New radiological approaches in lung cancer to evaluate tumor response to new treatments (targeted therapies and immunotherapy): morphological and functional imaging

Mariana Benegas Urteaga, I. Vollmer, N. Reguart, R. Perea, T. de Caralt, Marcelo Sanchez
Department of Radiology
Hospital Clínica de Barcelona, Barcelona, SPAIN
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Learning Objectives

- To show morphologic and functional changes in lung cancer treated with targeted and conventional chemotherapy
- To describe the role of multidetector CT and functional imaging (CT perfusion, Dual-Energy CT, positron emission tomography and MRI) in the evaluation of the treatment response
- To illustrate case-based lung cancer response evaluation approaches comparing anatomic and functional imaging with RECIST criteria
- To show Immune-Related Response Criteria in patients treated with immunotherapy
Introduction

- Treatment strategies in lung cancer changed over the past decade from cytotoxic chemotherapy to different targeted therapies.
- Targeted therapies are designed to interfere with specific aberrant biological pathways involved in tumourigenesis. Various mechanisms relevant in carcinogenesis are exploited by molecularly targeted therapies, such as angiogenesis, cell growth signalling and apoptosis.
- This change in development pattern of anti-cancer drugs is questioning traditional ways of assessing tumor response.

**RECIST 1 and 1.1** (response evaluation criteria in solid tumors) and **WHO** (World Health Organization) criteria for tumor evaluation were developed based in **uni or bidimensional measurements**. They are widely applied and well accepted.

**BUT:**
- The effects of the **new therapeutic modalities**, such as tyrosine kinase inhibitors, angiogenesis inhibitors and anti-vascular therapies, are complex
- **Necrosis and cavitation** without a change in size are frequently observed
- Thus, the **effect of targeted therapy is often underestimated by using tumor size based on RECIST evaluation**
The Evolution Of Non-small cell lung cancer (NSCLC) Approach

1999
Histology-driven selection

2002
Identification of oncogenic drivers*

2009
Consolidation of molecular-targeted agents in NSCLC treatment

<table>
<thead>
<tr>
<th>2008</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR Mu</td>
<td>ALK+</td>
</tr>
<tr>
<td>EGFR WT</td>
<td>BRAF Mu</td>
</tr>
<tr>
<td>EGFR Mu</td>
<td>ROS+</td>
</tr>
<tr>
<td>MET+, Ret, Her2,</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy (Checkpoints inhibitors)</td>
<td></td>
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</table>

Current standard of NSCLC care

*Incidence of mutations in adenocarcinoma provided as an example
**Chemotherapy**

- Bevacizumab (Avastin)
- Ramucirumab (Cyramza)

**Targeted Therapy**

**Drugs that target tumor angiogenesis**
- Bevacizumab (Avastin)
- Ramucirumab (Cyramza)

**Drugs that target cells with EGFR changes**
- EGFR inhibitors with *EGFR* gene mutations: Erlotinib (Tarceva), Afatinib (Gilotrif), Gefitinib (Iressa)
- EGFR inhibitors that also target cells with the T790M mutation: osimertinib (Tagrisso)
- EGFR inhibitors used for squamous cell NSCLC: Necitumumab (Portrazza)

**Drugs that target cells with ALK gene changes**
- Crizotinib (Xalkori), Ceritinib (Zykadia), Alectinib (Alecensa)

**Immunotherapy**

- Nivolumab (Opdivo) and pembrolizumab (Keytruda) target PD-1 protein
- Atezolizumab (Tecentriq) targets PD-L1 protein

**NSCLC response**

- Tumor size
  - Decreased blood flow
  - Tumor cavitation
  - Reduced tumor density
  - Tumor Hemorrhage
  - Pseudoprogression

**RECIST**
New tumor responses to new therapies

Conventional chemotherapy

Tumour reduction
Changes in size = response by RECIST criteria

No Changes in size = no response by RECIST

Targeted therapies

Reduced tumor density

Tumor cavitation

Growing with hemorrhage

Decreased blood flow

Cancer cell
Necrotic cell
Lymphocyte

Alternative methods
Functional imaging

Pseudoprogression

Immuno therapy
Evaluating treatment response

How?

