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NEW TRENDS IN CLINICAL ONCOLOGY

Recommendations for radiological diagnosis and assessment of treatment response in lung cancer: a national consensus statement by the Spanish Society of Medical Radiology and the Spanish Society of Medical Oncology

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Abstract The last decade has seen substantial progress in the diagnostic and therapeutic approach to lung cancer, thus meaning that its prognosis has improved. The Spanish Society of Medical Radiology and the Spanish Society of Medical Oncology have therefore produced a national consensus statement to make recommendations for radiological diagnosis and assessment of treatment response in patients with lung cancer. This expert group recommends multi-detector computed tomography as the technique of choice for investigating this disease. The radiology report should include a full assessment by the TNM staging system. Lastly, when the patient is on immunotherapy, response evaluation should employ not only response evaluation criteria in solid tumours, but also immune-related response criteria.

Keywords irRC · Lung neoplasm · MDCT · Radiology report · RECIST 1.1 · TNM staging

Introduction

In 2012, lung cancer had the highest incidence and mortality rates of any cancer worldwide. In Spain, 26,715 new cases were diagnosed. This represented 12.4 % of all cancer types, making it the malignancy responsible for the most deaths: 21,118 or 20.6 % of all cancer deaths [1]. These data illustrate the importance of this malignancy in the health-care arena. The last decade has seen substantial progress in the diagnostic and therapeutic approach to lung cancer, so its prognosis has improved, especially in certain

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patient subgroups. There have been advances in diagnostic accuracy thanks to the use of new technology in the areas of pathology and molecular biology, and also in imaging. Here, a good radiological diagnosis is a really important tool in caring for the patient with lung cancer.

In the treatment sphere, too, radiological techniques play a key role. Response assessment criteria must therefore be optimised, so that the efficacy of current therapies can be measured correctly, especially in the case of targeted therapy and immunotherapy. The administration of new treatments generates special situations, and we must know how to deal with these and thus make the right decisions. However, the existence of other imaging techniques, such as positron emission tomography (PET), magnetic resonance imaging (MRI) or scintigraphy, must not be forgotten, as these are also helpful in the diagnosis and treatment of lung cancer. Caring for cancer patients requires cooperation and coordination between the various professionals involved in this task, in a multidisciplinary team working together with the sole aim of helping the patient. In lung cancer, in particular, the radiologist plays a very important role in diagnosis, tumour staging, assessing the response to different therapies, and monitoring the patient.

Therefore, the Spanish Society of Medical Radiology (*Sociedad Española de Radiología Médica*, SERAM) and the Spanish Society of Medical Oncology (*Sociedad Española de Oncología Médica*, SEOM) have decided to issue the first national consensus statement. The ultimate aim of this document, drawn up by ten experts (five radiologists and five medical oncologists), is to make evidence-based recommendations for radiological diagnosis and assessment of treatment response in patients with lung cancer. In short, this document's raison d'être is to improve care for lung cancer patients, through optimised, state-of-the-art use of the radiological techniques needed to achieve the best oncological outcome.

Radiological diagnosis of lung cancer

Technical issues in radiological examination

Multi-detector computed tomography (MDCT) is an essential tool in oncology. Recent innovations have helped improve image quality and optimise the examination procedure, seeking to balance test quality against the radiation dose received. MDCT scanners must be able to examine the chest and abdomen in apnoea, with isotropic spatial resolution, enabling post-processing to be performed. Multi-planar reconstruction (MPR) and maximum intensity projection (MIP) reconstruction are always advisable for assessing central vascular invasion and the tumour's relationship to nearby structures. Minimum intensity projection (MinIP) reconstruction and virtual bronchoscopy may also be helpful. The most recent technological developments have brought dual-input, 256/320 detector scanners, with sub-millimetre isotropic spatial resolution and temporal resolution of $\leq$100 ms, permitting dynamic perfusion studies that help quantify and monitor tumour angiogenesis [2, 3].

In our opinion, the evaluation should be performed with intravenous contrast, approximately 90 mL being administered at 3–4 mL/s. This makes it possible to assess vascular and mediastinal structures and the abdomen in the portal phase in a single scan. The examination should cover the supraclavicular region to the iliac crests, in search of the most common extrathoracic sites for metastases.

MDCT is the radiodiagnostic technique that contributes most to the collective radiation dose. Dose modulation and iterative reconstruction can considerably reduce the effective dose by up to 70–75 % [4, 5, 6]. The new Euratom Directive 2013/59, published on 17 January 2014, urges member states to ensure the existence of quality assurance programmes and evaluation of patient dose ranges, which should be reflected in medical records [7].

It is advisable to use bismuth shields, which reduce the breast radiation dose by 40–60 % without compromising the examination results [8, 9]. In the case of pregnancy, the dose should be reduced as far as possible, by lowering both mAs and kilovolts. Only chest MDCT should be performed, and oral barium should be administered to minimise the dose that reaches the foetus. There are no human studies demonstrating foetal harm from the use of iodinated contrast material. The risk of thyroid dysfunction is accepted, so all neonates who have been exposed must undergo a thyroid screening test at birth. On the other hand, the most recent guidelines recommend not discontinuing breastfeeding [10, 11].

The toxicity reactions seen with this technique are nephrotoxicity, neurotoxicity, heart problems, and vasodilatation. Hypersensitivity reactions can be immediate (<1 h) or non-immediate (>1 h). Thirty percent (30 %) of non-immediate and 43 % of immediate reactions occur on first exposure [12]. Non-immediate reactions can appear up to 1 week after the radiological procedure. With severe immediate reactions, it is inadvisable to conduct further examinations with iodinated contrast agents. With mild and moderate immediate reactions, the patient's risk/benefit should be assessed, products should be chosen on the basis of negative allergy tests, and the use of premedication should be considered. With non-immediate reactions the product that triggered the reaction should be avoided, as should any others that test positive, and the use of premedication should be considered [13].

