

REVIEW ARTICLE

Radiological Diagnosis in Lung Disease

Factoring Treatment Options Into the Choice of Diagnostic Modality

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SUMMARY

Background: Chest X-ray, computed tomography (CT), and magnetic resonance imaging (MRI) each have characteristic advantages and disadvantages that need to be considered in clinical decision-making. This point is discussed in reference to the main types of lung disease that are encountered in practice.

Methods: A selective literature search was performed in the PubMed and Google Scholar databases. Existing clinical guidelines on the main types of lung disease and studies concerning radiological diagnosis were also considered in this review.

Results: There have been no more than a few large-scale, controlled comparative trials of different radiological techniques. Chest X-ray provides general orientation as an initial diagnostic study and is especially useful in the diagnosis of pneumonia, cancer, and chronic obstructive pulmonary disease (COPD). Multi-detector CT affords nearly isotropic spatial resolution at a radiation dose of only 0.2–5 mSv, much lower than before. Its main indications, according to current guidelines, are tumors, acute pulmonary embolism, pulmonary hypertension, pulmonary fibrosis, advanced COPD, and pneumonia in a high-risk patient. MRI is used in the diagnosis of cystic fibrosis, pulmonary embolism, pulmonary hypertension, and bronchial carcinoma. The positive predictive value (PPV) of a chest X-ray in outpatients with pneumonia is only 27% (gold standard, CT); in contrast, an initial, non-randomized trial of MRI in nosocomial pneumonia revealed a PPV of 95%. For the staging of mediastinal lymph nodes in bronchial carcinoma, MRI has a PPV of 88% and positron emission tomography with CT (PET/CT) has a PPV of 79%, while CT alone has a PPV of 41% (gold standard, histology).

Conclusion: The choice of radiological technique for the detection, staging, follow-up, and quantification of lung disease should be based on the individual clinical options, so that appropriate treatment can be provided without excessive use of diagnostic testing.

► Cite this as:

Wielpütz MO, Heußel CP, Herth FJF, Kauczor HU: Radiological diagnosis in lung disease—factoring treatment options into the choice of diagnostic modality. *Dtsch Arztebl Int* 2014; 111(11): 181–7.
DOI: 10.3238/arztebl.2014.0181

In the diagnosis of lung disease, assessing the pattern, location, and regional distribution of involvement is the domain of radiology. Complementing classical chest radiography, the tomographic imaging techniques of computed tomography (CT, today in the form of multidetector CT, MDCT) and magnetic resonance imaging (MRI) can demonstrate and quantify, not just morphology, but increasingly also functional processes such as perfusion, respiration, and metabolism, region by region. MDCT and MRI are also often used in treatment monitoring or disease monitoring to identify progression, to allow appropriate treatment alterations or further interventions to be initiated.

This review article will present both established and recommended radiological techniques and also newly introduced techniques used in the management of the most important lung diseases, indicating their advantages and disadvantages, how often they are used, remuneration details, and associated radiation dose (*Figure 1, Table*).

Methods

A selective literature search of the PubMed and Google Scholar databases was used to identify current German and European medical society guidelines on the most important lung diseases and reports of large controlled studies of diagnostic radiology. In addition, international review papers and original articles on smaller studies from the past 10 years were included for cases where the guidelines were not sufficiently up to date or detailed from the diagnostic radiology viewpoint.

Large controlled studies comparing different radiological techniques are rare, since technical innovations are introduced very quickly and the added value of a new technique often appears obvious. Comparison of two techniques involving radiation exposure can often not be ethically justified in the setting of a clinical study, or patients would not take part in a randomized study in which one study arm is intended to undergo the slower technique with the higher radiation exposure.

Technical aspects

Projection radiography: the chest radiograph

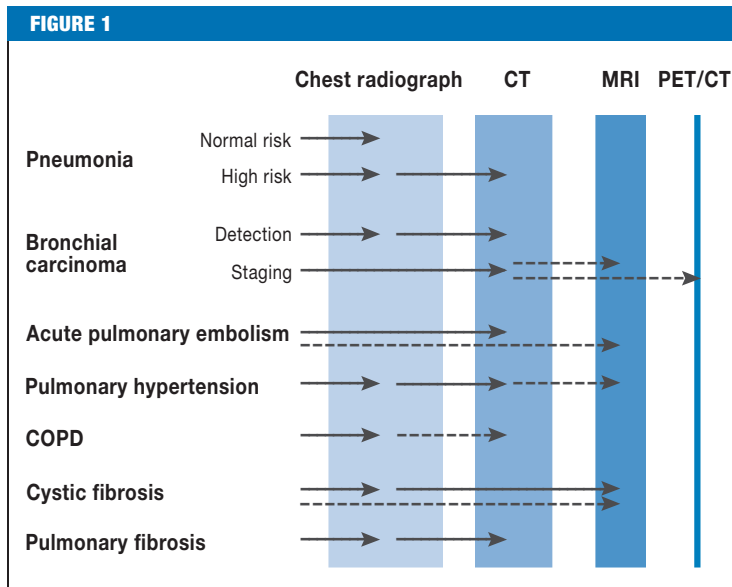
The chest radiograph is the oldest radiological procedure and the one most frequently used for diagnostic purposes in the lung. Chest radiography is generally

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Disease-specific choice of imaging modality. CT, computed tomography; MRI, magnetic resonance imaging; PET/CT positron emission tomography/CT; COPD, chronic obstructive pulmonary disease

carried out in two planes or projections (*Table*). In the projection image, in which all anatomical structures located in the path of the X-rays are superimposed on each other, about 70% of the lung volume can be freely seen in at least one projection. The sensitivity for the detection of lung nodules, infiltrates, and interstitial changes is therefore limited and the differential diagnosis of abnormal findings complicated. Modern X-ray equipment, both fixed and mobile, is now entirely digital, replacing the classical film–foil combinations.

