Evaluating Response of Lung Cancer to Treatment: The Role of Imaging
Theresa C. McLoud, MD

Question
- What is considered a partial response (PR) to therapy in lung cancer using the RECIST criteria?
  - A. 20% decrease in tumor diameter
  - B. 30% decrease in tumor diameter
  - C. 30% decrease in tumor volume
  - D. 50% decrease in tumor volume

Lung cancer staging and 5-year survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5-year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1-T2 N0 M0</td>
<td>60-80%</td>
</tr>
<tr>
<td>II</td>
<td>T1-T2 N1 M0</td>
<td>25-50%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3 N0-1 M0</td>
<td>25-40%</td>
</tr>
<tr>
<td>IIIB</td>
<td>Any T4 or any N3 M0</td>
<td>Less than 5%</td>
</tr>
<tr>
<td>IV</td>
<td>Any M1</td>
<td>Less than 5%</td>
</tr>
</tbody>
</table>

Chemotherapy provides only modest survival benefits in disseminated non-small cell lung cancer. With platinum-based chemotherapy the one and two year overall survival had still remained at 23% and 11%, respectively.


Thank you
- Dushant Sahani, MD.
- Umar Mahmood, MD, PhD.
- Victorine Muse, MD
- Amita Sharma, M.D.
- Mizuki Nishino, M.D.
Recurrent Mutations in NSCLC

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>15%</td>
</tr>
<tr>
<td>MET amplification</td>
<td>4%</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>1%</td>
</tr>
<tr>
<td>ALK translocation</td>
<td>3%</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>47%</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>30%</td>
</tr>
</tbody>
</table>

Genetic profiling and targeted agents (NSCLC-Adv)
- Genetic markers
  - EGFR mutations—targeted therapy with tyrosine kinase inhibitors TKI’s (gefitinib, erlotinib), and monoclonal antibodies -Cetuximab
  - Female, Asian, never smoked, adenocarcinomas

EGFR mutation and response to Erlotinib therapy

Genetic profiling and targeted agents
- Antiangiogenesis agents
  - Bevacizumab—monoclonal antibody inhibits activity of human Vascular endothelial growth factor (VEGF)

Response to Therapy

Radiation therapy
Targeted therapy
Chemotherapy

Tumor density
Cellular Angiogenesis
Immune cells
Matrix
Antiangiogenesis
Anti-angiogenesis
Antibodies
Small molecule inhibitor
Gene therapy

Tumor vasculature
Antiangiogenic vs Cytotoxic Therapy

**Antiangiogenic Therapy**
- Physiologic angiogenesis rare
- All tumors require angiogenesis
- Survival and growth factors produced by endothelial cells
- Provides oxygen and nutrition
- Wide spectrum
- Normal tissue spared
- Tumor cannot grow
- Improved delivery of chemotherapy

**Cytotoxic Therapy**
- Tumors have certain signatures with normal cell
- Tumor cells genetically unstable
- Biology of each tumor is different
- Endothelial cells recover quickly
- Do not spare normal tissue
- Wide spectrum
- Normal tissue spared
- Tumor cannot grow
- Improved delivery of chemotherapy
- Not ant angiogenic with usual schedule

In malignant tumors, angiogenesis represents a prerequisite for tumor growth, as the high metabolism of tumor cells requires large amounts of oxygen and nutrients. Disruption of angiogenesis pathways provides a therapeutic perspective in the treatment of primary malignant human tumors as well as their metastases.

