



# BREATHE EASY

HOW RADIOLOGY  
HELPS TO FIND AND  
FIGHT LUNG DISEASES

# BREATHE EASY

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## AN OVERVIEW OF CHEST IMAGING

BY CORNELIA SCHAEFER-PROKOP

**C**hest imaging, and imaging in general, serves many goals. It is initially used to diagnose or exclude a disease. During this process, imaging is frequently only one of many components and is combined with information provided by the physical examination, patient history, laboratory results and pathological findings, in order to come to the right diagnosis. Once a diagnosis has been made, imaging can be used to show the response to treatment, such as chemotherapy for tumours or antibiotic treatment for pneumonia. This is done to see whether response to treatment is adequate, or to see if a change of therapy is required in cases of inadequate or insufficient response. Similarly, imaging is used to look for complications or progression of disease if the clinical symptoms worsen or new symptoms arise.

Imaging can also be used for screening in order to detect diseases that are already present but do not yet cause symptoms. By doing this, the disease, such as lung cancer, can often be detected at such an early stage that it can be treated more successfully. Imaging can be helpful for detecting asymptomatic diseases that have nothing to do with cancer. Indications for such screening exams include an increased risk of inherited disease; contact with patients who have a highly infectious disease, such as tuberculosis; known diseases located outside the region that might involve the lung without creating symptoms. Radiologic imaging relies on the change of morphology of any of the anatomic structures in the chest to detect and characterise disease. For this reason, it is often the most

important diagnostic tool for suggesting the correct diagnosis and monitoring the course of treatment.

The most frequently used primary imaging technique to examine the chest is the chest radiograph. It is widely available, fast and relatively cheap. Many diseases can be diagnosed or excluded with a chest radiograph, for example pneumonia, pneumothorax or fluid overload due to heart problems. Tumours are also frequently diagnosed using a chest x-ray. Many suspicious abnormalities on the chest x-ray will trigger a further work-up, most of the time using a computed tomography (CT) examination. CT is superior to chest radiography at detecting small lesions and characterising them. That's because CT has a higher spatial resolution and it does not produce a shadow image like a chest radiograph. It creates a true cross-sectional image that does not suffer from superimposition of various structures. Certain diseases such as pulmonary embolism (a clot obstructing a pulmonary artery) can not be seen by radiography but require CT, MR or scintigraphy. Ultrasound is mainly used for pleural diseases (e.g. characterisation of pleural fluid) or diseases that are located close to the chest wall. Magnetic resonance (MR) is used for emerging indications such as further analysis of chest wall lesions or lesions located in the mediastinum. X-ray angiography uses a catheter that is introduced into a vessel and pushed to the region that needs to be examined. The technique is invasive and has a small but significant risk of bleeding or other serious complications. For the chest, it is normally substituted by CT angiography or MR angiography, which are much safer and only

require intravenous injection of a contrast agent and rapid imaging while the contrast agent passes the vessel territory of interest. CT angiography, for example, is the technique of choice for evaluating the lung arteries in suspected pulmonary embolism.

In some countries, screening programmes for lung cancer have been put in place or are currently being studied. A number of trials have been carried out over the past few decades to assess whether screening of a large part of the population can detect lung cancers early enough to make successful treatment possible and reduce the chances of dying from lung cancer (lung cancer-specific mortality). Chest radiography alone, or in conjunction with sputum analysis, was not found to be able to decrease mortality significantly; CT is much better suited to this purpose. CT screening has been endorsed in Japan, Korea, the United States and some European countries since the 1990s. However, no real scientific proof for the effectiveness of screening was available then. This changed two years ago, when the largest clinical study, the National Lung Screening Trial (NLST trial), involving around 50,000 smokers in the U.S., found a statistically significant reduction in lung cancer-specific mortality within the screening group. The results were published in 2011 in the prestigious *New England Journal of Medicine (NEJM)*. A number of European trials, all of them much smaller, were unable to find similarly positive results. The results of the largest European screening trial, the Dutch/Belgian NELSON trial, are expected to be published in 2016. While many professional medical societies in the U.S.

recommend screening, there has been no such recommendation in Europe.

Radiologists are the doctors responsible for imaging and image interpretation. They are trained to recognise the normal appearance of a chest radiograph, a CT or MR scan. This normal appearance includes changes that may occur with increasing age or as residuals of past disease, for example pneumonia, but that do not represent acute disease requesting treatment. Like a detective, a radiologist looks for any differences from that appearance and then works on finding potential reasons. Sometimes the changes are so typical that only one underlying disease is possible. Often, however, there are two or more possible underlying diseases. There are abnormalities that, for example, resemble pneumonia or a tumour. In these cases, following up over time, studying the effect of specific treatments, or imaging again can clarify the situation. The radiologist chooses the most appropriate test that provides the highest likelihood of a correct diagnosis. If imaging alone is insufficient, a biopsy might be needed to determine the underlying cause of disease.

To avoid mistakes in image interpretation, interdisciplinary conferences are held, in which all information regarding an individual patient is reviewed and discussed with various disciplines (surgery, oncology, pathology and radiology). Such conferences are very important to making the best diagnostic and therapeutic decisions in cancer patients, but are also held for

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diseases of the lung tissues (interstitial lung diseases), which require the specific skills of the radiologists and lung physicians. Such conferences may also include experts from different institutions.

Modern picture archive and communication systems (PACS) store all image data digitally, which means that images can be transferred to different institutions if a patient changes clinic, and they can also be used to consult external specialists in particularly difficult situations. Specific image interpretation workstations allow for interactive evaluation of the datasets, which in the case of chest CT may comprise hundreds of images. They can display current and previous images side-by-side, thus ensuring optimum evaluation of changes over time or after treatment.

Undergoing any kind of radiological exam involves little or no discomfort. The imaging process itself cannot be felt at all. Patients need to follow breathing instructions to make sure that images are not blurred, and they should try to lie still on the examination table. Patients with difficulties holding their breath can often continue breathing shallowly, although image quality will be somewhat reduced in this case. Many CT or MRI examinations require injection of an intravenous contrast agent, a dye that improves the display of vessels and various organs. These contrast agents often cause a warm sensation within the body that ceases after about 15–30 seconds. Patients may temporarily experience an unusual taste in this period. Precautions have to be taken in patients with

potential, or known, allergic reactions or limited renal function.

Radiological procedures very rarely have side effects. Most potential side effects stem from the medication applied to optimise image quality such as contrast agents. The strong magnetic field used in MRI examinations may influence pacemakers or other electronic implants. Thus anyone undergoing CT or MR examinations is asked about factors that may influence his or her individual risk of experiencing such side effects. In patients with an increased risk of side effects, imaging can be an option but may have to be adapted to their individual risk profile.

Some imaging modalities use ionising radiation in very low doses. Patients should keep in mind that their physicians have thoroughly weighed the benefits and risks of any diagnostic test; this is also true for imaging. In general the radiation exposure associated with x-rays is considerably lower than the exposure associated with CT. For both techniques, however, a single examination or even several examinations do not produce dose levels that put the individual patient at significant risk. Most risk estimates are derived from atomic bomb data, which can only provide a rough risk estimate for imaging procedures. The life-time risk for developing cancer in the general population varies between countries and is in the order of 30 percent. A single CT of the chest will lead to an estimated increase in cancer risk by 0.01–0.05%, depending on the imaging technique used, patient age and gender:

women have a higher risk associated with radiation than men, and risk decreases with old age and increases in children.

The benefits of imaging tests are their ability to help make the correct diagnosis, decide the most promising treatment and monitor the effect of treatment. Since the risks are so low, the benefit of an imaging test normally vastly outweighs the potential radiation risks. Radiologists and radiographers, who are specially trained operators of the imaging equipment, use the ALARA principle in their daily practice. This means that radiation exposure is kept 'as low as reasonably achievable'. Modern equipment for CT or chest radiography uses automated exposure control techniques and advanced processing to use only as high a dose as is required to gain a diagnostic image. Over the past decade, a significant reduction in radiation exposure has been achieved thanks to technical advances.

In general imaging techniques that involve no radiation at all, such as ultrasound or MRI, are preferred in children and used whenever possible. Air in the lungs, however, makes ultrasound and MRI examination difficult or even impossible. For this reason, CT will still be required. All examinations are specifically adapted for children: depending on their size and age, the medication and the radiation dose will be reduced. In very small children, who do not understand the instructions (breath hold and lying still) required for obtaining images of diagnostic quality, medication will be required to sedate them. In some cases, even anaesthesia will be

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necessary to gain the information needed for diagnosis or treatment decisions.

The future will bring new possibilities, as technological improvements continue. The technical performance of CT technology has doubled every two years over the past 20 years. This has led to a tremendous increase in diagnostic opportunities and has made it possible to avoid using more invasive and risky imaging techniques such as angiography. CT is, and remains, the most important imaging technique for the lung. Technological development in CT has recently switched from improving performance to decreasing radiation exposure. MRI techniques have been continuously evolving over the last few decades. MRI remains problematic for imaging of the lungs but new techniques look promising, although their diagnostic performance is still inferior to CT. Both CT and MRI will move from morphological imaging to functional imaging. Morphological imaging serves to evaluate anatomic and pathological details in the chest, while functional imaging focuses on evaluating and quantifying natural or disease processes. We will learn to quantify tissue perfusion, which can be expected to help differentiate various disease processes, predict response to treatment and select the most promising treatment. Currently computer programmes are being developed that can aid radiologists in better detecting or quantifying disease. These programmes will make image interpretation more effective and less expensive, contributing to the sustainability of high-quality healthcare services for future generations.

CHAPTER 1

# LUNG IMAGING: THE TECHNIQUES

## 1

## CHEST RADIOGRAPHY

BY JOSÉ VILAR

The chest radiograph (CXR) is the oldest radiographic technique and remains the most common radiological examination performed in the world today. Approximately 25 percent of all radiographic examinations are CXR. The enduring use of CXR can be explained by the advantages it offers. It is easy to perform and widely available. The radiograph provides instant information about the lung, the heart, the large vessels that bring blood to and from the heart (great vessels) and the chest wall. It also involves a low radiation dose and is relatively inexpensive.

Despite these apparent advantages, the technique also has some significant limitations. These limitations mainly relate to its limited spatial resolution and the fact that all structures, within the chest, lying in the path of the x-ray are projected over one another. These effects of 'overprojection' mean that some pulmonary lesions are difficult to see or analyse on a chest radiograph, and in these cases the usual response is to obtain a CT scan for further analysis. Conditions that are usually easy to diagnose with a chest radiograph are pneumonia, pneumothorax, symptomatic pleural effusion, cardiac enlargement with vascular congestion, and symptomatic tumours. Small nodules, a lung fibrosis and complex diseases affecting the mediastinum and the lung are often not entirely visible and require CT imaging.

CXR is usually performed with the patient in a standing position. Normally two views are obtained: one frontal and one lateral in order to improve the ability of the radiologist to localise pathology within the chest. If only one view is available, then visualisation is even more limited by the described projection effects.

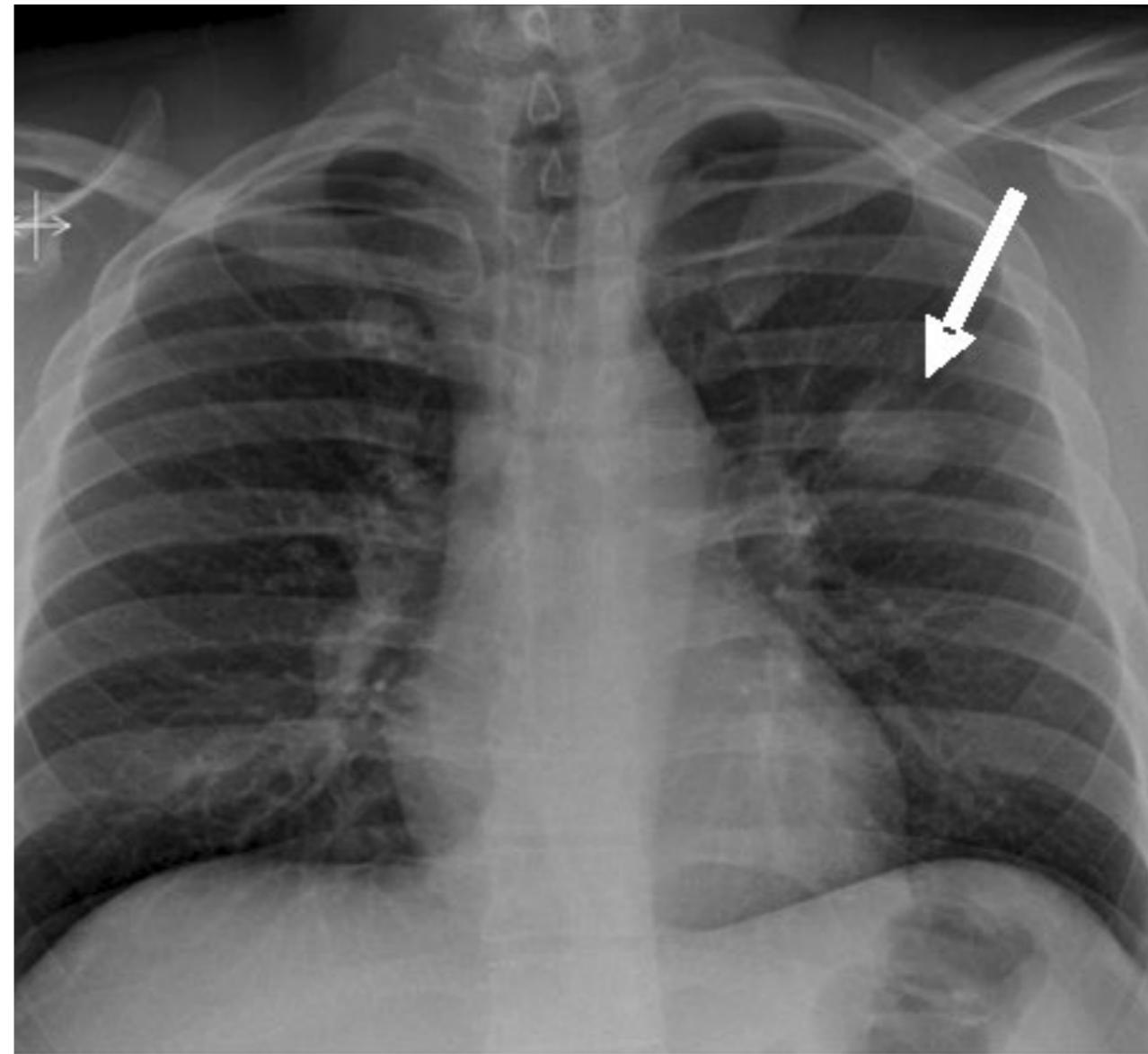
It is important that radiologists review and report the chest radiograph findings. This report will also indicate whether the patient needs further work-up such as a chest CT. In most cases the report will inform the referring physician that the patient has a pulmonary disease (e.g. pneumonia), triggering appropriate treatment or allowing the physician to rule out a suspected pulmonary disease.

In bed-ridden patients, CXR can be obtained using portable machines, which can be transferred to intensive care units. Portable CXR is essential in the evaluation of critically ill patients who frequently suffer from serious pulmonary diseases caused by pneumonia, heart failure or respiratory distress, requiring mechanical ventilation.

Recent advances in chest radiology include the transition from analogue to digital techniques, as in regular photography. The advantages of digital radiographic techniques include a more consistent and optimised image quality. Image data can be transferred anywhere and made instantly available in multiple locations at the same time. Elaborate computerised analysis of the data is becoming more available and has the potential to support radiologists in the detection of pathology, e.g. pulmonary nodules.

In conclusion it can be stated that chest radiography is still in everyday use. The technique has been constantly improved over the last few decades and it serves as a baseline examination for lung diseases worldwide and, as such – if wisely used by radiologists – is of great value.

CHEST RADIOGRAPH REVEALS A NODULAR LESION IN THE LEFT LUNG (ARROW).



## 2

## ULTRASOUND

BY FERGUS GLEESON

The most common method of imaging the chest is the CXR; in fact it is the most common radiological examination performed worldwide. Like CXR, ultrasound is also becoming more widely accessible, along with the ensuing benefits in diagnosis and treatment. As computing power increases and both software and hardware become cheaper and more readily available, ultrasound, previously a specialised and expensive technology, has become more widely available.

Thoracic ultrasound uses high-frequency sound waves, above the audible range of the human ear. These sound waves are passed from an ultrasound probe (transducer) into the body and their reflections, caused by differences in tissue density, are detected and converted into images for visual interpretation using dedicated computer algorithms. Because it has to pass through structures and be reflected back, ultrasound is unable to detect disease in an aerated lung, and requires either fluid or a solid mass abutting the chest wall to produce an image.

The main use of ultrasound in the chest is the detection and characterisation of pleural effusions. Multiple studies have shown ultrasound to be better than clinical

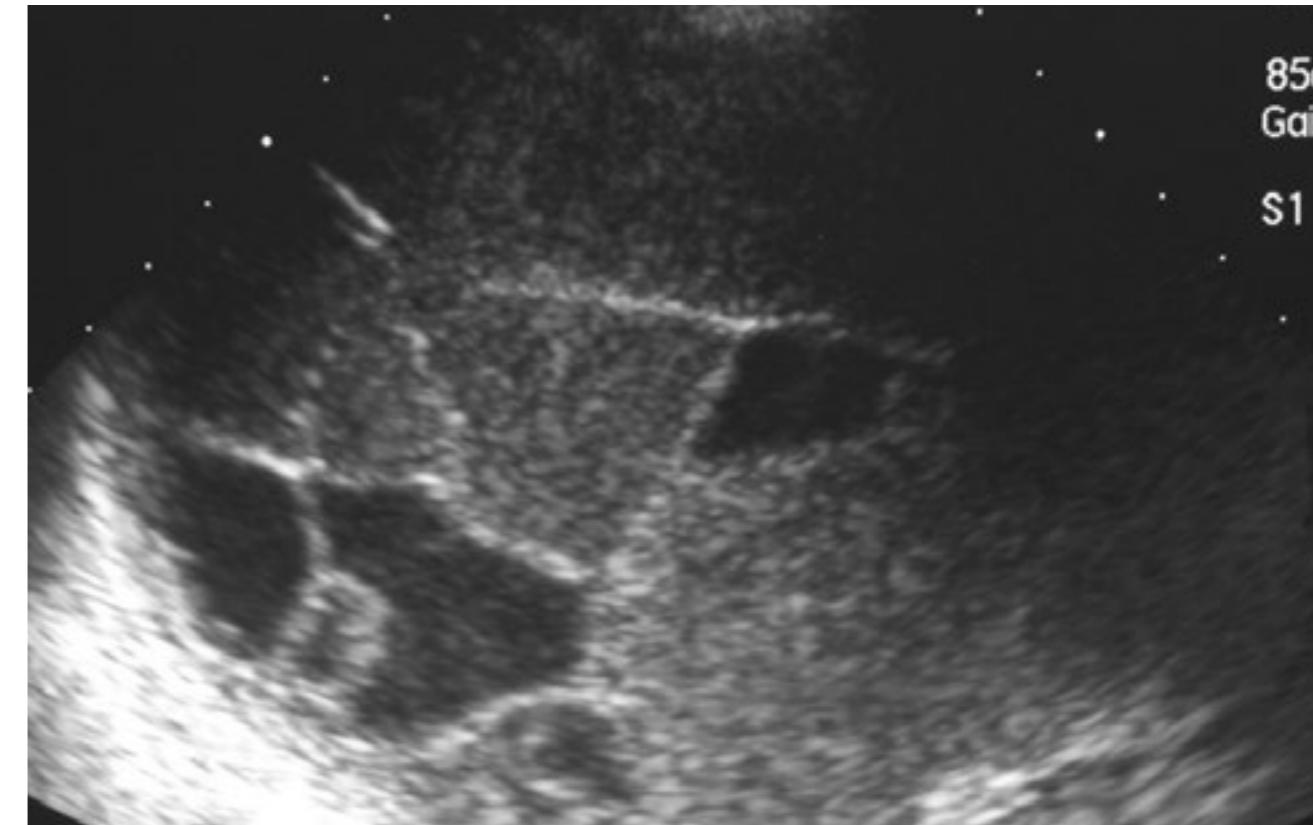
examination and to be more reliable than the CXR in detecting fluid. It has also been shown that ultrasound guidance is of substantial benefit when inserting chest drains. Unnecessary procedures can be prevented when there is only limited fluid present, or complications can be avoided, e.g. inadvertent puncture of organs, such as of the liver or spleen.

Initially, thoracic ultrasound was performed by radiologists, but it is now routinely used by physicians and surgeons in clinics and on the wards. It has become a standard of care in emergency departments, and many professional medical societies around the world have set up ultrasound training programmes for junior staff.

Although its primary use is in the diagnosis of pleural effusions and their drainage, it may also be used to assess and biopsy masses abutting the chest wall, and for the diagnosis of pneumothorax, especially in critically ill patients.

As computing power increases and sophisticated hardware becomes cheaper, ultrasound probes will become smaller and more portable, and may eventually become the 'stethoscope of the 21<sup>st</sup> century'.

ULTRASOUND IS PART OF THE DIAGNOSTIC WORK-UP; TRANSUDATE IS OFTEN ANECHOIC EXUDATE VARIES IN ECHOGENICITY; STRANDS AND SEPTAE ARE SUGGESTIVE OF EXUDATE, PUS IS RARELY ANECHOIC; 40% HAVE EFFUSION, 10% EMPYEMA



## 3

# CT, HRCT AND MDCT: COMPUTED TOMOGRAPHY OF THE LUNG

BY EVA CASTAÑER

**C**T (computed tomography) uses x-rays to produce detailed images of the inside of the body. As opposed to chest radiography, CT does not suffer from over-projection and it offers a spatial resolution in the submillimetre range. CT is by far the best method for evaluating very small lesions within the lungs. The abbreviation HRCT stands for high resolution CT, which is based on thin (1-1.5mm) sections. The abbreviation MDCT stands for Multidetector CT, which uses multiple detectors and provides a 3D volumetric examination of the whole thorax within seconds; it is the most modern type of CT scanner. MDCT also allows for the production of cross sections (slices) through the chest in any direction (axial, sagittal or coronal) and the production of 3D images.

CT is equally well-suited to examining the lungs, the thoracic vessels, the chest wall or the mediastinum. Depending on the clinical question and the type of suspected disease, a contrast agent may be injected intravenously to help enhance the visual contrast between vascularised and non-vascularised, or less vascularised, structures. CT can be used as the first imaging test (e.g. in emergency situations when a small and very subtle pathology is suspected), but most of the time it serves

for further analysis of findings that have been obtained with a chest radiograph. CT is the main tool for the diagnosis and staging of lung cancer.

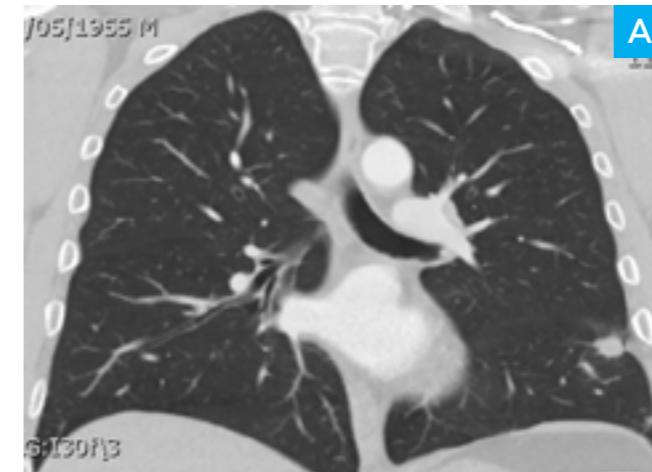
HRCT is the method of choice for assessing lung tissue. This technique is very useful for analysing diffuse lung diseases such as pulmonary fibrosis, emphysema or diseases affecting the airways. For diseases affecting the airways CT images are sometimes obtained during full inspiration and full expiration, in order to gain information about the functional aspects of ventilation. CT can also help locate the abnormality and suggest the most suitable location for a histological biopsy, if needed.

MDCT scanners have been available since the nineties. The development of MDCT after the introduction of the first spiral CT scanner at the end of the eighties was very fast: starting with four detector rings, then going up to 16 then 40, 64 and now a maximum of 256 to 320 detector rings, using one or two x-ray tubes at the same time, depending on the scanner type. These modern scanners can examine a chest within three seconds, acquire continuous volumetric data, assess perfusion and functional ventilation and, because they

are so fast, provide new insights into imaging of moving organs (cardiac imaging). This continuous volumetric assessment allows for the precise assessment of volumetric data of a whole lung, nodule or tumour.

The main drawback of CT is that it involves radiation. A CT examination should never be undertaken without very clear indications to do so and alternative techniques should always be considered, especially if children and pregnant women are involved. Over the last few years in particular, the industry has developed very elaborate techniques to drastically reduce the dose of radiation involved in an examination and to allow for the dose to be adapted to suit the indication, the body part to be examined and the individual body weight. This ensures that only the amount of radiation absolutely necessary to answer the diagnostic question is used.

In the future CT scanners will provide more detailed images, quicker and with less radiation. CT scanners are an essential tool in modern medicine and will certainly continue to play an important role for many years to come.



THREE CT IMAGES SHOWING THE COMPLETE CHEST BASED ON A VOLUMETRIC SCAN IN CORONAL (A AND B) AND SAGITTAL RECONSTRUCTION (C):

- (A) IS OPTIMISED TO SHOW THE LUNG PARENCHYMA,
- (B) THE SOFT TISSUES OF THE MEDIASTINUM WITH THE HEART AND THE LARGE VESSELS AND
- (C) TO ILLUSTRATE THE BONE STRUCTURES OF THE THORACIC SPINE.

## PET AND PET/CT: IMPROVING DETECTION AND ASSESSMENT OF LUNG CANCER

BY WALTER DE WEVER

**I**maging provided by computed tomography (CT) and magnetic resonance imaging (MRI) does not always give us all the information we need to diagnose and stage patients with lung cancer. Tumours or tumour relapses (reappearance of the tumour) can be missed or diagnosed too late. Tumours or other alterations may appear similar on CT or MRI images before and after treatment because functional or metabolic changes may occur, even in the absence of a noticeable change in appearance.

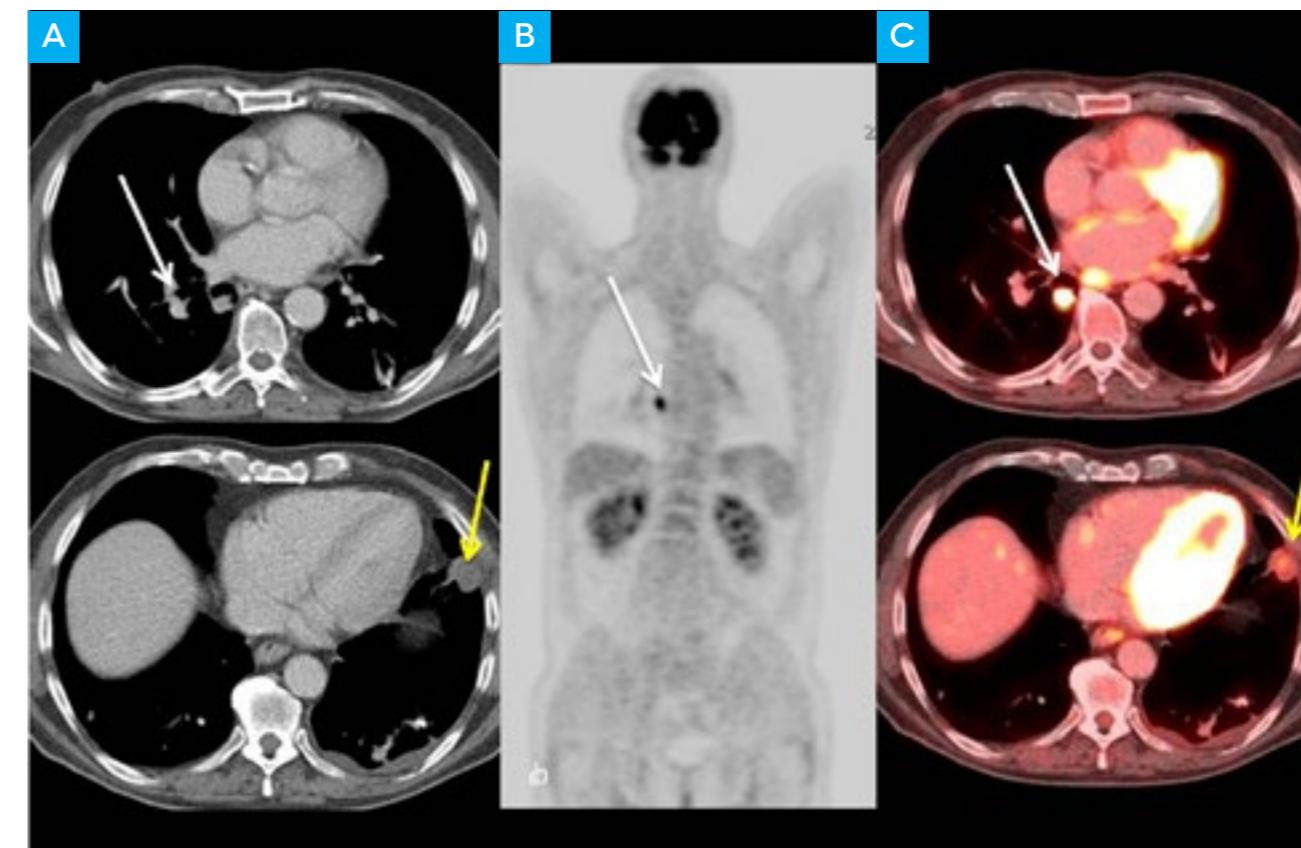
Positron emission tomography (PET) can image these functional processes by using radioactive tracers and photon detectors. PET is based on the injection of radioactive-labelled biomolecules (tracers), which are then followed and detected (enhancement). In oncology, <sup>18</sup>F-fluorodeoxyglucose (FDG), which is a glucose analogue, is the most widely used PET and PET/CT tracer. The disadvantages of PET are that small lesions (less than five millimetres) are difficult to detect and it can be hard to accurately pinpoint the location of the abnormality. But by combining PET and CT (PET/CT) functional and structural imaging are available in one machine. This 'anatomical-metabolic' imaging technique improves diagnostic accuracy for staging compared

with CT or PET. Improved diagnostic accuracy (Figure 3) allows for the detection of lesions not initially seen on CT or PET images; more precise lesion localisation and better delineation of the surrounding structures; and better characterisation of lesions as benign or malignant.