Gadolinium-enhanced MRI might be a useful supplement to MDCT in the case of allergy to iodinated contrast.

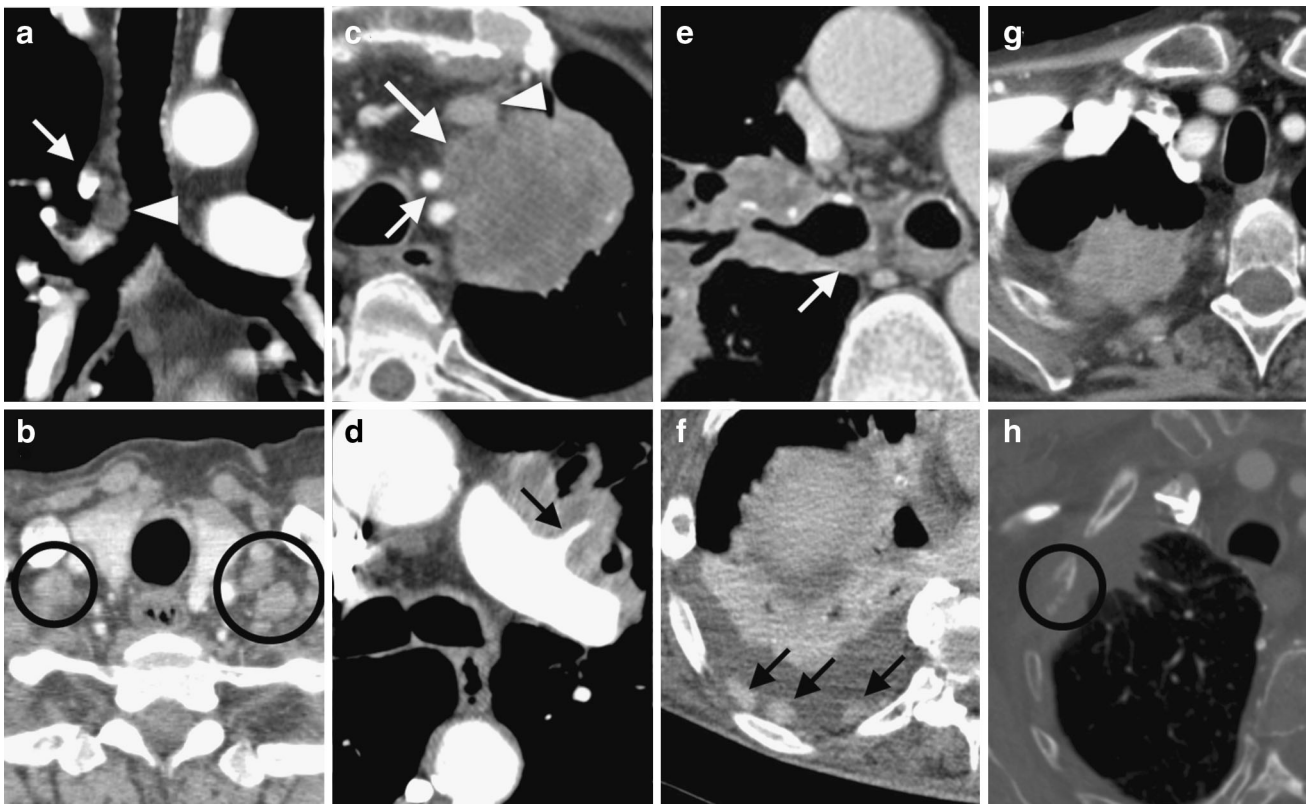

Fig. 1 TNM staging. **a** Hilar lymphadenopathy (N1) (*arrowhead*), caudad to the arch of the azygos vein (*arrow*); in a cephalad direction there are other lymph nodes, of small size, in 4R territory. **b** Bilateral supraclavicular lymphadenopathies (N3). **c** Invasion of the mediastinal fat (*large arrow*) (T4) in contact with the left subclavian and carotid arteries (*small arrow*) and the ipsilateral brachiocephalic vein (*arrowhead*). **d** Probable invasion of the left pulmonary artery (T4) with encasement of the superior lobar branch (*arrow*). **e** Invasion with stenosis of the right superior lobar bronchus and thickening of the posterior wall of the main bronchus (*arrow*) to within 2 cm of the carina (probable T3). **f** Right pleural effusion with nodular thickenings of the parietal pleura (*arrows*) (M1a). **g** Right upper lobe lesion protruding into the extrapleural fat (probable T3, but may represent associated inflammatory changes in some cases). **h** Right upper lobe lesion in extensive contact with the peripheral pleura and invasion with costal osteolysis (T3)

Gadolinium must not be used during pregnancy because foetal safety has not been demonstrated [14]. Patients with renal insufficiency should be categorised by their glomerular filtration rate [15]. Based on this, appropriate steps to take are: limit the contrast dose, discontinue nephrotoxic drugs, add isotonic saline solution (1 mL/kg every 12 h) pre- and post-contrast, use sodium bicarbonate, and consider the use of haemofiltration [16, 17].

Full description of the primary tumour

Radiological assessment in the diagnosis and staging of lung cancer should be based on the TNM classification, a system devised in the mid-twentieth century by Pierre Denoix and standardised in 1987 by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Its current version is the seventh, published in January 2010 [18, 19]. This classification is based on the analysis of three descriptors: (1) "T", which basically assesses the main tumour; (2) "N", which assesses lymph node involvement in the territories draining the tumour, and (3) "M", which assesses metastatic involvement. Based on this information, certain categories of the various descriptors are grouped together according to their prognosis into tumour stages (Fig. 1).

The T descriptor

This basically assesses the size and local invasiveness of the primary tumour. It is important for prognostic assessment and evaluating the resectability of the tumour.

T1 tumours are up to 3 cm in size, are surrounded by lung or visceral pleura, and show no bronchoscopic invasion of the main bronchus, with the uncommon exception of superficial spreading tumours, which show invasion confined to the bronchial wall. In this case, they are considered T1, although they affect the main bronchus. If they do not exceed 20 mm they are T1a, whereas those measuring 21–30 mm are T1b.