Computed tomography

Multidetector CT (MDCT) is widely available and is characterized by high, almost isotropic resolution (pixel size 0.5 to 1 mm in every spatial direction), allowing the image dataset to be viewed in any plane desired. Acquisition time ranges from 1 to 10 seconds, meaning that virtually artifact-free images can be obtained even of dyspneic patients or those unable to cooperate. The once classical incremental “high-resolution CT” (HRCT) has been replaced by MDCT, because it provides continuous imaging for the same radiation exposure, greatly facilitating disease monitoring (1). Indication-specific protocols for airway and lung parenchymal disease, and for lung nodules found during the follow-up of extrathoracic primary tumors, require studies without the use of intravenous contrast agent. For the staging of bronchial carcinoma, assessment of blood vessels, and cardiopulmonary interaction, on the other hand, intravenous contrast studies are required (1).

The disadvantage of CT is the radiation exposure (*Table*), although technical innovations have allowed this to be much reduced. These innovations include:

- Low tube current (e.g., 40 mAs): e.g., in disease monitoring, dose reduction (up to 80%) without any loss of diagnostic yield/validity
- Automatic dose modulation according to anatomy: low dose in the middle of the chest, higher dose for the shoulder girdle; dose saving approx. 30%
- Modern fixed-array detectors and interactive image reconstruction algorithms: reduced image noise; dose can be reduced by approx. 25% for the same image quality.

The newest MDCT scanners are equipped with dual-energy technology, meaning that two different energies/ tube voltages are used at the same time. Because of the energy dependence of absorption, this allows particular tissue characteristics to be emphasized, e.g., iodine distribution after contrast administration as a surrogate for regional perfusion (2).

Magnetic resonance imaging

MRI combines structural and functional information (3). Clinically informative MRI studies of the lung are obtained by fast sequences, parallel imaging, and respiratory and ECG triggering (3). Most lung diseases are accompanied by an increase in tissue and/or blood and displacement of air, resulting in higher signal on MRI (“plus pathology”). In addition to morphology, MRI enables complementary functional study of perfusion, ventilation, respiratory mechanics, and cardiac action and blood flow (3). With growing awareness about cardiopulmonary interaction, a chest MRI should cover both the lung and the heart, e.g., by means of “one-stop” diagnostic imaging in patients with pulmonary hypertension. Disadvantages of MRI are study acquisition time (15 to 30 min) and the spatial resolution (pixel size approx. 2 mm). The advantage is the absence of radiation exposure (*Table*).

Disease-specific imaging

Pneumonia

For the diagnosis of pneumonia, in addition to history, clinical findings, and laboratory test results, radiological proof of the presence of infiltrate is essential (4). According to German guidelines, in outpatient-acquired pneumonia, chest radiography in two planes is the procedure of choice (recommendation grade B) (4). This also applies for the initial diagnostic procedure for hospital-acquired pneumonia (≥48 h after hospital admission) in patients with immunocompetent status (strong recommendation, evidence level C) (5). Since the positive predictive value of chest radiography in comparison to CT is only 27% (6), for patients at higher risk—e.g., those with ventilation-associated pneumonia or the immune-compromised—non-contrast low-dose MDCT is indicated for detection and characterization of infiltrates (fungal?) (weak recommendation, evidence level C) (1, 5). In a non-randomized study in this patient group, MRI achieved a sensitivity of 95%, a specificity of 88%, and a positive predictive value of 95% in comparison to MDCT (*Figure 2*) (7).

TABELLE

Comparison of the most important diagnostic imaging techniques for lung disease

	Chest radiograph	Computed tomography	Magnetic resonance imaging
Advantages	Widely available Exploratory first study	High spatial resolution High sensitivity High speed Workflow	Intermediate spatial resolution High contrast resolution High temporal resolution Function No radiation exposure
Disadvantages	Low sensitivity Low specificity	Allergy to contrast agent Contraindications: impaired renal function, thyroid function	Availability Study acquisition time Allergy to contrast agent Contraindications: implants
Indications	Community-acquired + uncomplicated pneumonia, bronchial carcinoma (detection) Pulmonary hypertension COPD Cystic fibrosis Fibrosis	Complicated pneumonia, pneumonia in at-risk patients Bronchial carcinoma (staging) Acute pulmonary embolism Pulmonary hypertension COPD Fibrosis	Bronchial carcinoma Pulmonary hypertension Cystic fibrosis
Remuneration EBM points GoÄ rate (basic)	430 €26.23	1865; + 645 with contrast agent €134.06; with contrast agent €151.55 + additional consumables	3430; + 1260 with contrast agent €250.64; with contrast agent €326.42 + additional consumables
Dose	0.1 mSv * ¹	Low-dose-CT 0.2–1 mSv Routine now 1–5 mSv Routine 10 years ago 10 mSv * ¹	None
Number performed	15 million/year * ²	Total estimated 2 million/year * ² Inpatient 830 000/year * ³	Inpatient 12 000/year * ³