The radiologist should be aware that FDG not only enhances most malignant tumours, but can also enhance other non-malignant areas that are metabolically active, like inflammation or brown fatty tissue. Some tumours, like slowly growing adenocarcinoma or carcinoid tumours, often show little or no FDG-uptake, which may lead to misinterpretation.

The patient radiation dose from PET/CT is clearly an issue today. However, as long as a disease like cancer remains primarily a disease of the elderly and presents a life-threatening disease if not treated appropriately, then the benefits of nuclear and x-ray imaging will largely outweigh the risks. The fact that PET frequently provides indispensable information, with an impact on patient management in cases of malignant tumours, has meant that it increasingly represents an integral part of patient management, especially in oncology.

PATIENT WITH COLON CARCINOMA AND LUNG NODULES: ON CT (A) TWO LESIONS CAN BE SEEN: A SMALL LESION IN THE RIGHT LOWER LUNG (WHITE ARROW) AND A LARGER LESION IN THE LEFT LUNG (YELLOW ARROW). FDG-PET (B) ONLY SHOWS FDG UPTAKE (HOTSPOT) IN THE LESION IN THE RIGHT LUNG (WHITE ARROW). PET/CT (C) LOCALISED HOTSPOT ON RIGHT LUNG (WHITE ARROW) SUGGESTIVE OF LUNG METASTASIS BUT NOT ON THE LEFT LUNG (YELLOW ARROW). THEREFORE NOT SUGGESTIVE OF LUNG METASTASIS.



## 5

## LUNG MRI

BY JÜRGEN BIEDERER

Magnetic resonance imaging (MRI) is the latest technique for lung examinations. It uses the subtle resonant signal that can be obtained from hydrogen nuclei (protons) of water or organic substances when they are exposed to a strong magnetic field and excited by precise radio frequency pulses. Since the human body is made of proteins and fat, and contains a large amount of water, anatomic structures, as well as changes caused by diseases, can be easily visualised with MRI. In contrast to x-ray and computed tomography, images are acquired without any radiation exposure.

However, MRI of the lung is particularly challenging, since the lung contains a large volume of air with no signal and only small amounts of liquid and tissue, generating a low signal. This, in addition to a number of artefact sources (factors that lead to distortions in images), makes MRI of the lung a challenging endeavour that is less widely available and for which there is relatively little experience among the radiological community. This and many other issues, however, have been addressed by recent technological advances.

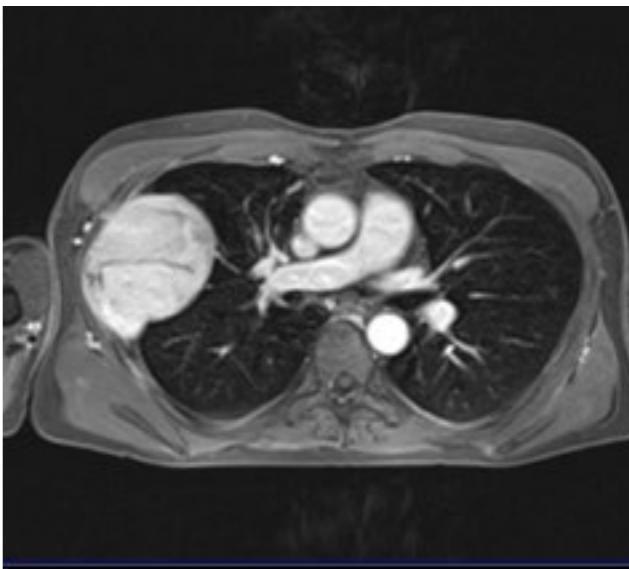
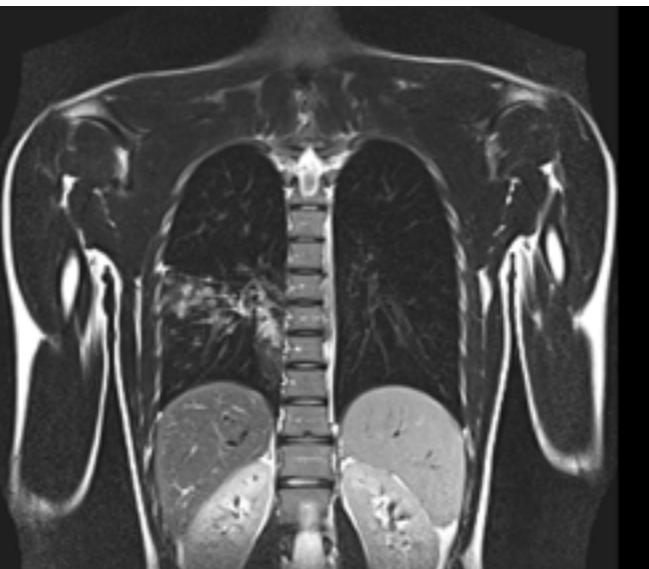
Today, modern MRI scanners produce images with great soft tissue contrast and they are well suited to neurological, musculoskeletal, abdominal, heart, and

lung imaging. Being a non-radiation alternative, lung MRI is particularly attractive for use in children, young patients, and pregnant women.

Furthermore, beyond its excellent morphological imaging capacities, MRI provides more functional information than any other technology. Blood circulation and air exchange inside the lung, as well as the movement of the lung and the breathing muscles (diaphragm, chest wall), can be studied with a routine examination. This makes MRI a preferred modality in specific clinical conditions such as cystic fibrosis (when the air flow inside the lung is blocked by large amounts of viscous mucus) and acute pulmonary embolism (when blood clots are blocking the pulmonary arteries). In other situations, e.g. tumours or pneumonia in children, lung MRI may be considered an alternative or adjunct to other modalities with similar diagnostic value.

Overall, MRI is more complex and more expensive than x-ray or CT. When resources were limited, it was important to define standardised protocols and clarify the indications in which MRI is preferred. This was a crucial step in introducing lung MRI into clinical use. This information is now widely available and makes it more likely that MRI will play a bigger role in lung imaging in the future.

## PNEUMONIA (WHITE SPOTS AND AREAS) IN A YOUNG MAN



YOUNG MAN WITH A LARGE TUMOUR OF THE CHEST WALL ORIGINATING FROM A RIB.

CHAPTER 2

# LUNG CANCER: DIAGNOSIS, STAGING, RADIOLOGICAL TREATMENT OPTIONS, FOLLOW-UP

## 1

# LUNG CANCER: HOW LUNG CANCER IS DIAGNOSED

BY CORNELIA SCHAEFER-PROKOP AND NIGEL HOWARTH

Patients with pulmonary symptoms, such as a cough or increasing dyspnoea, normally undergo a chest radiograph first, in order to diagnose or rule out any abnormal pulmonary opacification. Depending on the symptoms of the patient, e.g. increased temperature or sputum production, such an opacification may be caused by pneumonia, and so a control image following treatment will demonstrate adequate regression of the opacification. Certain morphological findings or a lack of therapy response, however, are indicative of lung cancer and will trigger immediate further diagnostic work-up. This is usually a CT examination with intravenous contrast injection.

Because of its 3D information and lack of overprojection, CT is superior to CXR in showing the exact location and size of a tumour. For tumours located in the centre of the lung it is important to analyse how extensively the tumour has grown into the central structures of the thorax, called the mediastinum, where the large vessels, the oesophagus and the central tracheobronchial system are located. The invasion of the tumour into the chest wall, the infiltration of lymph nodes or the presence of metastases in the bones, adrenals or liver are other important findings. The diagnostic process of determining the exact local extent of the

tumour, as well as the presence of distant metastases, is called 'staging' and determines whether the patient will undergo surgery, chemotherapy, radiotherapy, or some combination of the three.

Malignant cells show a pathologically increased glucose metabolism compared to non-malignant cells. This process is exploited by combining a PET scan with CT. While the CT provides the anatomic information (where the lesion is), the PET scan shows the pathological metabolism indicative of malignancy. Many studies have demonstrated the increased sensitivity of PET/CT for the detection of metastases compared to CT alone.

Nevertheless, any suspicious finding that determines the therapeutic management has to be histopathologically confirmed. Therefore, patients frequently have to undergo a biopsy, e.g. of a bone lesion or a liver lesion. There are several options for acquiring tissue from mediastinal lymph nodes for histological examination: via direct surgical access to the mediastinum under anaesthesia (mediastinoscopy), the tracheobronchial system (EBUS) or the oesophagus (EUS). Similarly, tissue from the tumour itself has to be examined by the pathologist in order to determine the best therapy for the patient, depending on tumour type and stage.

ACH, DASS DER  
MENSCH DOCH  
DURCHSICHTIG WÄRE  
WIE EINE QUALLE  
UND DASS MAN DEN  
SITZ SEINER LEIDEN  
SCHAUEN KÖNNTE.

**WILHELM CONRAD RÖNTGEN (1845 – 1923)**

## 2

# LUNG CANCER: VARIOUS RADIOLOGICAL APPEARANCES

BY PAUL FLECHSIG, CLAUS PETER HEUSSL AND HANS-ULRICH KAUCZOR

Lung cancer can appear with a huge variety of shapes and sizes. These appearances differ between tumour entities, types and stages, as well as between different imaging modalities.

One of the most common ways to examine lung diseases is with chest x-ray. In cases of doubtful findings from a chest x-ray, an additional CT examination is considered helpful. CT also captures the adjacent anatomic structures, i.e. the mediastinum, chest wall and heart. This helps to assess the local tumour burden and infiltration in patients suffering from lung cancer.

In the early stages, lung cancer appears as a small lung nodule; the larger the nodule or mass, the higher the stage. More advanced tumour stages are often accompanied by central necrosis, infiltration of the chest wall, ribs, or mediastinal structures, as well as metastases to the lymph nodes. Moreover, metastases in the lung, liver, brain, adrenal

glands and bones are signs of more advanced disease.

Figures 1 and 2 show two lung cancer patients with two very different radiological appearances. In the first patient, the chest x-ray (Figure 1a) shows a solid mass in the upper left lung (red arrow). The CT image (Figure 1b) reveals the chest wall as tumour free (blue arrows) on one side, but with close contact between the tumour and mediastinal structures (green arrows).

In the second patient, the chest x-ray (Figure 2a) shows many irregularly shaped nodules widely distributed in the lung (orange arrows). The mediastinum is widened, indicating enlarged lymph nodes (green arrows). The CT image (Figure 2b) shows a tumour consisting of a large cavitation (yellow arrow). The blue arrows indicate chest wall infiltration; green arrows show enlarged metastatic lymph nodes. The orange arrows indicate multiple lung metastases, correlating

with the irregularly shaped nodules seen in the chest x-ray (orange arrows).

To analyse chest wall infiltration, an additional MRI examination would be helpful. Figure 3 shows a mass in the upper right lung. In the x-ray (Figure 3a) and CT (Figure 3b), the tumour borders cannot be clearly assessed and infiltration into the ribs and chest wall muscles needs to be ruled out (Figure 3b, green arrows, question mark). The tumour borders are more clearly demarcated in the MRI image (Figure 3c, red line); the lung cancer is limited to the lung tissue while the ribs and chest wall muscles are unaffected.

Figure 4 shows chest x-ray (Figure 4a), CT (Figure 4b) and MR images (Figure 4c) of a lung cancer patient with a large mass in the upper left lobe (blue arrow). Local chest wall infiltration, including the destruction of the first and second rib can be seen on CT (Figure 4b, yellow arrows) as well as on the MR image (Figure 4c, yellow arrows).

FIGURE 1A



FIGURE 1B

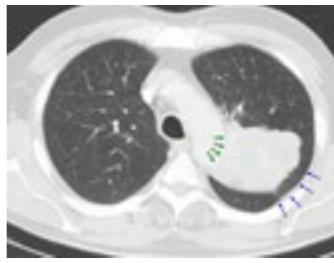


FIGURE 2A

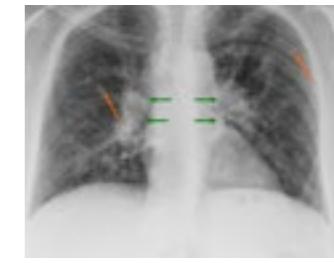


FIGURE 2B

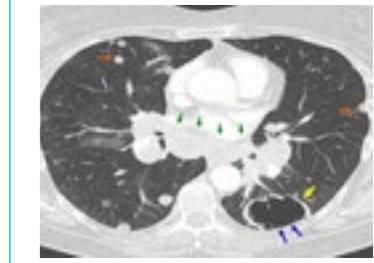


FIGURE 3A

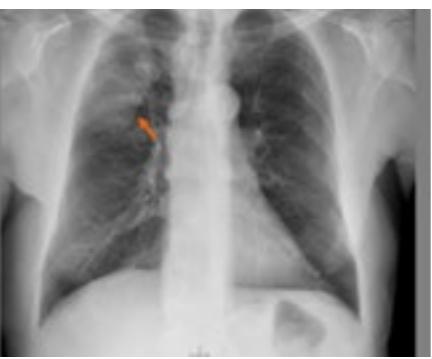


FIGURE 3B

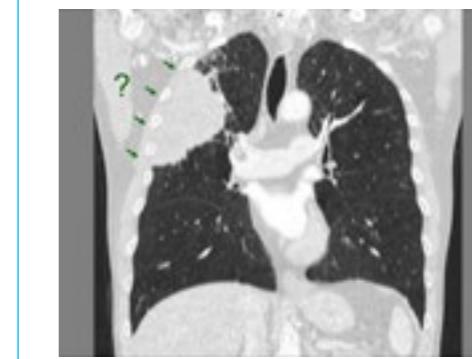


FIGURE 3C

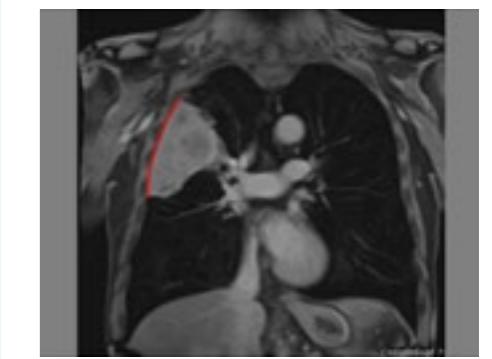


FIGURE 4A

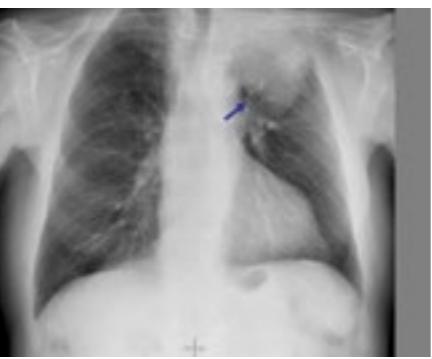


FIGURE 4B

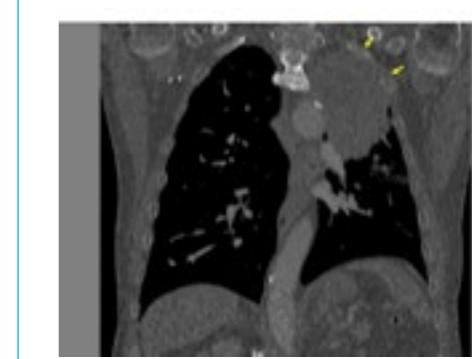
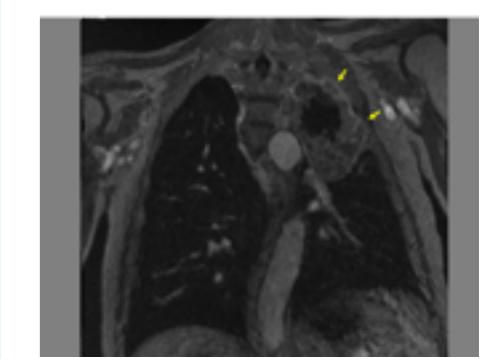


FIGURE 4C



## 3

## BIOPSY IN CHEST DISEASE

BY KATERINA MALAGARI AND DIMITRIOS FILIPPIADIS

The purpose of a biopsy procedure is to obtain a sample of tissue or cells from a diseased organ. A fine-needle aspiration is a procedure whereby cells are obtained using a very thin needle. Diagnostic interpretation of the cellular specimens or sample tissue from the lung, pleura, chest wall and other organs of the thorax is now practiced in virtually every major medical institution. These two procedures are performed in most patients suspected of having lung cancer, in order to confirm the final diagnosis and determine the histological type of the cancer, which is necessary for appropriate treatment planning.

These procedures are guided by suitable imaging modalities to ensure the needle is accurately inserted into the tissue, and to decrease the risk of side-effects such as bleeding or pneumothorax. In most cases, CT is used but other common alternatives include ultrasound or fluoroscopy. By using imaging guidance the physician can make sure that the sample is taken exactly from the suspicious mass, nodule or lesion and not from the surrounding organs, while avoiding injury to the neighbouring organs.

The indications for these procedures include the evaluation of lung nodules or masses, pleural masses, mediastinal lesions, lymph

adenopathy, chest wall masses and lytic bony cage lesions. Contraindications include a patient's refusal (the sole absolute contraindication), while other potentially correctable contraindications include bleeding diathesis; severe emphysema, especially if there is previous contralateral pneumonectomy; intractable cough; suspected echinococcal cyst (hydatid); possible arteriovenous malformation; and severe pulmonary hypertension.

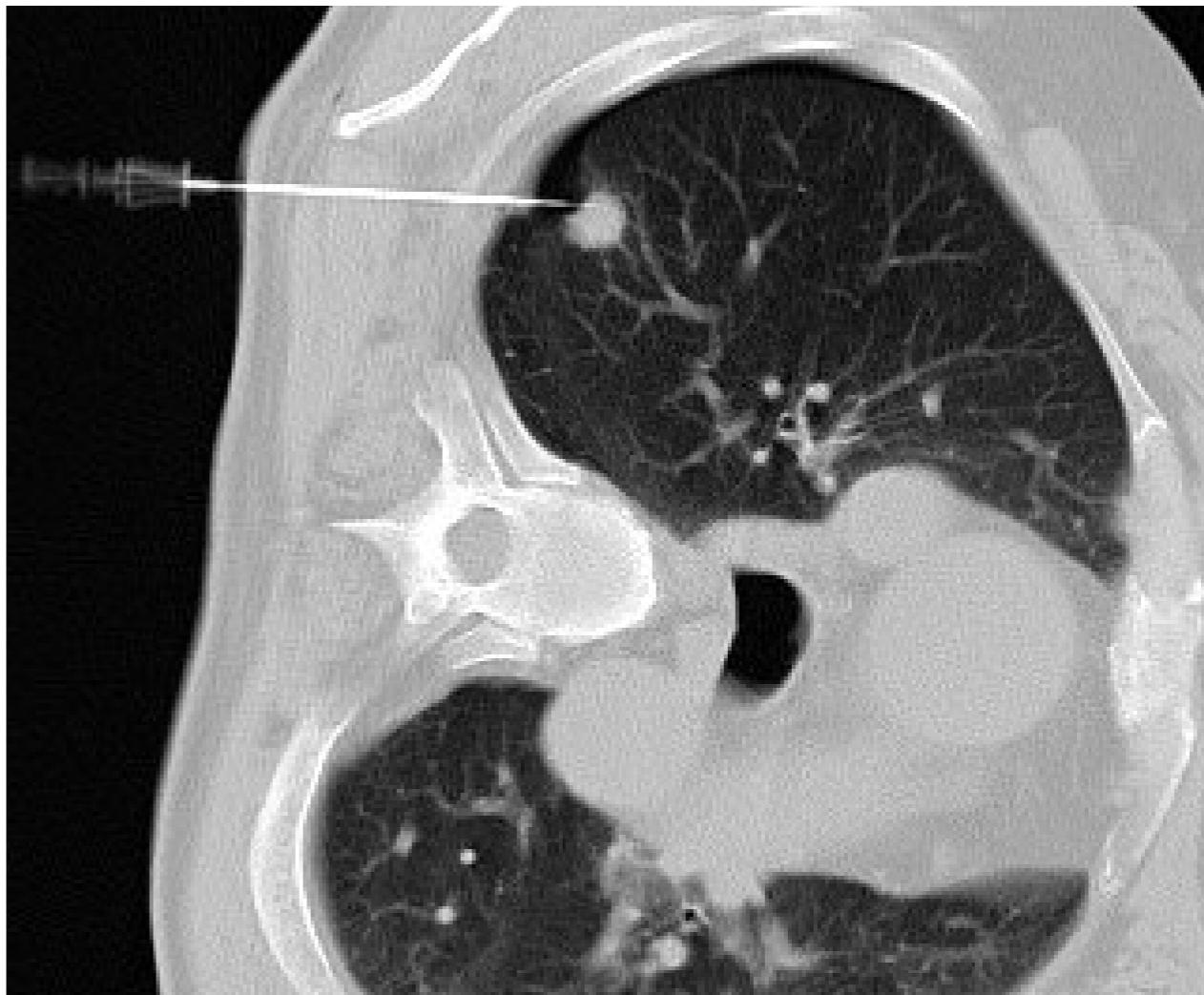
The patient is told about possible complications prior to the procedure and is given instructions to discontinue certain medication (e.g., aspirin or other non-steroidal anti-inflammatory drugs). Patients on oral anticoagulants should consult their physicians. A couple of hours before the procedure, clotting tests are performed to ensure proper coagulation and reduce the risk of bleeding. The patient should fast for six to eight hours prior to the procedure.

After placing the patient in the most suitable position, to access the tumour/lesion, the procedure is performed under local anaesthesia. Special needles are used to obtain the sample (cytological or actual tissue fragment in biopsy) and the sample is subsequently handled by pathology or cytology experts. After completing the procedure, additional views may be taken to rule out possible complications.

Complications are usually minor (some pain, or mild bleeding from the puncture site). The most serious, and also the most common, complication in lung biopsies is the insertion of air in the pleura room leading to a collapsed lung of varying severity (the latter is called pneumothorax). Pneumothorax occurs in 20–25 percent of lung biopsies, but only one in four of them require treatment by inserting a chest tube. Usually, the collapse is so minor that it can be managed conservatively with the administration of oxygen and a few hours of follow-up. Bleeding and haemoptysis occurs in less than 5–10 percent of cases and is self-limited. Fatal haemorrhaging occurs in less than one case in a thousand.

A biopsy is a highly accurate procedure yielding a definite (histological) diagnosis in more than 90 percent of cases. Diagnosis can be more difficult in benign lesions, especially since a negative result always needs to be considered critically to safely rule out a false negative result. In a certain percentage of cases, it might happen that the material aspirated was insufficient for the pathologist to make a diagnosis and it might be necessary to repeat the procedure, perhaps modifying the type of access or the type of needle.

THE PATIENT IS LYING ON HIS SIDE: A NEEDLE IS PLACED FROM THE BACK, CROSSING THE CHESTWALL TO APPROACH THE INTRAPULMONARY NODULE. THE NEEDLE IS PLACED IN SUCH WAY TO BYPASS THE BONES.



## LUNG CANCER TREATMENT OPTIONS: RADIOFREQUENCY AND MICROWAVE ABLATION

BY BENOÎT GHAYE

**A**bout one-third of patients with lung cancer are actually inoperable, even though the tumour itself is localised. This is usually because the patients present with poor overall condition, i.e. they have low cardiopulmonary function, which makes surgery too risky. In such cases, alternative therapies like radiation therapy or chemotherapy are applied, often accompanied with significant toxicity to the patient. Recently, minimally invasive treatments, including percutaneous thermal ablation, have been developed and appear to offer a valuable alternative.

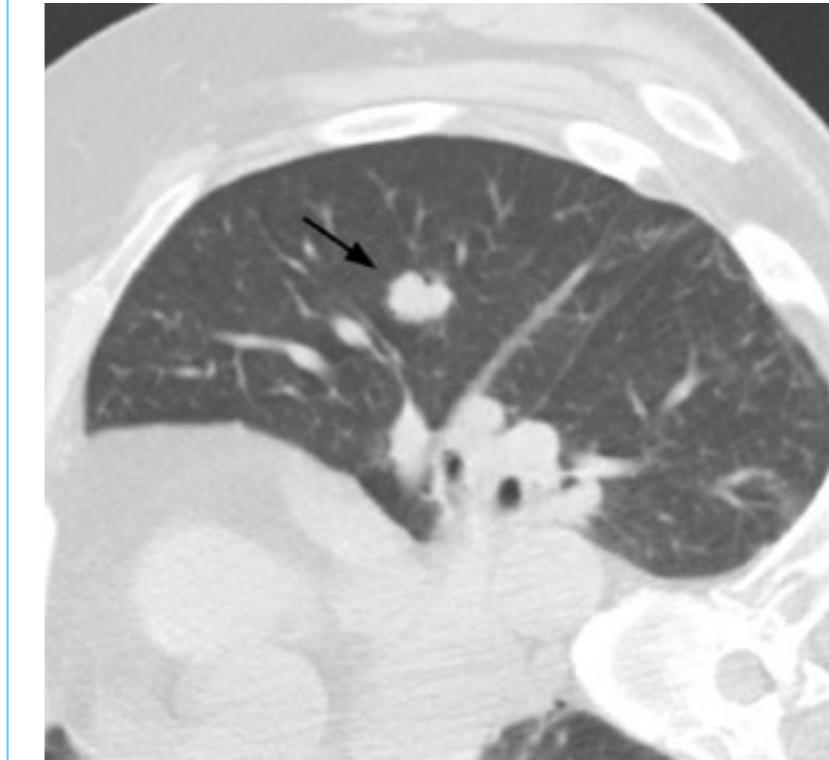
Thermal ablation is currently used as a substitute, or adjunct, to other therapeutic modalities for treating focal tumours in the liver, kidney, breast, thyroid, head and neck, bones and more recently, the lungs. The advantages of thermal ablation include reduced morbidity and mortality; faster recovery; earlier discharge from hospital; more outpatient treatment; lower costs; and a relative sparing of healthy peritumoural tissue, which is especially important for treating patients with reduced cardiopulmonary reserve.

Thermal ablation is performed by delivering either extreme heat (radiofrequency, microwave or laser) or extreme cold (cryotherapy) through a needle that

is inserted into the tumour under CT guidance. The type of energy and anaesthesia (general anaesthesia or conscious sedation) depend on the patient, tumour location, nature of the tumour, treatment goal, and operator experience or preference. The tumour should be no larger than two or three centimetres in diameter to be suitable for this type of treatment. The duration of the procedure varies from 30 minutes to three hours, depending on the number and type of lesions.

Indeed, as most patients treated with thermal ablation have contraindications to other treatments, the results of ablative therapy look very encouraging. Nevertheless, studies are still needed to accurately assess the role of ablation compared with other emerging techniques, like stereotactic radiotherapy, as well as its potential synergy with other treatments.

Complications are few and basically the same as for percutaneous lung biopsy. They mainly concern pneumothorax, which is easily treated during intervention. After intervention, patients are followed up with PET, and CT or MRI. When necessary, thermal ablations can be repeated to complete treatment in patients showing a persistence of viable tumour tissue.



NEW LUNG CANCER IN THE LEFT LUNG OF A PATIENT WHO UNDERWENT SURGICAL RESECTION OF A RIGHT-SIDED LUNG CANCER A FEW YEARS EARLIER.