**Molecular Targeted Therapy for Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>Response rate (%)</th>
<th>Median survival (months)</th>
<th>Progression on free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbst et al</td>
<td>Bevacizumab + erlotinib</td>
<td>20</td>
<td>12.6</td>
<td>6.2mos</td>
</tr>
<tr>
<td>Sandler et al</td>
<td>Paclitaxel + carboplatin + bevacizumab</td>
<td>27</td>
<td>12.5</td>
<td>6.4 mos</td>
</tr>
<tr>
<td>Paclitaxel + carboplatin + placebo</td>
<td>10</td>
<td>10.3</td>
<td>6.7 mos</td>
<td></td>
</tr>
<tr>
<td>Heymach et al</td>
<td>ZD6474 (50 mg) + docetaxel</td>
<td>16</td>
<td>NR</td>
<td>18.3 wks</td>
</tr>
<tr>
<td>Placebo + docetaxel</td>
<td>12</td>
<td>11.5</td>
<td>12 wks</td>
<td></td>
</tr>
</tbody>
</table>


Different ways to assess treatment response

- Tumor size
- RECIST
- Tumor volume
- CT Perfusion
- Lung cancer
- Metabolism
- Tumor Density (HU)
Quantitative Criteria

- **RECIST 1.0**
- **RECIST 1.1**
- **WHO**

**Major changes in RECIST 1.0 vs 1.1**

<table>
<thead>
<tr>
<th>RECIST guideline</th>
<th>RECIST 1.0</th>
<th>RECIST 1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of target lesions</td>
<td>Up to 5 per organ; up to 10 in total</td>
<td>Up to 5 per organ; up to 10 in total</td>
</tr>
<tr>
<td>Lymph node assessment</td>
<td>Short-axis measurements should be used and recorded; ≥ 15 mm, target lesions; ≥ 20 mm but &lt; 25 mm, non-target lesions; &lt; 10 mm, non-pathological</td>
<td>No clear guideline provided</td>
</tr>
<tr>
<td>Clarification of Disease progression</td>
<td>≤ 20% increase in the sum of target lesions and 5 mm absolute increase are required</td>
<td>≤ 20% increase in the sum of target lesions (no minimum absolute size increase is required)</td>
</tr>
<tr>
<td>FDG PET scan</td>
<td>Included only in the detection of new lesions</td>
<td>Not included</td>
</tr>
</tbody>
</table>

**Limitations of measurement by RECIST guidelines**

- Variability by lesion selection and measurement
- Tumor morphology
  - Confluent, irregular borders, cavitation
- Types of tumor (Mesothelioma)
- Types of treatment – Targeted therapy

**Conventional Size Measurement: Limitations of RECIST and WHO**

- Both criteria assume...
  - Tumor size changes in symmetric fashion
  - Tumor volume is simply related to a planar measurement
  - 4 discrete categories are sufficient to quantify disease response or progression
**Conventional Size Measurement: Limitations**

- In reality...
  - Tumors do not necessarily grow symmetrically
  - Different portions may grow at different rates
  - Substantial intra- and inter-observer variability in measurements
  - Cavitation or necrosis not taken into account

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**VOLUMETRIC ASSESSMENT**

**CT Volume Measurement**

- Recent rapid progress in MDCT technology enabled scanning of large anatomic volumes in a single breath hold with isotropic voxels and high resolution
- 3D methods for nodule and tumor volume measurement have been developed, aiming for more accurate and consistent tumor measurement and better determination of temporal change in a shorter interval

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**Lung ca with Metastasis disease treated with chemotherapy**

Pre treatment burden - 43.14cm³
Post treatment burden - 22.95cm³

**Why Volume?**
- Better reflective of tumor burden
- More sensitive for measuring changes after treatment
- Opportunity to predict outcome and customize chemo dose
<table>
<thead>
<tr>
<th>RECIST</th>
<th>WHO</th>
<th>Volumetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of metric</td>
<td>Uni-dimensional</td>
<td>Bi-dimensional</td>
</tr>
<tr>
<td>CR (Complete Response)</td>
<td>Total disappearance</td>
<td>Total disappearance</td>
</tr>
<tr>
<td>PR (Partial Response)</td>
<td>26% decrease</td>
<td>50% decrease</td>
</tr>
<tr>
<td>PD (Progressive Disease)</td>
<td>25% increase</td>
<td>25% increase</td>
</tr>
<tr>
<td>SD (Stable disease)</td>
<td>Neither PR or PD criteria met</td>
<td>Neither PR or PD criteria met</td>
</tr>
</tbody>
</table>