Sources: *¹Mettler FA, et al. (38); *²Federal Office for Radiation Protection (39); *³Federal Statistical Office (40)
COPD, chronic obstructive lung disease; EBM, uniform evaluation standard within the statutory health insurance scheme (Einheitlicher Bewertungsmaßstab); GoÄ, medical fee schedule (Gebührenordnung für Ärzte); CT, computed tomography

Bronchial carcinoma

Contrast-enhanced thoracic MDCT is the most important technique in the staging of bronchial carcinoma, according to the 2010 German guidelines (recommendation grade A) (8). In experienced centers, MRI delivers essentially similar results (evidence level 4) (8). Because of the high soft tissue contrast, MRI can better distinguish central tumor parts from poststenotic atelectasis, which is important for example in defining the target volume of radiation therapy (8). To assess infiltrations of the chest wall or mediastinum, MRI—including as a dynamic study—is likewise recommended by the guidelines (8, 9). In cases of superior sulcus tumor (Pancoast tumor) and cases where the tumor is in contact with the spine, MRI should even explicitly be carried out as part of the preoperative planning (evidence level 2a) (8).

In N-staging, the CT assessment relates to tumor stage only in terms of the short-axis diameter of the lymph nodes, leading to low sensitivity and specificity (52% to 62% and 62% to 69%, respectively) (evidence level 2a) (8). For this reason, for non-small-cell bronchial carcinoma, positron emission tomography (PET)/CT (sensitivity 74% to 85% and specificity 85% to 92%), combined with histological verification of relevant findings, is recommended (evidence level 1a) (8). Alternatively, MRI with special “diffusion-weighted”

sequences can be used, in which metastatic lymph nodes appear bright and fat-containing, healthy lymph nodes appear dark. Using these sequences, a sensitivity of 90%, specificity of 93%, and positive predictive value of 88% for MRI were obtained, and for PET/CT values of 77%, 88%, and 79%, respectively (with histology as gold standard) (10); whereas the values for CT alone, in less recent studies, were much lower (63%, 57%, 41%) (11).

For detection of distant metastases (M staging), whole-body PET/CT shows a sensitivity of 93% and a specificity of 96% (evidence level 2a, recommendation grade A); unexpected metastases were found in 15% of cases in comparison to diagnostic CT alone. In several comparison studies, dedicated whole-body MRI has achieved similar values to PET/CT (positive predictive values 53% versus 44%) (12)—in particular, distant metastases in brain and bones were better identified with MRI than with PET/CT (8)—and can, according to the guidelines, be carried out as an alternative, e.g., in patients with diabetic metabolic status (8). In every case, in addition to PET/CT, cranial MRI should be carried out to exclude brain metastases (recommendation grade A) (8).

It has long been known that chest radiography is not suitable as a screening technique for bronchial carcinoma (13). In contrast to this, however, in the first large,

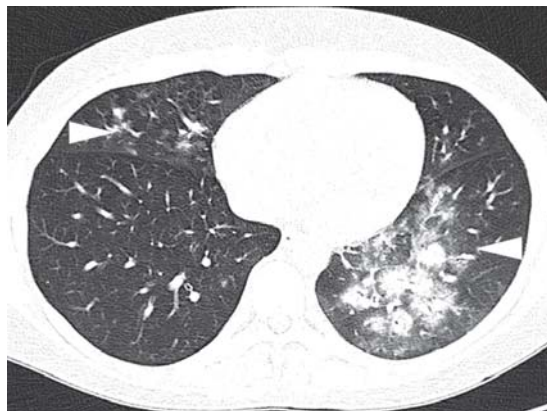


Figure 2: Diagnosis of infiltrates in an immunosuppressed patient. A 34-year-old woman after high-dose chemotherapy for B-cell lymphoma with neutropenic fever. Axial non-contrast computed tomography shows extensive peribronchovascular interstitial thickening (arrowheads)