# LUNG CANCER: FOLLOW-UP

BY ANNA RITA LARICI, LUCIO CALANDRIELLO AND LORENZO BONOMO

**S**urgery remains the mainstay of treatment with curative intent for patients with lung cancer in the early stages (with specific reference to non-small cell lung cancer = NSCLC). However, most patients are not eligible for surgery at the time of diagnosis, due to the advanced tumour stage or the coexistence of cardiopulmonary diseases limiting the indications for surgery. In these patients possible treatment options are combined (neoadjuvant) radio-chemotherapy, chemotherapy alone or local treatments, such as radiotherapy or tumour ablation, according to the extent of the disease.

Imaging plays an important role in the assessment of treatment response after radio-chemotherapy and in the follow-up of patients surgically treated for lung cancer. Computed tomography (CT) and positron emission tomography with computed tomography (PET/CT) with 18F-fluorodeoxyglucose (18F-FDG) are the imaging modalities commonly used in this context.

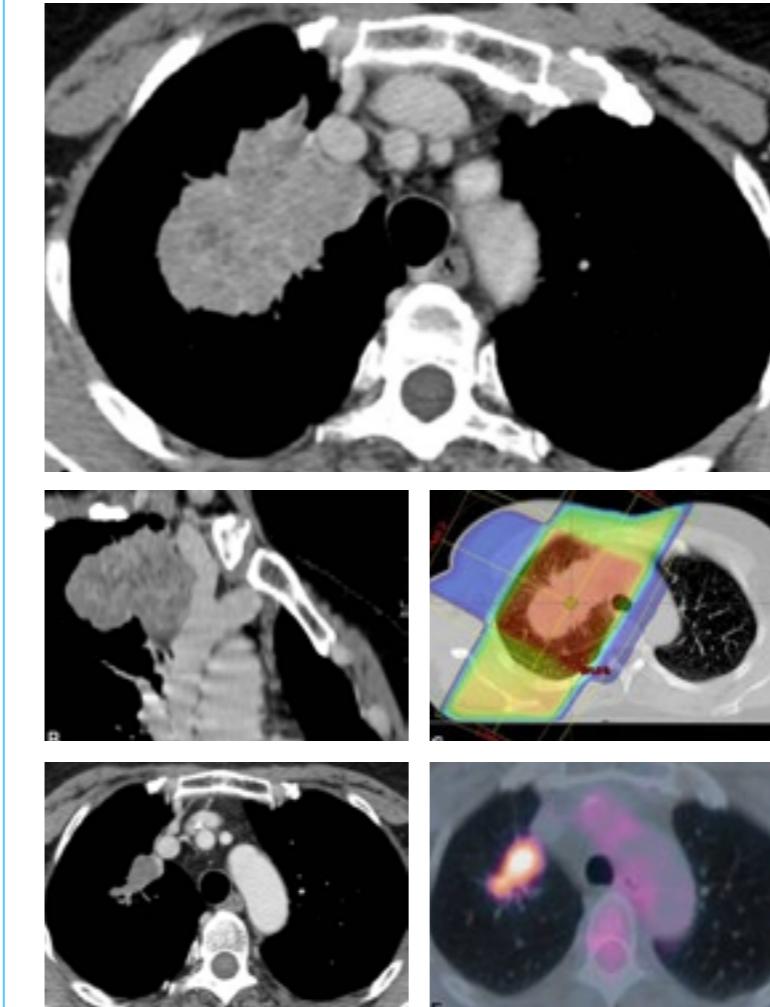
CT provides information on morphological changes affecting the tumour after treatment (Figure 1). According to dimensional criteria and following internationally accepted rules, radiologists and clinicians define the presence of 'complete' or 'partial response' to treatment as well as 'progression' or 'stability' of the disease. When a good response is seen after neoadjuvant radio-chemo-

therapy, selected patients may subsequently undergo surgery.

PET/CT is a highly accurate means of detecting residual disease after treatment (Figure 1) and for determining further treatment. It is known that metabolic-functional alterations precede morphological changes and, therefore, a reduction in the uptake of 18F-FDG by tumour cells after treatment is indicative of a reduction in the number of viable tumour cells. PET/CT is also useful for distinguishing metabolically active tumours from inactive scarring (fibrosis), which can occur after radiation therapy in the lung parenchyma surrounding the treated lesion.

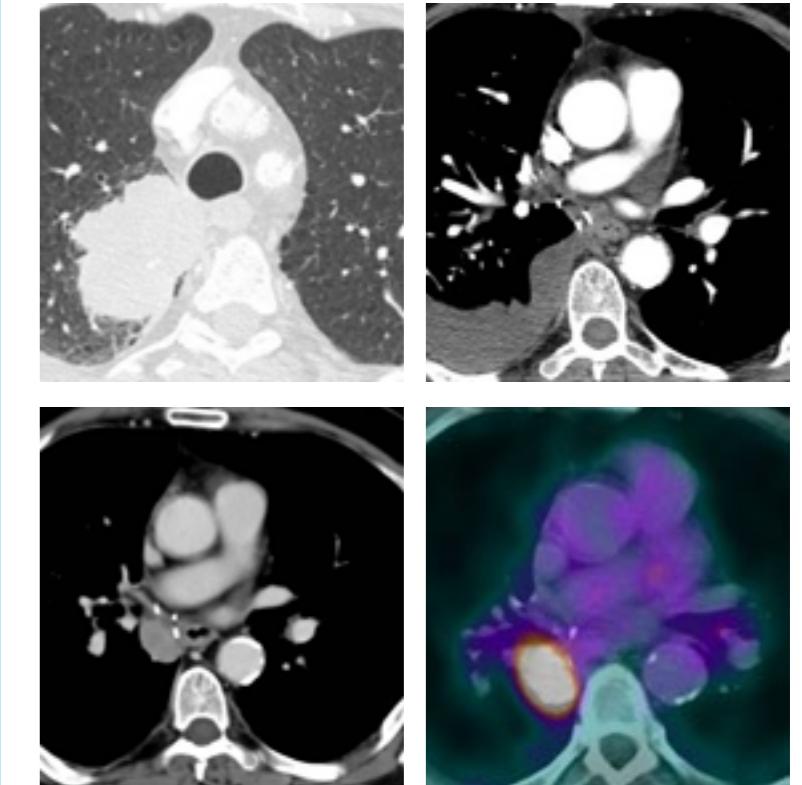
Even when treated with curative intent, lung cancer can recur, depending mainly on the pathological stage. Most recurrences occur within the first two years following completion of treatment. Therefore, it is important to schedule a tighter follow-up for the patient during that period. Radiology is essential for investigating both loco-regional (within the treated hemithorax) and distant recurrences. In particular, the integration between morphological and metabolic information obtained with PET/CT is useful for confirming a tumour recurrence (Figure 2), distinguishing lung abnormalities from tumour recurrence after treatment, and identifying distant metastases.

FIGURE 1



GOOD RESPONSE TO TREATMENT OF NSCLC. A 66-YEAR-OLD WOMAN WITH A LARGE RIGHT UPPER LOBE MASS INFILTRATING THE MEDIASTINAL FAT AND CLOSELY ADJACENT TO THE RIGHT INNOMINATE VEIN AND SUPERIOR VENA CAVA. VESSELS SHOW MILDLY IRREGULAR MARGINS (A, B). AFTER THREE MONTHS OF NEOADJUVANT COMBINED CHEMOTHERAPY AND RADIOTHERAPY (C), THE MASS SHOWED EVIDENT VOLUME SHRINKAGE (D) WITH RESIDUAL METABOLIC ACTIVITY IN THE PET/CT SCAN (E). PATIENT SUBSEQUENTLY UNDERWENT SURGERY.

FIGURE 2



RECURRENCE OF NSCLC. A 70-YEAR-OLD MAN UNDERWENT RIGHT UPPER LOBE LOBECTOMY FOR A LARGE MASS (A) WITH IPSILATERAL MEDIASTINAL AND SUBCARINAL LYMPHADENECTOMY. ONE MONTH AFTER SURGERY, THE BASELINE CT EXAM SHOWED A PLEURAL EFFUSION AND METAL CLIPS IN THE SUBCARINAL STATION (B). TWO YEARS LATER A ROUNDED SOFT TISSUE MASS IS SEEN CLOSE TO THE CLIPS ON CT (C) HIGHLY SUSPICIOUS FOR LOCO-REGIONAL RECURRENCE AND CONFIRMED BY PET/CT SCAN (D).

CHAPTER 3

# LUNG CANCER: SCREENING

# LUNG CANCER SCREENING: WHAT IS IT AND WHAT HAVE WE LEARNT SO FAR?

BY ANAND DEVARAJ

**L**ung cancer is still one of the deadliest diseases in the world today. It is the leading cause of death in many countries and is responsible for the largest number of cancer-related deaths worldwide. When detected early, however, there is a good chance of curing lung cancer through surgery. Unfortunately, lung cancer only has symptoms in more advanced stages, and most people suffering from lung cancer present at their doctor's office when their chances of being cured are slim.

Computed tomography (CT) scanning of the chest is a medical imaging technique that can detect early-stage lung cancer before symptoms become apparent (Figure 1b). Over the past decade, numerous investigations have studied whether CT can be used as an effective tool to detect these early stages of lung cancer in asymptomatic individuals. Many randomised controlled trials (either completed or in progress) have addressed the question of whether CT screening can reduce mortality in those who are at high risk of developing lung cancer.

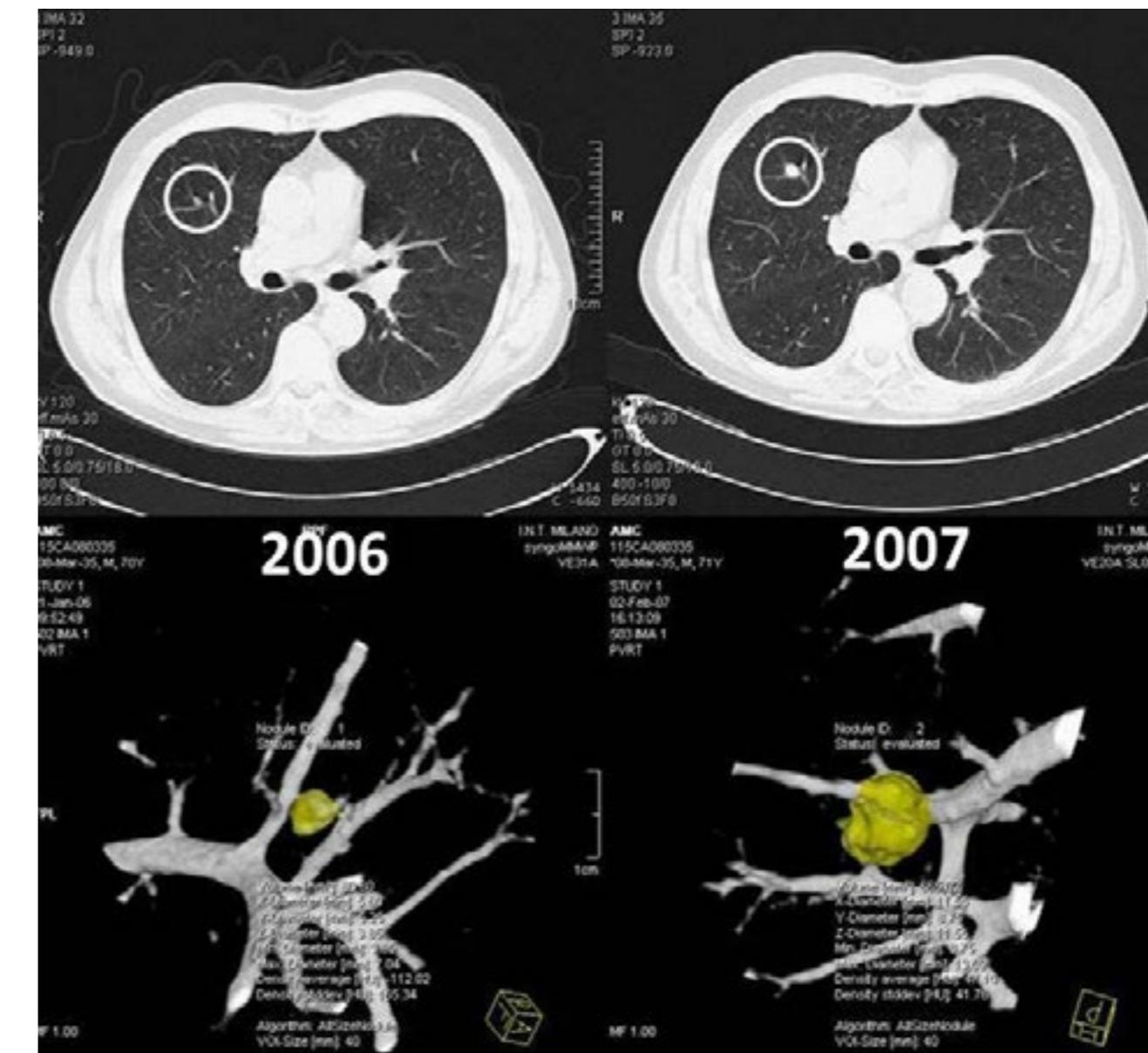
In 2002, the National Lung Screening Trial (NLST) embarked upon recruiting 53,454 former and current smokers to participate in a trial where participants were randomised to undergo annual screening with either CT or chest x-rays for three years. In 2011, six and a half years after the end of the trial, the investigators

reported 87 fewer deaths due to lung cancer among those individuals who were screened with CT, which corresponds to a 20 percent reduction in lung cancer-specific mortality.

Like in many trials before, the Prostate, Lung, Colorectal and Ovarian Randomized Cancer Screening Trial (PLCO), which was published at about the same time as the NLST, confirmed that screening with chest x-rays alone has no effect on lung cancer survival. No difference in mortality was identified between those receiving chest radiography and those who were not screened at all.

The results from the NLST have led many American national organisations to recommend the introduction of lung cancer screening in clinical practice. In Europe, however, smaller trials (MILD, DANTE and DLST) with approximately 2,500–4,000 patients each did not show any benefit from CT screening. In fact, these trials even suggested an increased mortality in those who underwent annual CT screening. The larger Dutch-Belgian NELSON lung cancer screening trial, with more than 15,000 participants, will publish its results in the next few years, and will help clarify whether CT screening should also be introduced in Europe.

TWO CTs AND AUTOMATIC VOLUMETRY SHOWING SIGNIFICANT GROWTH OF THE NODULE WITHIN ONE YEAR INDICATIVE OF AN EARLY LUNG CANCER.



## LUNG CANCER SCREENING: WHO SHOULD TAKE PART AND WHAT ARE THE CONCERNS?

BY NICOLA SVERZELLATI

The American National Lung Screening Trial (NLST) demonstrated a 20 percent reduction in death due to lung cancer among those who were screened with CT. Even the total number of deaths within the six-and-a-half year follow-up period was reduced by more than six percent. While these results are spectacular for any screening programme, the screening procedure itself has its risks. Careful selection is therefore necessary to identify those for whom the benefits outweigh the potential risks.

The risks are mainly due to false-positive results, suspicious lung lesions that are thought to represent lung cancer on screening CT, but are not actually malignant. Small lung nodules are common: in almost 20 percent of lung screening participants a lesion within the size range of 5–10 mm is detected. The vast majority of these lesions are in fact benign; less than 10 percent are cancerous. These lesions are usually followed up using CT to see whether they have grown. If lesions grow, their likelihood of being cancer is much greater, but many are still benign.

Invasive procedures such as biopsies or surgery are required to distinguish cancers from benign lesions. Participants with a benign lesion (false positive) will still have to undergo such procedures, along with their costs and potential complications. Anxiety is also an important consideration, particularly while waiting for screening results. False-positive results have been associated with depression and changes in overall perception of one's health<sup>4</sup>.

Other risks are overdiagnosis and the potential risk of radiation-induced cancer from the radiation used by CT<sup>1</sup>. Overdiagnosis refers to the detection of slow-growing non-fatal cancers, which if detected in a screening programme will cause unnecessary treatment because they would not have limited the patient's life expectancy nor effect his/her quality of life. The risk of cancer being induced by the low dose from lung cancer CT screening is unlikely, but cannot be completely ruled out. The average effective dose is comparable to the annual radiation dose from natural sources<sup>3</sup>.

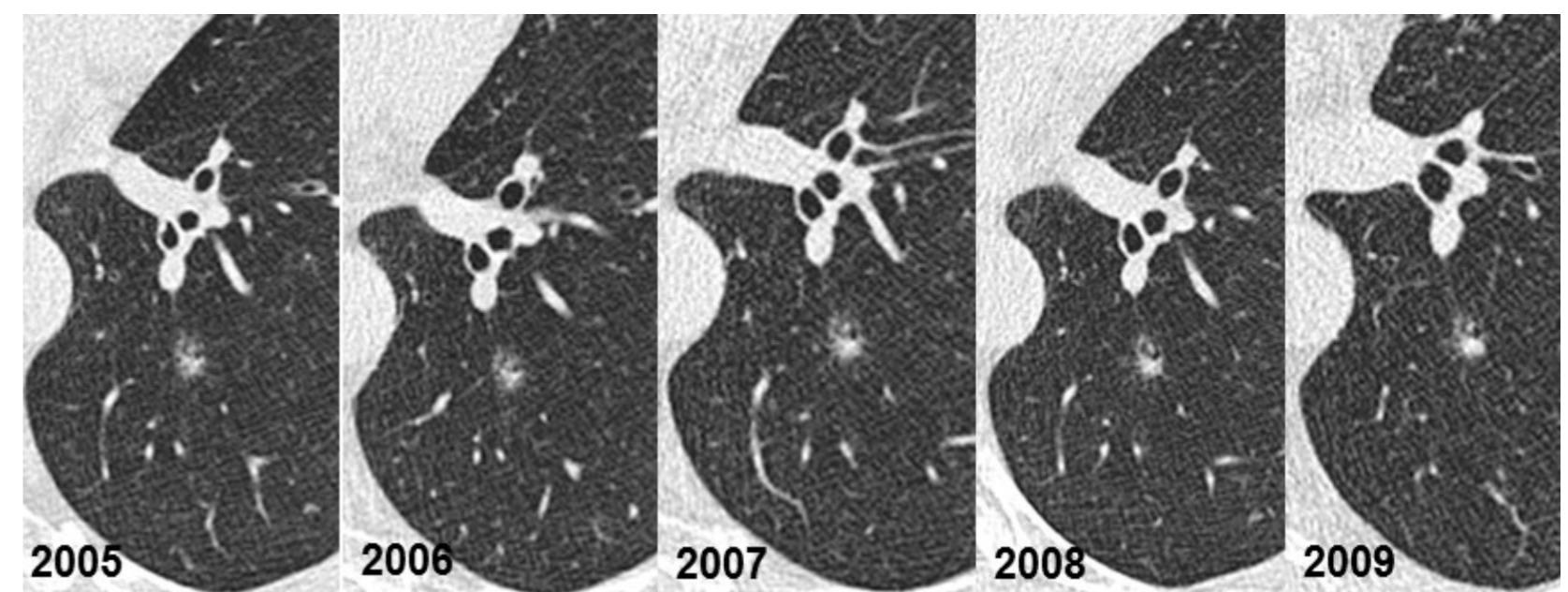
The discussion continues as to how best to identify those who are likely to benefit from screening. Lung cancer risk increases with age and with the number of pack-years smoked. The number of pack-years is calculated by multiplying the number of years a person has smoked by the average number of packets of cigarettes smoked per day. The NLST targeted high-risk smokers and former smokers between 50 and 75 years of age with at least 30 pack-years. Most European studies, which did not show a benefit from CT screening, also included individuals who had smoked less. It is also not clear whether screening might benefit individuals with other risk factors for lung cancer, such as various lung diseases, occupational exposure to asbestos or other carcinogens, or lung cancer in a first-degree relative.

Current research focuses on how to best select screening participants, how to reduce the number of false positives and cases of overdiagnosis, and how to keep radiation exposure to a minimum.

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**MINIMALLY INVASIVE LUNG ADENOCARCINOMA IN A 65-YEAR-OLD FEMALE LUNG CANCER SCREENING PARTICIPANT. BASELINE CT IMAGE (LEFT) SHOWS A GROUND-GLASS NODULE WITH A BARELY SOLID COMPONENT ON THE LEFT LOWER LOBE. CT IMAGES REPEATED ANNUALLY SHOW AN INCREASE IN THE SIZE OF A SMALL, CENTRAL AND SOLID COMPONENT. CHOOSING THE BEST WORK-UP FOR THIS TYPE OF SLOW-GROWING LESION CAN BE DIFFICULT DUE TO THE RISK OF OVERDIAGNOSIS.**



# LUNG CANCER SCREENING: AUTOMATED DETECTION & FOLLOW-UP

BY BRAM VAN GINNEKEN

Widespread implementation of CT lung screening would require millions of CT scans to be evaluated for the detection of potential lung cancers. Evaluation is normally carried out by radiologists, medical specialists who have been trained for many years to read such medical images. The demand for evaluations that would be brought about by widespread CT lung screening would create a major bottleneck: radiologists require five to fifteen minutes reading time to locate pulmonary nodules on a 3D CT dataset. This excludes the interaction time needed to locate the same nodule in prior exams and measure the size of the nodule. These tasks are fundamentally different from those required for mammography screening, the only widespread image-based screening implemented in the western world. Mammography screening uses 2D images and requires, on average, substantially less reading time for radiologists.

This reading bottleneck in CT lung screening could be solved by letting specially trained non-radiologists evaluate the images, but the effort involved would still be vast. A more promising solution would be to use computerised nodule detection software. Such software has been commercially available for about a decade, but literature reports that the sensitivity of these algorithms is too low.

Recently, it was shown that combining multiple algorithms for nodule detection in CT can substantially improve overall performance, far exceeding that of the best single algorithm<sup>1</sup>. Current research focuses on developing algorithms that are better than most human readers for detecting the locations of potential cancers, so that a human reader would only inspect locations selected by the computer. Specific software has to be developed for so-called 'subsolid' lesions that may rep-

resent slow-growing cancers, which could otherwise be easily missed. It is important to verify that no lesions requiring direct work-up or short term follow-up CT are missed by this procedure.

Workflow has to be optimised to increase throughput. For example, nodules in prior and current scans have to be automatically linked to ensure correct comparison. Automated measurement of their volume and their growth rate also needs to be optimised. For subsolid lesions in particular, automated assessment of lesion volume remains a challenge. Size and growth help in assessing the probability that a nodule is a cancer, which determines work-up.

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CHAPTER 4

# DIFFUSE LUNG DISEASES

# HIGH-RESOLUTION COMPUTED TOMOGRAPHY (HRCT) IN DIFFUSE INTERSTITIAL LUNG DISEASE: WHY IS HRCT BETTER THAN CHEST RADIOGRAPHY?

BY SUJAL R. DESAI AND DAVID M. HANSELL

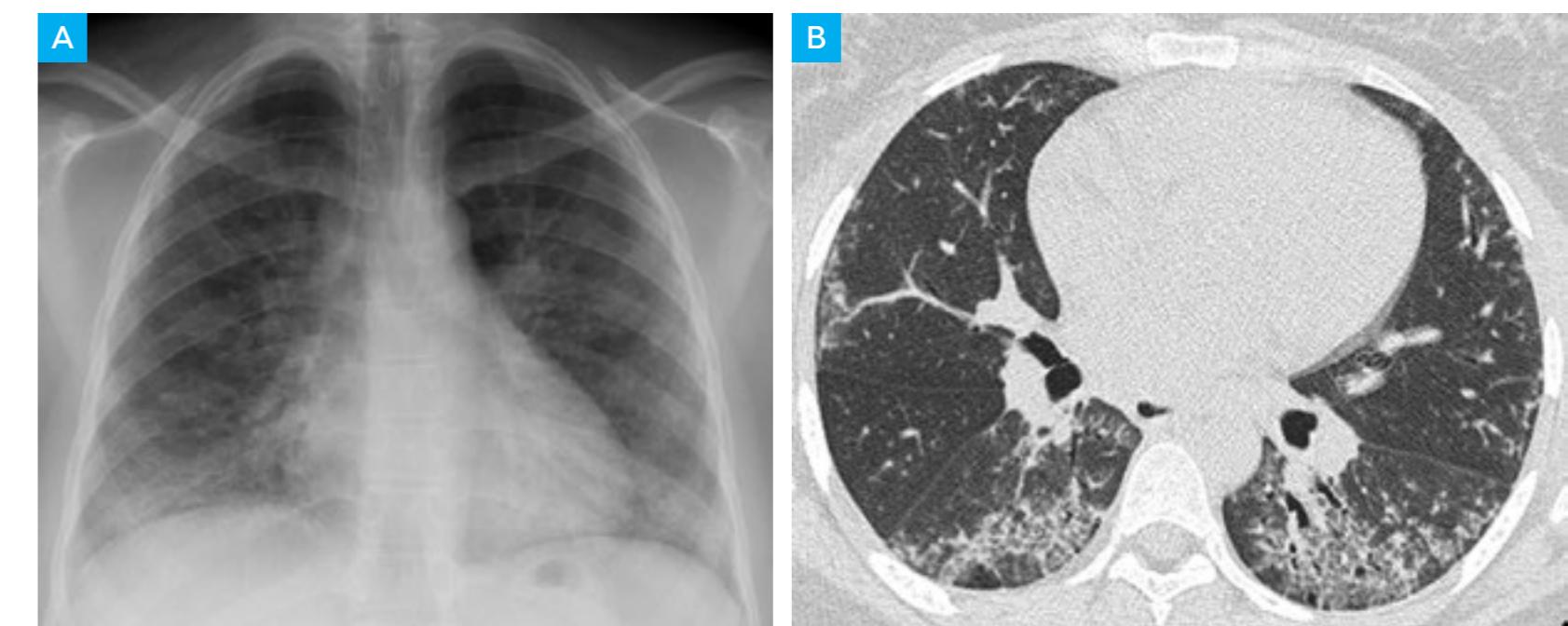
**D**iffuse interstitial lung diseases (DILD) are a challenging group of disorders. Patients with DILD often present to a physician with vague symptoms which include breathlessness and a cough. In most patients, a test of lung function and a chest x-ray (CXR) will be requested. While the CXR has the benefit of a low radiation dose, it has limitations. One of the main problems is that because of the way it is obtained, structures in the chest are superimposed on one another, causing some parts of the lung to be obscured. This can make interpretation difficult; more specifically, the characterisation of individual patterns, on which the diagnostic process hinges, becomes problematic. Another issue with the CXR is that its sensitivity is low; this means that disease is often at a quite advanced stage when it is first visible on a CXR.

The unique feature of all computed tomography (CT) imaging is that, because images are acquired from around the body, there is no anatomical overlap. In the technique of high-resolution CT (HRCT), the x-ray beam

is very narrow – of the order of 1.0 to 1.5mm. This has the effect of improving spatial resolution (which is the ability to distinguish one anatomical element from a neighbouring one) and making HRCT images appear much ‘sharper’ than images acquired with a wider x-ray beam (e.g. 5 or 10mm). The improved resolution and absence of any superimposition means that the patterns of disease and their distribution (another key characteristic that helps in making a diagnosis) and extent can be accurately evaluated.

In comparison to the CXR, radiologists are generally more confident when providing a diagnosis based on HRCT. More importantly, when experienced thoracic radiologists are confident about a diagnosis with HRCT, they are generally correct. This has had a major effect on clinical practice in certain disorders; where previously patients would have required an invasive surgical procedure, physicians now rely on a confident HRCT diagnosis (made by an experienced thoracic radiologist) to help with the management of their patients.

**A)** CHEST RADIOGRAPH (CXR) AND **B)** HIGH-RESOLUTION CT IN A PATIENT WITH A DIFFUSE LUNG DISEASE. THE CXR INDICATES THAT THERE IS AN ABNORMALITY IN THE LUNGS BUT ACCURATE CHARACTERISATION IS ONLY POSSIBLE ON THE CT IMAGE WHICH SHOWS THAT THERE IS ESTABLISHED LUNG FIBROSIS IN THIS PATIENT.



## 2

## DIFFUSE LUNG DISEASES CAUSED BY SMOKING: WHAT DO WE SEE?

BY SUJAL R. DESAI AND DAVID M. HANSELL

**I**t is widely known that cigarette smoking harms the lungs and the established link between smoking and lung cancer does not need to be repeated here. There is now a general awareness that smoking, over many years, can cause specific disorders such as emphysema and chronic bronchitis. What is less well appreciated is that there is a spectrum of other lung disorders that have more recently been attributed to cigarette smoking.