T2 tumours are between 31 and 70 mm in size, up to 50 mm for T2a and 51–70 mm for T2b. They must not involve the main bronchus within 2 cm of the carina. As the right main bronchus is very short, its involvement will often fail to meet the T2 criteria. This assessment, which will determine tumour resectability, is not very accurate by computed tomography (CT) [20] and is better by endobronchial ultrasound (EBUS). Tumours that invade the visceral pleura are also T2. Although this factor does not affect tumour resectability, it alters the disease prognosis [21]. CT is not very sensitive for its detection and ultrasound is an alternative technique in this case, although not yet validated. Transfissural invasion of a neighbouring lobe is included in this category, provided the size criterion is not exceeded [22]. Also categorised as T2 are central tumours invading only the hilar fat, and those causing atelectasis or pneumonitis from the hilum without involving the entire lung. It can be difficult to delimit the tumour radiologically and distinguish it from secondary obstructive lung changes.

T3 tumours include those greater than 70 mm, those associated with an additional tumour nodule in the same lobe, and those of any size with invasion of potentially resectable structures, such as the main bronchus less than 2 cm from the carina but not invading it, the chest wall, the diaphragm, the mediastinal pleura, the parietal pericardium or the phrenic nerve, as well as those causing atelectasis or pneumonitis of the entire lung. Parietal invasion does not rule out tumour resectability, but affects the prognosis and influences surgical management. Although the criteria for its assessment have been described (an obtuse angle with the wall, more than 3 cm contact with the pleural surface, pleural thickening, and no fat plane) [23], the only certain criterion is bone invasion. Ultrasound is a promising technique for assessing this [24]. On the other hand, invasion of the phrenic nerve can be suspected when the tumour makes contact with the course of the nerve, in association with a raised hemi-diaphragm.

Lastly, T4 tumours are malignancies with a tumour nodule located in another ipsilateral lobe, as well as tumours of any size invading unresectable neighbouring structures, such as the mediastinum (tumour extending to the mediastinal fat), recurrent laryngeal nerve, heart, visceral pericardium, trachea or carina, vertebral body, oesophagus, or great vessels (aorta, superior and inferior vena cava, main pulmonary artery, and intrapericardial portions of the right and left pulmonary arteries and pulmonary veins).

In central tumours, mediastinal invasion may be evident during CT or there may only be contact between the tumour and the mediastinum. Radiological features for distinguishing between contact and vascular invasion have been described, such as more than 3 cm contact, no separating fat plane, or more than 90° or 180° contact with the outline of the aorta, although their level of accuracy is very low [19, 25–27]. Since the advent of anti-angiogenic drugs, this issue has become crucially important because encasement or invasion of major blood vessels and bronchial vessels are the only radiological signs of bleeding risk associated with anti-angiogenic treatment [28]. On the other hand, although cavitation at baseline or on treatment is not included in TNM, and has not been shown to be a clear risk factor for bleeding [28], it is advisable to describe it. Therefore, until more well-defined criteria are established, it is recommended that all these parameters should be fully described in clinical practice, to enable the best possible treatment decision to be made.

The N descriptor

In radiological staging, lymph nodes with a short axis of over 10 mm are considered pathological with little diagnostic accuracy [29, 30]. The lymph node stations included are those that directly drain lung tumours, i.e. intrathoracic, scalene, supraclavicular and low cervical lymph nodes. Direct lymph node invasion by the tumour is regarded as N, and lymph nodes located above the lower margin of the cricoid cartilage are M1b, as are those of the extrapleural fat in cases of wall invasion. A new standardised lymph node map defines the anatomical boundaries of each station [31]. It is important to note that in paratracheal areas (2 and 4), the boundary between right and left does not lie on the anatomical mediastinal midline, but on the left border of the trachea or oncological mediastinal midline.

Tumours with lymphadenopathies in ipsilateral intrapulmonary, peribronchial, and hilar lymph nodes, i.e. lying within the visceral pleura (stations 10–14), are N1.

Tumours with lymphadenopathies in ipsilateral mediastinal and midline, prevascular, retrotracheal, and subcarinal lymph nodes (stations 2–9) are N2.

Tumours with lymphadenopathies in contralateral hilar or mediastinal and ipsi- or contralateral scalene, supraclavicular, and low cervical lymph nodes (station 1) are N3.

The M descriptor

This descriptor refers to metastases, which can be intra- or extrathoracic. Although lymphangitis carcinomatosis is not addressed in the current TNM, the worse prognosis it implies makes it advisable to consider it [19].

M1a tumours are those that have contralateral pulmonary nodules and malignant pericardial or pleural involvement not due to contiguity. This involvement may occur as thickenings or nodules, or take the form of an effusion. In this case ultrasound assessment is useful [32], making it easier to select where to aspirate fluid and detect solid foci,

Table 1 Suggested initial radiology report for lung cancer

Report order	
Specialist responsible: oncologist, radiotherapist, surgeon, or chest physician	
Descriptor parameter	Report features
Reason, treatment given, and purpose	Reason (screening, diagnosis, response assessment)
	Treatment given (surgery, chemotherapy, radiotherapy, targeted molecular therapies)
	Purpose of treatment (salvage surgery, radical, palliative)
Tumour characteristics	Histology
	TNM at diagnosis
	Molecular characteristics of tumour (EGFR, ALK)
Date of image to compare against	The order should include the date of the test against which to compare images (baseline, pre-treatment or, in the case of advanced disease, date of maximal RECIST 1.1 response)
Evaluation report	
Specialist responsible: radiologist	
Descriptor parameter	Report features
T	Longest diameter in the axial plane
	In the case of a pulmonary nodule with ground-glass opacity
	Diameter excluding ground-glass component
	Diameter including ground-glass component
	Airway involvement
	Most proximal involvement
	Trachea
	Main bronchus >2 cm from the carina
	Main bronchus <2 cm from the carina
	Lobar bronchus
	Interlobar bronchus
	Segmental bronchus
	Afferent bronchus
	Arterial involvement
	Supra-aortic trunks
	Aorta
	Pulmonary artery
	Main pulmonary artery
	Right or left pulmonary artery
	Superior lobar artery (anterior trunk) or interlobar artery
	Direct branches of interlobar artery (middle lobar/lingular or inferior lobar)
	Segmental arteries
	Venous involvement
	Superior vena cava
	Azygos vein
	Superior pulmonary vein
	Inferior pulmonary vein
	Left atrium
	Invasion of major vessels (arteries and/or veins): yes/no/indeterminate
	Peripheral invasion
	Pleural
	Extrapleural/chest wall
	Bone
	Transfissural

