UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE – UFCSPA
PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA

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COMPARAÇÃO DA ACURÁCIA DA RESSONÂNCIA MAGNÉTICA COM DIFUSÃO E DO 18F - FDG PET/CT NA DIFERENCIAÇÃO DE LESÃO PULMONAR MALIGNA DE BENIGNA: REVISÃO SISTEMÁTICA E METANÁLISE

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Dissertação submetida ao Programa de Pós-Graduação em Patologia da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Mestre.

Orientador: Dr. Bruno Hochhegger

Porto Alegre
2019

Catalogação na Publicação

Basso Dias, Adriano
COMPARAÇÃO DA ACURÁCIA DA RESSONÂNCIA MAGNÉTICA COM DIFUSÃO E DO 18F - FDG PET/CT NA DIFERENCIAÇÃO DE LESÃO PULMONAR MALIGNA DE BENIGNA: REVISÃO SISTEMÁTICA E METANÁLISE / Adriano Basso Dias. -- 2019.
50 p. :30 cm.

Dissertação (mestrado) -- Universidade Federal de Ciências da Saúde de Porto Alegre, Programa de Pós-Graduação em Patologia, 2019.

Orientador(a): Bruno Hochhegger.

1. Ressonância magnética. 2. Difusão. 3. PET/CT. 4. Nódulo pulmonar. I. Título.

Sistema de Geração de Ficha Catalográfica da UFCSPA com os dados fornecidos pelo autor (a).

Agradecimentos

Em primeiro lugar à minha noiva, Mariana, à minha mãe, Maria Joana, ao meu pai, Nilmar, e à minha irmã, Paula; meus maiores companheiros, pelos quais sinto e dos quais recebo amor incondicional.

Aos meus familiares, especialmente aos meus avós, e à família Paludo, por todo carinho, cuidado e por sempre se fazerem presentes na minha trajetória.

Ao meu orientador, Dr Bruno, brilhante professor e pesquisador, com quem tive a oportunidade de poder trabalhar e de quem sempre recebi todo incentivo e apoio.

Aos colegas Matheus, Stephan e Gabriel, que foram absolutamente imprescindíveis à elaboração de um estudo robusto, auxiliando de maneira ímpar na construção de todo o trabalho. Apesar do pouco tempo de estrada, impressionaram pela competência e experiência no que diz respeito à produção científica.

À colega Natália, que se envolveu neste trabalho desde que ele não passava apenas de uma ideia, e que trabalhou, sempre com prontidão, lado a lado na sua elaboração.

Aos estatísticos Guilherme e Anderson, que sempre se dispuseram a sanar as muitas dúvidas que surgiram durante todos os passos da metanálise. Os gráficos por eles elaborados superaram as expectativas e, certamente, contribuíram para o aceite do artigo em uma revista com alto fator de impacto.

À colega Tássia pelo auxílio com as referências na fase final do trabalho.

Ao Dr. Maciel, exemplo de ser humano, mestre e mentor. Uma das pessoas mais competentes, humildes e solícitas com quem tive o prazer de

conviver. Seu amor pela radiologia certamente influenciou a minha decisão de seguir por este caminho.

Aos preceptores, colegas de residência e funcionários da Santa Casa de Porto Alegre e UFCSPA, pela amizade e parceria cultivada durante estes três anos. Sem dúvida alguma foram pessoas indispensáveis à minha formação.

Resumo

Introdução: O câncer de pulmão é a principal causa de morte relacionada à malignidade no mundo, geralmente se apresentando como nódulo nos exames de imagem. A Tomografia por Emissão de Pósitrons com Tomografia Computorizada com 18F-Fluorodeoxiglicose (18F-FDG PET/CT) é um método não invasivo atualmente recomendado, em casos selecionados, para auxiliar na diferenciação de nódulo pulmonar maligno de benigno. Estudos mais recentes demonstram que a Ressonância Magnética com Difusão (DW MRI) possui acurácia semelhante a do PET/CT na caracterização de lesões pulmonares indeterminadas, com as vantagens de ser isenta de radiação ionizante e de apresentar um menor custo.

Objetivo: Realizar uma revisão sistemática e metanálise para comparar a performance diagnóstica do 18F-FDG PET/CT e da DW MRI na diferenciação de lesão pulmonar maligna de benigna.

Material e Métodos: Foi realizada uma busca em banco de dados relevantes de estudos publicados em inglês, até dezembro de 2017, sobre acurácia diagnóstica de PET/CT e/ou DW MRI. A análise primária consistiu de estudos que realizaram tanto o PET/CT quanto a DW MRI na mesma população, para redução da heterogeneidade entre os estudos. Os parâmetros de quantificação das lesões analisados foram razão lesão/medula (LSR) e coeficiente de difusão aparente (ADC) para DW MRI; e valor de captação padrão máximo (SUVmax) para PET/CT. Para cada um dos métodos, foram calculados sensibilidade, especificidade, razão de chance diagnóstica (DOR) e área sob a curva ROC (AUC) e seus intervalos de confiança de 95% (95%IC).

Resultados: Dentre os 1280 artigos encontrados inicialmente, 37 estudos atendiam os critérios de inclusão e foram selecionados, totalizando 4224 pacientes e 4463 lesões (malignas, n=3090, 69,2%). Na análise primária dos estudos com ambos os métodos (PET/CT e DW MRI) (n = 6), a sensibilidade e a especificidade foram, respectivamente, de 83% (75-89%) e 91% (80-96%) para DW MRI e 78% (70-84%, p=0,01 vs. DWI) e 81% (72-88%, p=0,056 vs. DWI) para PET/CT. A área sob a curva (AUC) foi de 0,93 (0,90-0,95) para a DW MRI e de 0,86 (0,83-0,89) para o PET/CT (p=0,001). A DW MRI apresentou razão de chance diagnóstica (DOR=50, 95%CI 19-132) superior comparada ao PET/CT (DOR=15, 95%CI 7-32) (p=0,006).

Conclusão: A performance diagnóstica da DWI-MRI é comparável ou superior ao PET/CT na diferenciação de lesões pulmonares malignas de benignas.

Palavras-chave: 1. Ressonância magnética. 2. Difusão. 3. PET/CT. 4. Nódulo pulmonar.

Abstract

Introduction: Lung cancer remains the number one cause of mortality worldwide, usually presenting as a nodule in the imaging exams. The 18F-FDG PET/CT is a noninvasive method currently recommended, in some cases, as a useful modality in differentiating malignant nodules from benign nodules. MRI with diffusion-weighted (DW) imaging has emerged more recently as a radiation-free and cost-effective alternative for the characterization of pulmonary lesions, with an accuracy comparable to that of PET/CT.

Aim of study: To perform a systematic review and meta-analysis of the literature to compare the diagnostic performance of 18F-FDG PET/CT and DW MRI in the differentiation of malignant and benign pulmonary lesions.

Materials and methods: Published English language studies on diagnostic accuracy of PET/CT and/or DW MRI in the characterization of pulmonary lesions were searched in relevant databases through December 2017. We primarily focused on studies that performed joint DW MRI and PET/CT in all study population to reduce inter-study heterogeneity. For DW MRI, lesion-to-spinal cord ratio (LSR) and apparent diffusion coefficient (ADC) were evaluated; for PET/CT, maximum standard uptake value (SUVmax) was evaluated. The pooled sensitivities, specificities, diagnostic odds ratios (DOR) and area under the ROC curve (AUC) of the summary receiver-operating curves for PET/CT and DW MRI with 95% confidence intervals were determined.

Results: 37 studies met inclusion criteria, with 4224 participants and 4463 lesions (malignant, n=3090, 69.2%). In the primary analysis of joint DW MRI and PET/CT studies (n=6), DW MRI had a pooled sensitivity and specificity of 83% (75-89%) and 91% (80-96%), compared to 78% (70-84%, p=0.01 vs. DWI)

and 81% (72-88%, p=0.056 vs. DWI) of PET/CT. DW MRI yielded an AUC of 0.93 (0.90-0.95) versus 0.86 (0.83-0.89) for PET/CT (p=0.001). The diagnostic odds ratio of DW MRI (DOR=50, 95%CI 19-132) was superior to that of PET/CT (DOR=15, 95%CI 7-32) (p=0.006).

Conclusion: Diagnostic performance of DW MRI is comparable or superior to 18F-FDG PET/CT in the differentiation of malignant and benign pulmonary lesions.

Keywords: 1. Magnetic Resonance Imaging. 2. Diffusion-Weighted Imaging. 3. PET/CT. 4. Pulmonary Nodule.

Lista de abreviaturas

18F-FDG PET/CT: tomografia por emissão de pósitrons com tomografia computadorizada com 18F-fluorodeoxiglicose

ADC: coeficiente de difusão aparente

AUC: área sob a curva

DOR: razão de chance diagnóstica

DW MRI: ressonância magnética com difusão

DWI: sequência de difusão

INCA: Instituto Nacional do Câncer

LSR: razão da intensidade de sinal entre lesão e medula espinhal

RM: ressonância magnética

SUV: valor padronizado de captação

SUVmax: valor padronizado de captação máximo

TC: tomografia computadorizada

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1. REFERENCIAL TEÓRICO

O câncer de pulmão é a principal causa de morte relacionada à malignidade no mundo (Siegel e cols., 2015). No Brasil, de acordo com as estimativas do Instituto Nacional do Câncer (INCA), a incidência deste câncer será de 18.740 casos novos entre homens e de 12.530 nas mulheres para cada ano do biênio 2018-2019 (Ministério da Saúde, 2018). Esses valores correspondem a um risco estimado de 18,16 casos novos a cada 100 mil homens, sendo o segundo tumor mais frequente; e com um risco estimado de 11,81 para cada 100 mil mulheres, ocupando a quarta posição (Ministério da Saúde, 2018).

Sem considerar os tumores de pele não melanoma, o câncer de pulmão em homens é o segundo mais frequente nas Regiões Sul (36,27/100 mil) e Centro-Oeste (16,98/100 mil), sendo, nas regiões Sudeste (19,22/100 mil), Nordeste (10,37/100 mil) e Norte (9,03/100 mil), o terceiro mais frequente (Ministério da Saúde, 2018). Para as mulheres, é o terceiro mais frequente nas Regiões Sul (20,59/100 mil) e Sudeste (12,72/100 mil) (Ministério da Saúde, 2018). Nas Regiões Centro-Oeste (11,52/100 mil), Nordeste (7,82/100 mil) e Norte (5,83/100 mil), ocupa a quarta posição (Ministério da Saúde, 2018).

Geralmente o câncer de pulmão se apresenta como nódulo (com até 3 cm de diâmetro) ou massa (maior que 3 cm de diâmetro) na radiografia simples ou na tomografia computadorizada (TC) de tórax (Hansell 2008 e cols., Li e cols., 2014).

Até o presente momento, a TC é considerada o melhor exame de imagem na detecção de nódulo pulmonar (Koyama e cols, 2013; Concatto e

cols., 2016). Entretanto, as características tomográficas deste achado, tais como forma, contornos, escavação e localização não demonstram adequada capacidade de diferenciação de nódulos malignos e benignos (Wang e cols., 2011). Desta forma, pacientes com lesões pulmonares benignas em muitos casos são submetidos a métodos diagnósticos invasivos (ex.: biópsia pulmonar) para afastar a possibilidade de malignidade (Lowe e cols., 1997).

Dentre as possibilidade de métodos não invasivos para avaliação de nódulo pulmonar sólido indeterminado, são recomendados, pela Fleischner *Society*, o controle evolutivo por TC e a Tomografia por Emissão de Pósitrons com Tomografia Computadorizada com 18F-Fluorodeoxiglicose (18F-FDG PET/CT), a depender do tamanho do nódulo e dos fatores de risco do paciente (MacMahon e cols., 2017).