### Limitations of quantitative approach to response to therapy

- Tumor shrinkage is slow as measured on CT
- Need early prediction of tumor response
- Targeted therapies—cytostatic not always cytoreductive

### Qualitative Approach of Response to Therapy

- **Tumor density (Choi Criteria)**
- **PET (FDG, FLT)**
- **CT tumor perfusion**

### Tumor density - Choi criteria

- **Complete Response (CR)**
  - Disappearance of all lesions
  - No new lesions
- **Partial Response (PR)**
  - A decrease in size of ≥ 15%
  - A decrease in tumor density (HU) ≥ 15% on CT
  - No obvious progression of non-measurable disease
- **Stable Disease (SD)**
  - Does not meet the criteria for CR, PR or PD
  - New intratumoral nodules or increase in the size of the existing intratumoral nodules
  - New lesions
- **Progressive Disease (PD)**
  - An increase in tumor size of ≥ 15% and does not meet criteria of PR by tumor density (HU) on CT
  - New symptomatic deterioration attributed to tumor progression

### Tumor density - Choi criteria

- **Good responder**
  - ≥ 15% decrease in tumor density
  - ≥ 15% decrease in tumor density
- **Poor responder**
  - ≤ 15% decrease in tumor density
  - ≤ 15% decrease in tumor density

### FDG-PET

- **PET**
  - **FDG**
  - **PET**

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**Choi criteria** – First use for response assessment in GIST treated with molecular targeted therapy

**Choi criteria** – Shown to be useful for response assessment in soft-tissue sarcomas and in carcinomas

Evaluation of Response to Therapy

- Normalization of FDG uptake after treatment is favorable indicator of good prognosis
- Decrease in FDG uptake after treatment may be better and earlier indicator of response to therapy than change in tumor size on CT

Evaluation of Response to Therapy and Detection of Recurrence PET--FDG

- Rx may result in hypermetabolic inflammatory changes- may be misinterpreted as residual tumor or recurrent disease
- Radiation changes may mask uptake of adjacent tumor
- Radiation and/or surgery may distort the anatomy- anatomic location inexact

Complete response after 2 cycles of carboplatin and pemetrexed

Post Treatment--Persistent apical pleural Thickening

No recurrence

Monitoring Response in Lung tumor: EORTC Criteria for FDG-PET

<table>
<thead>
<tr>
<th>PD</th>
<th>SUV increase &gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Rx</td>
<td>Visible increase of FDG uptake</td>
</tr>
<tr>
<td></td>
<td>Appearance of new focus</td>
</tr>
</tbody>
</table>
| SD | SUV increase 25% or decrease <15%
|       | No visible increase of the extent of FDG uptake |
| PR | SUV drop min 15-25% after one cycle; SUV <25% after more than one treatment cycle |
| CR | Complete resolution of FDG uptake |

EORTC = European Organization for Research and Treatment of Cancer

3 months post radiation
Recurrence 9 years after radiation therapy

What is 18F-FLT?

- 3-deoxy-3-[18F]fluorothymidine (FLT) is a thymidine analog used to assess cell proliferation.
- FLT is taken up and trapped intracellularly after phosphorylation by thymidine kinase 1.
- Although FLT is not incorporated into the DNA, its uptake is thought to track DNA synthesis because the concentration of thymidine kinase 1 increases up to tenfold during DNA synthesis.
- It was demonstrated that FLT has no tendency to accumulate in inflammatory lesions unlike FDG which has a high uptake in inflammatory tissue; which makes FLT a more specific earlier for assessment of neoplasms.

What is 18F-FLT?