Table 1 continued

Evaluation report	
Specialist responsible: radiologist	
Descriptor parameter	Report features
	Mediastinal
	Pericardial
	Additional nodules
	In the same lobe
	In another ipsilateral lobe
	Atelectasis/pneumonitis
	Part of the lung
	Entire lung
	Lymphangitis
	cLy0 (no lymphangitis)
	cLy1 (around tumour)
	cLy2 (at a distance in the same lobe)
	cLy3 (in another ipsilateral lobe)
	cLy4 (in the contralateral lung)
	Cavitation: yes/no
N	Lymph node territories by the TNM classification (7th edition) with lymph nodes displaying features suggestive of malignancy (size)
	Scalene/supraclavicular involvement
M	Additional nodule in the contralateral lung
	Pleural effusion
	Pleural nodule/thickening
	Pericardial effusion
	Pericardial nodule/thickening
	Extrapulmonary (lymph nodes not in N territories, adrenal, bone, hepatic, soft tissues, peritoneal, etc.)

EGFR epidermal growth factor receptor, *RECIST* response evaluation criteria in solid tumours

from which to take a needle biopsy for cytological or histological tests.

M1b tumours have distant metastasis, which includes lymphadenopathies located in territories other than those described for the N descriptor.

Description of the radiology report

In the management of lung cancer, the radiological evaluation is a key issue in the decision-making on which the oncologist bases his or her treatment strategy. Reports containing a full, correct description of the pathology are therefore crucial throughout the disease, and achieving them requires cooperation from both the professional who orders the investigations and the radiologist who interprets them. An order for radiological assessment must include the important information that enables the radiologist to interpret the findings correctly. The reason for ordering it should first be stated (screening, diagnosis, assessment of treatment response) together with treatment received, if applicable, and its purpose [surgery, chemotherapy, radiotherapy, new targeted therapies such as tyrosine kinase inhibitors (TKIs) or anti-angiogenics]. When possible, the order should include information both on the disease and on tumour histology and molecular features, such as epidermal growth factor receptor (EGFR), or anaplastic lymphoma kinase (ALK), and TNM at diagnosis. If ordering an assessment of treatment response, it is important to include the date of the earlier test against which to compare the images, as well as the target lesions selected and the date of maximal response.

The radiology report will define subsequent therapeutic approach, so correct, detailed interpretation of the images is important. Evaluation should be morphological, i.e. by CT, and define the levels of tumour involvement that affect TNM and assessment by response evaluation criteria in solid tumours (RECIST), if necessary. In diagnosis, radiological description of tumour characteristics is crucial when deciding on the initial therapeutic approach of the disease. The report must include a full assessment of TNM descriptor characteristics, as well as other relevant data (Table 1). In advanced disease, radiological description of

vascular invasion is an exclusion criterion for treatment with anti-angiogenic drugs, so it is essential for the radiology report to include an overall assessment of tumour invasion of major vessels.

Treatment response assessment criteria in lung cancer

Treatment scenarios in lung cancer

Radiology plays a key role in lung cancer, not just as a diagnostic and initial staging procedure, but as an excellent method for assessing treatment response. In lung cancer, the latest RECIST guideline (Version 1.1) is the universal method for assessing response to cancer treatment, whether chemotherapy, radiotherapy, or new targeted treatments. It basically concerns three possible treatment scenarios: (1) in early stages (I–II) treated with induction chemotherapy (before surgery) or adjuvant chemotherapy (after resection), (2) in locally advanced disease (N2–N3) treated with induction (chemotherapy ± radiotherapy), where assessment of treatment response will be vital for deciding on salvage surgery, and after radical treatment (chemotherapy + radiotherapy) for tumours not suitable for surgery, and lastly (3) in advanced disease (IV), for assessing the efficacy of cancer treatment for palliative purposes.

However, the last few years have seen major changes in the treatment of advanced lung cancer following the advent of a new generation of molecular therapies, such as TKIs (including erlotinib, gefitinib, afatinib and crizotinib) or anti-angiogenic therapy (such as bevacizumab), with very different mechanisms of action and response patterns from chemotherapy and radiotherapy. Nevertheless, the new revised version of the unidimensional criteria contained in RECIST 1.1 is still applicable for assessing the response to these new targeted therapies [33], although their anti-tumour activity is often not reflected accurately. Another incipient field of development in lung cancer is immunotherapy. Like molecular therapy, immunotherapy shows a specific response pattern which, in this case, is reflected in the bidimensional immune response criteria or immune-related response criteria (irRC) [34]. These criteria should be more representative than RECIST in assessing the immune response, so they are being used in the context of clinical trials of immunotherapy in lung cancer.

Application of RECIST criteria and inclusion in the report

The radiologist member of a multidisciplinary team devoted to lung cancer must be able to measure tumour burden in CT scans and degree of treatment response using RECIST, because these criteria are widely used in clinical trials and routine clinical practice, albeit with limitations in the case of the new cytostatic drugs. RECIST Version 1.1 is simpler than Version 1.0 because it involves measuring fewer lesions and contains other modifications that affect the radiology report on baseline and repeat scans, which must be done using the same modality and imaging parameters [33, 35–41].