1.1. Tomografia por Emissão de Pósitrons com Tomografia Computadorizada com 18F-Fluorodeoxiglicose (18F-FDG PET/CT)

Há mais de duas décadas, a tomografia por emissão de prótons (PET) utilizando 18F-fluorodeoxiglicose (18-FDG) vem se mostrando capaz de realizar a diferenciação de lesões pulmonares benignas de malignas (Lowe e cols., 1997; Lowe e cols., 1998; Gould e cols., 2001). Esta modalidade de exame quantifica a taxa de metabolismo de glicose pelas células, detectando, desta forma, a presença de nódulos metabolicamente ativos, com maior avidez à glicose e maior captação de 18F-FDG (Gupta e cols., 1996; Sim e cols., 2013). A combinação de 18F-FDG-PET e TC em uma imagem híbrida (18F-FDG-PET/CT) promove informações tanto sobre a morfologia quanto sobre o

metabolismo dos nódulos, o que tem mostrado aumento na acurácia da discriminação de nódulos pulmonares benignos e malignos (Kim e cols., 2007; Jeong e cols., 2008; Chang e cols., 2010; Ruilong e cols., 2016). O PET/CT pode ser analisado qualitativamente, através da comparação visual entre a captação nas lesões tumorais e nos tecidos normais; e, mais comumente, semiquantitativamente, por meio de um parâmetro denominado SUV (*Standardized Uptake Value*, Valor Padronizado de Captação, em g/mL), definido como a razão entre a concentração de atividade no tecido (kBq/mL) e a atividade injetada por massa do paciente (kBq/g), corrigida para o decaimento radioativo (Reinking e cols., 2009). Como regra geral, valores de SUVmáx ≥ 2,5 são considerados indicativos de lesões malignas, enquanto tumores com SUVmáx < 2,5 apresentam maior probabilidade de serem benignos (Hochhegger e cols., 2015) **(Figura 1).**

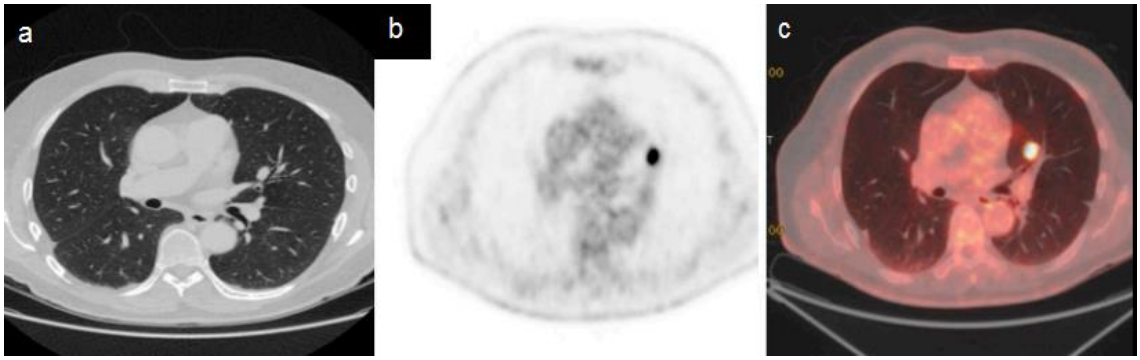

Figura 1. Paciente com histórico de neoplasia colorretal, com nódulo pulmonar que foi posteriormente confirmado, através de análise histopatológica, tratar-se de metástase. **a.** TC evidenciando nódulo no pulmão esquerdo. **b, c.** Imagens axiais de PET e PET/CT, respectivamente, mostrando alta avidez da lesão ao FDG, com SUVmax de 10.9. Figura adaptada de Sim e cols., 2013.

Entretanto, o PET apresenta resultados falso-negativos para adenocarcinoma bem diferenciado e falso-positivos para nódulos inflamatórios (Higashi e cols., 1998; Cheran e cols., 2004). Além disso, o PET/CT possui alto custo, além de expor os paciente à radiação ionizante (Ohba e cols., 2011; Li e cols., 2014). Por essas razões, um método alternativo, acurado e não radioativo para a detecção de lesão pulmonar maligna ainda se faz necessário (Li e cols, 2014).

1.2 Ressonância Magnética com Difusão (DW MRI)

Desde a introdução da ressonância magnética (RM) na prática clínica, a RM de tórax sempre apresentou indicações restritas, devido às limitações inerentes à avaliação pulmonar, como a baixa densidade de prótons do tecido celular normal, artefatos de suscetibilidade do ar, além de artefatos de

movimentos fisiológico (respiração, pulsação cardíaca e de vasos) (Barreto e cols., 2013; Hochhegger e cols., 2015).

Entretanto, nos últimos anos, houve uma evolução significativa da RM em virtude da criação dos equipamentos de alto campo magnético, novos *hardwares* e *softwares*, técnicas paralelas ultrarrápidas, sincronização dos movimentos respiratórios e cardíacos e de novas sequências dinâmicas e funcionais, o que promoveu um avanço significativo na qualidade das imagens, possibilitando, desta forma, uma evolução na performance diagnóstica das lesões torácicas (Kauczor e cols., 2009; Kauczor e cols., 2010). O desenvolvimento de parâmetros metabólicos e funcionais, como a perfusão e a difusão, foi capaz de acrescentar dados relevantes relacionados à atividade tumoral, o que possibilitou a utilização de tais parâmetros em diferentes etapas do manejo oncológico, como o diagnóstico, a avaliação de resposta terapêutica e o seguimento pós-terapêutico (Martí-Bonmatí e cols., 2010; Guimaraes e cols., 2015).

A sequência de difusão (DWI: *diffusion-weighted imaging*) por RM é uma técnica que possibilita a avaliação de características biomoleculares do comportamento tumoral, de forma análoga como ocorre com o PET/CT (Koh e cols., 2007). A DWI é capaz de detectar a restrição à difusão das moléculas de água nos tecidos em um nível celular, podendo ser avaliada de forma qualitativa, semi-quantitativa ou quantitativa (Koh e cols., 2007; Shen e cols., 2018). Qualitativamente, pode ser analisada através de escalas visuais em que se compara a intensidade de sinal da lesão com a de algum tecido, como por exemplo com a medula espinhal (ex. escala de 5 pontos, em que avalia a intensidade de sinal na sequência em difusão de uma lesão em relação à

medula espinhal torácica, classificando a lesão da seguinte forma: 1, hipointensa; 2, moderadamente hipointensa; 3, isointensa; 4, moderadamente hiperintensa; e 5, significativamente hiperintensa) (Satoh e cols., 2008; Çakir e cols., 2015; Shen e cols., 2018). Um método de avaliação semi-quantitativa é a chamada razão lesão/medula (LSR: *lesion-to-spinal cord ratio*), que corresponde a um valor numérico resultado da relação entre a intensidade de sinal, na sequência em difusão, da lesão e da medula espinhal torácica (Concatto e cols., 2016; Shen e cols., 2018). A análise quantitativa é realizada através da mensuração do valor absoluto do coeficiente de difusão aparente (ADC: *apparent diffusion coefficient*) no interior da lesão (Shen e cols., 2017).

O grau de restrição à difusão é inversamente proporcional à celularidade nos tecidos e à integridade das membranas celulares. (Liu e cols., 2010; Luna e cols., 2011). Lesões malignas, com alta celularidade, em geral apresentam restrição à difusão das moléculas de água, apresentando alto sinal na sequência em difusão e baixo sinal no ADC (Koh e cols., 2007; Padhani e cols., 2009; Padhani e cols., 2011) **(Figura 2).** Por outro lado, afecções benignas em geral não exibem restrição à difusão, demonstrando alto valor de ADC (Koh e cols., 2007; Padhani e cols., 2009; Padhani e cols., 2011). Devido a esta capacidade, a DWI emergiu nos últimos anos como uma alternativa acurada para a caracterização de lesões pulmonares indeterminadas, com a vantagem de ser isenta de radiação ionizante e apresentar menor custo quanto comparada ao PET/CT (Liu e cols., 2010; Luna e cols., 2011; Wu e cols., 2013; Li e cols., 2014; Concatto e cols., 2016).

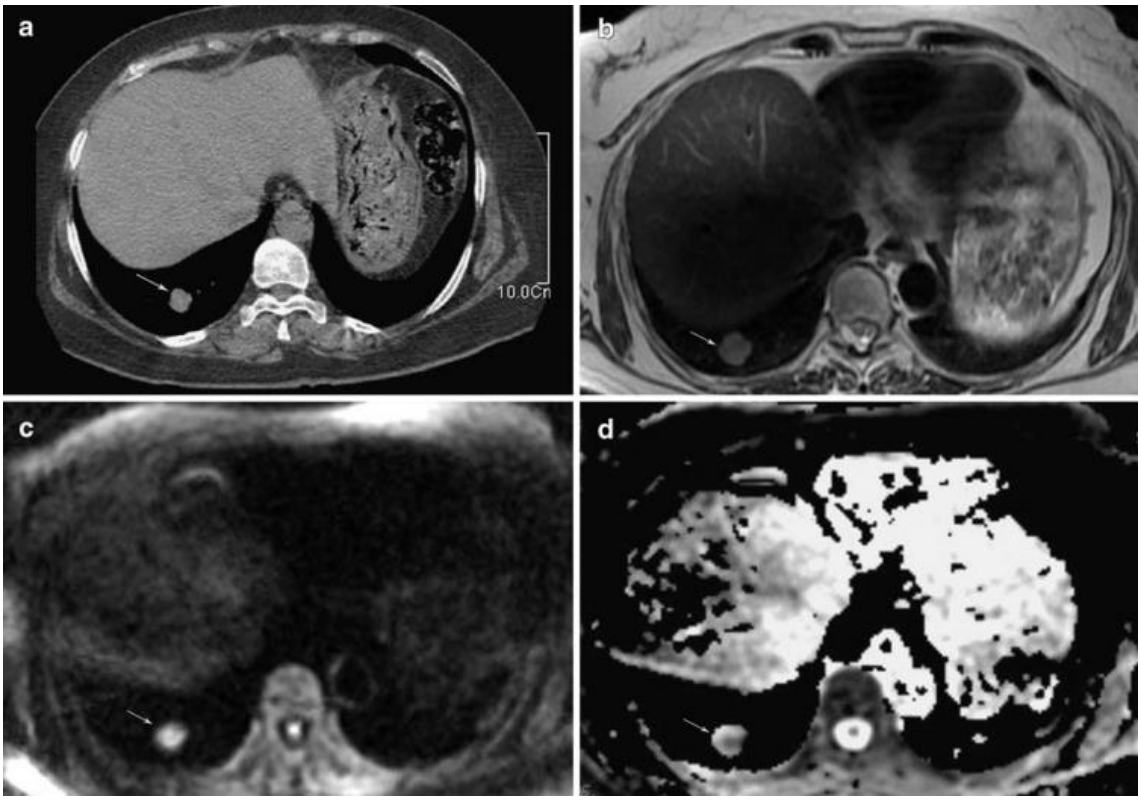

Figura 2. Paciente com adenocarcinoma pulmonar. **a**. TC evidenciado nódulo no lobo inferior direito. **b.** Imagem ponderada em T2 *fast recovery fast spin echo* demonstrando lesão levemente hiperintensa. **c**. Difusão com *b*=500 s/mm² evidenciando nódulo com alto sinal. **d.** Mapa de ADC revelando lesão com baixo valor de ADC. Figura retirada de Liu e cols., 2009.

1.3 Comparação de 18F-FDG PET/CT e DW MRI na diferenciação de lesão pulmonar benigna de maligna

Os poucos estudos que comparam a performance diagnóstica do PET/CT e da DWI na diferenciação de lesões pulmonares benignas e malignas apontam acurácias semelhantes (Mori e cols., 2008; Ohba e cols., 2009; Ohba e cols., 2011; Usuda e cols., 2014; Zhang e cols., 2014; Nomori e cols., 2015).

Não existe, entretanto, revisão sistemática e metanálise comparando estes dois métodos. Revisão sistemática e metanálise são metodologias integradoras de estudos individuais resumindo seus resultados e aumentando o poder estatístico para a resposta de questões clínicas (Sousa e cols., 2009).

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3. OBJETIVOS

3.1 Objetivo geral:

Realizar uma revisão sistemática e metanálise para comparar a performance diagnóstica da Tomografia por Emissão de Pósitrons com Tomografia Computadorizada com 18F-Fluorodeoxiglicose (18F-FDG PET/CT) e da Ressonância Magnética com Difusão (DW MRI) na diferenciação de lesão pulmonar maligna de benigna.

3.2 Objetivos específicos:

1. Comparar a performance diagnóstica (sensibilidade, especificidade, razão de chance diagnóstica e acurácia) do PET/CT e da DW MRI nos artigos (n=6) que utilizassem ambas as modalidades na mesma população (análise primária).
2. Comparar a performance diagnóstica do PET/CT e da DW MRI na totalidade dos artigos (n=37) incluídos neste estudo (análise secundária).
3. Na análise secundária, comparar a performance diagnóstica dos principais parâmetros de quantificação das lesões em cada modalidade (ADC e LSR para DW MRI) e SUVmax para PET/CT).
4. Realizar análise de subgrupo dos estudos com PET/CT e dos estudos com DW MRI para avaliação de possíveis fontes de heterogeneidade.