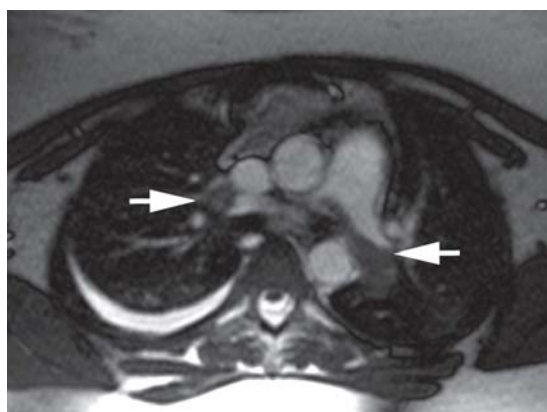


Figure 3: Magnetic resonance imaging (MRI) of pulmonary arterial embolism. A 23-year-old woman with a 2-week history of respiratory infection; current symptoms include hemoptysis, exercise dyspnea, and chest pain on breathing. Axial MRI without contrast administration shows central and peripheral filling defects, some of them partial, in the pulmonary artery (arrows), corresponding to extensive pulmonary embolism

controlled, prospectively randomized screening study of 53 454 smokers, low-dose MDCT showed a significant survival advantage. There were 20% fewer deaths from bronchial carcinoma in the MDCT group than in the control group (screening chest radiograph) (14). However, this was associated with many false-positive findings (17 702 = 96.4% in the CT group versus 4764 = 94.5% in the control group), which lead to follow-up investigations (12 757 = 72% versus 4211 = 85%) and complications due to invasive diagnostic procedures (61 = 0.4% versus 16 = 0.3%). It is still unclear how many indolent tumors are being treated that would have been irrelevant to the patient's survival ("overdiagnosis"). Moreover, results from the US cannot be simply extrapolated to Germany, and the results of the ongoing European studies must be awaited (15, 16).

Vascular diseases

Contrast-enhanced MDCT, which has the highest sensitivity (83% to 100%) and specificity (89% to 97%) and is easily available, has become universally established in the diagnosis of acute pulmonary embolism (APE), and has also replaced scintigraphy and invasive angiography as the primary imaging procedure in the current German guidelines (17, 18).

In patients with contraindications for MDCT (contrast allergy or pregnancy), MRI can be performed. In large, non-randomized studies (PIOPED III), it has been shown that MRI can be almost equivalent to MDCT, with sensitivity and specificity rates of 78% to 90% and 99% to 100%. Its high negative predictive value of 97% for a follow-up period of 3 months (19) has clinical relevance. This investigation should be carried out first without contrast administration, using contrast-rich fast imaging sequences, to show a central pulmonary embolism within a few seconds (Figure 3). If no central pulmonary embolism is shown, the MRI is continued as a perfusion study and MR angiography, with administration of gadolinium-based contrast agent (20).

According to the European guidelines, contrast-enhanced MDCT angiography is used to rule out causative diseases in patients with pulmonary hypertension, e.g., interstitial lung disease, emphysema, or chronic thromboembolic pulmonary hypertension (CTEPH); and to identify dilated bronchial arteries and right heart dilatation and hypertrophy (21). If signs of CTEPH are found, according to the 2010 German consensus conference, the findings of ventilation perfusion scintigraphy, MDCT, and invasive pulmonary artery angiography should be interpreted together to decide whether surgery (curative pulmonary thrombendarterectomy) is possible (recommendation grade 2a, evidence level C) (22). Morphological MRI (central thrombus burden, webs and bands, vascular stenosis) and functional MRI (peripheral perfusion deficits) achieved a sensitivity, specificity, and positive predictive value of 98%, 94%, and 96% in comparison with MDCT (23), and 93% sensitivity in comparison to pulmonary arterial angiography (gold standard) in imaging the subsegmental pulmonary arteries (24). For comprehensive diagnostic investigations, functional MRI techniques that quantify cardiac action, blood flow in the great vessels, and lung perfusion with high reproducibility are available (25).

Obstructive airways disease

Cystic fibrosis is the most common life-limiting autosomal recessive disease of fair-skinned people, and its prognosis is determined by the severity of lung involvement (26). From what age and at what intervals routine diagnostic imaging should be performed has not yet become firmly established. According to the German guidelines, chest radiograph, MDCT, and MRI should be performed depending on local expertise and the clinical situation (recommendation grade B) (27). MDCT is more sensitive than the chest radiograph in