Radiology report on the baseline scan

The radiology report on the baseline scan should include information on the following issues:

- Selection and unidimensional measurement of the longest diameter of target lesions, with a maximum of 5 lesions and 2 per organ (RECIST 1.0 said a maximum of 10, and 5 per organ), choosing the largest and most easily reproducible lesions. These lesions must be measurable, i.e. longest diameter $\geq$10 mm (assuming a CT slice thickness of $\leq$5 mm) in the axial plane. RECIST 1.1 accepts sagittal or coronal measurements if reconstructions are isotropic.
- Lymphadenopathies are measured along the short axis and can be target lesions, if $\geq$15 mm in size. Lytic or mixed bone metastases can also be target lesions, if they have a measurable soft tissue component. Cystic metastases can be target lesions, but it is preferable to use solid lesions.
- Description of the other lesions (non-target), without measurements, including measurable and non-measurable lesions, i.e. with longest diameter <10 mm, lymphadenopathies with short axis $\geq$10 and <15 mm, ascites, pleural and pericardial effusion, lymphangitis carcinomatosa, leptomeningeal metastases, bone metastases with no soft-tissue mass, and lesions previously irradiated or treated locally.
- The sum of target lesion diameters, which will serve as a reference for repeat examinations. Figure 2 shows target and non-target lesions in the baseline scan of an adenocarcinoma of the lung.

Radiology report on follow-up scans

The radiology report on follow-up scans should include information on the following issues:

- Measurement of the longest diameter of target lesions, which may differ in orientation from the baseline scan. If lesions are confluent, the longest diameter of the resulting lesion should be measured. If a target lesion becomes fragmented, the sum of the longest diameters of the resulting lesions should be measured. If a lesion shrinks so much that it cannot be measured, it is

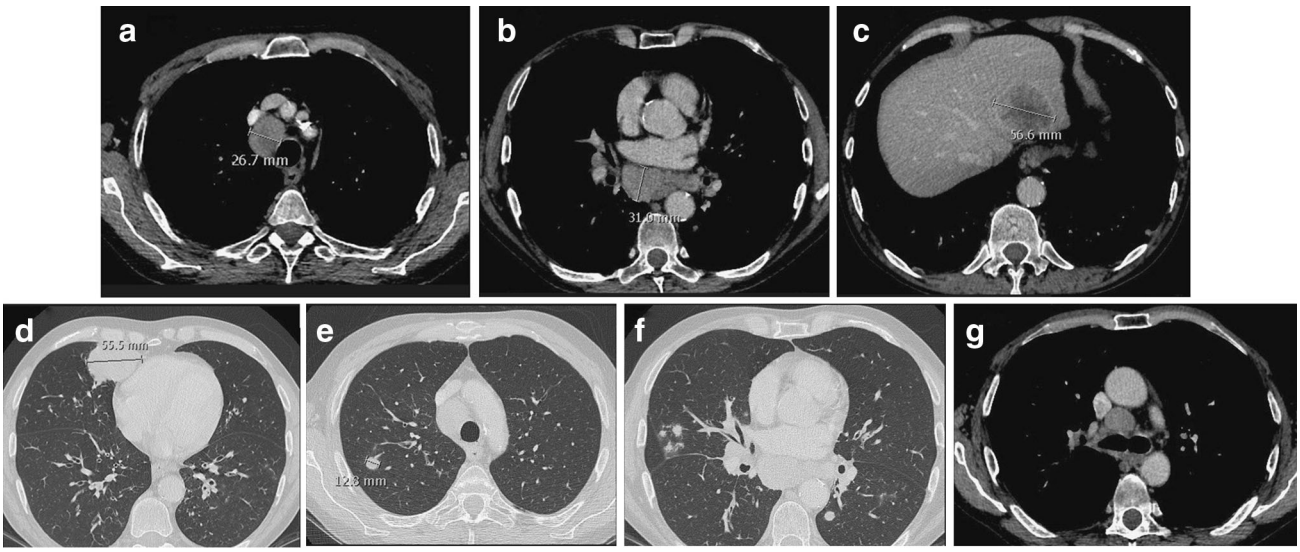

Fig. 2 Target (**a**–**e**) and non-target (**f**–**g**) lesions in the baseline scan of an adenocarcinoma of the lung. **a**, **b** Mediastinal lymphadenopathies measured along the short axis. **c** Hepatic metastasis. **d** Mass in middle lobe. **e** Metastatic pulmonary nodule. **f** Bilateral multiple pulmonary nodules. **g** Mediastinal lymphadenopathy. The sum of target lesions is 181 mm

assigned a measurement of 5 mm. In the case of lymphadenopathies, their short axis measurement is recorded, even if <10 mm (Table 2).

- The appearance of necrosis within lesions, if necessary. This is not a RECIST treatment response criterion, but these criteria are suggested in Appendix III of the guideline.
- Assessment of treatment response according to the sum of target lesions and qualitative assessment of non-target lesions.
- For target lesion progression to be established, based on the smallest measurement obtained throughout the study (nadir) and RECIST 1.1, the increase must be ≥5 mm and ≥20 %.
- The unequivocal appearance of new malignant lesions is considered progressive disease. The appearance of new lesions seen by PET, not present in the baseline CT scan and confirmed by CT, is also considered disease progression according to RECIST 1.1. The appearance of lesions in areas not included in the baseline scan is also regarded as progressive disease.
- In the case of progression of "non-target" lesions with stabilisation or treatment response by "target" lesions, careful assessment by the clinician is advised, for example, on the appearance of pleural effusion.

Post-radiotherapy response assessment

Radiation pneumonitis

Radiation pneumonitis can occur 1–6 months after external radiotherapy of the chest [42–44]. It is estimated that 13–37 % of patients develop clinically meaningful pneumonitis after radical doses of radiotherapy and may require steroid treatment.