Pathologists have known since the 1970s that smoking can provoke the build-up of particular cells (macrophages) in the lungs. Such an accumulation (which tends to be most florid around the small airways), has been termed 'respiratory bronchiolitis' (RB). In the majority of patients RB causes no symptoms. However, a minority of smokers will develop symptoms of a diffuse interstitial lung disease (DILD). Respiratory bronchiolitis-interstitial lung disease (RBILD) is the clinical

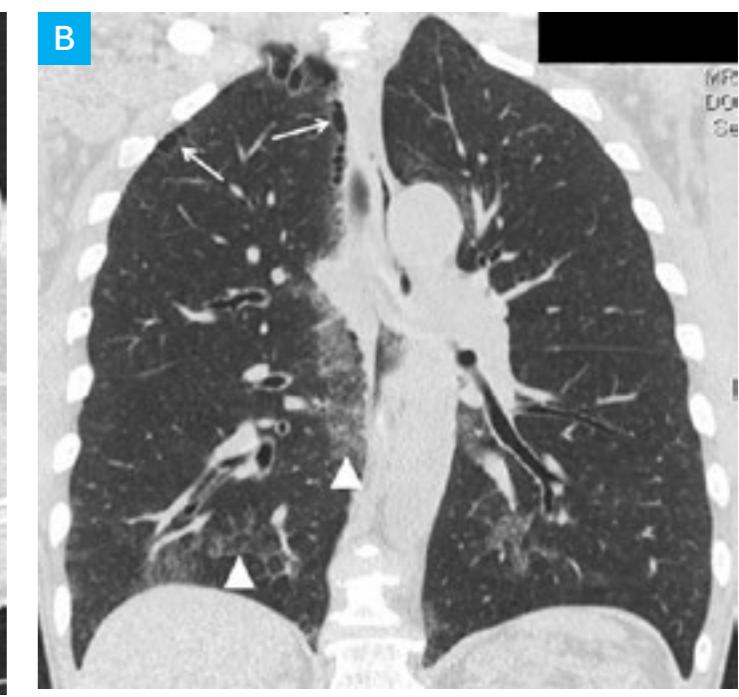
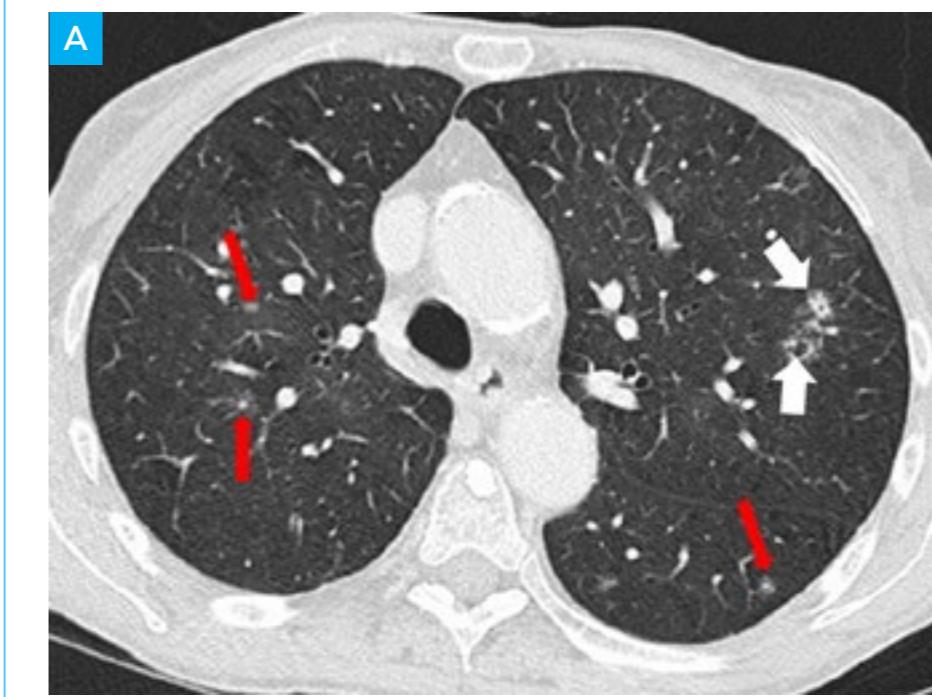
manifestation of interstitial lung disease in smokers who have the pathological abnormality of RB.

Other DILDs known to be caused by, or associated with, cigarette smoking include Langerhans' cell histiocytosis, desquamative interstitial pneumonia and acute eosinophilic pneumonia. Additionally, patients with certain types of fibrosing DILD (notably idiopathic pulmonary fibrosis) are, more often than not, smokers.

The high-resolution CT (HRCT) appearances of smoking-related DILDs can be non-specific: a general increase in density (termed 'ground-glass opacification') is a common feature in smoking-related infiltrative diseases, but this can be seen in a variety of other disorders. However, in the appropriate clinical setting, an experienced thoracic radiologist may be able to suggest the diagnosis of smoking-related interstitial lung disease.

CT IMAGES SHOWING TWO DIFFERENT DISEASES CAUSED BY SMOKING.

- A)** LANGERHANS' CELL HISTIOCYTOSIS (WITH MULTIPLE SOLID NODULES [RED ARROWS] AND SOME WHICH ARE CAVITATING [WHITE ARROWS]) AND
- B)** DESQUAMATIVE INTERSTITIAL PNEUMONIA - RECONSTRUCTED CT IMAGE SHOWS PATCHY AREAS OF GROUND-GLASS OPACIFICATION ('WHITE LUNG', ARROWHEADS).



## FIBROSING LUNG DISEASES: EFFECTS ON STRUCTURE AND FUNCTION

BY SUJAL R. DESAI AND DAVID M. HANSELL

**I**n nature, structure and function are linked. Research studies that have investigated structural alterations and their relationship to physiological (functional) alterations have provided many valuable insights into the pathogenesis and behaviour of fibrosing lung diseases.

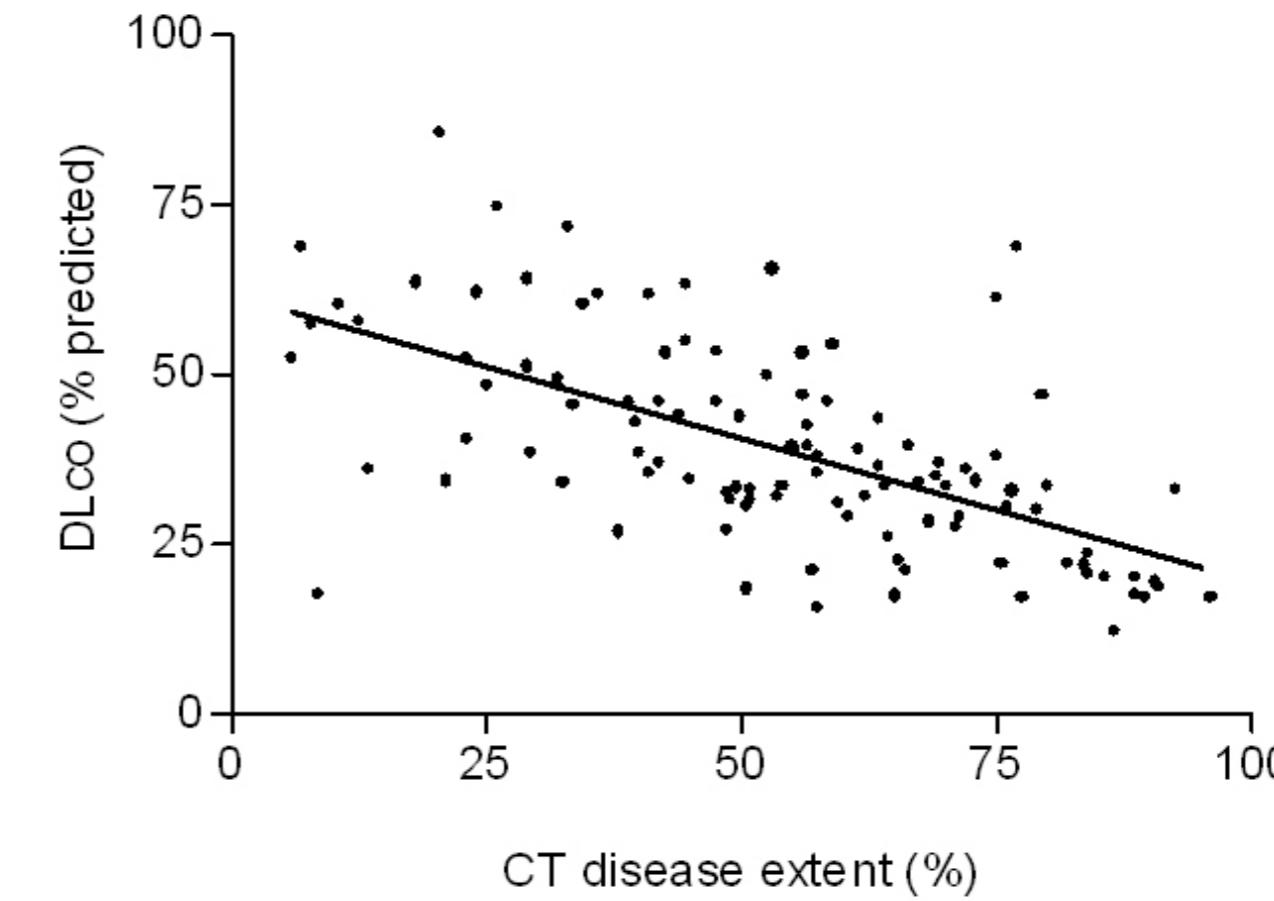
Investigation into structural-functional relationships has been made possible, largely because of the quality of images provided by high-resolution computed tomography (HRCT) and the ability of radiologists to accurately quantify different patterns of disease. Approaches to the quantification of CT abnormalities vary, but one of two methods is usually adopted: CT patterns are scored visually or with sophisticated computer-aided techniques. Both have their advantages and disadvantages.

Whichever method is used, there is no doubt that studies based on CT observations have provided many

insights. For instance, in one of the archetypal fibrosing lung diseases (idiopathic pulmonary fibrosis), correlative studies have shown that, among the plethora of lung function indices that are available to a physician, there is one – a measure of the gas transfer in the lungs – which is the best single predictor of the extent of disease. In other disorders (sarcoidosis being a notable example), there may be a mixture of patterns with opposing functional consequences. In such cases, CT can provide the morphological explanation for seemingly complex physiological patterns.

With accurate quantification and characterisation of disease, the role of CT in predicting long-term outcome has also been explored more recently. A number of investigators have shown that there may be a strong prognostic 'signal' in CT images. Indeed, some recent studies have shown the value of individual CT signs (for instance, the dilatation of airways present in scarred lung) in predicting mortality.

GRAPH PLOTTING THE RELATIONSHIP BETWEEN THE EXTENT OF LUNG FIBROSIS AND AN IMPORTANT MEASURE OF LUNG FUNCTION IN A GROUP OF PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS.



# IMAGING OF AIRWAYS DISEASES

BY SUJAL R. DESAI, ARJUN NAIR AND PHILIPPE GRENIER

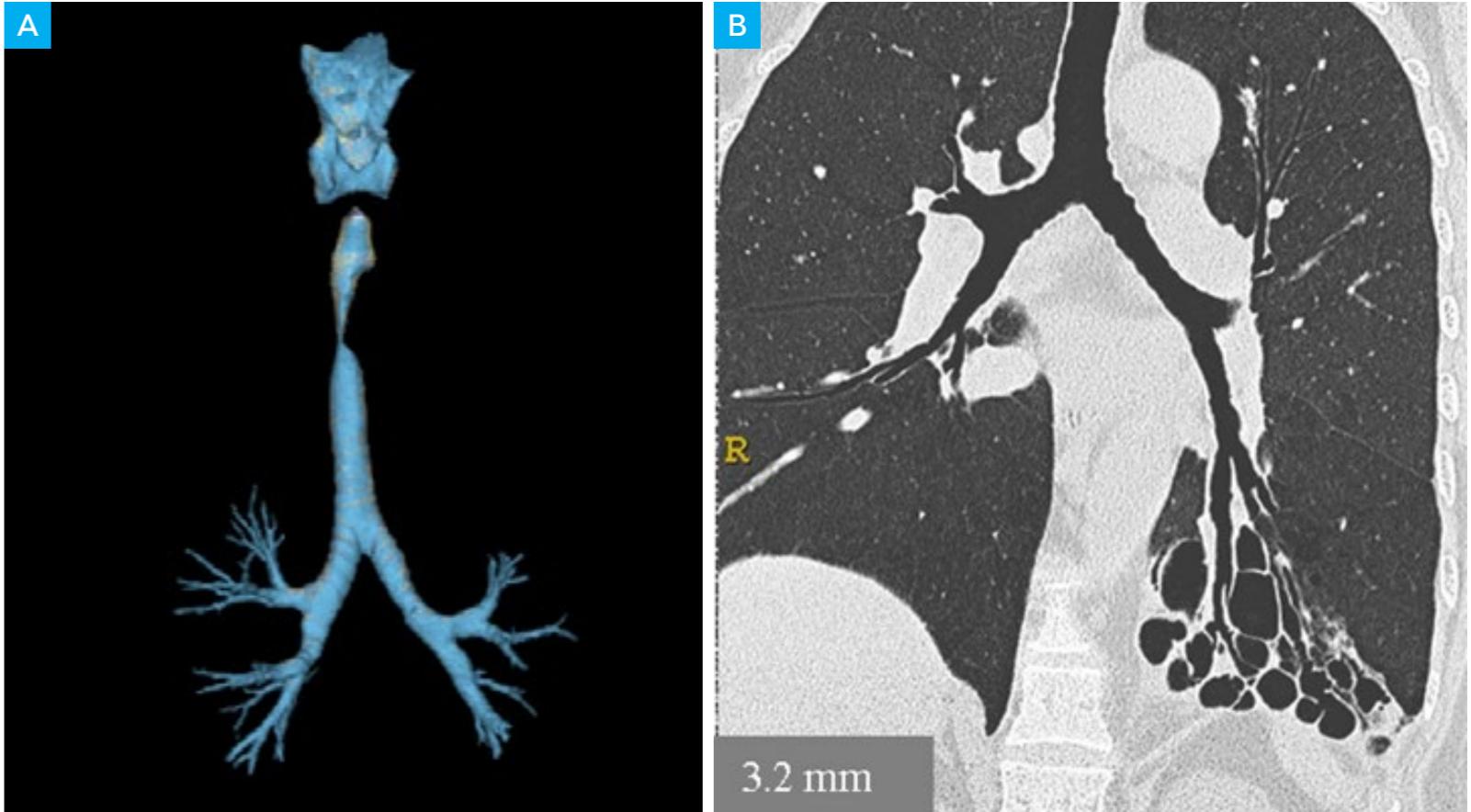
**D**iseases of the airways are incredibly common and radiological tests play a central role. The spectrum of pathologies is wide and can affect the entire length of the bronchial tree from the largest (called the trachea) to the very smallest airways. Some of the most common diseases that have a worldwide significance include asthma and chronic obstructive pulmonary disease (COPD).

When faced with a patient with suspected or established airways disease, it is likely that a chest physician will request an imaging study. More often than not, a chest x-ray (CXR) will be performed as one of the initial tests. However, in modern clinical practice it is increasingly likely that computed tomography (CT) will also be requested. In specialist centres, magnetic resonance imaging (MRI) is being increasingly used, and the technique of ultrasound imaging has been combined with standard bronoscopes to revolutionise the 'targeting' of tissues for biopsy.

In most instances, however, CT will be the key investigation. The availability of superfast and sophisticated CT machines means that images of the chest can now be captured within a single breath-hold; this has particular significance in patients who may already be breathless because of their underlying lung problem. Over the last two decades, such advances have been nothing short of staggering. The data acquired with modern CT machines is used to visualise pathology in a number of different planes and formats.

In addition to traditional cross-sectional images, doctors can now view images which show the bronchial tree in three-dimensions, from the outside or inside, by using the technique of virtual bronchoscopy (VB). Indeed, VB may be an invaluable 'roadmap' when planning invasive procedures with the bronchoscope. More recently, an exciting development has been the guidance, in real-time, of bronchoscopic needles using electromagnetic maps 'overlaid' on VB images.

THE VALUE OF DIFFERENT CT RECONSTRUCTION TECHNIQUES IN THE DIAGNOSIS OF AIRWAYS DISEASE. **A)** VOLUME RENDERED IMAGE SHOWING NARROWING OF THE UPPER TRACHEA AND **B)** MINIMUM-INTENSITY PROJECTION IN A PATIENT WITH SEVERE BRONCHIECTASIS IN THE LEFT LOWER LOBE.



## AIR SPACE DISEASES: IS CT ALWAYS NECESSARY?

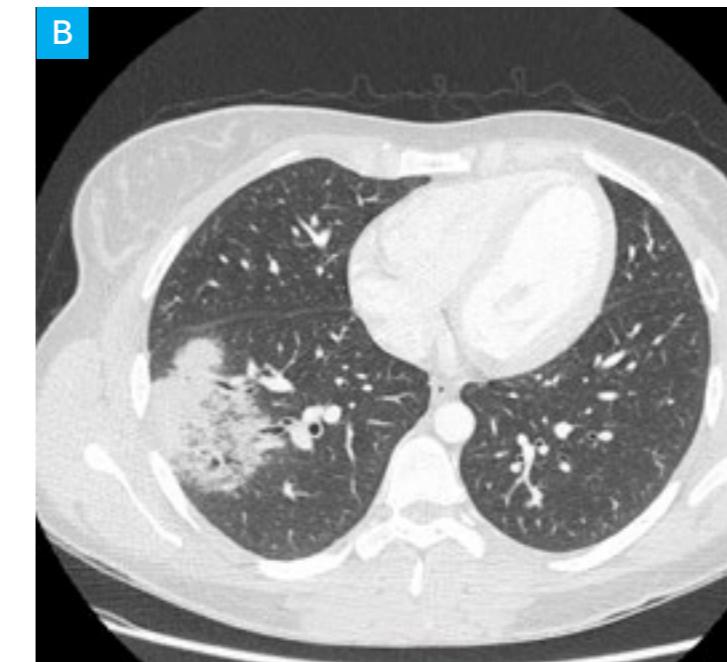
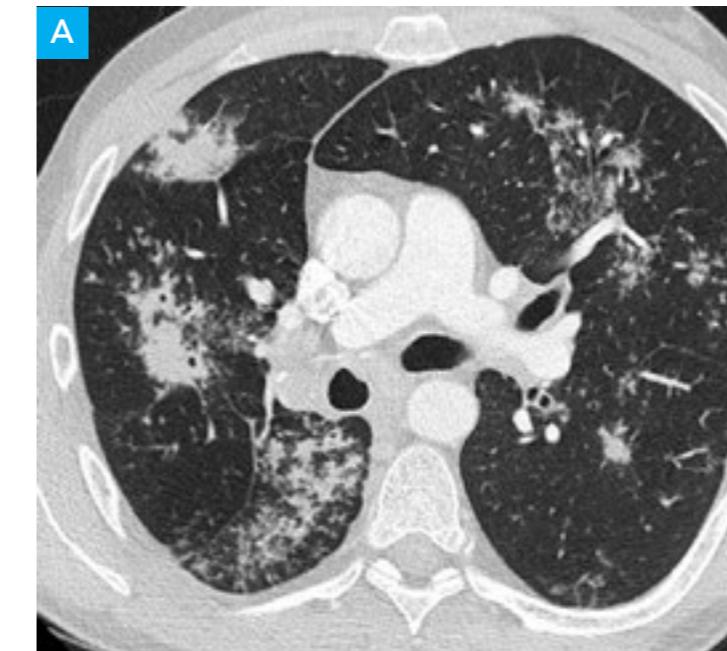
BY SUJAL R. DESAI

**D**iseases that principally affect the air spaces are incredibly common. The term 'air space disease' refers to the fact that the alveolar spaces of the lung – usually filled with air – are now filled with some type of fluid, cells or tissue to a variable extent and composition. Not surprisingly, physicians and radiologists frequently face a diagnostic conundrum in patients presenting with conditions that predominantly involve the air spaces. One of the main difficulties is that the list of possible causes is long: infections are probably the most common cause in day-to-day practice worldwide, but there are a plethora of other conditions which also manifest with this radiological pattern. Certain subtypes of cancer (for instance, adenocarcinoma and lymphoma) and some diffuse lung diseases (e.g. organising pneumonia) are specific non-infectious examples of conditions that cause a pattern of air space opacities on radiological tests.

In the world of interstitial lung disease, computed tomography (CT) – and specifically, high-resolution CT – reigns supreme. However, whether the same can be said of CT in patients with predominant air space disease can be legitimately questioned. Nevertheless, there are

occasional patients in whom an accurate diagnosis of an air space disease will be made on the basis of CT appearances: for instance, a pattern bearing more than a passing resemblance to a Pacific atoll can be seen in patients with a pathological process called organising pneumonia. In the appropriate clinical context, the recognition of this sign on CT may allow the radiologist to suggest the diagnosis with a reasonable degree of confidence. The visualisation of cavitation, which may not be clearly visible on chest x-ray, is another example in which CT can benefit the diagnostic process.

However, barring a few examples, there is often little additional information to be gleaned from CT. Indeed, reviewing a series of chest x-rays, as opposed to CT, can often provide the vital clue to the diagnosis. In patients with a build-up of fluid (oedema) in the lungs – a common problem in clinical practice – chest x-ray appearances may change relatively rapidly, sometimes just over a period of hours, and this will be the important diagnostic pointer. Needless to say, an important benefit of utilising chest x-rays is the significant reduction in radiation dose.



TWO DIFFERENT  
CT PATTERNS  
OF AIR SPACE  
OPACIFICATION.

**A)** A PATIENT WITH  
DISSEMINATED  
TUBERCULOSIS  
AND

**B)** ANOTHER  
PATIENT WITH  
THE 'ATOLL SIGN'  
CAUSED BY  
ORGANISING  
PNEUMONIA.

CHAPTER 5

# PULMONARY EMBOLISM

1

# HOW DOES ACUTE PULMONARY EMBOLISM DIFFER FROM CHRONIC PULMONARY EMBOLISM?

BY MARTINE REMY-JARDIN, FRANCESCO MOLINARI, FRANÇOIS PONTANA

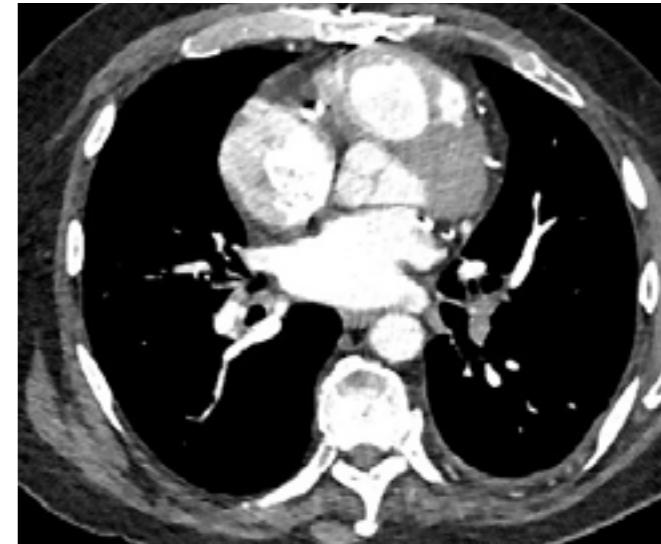
**A** diagnosis of acute pulmonary embolism means that the patient suffers from an obstruction of the pulmonary arteries caused by fresh clots (Figure 1). These clots are responsible for an interruption in the arrival of blood to the lung, which hampers the normal oxygenation of blood. These clots usually come from the veins of the lower extremities; they then migrate from the legs to the lungs where they become lodged. This acute obstruction of pulmonary arteries by fresh clots is called acute pulmonary embolism. It is usually diagnosed when the patient suddenly suffers from chest pain and/or shortness of breath. The usual outcome of fresh clots is that they dissolve, allowing

pulmonary arteries to recover their normal flow which, in turn, restores normal blood oxygenation. In a small percentage of patients fresh clots do not disappear but remain within pulmonary arteries for years. Their permanent presence creates a chronic obstruction of the pulmonary arteries (Figure 2) and this leads to a different disease called chronic pulmonary embolism. This disease is very difficult to recognise because the patient does not present with the acute symptoms as previously described for acute pulmonary embolism. The key symptom of chronic pulmonary embolism is shortness of breath, progressively worsening over time. As this symptom can be observed in many respiratory

FIGURE 1



FIGURE 2

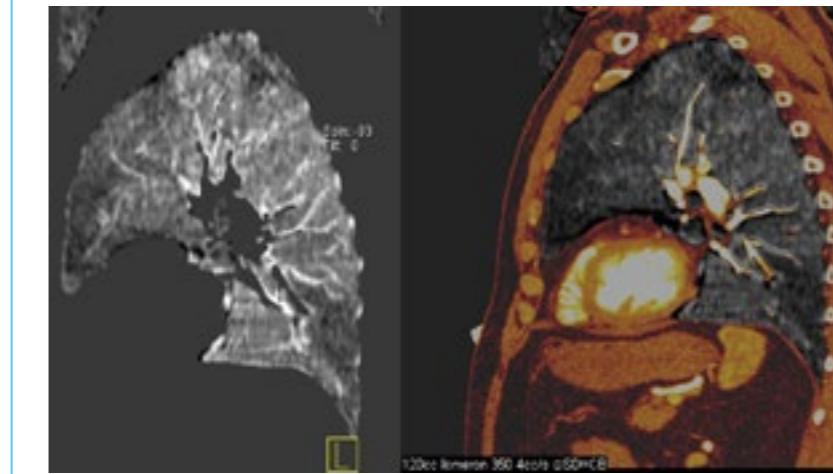


## HOW IS ACUTE PULMONARY EMBOLISM DIAGNOSED? (CT, V-Q)

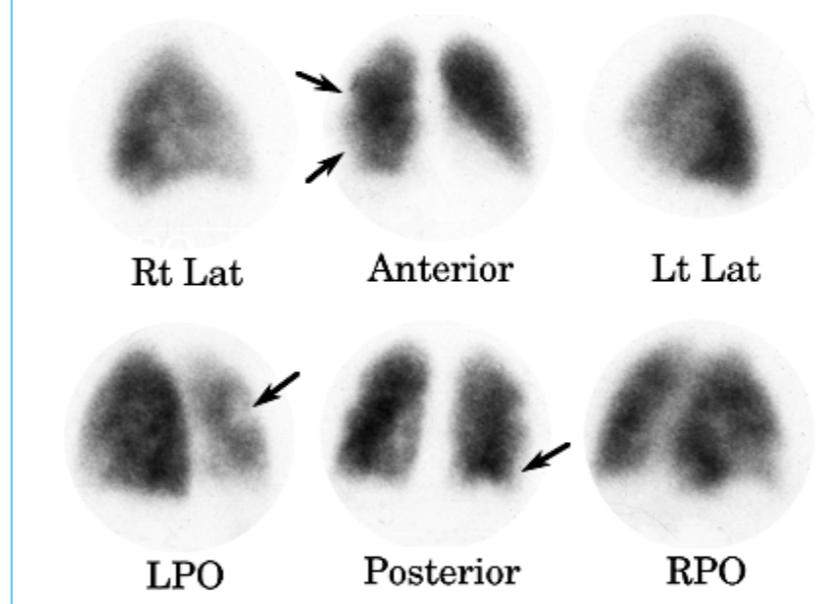
BY MARTINE REMY-JARDIN, FRANCESCO MOLINARI, FRANÇOIS PONTANA

When acute pulmonary embolism is suspected, the patient is referred to the radiologist for a chest CT examination (an examination using x-rays and an injection of intravenous contrast material – usually iodine – to examine the pulmonary circulation) or to a nuclear medicine department for a scintigraphic examination (an examination using radioactive material to analyse the pulmonary circulation and ventilation). In each of these examinations, the objective is to find abnormalities within pulmonary arteries that characterise acute pulmonary embolism. On CT images, the radiologist can directly identify the clots which are surrounded by the intravenously administered iodine. On scintigraphic images, it is possible to detect zones devoid of perfusion (a result of the clots, with normal lung ventilation; this association is highly suggestive of acute pulmonary embolism. The

advantage of CT is that it can visualise the actual clots, whereas scintigraphy only provides indirect clues to the diagnosis. The additional advantage of CT is the ability to visualise diseases which cause symptoms similar to those of acute pulmonary embolism, known as alternative diagnoses. The alternative diagnoses that are identifiable using CT are described in the next chapter. CT imaging is the main diagnostic tool for the diagnosis of acute pulmonary embolism. Even though it uses x-rays, there are numerous effective methods for reducing the radiation delivered to patients, and this limitation is no longer a problem for the radiological community. When CT is contraindicated due to an allergy to iodine or renal insufficiency, then scintigraphy is performed. It also has a range of indications in pregnant patients as described later in this chapter.



Lung Perfusion



07/09/90

THESE IMAGES SHOW A TRIANGULAR AREA IN THE POSTERIOR PART OF THE LUNG (ARROWS), DEVOID OF PERFUSION THAT IS TYPICAL OF ACUTE PULMONARY EMBOLISM.

THESE IMAGES SHOW NUMEROUS AREAS DEVOID OF PERFUSION (ARROWS), SUGGESTIVE OF ACUTE PULMONARY EMBOLISM.