Are you evaluating treatment response in Lung Cancer?

Conventional therapy

Target Therapy

Immuno Therapy

RECIST 1.1

Molecular therapies
EFGR/ALK/ROS

PET
PERCIST or EORTC

Antiangiogenic therapy

Modified RECIST by cavitation or density
Perfusion CT

irRC
irRECIST
iRECIST

Alternative methods: Functional Imaging
The first criteria to be proposed for the standardization of methodologies for assessing treatment response were the World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors (RECIST). Both were developed to assess response to cytotoxic chemotherapeutic agents and to monitor only changes in tumor size.

The use of tumor size alone has certain pitfalls and limitations, especially in the evaluation of targeted therapies. Changes in tumor dimension do not necessarily reflect tumor response.

Over the years, WHO and RECIST criteria have been modified by combining new and alternative morphologic methods and functional imaging with also specifics criteria for immunotherapy.
<table>
<thead>
<tr>
<th>Bi/Unidimensional</th>
<th>WHO</th>
<th>RECIST1.0</th>
<th>RECIST1.1</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of measurement</td>
<td>Bidimensional</td>
<td>Unidimensional</td>
<td>Unidimensional</td>
<td>Bidimensional</td>
</tr>
<tr>
<td>N target How many?</td>
<td>10 (max. 5 x organ)</td>
<td>10 (max. 5 x organ)</td>
<td>5 (max. 2 x organ)</td>
<td>10 visceral (max 5 x organ, 10 visceral, 5 cutaneous)</td>
</tr>
<tr>
<td>Target lesion</td>
<td>&gt;10x10mm (Node &gt;15x15mm)</td>
<td>&gt;10mm</td>
<td>&gt;10mm (Node &gt;15mm shortest diameter)</td>
<td>&gt;10x10mm (Node &gt;15x15mm)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>No lesions</td>
<td>No lesions</td>
<td>No lesions</td>
<td>No lesions</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>≤50% SPD</td>
<td>≤30% in sum of longest diameter (SLD)</td>
<td>≤30% SLD</td>
<td>≤50% SPDir New lesions (&gt;5x5mm)</td>
</tr>
<tr>
<td>Progression disease (PD)</td>
<td>≥ 25% SPD</td>
<td>≥ 20% SLD</td>
<td>≥ 20% SLD (&gt;5mm)</td>
<td>≥ 25% SPDir</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>No CR, PR, PD</td>
<td>No CR, PR, PD</td>
<td>No CR, PD, PD</td>
<td>No CRir, PRir, ni PDir New lesions (&gt;5x5mm)</td>
</tr>
<tr>
<td>Confirmation</td>
<td>CR, PR &gt; 4Wk</td>
<td>RC, RP, PD &gt; 4Wk</td>
<td>CR, PD, SD, PD &gt; 6 Wk</td>
<td>CR, PR, PD &gt; 4 Wk</td>
</tr>
</tbody>
</table>
Alternative methods to tumor size

**Tumor volume**

There are some trials where correlations with clinical outcomes have been higher for **volumetric-based measures** than for unidimensional or bidimensional diameters.

Value in clinical practice settings and clinical trials has been suggested, but not proven.


**Tumor density**

- **CHOI criteria** were described as response criteria in the evaluation of GIST. These criteria are based on size and tumor density in Hounsfield units. 

  Decreased density of the responding tumors on CT is correlated with the development of tumor necrosis or cystic or myxoid degeneration.


- **Lee et al.** approach according to changes in density in lung lesions.


- **Crabb et al.** Alternate method incorporating cavitation into volume assessment for target lesions, potentially altering outcomes.

  Crabb S J et al. JCO 2009;27:404-410

**Tumor cavitation**
Anti-angiogenic therapy sometimes cause intratumoral hemorrhage, necrosis or cavitation which usually represents a good response to the agents.

CT performed before (a) and after (b) anti-angiogenic treatment. Tumor density in (a) is 23 HU and in (b) is 8 HU with no changes in size. According to Choi a combined criteria with a decrease in tumor density ≥15% corresponds to partial response with stable disease according to RECIST.