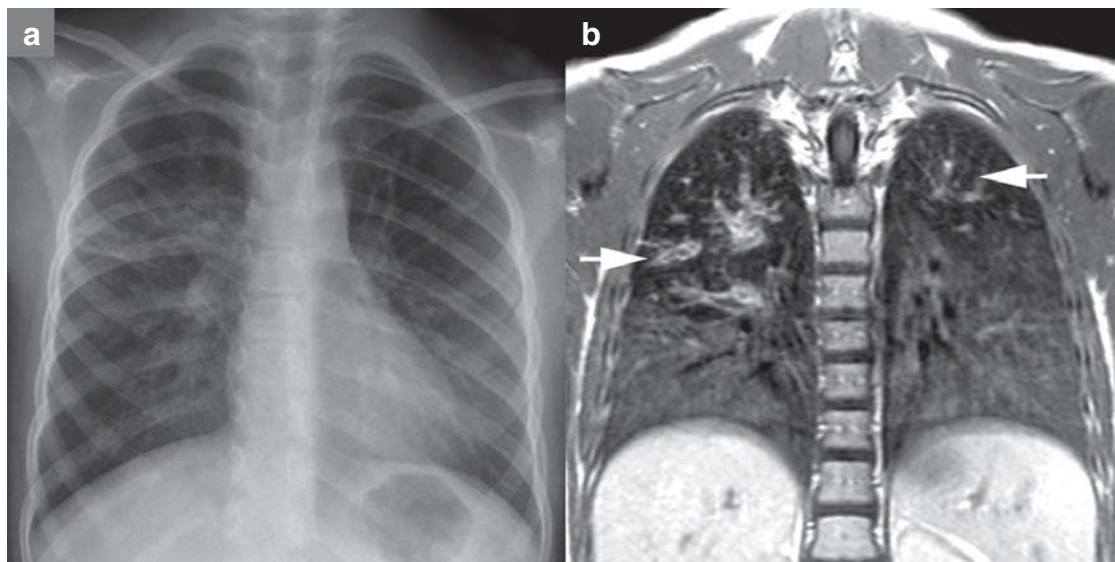


Figure 4: Magnetic resonance imaging (MRI) in cystic fibrosis. A 7-year-old girl in long-term treatment for cystic fibrosis at a pediatric pneumology center. a) Chest radiograph. b) MRI on the same day; the patient was sedated but free breathing. The T1-weighted contrast studies show clear bronchial wall thickening and varicose bronchiectasis, most pronounced in the upper lobes (arrows), and reduced signal apically compared to basally

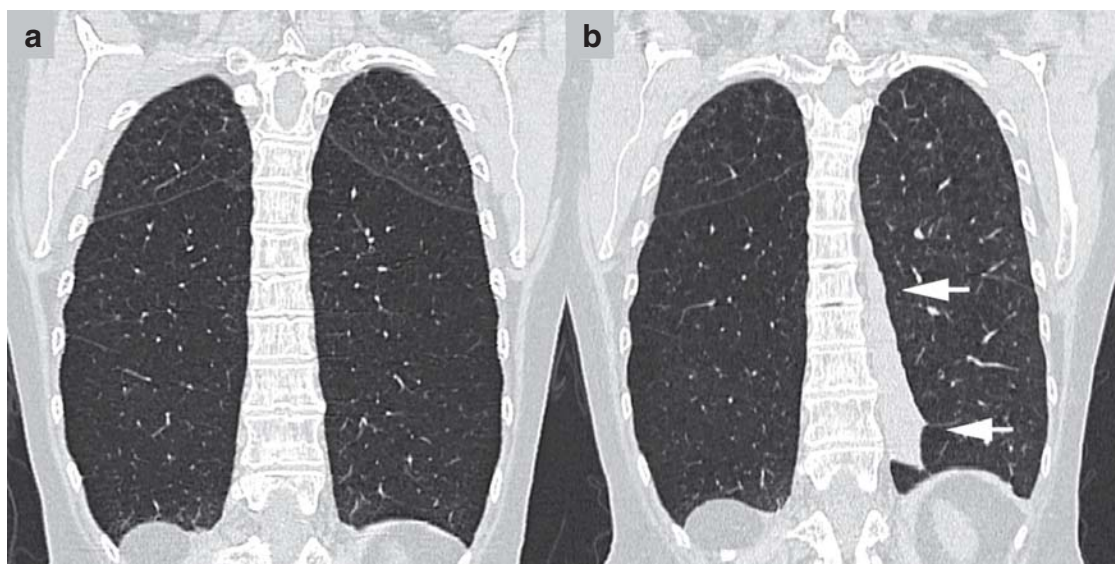


Figure 5: Phenotyping in chronic obstructive pulmonary disease (COPD). A 60-year-old woman with a long history of nicotine abuse. a) Multidetector computed tomography (MDCT) without contrast administration and with coronary reconstruction, showing very severe centrilobular pulmonary emphysema, most pronounced in the lower lobe. The left lower lobe, with an intact lobar fissure, was identified as the target structure for endoscopic pulmonary volume reduction. b) Outcome 3 months after the intervention, with atelectasis of treated segments 8–10 on the left side (arrows)

showing typical lung changes (28). In patients identified at neonatal screening, MDCT shows typical bronchiectasis in 27% of cases, before they become clinically manifest or show any changes in lung function tests (29). MRI is increasingly replacing MDCT as the technique for diagnosing complications or monitoring the disease (30). It shows the typical changes of bronchiectasis, wall thickening, mucus plugging, and

infiltrates (“plus pathologies” on MRI) sensitively and with comparable clinical relevance to MDCT (31). In addition, MR perfusion imaging making use of hypoxic pulmonary vasoconstriction (Euler–Liljestrand reflex) shows potentially reversible perfusion and ventilation impairment (Figure 4) (30). The necessity of radiation-free diagnosis using MRI is particularly significant given the potentially high cumulative lifetime radiation

exposure of cystic fibrosis patients. At present, MRI is being used for the first time in a German multicenter study in the framework of the neonatal cystic fibrosis screening program, providing a secondary surrogate endpoint for preventive treatment strategies.