- 18F-FLT compared to 18F-FDG is:
  - Less sensitive
  - More specific
  - Has a higher positive predictive value
  - Has a higher rate of false negative and lower rate of false positive
  - Is negative in inflammatory lesions
  - Has a higher correlation with cell proliferation

Assessment of Lung nodules

RESPONSE TO THERAPY

- Early prediction of tumor response
- Can distinguish inflammation (radiation pneumonitis) from tumor cell proliferation

NEW PET AGENTS
FLT and FMISO

NEW PET AGENTS
FLT and FMISO

The proliferation marker of choice is 18F-FLT.
Assessment of response to therapy using 18F-FLT PET

- PET images of a patient (A) show markedly decreased FLT uptake (SUVmax = 4.8 vs 2.3) at 7 days after gefitinib therapy. CT scan at 6 weeks reveals tumor shrinkage.
- PET images of another patient (B) show no visible change at 7 days after gefitinib therapy (SUVmax = 7.2 vs 8.0) and increase in tumor size at 6 weeks.
- Kaplan-Meier plots showing TP (C) and CS (D) according to FLT-PET response.

FLT-PET can predict response to gefitinib 7 days after treatment in patients with advanced adenocarcinoma of the lung. The change in tumor SUVmax obtained by FLT-PET seems to be a promising predictive variable.


Perfusion CT in advanced NSCLC

- Correlation between baseline perfusion parameters and therapeutic response
- Parameters:
  - Blood flow
  - Blood volume
  - Mean transit time
  - Permeability-surface area product

Monitoring early anti-angiogenic response: Perfusion CT

- Case 1: Ca Lung
  - Pre: BF = 109.6 ml/100gm/min
  - Post BVZ 2 wks: BF = 61.5 ml/100gm/min

- Case 2: Ca Lung
  - Pre: BF = 68.1 ml/100gm/min
  - Post BVZ 2 wks: BF = 92.7 ml/100gm/min

- Case 3: Ca Lung with metastatic LN
  - Pre: BF = 78 ml/100gm/min
  - Post BVZ 2 wks: BF = 59 ml/100gm/min


CT Perfusion

Tumor density 56%
Tumor density 35%
Tumor density 25%

CT Perfusion BF 64.30
CT Perfusion BF 101.6/67.46
CT Perfusion BF 43.0.001

FDG PET Mean SUV 7.62
FDG PET Mean SUV 4.01
FDG PET Mean SUV 2.1

Early changes 12 days after start of bevacizumab

TP: Time point

Measureable Drop in CT parameters (BF, BV and PS: p<0.05), SUV (P<0.05), tumor density (p<0.05) and insignificant changes in RECIST (P>0.05).
Treatment Customization

Low risk of recurrence
Drug not beneficial, toxic

High risk of recurrence
Drug beneficial, not toxic

Late changes following treatment with combination chemotherapy (18 wks)

Following the completion of treatment significant reduction in tumor perfusion [-42 to 72%, \(p<0.05\)], SUV (-48.8%, \(p<0.01\)) and RECIST (-40%, \(p<0.05\)) was seen.

Insignificant difference in Baseline CTP, SUV, tumor density and RECIST between patients with PFS > and < 6M (\(p>0.05\)).

RESPONSES TO TARGETED THERAPY

Lung Adenocarcinoma
EGFR(+)
EGFR mutation and response to Erlotinib therapy

EGFR mutant positive

Pre-Post treatment

EGFR mutant negative

Pre-Post treatment

Tumor cavitations: Predictor of favorable outcome following targeted therapy
PRETREATMENT  EGFR MUTATION  ERLOTINIB  
RECURRENCE, RELAPSE  
SAMPLE – TRANSLOCATION – RESISTANCE TO THERAPY  

Genomic: 
TL-09-267  20 ng/panel DNA  
TL-09-285  1.04 ng/panel DNA  

Courtesy of Jo-Anne O. Shepard, MD and John Iafrate, MD
Tumor cavitations following targeted therapies