4. ARTIGO CIENTÍFICO REDIGIDO EM INGLÊS

“Fluorine 18–FDG PET/CT and Diffusion-weighted MRI for Malignant versus Benign Pulmonary Lesions: A Meta-Analysis”

Adriano Basso Dias, Matheus Zanon, Stephan Altmayer, Gabriel Sartori Pacini, Natália Henz Concatto, Guilherme Watte, Anderson Garcez, Tan-Lucien Mohammed, Nupur Verma, Tássia Medeiros, Edson Marchiori, Klaus Irion, Bruno Hochhegger

Publicado na Revista RADIOLOGY

(Radiology 2019; 00:1–10 • https://doi.org/10.1148/radiol.2018181159)

Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

Fluorine 18–FDG PET/CT and Diffusion-weighted MRI for Malignant versus Benign Pulmonary Lesions: A Meta-Analysis

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Conflicts of interest are listed at the end of this article.

See also the editorial by Schiebler in this issue.

Radiology 2019; 00:1–10 • https://doi.org/10.1148/radiol.2018181159 • Content codes: CH MR OI

Purpose: To perform a meta-analysis of the literature to compare the diagnostic performance of fluorine 18 fluorodeoxyglucose PET/CT and diffusion-weighted (DW) MRI in the differentiation of malignant and benign pulmonary nodules and masses.

Materials and Methods: Published English-language studies on the diagnostic accuracy of PET/CT and/or DW MRI in the characterization of pulmonary lesions were searched in relevant databases through December 2017. The primary focus was on studies in which joint DW MRI and PET/CT were performed in the entire study population, to reduce interstudy heterogeneity. For DW MRI, lesion-to–spinal cord signal intensity ratio and apparent diffusion coefficient were evaluated; for PET/CT, maximum standard uptake value was evaluated. The pooled sensitivities, specificities, diagnostic odds ratios, and areas under the receiver operating characteristic curve (AUCs) for PET/CT and DW MRI were determined along with 95% confidence intervals (CIs).

Results: Thirty-seven studies met the inclusion criteria, with a total of 4224 participants and 4463 lesions (3090 malignant lesions [69.2%]). In the primary analysis of joint DW MRI and PET/CT studies (n = 6), DW MRI had a pooled sensitivity and specificity of 83% (95% CI: 75%, 89%) and 91% (95% CI: 80%, 96%), respectively, compared with 78% (95% CI: 70%, 84%) (P = .01 vs DW MRI) and 81% (95% CI: 72%, 88%) (P = .056 vs DW MRI) for PET/CT. DW MRI yielded an AUC of 0.93 (95% CI: 0.90, 0.95), versus 0.86 (95% CI: 0.83, 0.89) for PET/CT (P = .001). The diagnostic odds ratio of DW MRI (50 [95% CI: 19, 132]) was superior to that of PET/CT (15 [95% CI: 7, 32]) (P = .006).

Conclusion: The diagnostic performance of diffusion-weighted MRI is comparable or superior to that of fluorine 18 fluorodeoxyglucose PET/CT in the differentiation of malignant and benign pulmonary lesions.

Online supplemental material is available for this article.

Lung cancer remains the number one cause of cancer mortality worldwide (1). In most cases, the diagnosis is initially made through the detection of a nodule or a mass at chest radiography or CT (1,2). Although CT is the best imaging modality for the detection of pulmonary lesions, in some cases, this modality is not sufficient to accurately distinguish malignant nodules from benign nodules (3–5). Thus, patients with benign nodules might undergo invasive diagnostic methods, such as lung biopsy or video-assisted thoracoscopic surgery, to rule out a malignancy (6).

PET/CT performed by using the radiotracer fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) is a noninvasive alternative that combines both metabolic and morphologic parameters for the characterization of pulmonary nodules (6–12). However, PET/CT has some disadvantages, such as nondetection of some well-differentiated pulmonary adenocarcinomas, misclassification of benign inflammatory nodules, high costs, and patient exposure to radiation (13–17). MRI performed by using diffusion-weighted (DW) imaging allows quantification of restriction to water diffusion in biologic tissue. In malignant tumors, restriction of water motion is inversely correlated with increased cellularity and reduced extracellular space (18,19). For this ability, DW MRI has emerged as a radiation-free alternative for the characterization of pulmonary nodules (18,19).

The few studies that compared DW MRI and PET/CT for differentiation of malignant from benign pulmonary nodules demonstrated similar accuracies

Abbreviations

ADC = apparent diffusion coefficient, AUC = area under the summary receiver operating characteristic curve, CI = confidence interval, DOR = diagnostic odds ratio, DW = diffusion weighted, FDG = fluorodeoxyglucose, FN = false-negative, FP = false-positive, LSR = lesion-to–spinal cord signal intensity ratio, NLR = negative likelihood ratio, PLR = positive likelihood ratio, QUADAS = Quality Assessment of Diagnostic Accuracy Studies, SUV-CR = contrast ratio of SUV, SUV_{max} = maximum SUV, SUV = standardized uptake value, TN = true-negative, TP = true-positive

Summary

The diagnostic performance of diffusion-weighted MRI is comparable to that of fluorine 18 fluorodeoxyglucose PET/CT for the characterization of pulmonary lesions as malignant or benign.

Implication for Patient Care

MRI with diffusion-weighted imaging and PET/CT can be used in the evaluation of indeterminate pulmonary nodules and masses with similar accuracy.

between the two modalities (17,20–24). However, to our knowledge, there are no meta-analyses on this topic. The aim of this systematic review and meta-analysis was to compare the diagnostic performance of ^{18}F-FDG PET/CT and DW MRI in the characterization of pulmonary nodules and masses as malignant or benign.

Materials and Methods

Search Strategy

This study was reported by following the Enhancing the Quality and Transparency of Health Research, or EQUATOR, reporting guidelines, including the Preferred Reporting Items for Systematic Reviews, or PRISMA, and the Meta-analysis of Observational Studies in Epidemiology, or MOOSE, guidelines (25). We searched all available literature published through December 2017 in the PubMed-MEDLINE, EMBASE, and Cochrane databases. The databases were comprehensively searched by using the equivalent terms included in Appendix E1 (online).

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if all of the following applied: *(a)* the diagnostic performances of DW MRI and ^{18}F-FDG PET/CT to differentiate malignancy of pulmonary lesions were clearly identified in the study; *(b)* the number of true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results could be obtained from the article; and *(c)* the reference standard parameter for malignancy was either histopathologic analysis or imaging follow-up.

We excluded the following kinds of articles: *(a)* studies not published in English; *(b)* studies focusing on staging, prognosis, or therapy response rather than on nodule differentiation; *(c)* case reports, letters to the editor, studies with animals; *(d)* studies in which FDG PET was not integrated with CT; and *(e)* studies using radiotracers other than ^{18}F-FDG.

Study Quality Assessment

Two reviewers (M.Z. and S.A.) assessed the quality of all eligible studies with the current Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2, tool (26). This tool is composed of four major domains: patient selection, index test, reference standard, and flow and timing. These domains were then further assessed on the basis of the risk of bias and were rated regarding applicability as "high," "low," or "unclear" (26). We decided to include only studies that had at least four domains rated as low risk. A third reviewer (B.H.) was consulted to resolve disagreements between the two reviewers by consensus.

Data Extraction

Three reviewers independently reviewed all included articles to collect all key information (eg, study design, country of recruitment, technical specifications). Any disagreements were resolved by consensus. The numbers of TP, FP, TN, and FN results were obtained or derived from the studies.

Endemic Zones of Granulomatous Disease

We stratified studies that were performed in endemic zones of granulomatous disease. They were considered to be from an endemic zone in the following instances: *(a)* this information was explicitly stated in the study; *(b)* when granulomas with infectious etiologies consisted of at least 50% of all benign lesions; and *(c)* when the study was from a country on the high burden list for tuberculosis according to the World Health Organization for the period 2016–2020 (27).

Diagnostic Performance Analyses

Our primary diagnostic performance analysis of DW MRI and PET/CT included only studies in which both modalities were performed in the same population as an attempt to reduce the clinical (ie, pretest probability of malignancy) and methodologic interstudy heterogeneity. The secondary analysis investigated the diagnostic performance of each method of lesion qualification of DW MRI and PET/CT (quantitative: apparent diffusion coefficient [ADC], maximum standardized uptake value [SUV] [SUV_{max}], SUV contrast ratio [SUV-CR]; semiquantitative: lesion-to–spinal cord signal intensity ratio [LSR]; and qualitative: five-point scale–ordinal scale of the radiologist's certainty of the benign or malignant nature of a lesion using all available imaging features).

Statistical Analysis

The pooled sensitivities and specificities and 95% confidence intervals (CIs) were calculated by using random-effect analysis. The pooled positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratios (DORs) were also obtained. Summary receiver operating characteristic curves were constructed, and the areas under the curve (AUCs) were obtained. The Z test was performed for direct comparison of diagnostic accuracy of the joint PET/CT and MRI studies, and a two-tailed *P* value of less than .05 was considered to indicate a significant difference. To assume an approximate normal

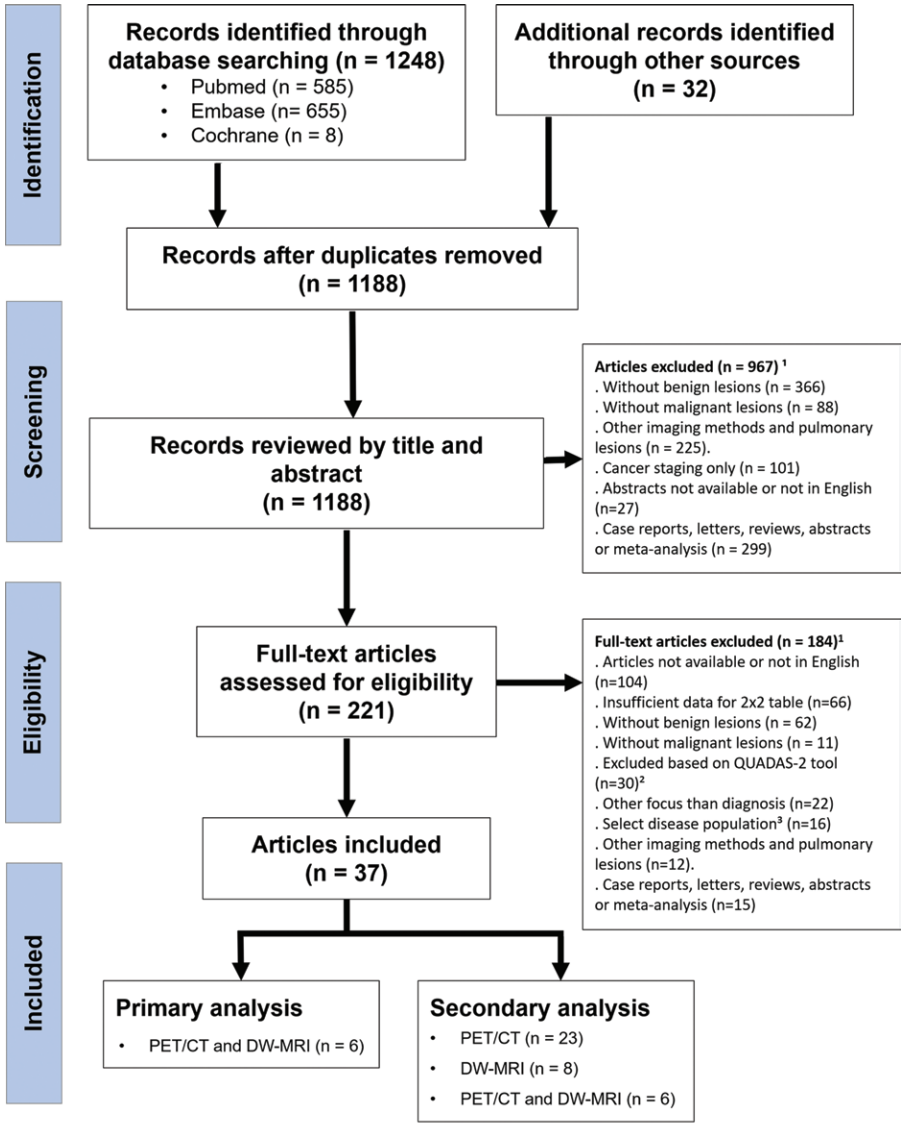
distribution, we used the distribution of logit-transformed sensitivity and specificity and the natural logarithm of DOR (28–30). To identify potential sources of heterogeneity, we stratified our secondary analysis in subgroups according to characteristics such as sample size, study design, and those studies performed in known areas of endemic granulomatous disease. The threshold effect between sensitivity and 1 − specificity was calculated with the Spearman correlation coefficient, and a positive coefficient (ρ) of 0.6 or greater was considered to indicate a significant correlation (31). The Deeks funnel plot was used to display possible publication bias. Interstudy heterogeneity was also evaluated by using Galbraith plots (32). Studies outside the 95% boundaries of the regression line may be considered outliers accounting for interstudy heterogeneity (32). All analyses were performed by using Stata, version 12.0 (Stata, College Station, Tex).