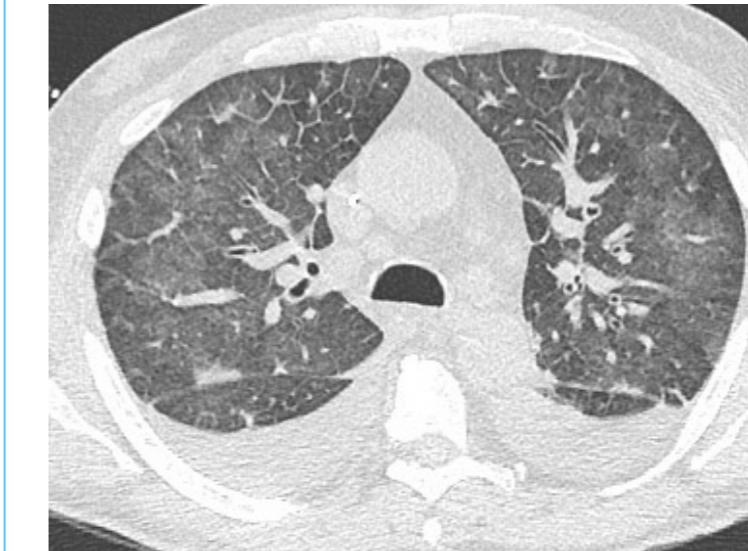
3

# WHAT ARE THE ALTERNATIVE DIAGNOSES WHEN PULMONARY EMBOLISM IS SUSPECTED?

BY MARTINE REMY-JARDIN, FRANCESCO MOLINARI, FRANÇOIS PONTANA

Pulmonary embolism (PE) is a common and potentially lethal disease and can be difficult to diagnose because of its various clinical presentations. Proper diagnosis and treatment can significantly reduce the mortality and morbidity associated with this condition. The diagnostic challenge is that the textbook presentation, with an abrupt onset of chest pain, shortness of breath and hypoxia is rarely seen. The differential diagnoses of PE are extensive, and should be considered in any suspected case of pulmonary embolism. Chest computed tomography (CT) is now the reference imaging modality for the diagnosis of PE. It allows the radiologist to directly visualise clots within the pulmonary arteries and exclude other potential causes of the patient's symptoms (also called differential diagnosis). These differential diagnoses can be divided into three main groups: pulmonary disease, acute aortic syndrome and cardiac disease. Pulmonary diseases include pneumonia, which presents as a lobar lung consolidation; pleural effusion, diagnosed as fluid sur-

rounding the lungs or pneumothorax; or as air within the pleural space. In long-term smokers, the radiologist can also detect signs of tobacco-related disease, such as chronic obstructive pulmonary disease (COPD), with lung destruction (emphysema) and airway disease. The clinical presentation of an exacerbation of COPD may mimic an acute pulmonary embolism, and about 20 percent of COPD exacerbations are associated with a concomitant PE. On CT angiography performed in cases of suspected PE, the radiologist can diagnose aortic dissection, corresponding to a tear within the aortic wall, through the visualisation of a flap dividing the different layers of the aortic wall. This is possible with the CT examination as it allows for the simultaneous analysis of the pulmonary and aortic circulations during the same acquisition. Finally, even if cardiac disease remains the domain of echocardiography and MRI, CT can in some cases be useful for diagnosis, demonstrating pericardial effusion (fluid surrounding the heart) and signs of cardiac failure (acute pulmonary oedema).



THIS IMAGE OF THE LUNG PARENCHYMA SHOWS ABNORMAL LUNG FEATURES AND PRESENCE OF FLUID IN THE PLEURAL SPACE, BOTH SUGGESTIVE OF CARDIAC FAILURE.



THIS IMAGE SHOWS A TEAR WITHIN THE AORTIC WALL AND FLUID IN THE PERICARDIAL CAVITY THAT SUGGESTS THE PRESENCE OF AORTIC DISSECTION.

## HOW IS IMAGING USED TO ASSESS THE SEVERITY OF ACUTE PULMONARY EMBOLISM AND ITS PROGNOSIS?

BY MARTINE REMY-JARDIN, FRANCESCO MOLINARI, FRANÇOIS PONTANA

**B**efore discussing the imaging modalities necessary to assess the severity and prognosis of acute pulmonary embolism, it is important to describe the meaning of each of these terms. Regarding the severity of pulmonary embolism, this refers to the immediate tolerance of clots within pulmonary arteries. A small number of clots in an otherwise normal lung are often well tolerated by the patient. On the contrary, a large number of clots in a patient already suffering from another lung disease may be associated with severe clinical consequences. The number of clots can easily be determined by the radiologist on the CT examination used to recognise this disease. Regarding the prognosis of pulmonary embolism, this refers to the patient's survival after the pulmonary circulation has been obstructed by clots. The heart is an important factor in a patient's prognosis. This organ has to produce more power than usual in order to send blood through the obstructed pulmonary arteries. If previously altered

by a chronic disease, the heart will not be able to adapt easily. Cardiac function can be analysed by echocardiography, but it is also available on the CT examination used for the diagnosis of pulmonary embolism. The patient also runs the risk of the pulmonary embolism recurring. Because clots originate in the lower extremity veins it is important to examine these veins, which can easily be done with Doppler ultrasonography. The last important point in a patient's prognosis concerns their medical condition before the pulmonary embolism. If healthy, the patient has no risk of adverse events after pulmonary embolism. The situation is more complex if the patient also suffers from a pre-existing cardiac or pulmonary disease, as pulmonary embolism can decompensate the pre-existing disease. In summary, two non-invasive tests, i.e. chest CT examination and Doppler ultrasonography, enable the radiologist to provide useful diagnostic and prognostic information to clinicians.

THIS CT SECTION SHOWS THE CARDIAC CAVITIES WITH A LARGE RIGHT VENTRICLE COMPARED TO THE LEFT VENTRICLE. THIS APPEARANCE SUGGESTS RIGHT VENTRICULAR DYSFUNCTION.



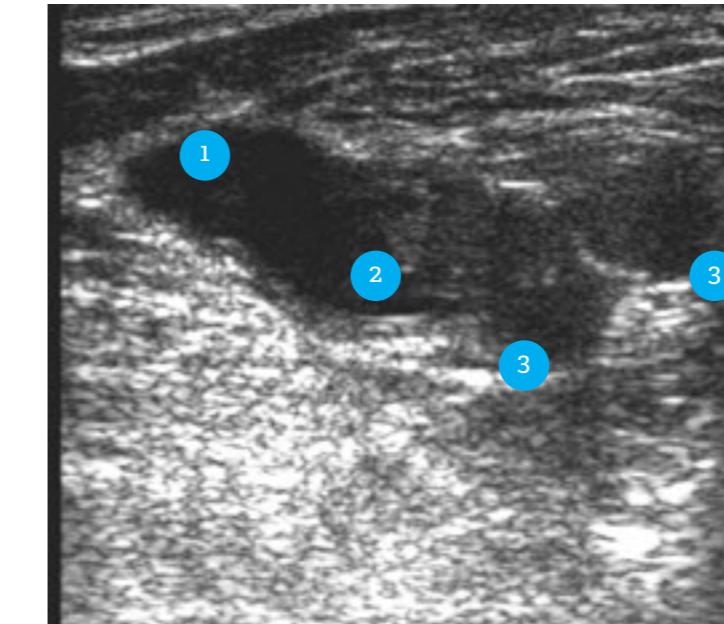
# PULMONARY EMBOLISM DURING PREGNANCY: WHAT'S THE BEST APPROACH?

BY MARTINE REMY-JARDIN, MARIE-PIERRE REVEL, FRANCESCO MOLINARI, FRANÇOIS PONTANA

Pregnancy is associated with an increased risk of pulmonary embolism (clots within the pulmonary arteries) and deep venous thrombosis (clots within the deep veins of the legs). Pulmonary embolism and deep venous thrombosis are frequently associated. As previously described, pulmonary embolism usually results from the migration of clots formed within the deep veins of the legs. Clinical symptoms such as chest pain, shortness of breath or leg swelling are insufficient for establishing the diagnosis. It is thus necessary to confirm or rule out the condition in the pregnant patient by using the appropriate imaging tests. Compression ultrasound is the appropriate test in patients with leg symptoms suggesting deep venous thrombosis, and it is also radiation free. It consists of performing serial compressions of the deep veins of the legs. They collapse if patent and remain uncompressible if obstructed (Figure 9). In pregnant patients with thoracic symptoms suggesting pulmonary embolism, compression ultrasound can also be performed as a first-line imaging test, as pulmonary embolism and deep venous thrombosis are usually associated and similarly treated. However, the ultrasound examination is usually negative when there are no leg symptoms.

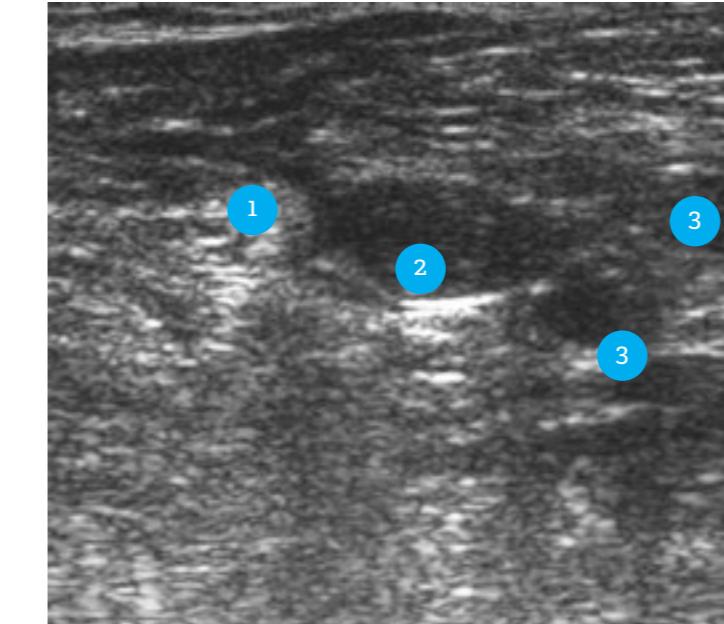
A chest radiograph must then be performed as it can show abnormalities suggesting an alternative diagnosis (a condition clinically mimicking pulmonary embolism) such as pneumonia. In such cases, there is no longer any suspicion of pulmonary embolism and the investigations cease. If a diagnosis is not reached after the chest radiograph, especially if it is normal, the next test is usually lung scintigraphy, which requires venous injection of a radioactive tracer to the mother. A homogeneous tracer distribution throughout the lungs excludes pulmonary embolism. If there are perfusion defects on the scintigram, pulmonary embolism is diagnosed. In 20 percent of pregnant patients, the scintigraphic result is inconclusive. In these cases, suspected pulmonary embolism requires a chest CT examination. Both lung scintigraphy and chest CT expose the foetus to a low radiation dose, so they do not present any harm to the foetus. Regarding the radiation dose delivered to the maternal breast, it is higher with CT than with scintigraphy which justifies the preference for scintigraphy in analysing the pulmonary circulation in pregnant patients.

## COMPRESSION ULTRASOUND OF THE LEFT GROIN



### WITHOUT COMPRESSION

- 1 GREAT SAPHENOUS VEIN
- 2 LEFT COMMON FEMORAL VEIN  
CONTAINING HYPERECHOIC MATERIAL (\*)
- 3 FEMORAL ARTERY BIFURCATION



### WITH COMPRESSION

- 1 THE GREAT SAPHENOUS VEIN IS PATENT AND HAS COLLAPSED
- 2 THE LEFT COMMON FEMORAL VEIN DOES NOT COLLAPSE FOLLOWING COMPRESSION: THIS IS ABNORMAL AND IS DUE TO THE PRESENCE OF CLOTS (HYPERECHOIC MATERIAL) INSIDE THE LUMEN
- 3 FEMORAL ARTERY BIFURCATION  
NOTE THE ARTERIES DON'T COLLAPSE ON COMPRESSION, AS USUAL, THIS IS DUE TO THE HIGHER STIFFNESS OF THE ARTERIAL WALL

CHAPTER 6

# CT LUNG CANCER SCREENING: A POWERFUL EXAMPLE OF HOW RESEARCH ADVANCES RADIOLOGY

By [Denise R. Aberle](#) and [Bruce J. Hillman](#) (American College of Radiology)

## THE VALUE OF RESEARCH TO RADIOLOGY

It is no exaggeration to assert that the remarkable rise of radiology over the past four decades is nearly entirely attributable to imaging research. Research has fueled the development of a remarkable procession of imaging innovations that has advanced the specialty from a sleepy medical backwater to a central position in the delivery of health care. Ultrasonography, x-ray computed tomography, magnetic resonance imaging, positron emission tomography, and a long succession of image-guided therapeutic procedures have transitioned from concept to working model to commercial product<sup>1</sup>. Continuing research and the further development of these same technologies into the present has resulted in higher spatial, contrast, and temporal resolution and led to new capabilities like CT angiography, CT colonography, and MR-guided tissue ablation. In concert with leaps in computing power, electronic connectivity, and improved visualization software, modern cross-sectional imaging technologies have become faster, safer, and more reliable in the detection, characterization, and treatment of important disease states. Patients have benefitted. The manufacturers and providers of imaging technology have prospered.

The research-driven expansion of radiology practice is unparalleled by any other medical specialty. Unlike most new medical technologies, which usually are directed at one or just a few applications, imaging technologies are broad-based, suitable for interrogating nearly every organ system, and capable of addressing five key applications: screening and early detection; diagnosis and staging; image-guided therapy; following the progression of disease; and gauging the impact of treatment. Each imaging application has had an important enough impact on improving medical care that a *turn-of-the-century* poll of physicians ranked CT and MRI the most important advances of the last quarter of the twentieth century (1).

The recognition of the benefits to be gained from cross-sectional imaging did not occur instantaneously, magically cut from whole cloth. Rather, each technology had to overcome the suspicion of regulators, payers, and policy-makers that its capabilities were overhyped. Study-by-study, clinical researchers translated the applications of imaging technologies to improving patient care and assessed their impact. Their results provided the basis for Food and Drug Administration (FDA) applications to market new technologies, supported bids for payer coverage, and set the foundations of modern radiologic practice. The work continues as a new generation of clinical researchers – radiologists, statisticians, sociometrists, and others – continue to assess the worth of imaging innovations and their evidence-based implementation.

## IMAGING TO SCREEN FOR SERIOUS DISEASES

The use of CT to detect important conditions like cancer and cardiovascular disease stands out as a particularly interesting story of how research has generated a new role for radiologists – screening for asymptomatic but important diseases. The introduction of faster and higher resolution multi-slice scanners during the 1990s and early observational publications generated interest in using CT to screen for the great killers of developed countries: cancer and cardiovascular disease. Entrepreneurial CT screening businesses touted the benefits of finding disease early, when it would be more treatable. In the absence of data to either support or deny their claims, screening centers flooded the airwaves with promotional messages, rolled mobile CT systems into shopping centers, and offered discounts to church and civic groups (3). Most services featured whole-body screening, on demand, without a physician referral.

The CT screening businesses were built on the American public's fear of cancer and an overwhelming belief that screening for disease is always better than waiting for a condition to become symptomatic (4). The few voices that challenged the effectiveness of screening CT were largely drowned out by apologists who considered only the possible benefits and not the risks and costs. In retrospect, this was short-sighted. Whole-body CT screening was identifying suspicious areas in up to 95% of the healthy adults undergoing the procedure at some centers, leading them to undergo further testing and, in some cases, unnecessary treatment. In time, the medical community began to grasp that imaging screening is not such a benign process and that CT screening should be reserved for circumstances where the procedure can be definitively and rigorously demonstrated to have an important effect in improving important population-based health outcomes. A brief review of the possible results of screening makes the point that not all outcomes of screening are good for the individual being screened or for society at large:

- » **True negative screening** – the CT scan is negative in a patient who has no serious disease. There is benefit in being reassured of good health and the individual pays the cost for a screening exam out of his own pocket<sup>2</sup>. There are no downstream costs.
- » **False negative screening** – the CT scan is negative, but the individual actually has a treatable serious condition. The individual is falsely reassured and may ignore warning signs when symptoms appear. In doing so, he may wait too long to seek medical care and suffer a poorer outcome.
- » **False positive screening** – the individual is healthy but the CT scan is interpreted as showing a serious disease. The individual

inevitably is subjected to further testing and may be treated for a condition that does not actually exist. There is a risk of harm, and no benefit accrues to the individual. Once an abnormality is found, the costs of subsequent medical care are, for most patients, paid by government and private insurers, such that the costs of false positive screenings are borne by us all.

» **True positive screening** has the potential for driving several outcomes:

- The patient has a serious disease which is treatable and the patient is cured. This, of course, is why screening is performed. There is cost, but there is also great value to the patient and society.
- The patient has a serious condition for which there is no treatment, and the patient succumbs at around the same time as if the disease had not been discovered by screening. In this circumstance, there may be added cost without any additional benefit.
- The patient has a target abnormality, which on biopsy appears to represent serious disease. However, the biological aggressiveness is quite low, such that the condition would not have affected the patient in his lifetime. Subsequent follow-up and treatment pose risks to the patient without benefit, and there are significant downstream costs.
- An abnormality is found that is unrelated to the target condition for which the screening is performed (sometimes referred to as an incidentaloma). Some fraction of incidentalomas will eventually prove to be both important and treatable. However, the vast majority do not threaten the patient's health or life. As such, the finding of incidentalomas will result in downstream costs to society. However, only a minority of patients benefit.

Recognition of the complexity of screening led to reconsideration and more critical scrutiny directed at identifying clinical circumstances where CT screening might be beneficial. One area where CT screening attracted considerable attention was lung cancer. All the qualifications for successful screening seemed to be aligned: the disease is a deadly one, the most common cause of cancer death for both men and women in developed societies; from simple anecdotal experience, there could be no doubt about the capability of CT to detect lesions that might be lung cancer; the test can be safely repeated over time; when lung cancer is found and treated at an early stage, patient health outcomes are better than when it is found later in the course of disease. How these factors played into provider and patient expectations, energized the politics of funded research, and influenced the research design is a fascinating story that both encourages future research and cautions us about research biases that can lead to erroneous conclusions.

## A SELECTIVE HISTORY OF RESEARCH INTO LUNG CANCER SCREENING

In 2013, it is estimated that lung cancer will account for 26% of all female and 28% of all male cancer deaths in the United States, accounting for more deaths than from breast, prostate, colorectal, and pancreatic cancers combined (5). Tobacco smoking is associated with roughly 85% of all lung cancers. Although lung cancer mortality rates have fallen in the US over the past decade in conjunction with declining tobacco use, more than half of current lung cancer victims are former smokers. Thus, while smoking cessation remains the single best way to prevent a lung cancer death and other co-morbidities like obstructive lung and cardiovascular diseases, it will not eliminate the dominance of lung cancer as the foremost cause of cancer death for years to come.

Due to the paucity of symptoms early in the course of disease, the majority of lung cancers are diagnosed in advanced stages. Stage is a primary determinant of both treatment options and long-term survival, with advanced stage disease resulting in notoriously poor five-year survival rates (6). In contrast, patients undergoing resection for early-stage lung cancer have five-year survival rates of up to 70%. Thus, the rationale for lung cancer screening is to evaluate ostensibly healthy, asymptomatic individuals at high risk of lung cancer to find pre-clinical, early-stage disease that can be surgically resected for cure.

Assessing the value of a potential screening test for lung cancer requires the conduct of randomized controlled trials. In a randomized controlled trial, the subjects assigned to an 'intervention' arm receive the screening test and those in a 'control' arm do not. The randomization of subjects is critical, because it distributes the participants with respect to age, sex, smoking history, and other factors that influence cancer risk equally into the two arms of the trial. All individuals enrolled in the trial must fit the eligibility criteria for the study, and clinical and other information is captured systematically in both the intervention and control arms. In this way, randomized trials eliminate many biases that erroneously affect analyses, and any potential effects of the intervention on key outcomes can be ascribed to the intervention. This is not the case with single-arm observational studies, wherein inherent biases can confuse the results.

<sup>1</sup> For brief histories of how these technologies came into being and how they produce medical images, see Hillman and Goldsmith's *The Sorcerer's Apprentice – How Medical Imaging is Changing Health Care* (2).

<sup>2</sup> Few insurance companies paid for CT screening, citing it as an unproven technology.

breathe easy

## CHEST X-RAY SCREENING TRIALS

Based on the fact that lung cancer survival is more favorable with early-stage diagnosis, four randomized trials of lung cancer screening were conducted in the United States and Europe (7–10) during 1960–1980, to determine whether screening could improve outcomes. Each trial used various combinations and frequencies of chest x-ray (CXR) and sputum cytology to screen high-risk individuals. Perhaps the most widely known of these is the Mayo Lung Project. The Mayo trial randomized 9,211 male smokers, 45 years or older and initially determined to be cancer free by baseline screening. The intervention arm received intensive screening by CXR and sputum cytology every four months for 6 years (8). The subjects assigned to the control arm received no trial-related screening, but were advised to receive annual screening with CXR and sputum. At trial's end in 1983, researchers found there to be an increased number of early-stage lung cancers and better survival (as had been observed in previous studies) among subjects in the intervention arm. However, the numbers of advanced-stage lung cancers and lung cancer mortality rates were the same in the screening and control arms. Extended follow-up of the participants through 1996 also showed no mortality benefit from screening.

Based on these data and similar results from the other major randomized trials of CXR screening, no medical organization has recommended lung cancer screening in any form until very recently. Despite this, many primary care providers have continued to perform annual CXR on smokers because of methodological shortcomings of these early trials (11). Critics have blamed the outcome on a range of methodological shortcomings, including small numbers of participants with low statistical power to detect small benefits, and contamination due to participants in the control arm receiving CXR or sputum screening outside the trial.

A critical caveat here is that the valid measure of screening benefit, unlike treatment benefit, depends upon the rates of lung cancer *mortality* and not lung cancer survival. Screening can improve the length of survival (the time between diagnosis and death) independent of improving longevity (delaying the time of death) due to several well-known biases associated with observational studies of screening tests. These are known as lead-time bias, length bias, and overdiagnosis (12). For example, when a symptomatic lung cancer is diagnosed, survival time is measured from the time of diagnosis to the time of death. If that same lung cancer is detected by screening prior to symptoms, the time of diagnosis occurs earlier, such that the amount of time a person lives after knowing he has lung cancer increases, even without a change in the time of death.

breathe easy

The patient appears to live longer even if he dies at the same time as if no screening had occurred. This 'lead-time bias' and other confounders unique to screening make the measure of survival rates misrepresentative of screening benefit. Valid benefits of screening can only be measured by looking at differences in mortality rates, specifically in the context of a randomized trial that has a contemporaneous control arm.

The lingering ambiguity over whether there might actually have been a benefit to screening in the early CXR screening trials provided the impetus to include lung cancer screening in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial sponsored by the American government's National Cancer Institute (NCI). Initiated in 1993, the PLCO trial enrolled 77,464 men and women aged 55–74 years, across the United States, and randomized them to receive screening with a baseline and three annual CXR screens in the intervention arm and no screening as the control (13). After follow-up for a median of nearly 12 years, there was no significant difference in mortality rates between the CXR-screened and non-screened arms. A subset analysis performed in 30,321 older heavy smokers in the PLCO also showed no mortality benefit. The PLCO trial has reinforced the observation that CXR screening provides no significant decrease in death rates from lung cancer in individuals at high risk (14).

## SINGLE ARM TRIALS OF LOW-DOSE HELICAL CT

Over the past 20 years, technological advances in computed tomography (CT) prompted the notion of CT as a potential imaging-based screening test for lung cancer. Multidetector helical CT enables the entire lung to be imaged as a single volume of tissue while the patient holds their breath. Unlike CXR, CT affords inherently high visibility between normal aerated lung and soft tissue nodules. Although radiation doses with CT are several times higher than with CXR, low radiation-dose CT (LDCT) holds the radiation dose to the minimum that allows for interpretable images for the purpose of detecting focal lung nodules. Early studies in the US and Japan began looking at LDCT as a potential screening tool.

Between 1995 and 2002, researchers conducted several prospective, single arm studies of LDCT lung cancer screening (15–21). The findings from these studies varied due to: [a] differences in cohort sizes, demographics, smoking status, and risk profiles; [b] differing criteria for the size of lung nodules that defined a positive screen; [c] and details about follow-up methods. Across all studies, the prevalence of detected lung

cancer varied from 0.40% to 2.70%. A disproportionate number of lung cancers were adenocarcinomas, suggesting that CT may preferentially detect this cell type over others. Two studies in which participants underwent both LDCT and CXR screening showed that there was a three-fold or greater increase in the nodule detection rate with LDCT (15, 19) and an overall increase in the number of lung cancers detected. Although LDCT-detected lung cancers were predominantly early stage, there was no decrease in late-stage lung cancers with LDCT relative to CXR. This suggested that LDCT screening may not meaningfully shift the stage of screening-detected lung cancers from advanced to early stages – essential to reducing mortality – but may simply detect more lung cancers, some of which would never have been diagnosed or affected health were it not for screening (i.e. pseudodisease) (22).

Although these early studies of LDCT screening were inconclusive, they were important in defining both the challenges and potential of CT-based screening and set the stage for more substantive research to follow. In 1999, the Early Lung Cancer Action Program (ELCAP) published the initial results of its observational (single arm) study, catapulting CT screening for lung cancer onto the scientific radar of both the American public and the National Cancer Institute. The very positive findings of the ELCAP study were an early driver of interest in conducting a randomized control trial, which eventually became the National Lung Screening Trial.

## THE AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK AND THE NATIONAL LUNG SCREENING TRIAL

Because of the infrequency of serious disease among asymptomatic adults, rigorous, adequately powered clinical trials to assess the value of imaging screening require large numbers of subjects. Even restricting accrual to subjects with elevated risk of disease – older age and a history of heavy smoking in the case of lung cancer – still means conducting large, complex, and expensive research studies. Screening trials also need the scientific personnel necessary to develop methods to address the aims of the study; an organizational structure and information technology capable of handling copious image and non-image data; personnel to ensure data quality, manage the data, and administer the study; a sizable number of participating sites trained to accrue

subjects according to the protocol; and individuals to qualify sites, monitor site compliance, and respond to queries. These resources were lacking in radiology until quite recently.

The first continuing, federally-funded organization for multi-center clinical trials of imaging technologies developed in the late 1980s under the aegis of the Diagnostic Radiology Oncology Group (RDOG). RDOG was led by Barbara McNeil, MD, PhD, as group primary investigator (PI). The RDOG conducted five clinical trials of imaging in cancer before NCI funding terminated in the 1990s.

In 1998, The NCI developed the idea for a new program focused on medical imaging and its application to cancer, now known as the Cancer Imaging Program (CIP). CIP's director, Daniel Sullivan, MD, convinced NCI leadership of the need to set aside a substantial amount of money to fund an ongoing 'network' that, like the long-standing NCI therapeutic cooperative groups (examples include the Eastern Cooperative Oncology Group (ECOG) and the Radiation Therapy Oncology Group (RTOG)), would set its own research agenda and have the resources to pursue clinical trials. CIP issued a request for applications (RFA) with initial five-year funding of more than \$20 million. The PI of the winning proposal, Bruce J. Hillman, MD, submitted on behalf of the American College of Radiology (ACR), named the organization the ACR Imaging Network (ACRIN), and included as an 'example protocol' in ACRIN's submission a proposal to conduct a trial of CT screening for lung cancer written by Denise R. Aberle, MD, a UCLA radiologist subspecializing in thoracic radiology. Dr. Aberle eventually became the PI of the National Lung Screening Trial (NLST).

Initially funded with \$20 million between 1999 and 2004, ACRIN provided the financial wherewithal, scientific talent, committee organization, and infrastructure that the specialty of diagnostic radiology needed to design and conduct approximately 30 multi-center clinical trials of imaging screening modalities. During 1999–2007, NCI leadership provided additional funding of roughly \$150 million to conduct large screening trials. Among these were trials of digital mammography, CT colonography, and lung cancer screening using CT. Each trial had its own challenges, but, by far the longest-lasting and most complex trial was the NLST. The NLST was a collaboration between ACRIN and the researchers guided by the leadership of the NCI Division of Cancer Prevention and the same sites that were conducting the PLCO trial.

## THE BIRTH OF THE NLST

In the wake of the findings of the ELCAP screening trial, ACRIN leadership drafted the initial protocol for a randomized controlled trial

of LDCT screening. Due to the considerable gap between what could be afforded out of ACRIN's base budget and the expected cost of running a CT screening trial for lung cancer, the trial's authors proposed to randomize just 7,000 subjects to receive either annual LDCT screening or no screening for five years. As such, the trial would have been under-powered to detect a difference in lung cancer mortality between the two arms. Rather, the trial was expected to show proof of concept while measuring such endpoints as differential quality of life resulting from screening and lung cancer diagnosis between the two arms; establishing a specimen archive of blood, sputum, and urine that could be used to validate biological markers of lung cancer; and an analysis of the cost effectiveness of LDCT screening from a societal perspective.

However, also in 1999, and paralleling the ACRIN activities, six of the ten screening sites associated with the PLCO trial initiated a study called the Lung Screening Study (LSS) (23). Intended to be a trial demonstrating feasibility, the LSS accrued 3,000 individuals at high risk for lung cancer and convincingly showed that such individuals would agree to be randomized to receive LDCT or CXR. The LSS investigators proposed a larger, randomized trial that would add another 12,000 subjects with the aim of detecting a 50% mortality reduction associated with LDCT screening.