Volumetric assessment in lung lesion

Limitations of unidimensional measurement
Zhao et al. suggested that measuring volumetric changes in tumor dimension may hold the potential to be an earlier or better biomarker of tumor regression or progression.
Radiology 2006;241:892-898

Anti-angiogenic
Anti-angiogenic therapy
Tumor Cavitation

- Cavitation is common in lung cancer treated with angiogenesis inhibitors
- Incorporating an assessment of cavitation when measuring target lesions might more accurately reflect changes in tumor volume

(a). CT demonstrating pulmonary mass at baseline with cavitation after subsequent cycles of chemotherapy and angiogenesis inhibitor (b) with posterior refilling, indicating progression (c).

**Alternate measurement**

- RECIST measurement = x
- Alternative measurement = x - y

Crabb S J et al. JCO 2009;27:404-410
Immunotherapy

- Lung cancer has recently emerged as an exciting new target of immune-based therapies
- **Immune treatments**
  - PD-1 and PD-L1 blockers
  - Cancer vaccines
  - Others: Ipilimumab
- **RECIST** criteria are not adequate to evaluate response to immunotherapy. Tumor volume may even increase during the early phases of treatment or appear new small lesions.
- **Functional imaging** may be useful to evaluate response to these new treatments


<table>
<thead>
<tr>
<th></th>
<th><strong>RECIST 1.1. Unidimensional</strong></th>
<th><strong>irRC Bidimensional</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>New, measurable</td>
<td>• Always PD</td>
<td>• irRC Incorporated into tumor burden</td>
</tr>
<tr>
<td>lesions(≥5 × 5 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New, nonmeasurable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesion(&lt;5 × 5 mm)</td>
<td>• Always PD</td>
<td>• Do not define progression</td>
</tr>
<tr>
<td>CR</td>
<td>• Disappearance of all lesions in two consecutive</td>
<td>• Disappearance of all lesions in two consecutive observations not less than 4 wk apart</td>
</tr>
<tr>
<td></td>
<td>observations not less than 6 weeks</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>• Decrease &gt;30% nadir.</td>
<td>• ≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart</td>
</tr>
<tr>
<td></td>
<td>• No new lesions or unequivocal progression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Confirmation ≥ 6 weeks</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>• No criteria for CR, PR o PD</td>
<td>• 50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir</td>
</tr>
<tr>
<td>PD</td>
<td>• Increase &gt;20% nadir(at least 5mm) o or new lesions or unequivocal progression non target lesions</td>
<td>• At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart</td>
</tr>
</tbody>
</table>
Immunotherapy: Immune Response Criteria


Subsequent modifications proposed Based on RECIST/RECIST 1.1:


<table>
<thead>
<tr>
<th></th>
<th><strong>RECIST 1.1</strong></th>
<th><strong>irRC</strong></th>
<th><strong>irRECIST</strong></th>
<th><strong>iRECIST</strong></th>
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</thead>
<tbody>
<tr>
<td>Bi/unidimen.</td>
<td>Unidimensional</td>
<td>Bidimensional</td>
<td>Unidimensional</td>
<td>Unidimensional</td>
</tr>
<tr>
<td>N target</td>
<td>5</td>
<td>5; (≥5 x 5mm)</td>
<td>10/5 (≥10 mm/≥10 mm (15 for nodes)</td>
<td>5</td>
</tr>
<tr>
<td>New target lesions added to sum or measures (SOM)</td>
<td>NO</td>
<td>(≥5 x 5 mm); Yes—does not automatically define PD</td>
<td>(RECIST or RECIST 1.1 rules)</td>
<td>New lesions recorded separately. Not included in the summatory of baseline target lesions.</td>
</tr>
<tr>
<td>How many?</td>
<td>NA</td>
<td>10 visceral, 5 cutaneous</td>
<td>10 / 5 (RECIST 1.1 rules)</td>
<td>5</td>
</tr>
<tr>
<td>Definition of progression (PD)</td>
<td>≥ 20% ↑ compared to nadir (≥ 5mm ↑)</td>
<td>≥ 25% ↑ compared to baseline (BL), nadir/reset BL</td>
<td>≥ 20% ↑ compared to nadir (≥ 5mm ↑)</td>
<td>Assess by RECIST 1.1 and confirmed progression disease. It has to be confirmed in the next assessment</td>
</tr>
<tr>
<td>Confirmation?</td>
<td>No</td>
<td>Yes, required</td>
<td>Yes, recommended</td>
<td>Yes, always required Confirmation in 4-8 weeks</td>
</tr>
<tr>
<td>How confirmed?</td>
<td>NA</td>
<td>Not defined</td>
<td>Not defined; not improved? Imager feels is worse?</td>
<td></td>
</tr>
</tbody>
</table>
Immunotherapy: RECIST and Immune Response Criteria