Results

Study Selection and Description

The initial search yielded 1280 articles (Fig 1), from which 221 articles were reviewed and a total of 37 articles were considered eligible: 23 studies for ^{18}F-FDG PET/CT (9,11,12,33–52), eight for DW MRI (3,19,53–58), and six studies that included both modalities (17,20–24).

The characteristics of the included studies are summarized in Tables E1–E4 (online). The methods of lesion qualification were heterogeneous for both imaging modalities. The most common parameter in PET/CT studies was SUV_{max} (n = 24). In DW MRI studies, ADC (n = 12), LSR (n = 4), and a five-point scale (n = 2) were used. The studies using DW MRI had a total of 1008 subjects with 1116 pulmonary lesions (74.6% malignant, 25.4% benign). For the studies using PET/CT, the total sample size was 3867 with 4075 pulmonary lesions (69.3% malignant, 30.7% benign). In the studies of joint DW MRI and PET/CT, the total sample size was 651 patients and 728 lesions (77.3% malignant, 22.7% benign). The median lesion size was 18.5 mm (interquartile range, 16.0–22.5 mm; n = 19) in PET/CT studies and 22.0 mm (IQR, 18.4–28.7; n = 11) in DW MRI studies. One of the PET/CT studies reported the results according to lesion size (for small nodules [>0.8 to 1.5 cm] vs large nodules [>1.5 to 3 cm]), and its results were analyzed separately (49).



1. The same study could be excluded for multiple reasons.
2. Studies with ≥ 4 domains considered high/nuclear risk were excluded
3. Studies with populations subjected to preselection of specific histology (e.g., adenocarcinoma) or tumor characteristics in imaging (e.g., ground-glass opacity, atelectasis, consolidation) were excluded

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, or PRISMA, flow diagram of the meta-analysis. *DW* = diffusion weighted, *QUADAS* = Quality Assessment of Diagnostic Accuracy Studies.

QUADAS-2 Assessment

All the methodologic results of the QUADAS-2 assessment are presented in Figure E1 (online) (for joint PET/CT and DW MRI), Figure E2 (online) (for DW MRI), and Figure E3 (online) (for PET/CT). For the joint PET/CT and DW MRI studies, participant selection was considered at low risk of bias in 50% of studies (n = 3) and at high risk of bias in 16.7% of studies (n = 1), while for the remaining 33.3% of studies, subject selection was unclear. Regarding the reference standard, all studies were judged as having low risk of bias because they used

histopathologic analysis, follow-up for at least 2 years, or both. Most studies (n = 4, 66.7%) could not be evaluated in terms of risk of bias for flow and timing because they did not provide the appropriate interval between the index test and reference standard.

Table 1: Diagnostic Performances of Six Studies Using Both DW MRI and PET/CT as Imaging Modalities for the Evaluation of Indeterminate Pulmonary Lesions

Parameter	DW MRI	95% CI	PET/CT	95% CI	*P* Value
No. of TP results	454	…	429	…	…
No. of TN results	147	…	133	…	…
No. of FP results	19	…	33	…	…
No. of FN results	109	…	140	…	…
Sensitivity (%)	83	75, 89	78	70, 84	.018
Specificity (%)	91	80, 96	81	72, 88	.056
PPV (%)	89	83, 94	79	73, 84	…
NPV (%)	83	78, 88	77	71, 82	…
PLR	9.1	4.0, 20.8	4.1	2.6, 6.5	…
NLR	0.18	0.12, 0.28	0.28	0.19, 0.40	…
DOR	50	19, 132	15	7, 32	.001
AUC	0.93	0.90, 0.95	0.86	0.83, 0.89	.001

Note.—Data are pooled estimates for all six studies (17,20–24) of joint DW MRI and PET/CT in the same population for the evaluation of indeterminate pulmonary lesions. AUC = area under the summary receiver operating characteristic curve, CI = confidence interval, DOR = diagnostic odds ratio, DW = diffusion weighted, FN = false-negative, FP = false-positive, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value, TN = true-negative, TP = true-positive.

Diagnostic Accuracy of ^{18}F-FDG PET/CT and DW MRI

The pooled analyses of the studies that performed joint PET/CT and DW MRI in the same patient population are summarized in Table 1. Diagnostic performances were analyzed per lesion in all the included studies. The sensitivity and specificity of DW MRI were 83% (95% CI: 75%, 89%) and 91% (95% CI: 80%, 96%), whereas the sensitivity and specificity for PET/CT were 78% (95% CI: 70%, 84%; P = .01 compared with DW MRI) and 81% (95% CI: 72%, 88%; P = .056 compared with DW MRI), respectively (Fig 2). DW MRI yielded a higher AUC of 93% (95% CI: 90%, 95%), compared with 86% (95% CI: 83%, 89%) for PET/CT (P = .001) (Fig 3). The DOR for DW MRI was significantly higher than that for PET/CT (50 vs 15, P = .001).

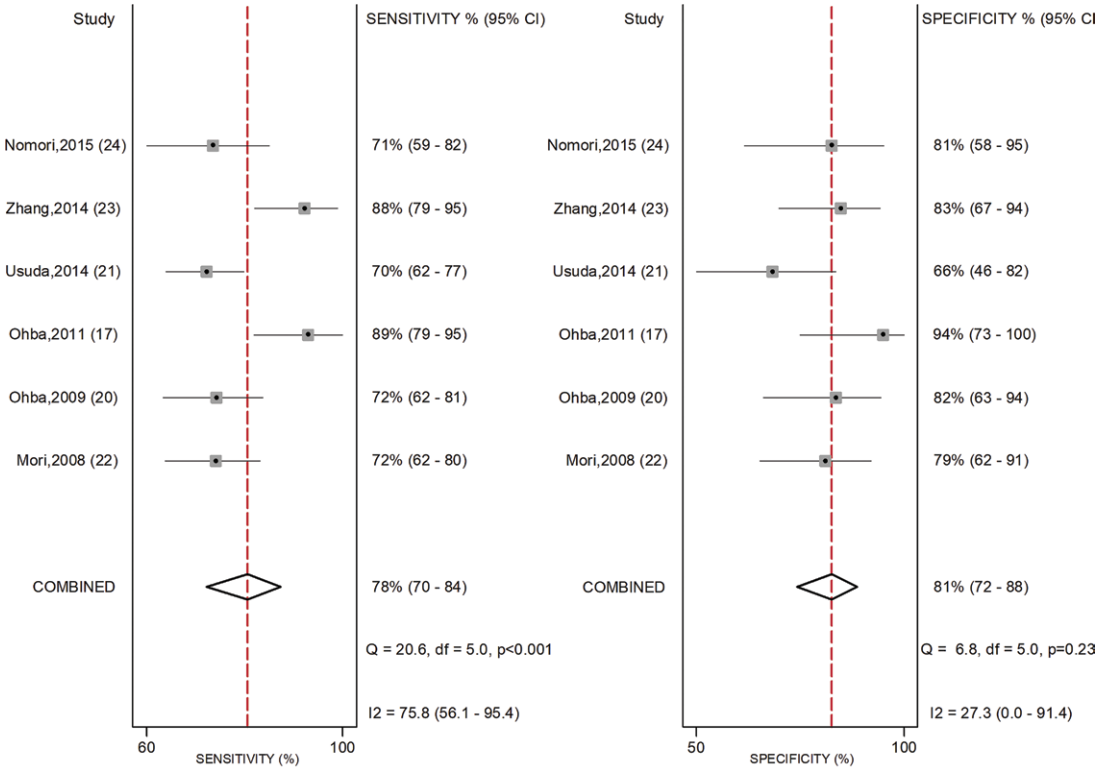
The secondary analysis to investigate each imaging parameter by modality included a total of 37 articles. The pooled analyses of the main parameters (ADC, LSR, and SUV_{max}) are summarized in Table E5 (online). The pooled sensitivity and specificity of ADC at DW MRI were 83% (95% CI: 77%, 88%) and 86% (95% CI: 76%, 92%), respectively (Fig E4, *A* [online]). The combination of the DW LSR studies revealed a sensitivity of 81% (95% CI: 71%, 88%) and a specificity of 90% (95% CI: 79%, 95%). In comparison, SUV_{max} had a sensitivity of 86% (95% CI: 82%, 90%) but a specificity of 73% (95% CI: 62%, 82%) (Fig E4, *B* [online]). The summary pooled analyses of each method were charted on summary receiver operating characteristic curves, as shown in Figure E5 (online). Analyses of use of a five-point scale at PET/CT, SUV-CR, and a five-point scale at DW MRI scale were not possible because of the limited number of studies.

Heterogeneity Analysis (Subgroup Analysis)

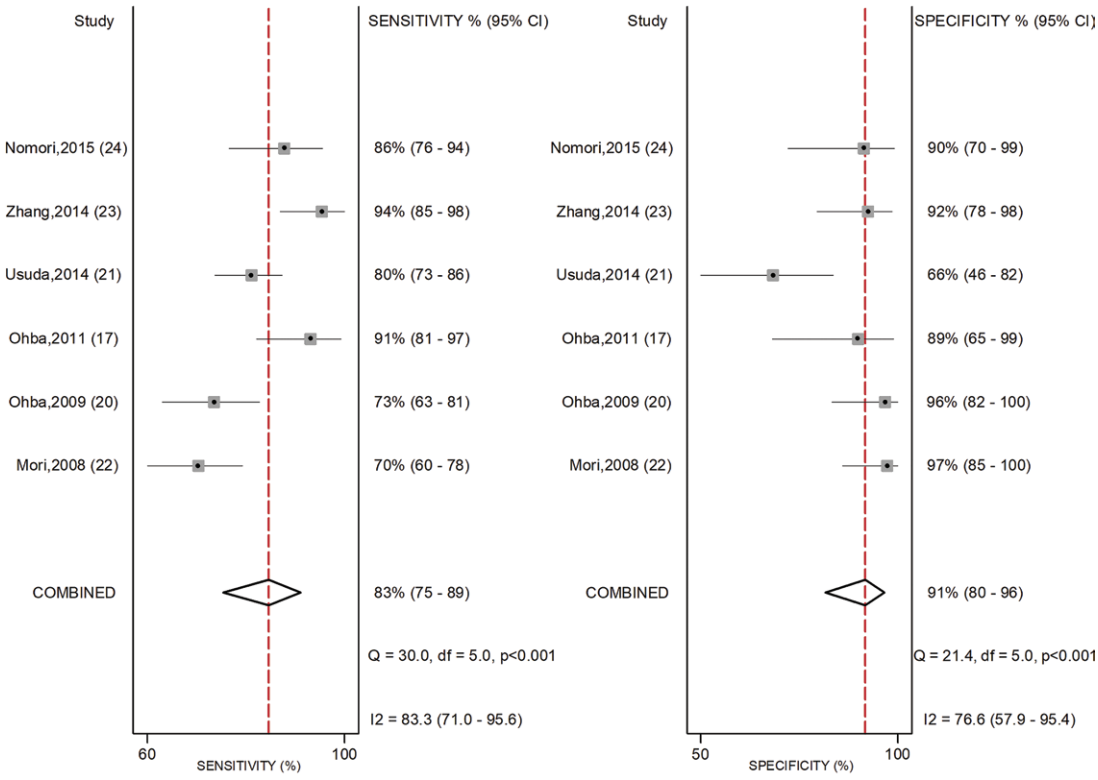
In the primary analysis, there was a strong, significant heterogeneity for DW MRI sensitivity (I^2 = 83.4%) and specificity (I^2 = 76.7%), with a nonsignificant threshold effect (ρ = 0.486, P = .329). The heterogeneity for PET/CT was also strong for sensitivity (I^2 = 75.8%, P < .001) and nonsignificant for specificity (I^2 = 27.3%, P = .23), with no evidence of a threshold effect given the negative direction of the negative correlation (ρ = −0.899, P = .015). Although the limited number of articles did not permit a subgroup analysis, we visually assessed the bivariate forest plots for potential sources of heterogeneity (Fig 2). The study by Usuda et al (21) consistently yielded a lower-than-predicted specificity for both methods. Also, the study by Zhang et al (23) provided higher-than-predicted sensitivities for both methods, which could be explained, as this was the only study performed in an endogenous zone of granulomatous disease. Visual assessment of the DW MRI summary receiver operating characteristic curve (Fig 3, *A*) shows that with removal of the study by Usuda et al, heterogeneity would be largely explained by the threshold effect (ρ = 0.7, P = .188) (21). Analysis of the Galbraith plots for interstudy heterogeneity also supports the idea that the studies by Usuda et al and Zhang et al are outliers for both imaging modalities (Fig 4).