Post-radiotherapy fibrosis

Post-radiotherapy fibrosis in the irradiated area tends to be seen 6–12 months after this treatment is administered, often with no previous clinical features of radiation pneumonitis [42, 43]. CT manifestations consist of an area of atelectasis with traction bronchiectasis confined to the irradiated area. This may progress for up to 24 months, and thickening or pleural effusion may also develop. To assess this condition, it is important to know the radiotherapy technique used on the patient (Fig. 3).

Tumour response assessment

CT assessment of post-radiotherapy tumour changes is hindered by surrounding alterations caused by pneumonitis or fibrosis. Evaluation relies on the availability of follow-up CT scans performed using a similar technique following the injection of iodinated contrast material. In the first few months, performing a PET/CT scan of the patient is not helpful, as there may be false positives due to pneumonitis [45]. When complete disease remission is achieved, early CT detection of tumour recurrence in irradiated areas is difficult. It is important to compare repeat CT scans against each other; tumour recurrence is manifested as the appearance or growth of a soft tissue opacity within the area of post-radiotherapy fibrosis. In dubious cases, the

Table 2 Suggested follow-up radiology report for lung cancer

Give measurements of all target lesions, including lymphadenopathies even if the short axis has decreased to <10 mm, and their S. Include description of possible necrosis/cavitation
Radiological interpretation of target lesion response
CR: disappearance of all lesions and all lymph nodes <10 mm along the short axis
PR: ≥30 % decrease in S compared with baseline scan
SD: non-PR, non-PD
PD: increase in S of ≥20 % and ≥5 mm compared with the smallest sum obtained during follow-up
Radiological interpretation of non-target lesion response
CR: disappearance of all lesions and all lymph nodes <10 mm along the short axis
Non-CR, non-PD: persistence of lesions
PD: unequivocal increase in measurable and/or non-measurable lesions
New-onset lesions
Yes → progression
No
Dubious → Assess at the next checkup
Interpretation of radiological overall response
CR: CR of target and non-target lesions
PR
CR of target lesions; non-target lesions non-CR, non-PD, or NE
PR of target lesions; non-target lesions non-CR, non-PD, or NE
SD: SD of target lesions; non-target non-PD/NE
PD: PD target lesions and/or PD non-target lesions and/or new lesions
NE: target lesions NE

CR complete response, *NE* not evaluable, *PD* progressive disease, *PR* partial response, *S* sum, *SD* stable disease

patient can have a PET/CT scan. Using this test, disease recurrence shows up as high uptake of fluorodeoxyglucose (FDG) within the irradiated area.

Special situations

The development of targeted cancer therapies represents a major advance in cancer treatment. Targeted molecular therapies with non-cytotoxic drugs are intended to specifically disrupt the aberrant biological pathways involved in tumorigenesis, in contrast to the generalised cytotoxic effect of conventional chemotherapy. Although they have some limitations, the RECIST criteria, based on tumour size, are widely used and well accepted for evaluating the treatment response of solid tumours treated with conventional cytotoxic chemotherapy [46]. However, these criteria take no account of modest, long-term tumour responses or prolonged disease stabilisation, which drugs such as gefitinib, erlotinib, and bevacizumab are known to be capable of producing [47]. The effects of new treatment modalities, such as angiogenesis inhibitors and antivascular therapies, are more complex than simple size changes. These drugs often produce necrosis and cavitation in the tumour, without any significant change in its size. This means that the effect of targeted therapy is often underestimated when evaluated by RECIST. Alternative methods have therefore been suggested to measure tumour treatment response using new imaging techniques, such as functional and molecular imaging techniques.

Cavitation

Cavitation can occur initially in lung cancer, especially squamous cell carcinomas, but also less commonly in adenocarcinomas. The development of tumour cavitation is common in lung lesions treated with anti-angiogenic drugs. In one study, cavitation was observed in 24 % of patients treated with anti-angiogenic drugs and none of those treated with classical chemotherapy [48]. It was suggested that the diameter used should not be the one defined by the RECIST criteria, but the Crabb diameter, which is obtained by subtracting the longest cavitation diameter from it. This method allowed better assessment of treatment response, by including cavitation in the size measurement of target lesions [48] (Fig. 4).

Necrosis

In addition to lesion size changes and cavitation, changes in tumour attenuation can appear due to the presence of necrosis and bleeding. In a study on gastrointestinal stromal tumours (GISTs) [49], tumour necrosis was assessed by measuring CT attenuation in Hounsfield units in pre- and post-treatment contrast-enhanced CT scans. Based on the results of this study, a set of response criteria incorporating tumour attenuation, called the Choi criteria, have been proposed. These criteria have been included in some studies assessing lung response to anti-angiogenic drug treatment [50].

Perfusion

Many functional imaging techniques exist, involving CT, MRI, PET, or ultrasound [46]. In lung cancer, the functional imaging technique most widely used at present is CT perfusion imaging. This technique makes it possible to evaluate tumour vascularisation by means of temporal analysis of attenuation changes in blood vessels and tissues during the rapid acquisition of several series of images using intravenous contrast [51]. The parameters most commonly assessed are blood flow, blood volume, and