(A) Progression by RECIST and by irRC confirmed at 16 weeks with the increase of total lesions (subcutaneous nodules, pulmonary nodule and subcarinal lymph node) in a 50 year-old woman with advance NSCLC.

(B) Reduction of the right lung lesion but appearance of new lesions, meaning progression disease by RECIST. In irRC new target lesions are added to sum or measures (SOM).
Immune-related response patterns have been observed including development of new lesions associated with edema and infiltrates of immune cells and transient increases in baseline tumor lesions.

Delayed clinical responses were also observed in studies of immunotherapeutic agents, such that an increase in total tumor burden was later followed by tumor regression.

Pseudoprogression would have been classified prematurely as progressive disease by historic WHO or RECIST criteria and have prompted the development of the immune-related response criteria.

Immunotherapy

- Evaluating response to immunotherapy is important to have a knowledge of radiologic manifestations of immune-related adverse events

Four patients with lung cancer treated with immunotherapy with pneumonitis induced by treatment

- Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell-lung cancer. Lung Cancer. 2017 Feb;104:111-118
Imaging techniques - Functional imaging

- With the development of new anti-cancer drugs, various diagnostic imaging modalities are emerging in the assessment of tumor response to treatment.
- In addition to Anatomic or Morphological approaches, new functional and metabolic imaging techniques are now potentially available.

Characteristics:
- Differentiation of Malignant and Benign Pulmonary Nodules
- Prognostic and predictive biomarkers of response to targeted therapies
- Identification of “early responders”

- An ideal biomarker in functional imaging
  - Characterize the tumor from initial diagnosis throughout therapy
  - Understand tumor physiology
  - Make therapy success/failure measurable early in the treatment

- And they should be:
  - Fast to measure
  - Reliable
  - Accessible
  - Easy to incorporate in standard workflow
Many imaging techniques can provide functional information and they could be a oncologic biomarker

- **Targeted** (using molecularly targeted probes):
  - MRI, PET, US, optical imaging

- **Functional** (using contrast):
  - Dynamic Ultrasound (DCE-US)
  - Dynamic, Functional, Contrast-Enhanced (DCE-CT) or Perfusion CT (CTP)
  - Dynamic Contrast-Enhanced MRI (DCE-MRI)
  - Functional PET (FDG, FLT, F-Miso, O-water)
### Functional imaging - DWI

- **Diffusion-weighted MRI (DWI)** allows the analysis of tissue characteristics based on the diffusivity of water molecules within tissue.
- Provides information on extracellular-space tortuosity, tissue cellularity and the integrity of cellular membranes.
- **DW-MRI** in the characterization of malignancy, including determination of lesion aggressiveness and monitoring response to therapy.
- Advantages: no ionizing radiation, no contrast medium.
- ADC seems to be a promising tool for monitoring the early response to or predicting prognosis after chemotherapy of NSCLC.