In the secondary analysis including all PET/CT and DW MRI studies, subgroup analysis was possible for DW ADC and SUV_{max} but not for other parameters, given the small number of studies. For DW ADC, sample size, blinding, endemic zone of granulomatous disease, ADC cutoff value, and b value were identified as potential factors accounting for the between-study heterogeneity (Table 2). On the other hand, for SUV_{max} at PET/CT, only blinding and endemic zone of granulomatous disease were significant factors (Table 3). Notably, studies from endemic zones of granulomatous disease had significantly higher pooled sensitivity but lower pooled specificity for both DW ADC and SUV_{max} at PET/CT.

The Deeks funnel plot regression revealed no statistical evidence of asymmetry for DW ADC and PET/CT SUV_{max} studies (P = .19 and P = .09, respectively) (Fig E6 [online]). This suggests that no major publication bias was present, although this cannot be entirely excluded by funnel plot regression. There was an insufficient number of DW LSR and joint DW MRI/PET studies to allow assessment of reporting bias.



a.



b.

Figure 2: Forest plots of **(a)** diffusion-weighted (DW) MRI and **(b)** PET/CT studies, including the six studies performing DW MRI and PET/CT in the same population. Compared with PET/CT, DW MRI had a superior pooled sensitivity (83% vs 78%, $P = .01$) and specificity (91% vs 81%, $P = .056$). The Q statistic and I^2 are measurements of heterogeneity. Heterogeneity was strong and significant for all pooled analyses, except for specificity for PET/CT. The study by Usuda et al (21) consistently reported lower specificity and was responsible in part for the heterogeneity for both imaging modalities.

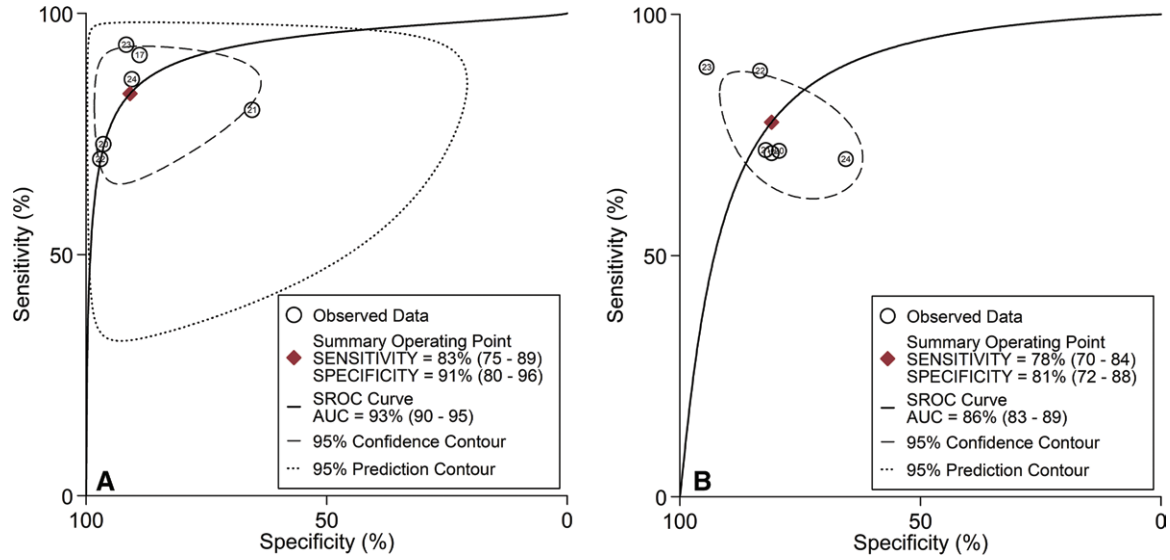


Figure 3: Summarized receiver operating characteristic *(SROC)* curves for, *A*, diffusion-weighted (DW) MRI and, *B*, PET/CT for the six studies in which joint DW MRI and PET/CT were performed in the same population. The estimated SROC of DW MRI provided a significantly higher area under the curve *(AUC)* compared with PET/CT (0.93 vs 0.88, $P < .001$), which suggests an overall higher diagnostic performance of the method. Visual analysis of the curves reveals that the study of Zhang et al (23) reported a higher-than-expected sensitivity for both present models (DW MRI and PET/CT). Numbers within circles = references.

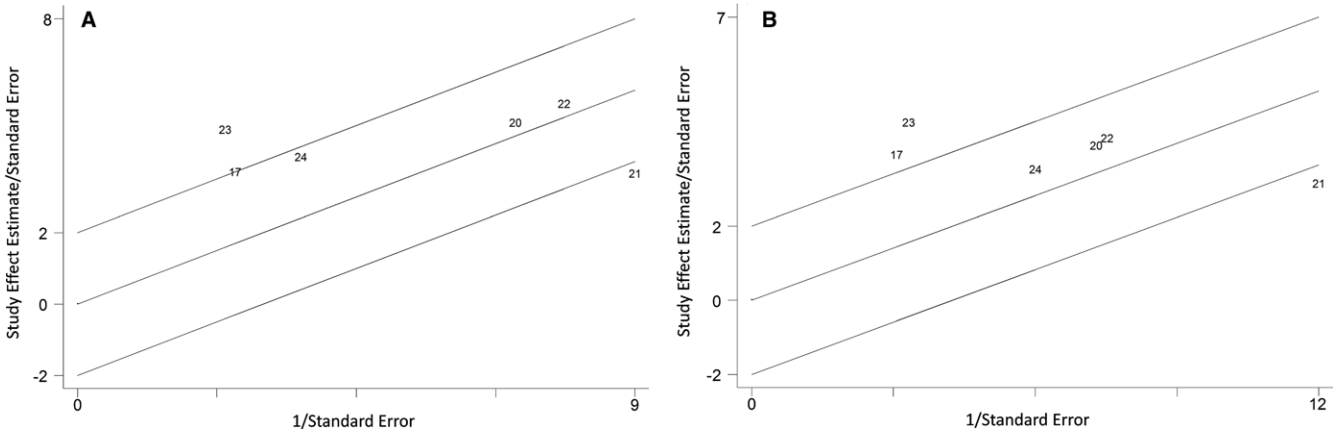


Figure 4: Galbraith plots for the, *A*, diffusion-weighted (DW) MRI and, *B*, PET/CT studies included in the primary analysis. The Galbraith plot is an alternative to the Forest plot to identify the sources of interstudy heterogeneity by incorporating the effect size of each study compared with the pooled analysis. The y-axis represents the test statistics (effect/standard error of the estimate) of each study, which are expected to fall within 2 units of the pooled effects for 95% of the studies. The x-axis plots 1/standard error of the pooled study estimate. The studies by Usuda et al (21) and Zhang et al (23) were identified as sources of heterogeneity for both DW MRI and PET/CT. For PET/CT, the study by Ohba et al (17) was also implicated in the interstudy heterogeneity. All studies are identified according to their reference number.

Discussion

The 2017 guidelines for evaluation of incidental solitary pulmonary nodules (SPNs) by the Fleischner Society did not include MRI as a potential diagnostic tool for the evaluation of an SPN (59). The results of the primary analysis indicate that DW MRI is comparable or even superior to PET/CT, which would support the inclusion of MRI as an alternative to the diagnostic work-up of indeterminate pulmonary lesions. DW MRI yielded a higher pooled sensitivity (83% vs 78%, $P = .018$), specificity (91% vs 81%, $P = .056$), DOR (50% vs 15%, $P = .001$), and AUC (0.93 vs 0.86, $P = .001$) compared with PET/CT. Although individual comparisons of sensitivity and specificity in the meta-analysis with different thresholds were limited, the significant difference in DOR supports a possible higher diagnostic accuracy of DW MRI compared with PET/CT. Our primary analysis, to limit clinical and methodologic heterogeneity, concentrated on those studies that evaluated the same population with DW MRI and PET/CT (six studies, 651 patients, 729 lesions) and found good agreement with the larger secondary analysis where all relevant studies were included (37 studies, 4224 patients, 4463 lesions).

Table 2: Subgroup Analyses of the Diagnostic Performance of DW MRI ADC for Evaluation of Indeterminate Pulmonary Lesions in 12 Studies

Characteristic	No. of Studies	No. of Patients	No. of Lesions	Sensitivity (%)	Specificity (%)
Sample size*					
<100	8	368	410	87 (80, 94)	88 (79, 97)
≥100	4	516	565	86 (80, 91)	85 (78, 93)
Study design					
Prospective	9	659	737	91 (82, 99)	77 (54, 99)
Retrospective/unclear	3	221	238	85 (80, 90)	88 (82, 93)
Consecutive enrollment					
Yes	6	260	286	87 (82, 93)	82 (72, 92)
No/unclear	6	620	689	84 (78, 91)	90 (84, 97)
Blind*					
Yes	10	795	875	86 (81, 92)	87 (80, 93)
No/unclear	2	85	100	85 (76, 94)	86 (74, 99)
Endemic zone of granulomatous disease*					
Yes	5	294	301	87 (79, 92)	83 (72, 90)
No	7	586	674	80 (73, 85)	88 (70, 96)
ADC cutoff value (10^{-3} mm^2/sec)*†					
<1.1	4	394	452	84 (73, 92)	87 (69, 95)
≥1.1	8	486	523	80 (75, 84)	85 (71, 93)
Mean lesion size (mm)*‡					
≤20	4	238	270	84 (76, 90)	84 (68, 93)
>20	5	435	491	80 (72, 87)	88 (73, 95)
b Value (sec/mm^2)*					
<1000	6	411	436	83 (76, 88)	75 (57, 87)
≥1000	6	469	539	83 (73, 90)	93 (87, 97)

Note.—Data are pooled estimates for all 12 studies (3,17,19–23,54–58) that used DW MRI ADC for the evaluation of indeterminate pulmonary lesions. Five factors were associated with the heterogeneity in studies of DW MRI: sample size, studies performed in areas of known granulomatous disease, ADC cutoff value, lesion size, and *b* value. Data in parentheses are 95% confidence intervals. ADC = apparent diffusion coefficient, DW = diffusion weighted.

* There was a statistically significant difference between these subgroups ($P < .05$).

† ADC cutoff value was not available in two studies.

‡ Mean lesion size was not available in three studies.

MRI has emerged as a promising modality in chest imaging to differentiate benign and malignant pulmonary lesions (60,61). Some authors have speculated that pulmonary MRI could even be used as a screening modality for lung cancer (62). According to data obtained from the searchable Medicare physician fee schedule in 2018, the average national facility reimbursement for ambulatory PET/CT was $1411.18, compared with $307.08 for chest MRI without contrast material (63). Thus, in the setting of lung cancer screening and diagnosis, MRI has advantages over PET/CT. These include the lack of ionizing radiation and a lower cost (60,61,63).

The diagnostic performance of DW MRI varied according to the parameter evaluated, which could be qualitative using a five-point scale, semiquantitative (eg, LSR), or quantitative (eg, ADC) (2,63–66). Shen and colleagues (66) were the first to publish a meta-analysis of DW MRI in pulmonary lesions stratified by each DW MRI diagnostic parameter. Our secondary analysis of DW MRI found similar results to those of Shen et al, even though we did not include Chinese studies (n = 14, 1206 patients) for which English text was not available.

Previous meta-analyses that investigated the use of ^{18}F-FDG PET/CT for pulmonary lesions combined very heterogeneous studies (eg, PET alone and hybrid PET/CT were combined) (8,67–69). Despite our attempt to control for those factors, our analysis demonstrated that there remains a large degree of heterogeneity among PET/CT studies in the literature. Thus, the current data on PET/CT is not more robust than that available for DW MRI to support one modality over the other.