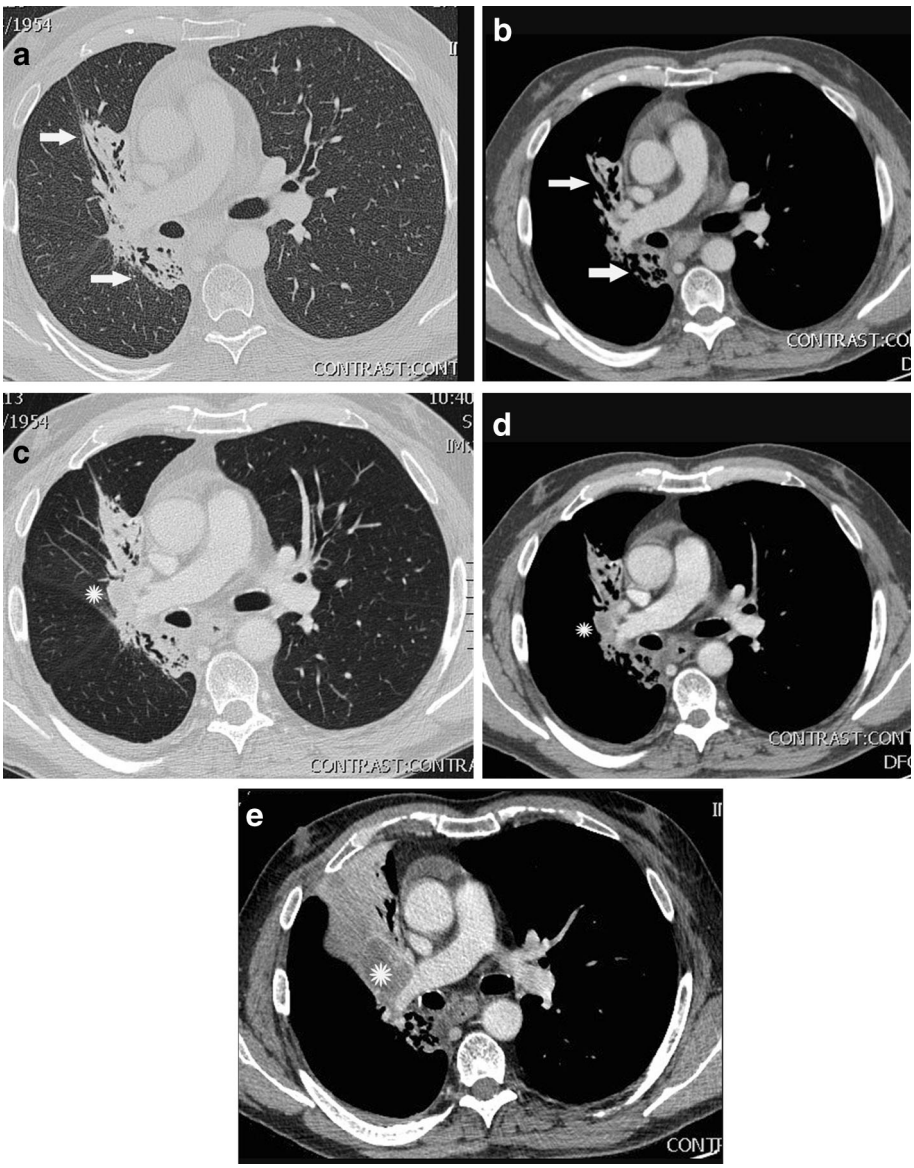

Fig. 3 Post-radiotherapy fibrosis and subsequent tumour recurrence in a 54-year-old man treated with chemotherapy/radiotherapy for small cell lung carcinoma. Multidetector CT scans with intravenous contrast. Lung (**a**) and mediastinal (**b**) windows in a CT scan done 2 years after chemotherapy/radiotherapy. The patient was in complete remission. Post-radiotherapy fibrosis with atelectasis and traction bronchiectasis confined to the irradiated field can be seen (*arrows*). Lung (**c**) and mediastinal (**d**) windows in a CT scan done 3 years 6 months after chemotherapy/radiotherapy. A rounded opacity of soft tissue density can be seen in a right parahilar position. This was not visible in earlier serial CT scans and is consistent with tumour recurrence (*asterisks*). There were no other CT findings. **e** Mediastinal window in a CT scan done 3 years 10 months after chemotherapy/radiotherapy, showing marked growth of the right hilar mass (*asterisk*) and associated obstructive atelectasis. There were also multiple liver metastases (not shown). *CT* Computed tomography

permeability. These parameters have been correlated in terms of pathology with angiogenesis, tumour vascularisation, and necrosis [52–55], and are helpful in assessing tumour response in patients treated with anti-angiogenic drugs [56–58]. The latest studies agree that CT perfusion imaging is not just a suitable technique for assessing treatment response, but is also sensitive enough to detect early changes in tumour vascularisation that may predict treatment response (Fig. 4). The main limitation to extending the use of CT perfusion imaging in clinical trials is the lack of consistency between existing protocols and differences between the various commercial brands. The first clinical guidelines designed to standardise the approach were recently published, and protocols have been drawn up for the use of CT perfusion imaging in clinical trials [51].

Follow-up frequency in patients with lung cancer

Follow-up frequency in patients with lung cancer is a controversial issue that must be tailored to the individual. In patients who have had surgery, follow-up CT is recommended every 6–12 months for the first 2 years and annually thereafter [59].

In first-line treatment, it is recommended that treatment response be evaluated 9 or 12 weeks after treatment begins. Depending on individual clinical judgement, a repeat scan might be perfomed after 6 weeks, but this tends to be indicated when there is suspicion of early disease progression or toxicity, or when it is desirable to evaluate treatment response earlier than usual for any reason.

The optimal clinical and radiological monitoring for patients with advanced non-small cell lung cancer

