were assessed according to their potential for consisting of information relevant to the review, 18 were found to match the selection criteria and were selected for study inclusion. ¹⁸FDG-PET/CT scanning had been performed in addition to the clinical staging with or without conventional imaging in those 18 studies, either through a retrospective review or within a prospective protocol.

As none of the studies was randomized, bias could not be excluded. Publications reviewing patients with early stage invasive breast cancer were included.

Prevalence of DM diagnosed by ¹⁸FDG-PET/CT scan according to patient characteristics

Clinical stage: The rates of DM ranged from 0% to 30%^[17-34] for the entire group of reported patients. However, only 9 of the studies correlated DM rates detected by ¹⁸FDG-PET/CT with the clinical stage^[17,22-24,27,29,31,32,34]. The rate of DM was lowest among studies of patients with invasive lobular cancer compared to studies that had included a mixture of other histologies, such as invasive ductal carcinoma^[18] (Tables 1 and 2).

Overall, the rate of DM for presumed stage I was low for all cancer types but non-negligible, ranging from 0% to 8.3%^[22,27,29,31,32,34]. Among the 9 studies that reported the rate of DM in patients with stage II breast cancer separately, the prevalence ranged from 0% to 12.4%^[17,22,24,27,29,31,32,34]. Patients with large tumors and/or axillary lymph node metastases appeared to be at increased risk of DM; specifically, the rate of DM was 7.2% (range, 0%-19.6%) and 15.8% (range, 0%-40.8%) for stage II A and stage II B, respectively^[17,22,24,27,31,32,34].

Tumor size: Among studies that included a significant proportion of patients with large tumors (T2 and/or T3), the DM rate was higher and ranged from 8% to 8.4%^[18,19], as compared to the range of 1.5% to 4.8% in studies including patients with smaller tumors^[21,23,28]. However, since those latter studies also included a small proportion of patients with stage III disease and did not analyze the metastatic rate in relation to the clinical stage, the correlation between tumor size and DM rate remains unclear.

Nodal status: Patients who presented with N1 disease also presented with a higher risk of having DM. The rate of DM was 6% and 20% for N0 and N1 disease, respectively^[31].

Receptor status: Among the 232 patients with triple-negative breast cancer, the DM rate was 0% and 10.9% for clinical stage I and stage II diseases, respectively, but there was no comparison performed with receptor-positive cases^[32]. Other studies did not report the rates of DM according to receptor status.

Age: Two studies reported the influence of age on DM rate^[27,33]. In the first study, among 134 young patients (< 40-year-old), the DM rate was 5% and 10.9% for clinical stage I and stage II, respectively^[27]. In the second study, among 214 stage I-III patients, the DM rates did not differ significantly between the age groups of < 40-year-old and ≥ 40-year-old^[33]. However, the DM rates in the younger age group were 8% in stage I, 9% in stage II A and 17% in stage II B, equating to 2x's

Table 1 Prevalence of distant metastases in patients with invasive breast cancer who had [¹⁸F]fluorodeoxyglucose-positron emission tomography scan as part of the workup before or immediately after surgery