Both LSS and ACRIN concepts were presented to the Board of Scientific Advisors (BSA) of the NCI in June 2001 (24). Several concerns were raised. In particular, BSA members believed that a 50% mortality reduction was unlikely. If they were correct, a larger number of subjects would be necessary to detect smaller, more realistic differences in lung cancer mortality. Other concerns included that insurance providers might not cover the cost of downstream diagnostic testing in participants with positive screens and that the impact of screening on smoking cessation was not known. The Board voted to appoint a subcommittee to help meld the proposals into a joint ACRIN and LSS lung cancer screening concept for reconsideration later that year.

At the November 2001 BSA meeting, ACRIN and LSS investigators proposed a trial in which 50,000 high-risk individuals would be randomized to receive either LDCT or CXR screening for three annual screens, with a maximum follow-up of eight years to determine outcomes. ACRIN and LSS protocols and data collection would be harmonized such that results could be combined for analysis. The trial would be overseen by one Data and Safety Monitoring Board with early stopping rules so that the trial would end early if results were strongly negative or positive. Enduring concerns were the high cost of the trial, estimated at roughly \$200 million dollars, and its effect on the NCI's ability to fund other significant research projects. Some suggested delaying until partners willing to share the cost of the trial could be

identified. In addition, some members feared that a screening trial could detract from the primary goal of smoking cessation. Ultimately, though, the scientifically rigorous study design of the proposed trial, the severe burden of lung cancer deaths in the United States, and the potential of LDCT screening to positively impact the NCI goal of reducing lung cancer mortality won over the majority of the BSA. The motion to approve the joint concept was approved, which led to the birth of the NLST (25).

## MAKING IT WORK

With the approval of the concept for the NLST, ACRIN and LSS teams began in earnest to harmonize trial procedures, image acquisition protocols, interpretation guidelines, and the data elements to be obtained. ACRIN successfully engaged the American Cancer Society to assist with initial trial advertising and subject accrual (26).

Given the unusual marriage between an NCI-sponsored contract (the LSS) and an external grant (ACRIN), an Oversight Committee of scientists, chosen by NCI leadership, was created to ensure that the LSS and ACRIN groups would conform to common practices necessary to preserve the scientific validity of the trial. The Oversight Committee was chaired by Robert C. Young, MD, a renowned medical oncologist, as well as the chair of the NCI BSA, who had advocated for the approval and funding of the NLST. The Oversight Committee held regular teleconferences for the duration of the trial and assumed major roles in responding to criticisms leveled at the trial over the course of eight years.

The process of harmonization proved to be a complex choreography between the LSS investigators – whose sites had existing infrastructure from the PLCO trial that could be modified for NLST – and the new ACRIN investigators, predominantly radiologists, who had no existing site infrastructure but were experts in CT technology, imaging interpretation, and clinical practice patterns. ACRIN took the lead in standardizing imaging protocols across different CXR units and CT scanner platforms. A committee of experienced medical physicists worked with the radiologists to standardize 18 unique imaging parameters across 14 different scanner platforms from four CT manufacturers (27). This proved to be a critically important process that would guarantee not only consistent quality of imaging across the 33 NLST sites, but would refute future criticisms that the NLST imaging technology was obsolete. Indeed, because of the efforts of these medical physicists, the NLST had arguably the most rigorous, standardized imaging protocols of any clinical trial to that time.

The ACRIN investigators were intent on answering questions beyond the basic epidemiologic concern of mortality reduction. They approached the trial as an opportunity to collect data that could: be used to better define risk cohorts for screening; collect and store biological specimens for the future validation of molecular biomarkers of lung cancer; and enable a formal cost-effectiveness analysis of screening should the trial show that LDCT reduced lung cancer death rates.

These secondary aims came at great cost with respect to both human resources and financial burden. To contain costs, the study teams, rather than local laboratories, would perform any additional procedures required for ACRIN's secondary aims. In these regards, site principal investigators and study coordinators were trained to administer pulmonary function tests to characterize the prevalence of chronic obstructive pulmonary disease (a known risk factor for lung cancer), collect, process, and archive tissue specimens, and collect additional data elements to capture quality of life measures and medical costs.

The ACRIN secondary aims were risky. They added sufficient complexity to generate concerns on the part of the NLST Oversight Committee, the Data and Safety Monitoring Board, and the site investigators that there was the potential to derail ACRIN sites overburdened by data collection processes. When subject accrual at the ACRIN sites began to lag behind those of the LSS, ACRIN leadership put into place several new provisions to bolster data collection: the creation of a regularly convened ACRIN Operational Committee that paired NLST study coordinators with trial leadership to ground logistical and process decisions; deployment of rapid response teams to struggling sites to assist with data collection and data entry efforts; nearly daily contact between the NLST ACRIN Project Manager, Irene Mahon, RN, MPH, and the 23 ACRIN sites with trial leadership; and overall greater involvement of ACRIN's leaders. Finally, the ACRIN Program Director of the NCI Cancer Imaging Program, Barbara Galen, MSN, CRNP, a seasoned administrator and continuous advocate for ACRIN, increasingly imparted her insights and involved herself in NLST activities. Her dedication to the scientific objectives of the NLST was in no small measure at the heart of the ultimate success of the trial.

## THE POLITICS OF SCIENCE

The blending of the very different LSS and ACRIN cultures was delicate. The LSS involvement was based on a long-standing contract from the Division of Cancer Prevention to ten PLCO sites, while ACRIN's participation derived from a funded supplement to the ACRIN grant. As such, the motives for participation of the two entities differed con-

siderably. The LSS was a highly experienced, well-oiled machine in the screening arena. ACRIN investigators were untried clinical trialists, working within a newly funded cooperative network that also was involved in a host of other important, imaging-based clinical trials. However, notwithstanding these differences, all parties understood that by virtue of its sheer size and cost, the NLST would be under microscopic scrutiny by the scientific and lay cancer advocacy communities. In this regard, the NLST investigators were very sensitive to the significance the trial held for ACRIN's expectations for the future.

In the early stages of trial launch, skeptics of the NLST successfully petitioned the NCI for an audience with the NCI Director, Andrew von Eschenbach, MD, who met with NLST investigators and the opposing factions to discuss the critics' concerns about study size, statistical approach, and the logistics of the trial. NLST investigators were collectively persuasive in defending the methodological strengths and importance of the trial. In addition, ACRIN achieved a major paradigm shift. The original proposal approved by the BSA provided for ACRIN to accrue 10,000 of the total 50,000 individuals enrolled in the NLST. The scientific credibility and broader goals of the ACRIN investigators convinced the NCI Director that accrual should not be prescriptive; ACRIN and LSS were free to enroll as many subjects as possible to increase the speed of accrual. Ultimately, this fostered a healthy competition, such that the 23 ACRIN sites ultimately accrued 19,000 participants to the NLST, and the trial was fully subscribed four months in advance of the projected date for trial completion.

However, this first meeting turned out to be just the opening salvo. The NLST became a lightning rod for conflicting philosophical and scientific views about lung cancer screening extant in the imaging, medical oncology, and advocacy communities (28–30). Opponents of the NLST argued that the single arm cohort studies (particularly the ELCAP studies) had validated LDCT screening beyond all reasonable doubt, even without the demonstration of a mortality benefit. ELCAP advocates heavily lobbied the NCI leadership and the federal government to abandon a trial that they called 'unethical'. The NLST trialists and a broad base of the imaging and scientific community argued that it was not only necessary to demonstrate a mortality benefit, but that the future adoption of lung cancer screening as a covered procedure by private insurers and the Centers for Medicare and Medicaid Services (CMS) depended upon this evidence, as well as the rigorous estimate of cost-effectiveness planned as part of the ACRIN participation in the trial. The NLST became the fulcrum of these polarizing and contentious debates, which took on the tenor of religion. Sadly, in all of this, it was the lung cancer community that suffered the most, garnering for itself the unwanted reputation of being divisive and sending mixed messages to the public.

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## THE NATIONAL LUNG SCREENING TRIAL: ESTABLISHING THE RULES OF PLAY

The LSS and ACRIN investigators each established independent and regular teleconferences at the leadership and site investigator levels to monitor accrual, protocol adherence, data collection efforts, and logistical concerns. At the same time, a global NLST Executive Committee bridging the two groups communicated by monthly teleconference calls and face-to-face meetings held during the annual ACRIN meeting, bi-annual DSMB meetings, and ad hoc conferences. Relatively early in the trial, the leadership of the LSS group transitioned from Dr. John Gohagen to Dr. Christine Berg, chief of the Early Detection Research Group in the NCI's Division of Cancer Prevention. The respective ACRIN and LSS principal investigators established close and regular communication, which engendered a culture of collaboration that permeated the trial. The annual meetings of the Radiological Society of North America (RSNA), one of the largest international societies of radiologists and medical physicists, provided a backdrop for collaboration among the radiologists across the 33 combined LSS and ACRIN sites. The radiology investigators were the glue that cemented a unified research effort.

## FINAL DECISIONS CONCERNING TRIAL DESIGN

The NLST was a fundamentally simple trial design: individuals at high risk for lung cancer would be randomized to receive either LDCT or CXR screening annually for a total of three years. Follow-up for endpoints – including diagnostic procedures, diagnoses, screening-related complications, lung cancer treatments, and vital status – would be collected on all participants for an average of 6.5 years (Figure 1). The primary analysis compared lung cancer mortality between the two arms using an intent-to-screen analysis. The study was sized for 90% power to detect a 20% decrease in mortality from lung cancer in the low-dose CT group compared with the CXR group. Secondary analyses compared the overall mortality rates from any cause and lung cancer incidence in the two screening arms.

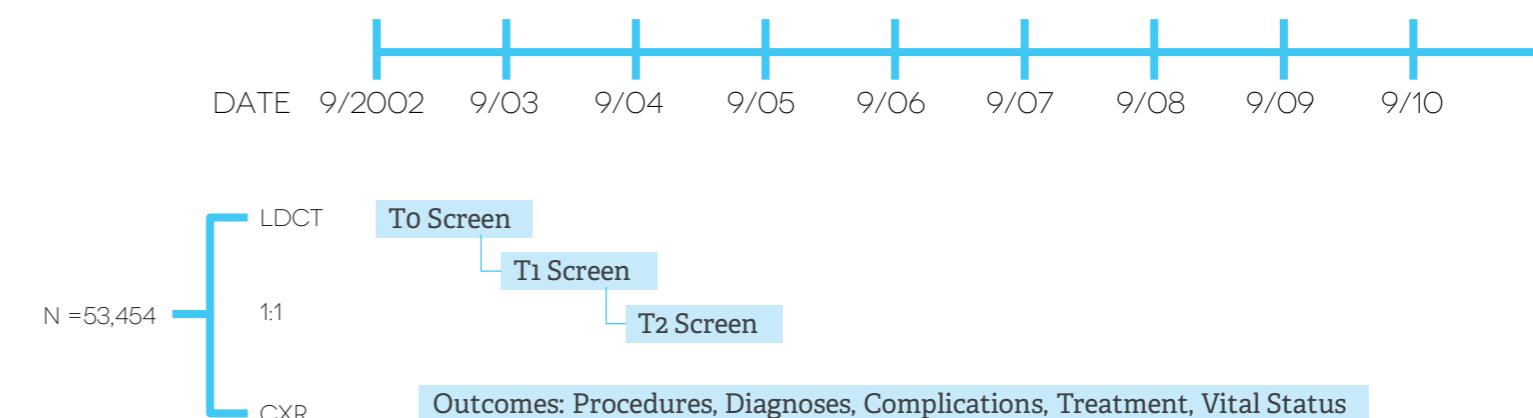
A major trial design consideration that lingered very late into protocol development was a control arm in which no screening was provided. This idea was abandoned in favor of the control arm receiving frontal CXR (31). The reasons for this were many:

1. There was no 'standard of care' for lung cancer screening in the US. As noted earlier, however, many physicians routinely performed CXRs on their current and former smoking patients. Findings in control subjects who underwent CXR screening at the behest of their primary physicians could confound the results of a trial design in which the control arm received no screening.
2. The NLST was launched at a time when early adopters of screening and entrepreneurial imaging groups were setting up screening centers across the country in clinics and shopping malls. There was high interest in screening and fundamental misunderstanding about the known risks and benefits of LDCT. These factors would have made it difficult for potential enrollees to appreciate scientific balance between LDCT and no screening arms.
3. The PLCO, which predated the NLST by nearly a decade, had a study component that was comparing CXR to no screening. The outcomes of this trial were not known during the design phase of the NLST. Had the PLCO shown a mortality benefit from CXR screening, the outcomes of NLST using a control arm with no screening would be indeterminate relative to the validated new standard of CXR. Finally it was reasoned that if the PLCO trial were to show no lung cancer mortality benefit from CXR screening (which proved to be the case), the incorporation of CXR into the NLST control arm should have little effect on the measure of differential death rates. Combined, these considerations were daunting enough that CXR was chosen as the control arm.

Eligibility criteria were designed to include those at highest risk of lung cancer, based on age and smoking history, who would tolerate resection of the lung. Subjects were between the ages of 55 and 74 years, corresponding to the peak-age range associated with lung cancer, and had to be current or former heavy smokers with a minimum smoking history of 30 pack-years (number of packs smoked per day  $\times$  number of years smoked). Former smokers must have quit smoking within the preceding 15 years. Exclusion criteria were designed to eliminate individuals with symptomatic lung cancer, those who would be at highest risk of complications from lung cancer surgery, and individuals in whom other cancers, metal implants, or prior lung surgery could confound screening interpretation (32, 33). Data on other known risk factors for lung cancer, such as a history of chronic obstructive pulmonary disease (COPD), family history of lung cancer, and occupational exposure to asbestos, radon, and other carcinogens were collected on all subjects, but did not factor into eligibility. The ACRIN sites performed spirometry at baseline on enrolled participants to ascertain the presence of COPD, but did not use this as a criterion for enrollment.

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**FIGURE 1:  
NATIONAL LUNG SCREENING TRIAL DESIGN.  
NLST ACCRUAL BEGAN IN SEPTEMBER 2002.  
OVER 20 MONTHS, 53,454 PARTICIPANTS WERE  
RANDOMLY ASSIGNED TO RECEIVE EITHER  
LOW-DOSE COMPUTED TOMOGRAPHY (LDCT) OR  
CHEST X-RAY (CXR) FOR THREE ANNUAL SCREENS.  
OUTCOMES THROUGH DECEMBER 31, 2009 WERE  
COLLECTED ON PARTICIPANTS, AN AVERAGE OF  
6.5 YEARS.**



## PARTICIPANT CHARACTERISTICS AND SUCCESS OF RANDOMIZATION

NLST enrollment began in September 2002 and was completed in April 2004, four months ahead of the targeted completion date. The trial enrolled 53,454 participants who were randomly assigned to LDCT or CXR screening arms. Targeted recruitment plans to accrue minority groups were implemented at specific sites on the basis of regional demographic data and site-specific strategies. These strategies were developed in collaboration with the NCI Cancer Information Service Partnership Program, the American Public Health Association's Black Caucus of Health Workers, the NCI Spirit of Eagles Program, and the American Cancer Society. These efforts added considerable cost to recruitment, but were highly successful; the seven ACRIN sites that implemented targeted strategies enrolled 77.6% of all minority participants in the ACRIN NLST (34).

Randomization was stratified by sex and five-year age groups, such that participant numbers in the two arms were virtually identical within these categories. The success of randomization (e.g., equally distributing the demographic, smoking, and health characteristics of participants between the two arms) was evidenced by strong similarities between the arms with respect to race, ethnicity, educational status, smoking histories, occupational exposure, and family history of lung cancer (Table 1) (33).

To determine how well the NLST population matched that of the screening-eligible U.S. population, the demographic features of NLST participants were compared to respondents who completed the Tobacco Use Supplement of the most recent US Census Survey, restricting the survey population to those who met the NLST criteria of age and smoking eligibility (Table 1). Sex, median pack-years of smoking, race, and ethnicity for NLST subjects were quite similar to those represented by the Tobacco Use Supplement; however, the NLST cohort tended to be younger, more frequently former smokers and better educated, all of which would tend to make the NLST cohort somewhat healthier than the eligible US population.

## SCREENING TESTS AND RESULTS

LDCT screening tests were considered positive (i.e. a finding potentially related to lung cancer was detected) if at least one non-calcified nodule of at least 4mm or other suspicious abnormality was observed. CXR screens were called positive if any non-calcified nodule or mass was observed. For all positive screens, providers at the sites recommended some form of follow-up. Diagnostic guidelines were developed, trial-wide, for positive screens based on the level of suspicion of the finding, determined largely by nodule size and consistency (density). These guidelines were not mandated but could be used at the discretion of the interpreting radiologist. Both subjects and their primary care providers received a description of the screening findings and recommendations for follow-up.

The rates of positive screens were more than three times higher in the LDCT arm – 24.2% of LDCT screens versus 6.9% of CXR screens (35). Among participants who received all three LDCT screens, 39% had at least one positive screen. The rate of positive exams decreased at the final screen, largely because persisting nodules that were stable across all three screens could be considered negative at the discretion of the radiologist.

## DOWNTREAM DIAGNOSTIC TESTING AND COMPLICATIONS

More than 90% of positive screens at baseline (T0) resulted in further diagnostic testing. Rates of diagnostic evaluation dropped in the subsequent screens (Table 2). Among positive LDCT screens, less than 4% were associated with a diagnosis of lung cancer. This translates into a high number of false positive screens that prompted downstream diagnostic testing. The majority of diagnostic tests were follow-up imaging procedures, most commonly a repeat LDCT at 3–6 months to determine whether the nodule exhibited change over time that would suggest malignancy. Many fewer invasive procedures were performed following positive screen. Those that were performed mostly consisted of some form of surgical procedure, bronchoscopy, or percutaneous lung biopsy, in which suspicious nodules were biopsied by inserting a needle from the skin surface into the lesion (35).

**TABLE 1:  
DEMOGRAPHIC FEATURES OF THE NLST COHORT RELATIVE  
TO THE NLST-ELIGIBLE US POPULATION<sup>1</sup>**

Characteristic	LDCT Arm	CXR Arm	Tobacco Use Supplement <sup>1</sup>
<b>Male (%)</b>	15,770 (59.0%)	15,763 (59.0%)	58.5%
<b>Smoking History</b>			
Median pack-years	48.0	48.0	47.0
Former smoker (%)	13,853 (51.8%)	13,823 (51.7%)	42.9%
<b>Age group (%)</b>			
55-59 yrs.	11,440 (42.8%)	11,421 (42.7%)	35.2%
60-64 yrs.	8170 (30.6%)	8198 (30.7%)	29.3%
65-69 yrs.	4756 (17.8%)	4762 (17.8%)	20.8%
70-74 yrs.	2352 (8.8%)	2345 (8.8%)	14.7%
<b>Race   Ethnicity %</b>			
White	24,289 (90.9%)	24,260 (90.7%)	
Black or African American	1196 (4.5%)	1182 (4.4%)	5.5%
Hispanic or Latino	479 (1.8%)	456 (1.7%)	2.4%
<b>Education Status</b>			
Less than high school	1642 (6.2%)	1610 (6.1%)	21.3%
College degree or higher	8433 (31.6%)	8406 (31.4%)	14.4%

Abbreviations: LDCT = low-dose CT; CXR = Chest x-ray

<sup>1</sup> Estimates were derived from the Tobacco Use Supplement of the US Census Bureau Current Population Survey for the years of NLST enrollment, restricting the survey population to those respondents who met the NLST criteria of age and smoking eligibility.

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**TABLE 2:**  
**DIAGNOSTIC FOLLOW-UP OF POSITIVE SCREENING**  
**RESULTS BY STUDY ARM IN THE THREE SCREENING ROUNDS**

	Low-Dose CT				Chest Radiography			
	To	T1	T2	Total	To	T1	T2	Total
<b>Total positive tests</b>	7191 (100.0%)	6901 (100.0%)	4054 (100.0%)	18,146 (100.0%)	2387 (100.0%)	1482 (100.0%)	1174 (100.0%)	5043 (100.0%)
Lung cancer confirmed	270 (3.8%)	168 (2.4%)	211 (5.2%)	649 (3.6%)	136 (5.7%)	65 (4.4%)	78 (6.6%)	279 (5.5%)
Lung cancer not confirmed <sup>1</sup>	6921 (96.2%)	6733 (97.6%)	3843 (94.8%)	17,497 (96.4%)	2251 (94.3%)	1417 (95.6%)	1096 (93.4%)	4764 (94.5%)
<b>Positive screens with complete diagnostic follow-up information</b>	7049 (100.0%)	6740 (100.0%)	3913 (100.0%)	17,702 (100.0%)	2348 (100.0%)	1456 (100.0%)	1149 (100.0%)	4953 (100.0%)
<b>Any diagnostic follow-up</b>	6369 (90.4%)	3866 (57.4%)	2522 (64.5%)	12757 (72.1%)	2176 (92.7%)	1078 (74.0%)	957 (83.3%)	4211 (85.0%)
<b>Imaging exam</b>	5717 (81.1%)	2520 (37.4%)	2009 (51.3%)	10,246 (57.9%)	2010 (85.6%)	968 (66.5%)	906 (78.9%)	3884 (78.4%)
CT chest	5153 (73.1%)	2046 (30.4%)	1608 (41.1%)	8807 (49.8%)	1546 (65.8%)	745 (51.2%)	712 (62.0%)	3003 (60.6%)
FDG-PET or PET-CT	728 (10.3%)	350 (5.2%)	393 (10.0%)	1471 (8.3%)	179 (7.6%)	105 (7.2%)	113 (9.8%)	397 (8.0%)
<b>Percutaneous lung biopsy</b>	155 (2.2%)	74 (1.1%)	93 (2.4%)	322 (1.8%)	83 (3.5%)	37 (2.5%)	52 (4.5%)	172 (3.5%)
<b>Bronchoscopy</b>	306 (4.3%)	178 (2.6%)	187 (4.8%)	671 (3.8%)	107 (4.6%)	56 (3.8%)	62 (5.4%)	225 (4.5%)
<b>Surgical Procedure</b>	297 (4.2%)	197 (2.9%)	219 (5.6%)	713 (4.0%)	121 (5.2%)	51 (3.5%)	67 (5.8%)	239 (4.8%)

Abbreviations: FDG PET = 18-Fluorodeoxyglucose positron emission tomography.

<sup>1</sup> Positive tests with incomplete diagnostic follow-up are included in this category.

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Adverse events following a positive screen occurred primarily at the time of follow-up rather than at the actual screening exam. These were divided into minor, intermediate and major complications (35). The rate of at least one complication was 1.4% in the LDCT arm and 1.6% in the CXR arm. Major complications were typically due to cardiac events, such as heart failure or myocardial infarction, respiratory failure, pulmonary embolism, or complications of surgery. In the LDCT arm, major complications were observed in 75 of 649 (11.6%) participants with positive screens in whom lung cancer was diagnosed, and in 12 of 17,053 (0.1%) in whom no lung cancer was found. Correspondingly, in the CXR arm, major complications occurred in 24 of 279 (8.6%) participants with a positive screen in whom lung cancer was diagnosed, and in 4 of 4764 (< 0.1%) with no diagnosis of lung cancer. Deaths were observed within 60 days of an invasive procedure in 16 participants in the LDCT arm, ten of whom had lung cancer, and in ten participants in the CXR arm, all of whom had lung cancer. It is unknown whether the deaths were due to complications of the diagnostic procedures, but the low frequency of such deaths suggests that this was a rare occurrence.

## LUNG CANCER DIAGNOSES, STAGES, AND HISTOLOGIES

Lung cancers were analyzed through the entire period of observation. Each cancer was assigned to having been found in the setting of a positive screen, a negative screen, or absent screening (35). More lung cancers were observed in the LDCT arm ( $N = 1060$ ; 645 per 100,000 person years) than in the CXR arm (941; 572 per 100,000 person-years). Among lung cancers of known stage, stage IA cancers were more than two times greater in the LDCT arm, the majority of which were screen-detected (Figure 2). There were fewer lung cancers diagnosed following negative LDCT screens (i.e. interval cancers) ( $N = 44$ ) than with CXR ( $N = 137$ ). In both arms, most interval lung cancers were advanced, supporting the likelihood that such cancers are biologically more aggressive and arise quickly between scans. Finally, there were fewer stage IV lung cancers in the LDCT arm compared with the CXR arm, showing that LDCT promoted a stage shift from more advanced stages to earlier stages of lung cancers.

Adenocarcinoma was the most common lung cancer cell type found in both arms; squamous cell carcinomas were the second most common, followed by small-cell lung cancers and non-small cell carcinomas not otherwise specified. The majority of small-cell carcinomas were in an advanced

stage at diagnosis, in keeping with the belief that imaging screening is inadequate for the early detection of this form of lung cancer.

## LUNG CANCER-SPECIFIC AND ALL-CAUSE MORTALITY

Trial-wide, the major causes of death in the NLST were lung cancer, other cancers, cardiovascular disease, and respiratory disease. These conditions accounted for over 80% of all deaths (Table 3). Based on verification of cause of death by a separate committee that reviewed all medical records of decedents, there were 356 and 443 lung cancer deaths in the LDCT and CXR arms, respectively. This corresponds to death rates of 247 per 100,000 person-years in the LDCT arm and 309 per 100,000 person-years in the CXR arm. The relative reduction in lung cancer-specific mortality in the LDCT arm was 20% (95% confidence interval (CI), 6.8–26.7;  $P = 0.004$ ). The number of individuals that had to be screened with LDCT to prevent one death from lung cancer was 320.

What was not expected, and has never previously been shown in a screening trial, was a modest reduction in all-cause (overall) mortality (35). There were 1,877 deaths in the LDCT arm and 2,000 deaths in the CXR arm. These results translate into a 6.7% (95% CI, 1.2 to 13.6;  $P = 0.02$ ) reduction in overall mortality in the LDCT arm. Lung cancer accounted for 24.1% of all deaths in the NLST, but 60.3% of the excess deaths in the CXR arm. Excluding the lung cancer deaths in the CXR arm, the differences in overall mortality between the two arms is not significant.

## SUMMARY OF FINDINGS FROM THE NLST

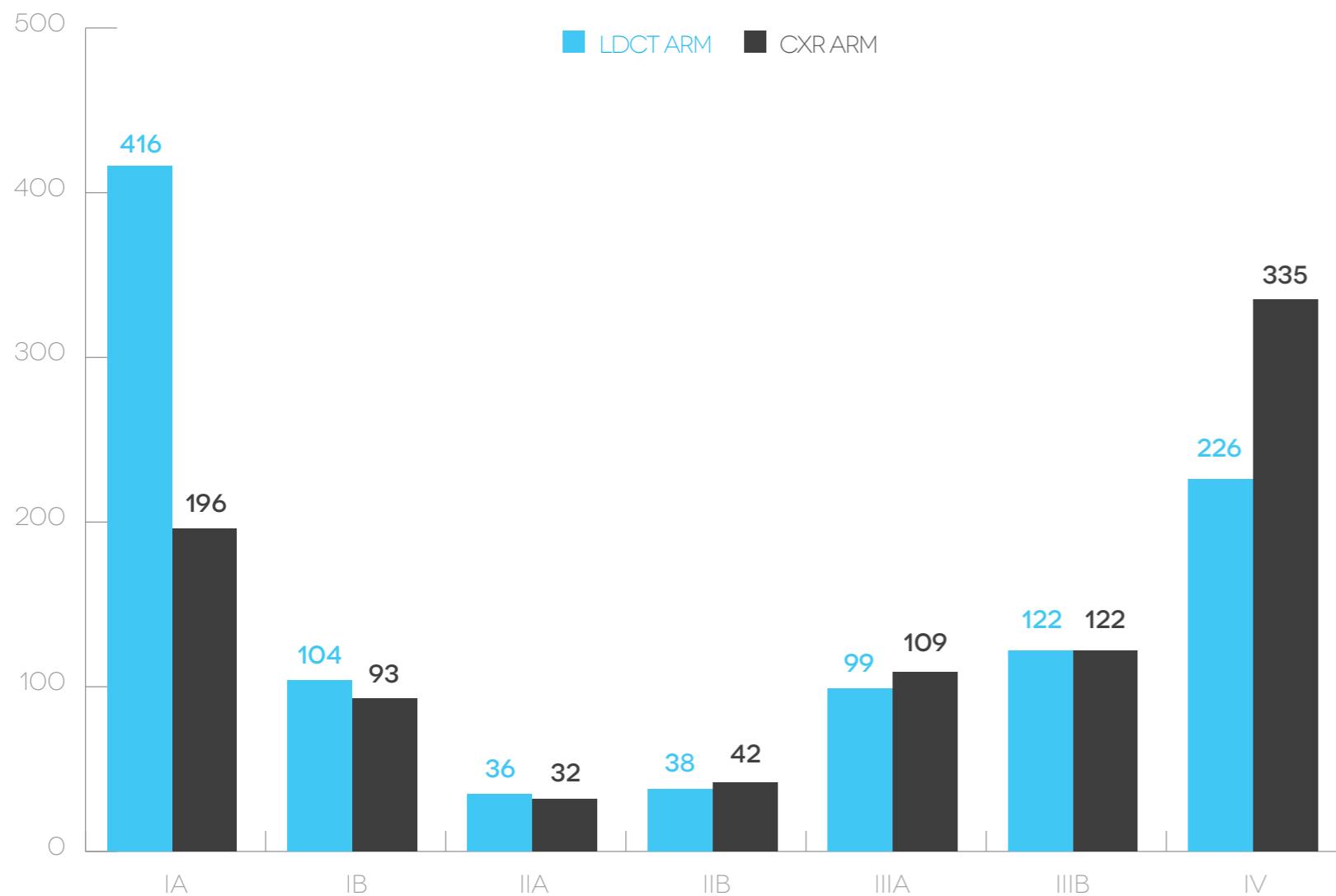
To summarize, the single most critical finding of the NLST is that LDCT screening reduces lung cancer specific mortality in older, heavy, current or former smokers by 20% relative to CXR screening. With LDCT there is a three-fold increase in initial nodule detection (which diminishes in subsequent screens) and an increase in detected lung cancers. There is a favorable stage shift from advanced to early-stage disease with LDCT. These benefits come at the cost of a high false positivity rate, such that less than 4% of LDCT-screen detected nodules represent lung cancer. Complications from diagnostic tests

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## FIGURE 2: STAGE DISTRIBUTION OF LUNG CANCERS BY SCREENING ARM

ABBREVIATIONS: LDCT = LOW-DOSE COMPUTED TOMOGRAPHY; CXR = CHEST X-RAY

NOTE: OF 1060 LUNG CANCERS IN THE LDCT ARM, 20 WERE OF UNKNOWN STAGE AND ARE NOT INCLUDED.  
OF 941 LUNG CANCERS IN THE CXR ARM, TWELVE WERE OF UNKNOWN STAGE AND ARE NOT INCLUDED.