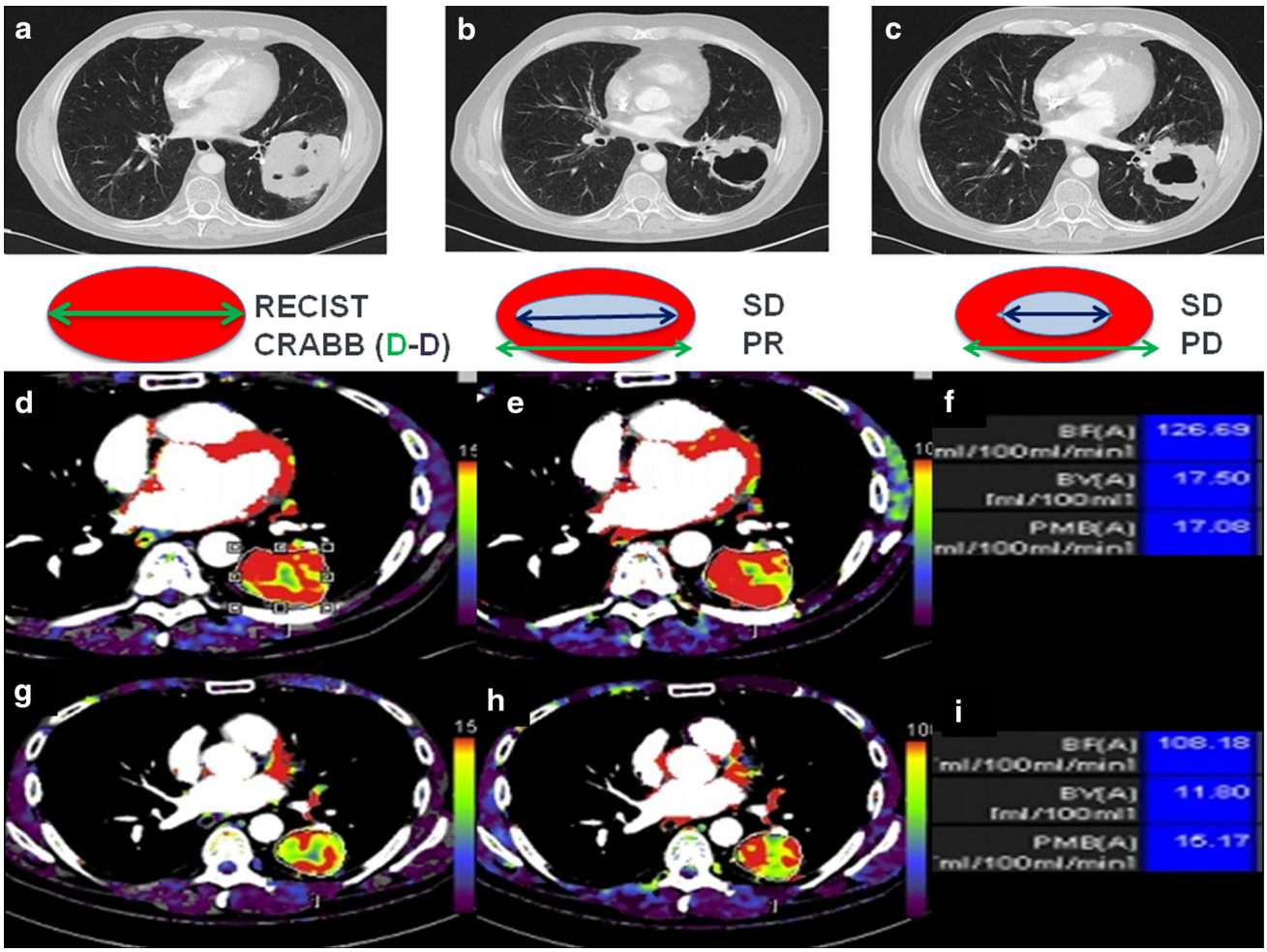

Fig. 4 RECIST and Crabb diameters and CT perfusion imaging of an LLL lung mass. **a** LLL lung mass with minimal cavitation with the same diameter as measured by RECIST and the Crabb method. **b** Post-treatment the lung mass displays a large cavitation. By RECIST, which considers only tumour size, this is stable disease, whereas subtracting the cavitation diameter from the RECIST diameter, according to Crabb, gives a partial response. **c** At a subsequent check-up the solid component of the lesion has visibly increased, representing stable disease by RECIST and progression according to Crabb. CT perfusion imaging of other lung neoplasm in LLL prior to commencing treatment: **d** blood volume imaging; **e** blood flow imaging; **f** numerical values for blood volume, blood flow and permeability. CT perfusion imaging 10 days after commencing anti-angiogenic treatment: **g** blood volume map; **h** blood flow map; **i** numerical values for blood volume, blood flow and permeability, showing a reduction in all perfusion parameters with no visible changes in lesion size by RECIST. *CT* Computed tomography, *LLL* left lower lobe, *PD* progressive disease, *PR* partial response, *RECIST* response evaluation criteria in solid tumours, *SD* stable disease

(NSCLC), once the proposed cancer treatment has finished, is not very clear, because there is limited evidence available in the literature. The type of follow-up a patient has should essentially be based on the treatment plan decided at the time of disease progression [60]. Patients not eligible for active cancer therapy in successive lines of treatment should not undergo follow-up with additional radiological investigations. In view of the proven survival benefit in patients treated with second-line chemotherapy, and the fact that only 60–65 % of them reach this treatment scenario because of the aggressive nature of this cancer, these patients need to be monitored closely after they finish first-line chemotherapy. It is advisable for them to undergo clinical and/or radiological evaluation 6 weeks after finishing treatment and then every 6–12 weeks to enable second-line therapy to commence promptly.

Conclusions

MDCT is the technique of choice for investigating lung cancer. It should be done with intravenous contrast to assess vascular and mediastinal structures and the abdomen in the portal phase.

The examination and subsequent radiology report should include a full assessment of the characteristics of

the TNM staging system descriptors. The primary tumour should be described thoroughly, providing information on location, measurement, involvement of adjacent structures, and potential vascular invasion. Radiology is also the method of choice for evaluating treatment response using the latest RECIST guideline (Version 1.1). It is important to assess treatment response in target and non-target lesions, describe whether any new lesions have appeared, and give an overall interpretation. Clinicians should therefore provide the necessary information about the patient, disease type, and treatments received. On the other hand, when the patient is on immunotherapy, bidimensional immune response criteria (irRC) should also be used. Lastly, although tumour response test frequency is a controversial issue, a first assessment is recommended 6–12 weeks after commencing treatment. Subsequently, evaluations should be done every 6–12 weeks after finishing treatment and, in any case, the type of follow-up a patient has should essentially be based on the treatment plan decided at the time of disease progression.

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