Pre Sorafenib

Post Sorafenib

Cavitations in lung tumor of patient receiving Bevacizumab

Pre Post Bevacizumab

Cavitations can potentially lead to pneumothorax in peripherally tumors

Late changes following treatment with combination chemotherapy (18 wks)

Following the completion of treatment significant reduction in tumor perfusion [-42 to 72%, p<0.05], SUV (-48.8%, p<0.01) and HU (-37.2%, p<0.023) and RECIST (-40%, p<0.05) was seen.
Pre and post BVZ

Post BVZ Base line

Contrast enhanced CT (RECIST)

Tumor density

CT Perfusion

BF 33.78 ml/100g/min

FDG PET Mean SUV 7.4

FDG PET Mean SUV 5.2
**EORTC criteria**

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>Complete resolution of FDG uptake (&lt;100% SUV)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>Reduction of minimum of 15% -25% in tumor SUV after 1 cycle of chemotherapy, and &gt;25% after more than 1 treatment cycle;</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Increase in SUV or decrease of &lt; 15% and no visible increase in extent of tumor uptake (20% in longest dimension)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>Increase in tumor SUV of &gt;15% within tumor region defined on baseline scan; Visible increase in extent of tumor SUV uptake (20% in longest dimension)</td>
</tr>
</tbody>
</table>

There is enhanced uptake of 18F-fluoroamygin (18FGD) in majority of malignant tumors which in turn can be measured with positron emission tomography (PET-CT) is usually combined with CT to provide both anatomical and functional information. At present combined PET-CT response criteria is not available. PET guidelines for response assessment in solid tumors was introduced by EORTC. According to recommendations by EORTC the standardized uptake value (SUV) is measured and treatment response is categorized based on percentage change in SUV.

**Lung ca with Metastasis disease treated with chemotherapy**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Post BVZ</th>
<th>Post Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment burden - 41.24cm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre treatment burden - 22.95cm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post BVZ Base level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post BVZ Post treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre treatment burden - 22.95cm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CT Perfusion**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Post BVZ</th>
<th>Post Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF 23.33 ml/100g/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BF 13.78 ml/100g/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BF 7.59 ml/100g/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BF 13.78 ml/100g/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BF 3.26 ml/100g/min</td>
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<td></td>
</tr>
</tbody>
</table>

**FDG PET**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Post BVZ</th>
<th>Post Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SUV 7.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SUV 4.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SUV 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SUV 9.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SUV 6.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SUV 2.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The fundamental principle of perfusion CT (CTp) is based on the temporal changes in tissue attenuation after intravenous administration of iodinated CM.

**Initial phase (First pass)**
- Based on contrast distribution in intravascular compartment
- Enhancement is determined to a great extent by the tissue blood flow (BF) and blood volume (BV)

**Second phase (Delayed phase)**
- Contrast pass from intravascular to extravascular compartment
- Influenced by vascular permeability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF (mL per 100 g/min)</td>
<td>Flow rate through vasculature in tissue region</td>
<td></td>
</tr>
<tr>
<td>BV (mL per 100 g)</td>
<td>Volume of flowing blood within a vasculature in tissue region</td>
<td></td>
</tr>
<tr>
<td>PS (mL per 100 g/min)</td>
<td>Total flux from plasma to interstitial space</td>
<td></td>
</tr>
</tbody>
</table>

**Tumor metabolism – PET-CT**

1. FDG-PET best assessed in conjunction with anatomical imaging (CT) to reduce errors in interpretation
2. Has limited value in tumors with low metabolic activity

**Molecular Targeted Therapy for Cancer**

- EGFR mutation and response to Erlotinib therapy
- Pre-post treatment comparison
  - EGFR mutant positive
  - EGFR mutant negative
Lung Adenocarcinoma
EGFR(+)

267