Ref.	Subjects, <i>n</i>	Stage	Age, median	Histology	Tumor grade	Tumor receptors	Distant metastases	2 nd primaries
Groheux <i>et al</i> ^[17]	131	II: 84 III: 47 T1: 2 T2: 71 T3: 58 N0: 50 N1: 59 N2: 18	NS	IDC: 114 ILC: 8 Other: 9	1: 9 2: 5 3: 53 NS: 4	ER+: 82 HER2+: 30	5.90% (II)	1% (II)
Bernsdorf <i>et al</i> ^[18]	103	T2 or higher	55 (24-81)	IDC: 83 ILC: 14 Other: 6	1: 11 2: 54 3: 37 NS: 1	ER+: 74 HER2+: 22 TN: 13	8%	1.90%
Choi <i>et al</i> ^[19]	154	I: 69 II: 51 III: 21 IV: 13 T1: 89 T2: 51 T3: 14	52 (30-81)	IDC: 141 ILC: 4 Other: 9	NS: 154	NS	8.40%	NS
Garami <i>et al</i> ^[20]	115	T1: 56 T2: 48 NS: 11 N0: 57 N+: 46 NS: 12	55.7	IDC: 92 ILC: 11 Other: 12	1: 16 2: 50 3: 48 NS: 1	ER+: 89 ER-: 26	6.90%	2.60%
Groves <i>et al</i> ^[21]	70	T1: 34 T2: 30 N1: 24	61	IDC: 45 ILC: 10 Other: 5	1: 02 2: 33 3: 25	ER+: 64 HER+: 15	2.80%	NS
Gunalp <i>et al</i> ^[22]	141	I: 19 II: 100 III: 14	47 (28-78)	NS	2 + 3: 141	NS	5% (I) 30% (II)	NS
Pritchard <i>et al</i> ^[23]	325	T1: 207 T2: 110 T3: 8 N0: 325	56 (28-83)	IDC: 290 ILC: 35	1: 68 2: 158 3: 92	NS	1.50%	NS
Cochet <i>et al</i> ^[24]	142	II: 79 III: 46 IV: 17 T2 or Higher	51 (25-85)	IDC: 128 ILC: 11 Other: 3	1+2: 81 3: 56 NS: 3	ER+/HER2-: 63 HER2+: 33 TN: 31	7.5% (II)	NS
Jeong <i>et al</i> ^[25]	178	N0: 178 T1: 108 T2: 64 T3: 6	54.9 (33-82)	IDC: 145 ILC: 11 DCIS: 12 Other: 10	NS	NS	0%	2.80%
Koolen <i>et al</i> ^[26]	62	I: 35 II: 25 III: 2 T1: 62	59.8 (26-75)	IDC: 58 ILC: 1 Other: 3	1: 21 2: 29 3: 09 NS: 3	ER+/HER2-: 48 TN: 7 HER2+: 7	16%	3%
Riedl <i>et al</i> ^[27]	134	I: 20 II: 91 III: 19	36.2 (22-39)	IDC: 124 ILC: 1 Other: 9	1: 01 2: 23 3: 110	ER+/HER2-: 75 HER2+: 26	5% (I) 10.9% (II)	4%
Zhang <i>et al</i> ^[28]	164	T1: 127 T2: 35 T3: 2 N0: 123 N1: 29 N2: 9 N3: 3	45 (21-70)	IDL: 150 ILC: 14	1: 23 2-3: 141	ER+: 140 HER2+: 18	4.80%	NS
Hogan <i>et al</i> ^[29]	146	I: 8 II: 50 III: 88	57 (34-92)	ILC: 146	NS	ER+/HER2-: 132 HER2+: 8 TN: 5	0% (I) 4% (II)	NS
Krammer <i>et al</i> ^[30]	101	II: 75 III: 15 IV: 11 T1: 7	54	IDC: 80 ILC: 15 Other: 9	1: 05 2: 48 3: 45 NS: 6	ER+: 67 HER2+: 56	15.80%	NS

Nursal <i>et al</i> ^[31]	419	T2: 69 T3: 4 T4: 5	51.5	IDC: 305 ILC: 29 Other: 85	NS	NS	2.9% (I) 12.4% (II)	NS
		I : 104 II : 315 T1: 127 T2: 270 T3: 20						
		I : 23 II : 169 III: 40						
		I : 24 II : 124 III: 66						
Ulaner <i>et al</i> ^[32]	232	I : 23 II : 169 III: 40	51 (25-93)	IDC: 217 ILC: 2	2: 8 3: 217 NS: 7	TN: 232	0% (I) 10% (II)	NS
		I : 24 II : 124 III: 66						
		I : 24 II : 124 III: 66						
		I : 24 II : 124 III: 66						
Lebon <i>et al</i> ^[33]	214	I : 24 II : 124 III: 66	45.2	IDC: 181 ILC: 10 Other: 23	1: 13 2: 68 3: 133	HR+/HER2-: 89 HER2+: 61 TN: 63 NS: 1	8.3% (I) 12.9% (II)	NS
		I : 24 II : 124 III: 66						
		I : 24 II : 124 III: 66						
		I : 24 II : 124 III: 66						
Ulaner <i>et al</i> ^[34]	483	I : 36 II : 331 III: 116	52.7 (23.6-89.5)	IDC: 414 ILC: 41 Other: 28	1: 5 2: 55 3: 400 NS: 23	ER+: 402 HER2+: 245 TN: 0	2.8% (I) 9.7% (II) 24.1% (III)	1.40%
		I : 36 II : 331 III: 116						
		I : 36 II : 331 III: 116						
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DCIS: Ductal carcinoma *in situ*; ER: Estrogen receptor; ¹⁸FDG-PET: [18]fluorodeoxyglucose-positron emission tomography; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; NS: Not specified; PR: Progesterone receptor; TN: Triple-negative.