Our primary analysis demonstrated significant statistical heterogeneity, which is expected because of the threshold effect, as the pair of sensitivity and specificity will vary in opposite directions according to the cutoff threshold (31). Other factors (nonthreshold) may also account for the statistical heterogeneity, as seen in the primary analysis with the studies of Usuda et al (21) and Zhang et al (23). The subgroup analyses identified other possible sources of heterogeneity for DW MRI (sample size, blinding, endemic zone of granulomatous disease, ADC cutoff, *b* value) and also for PET/CT SUV_{max} (lack of reader blinding and endemic zones of granulomatous disease and other pulmonary infectious agents). In areas with a high prevalence of granulomatous lung disease, both DW ADC and PET/CT

Table 3: Subgroup Analyses of the Diagnostic Performance of PET/CT SUV_{max} for Evaluation of Indeterminate Pulmonary Lesions in 24 Studies

Characteristic	No. of Studies	No. of Patients	No. of Lesions	Sensitivity (%)	Specificity (%)
Sample size					
<100	12	710	811	84 (78, 90)	82 (73, 91)
≥100	12	2448	2495	86 (81, 91)	71 (60, 83)
Study design					
Prospective	13	2280	2411	85 (79, 90)	70 (58, 82)
Retrospective/unclear	11	978	995	85 (80, 91)	82 (74, 91)
Consecutive enrollment					
Yes	12	1648	1778	86 (8, 91)	67 (54, 79)
No/unclear	12	1610	1628	84 (79, 89)	83 (75, 91)
Blind*					
Yes	18	2136	2171	85 (80, 90)	82 (75, 88)
No/unclear	6	1122	1235	85 (78, 92)	61 (45, 77)
Endemic zone of granulomatous disease*					
Yes	8	1141	1163	92 (88, 95)	61 (43, 77)
No	16	2117	2243	82 (77, 87)	79 (66, 88)
SUV_{max} cutoff value†					
≤2.5	16	2127	2275	87 (82, 91)	72 (58, 82)
>2.5	6	1131	1131	85 (76, 91)	76 (63, 85)
Mean lesion size (mm)‡					
≤20	11	1144	1274	87 (81, 91)	73 (59, 84)
>20	6	682	700	85 (78, 90)	72 (57, 84)

Note.—Data are pooled estimates for all 24 studies (9,11,12,17,21,23,33–45,47–49,51,52) that used PET/CT maximum standardized uptake value (SUV_{max}) for the evaluation of indeterminate pulmonary lesions. We identified three potential factors for the heterogeneity among the studies, including lack of reader blinding, SUV_{max} cutoff value, and studies performed in areas with high incidence of granulomatous disease. The specificity of PET/CT SUV_{max} was consistently lower in those studies in known areas of granulomatous disease. Data in parentheses are 95% confidence intervals.

* There was atatistically significant difference between these subgroups ($P < .05$).

† SUV_{max} cutoff value was not available in two studies.

‡ Mean lesion size was not available in six studies.

SUV_{max} were less specific (5% and 18%, respectively) for lung nodule characterization, although DW ADC was much less affected than SUV_{max} by the presence of infection.

In a previous meta-analysis on this topic, Deppen et al (68) also reported lower mean specificity of ^{18}F-FDG PET for lung nodule characterization in regions with endemic infectious lung disease (specificity, 61% [95% CI: 49%, 72%]), which discouraged the use of PET to evaluate suspicious pulmonary lesions in endemic areas. In the work of Deppen et al, a zone was considered as endemic of granulomatous disease if this was either explicitly stated in the study or if more than 50% of benign lesions were of infectious lung disease etiology (68). However, the latter may have been underestimated in the studies that classified a nodule as benign only according to follow-up (and not histopathologic examination). For this reason, we extended the criteria used by Deppen et al and considered all studies with samples from the top 30 countries with a high burden for *Mycobacterium tuberculosis* listed by the World Health Organization as from endemic areas.

Our study had some limitations that warrant discussion. First, our primary analysis was limited because of the small number of studies assessing joint DW MRI and PET/CT in the same population. The overall heterogeneity was high; thus, it is possible that other institutions might encounter similar deviations from the pooled results in prospective studies. Second, there were limitations inherent to any meta-analyses evaluating diagnostic tests (eg, publication bias, selection bias, missing information from some studies, and potential for ecologic fallacy). Also, the exclusion of studies not available in English could have increased the probability of publication bias. Although the Deeks funnel plot regression suggested no major publication bias for both DW MRI and PET/CT studies, this does not entirely exclude this possibility. Third, combining data from studies that lack standardized methodologic techniques (eg, different DW MRI *b* values) and cutoffs may be difficult to interpret and translate to real practice and can result in spectrum bias. Fourth, information about the blinding of observers to histologic and clinical data was not reported in some of the studies. Finally, few data were available from each study about the diagnostic performance of the tests according to lesion size.

In summary, we found that the diagnostic performance of diffusion-weighted (DW) MRI was comparable or even superior to that of fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) PET/CT for the noninvasive work-up of suspicious pulmonary nodules and masses. This meta-analysis supports

the inclusion of DW MRI as a radiation-free and less costly imaging modality for the primary noninvasive diagnostic work-up of suspicious pulmonary lesions. Despite the heterogeneity and limitations found in this study, these data suggest the need for larger scale randomized controlled trials for the direct comparison of DW MRI and ^{18}F-FDG PET/CT in the setting of suspicious lung pathologic findings.

Author contributions: Guarantors of integrity of entire study, A.B.D., M.Z., G.S.P., G.W., T.L.M., T.M., B.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.B.D., M.Z., S.A., N.H.C., G.W., T.L.M., N.V., T.M., E.M., B.H.; clinical studies, A.B.D., M.Z., S.A., T.L.M., N.V., K.I.; statistical analysis, M.Z., S.A., N.H.C., G.W., A.G., T.L.M., B.H.; and manuscript editing, A.B.D., M.Z., S.A., G.S.P., N.H.C., G.W., T.L.M., N.V., T.M., E.M., K.I., B.H.

Disclosures of Conflicts of Interest: **A.B.D.** disclosed no relevant relationships. **M.Z.** disclosed no relevant relationships. **S.A.** disclosed no relevant relationships. **G.S.P.** disclosed no relevant relationships. **N.H.C.** disclosed no relevant relationships. **G.W.** disclosed no relevant relationships. **A.G.** disclosed no relevant relationships. **T.L.M.** disclosed no relevant relationships. **N.V.** disclosed no relevant relationships. **T.M.** disclosed no relevant relationships. **E.M.** disclosed no relevant relationships. **K.I.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: Roche waived fees for lecture on interstitial lung diseases for £500.00. Other relationships: disclosed no relevant relationships. **B.H.** disclosed no relevant relationships.

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Supplemental material

Appendix E1: Search Strategy in the Online Databases

("lung cancer"[All Fields] OR "lung neoplasm"[All Fields] OR "solitary pulmonary nodules"[All Fields] OR "spns"[All Fields] OR "pulmonary nodules"[All Fields] OR "pulmonary mass"[All Fields]) AND ("FDG"[All Fields] OR "18F-FDG"[All Fields] OR "FDG-^{18}F"[All Fields] OR "fluorodeoxyglucose"[All Fields] OR "PET/CT"[All Fields] OR "positron emission tomography/computed tomography"[All Fields] OR "PET-CT"[All Fields] OR "positron emission tomography-computed tomography"[All Fields] OR "DW-MRI"[All Fields] OR "diffusion-weighted magnetic resonance imaging"[All Fields]) AND ("specificity"[All Fields] OR "sensitivity"[All Fields] OR "false-positive"[All Fields] OR "false-negative"[All Fields] OR "detection"[All Fields] OR "diagnosis"[All Fields] OR "accuracy"[All Fields]).

Figure E1: Methodological quality of all eligible PET/CT studies according to the QUADAS-2.

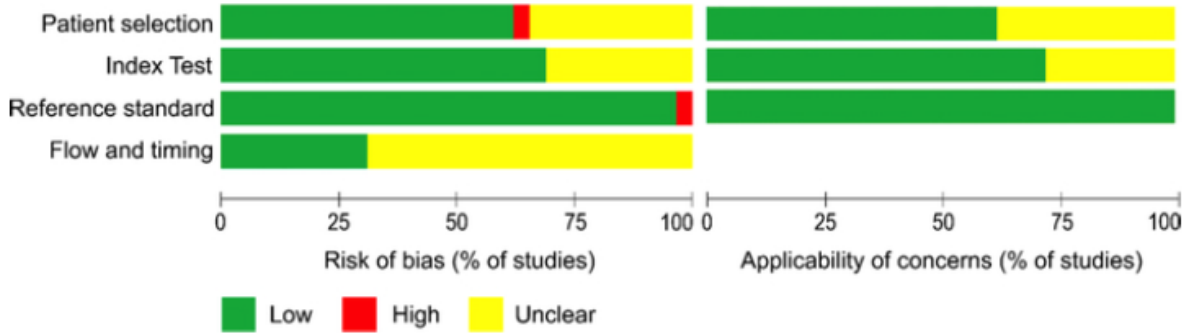

Figure E2: Methodological quality of all eligible DW MRI studies according to the QUADAS-2.

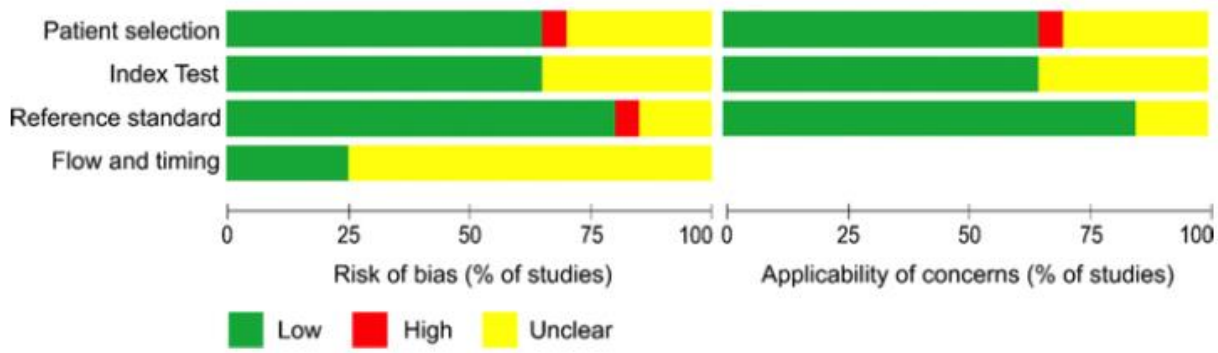

Figure E3: Forest plot of all individual DW ADC (A) and PET/CT SUVmax (B) studies of the secondary analysis. Heterogeneity (represented by Q-statistic and I2) was high and significant for pooled sensitivity and specificity for both DW ADC and PET/CT SUVmax studies.