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## TABLE 3: CAUSE OF DEATH ON DEATH CERTIFICATE BY SCREENING ARM<sup>1</sup>

	LDCT Group	CXR Group	Total
Neoplasm of lung   bronchus <sup>2</sup>	427/1865 (22.9%)	503/1991 (25.3%)	930/3856 (24.1%)
Other neoplasm	416/1865 (22.3%)	442/1991 (22.2%)	858/3856 (22.3%)
Cardiovascular illness	486/1865 (26.1%)	470/1991 (23.6%)	956/3856 (24.8%)
Respiratory illness	175/1865 (9.4%)	226/1991 (11.4%)	401/3856 (10.4%)
Complications of medical or surgical care	12/1865 (0.6%)	7/1991 (0.4%)	19/3856 (0.5%)
Other	349/1865 (18.7%)	343/1991 (17.2%)	692/3856 (17.9%)
Known deaths among death certificates reviewed <sup>3</sup>	1865/1877 (99.4%)	1991/1998 (100%)	3856/3875 (99.5%)
Unknown cause of death	12/1877 (0.6%)	7/1998 (0.4%)	19/3875 (0.5%)

Abbreviations: LDCT = Low dose computed tomography; CXR = chest x-ray.

<sup>1</sup> Among 3,875 death certificates received, cause of death was unknown for 19 participants (12 in the LDCT arm and 7 in the CXR arm). Denominators for known cause of death represent only the deaths for which cause of death was known.<sup>2</sup> Deaths from neoplasm of lung and bronchus include all death certificates received by 12/31/2009, and is not equal to the number of lung-cancer deaths in the calculation of lung-cancer specific mortality, which factored only those deaths reviewed by an endpoint-verification team.<sup>3</sup> Death certificates were unavailable for two deaths in the CXR arm, but the occurrence of death was confirmed by the endpoint verification committee.

occurring downstream from a positive screen were uncommon. Severe complications and/or death occurred rarely, particularly in those without lung cancer. The decrease in the overall death rate suggests that LDCT screening does not promote deleterious consequences and that patients who are spared a lung cancer death do not, in the short term, die from competing causes.

Earlier claims based on single arm observational studies of high mortality reduction on the order of 50–80% (36, 37) were not realized in the NLST. Nonetheless, LDCT screening in appropriate high-risk cohorts is the most powerful new weapon we have to reduce the burden of lung cancer in the United States since the 1964 Surgeon General's report on cigarette smoking and lung cancer (38). By comparison, individualized therapies for lung cancer with therapeutic agents targeted to specimen gene mutations have achieved incremental median increases in survival on the order of only months (39).

## HARMS OF LDCT SCREENING

Screening with LDCT has inherent risks. A major concern is the high false positivity rate that was observed in the NLST, which leads to diagnostic testing that is unnecessary, potentially harmful, anxiety-provoking and costly. A focus of current and future research will be to establish practices to reduce high false positivity rates. Potential solutions fall into four categories: [a] to establish different criteria for screening positivity; [b] to consider screening interpretation as a two-step process of detection and diagnosis rather than a dichotomous choice of positive or negative; [c] to better determine the risk cohort that should undergo screening using available clinical and epidemiologic profiling; and [d] to incorporate validated biomolecular markers of lung cancer risk to better stratify screening cohorts.

The NLST used 4mm as the nodule threshold size for defining a positive screen potentially signaling lung cancer. The vast majority of actual lung cancers were in nodules larger than 5mm. Increasing the size threshold would reduce the rate of both true positive and false positive screens. This outcome has been validated in a retrospective study (40). Of course, the concern over this approach is delayed diagnosis for the smallest cancers, the impact of which could not be measured retrospectively. Moreover, differences in the demographics and risk profiles of the cohort limit generalizability to a higher-risk population. Nonetheless, recent guidelines for managing indeterminate nodules in the screening setting use minimum thresholds of 5mm diameter to trigger diagnostic work-up (41, 42).

Unlike the NLST, which required radiologists interpreting the screening studies to declare the exams positive or negative for lung cancer, the Dutch-Belgian randomized lung cancer screening trial (Nederlands-Leuven Longkanker Screenings Onderzoek [NELSON]) categorized screens as 'negative' with nodules less than 5mm diameter, as 'positive' with nodules greater than 10mm, and as 'indeterminate' with nodules ranging from 5 to 10mm (43). Indeterminate nodules were reassessed by repeat LDCT at 3 months; growth based on volumetric analysis at follow-up was used to classify the scan as negative or positive. Using this strategy, the positive predictive value of positive screens improved significantly (up to 42.2% at incidence screens). Although the volume of downstream diagnostic tests was not significantly different from the NLST, the two-step process provides interpretations more representative of the true risk of lung cancer. This has implications for both the individuals undergoing screening and the physicians who assist with their management.

The false positivity rate and other performance characteristics of LDCT are also influenced by the risk of lung cancer in the population to be screened. Several risk prediction models have been developed to improve the selection of individuals who should undergo screening (44–47). For example, the currently accruing UK Lung Screen Trial uses a risk algorithm as the basis for determining eligibility (48). As our knowledge evolves, screening guidelines will be informed by integrating multiple demographic and clinical risk factors, imaging features, and validated biological markers of lung cancer predisposition in blood or other readily accessible specimens (49).

Radiation exposure and risk of carcinogenesis is another concern with LDCT screening, owing to both consecutive screens over time and downstream imaging follow-up of positive screens. Although individual risk may be acceptable, the large number of individuals who would be exposed to consecutive screening over years could translate into measurable increases in radiation-induced cancers (50). The radiology community and industry partners have been aggressive in addressing these concerns by using contemporary scanners at lower exposures with the body-mass index as a guide, employing new image reconstruction algorithms that enable significantly lower exposures, reducing the scan field to that necessary to cover the lungs only, and using tube current modulation techniques that reduce exposure when the x-ray beam is passing over sensitive anatomic regions such as the breast (51, 52).

Finally, an enduring concern with any screening test is the notion of overdiagnosis, referring to the diagnosis of a cancer that would not have gone on to cause symptoms or death. Overdiagnosis occurs in two settings: [a] the screen-detected cancer is so biologically indolent that it will not result in the death of the individual, or [b] the cancer is treated or progresses sufficiently slowly that the individual dies of competing conditions such as cardiovascular or respiratory disease (53). The mod-

adding what is likely to be tens of billions of dollars to a federal health-care budget is worth the cost. Employing the vast secondary data ACRIN collected during the NLST, ACRIN researchers are nearing an estimate of cost-effectiveness. The outcome of this analysis is essential to rational decisions concerning insurance coverage for the screening examination.

Regardless of coverage, LDCT screening for lung cancer is certain to diffuse into medical practice. The risk is that without broad public coverage some populations will be excluded from the benefits of LDCT screening. To be truly effective, lung cancer screening must cross socioeconomic strata to encompass all high-risk individuals. Failure to take directed steps to assure access to all economic strata threatens to relegate lung cancer to a disease of poor and underserved populations. Inclusion of the underserved will require a multipronged approach in which information strategies are used to educate across demographic divides through dialogue among community organizations, healthcare providers and patients. The medical community must come to terms with its own racial and class misperceptions of lung cancer and smoking-related diseases (55), thus assuaging community mistrust of the medical profession. The stigma of smoking and lung cancer must be exorcised from our professional consciousness (56).

## CONCLUSIONS

Designed and led by radiology researchers, the NLST was more than a decade in the making. It was an extraordinarily complicated trial in every regard – scientifically, financially, politically, and culturally. However, the outcomes of the NLST were worth the effort. First and foremost, many individuals who are at the highest risk of dying of lung cancer have greater hope than they previously had that their cancers will be found at an early, curable stage. Secondly, radiologists will likely see a considerable expansion of their thoracic imaging services as lung cancer screening disseminates across the country. At-risk individuals increasingly will seek screening hospitals and outpatient services will provide it, and providers will be reimbursed for both the screening and inevitable associated downstream imaging. Very significantly from the perspective of future imaging research, the NLST stands as perhaps the most glowing of ACRIN's accomplishments. ACRIN's joint ownership of the trial with LSS once and for all puts the lie to a common misapprehension among other specialists that radiologists are not interested in or capable of performing high quality, rigorous, multi-institutional research. Radiologists asked the key question, organized the 32 sites and the complex infrastructure essential to the trial's success, designed and implemented the protocol; and achieved a positive result that has critical implications for our nation's health.

Inevitably, the NLST generated several new and important research questions to be addressed by future radiology researchers. The most pressing of these questions asks whether LDCT screening can be done cost-effectively. There are legitimate concerns about whether our society can afford to develop a national lung cancer screening program similar to mammography for breast cancer. Restricting the procedure to the highest-risk individuals would help ameliorate only some of the costs. The very high rate of false positive findings ensures follow-on procedures and their associated expenditures. Policy-makers will have to decide whether

In summary, research leading to the development of modern CT technology, image display systems and computational connectivity advanced clinical CT to the point where it is practical to employ the modality for screening for curable lung cancer. The simultaneous development of a clinical research infrastructure and the talents of radiologist researchers and their research colleagues has proven the value of CT lung cancer screening in reducing our national burden of lung cancer-related mortality.

LDCT lung cancer screening offers a prime opportunity for radiologists to take the lead in establishing collaborative clinical programs with their physician colleagues. Organizations that establish lung cancer screening within a broad programmatic, transdisciplinary context will achieve better care and greater efficiencies through close communication among providers, avoidance of redundancies, and consensus in approach to diagnostic follow-up and early referral for treatment.

These are exciting times in medicine. If we work smart, we can use lung cancer screening to combat the most common cause of cancer death worldwide and simultaneously use it as a blueprint for how to efficiently and effectively implement evidence-based medical practice. It is highly gratifying to look back and realize the roles highly motivated radiologists and their collaborators played in taking us from concept to evidence and anticipate radiologists' roles as we implement the lessons learned going forward.

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OH, IF ONLY MAN  
WERE TRANSPARENT  
LIKE A JELLYFISH  
SO THAT ONE  
COULD SEE WHERE  
HIS SUFFERING LIES.

WILHELM CONRAD RÖNTGEN (1845 - 1923)

CHAPTER 7

# IMAGING PATIENTS WITH LUNG DISEASE: A ROUNDTABLE INTERVIEW

A panel of world-renowned thoracic radiologists took part in IDoR 2013 to make the benefits of medical imaging clearer to the public. They explained what exactly imaging can do for lung patients, the role played by radiologists in healthcare and what patients should know before undergoing a chest examination.

**How does imaging help in the management of lung disease? Diagnosing disease might be the best-known use of imaging, but can imaging be employed in other areas of healthcare?**

**Johny A. Verschakelen:** Imaging plays an important role in the detection of lung diseases, as it does in many other parts of the body. Pathology (microscopic examination of tissue) used to be the gold standard for the diagnosis of diffuse and interstitial lung disease. However, this is no longer the case. Diffuse and interstitial lung diseases are diagnosed by a multidisciplinary team, in which the radiologist has an important role. Imaging is also successfully used to follow up patients once the diagnosis has been made and treatment has started. Screening is another story. Many studies are being carried out to examine whether computed tomography (CT) could be a good technique for the early detection of lung cancer. The initial results are promising but need to be confirmed.

**Tomás Franquet:** There are many reasons why medical professionals request a chest x-ray, one of the most widely used diagnostic imaging techniques in Western societies (on average 236 chest x-rays per 1,000 patients are performed each year and this technique accounts for 25 percent of the annual number of diagnostic imaging procedures). Conventional radiography may be useful for follow-up lung infections, invasive thoracic procedures (drainage) and intrathoracic catheters, tubes and wires. The frequency with which even relatively inexpensive and non-invasive diagnostic tests are performed leads to high costs in healthcare.

**Arthur Soares Souza:** Imaging helps not only by diagnosing lung diseases but also by identifying the complications and associated lesions. It is an important tool for monitoring the treatment, follow-up and screening of different lung diseases.

**What kind of lung diseases can be detected and monitored with imaging?**

**Santiago Rossi:** Imaging can detect different lung diseases such as lung cancer, emphysema, interstitial pneumonia, mediastinal masses, infectious diseases and small airways disease, among others. It also plays a role in the diagnosis of systemic disorders such as collagen vascular disease, sarcoidosis and vasculitis; the diagnosis and follow-up of vascular disorders such as pulmonary embolism (PE), aneurysms or arteriovenous malformations; diagnosis of effusions; and in interventional procedures.

**Richard Pitcher:** Globally, imaging plays a pivotal role in the detection and monitoring of the full spectrum of lung pathology. In any particular region, the pathology detected is dictated by the local burden of disease. If we consider sub-Saharan Africa, where there is a high prevalence of HIV-infection but very limited access to HIV-testing, the chest x-ray may provide the first clue to the presence of HIV infection, by demonstrating features of pneumocystis jirovecii pneumonia, suggesting underlying immune compromise requiring further investigation. In addition, in resource-limited environments, where there is poor access to immunisation as well as delays in the treatment of lung infections, the complications of pneumonia, particularly bronchiectasis, are seen more often than in well-resourced countries.

# Imaging plays an important role

in the management of lung diseases as part of a multidisciplinary approach. Imaging is also used in lung cancer screening, and plays an important role in lung cancer patients, for staging and treatment response. Another area where imaging is starting to play a role is in chronic obstructive pulmonary disease (COPD) patients, by focusing on lung density and airway evaluation.

**Santiago Rossi** (How does imaging help in the management of lung disease? Diagnosing disease might be the best-known use of imaging, but can imaging be employed in other areas of healthcare?)

Imaging is very valuable for the **detection and characterisation** of a multitude of different disease processes of the lung, for example pulmonary infections, lung malignancies, and staging of extra-thoracic malignancies. Chest imaging is also an essential tool in the evaluation of patients suffering from traumatic injuries.

**Eric J. Stern** (What kind of lung diseases can be detected and monitored with imaging?)

Lung cancer is one of the most common types of cancer. What kind of lung screening programmes are in place around the world?

**Johny A. Verschakelen:** There are screening programmes that, in a randomised way, examine whether people who are screened with CT live longer than people who are not screened. American studies have been positive, although European studies have not yet confirmed this.

**Santiago Rossi:** The main thoracic societies recommend low-dose CT in patients between 55–74 years with 30 pack years, or who have quit smoking within the last 15 years and have no history of lung cancer. A lung screening programme should be performed through a multidisciplinary approach.

**Eric J. Stern:** Lung cancer is the most common malignancy in the industrialised world, with increasing frequency in the developing world as well. Recent research studies have shown that early detection of lung cancer has been shown to reduce overall mortality. However, for a variety of reasons, CT lung cancer screening programmes currently have limited availability, although some centres are offering this service to their communities. Such programmes would include a low-dose CT technique as part of a more comprehensive cancer evaluation centre with a dedicated multispecialty team.

**Tomás Franquet:** Currently, routine chest x-rays and other screening tests for lung cancer are not recommended, even for smokers. It has been widely accepted that CT scans are more sensitive than routine chest x-rays in demonstrating early lung cancer. The National Cancer Institute (NCI) recommends low-dose computed tomography (CT) as the best non-invasive diagnostic imaging examination for detecting lung cancer early. This technique has about one-tenth of the radiation dosage of a standard-dose CT scan.

**Richard Pitcher:** Screening programmes are determined by both the prevalence of the disease and the

available resources. In Africa, screening for lung disease is largely limited by a lack of available funding and more pressing healthcare imperatives. In Africa, screening programmes are principally focused on industrial lung disease, such as asbestosis and silicosis, associated with mining activity. There is scope for broader implementation in this regard.

How do radiologists image lung disease? What kind of technology do they have at their disposal?

**Arthur Soares Souza:** Radiologists image the lungs with x-ray, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography CT (PET/CT), nuclear medicine and angiography. The x-ray is still the number one tool used to evaluate lung disease and the most common imaging investigation worldwide. Ultrasound can evaluate pleural effusions, while CT and MRI can evaluate focal and diffuse lung disease, vascular diseases, the thoracic wall, etc. PET/CT is a good tool for staging neoplastic diseases. A nuclear medicine scan can assess ventilation and perfusion of the lungs. The intra-arterial catheter is almost only used for treatment.

**Johny A. Verschakelen:** Given the anatomy of the lung, predominantly air, very small lesions can become visible when their density is higher than that of air, at least when techniques that work with x-rays, like chest radiography and especially CT, are used. Air in the lung and the fact that small lesions induce little signal are the main reasons why MRI is not so frequently used for imaging of the chest in daily practice anymore. Air in the lung also prevents the use of ultrasound. CT offers highly detailed imaging of the lung, and this detail is not only used to detect disease, but also to diagnose disease.

**Jung-Gi Im:** MRI has been used mainly as a complementary modality due to its many limitations in lung imaging, but it may be used as a primary modality in pulmonary vascular and oncologic imaging given recent

technical improvements. As a fusion imaging modality, PET/CT has shown excellent performance in the evaluation of lung malignancies and the recently introduced PET/MRI may have strengths from both PET and MRI as a whole-body imaging tool for lung malignancies.

**Richard Pitcher:** In sub-Saharan Africa there are some well-resourced healthcare environments, mostly in the private or corporate sector, that have the full spectrum of radiologist-driven imaging modalities. Radiologists can use fluoroscopy, ultrasound or CT scans to guide the accurate performance of diagnostic and interventional procedures in lung disease, such as drainage of fluid from around the lung and biopsy of lung tumours. However, in many parts of Africa, particularly in the public healthcare sector, plain film radiography is the only imaging modality. Furthermore, there is a global shortage of radiologists. In many parts of Africa, general medical practitioners are responsible for interpreting plain radiographs.

### How do radiologists interpret images from radiological exams and how does their interpretation help in reaching a diagnosis?

**Richard Pitcher:** Radiologists are medical specialists who spend an additional four or five years training after their basic undergraduate medical degree in order to acquire the skills necessary for interpreting radiological images. An important aspect of the interpretation process is knowledge of the clinical setting behind the radiological findings. This means that it is important for a radiologist to be provided with accurate clinical details by the referring healthcare worker. In cases of lung disease, important information includes the patient's smoking habits, occupation, medication, and whether the patient has a cough, high temperature, night sweats, chest pain, weight loss, or is immune compromised. In areas with a high prevalence of pulmonary tuberculosis (PTB), it is also important to know if any household contacts have pulmonary tuberculosis. The results of any laboratory tests may

also help in interpretation. Knowing whether the patient has a high white blood cell count in the peripheral blood, anaemia, or is in renal failure, is important.

The radiologist may also use the findings from the patient's previous x-ray examinations to assist in the interpretation of the findings from the current study. An abnormality on a plain chest x-ray may be difficult to interpret with confidence, so the radiologist may need to use a range of imaging examinations to establish a final diagnosis. This may prompt the use of more sophisticated and expensive imaging studies such as CT or MRI, which may allow the radiologist to make a more accurate diagnosis. A radiologist needs to know the strengths and weaknesses of each imaging modality and when to seek further imaging.

**Eric J. Stern:** In most parts of the developed world, after images are obtained by the technologists, radiologists evaluate patient images electronically through the use of computers and monitors. Images are typically stored and retrieved in computer archive systems. In other parts of the world, images are still created and stored on hard copy film for interpretation.

### What kind of safeguards are generally put in place to avoid mistakes in image interpretation and ensure consistency between the opinions of different consultants?

**Jung-Gi Im:** Each radiological society provides continuing medical education through seminars, classes, workshops, lectures, conferences and webinars. There are also many guidelines and quality assurance programmes for the radiologists to ensure consistency and to provide high quality interpretation or readings. In addition to that, for example, the ACR (American College of Radiology) provides evidence-based guidelines to assist referring physicians and other providers in making the most appropriate imaging or treatment decision

**The radiologist detects, localises (study distribution) and studies** appearance pattern of the abnormalities. The radiologist correlates these abnormalities with clinical findings and suggests a diagnosis or differential diagnosis. This is increasingly done through a multidisciplinary approach.

**Johny A. Verschakelen** (How do radiologists interpret images from radiological exams and how does their interpretation help in reaching a diagnosis?)

In making a diagnosis and determining a treatment plan, a multidisciplinary approach ensures more **consistency** and more **standardised decisions.**

Other approaches to reducing the number of lesions missed and the variability of measurements includes computer-aided detection (CAD) and computer-assisted quantification.

**Jung-Gi Im** (What kind of safeguards are generally put in place to avoid mistakes in image interpretation and ensure consistency between the opinions of different consultants?)

for a specific clinical condition. Employing these guidelines helps providers enhance the quality of patient care and contribute to the most effective use of radiology.

**Arthur Soares Souza:** You need an initial evaluation to recognise the primary patterns of lung disease using each technology, a clear and easy to understand report and double reading (signature).

**Santiago Rossi:** In our practice, we use double reading in order to avoid interpretation mistakes. We also have conferences, in which we discuss the most difficult cases before contacting the referring doctor. In the future, we will be adding CAD to help us detect small lesions.

**Eric J. Stern:** Our computer archive systems (PACS) are very accurate in storing and retrieving patient health records. Most institutions are using peer review quality assurance programmes.

What should patients keep in mind before undergoing an imaging exam? Do patients undergoing radiological exams generally experience any discomfort?

**Eric J. Stern:** Patients should consider asking their primary care physicians if they are receiving the right exam at the right time, for the right reason. X-rays themselves cause no discomfort. If intravenous contrast material is administered, some patients may experience a warm, flushing feeling.

**Richard Pitcher:** When embarking on any imaging procedure, the radiologist is committed to serving the patient's best interests and ensuring that the potential benefit always exceeds the cost and potential risk. Part of the training in the field of radiology is in balancing of these imperatives. The patient needs to know that these considerations will be carefully weighed by the radiologist when undertaking any imaging procedure. This is

particularly true as the number of imaging modalities is increasing and the costs of healthcare are climbing. There are examinations that may involve a small degree of discomfort, such as contrasted CT scans and angiographic procedures, where patients can possibly experience some nausea during the injection of contrast. MR examinations may be uncomfortable due to the need for complete immobility for relatively long periods of time, mammography is uncomfortable due to breast compression and fluoroscopy studies of the gastrointestinal tract may result in discomfort due to bowel distension.

Some imaging technology, such as x-ray and CT, uses ionising radiation. How high is the risk associated with radiation exposure and how does it compare with the benefits? How can patient safety be ensured when using these modalities?

**Jung-Gi Im:** One of the most critical and well-known potential adverse effects of radiation exposure is cancer. The radiologist takes great care to identify the patients who should and should not undergo radiological examinations. And we radiologists have been trying to lower the radiation dose needed for exams. However, the risk should not be over-estimated and the benefit and harm from radiological exams should be checked and balanced. In most cases, particularly patients with disease or adult population at high risk of critical diseases, we do not think that there is any reason for them to avoid radiological exams that are proven to be beneficial. The dose used in medical examinations is very low. According to recent estimates, the average person in the U.S. receives an effective dose of about 3mSv per year from naturally occurring radioactive materials and cosmic radiation from outer space. The radiation exposure from one chest x-ray is the equivalent to the amount of radiation exposure one experiences from natural sur-

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Physical discomfort, anxiety, embarrassment, and other aspects of patient experience impact on future compliance for some diagnostic imaging tests.

## **Patients have a moderate amount of anxiety**

about interventional and invasive procedures and anticipate some discomfort. It's really important for the patient to receive all the information and support before and during the diagnostic procedure.

A friendly atmosphere in the interventional room and supportive staff are crucial to making patients more relaxed and distracted from pain.

**Tomás Franquet** (What should patients keep in mind before undergoing an imaging exam? Do patients undergoing radiological exams generally experience any discomfort?)

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As there is a 'linear no threshold' relationship between cancer and radiation dose it is

**essential** that doses for medical diagnostic purposes be kept **as low as possible.**

This was outlined in the 1977 recommendations of the International Commission on Radiation Protection (ICRP), which proposed keeping radiation exposures 'As Low As is Reasonably Achievable' – the so-called ALARA principle.

**Richard Pitcher** (Some imaging technology, such as x-ray and CT, uses ionising radiation. How high is the risk associated with radiation exposure and how does it compare with the benefits? How can patient safety be ensured when using these modalities?)

roundings in 10 days. CT radiation is about 6–7mSv and low-dose screening chest CT radiation is about 1–2mSv.

**Arthur Soares Souza:** There are risks, more for some populations than for others, but the benefits are greater than the risks in a well-indicated test using ionising radiation. Mainly at risk are the paediatric population and patients with chronic disease. The pelvic, breast and thyroid regions are also at risk when exposed to radiation.

**Johny A. Verschakelen:** There is radiation exposure but this can be minimised given the fact that for lung imaging dose can be kept very low. The risks from the exam and advantages of making or trying to make a diagnosis through this exam should be balanced. The examination should only be performed when really indicated and when decision-making is influenced. But once an exam is to be performed, the radiologist should then choose the optimal technique.

**Richard Pitcher:** When compared to plain radiographs, CT scans involve relatively large doses of ionising radiation, which are potentially harmful to human tissue. For example the effective radiation dose for a plain skull x-ray is 0.03 millisievert (mSv) while that of a CT head scan is approximately 2mSv. As there is a 'linear no threshold' relationship between cancer and radiation dose it is essential that doses for medical diagnostic purposes be kept as low as possible. This was outlined in the 1977 recommendations of the International Commission on Radiation Protection (ICRP), which proposed keeping radiation exposures 'As Low As is Reasonably Achievable' – the so-called ALARA principle. These recommendations included the principles of justification for all diagnostic procedures such that no exposure to ionising radiation should be adopted unless it produces a net benefit; is based on optimisation, whereby all exposures are kept as low as reasonably achievable; and stays within dose limits, where individual doses do not exceed the limits recommended for the specific circumstance. In addition to international guidelines on the limitation of radiation dose, most countries have implemented government control of the registration, licencing and use of diagnostic imaging equipment. Thus, in South Africa, all diagnostic imaging equipment is controlled and registered by the Radiation Control Board and all users of diagnostic imaging equipment are required to be duly qualified and registered for this purpose.

## How do radiological exams for children differ from those for adults?

**Eric J. Stern:** The examinations are very similar. In recognition of the Image Gently and Image Wisely campaigns, radiologists use the lowest radiation dose as possible to generate the corporate examinations in all patients, especially in children.

**Jung-Gi Im:** Children are more likely to be affected by radiation. Furthermore, children are at an earlier stage of life than adults, which means the probability of cancer occurring due to radiation increases during their lifetime. So the radiological examination should be carried out with this in mind. We avoid radiation exposure, or substitute the radiological tests with non-radiation tests such as MR or US, whenever possible. If we cannot do that, we have to try to lower the radiation exposure during the test. We should take into consideration the radiation hazard as well as the accuracy and diagnostic quality of the tests, particularly in children.

## Do other radiological procedures have any side effects? How can these side effects be minimised?

**Jung-Gi Im:** Intravenous contrast media used for CT or MRI may cause adverse reactions ranging from the very trivial to the serious. Fortunately, the incidence of serious reactions is, however, extremely rare. Most adverse reactions are minor and self-resolving events. Patients who undergo the radiological exams should know and be aware of this prior to the exam. Interventional procedures such as percutaneous needle aspiration or biopsy, and percutaneous catheter drainage may cause pneumothorax, haemothorax, haemoptysis, etc. However, these side effects can be minimised by patient preparation, patient cooperation and precise image guidance.