Table 2 Prevalence of occult distant metastases in clinical stage II patients who had [18]fluorodeoxyglucose-positron emission tomography scan as part of a staging workup before or immediately after surgery

Ref.	Subjects, <i>n</i>	Age, median	Distant metastases rate		
			II A	II B	All
Grobeux <i>et al</i> ^[17]	84	NS	2.80% (1/36)	8.30% (4/48)	5.95%
Gunalp <i>et al</i> ^[22]	100	51	19.60% (10/51)	40.80% (20/49)	30%
Cochet <i>et al</i> ^[24]	142	51	9.10% (2/22)	7.00% (4/57)	7.60%
Jeong <i>et al</i> ^[25]	70	54.9	0% (0/64)	0% (0/6)	0%
Riedl <i>et al</i> ^[27]	91	36.2	5% (2/44)	17% (8/47)	10.90%
Nursal <i>et al</i> ^[31]	315	51.5	9.50% (19/199)	17.20% (20/116)	12.40%
Ulaner <i>et al</i> ^[32]	169	51	5% (4/82)	15% (13/87)	9.50%
Lebon <i>et al</i> ^[33]	124	45.2	11% (7/64)	15% (9/60)	12.90%
Ulaner <i>et al</i> ^[34]	483	52.7	4.20% (6/143)	13.80% (26/188)	9.70%
All	1578	47.8	7.20% (0%-19.6%)	15.80% (0%-40.8%)	11.40% (0%-12.9%)

¹⁸FDG-PET: [18]fluorodeoxyglucose-positron emission tomography; NS: Not specified.

higher than those found in the first study.

Histologic grade: Histologic grade of the tumor may also be associated with increased risk of developing DM. Among 141 patients with moderate to poorly differentiated invasive breast cancers, the rate of DM was 30% for stage II patients^[22]. However, correlation between tumor histologic grade and DM risk was not investigated in other studies^[17-21,23,24,26-33].

DISCUSSION

This article reviews the role of ¹⁸FDG-PET/CT scan in the detection of DM in patients with early stages (*i.e.*, I and II) of invasive breast cancer. The findings might represent important information applicable to discussions with patients about the utility of the scan. In contrast to stage III breast cancer, the role of ¹⁸FDG-PET/CT scan in identifying patients with clinical stages I and II who are at high risk of DM is

controversial. Even though ¹⁸FDG-PET/CT scan may also be capable of identifying a second primary cancer, its main role in patients with breast cancer is the detection of DM, which could preclude upfront surgery^[16]. Furthermore, the detection of DM could be of critical importance for the correct classification of patients and in the evaluation of treatment outcomes.

As the risk of DM is low in "early stage" asymptomatic breast cancer patients, an expensive imaging study, such as with the ¹⁸FDG-PET/CT scan, is not justified for the staging workup of all patients^[6,35]. However, breast cancer is a heterogeneous disease, with some subgroups of patients at risk of developing DM even at the early stage. Subgroups of breast cancer patients with worse outcome include younger patients^[36] and patients that have tumors with a more aggressive biological profile^[37]. Rare histologic subtypes, such as metaplastic carcinoma of breast and invasive micropapillary carcinoma, are also more frequently associated with poor prognosis because of the high

rate of axillary lymph node involvement and DM^[38,39]. Genomic classification of risk, such as the oncoprint DX and Perou's studies, also identified the risk of distant recurrence^[40-42]. Thus, those patients at high risk of systemic spread may benefit from early diagnosis of DM, for which chemotherapy may be initiated in a timely manner and unnecessary surgery may be avoided. The benefit of ¹⁸FDG-PET scan may outweigh its cost in those circumstances.