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**DWI images and ADC map in a patient with lung cancer with a mass in LUL and a hilar lymphadenopathy. Lesions are hyperintense in DWI with ADC restriction**
Functional imaging - PET/CT

- **18F-FDG** is the most used radiotracer in oncologic imaging.
- Criteria to evaluate response in PET-FDG are based in **SUV** (standard uptake value) and metabolic response. There are no generally accepted criteria for a metabolic response in FDG PET studies. Proposed classifications are:
  - PERCIST (PET Response Criteria in Solid Tumors)
  - EORTC (European Organization for Research and Treatment of Cancer)
- Other specific radiotracers could be used in lung cancer (Table)

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Biologic property</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F-FDG</td>
<td>Glucose metabolism</td>
</tr>
<tr>
<td>18F-Choline/11C-Choline</td>
<td>Metabolism</td>
</tr>
<tr>
<td>18F-Thymidine</td>
<td>Cellular proliferation</td>
</tr>
<tr>
<td>15O-Water</td>
<td>Perfusion</td>
</tr>
<tr>
<td>11C-Methionina</td>
<td>Proteic synthesis</td>
</tr>
<tr>
<td>18F-misonidazole</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>18F–fluoro annexin V</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>EGFR- or VEGFR linked radiotracers(11C)</td>
<td>Receptor expression</td>
</tr>
</tbody>
</table>
Functional imaging - PET/CT

- An effect of several new agents such as gefitinib, erlotinib and crizotinib are **durable modest regressions or prolonged disease stability**

Patient with lung cancer ALK traslocated treated with crizotinib: a) Basal PET-CT with multiple hilar and mediastinal lymphadenopathies and bone metastases, b) PET-CT one month later with an important metabolic response with stabilization according to RECIST criteria. c) Basal CT and a 18 month later CT with RECIST stabilization (25% reduction) and d) persistent metabolic response in PET
Dual energy-CT (DECT)

- DECT could be a useful functional imaging test for NSCLC because it provides information on tumor angiogenesis and its relationship with tumor metabolism by showing a close correlation between maximum iodine-related attenuation and SUV max on FDG-PET-CT (Schmid-Bindert Get al Eur Radiol 2012;22:93-103).
- DECT may serve as a useful tool for response evaluation after anti-angiogenic treatment (Kim YN et al Korean J Radiol 2012;13(6):702-710).

Lung cancer in LUL with distal atelectasis. a)PET-CT before treatment showing intense FDG uptake. DECT after radiotherapy b) lung window c)virtual non contrast imaging d)iodine enhanced image and e)iodine enhanced image with measurements. It is possible to distinguish between the atelectasis (white arrow) and the hypodense tumor (yellow arrow), and the markedly hypodense right paratracheal image secondary to previous mediastinoscopy (green arrow). In the image (e) we can see the differences in iodine density. Therapy monitoring is possible with iodine attenuation.
Perfusion CT and angiogenesis

- Many studies* relating pathological assessments of angiogenesis to DCE-CT parameters have shown that perfusion-CT parameters correlate closely with the expression of vascular endothelial growth factor (VEGF) and microvessel density (MVD) in lung cancer.

- Whole-tumor perfusion analysis is achievable with CT, enabling qualitative and quantitative assessment of lung tumor vascularization.

Kinetic parameters measured by CT perfusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Physiopathology correlation</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Flow (BF)</td>
<td>Flow rate through vasculature in tissue region</td>
<td>Tumor vascularity</td>
<td>ml/100g/min</td>
</tr>
<tr>
<td>Blood Volume (BV)</td>
<td>Volume of flowing blood within vasculature in tissue region</td>
<td>Tumor vascularity</td>
<td>ml/100g</td>
</tr>
<tr>
<td>Permeability</td>
<td>Total flux plasma to interstitial space</td>
<td>Immature leaky vessels</td>
<td>ml/100g/min</td>
</tr>
<tr>
<td>Time to peak (TTP)</td>
<td>Time from arrival of contrast in major arterial vessels to the peak enhancement</td>
<td>Perfusion pressure</td>
<td>seconds</td>
</tr>
<tr>
<td>Mean Transit Time</td>
<td>Average time taken to traverse the tissue vasculature</td>
<td>Perfusion pressure</td>
<td>seconds</td>
</tr>
</tbody>
</table>

*Studies in lung cancer with Perfusion-CT with pathological correlation:
- Tacelli et al. Radiology. 2010 Dec;257(3):863-71
- Spira D et al.. JCAT 2013; 37:15-21
Clinical applications in Oncology