In patients with smoking-related COPD, the guideline states that at first diagnosis chest radiography should be carried out as the initial study (32). To investigate the indication for endoscopic or operative treatment of severe pulmonary emphysema, and to plan these, thin-slice, non-contrast MDCT is recommended (32). This allows the severity and distribution of the emphysema to be quantified and the integrity of the lobar fissures to be determined (*Figure 5*) (33, 34). MDCT is also desirable when bronchial carcinoma is suspected (35). The question of whether functional MRI can yield clinically relevant functional information in COPD patients is currently being investigated in a nationwide multicenter study in Germany (“COSYCONET”) (www.asconet.net).

Diffuse interstitial lung disease—pulmonary fibrosis

In the diagnosis of idiopathic pulmonary fibrosis (IPF), since 2011 in parallel with the revision of international and national guidelines, the single gold standard—histology—has been abandoned in favor of interdisciplinary diagnostic procedures (pneumology, radiology, and pathology) mainly based on the predominant pattern on MDCT (non-contrast, slice thickness ≤ 2 mm) (36, 37). The pattern of usual interstitial pneumonia (UIP) with a honeycomb structure and traction bronchiectasis dominating in the dorsobasal periphery is the main indicator. If this is seen together with typical clinical presentation and other causes are ruled out, IPF can be reliably diagnosed without histological confirmation.

KEY MESSAGES

- Chest radiography is the first diagnostic step in patients with pneumonia, cancer, and chronic obstructive pulmonary disease (COPD).
- Among the subsequent targeted radiological and pneumological diagnostic techniques that proceed according to risk and clinical significance, and are also used for treatment planning and monitoring, tomographic imaging techniques (CT and MRI) predominate.
- CT should be carried out in patients with tumors, acute pulmonary embolism, pulmonary hypertension, pulmonary fibrosis, and advanced COPD, and in at-risk patients with pneumonia.
- MRI of the lungs yield clinically relevant extra information and avoids radiation exposure. It is most clinically useful in diagnosing cystic fibrosis, acute pulmonary embolism, pulmonary hypertension, and bronchial carcinoma.
- The positive predictive value (PPV) for diagnosing community-acquired pneumonia by chest radiography is 27% in comparison with CT as the gold standard.
- For lymph node staging in bronchial carcinoma, MRI achieves a PPV of 88% and PET/CT a PPV of 79% compared to histology.

Acknowledgment

This work was supported by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung) (82DZL00401, 82DZL00402, 82DZL00404).

Conflict of interest statement

Dr. Wielputz has received lecture fees from Activaero GmbH, Gmünden.

Professor Heussel owns shares in Stada and GSK, and patent shares in Method and Device for Representing the Microstructure of the Lungs. IPC8, Class: AA61B5055F1, PAN: 20080208038. He has received consultancy fees from Schering-Plough, Pfizer, Basilea, Boehringer Ingelheim, Novartis, Roche, Astellas, Gilead, MSD, Lilly, and Intermune. He has received research funding (third-party account) from Siemens, Pfizer, and MeVis. He has received lecture fees from Gilead, Essex, Schering-Plough, AstraZeneca, Lilly, Roche, MSD, Pfizer, Bracco, MEDA Pharma, Intermune, Chiesi, Siemens, Covidien, Pierre Fabre, Boehringer Ingelheim, Grifols, and Novartis.

Professor Kauczor has received consultancy fees from Siemens. He has received lecture fees from Boehringer Ingelheim, Bracco, Siemens, and Bayer.

Professor Herth declares that no conflict of interest exists.

Manuscript received on 12 July 2013, revised version accepted on 6 January 2014.

Translated from the original German by Kersti Wagstaff, MA.

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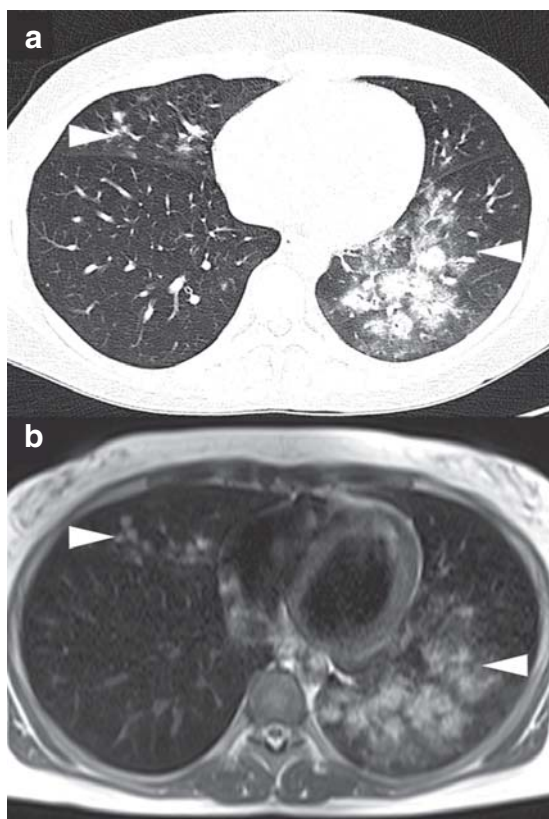
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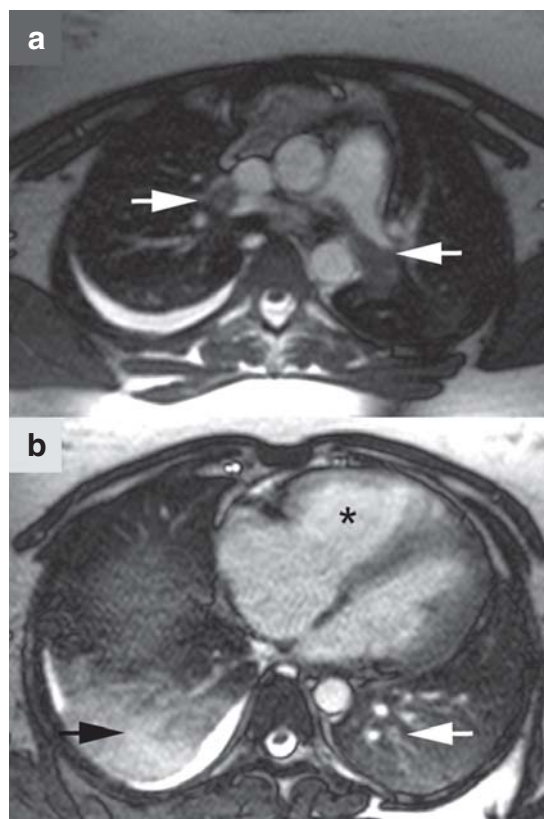
Radiological Diagnosis in Lung Disease