In patients with clinical stage I breast cancer, regardless of age, tumor grade or aggressive histology, the risk of DM as diagnosed by ¹⁸FDG-PET scan ranged from 0% to 8.3%^[22,27,29,31-34]. This low, though not negligible, metastatic rate has been corroborated in studies with a high proportion of patients with T1 and N0 disease^[21,23]. Even though the number of patients with stage I disease in those studies was small, preliminary evidence suggested that ¹⁸FDG-PET scan may not be cost effective for clinical stage I patients.

In patients with clinical stage II breast cancer, the prevalence of occult DM detected through ¹⁸FDG-PET scan ranged from 0% to 12.4%^[17,22,24,27,29,31,32,34]. As stage II breast cancer patients also comprise a heterogeneous group, the risk of DM is higher for patients with stage II B disease (T3N0M0, T2N1M0) than for those with stage II A (T1N1M0, T2N0M0) disease. Discounting the one study that included only 6 patients with stage II B disease^[25], the risk of unsuspected DM diagnosed by ¹⁸FDG-PET scan ranged from 2.8% to 19.6% for stage II A and 9.1% to 40% for stage II B, respectively^[17,22,27,31,32,34] (Table 2).

Patients with stage II B have larger tumors than those with stage II A. As tumor size has been reported to be correlated with an increased risk of DM, this may be one of the reasons underlying the higher rate of DM at diagnosis^[43]. Other studies have corroborated the increased prevalence of DM diagnosed with ¹⁸FDG-PET scan for patients with large tumors compared to those with smaller tumors^[18-21,23,28]. It is likely that other factors, like axillary lymph node metastases and tumor biology, may also lead to a high rate of DM at diagnosis^[22,24,27,29,31].

Patients with triple-negative breast cancer frequently have a worse prognosis than their counterparts who harbor other subtypes because of the high rate of DM^[44]. A 10% rate of unsuspected DM was seen on ¹⁸FDG-PET scan compared to conventional imaging for patients with clinical stage II breast cancer^[32]. However, even among those triple-negative breast cancer patients, the rate of DM remained low for stage II A disease. Specifically, the DM rate was 5% and 15% for stage II A and II B triple-negative breast cancers, respectively.

Another prognostic factor that has been reported in the literature is the patient age at diagnosis. Young patients (< 40-year-old) may have a more aggressive tumor biology that translates to a lower survival rate compared to older patients^[36]. Among young patients with breast cancer, those with stage II B disease had

a 17% rate of DM compared to 5% for stage II A. The incidence of DM in patients with clinical stage II A with moderate to poorly differentiated grade carcinoma climbs to 19.6% after ¹⁸FDG-PET scanning^[22]. Tumor biology needs to be taken into account beyond the conventional TNM staging. In patients with invasive micropapillary carcinoma, for example, a high rate of DM detected by ¹⁸FDG-PET scan before surgery has been reported. Among 16 patients with invasive micropapillary carcinoma who underwent ¹⁸FDG-PET scan when the tumor was diagnosed, axillary lymph node metastases and DM were observed in 12 (75% of cases)^[45].

To date, this is the first study looking at the impact of ¹⁸FDG-PET on the management of invasive micropapillary carcinoma, a rare tumor with a high rate of axillary lymph node invasion and DM, even in the case of a relatively small tumor. Moreover, no study has been performed yet to investigate the role of ¹⁸FDG-PET scan for the diagnosis of occult DM in patients who had surgery for metaplastic carcinoma of the breast, another rare tumor with a poor survival rate associated with a high propensity to metastasize to distant sites.

Our study was restricted by the limited availability of the data correlating clinical stages and biology with the risk of DM diagnosed with ¹⁸FDG-PET/CT scan in patients with early stage breast cancer. Ki-67 is a known prognostic marker^[46] but was not reported in any of the recent and largest studies^[31-34]. Most studies were retrospective. The classification of patients into stages was usually done after the ¹⁸FDG-PET/CT image acquisition, which might have affected the selection of patients. Some studies included the more advanced stages, stage III and IV, and a few studies included post-operative patients. Many issues of importance are relevant for breast cancer, notably the emerging role of PET/MRI and its comparison with PET/CT^[47], the use of PET in the monitoring of neoadjuvant therapy^[48], the use for staging and restaging^[49], the standardized uptake values (commonly known as SUVs) and how they relate to lymph node status^[50], the prognostic role of FDG-PET^[51] and the suitability for treatment planning^[52]; all these represent immensely exciting domains of breast cancer research, but would have confused the scope of the present study, namely the rates of DM.