- The advantages of Perfusion CT in Oncology are:
  - wide availability
  - low cost
  - easy to incorporate in the standard workflow
  - can be combined with CT assessments using RECIST or WHO morphological criteria

- Possible applications of Perfusion CT:
  - Differentiation benign and malignant lesions (Fig)
  - Tumor characterization
    - Prediction of response
    - Prognostic information
  - Assessment of therapeutic response
    - Antiangiogenic treatment

Lung cancer treated with radiofrequency ablation (RFA). Follow-up perfusion CT showing high blood flow (red color) in the periphery of the lesion suggesting tumor activity. Lesion was retreated with RFA.
Multifunctional profiling: PET-CT combined with Perfusion CT

- New PET-CT equipment allows to do **perfusion CT and PET** in the same exam. It is also possible to do both exams separately (Fig).

- **18F-FDG** uptake and perfusion parameters provide complementary functional information\(^1\)

- Improving the tumor profiling will be beneficial for both prognosis and therapy response evaluation


Perfusion CT and **18F-FDG** PET-CT pretreatment in a patient with lung adenocarcinoma in LLL. Perfusion parameters are different biomarkers:

- **SUV** correlates with Ki67 (proliferation marker)
- **CT perfusion parameters** correlate with MVD (angiogenic marker)
Assessment of therapeutic response

- Different trials have shown that Perfusion CT demonstrates early changes in lung cancer vascularity under anti-angiogenic chemotherapy\(^1,2,3\)
- These changes may help to predict therapeutic response
- Responders have higher basal perfusion

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Metastatic lung cancer treated with antiangiogenic therapy. PET-CT shows a necrotic mass in RUL and a metastatic periaortic and right paratracheal lymph node. Basal and 1 week after treatment perfusion CT

<table>
<thead>
<tr>
<th>Baseline</th>
<th>BF 89.32</th>
<th>BV 11.58</th>
<th>PMB 26.64</th>
</tr>
</thead>
<tbody>
<tr>
<td>After</td>
<td>BF 26.02</td>
<td>BV 6.24</td>
<td>PMB 10.84</td>
</tr>
</tbody>
</table>

\(^3\)Tacelli N et al. Eur Radiol. 2013 Aug;23(8):2127-3
CASE 1

Two lung cancer treated with antiangiogenic therapy. Perfusion CT performed just before the beginning of the treatment and one week later. Case 1 has all decreased perfusion parameters indicating probably good response and prognosis.

CASE 2

Case 2 has an increase in BF and PMB indicating poor response and prognosis. Both cases without tumor shrinking.
A 63-year-old male patient with a right upper lobe adenocarcinoma. Transverse CT image at baseline, at day 7 and at day 42 and their corresponding functional CT maps of Blood Flow (BF), Blood Volume (BV) and Permeability (PMB) demonstrating a decrease in tumour vascularity.

Partial response RECIST day+42
A 67-year-old male patient with a left lower lobe adenocarcinoma. Transverse CT at baseline, at day 7 and at day 42 and their corresponding functional CT maps of Blood Flow (BF), Blood Volume (BV) and Permeability (PMB) demonstrating a decrease in tumour vascularity.
A 60-year-old male patient with a subcarinal adenopathy. Transverse CT image at baseline, at day 7 and at day 42 and their corresponding functional CT maps demonstrating a minimum decrease in BF and PMB and an increase in values even compared to baseline at day 42.

Progression disease RECIST day+42
Summary

- New oncologic treatments bring new patterns of response
- Classic morphological response criteria are no adequate for new or future targeted therapy in lung cancer
- Alternative morphological methods have been developed
- Immunotherapy has an own immune-related response assessment and specific immune-related adverse events
- Functional and molecular imaging may have an important role evaluating response to these therapies. Especially for early response
References


Contact information

Mariana Benegas Urteaga, MD
Thoracic Radiology
Department of Radiology
Hospital Clínic de Barcelona

mnbenegea@clinic.cat
benegasmariana@gmail.com