Factoring Treatment Options Into the Choice of Diagnostic Modality

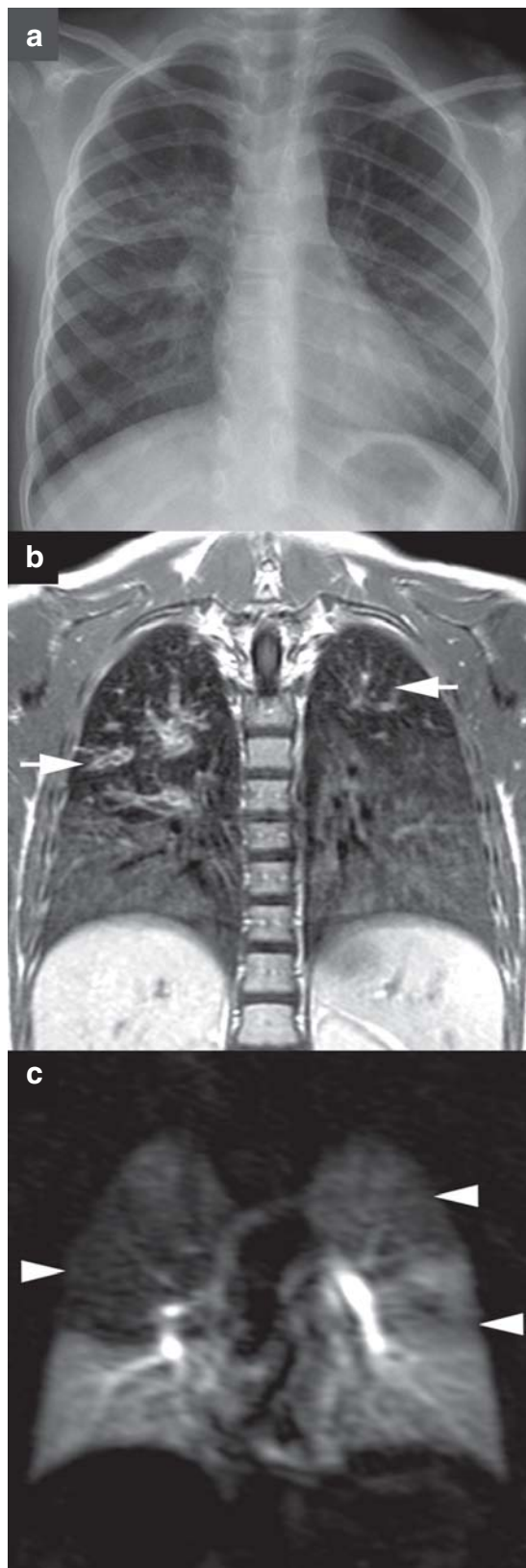
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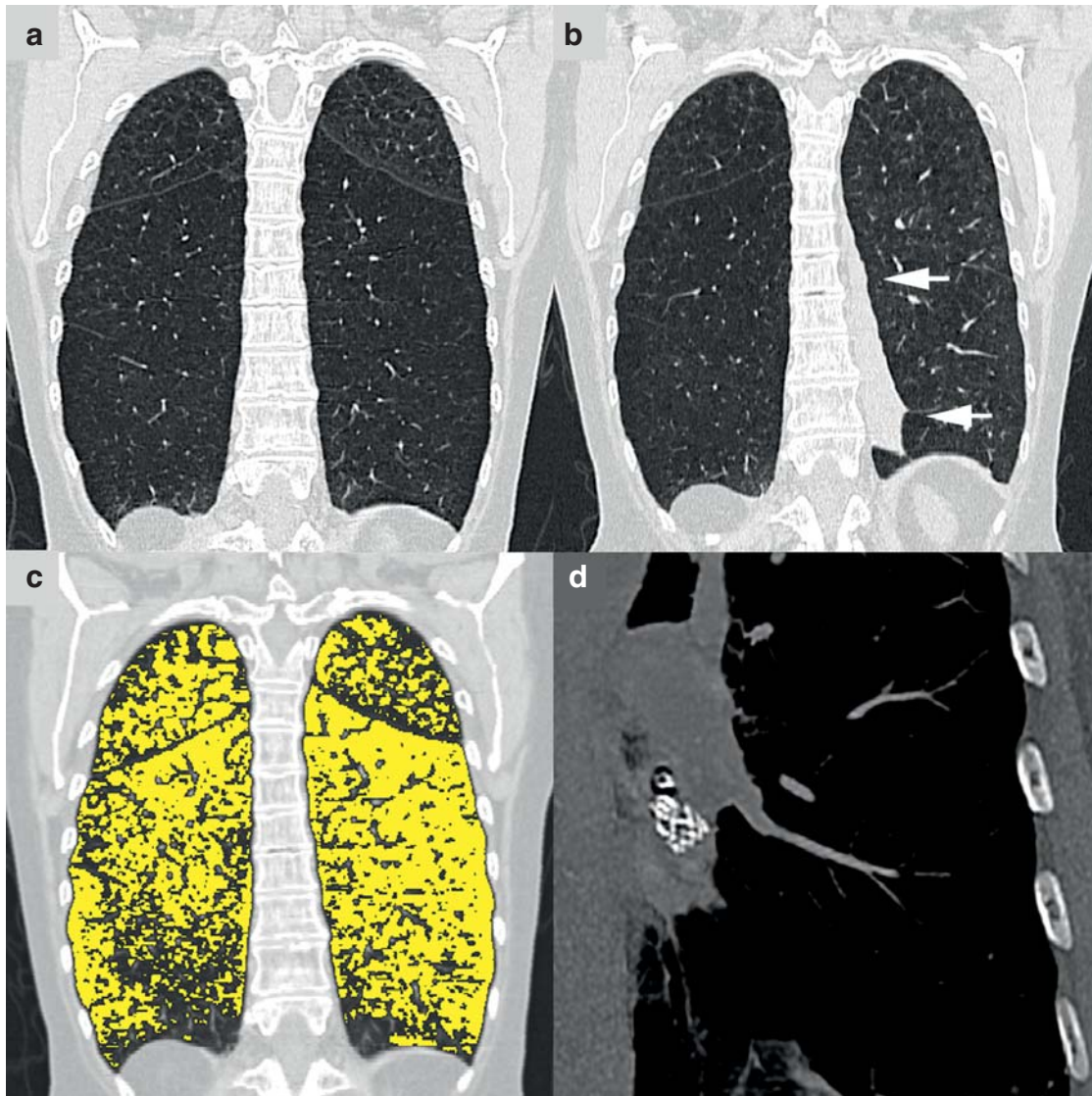
eFigure 1: Diagnosis of infiltrate in an immunosuppressed patient. A 34-year-old woman after high-dose chemotherapy for B-cell lymphoma with neutropenic fever. a) Axial non-contrast computed tomography shows extensive peribronchovascular infiltrates (arrowheads). b) The infiltrate morphology is shown identically by non-contrast T2-weighted magnetic resonance imaging