In summary, the current review suggests a need for future prospective studies looking at subgroups of patients who would most likely benefit from PET scan before surgery-stage II B, poorly differentiated tumors, rare tumors with aggressive biology, such as invasive micropapillary carcinoma, and young age. These patients would most likely receive systemic therapy. Detection of DM could help in selecting the optimal sequence of therapies and the monitoring thereof. Incorporating biomarkers such as c-erbB2 and genetic arrays in those studies may further help the clinician to define the risk of DM at diagnosis for patients with early stage breast cancer.

Conclusion

In patients with clinical stage I breast cancer, the systematic use of ¹⁸FDG-PET/CT scan for staging is not cost effective because the yield of ¹⁸FDG-PET/CT-detected DM in clinical stage I is low. In young patients with stage II B triple-negative and/or poorly differentiated breast cancer, ¹⁸FDG-PET/CT scan identifies a substantial rate of DM and should therefore be considered for these patients. Finally, the role of ¹⁸FDG-PET for stage II breast cancer and for rare tumors with aggressive biology needs to be defined in future prospective studies.

ACKNOWLEDGMENTS

The authors would like to express their heartfelt gratitude to Carl Leak, for revising the language of this manuscript, to Jessica Malki, Olga Morgan, Brentwood Oftedal, Yeoshina Pillay and Andrew Westfall of the RUSM Oncology Society, Ross University School of Medicine, Dominica, West Indies for their enthusiastic interest and partaking in the discussion and the writing.

COMMENTS

Background

Staging of cancer is the process of identifying and classifying the extent of the disease. Staging is important to aid the clinician in planning treatment, to inform the patient on prognosis, to evaluate the results of treatment, and to facilitate the exchange of information between treatment centers. Initial staging is based on all evidence acquired before treatment. The evidence arises from physical examination, imaging, pathology, and/or endoscopic or surgical exploration.

Research frontiers

In early breast cancer (small tumor and no symptom), previous diagnostic studies rarely detected metastases. The contentious issue is that the earlier studies were based on the use of conventional imaging with poor detection performance. Metastatic disease might have been missed.

Innovations and breakthroughs

[¹⁸F]fluorodeoxyglucose-positron emission tomography/computed tomography (¹⁸FDG-PET/CT) combines metabolic and anatomic imaging. It requires a dual competence in radiology and in nuclear medicine. Negative reviews of its role in breast cancer confounded it with ¹⁸FDG-PET alone, did not have the joint nuclear-radiologist's expertise to analyze the images, or focused only on the detection of regional lymph node involvement. There has been no pooled evaluation of the rates of distant metastases detected with ¹⁸FDG-PET/CT. This study fills the gap.

Applications

The present review identifies groups of patients with early breast cancer, who are at high risk for distant metastases, notably those with stage II B or aggressive histologies, in whom it might be prudent to reconsider the role of ¹⁸FDG-PET/CT.

Terminology

¹⁸FDG is a radioactively labeled glucose analog. It allows the detection of tissues that have a high glucose uptake, such as tumors with a high metabolic activity. Imaging with ¹⁸FDG, the ¹⁸FDG-PET, shows areas of high activity. The ¹⁸FDG-PET imaging combined with CT imaging shows where the areas of high activity are distributed in the body; N1 disease: Cancer that has spread to regional lymph nodes; Distant metastases: Cancer that has spread beyond the breast and regional lymph nodes to distant organs or distant lymph nodes;

Triple-negative breast cancer: Breast tumor that tested negative for the estrogen receptor, the progesterone receptor, and the human epidermal growth receptor HER2. Triple negative tumors might respond to chemotherapy but will not to receptor targeted treatments.

Peer-review

A well-written review article, summarising important information to the field.

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P- Reviewer: Bilir C, Wang L, Wang SK **S- Editor:** Ji FF

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