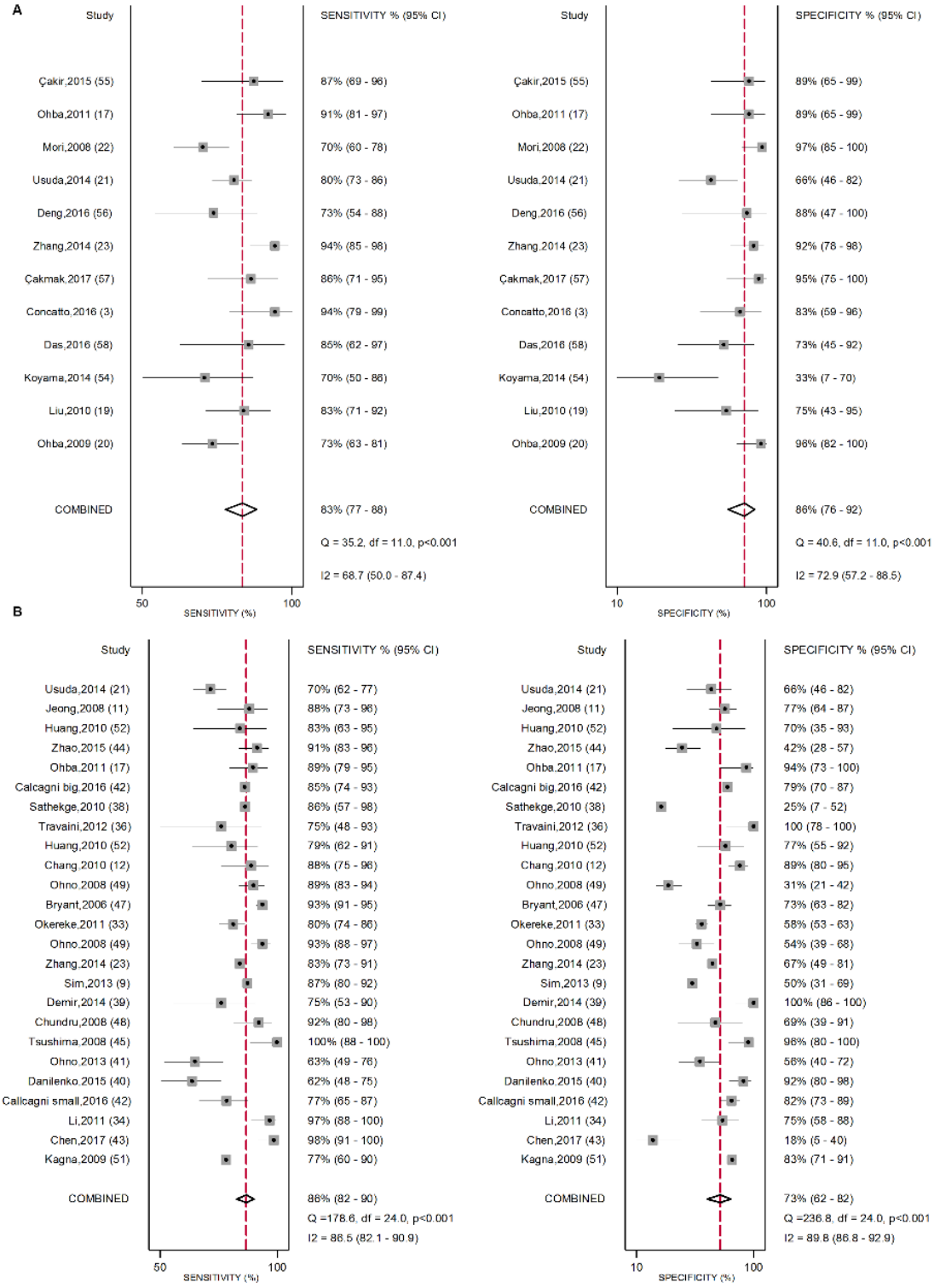

Figure E4: Summarized receiver-operating curves of PET/CT SUVmax (A), DW ADC (B), and DW LSR (C). Numbers within the circles correspond to the references.

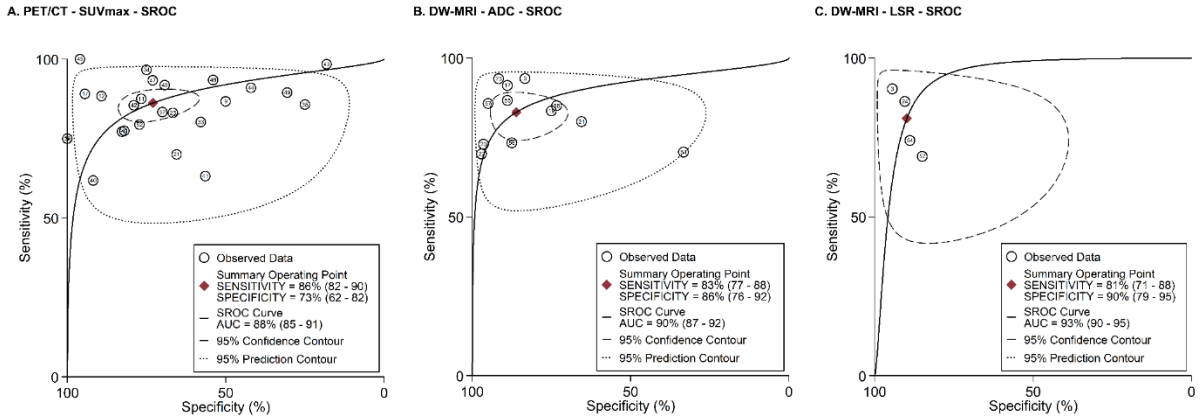

Figure E5: Deeks' funnel plot of the PET/CT (A) and DWI studies (B). The slopes were not significant for both DW ADC (*P* = .09) and PET/CT SUVmax (*P* = .18), indicating no major publication bias.

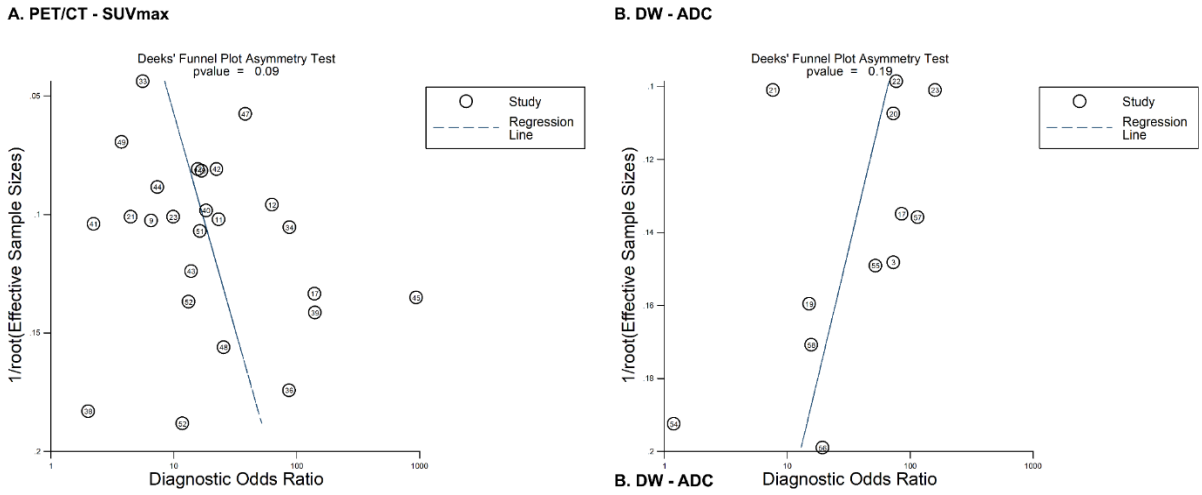

Table E1: Main Characteristic for PET/CT Parameters for the Six Studies with Joint PET/CT and DW MRI Performed in the Same Patient Population

Study	Year	Country	Study Design	Blind	Reference Standard	Dose (MBq)	Number of patients, lesions	Type of lesion	Mean size (mm)	Endemic region	Parameters	Cutoff value
Mori (22)	2008	Japan	P	Yes	His/Fol	3.7/kg	104,140	106M, 34B	22	No	SUV CR	0.37
Ohba (20)	2009	Japan	R	Yes	His/Fol	3.7/kg	110,124	96M, 28B	16	No	SUV CR	0.31
Ohba (17)	2011	Japan	P	Yes	His/Fol	3.7/kg	58,76	58M, 18B	23	No	SUVmax	1.7
Zhang (23)	2014	China	P	Yes	His	370	113,113	77M, 36B	NA	Yes	SUVmax, 5-point	6.5, ≥ 4
Usuda (21)	2014	Japan	P	Yes	His/Fol	3.7/Kg	189,189	160M, 29B	30.1	No	SUVmax	3.43
Nomori (24)	2015	Japan	P	NA	His/Fol	185–230	77,87	66M, 21B	21	No	SUV CR	2.65

P = prospective, R = retrospective, NA = not available, His = histologic, Fol = follow-up, MBq = megabecquerels, M = malignant, B = benign, SUVmax = maximum standard uptake value, SUV CR = contrast ratio of standard uptake value, 5-point = five-point visual scale of probability of a malignant lesion, DW MRI = diffusion-weighted magnetic resonance imaging, PET/CT = positron emission tomography with compute tomography.

Table E2: Main Characteristic for DW MRI Parameters for the Six Studies with Joint PET/CT and DW MRI Performed in the Same Patient Population

Study	Year	Country	Study Design	Blind	Reference Standard	MRI Field	Number of patients, lesions	Type of lesion	Mean lesion size (mm)	Parameters	Cutoff Values (x 10^{-3} mm^2/s)	b-value (s/mm^2)
Ohba (17)	2011	Japan	P	Yes	His/Fol	1.5T	104,140	58M, 18B	23	ADC	1.1	1000
Ohba (20)	2009	Japan	R	Yes	His/Fol	1.5T	110,124	96M, 28B	16	ADC	1.2	1000
Mori (22)	2008	Japan	P	Yes	His/Fol	1.5T	58,76	106M, 34B	22	ADC	1.1	1000
Zhang (23)	2014	China	P	Yes	His	3.0T	113,113	77M, 36B	NA	ADC	0.991	1000
Usuda (21)	2014	Japan	P	Yes	His/Fol	1.5T	189,189	160M, 29B	30.1	ADC	1.44	800
Nomori (24)	2015	Japan	P	NA	His/Fol	1.5T	77,87	66M, 21B	21	LSR	0.45	800

Note.—All authors used a spin-echo echo-planar imaging sequence. P = prospective, R = retrospective, NA = not available, His = histologic, Fol = follow-up, T = tesla, M = malignant, B = benign, ADC = apparent diffusion coefficient, LSR = lesion-to-spinal ratio, DW MRI = diffusion-weighted magnetic resonance imaging.

Table E3: Principal Characteristics of the 23 Studies Using Only PET/CT for the Evaluation of Indeterminate Pulmonary Lesions

Study	Year	Country	Study Design	Blind	Reference Standard	Dose (MBq)	Number patients, lesions	Type of lesion	Mean size (mm)	Endemic region	Parameters	Cutoff value
Bryant (47)	2006	USA	P	NA	His	555	585,585	496M, 89B	Na	Yes	SUVmax	4.1

Kim (46)	2007	USA	R	Yes	His	7.5/kg	42,42	29M, 13B	15	Yes	5-point scale	ND
Jeong (11)	2008	Korea	R	Yes	His/Fol	370	100,100	40M, 60B	20.8	No	SUVmax	ND
Ohno (49)	2008	Japan	P	NA	His/Fol	4.44/kg	175,202	152M, 39B	15.7	No	SUVmax	1.8
Chundru (48)	2008	USA	P	Yes	His	555	62,62	49M, 13B	NA	Yes	SUVmax	3.5
Pauls (50)	2008	Germany	P	Yes	His/Fol	370–550	276,276	216M, 60B	41	No	5-point scale	≥4
Tsushima (45)	2008	Japan	R	Yes	His	370	53,53	28M, 25B	18.4	No	SUVmax	1.5
Kagna (51)	2009	Israel	R	Yes	His/Fol	370–550	93,93	35M, 58B	16	No	SUVmax	2.2
Chang (12)	2010	Taiwan	R	Yes	His/Fol	370	117,117	43M, 74B	NA	Yes	SUVmax	2
Huang (52)	2010	USA	P	Yes	His/Fol	370–550	56,56	34M, 22B	17.9	No	SUVmax	2.1
Okereke (33)	2011	USA	P	Yes	His	ND	584,584	414M, 170B	NA	No	SUVmax	2.5
Li (34)	2011	China	P	Yes	His/Fol	185–370	96,96	60M, 36B	17.6	Yes	SUVmax	2.5
Huang (35)	2012	Taiwan	ND	Yes	His	5.2/kg	34,34	24M, 10B	26	Yes	SUVmax	5.05
Travaini (36)	2012	Italy	R	Yes	His	5/Kg	14,31	16M, 15B	13.2	No	SUVmax	2
Sim (9)	2013	UK	R	Yes	His	350–400	186,186	158M, 28B	18	No	SUVmax	2.5
Ohno (37)	2013	Japan	P	NA	His/Fol	3.3/kg	52,96	57M, 39B	15.9	No	SUVmax	2.5
Sathekge (38)	2010	South Africa	P	NA	His	3.7/Kg	30,30	14M, 16B	18.9	Yes	SUVmax	2.5
Demir (39)	2014	Turkey	R	Yes	His/Fol	259–407	48,48	18M, 30B	NA	No	SUVmax	2.75
Danilenko (40)	2015	Canada	P	NA	His/Fol	370–555	82,104	55M, 49B	16	No	SUVmax	2.5
Ohno (41)	2015	Japan	P	NA	His/Fol	3.3/kg	198,218	133M, 85B	18.5	No	SUVmax	2
Zhao (44)	2015	China	R	Yes	His/Fol	5–6/Kg	139,139	89M, 50B	44.3	Yes	SUVmax	2.5
Calcagni (42)	2016	Italy	R	Yes	His/Fol	185–333	162,162	62M, 100B	12, 22	No	SUVmax	1.3
Chen (43)	2017	China	R	Yes	His/Fol	5.55/kg	85,85	63M, 22B	NA	Yes	SUVmax, 5-point	2.5, ≥ 3.5

P = prospective, R = retrospective, NA = not available, His = histologic, Fol = follow-up, MBq = megabecquerels, M = malignant, B = benign, SUVmax = maximum standard uptake value, SUV CR = contrast ratio of standard uptake value, 5-point = five-point visual scale of probability of a malignant lesion, PET/CT = positron emission tomography with compute tomography.