eFigure 2: Magnetic resonance imaging (MRI) of pulmonary embolism. A 23-year-old woman with a 2-week history of respiratory infection; current symptoms include hemoptysis, exercise dyspnea, and chest pain on breathing. Axial MRI without contrast administration shows central and peripheral filling defects, some of them partial, in the pulmonary artery (white arrows), corresponding to extensive pulmonary artery embolism. b) Dilatation of the right atrium and ventricle (*), signs of right heart strain. In addition, infarction pneumonia of the right upper lobe accompanied by pleural effusion (black arrow)



eFigure 3: Magnetic resonance imaging (MRI) in cystic fibrosis. A 7-year-old girl in long-term treatment for cystic fibrosis at a pediatric pneumology center. a) Chest radiograph. b) MRI on the same day; the patient was sedated but free breathing. The T1-weighted contrast studies show clear bronchial wall thickening and varicose bronchiectasis, most pronounced in the upper lobes (arrows), and reduced signal apically compared to basally. c) Perfusion imaging subtraction map shows the corresponding perfusion defects of the upper fields in both lungs (arrowheads)



eFigure 4: Phenotyping in chronic obstructive pulmonary disease (COPD). A 60-year-old woman with a long history of nicotine abuse. a) Multidetector computed tomography (MDCT) without contrast administration and with coronal reconstruction, showing very marked centrilobular pulmonary emphysema, most pronounced in the lower lobe. The left lower lobe, with an intact lobar fissure, was identified as the target structure for endoscopic pulmonary volume reduction. b) Outcome 3 months after the intervention, with atelectasis of treated segments 8–10 on the left side (arrows). c) Results of densitometry performed as image postprocessing (Oliver Weinheimer, Heidelberg) with emphysema map overlaid on the MDCT image. The emphysema (48% of lung volume) is colored yellow. d) Visualization of a valve at the take-off of the S9/10 bronchus