**Tomás Franquet:** While angiographic procedures always use iodine-containing contrast medium (ICCM), some

but not all computed tomography (CT) scans require the use of intravenous contrast agents. Depending on the procedure and the type of contrast agent used, some patients do experience temporary mild adverse side effects, such as a metallic taste in their mouth or flushing (a warming sensation). Conversely, allergic reactions (anaphylactoid) are unpredictable and although people who know they have asthma or allergies to certain drugs, foods, pollen, dust or chemicals are more likely to have an allergic reaction; however, no one can predict whether any individual person will have a reaction.

## Like many other areas of healthcare, imaging is constantly developing. How do you think lung imaging will evolve over the next decade and how will this change patient care? How involved are radiologists in these developments and what other physicians are involved in the process?

**Santiago Rossi:** In my opinion thoracic radiology will continue evolving through more dynamic and functional studies, with a special focus on patient care. Thoracic imaging will play an important role in the diagnosis and treatment follow-up of patients with COPD, asthma and lung fibrosis. PET/CT and PET/MR will continue to develop and new agents will become available. Imaging will play an important role in drugs administration, delivery and monitoring during the next decade.

**Eric J. Stern:** There have been many rapid technological advances in imaging. Lung imaging will continue to evolve in terms of technologies that allow for radiation dose reduction without a loss in quality, especially for CT scanning. These CT dose reduction techniques

should help alleviate any referring physician or patient concerns about radiation dosage. Radiologists are heavily involved in the development of these techniques, as well as radiation physicists, and our corporate partners.

**Tomás Franquet:** Although imaging technologies have undergone dramatic evolution over the past century, radiology reporting has remained largely static, in both content and structure.

Radiology has achieved importance as one of the most powerful diagnostic approaches in clinical medicine. However, another type of radiologist is also needed for the discipline to survive in an era of managed care. The primary care physician, whether a general internist, general paediatrician, or family practitioner, will also need help from the general radiologist.

**Richard Pitcher:** From the African perspective, an important development has been the evolution of digital imaging, with the capacity to transmit images for reporting at a distance, thus affording rural general practitioners much needed radiological support.

Remote reporting will go a long way to addressing the global shortage of radiologists, increasing the efficiency of service delivery and allowing radiologists to play a more effective role in monitoring and managing radiological services in rural areas. This will also allow the deployment of more sophisticated imaging modalities in these rural areas, while allowing the radiologist to maintain a pivotal role in quality assurance and the rationalisation of utilisation.

**Jung-Gi Im:** Imaging will evolve to include more advantages and eliminate many current disadvantages: The radiation dose of CT will be reduced while maintaining its image quality, rapid acquisition with reduced motion-related artefacts will be possible with MRI, and more effective combination of fusion imaging will become available. Quantification using images will become a clinical routine beyond research fields. Protocols and scanners should be standardised for this, which requires input from radiologists. In addition to generating better images, handling imaging-based information will become an important issue for extracting more value from images, and this process will be developed closely with processes dealing with patient information and laboratory data.

CHAPTER 8

# IDOR AND PATIENTS' ORGANISATIONS: NEW COLLABORATIONS TO BENEFIT ALL

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# THE ESR AND THE EUROPEAN PATIENTS' FORUM

NICOLA BEDLINGTON, EXECUTIVE DIRECTOR OF THE EUROPEAN PATIENTS' FORUM (EPF), SHARED HER VIEWS ON HEALTHCARE IN THE EU AND EXPLAINED WHY SHE CHOSE TO PARTICIPATE IN IDOR 2013.

**What is the overall aim of your organisation?**

**Nicola Bedlington:** Our vision is high quality, patient-centred and equitable healthcare for all patients throughout the European Union.

The European Patients' Forum is an umbrella organisation that works with patients' groups in public health and health advocacy across Europe. Our members represent specific chronic disease groups at EU level, or are national coalitions of patients. We currently represent almost 60 such organisations.

Our mission is to be the collective patients' voice at EU level, manifesting the solidarity, power and unity of the EU patients' movement, and to provide a strong and united patients' voice in order to put patients at the centre of EU health policy and programmes. In this regard we are the key interlocutor with EU institutions on cross-cutting issues affecting all patients.

**What exactly does your organisation do to meet this aim?**

**Nicola Bedlington:** The EPF helps to empower patients' organisations through educational seminars,

policy initiatives and projects. We coordinate best practice exchanges between patient organisations at European and national levels. Our programmes also help to strengthen organisational and advocacy capacity.

**Your organisation has experience working with various chronic disease groups. Do many patients suffer from chronic diseases in the EU?**

**Nicola Bedlington:** Following consultation with our members we estimate there are at least 150 million patients with chronic conditions across the European Union. This figure is likely to increase given the ageing population.

**Many EU countries face significant health budget cuts, leading to shorter hospital stays and less access to modern equipment (i.e. long waiting lists for MRI exams).**

**How can patient care be promoted in this context?**

**Nicola Bedlington:** The EPF is working with its member organisations to ensure health is seen as an investment, and patients are not perceived as purely cost drivers. Major health inequalities exist across the EU which impact enormously on patients' access to care.

Building on the three pillars of quality information, health literacy and empowerment, patients can be agents of change and sources of innovation, particularly in terms of equity and sustainability of care. There need to be meaningful opportunities for patient involvement throughout the healthcare sector. We promote meaningful patient involvement in all forms of innovation, whether it is in high or low technology, pharmaceuticals, information technology, social change or systems change. The patient community seeks partnerships with researchers, policy-makers and industry in order to achieve greater impact in this arena.

**Do you think most patients in the EU are well-informed about disease management? For instance, do they know about the latest available treatment options?**

**Nicola Bedlington:** This varies across the European Union, but access to quality information about treatment options and health literacy, more generally, are core aspects of our work. There is a vast disparity in access to information on, for instance, research and

development in medicine, and the EPF is addressing this through projects such as the European patients' academy on therapeutic innovation.

**What does your organisation hope to achieve by taking part in IDoR 2013?**

**Nicola Bedlington:** This is part of a wider collaboration with the European Society of Radiology, which has set up a specific patient advisory board, chaired by the EPF, in order to embed a stronger patient perspective in its work. This is strongly welcomed by the EPF and all patient organisations with a particular interest in medical imaging. This initiative could, moreover, provide an excellent model for other medical societies to replicate.

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## ELF JOINS IDOR 2013

THE EUROPEAN LUNG FOUNDATION (ELF) WAS FOUNDED BY THE EUROPEAN RESPIRATORY SOCIETY (ERS) TO BRING TOGETHER PATIENTS, THE PUBLIC AND RESPIRATORY CARE PROFESSIONALS. ELF CHAIR MONICA FLETCHER AND ERS PRESIDENT PROFESSOR FRANCESCO BLASI PRESENTED THEIR REASONS FOR PARTICIPATING IN IDOR 2013.

### **What is the overall aim of your organisation?**

**Monica Fletcher & Francesco Blasi:** We work to bring together patients, the public and respiratory care professionals to positively influence respiratory medicine. To this end, we work to communicate respiratory research and news to those outside the field of respiratory medicine, and to translate this information into different languages. The ELF website ([www.european-lung-foundation.org](http://www.european-lung-foundation.org)) provides lung information to the public, and our factsheets, developed with patients and ERS experts, provide reliable and accurate patient information. We produce press releases and summaries to allow the media and the public to access papers from the European Respiratory Journal (ERJ) and abstracts from the ERS congress. We organise public awareness campaigns, such as World Spirometry Day, to encourage people to care about their lung health, and we also develop websites for EU projects.

The ELF also works to ensure that people with lung diseases and the general public have the opportunity to influence respiratory research and guidelines at the European level. We are a network and advisory group of patient organisations across Europe covering all areas of respiratory disease. We offer an online training programme for patients to help them in their interactions with doctors, policymakers and the media. We manage patient involvement in ERS guidelines through patient-orientated literature searches, online questionnaires, focus groups and patient versions of final guidelines. We also source patients to speak at ERS symposia,

and we encourage them to discuss the issues important to them with policymakers.

### **How many patient organisations do you work with?**

The ELF has a patient advisory committee comprising of 18 organisations who contribute to ELF activities. These organisations attend the ERS annual congress and advise the ELF on all its key and strategic issues. The ELF then has a wider network of more than 150 patient organisations. These organisations receive a monthly newsletter to update them on activities, they participate in surveys and patient input opportunities, and they share their latest activities with the ELF.

### **How many patients suffer from chronic airways diseases?**

According to the World Health Organisation, four respiratory disease categories – lower respiratory infections; COPD; tuberculosis; trachea, bronchus and lung cancer – appear in the global top ten causes of mortality, together accounting for one in six deaths, as well as one in ten disability-adjusted life-years lost. In Europe, these diseases account for one death in ten.

**Chronic diseases like COPD or asthma affect an increasing number of people worldwide. Do you know how many patients are affected by these conditions in Europe? Do you think current European health policies are well-suited to tackling the issue? What kind of feedback have you received from patient groups?**

The European Respiratory Society (ERS), together with the ELF, will publish an update on its European Lung White Book in September – with facts and figures about the burden and economic impact of lung disease in Europe. This publication will provide updated figures on COPD and asthma mortality and morbidity. The figures from the last edition, published in 2003, estimated that there were 3.4 million people living with asthma in the UK and four million in Germany. The prevalence of COPD was estimated as 4–10% of the adult population in Europe. However, we know that this figure is probably an underestimation.

The issue of non-communicable disease is of the utmost importance at the moment. The ELF has been working closely with the ERS to ensure that it is high on the EU agenda. The ELF and ERS have, for many years, called for a coordinated EU strategy on chronic diseases. We believe that more could be done at the EU level to ensure that healthcare systems are prepared to deal with the chronic disease epidemic, which we are seeing in Europe and across the globe. Patient groups are very aware of the chronic disease issue; specifically they have concerns about co-morbidities – people living with several conditions.

**Lung cancer also affects an increasing number of people. Do you think current EU health policies are capable of dealing with the issue? Is there enough emphasis on prevention and early detection? What kind of feedback have you been getting from patient groups?**

With regards to lung cancer, more needs to be done on prevention. As cigarette smoking is the primary cause of lung cancer this work must focus on tobacco control legislation. Unfortunately, legislators all too often listen to the arguments of the industry rather than to patients – who support strong and effective legislation on tobacco, and the health and economic benefits that would bring.

**Many EU countries face significant health budget cuts, leading to shorter hospital stays and less access to modern equipment (i.e. long waiting lists for MRI exams). How can patient care be promoted in this context?**

Last year the ERS held a summit on health inequalities. What came out loud and clear from that event was that cutting health budgets in times of austerity is a false economy. There is a danger that it will lead to greater health divides across Europe. Short-term savings will also have a great negative impact on health in the future. Health is in fact a big driver for the economy – better health means more wealth.

**Do you think most patients in the EU are well-informed about disease management? For instance, do they know about the latest available treatment options?**

The ELF believes that patients are not well informed about available treatment options, and that much more could be done to improve this. Often, treatment guide-

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lines are inaccessible to patients as they are written in technical language with complicated terms and are not published widely. The ELF is working to ensure that ERS guidelines and recommendations for respiratory patients are always developed with patient input – be that through working with patients on the main task force group, using surveys and questionnaires to ask specific questions or holding focus groups. The recommendations made will also be reviewed by patients and a clear and simple version of the guidelines will be written and translated into other European languages. This way it is hoped that guidelines will be more relevant to patients and that their preferences will be taken into account.

The ELF has developed an online training programme for patients to learn more about guidelines and other healthcare issues to help them become patient ambassadors ([www.EPAPonline.eu](http://www.EPAPonline.eu)).

**Do you think patients are well informed about the benefits imaging has to offer in lung disease management? Do they have an accurate idea of what radiology has to offer today?**

In general, patients are not well informed about imaging and the benefits it has to offer. The ELF is a member of AirPROM, an EU project concentrating on imaging of the airways. It has been a real eye-opener to what is now possible with imaging and what the future may hold for more personalised medicine. Patients have also been involved in this project and they are keen to make this kind of information more readily available to others.

**Do you think an initiative like IDoR 2013 can help in this regard? If yes, then how?**

IDoR can raise awareness among the public and patients of the different techniques that are available with regards to imaging that can help determine diagnosis and appropriate treatment of lung conditions. The ELF holds a biennial awareness day called World Spirometry Day, which aims to inform the public about lung health and how conditions such as COPD can be identified early on in their progression. We have certainly found, from these events, that patients are happy to learn more about their health and are empowered to go to speak further with their healthcare provider.

**What does your organisation hope to achieve by taking part in IDoR 2013?**

The ELF is happy to work with other health organisations that are trying to empower patients. As imaging can play a role in the diagnosis and treatment of lung disease then it is important to support this initiative.

**What kind of information do you think is the most important to lung / airways patients regarding medical imaging?**

Information provided should be clear, balanced, reliable and trustworthy. Respiratory patients should be aware of which imaging options should be available to them.

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**Nicola  
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joined the European Patients' Forum as its first executive director in June 2006. She was the founding director of the European Disability Forum, an umbrella organisation uniting over 70 European disability NGOs and national councils for disabled people to advocate for the human rights and inclusion of disabled citizens in Europe. She previously headed the NGO unit within the HELIOS Programme, a European Commission Action Programme promoting equal opportunities for disabled people. Prior to that, she led the Environment and Schools Initiatives Secretariat, an international government-based network set up by OECD focusing on innovation, action research and policy development in the field of Education for Sustainable Development. She has also worked as an independent consultant/evaluator, specialising in European social and development policy and health advocacy whilst in Switzerland.


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**Tomás  
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is associate professor of radiology and head of the thoracic radiology section at the Autonomous University of Barcelona. He is currently president elect of the European Society of Thoracic Imaging, from which he also received honorary membership. He also holds membership of the Fleischner Society, the European Society of Radiology, the Radiological Society of North America, the American Roentgen Ray Society (ARRS), the Society of Thoracic Imaging and the Spanish Society of Radiology. He is an editorial member of the *Journal of Thoracic Imaging* and reviewer for *Radiology*, *American Journal of Radiology*, *European Radiology* and *Journal of Thoracic Imaging*. He has received 28 international awards from prestigious organisations, including the European Society of Radiology and the ARRS. He has co-authored six books and authored 28 book chapters, over 150 papers in radiological journals and 91 peer-reviewed articles.


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is professor of radiology and chairman of the department of diagnostic radiology at the Hôpital Pitié-Salpêtrière in Paris, France. He is a former president of both the European Society of Thoracic Imaging and the Fleischner Society, and was president of the European Congress of Radiology in 2002. A pioneer in the diagnosis of chronic airway disease and chronic diffuse infiltrative lung disease using high-resolution CT, and a respected expert in chest imaging and respiratory disease, Prof. Grenier is author or co-author of almost 200 peer-reviewed articles and 60 books or book chapters. He is or was a member of the editorial boards for *European Radiology*, *Journal of Thoracic Imaging* and *Academic Radiology*. He is an honorary member of the Swedish Society of Medical Radiology, the Japan Radiological Society, the Radiological Society of North America, the Société Canadienne Française de Radiologie, the Austrian Society of Radiology, the Italian Society of Radiology, and he is also Honorary Fellow of the Royal College of Radiologists. Furthermore, he is a founding member of the Société d'Imagerie Thoracique and the European Society of Thoracic Imaging.



**David  
Hansell**

is consultant radiologist at the Royal Brompton Hospital and was appointed professor of thoracic imaging at the National Heart and Lung Institute, Imperial College, London in 1998. He has a particular interest in high resolution computed tomography (HRCT) of diffuse lung diseases, on which he has published widely. He is sent challenging HRCT scans for his opinion from every continent (except Antarctica). Prof. Hansell is the senior author of a highly regarded textbook, *Imaging of Diseases of the Chest* (5<sup>th</sup> edition, 2010, Elsevier). He has been president of the European Society of Thoracic Imaging (2005) and the Fleischner Society (2012). As well as supervising higher degrees of many research fellows, Prof. Hansell has also been host to visiting radiologists from all over the world. In 2013 he was appointed to the National Institute of Health's Senior Investigator Faculty, an award made to only 200 clinical academics across the UK.



**Claus Peter  
Heussel**

is head of diagnostic and interventional radiology with nuclear medicine at Ruprecht Karls University in Heidelberg, Germany. He has carried out research in the areas of computer-assisted quantitate image analysis of lung tissue, airway morphology and function, as well as functional CT and MRI for ventilation, perfusion and dynamic real-time imaging of the respiratory tract. Prof. Heussel is also a member of the German Centre for Lung Research and a faculty member of the European Society of Thoracic Imaging.



**Bruce J.  
Hillman**

is the founding editor and editor-in-chief of the Journal of the American College of Radiology and founder and chief scientific officer of the imaging contract research organisation, ACR Image Metrix. He is professor and former chair of the Departments of Radiology and Medical Imaging and Public Health Sciences, the University of Virginia, Charlottesville, Virginia. He has published more than 300 original articles, reviews, and editorials, including his 2010 book with Jeff Goldsmith, *The Sorcerer's Apprentice – How Medical Imaging is Changing Health Care*. He has received 22 grants as principal investigator or co-investigator, including the National Cancer Institute (NCI) UO-1 award, which led to the founding of the American College of Radiology Imaging Network®, which he chaired during 1999–2007. Dr. Hillman has presented more than 40 named and keynote lectures, is an honorary fellow of three foreign radiological societies, and has been honoured with the Gold Medals of the Radiological Society of North America, the Association of University Radiologists, and the Society of Uroradiology. He is a member of the ACR Board of Chancellors.



**Nigel  
Howarth**

is consultant radiologist responsible for chest radiology at the Clinique des Grangettes and the University Hospital of Geneva, Switzerland. He has been treasurer of the European Society of Thoracic Imaging since 2005. He is a fellow of the Royal College of Radiologists and member of the Swiss and French Radiology Societies. He has also been responsible for chest radiology on the Board of Examiners for the Swiss radiology examinations since 2002. He has co-authored more than 30 papers and book chapters. He has given more than 100 invited presentations and is a regular reviewer for *European Radiology*.



**Jung-Gi  
Im**

is professor of medicine at the Department of Radiology, College of Medicine, Seoul National University, and executive vice-president of Seoul National University. He previously served as dean of medicine at Seoul National University. His major research areas include imaging of pulmonary infections and lung cancer. Professor Im has held a number of executive positions, including president of the Korean Association of Medical Colleges and president of the Korean Council for Medical Education. He also served as president of the Organising Committee of the third World Congress of Thoracic Imaging, which was held in Seoul in 2013. He is an active member of the Fleischner Society and a fellow of the Society of Computed Body Tomography and MR. He has served as editor of the *Korean Journal of Radiology* and associate editor of the *Journal of Thoracic Imaging*.



**Hans-Ulrich  
Kauczor**

did his residency in radiology and received his habilitation degree at the University of Mainz. In 2003, he became full professor of radiology and head of the department of radiology at the German Cancer Research Center (DKFZ) in Heidelberg before being appointed chairman of radiology at the University of Heidelberg in 2008. Since then he has also been working as medical director of the department of diagnostic and interventional radiology. The main focus of his scientific work is on the field of CT & MRI of the chest and oncology. Since 1990 he has published more than 350 publications in this field. He served as president of the European Society of Thoracic Imaging in 2011. Currently, he chairs the European Society of Radiology's Research Committee and serves as president of the German-Japanese Radiological Affiliation, as well as vice-president of the Fleischner Society.



**Anna Rita  
Larici**

is a researcher in radiology and clinical radiologist in the department of radiological sciences at the Catholic University of Rome. Her main field of research is chest imaging, with particular regard to MDCT applications in lung cancer and pulmonary nodule imaging, lung perfusion, interstitial lung diseases and CAD systems. She completed a postdoctoral fellowship in chest radiology at the department of radiology at the University of California in San Francisco in 2001. She is currently a counsellor for the European Society of Thoracic Imaging and the Italian Society of Thoracic Imaging. She is a reviewer for the *European Journal of Radiology*, *European Radiology*, *Diagnostic and Interventional Radiology* and *La Radiologia Medica*. She is author and co-author of five book chapters and 20 peer-reviewed papers in radiological journals.



**Katerina  
Malagari**

is associate professor of radiology and specialises in chest radiology and interventional radiology at the 2<sup>nd</sup> department of radiology, the University of Athens, Greece. She served as a member of the Executive Committee of the European Society of Thoracic Imaging (ESTI) from 2004 to 2009 and president of ESTI in 2007. She is also a fellow of the Cardiovascular and Interventional Radiological Society of Europe and a European Board of Interventional Radiology (EBIR) diploma holder. She is the author of several chapters in five international books and 74 articles in peer-reviewed international journals. She has also served, or currently serves, as reviewer for the *Journal of Cardiovascular and Interventional Radiology*, the *European Respiratory Journal*, *Hepatology* and several Greek journals.



**Francesco  
Molinari**

is an attending radiologist and PhD fellow at the department of cardio-thoracic imaging at the University Centre of Lille. His fields of interest include HRCT of diffuse infiltrative lung diseases, pulmonary vascular diseases, and cardiac imaging, but his major focus is imaging of cardiopulmonary function. He received his board certification at the Catholic University of Rome, Italy and received additional education as a thoracic radiologist and research fellow at two major academic institutions: the German Cancer Research Center in Heidelberg, Germany, and the Beth Israel Deaconess Medical Center, Boston, MA, US. He is the author of 36 peer-reviewed publications and 100 scientific abstracts and papers. He has been a regular reviewer for several journals, including the *Journal of Magnetic Resonance Imaging*, *European Radiology*, *Investigative Radiology* and the *European Journal of Radiology*. He is a member of several professional and scientific societies, including the European Society of Radiology, European Society of Thoracic Imaging, and the Italian Society of Thoracic Imaging.



**Arjun  
Nair**

was appointed consultant radiologist with a subspecialty interest in cardiothoracic imaging at Guy's and St Thomas' NHS Foundation Trust in 2013. After completing a one-year subspecialty cardiothoracic radiology fellowship at St George's Hospital, Dr. Nair was awarded the Thoracic Imaging Fellowship at the Royal Brompton Hospital between 2011 and 2013, where he has just completed his MD thesis on computed tomography reading strategies in lung cancer screening. During his research, Dr. Nair has been actively involved in the UK Lung Screen pilot trial on lung cancer screening. He has presented at various national and international meetings and has been awarded prizes from the Radiological Society of North America, European Society of Thoracic Imaging, World Congress of Thoracic Imaging and the London School of Radiology for his presentations. He is also the author and co-author of several peer-reviewed scientific papers and book chapters on cardiothoracic imaging.



**Richard  
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is professor of radiology, executive head of the Department of Medical Imaging and Clinical Oncology, as well as chief specialist and head of the radiodiagnosis division at the Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital in Cape Town, South Africa. He is also secretary of the College of Radiologists at the Colleges of Medicine of South Africa. He previously served as head of the paediatric radiology division at the School of Child and Adolescent Health, Faculty of Health Sciences, University of Cape Town. His main research interest is the chest radiograph in HIV-infected children.



**François  
Pontana**

is assistant professor in the department of cardiovascular imaging at the University Hospital Centre of Lille. After a very productive fellowship in thoracic imaging, he oriented his medical and academic career in cardiovascular imaging towards participating actively in European and international societies devoted to this subspecialty. His key areas of research in thoracic imaging include dual-energy CT and radiation dose reduction.



**Martine  
Rémy-Jardin**

is professor of radiology and head of the department of cardio-thoracic imaging at the University Centre of Lille. Her fields of interest include HRCT of diffuse infiltrative lung diseases, pulmonary vascular diseases, and cardiac and pulmonary functional imaging, but the major focus of her research has been spiral CT imaging. Her published works comprise 220 peer-reviewed publications, 75 postgraduate publications, 377 scientific papers, and 39 books and chapters. She has been a regular reviewer for several journals, currently including *European Radiology*, and is a member of numerous professional and scientific societies, including the American Thoracic Society, the Society of Thoracic Radiology, the European Society of Thoracic Imaging (of which she is Past President), the European Respiratory Society, the French Society of Thoracic Imaging, and the French Society of Radiology, for which she served as President of the Scientific Committee from 1995 to 2006.



**Marie-Pierre  
Revel**

is professor of radiology at the Paris Descartes University, France. She is a specialist in thoracic imaging and she also works in the radiology department at the Cochin Hospital in Paris. She currently chairs the European Society of Thoracic Imaging's (ESTI) Congress Programme Committee. Her main areas of research are computer-aided diagnosis in CT, especially lung nodule volumetry, and thrombo-embolic disease. She is a member of the French Society of Radiology and the European Society of Thoracic Imaging. She is also a reviewer for *European Radiology* and the *European Respiratory Journal*. She has authored 42 peer-reviewed articles, including 7 as first author, for *Radiology* and delivered more than 100 scientific presentations and lectures.



**Santiago  
Enrique Rossi**

is head of the thoracic imaging section and chairman of the Dr. Enrique Rossi Diagnostic Centre, which is affiliated with Buenos Aires University. He has served as secretary of the Argentinean Association of Respiratory Medicine and is member of the Society of Thoracic Radiology. He sits on the editorial board of the *Journal of Thoracic Imaging*, and serves as a reviewer for various journals including *Radiographics*, *Journal of Thoracic Imaging*, *American Journal of Radiology* and *Chest*.


**Cornelia  
Schaefer-Prokop**

teaches as associate professor of radiology at Hanover Medical School, Germany. She works as clinical radiologist at the Radiology Department of Meander Medical Hospital, Amersfoort, the Netherlands, and has a research affiliation with Radboud University in Nijmegen, the Netherlands. Her main areas of research are digital radiography (image processing and dose containment), computer-aided diagnosis in CT and radiography, high resolution CT of interstitial lung diseases, and diagnosis and staging of bronchogenic carcinoma. A respected thoracic radiologist, she is currently president of the European Society for Thoracic Imaging, where she previously served as general secretary, and is an active member of the Fleischner Society. She serves as reviewer for multiple journals and is editorial member of *European Radiology*, *Radiology* and *Journal of Thoracic Imaging*. She has authored two books, numerous book chapters, and more than 100 publications in peer reviewed journals, and has delivered around 230 scientific presentations and more than 200 invited presentations.


**Arthur Soares  
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is professor of radiology at the São José do Rio Preto Medical School in Brazil. He is a member of the Society Paulista of Radiology's Scientific Committee and the Global Relations Committee of the Society of Thoracic Radiology. He is also director of the Institute Radiodiagnóstico Rio Preto. Dr. Souza has substantial experience in thoracic MRI, CT and PET/CT. He has published over 100 peer-reviewed articles and has lectured at 415 national and international conferences.


**Eric J.  
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is professor of radiology, medicine, medical education and global health, and vice-chairman of academic affairs in the Department of Radiology at the University of Washington, Seattle. He is a specialist in thoracic imaging and the author of over 100 papers, as well as seven textbooks, on chest radiology. He was the founding president of the AUR Alliance of Clinician-Educators in Radiology, is the current editor-in-chief of the journal *Current Problems in Diagnostic Radiology*, and previously served as deputy editor of the *American Journal of Roentgenology*. He is also the founding editor-in-chief of GO RAD, a global outreach journal of the International Society of Radiology. He currently serves as president of the Society of Thoracic Radiology, vice-president of the Washington State Radiology Society, chairman of the Board of Directors of the Pacific Northwest Radiology Society, and vice-chair of the International Commission on Radiology Education.


**Nicola  
Sverzellati**

has been a researcher and consultant at the University Hospital of Parma since 2010. Dr. Sverzellati's research activity is focused on imaging of interstitial lung disease, chronic obstructive pulmonary disease and lung cancer. He is also involved in a lung cancer screening trial (Multicentric Italian Lung Detection trial). He is currently secretary-general of the European Society of Thoracic Imaging (ESTI) and an elected member of the Fleischner Society. He is the author, or co-author, of 80 peer-reviewed articles, numerous abstracts for international congresses and book chapters. He is also a regular reviewer for several journals, including *Radiology*, *European Radiology*, and *Clinical Radiology*.


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**Johny A.  
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**José  
Vilar**

is head of the radiology department at Dr. Peset University Hospital in Valencia and former associate professor at the University of Valencia. He has previously served as president of the European Society of Thoracic Imaging and the Second World Congress of Thoracic Imaging. He is an honorary member of the European Society of Thoracic Imaging and the Spanish Society of Radiology (SERAM). He also holds membership of the ESR, RSNA and SERAM. He has been on the editorial board of *European Radiology* and *Radiología*. He has also been very active in thoracic radiology and management in radiology over the last 20 years, with publications in both fields and lectures at the ESTI and Management in Radiology (MIR) meetings, as well as participating in ESR, RSNA and SERAM Congresses, among others. Prof. Vilar is a frequent lecturer at European School of Radiology courses and has been responsible for the organisation of the interactive lectures at the ECR in Vienna since 2004. He has written three radiology books and numerous chapters on thoracic imaging and management. In 2010 he was appointed member of the Royal Academy of Medicine in Valencia.

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