Table E4: Principal Characteristics of the 8 Studies Using Only DW MRI for the Evaluation of Indeterminate Pulmonary Lesions

Study	Year	Country	Study Design	Blind	Reference Standard	MRI Field	Number of patients, lesions	Type of lesion	Mean lesion size (mm)	Parameters	Cutoff Values (x 10^{-3} mm^2/s)	b-value (s/mm^2)
Liu (19)	2010	China	NA	Yes	His/Fol	1.5T	62,66	54M,12B	NA	ADC	1.4	500
Satoh (53)	2008	Japan	R	Yes	His/Fol	1.5T	51,54	36M,18B	33.8	5-Point	3	1000
Koyama (54)	2014	Japan	P	Yes	His/Fol	1.5T	32,36	27M,9B	16.8	ADC, LSR	0.4, 0.4	500
Çakir (55)	2015	Turkey	P	Yes	His/Fol	1.5T	46,48	30M,18B	27.4	ADC, 5-point	1.5, ≥ 3	1000
Deng (56)	2016	China	P	NA	His/Fol	3T	38,38	30M,8B	32.1	ADC	1.022	1000

Çakmak (57)	2017	Turkey	P	NA	His/Fol	1.5T	47,62	42M,20B	20	ADC, LSR	1.78, 0.86	600
Concatto (3)	2016	Brazil	NA	Yes	His/Fol	1.5T	49,49	31M,18B	12	ADC, LSR	1.08, 1.2	800
Das (58)	2016	China	P	Yes	His	3.0T	32,35	20M,15B	NA	ADC	1.26	800

Note.—All authors used a spin-echo echo-planar imaging sequence. P = prospective, R = retrospective, NA = not available, His = histologic, Fol = follow-up, T = tesla, M = malignant, B = benign, ADC = apparent diffusion coefficient, 5-point = five-point visual scale of probability of a malignant lesion, LSR = lesion-to-spinal cord ratio, DW MRI = diffusion-weighted magnetic resonance imaging.

Table E5: Diagnostic Performances of the Main Parameters Used in DWI and PET/CT for the Entire Group of Studies

	ADC (DW MRI)	95% CI	LSR (DW MRI)	95% CI	SUVmax (PET/CT)	95% CI
TP	591		134		1886	
TN	208		61		479	
FP	37		7		306	
FN	140		32		956	
Sensitivity (%)	83	77–88	81	71–88	86	82–90
Specificity (%)	86	76–92	90	79–95	73	62–82
PPV (%)	84	78–90	87	82–93	74	69–80
NPV (%)	82	76–88	81	76–86	82	76–89
PLR	6.0	3.3–10.7	8.0	3.6–17.5	3.2	2.2–4.5
NLR	0.20	0.14–0.27	0.21	0.13–0.34	0.19	0.14–0.25
DOR	30	14–66	38	12–115	17	10–28
AUC	0.90	0.87–0.92	0.92	0.90–0.95	0.88	0.85–0.91

Note.—Data are pooled estimates for the entire group of studies using DWI ADC (3,17,19–23, 54–58), DWI LSR (3,24,54,57) and PET/CT SUVmax (9,11,12,17, 21,23,33–45, 47–49,51,52) for the evaluation of indeterminate pulmonary lesions. Analysis of 5-point scale (DWI and PET/CT) and SUV-CR (PET/CT) were not possible due to the limited number of studies. DW MRI = diffusion-weighted magnetic resonance imaging, ADC = apparent diffusion coefficient, LSR = lesion-to-spinal cord ratio, PET/CT = positron emission tomography with computed tomography, SUVmax = maximum standardized uptake value, CR = contrast ratio, TP = true positive, TN = true negative, FP = false positive, FN = false negative, PPV = positive predictive value, NPV = negative predictive value, PLR = positive likelihood ratio, NLR = negative likelihood ratio, DOR = diagnostic odds ratio, AUC = area under the curve.

5. CONCLUSÕES

Através deste estudo, demonstrou-se que a acurácia diagnóstica da Ressonância Magnética com Difusão (DW MRI) é semelhante ou superior a da Tomografia por Emissão de Pósitrons com Tomografia Computadorizada com 18F-Fluorodeoxiglicose (18F-FDG PET/CT) na diferenciação de lesão pulmonar maligna de benigna.

Desta forma, esta metanálise reforça a inclusão da DW MRI como um método acurado, não invasivo, isento de radiação ionizante e com um custo menor em relação ao PET/CT na avaliação de lesões pulmonares indeterminadas.

Em anexo, segue o editorial publicado na revista *Radiology*, em que o editor-adjunto, Dr. Mark L. Schiebler, comenta os principais resultados deste artigo, as implicações práticas decorrentes deste estudo e as perspectivas futuras na avaliação dos nódulos pulmonares indeterminados.

6. APÊNDICES

6.1. Editorial escrito pelo editor-adjunto da revista *Radiology* sobre o artigo publicado.

Radiology

REVIEWS AND COMMENTARY • EDITORIAL

Can Solitary Pulmonary Nodules Be Accurately Characterized with Diffusion-weighted MRI?

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Conflicts of interest are listed at the end of this article.

See also the article by Basso Dias et al in this issue.

Radiology 2019; 00:1–2 • https://doi.org/10.1148/radiol.2018182442 • Content codes: CH MR OI •

Lung cancer is the leading cause of cancer death in the world, at a rate of 1.2 million persons per year (1,2). For more than 25 years, lung and bronchus cancer deaths have led all cancer types in both male patients (83 550 estimated deaths in 2018) and female patients (70 500 estimated deaths) (3). The National Lung Screening Trial in the United States showed that low-radiation-dose CT is cost-effective and saves lives (4). The efficacy of lung cancer screening with low-dose CT was also recently confirmed at the International Association for the Study of Lung Cancer meeting in Toronto, where an oral presentation by Harry de Koning, MD, PhD, of Erasmus University in Rotterdam, the Netherlands, presented the European NELSON trial results on the effectiveness of low-dose CT screening in men at high risk for lung cancer. The NELSON trial showed a 26% reduction in cancer-specific mortality after 10 years of follow-up. Suffice it to say that we now have good evidence that screening for lung cancer is beneficial for an at-risk cohort of patients.

Noninvasive characterization of solitary pulmonary nodules (SPNs) is important because lung cancer can be cured if caught early. After we find a lung nodule (with CT or chest radiography), what noninvasive ways are there to determine whether the nodule is malignant? The most common way to deal with SPNs is to use the current Fleischner guidelines (5). Frequently, this means ordering a follow-up CT study (5). More expensive ways include biopsy or the use of fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) PET. For low-dose CT lung cancer screening examinations, the Lung Imaging Reporting and Data System, or Lung-RADS, follow-up recommendations should be used.

In this issue of *Radiology*, a meta-analysis by Basso Dias et al helps to answer the question of the possible role of diffusion-weighted (DW) MRI in the noninvasive determination of whether a pulmonary nodule is benign or malignant (6). A total of 37 studies that evaluated the diagnostic performance of ^{18}F-FDG PET/CT or DW MRI for characterizing SPNs were initially considered. Of these studies, only six were head-to-head comparisons of the two modalities in the same study population. The pooled estimates of sensitivity were 78% for PET/CT and 83% for DW MRI. The difference between PET/CT and DW MRI was statistically significant at the $P = .01$ level. For specificity, the estimates for were 81% for PET/CT and 91% for DW MRI, for a near-significant difference ($P = .056$).

The overall diagnostic performance of the modalities for the same nodules was evaluated with the area under the receiver operating characteristic curve (AUC). For PET/CT, the AUC was 0.86; for DW MRI, the AUC was 0.93, which was statistically greater than that of PET/CT at a P value of .001. Overall, the results of this meta-analysis show that DW MRI is of similar or greater value to ^{18}F-FDG PET/CT for the classification of a lung nodule as malignant (6).

The reader can justifiably ask whether this result is plausible (ie, DW MRI being superior to ^{18}F-FDG PET/CT for the detection of a malignant SPN) and applicable to their clinical practice. I believe these questions remain to be definitively answered. Both MRI and PET continue to have hardware and software improvements that affect diagnostic utility at individual sites. The recent introduction of PET/MRI imaging unit configurations with simultaneous acquisition of the PET and MRI images will further improve the quality of ^{18}F-FDG PET for lung nodules. With PET/MRI, volume averaging due to respiratory motion can be limited by binning the ^{18}F-FDG PET data according to changes in the respiratory cycle found at MRI.

Major factors that must be considered in the meta-analysis by Basso Dias et al (6) are *(a)* nodule size, *(b)* histopathologic data, and *(c)* metabolic activity. For example, when comparing the efficacy of DW MRI with that of ^{18}F-FDG PET/CT for the evaluation of SPNs, comparable nodules must be studied with both modalities. However, these critical cofounders (equivalent sizes, histopathologic features, and metabolic activity) were taken into account by the authors by selecting efficacy studies in which ^{18}F-FDG PET/CT and DW MRI were both performed on the same nodules.

For those patients who are not able to undergo biopsy, clinical staging using the combination of ^{18}F-FDG PET/CT and brain MRI is the most critical study. DW MRI can also help in this work-up. DW MRI has a long track record in the noninvasive characterization of malignancy. Malignant tissues with more densely packed, smaller cells have more restricted diffusion than normal cells. The use of DW MRI is a mainstay of neuroimaging for the findings of ischemia and malignancy (7). In the chest, the use of DW MRI for SPN analysis has been problematic because of the presence of respiratory and cardiac motion, which can limit its applicability for small nodules that move during the respiratory and/or cardiac cycle. The meta-analysis by Basso Dias et al helps to show that this is no longer a substantial drawback. However, we still need to be careful, because not all SPNs are the same. Specifically, the size,

location, motion, tumor biology/metabolism/hypoxia, host immune response, tumoral genetic heterogeneity, tumor phenotype, tumor mutations, and histopathologic features all serve to influence the various parameters found at noninvasive imaging.

There are future considerations we must consider. First, most individuals with non–small cell lung cancer (NSCLC) are able to undergo biopsy and therefore can have their disease pathologically staged. However, for patients with comorbidities that increase the risk of surgery or biopsy, we must use clinical staging methodologies. At present, ^{18}F-FDG PET is the reference standard for the clinical staging of NSCLC. However, the meta-analysis by Basso Dias and colleagues indicates an emerging role for DW MRI in characterizing SPNs and possibly playing a role in the clinical staging of NSCLC as well.

There is a single report by Usuda et al (8) that shows that DW MRI can be used to adequately stage NSCLC. In their study of 67 patients with NSCLC, PET/CT plus brain MRI showed a pathologic staging accuracy of .69, while in the same group, whole-body DW MRI had a pathologic staging accuracy of .75. These data (8) clearly point to a need for an adequately powered prospective randomized trial to help definitively answer this question. Specifically, if whole-body DW MRI can be shown to have equipoise with ^{18}F-FDG PET for the clinical staging of NSCLC, this would reduce the costs of patient work-up because ^{18}F-FDG PET would no longer be needed. Perhaps in the near future, only whole-body DW MRI will be needed for clinical staging in patients with a new diagnosis of NSCLC.

Disclosures of Conflicts of Interest: M.L.S. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a shareholder in Stemina Biomarkers and Healthmyne. Other relationships: disclosed no relevant relationships.

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6.2. Certificado de apresentação do tema do artigo no *Radiological Society of North America* (RSNA) 2018 e de recebimento do prêmio "*Student Travel Stipend Award*".

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Public ID: SSJ05-03

Time: 27 Nov 2018 3:20 PM

Title: 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (PET/CT) and Diffusion-Weighted Magnetic Resonance Imaging (DWI-MRI) Diagnostic Performance in the Evaluation of Pulmonary Lesions: A Systematic Review and Meta-Analysis

Author List: Adriano Basso Dias MD, Matheus Zanon, Stephan Altmayer, Gabriel Sartori Pacini, Natalia Concatto MD, Tassia Medeiros, Anderson Garcez, Ricardo Do Amaral, Irai Giacomelli MD, Edson Marchiori MD, PhD, Klaus Irion MD, PhD, Nupur Verma MD, Tan-Lucien Mohammed MD, Guilherme Watte, Bruno Hochhegger MD, PhD

Presenter: Adriano Basso Dias MD

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Vijay M. Rao

Vijay M. Rao, MD
2018 RSNA President