Evaluation of Lung Cancer Response: Current Practice and Advances

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I have no financial relationships, arrangements or affiliations and this presentation will not include discussion of investigational or off-label use of a product.
Assessing Tumor Response

Objectives

• Review RECIST and WHO criteria for response
• Review immune-related response criteria (irRC)
• Describe the role and limitations of CT and PET in the assessment of therapeutic response
Assessing Tumor Response

World Health Organization (WHO)

- Partial Response (PR) > 50% decrease in sum of products
- Progressive Disease (PD) > 25% increase

Response Evaluation Criteria in Solid Tumors (RECIST)

- Partial Response (PR) > 30% decrease in longest diameter
- Progressive Disease (PD) > 20% increase in diameter
Assessing Tumor Response

RECIST 1.1

- Progressive Disease: > 20% increase in diameter but also a 5 mm absolute increase now required
- Maximum lesions to determine response reduced to 5
- Maximum lesions per organ reduced to 2
- Assessment of lymph nodes now incorporated: nodes with short axis > 15 mm can be target lesions
- Interpretation of FDG-PET assessment now included

Assessing Tumor Response

- Treatment of NSCLC is evolving with increasing use of targeted agents, including inhibitors of angiogenesis.
- Anti-angiogenesis agents that target VEGF factor receptor tyrosine kinase pathway commonly result in cavitation.
- Cavitation can be associated with response.
- Incorporating an assessment of cavitation when measuring target lesions may be important in determining response.

Crabb Methodology

**Crabb Measurement of Response** = \(x - y\)
Assessing Tumor Response

- 57 patients with non-small cell lung cancer
- TNM - stage II (n=2), III (n=11), IV (n=44)
- CT within a month of chemotherapy (mean, 24 days)
- Response assessed using uni-dimensional measurements according to RECIST

Assessing Tumor Response

- Significant change in tumor size in 8 (14%) patients
- Tumor regression in 2 (3%), progression in 6 (11%)
- Early detection of therapeutic failure resulted in a change/discontinuation of therapy in 5/6 patients
- Early CT is useful in evaluating response in NSCLC

Assessing Tumor Response

Variability in Measurements

- 33 patients with NSCLC
- 40 tumors, average size of 1.8-8 cm (mean, 4.1)
- 23 tumors well marginated, 17 irregular
- Bidimensional and unidimensional measurements according to WHO criteria and RECIST
- Measurements performed independently by 5 radiologists and repeated after 5-7 days

Assessing Tumor Response

Variability in Measurements

**Progressive Disease** *(RECIST > 20%, WHO > 25%)*
- Intraobserver misclassification: 9%, 22%
- Interobserver misclassification: 31%, 43%

**Response** *(RECIST > 30%, WHO > 50%)*
- Intraobserver misclassification: 3%, 4%
- Interobserver misclassification: 10%, 15%
Variability in Measurements

Reader 1  3.7 x 2.7 cm  
Reader 2  3.3 x 3.1 cm  
Reader 3  3.7 x 2.2 cm  
Reader 4  4.8 x 2.5 cm  
Reader 5  5.1 x 3.8 cm

Max diameter difference: 57%
Product size difference: 138%
Assessing Tumor Response

• 160 patients, CT before/after neoadjuvant Rx followed by resection/histopathologic assessment of tumor response

• % change in size calculated between pre-chemotherapy and post-chemotherapy measurements

• CR or PR by RECIST defined as radiologic responders, SD or PD non-responders

• Pathologic responders if <10% viable tumor cells, non-responders if >10%

Assessing Tumor Response

- 2 (1%) had CR, 78 (49%) PR, 75 (47%) SD, 5 (3%) PD
- 41% discordance rate between HR and CT RECIST
- 8/80 had HR despite being classified as SD/PD by CT
- 58/80 no HR despite being classified as PR by CT
- CT RECIST sensitivity 73%, specificity 55% for HR
- CT RECIST response is unreliable predictor of OS (p=0.03), HR (p = 0.002)

CT Pre- and Post-Chemoetherapy
Assessing Tumor Response

- Novel response patterns are being observed with immunotherapeutic agents
- SD can be indicator of meaningful therapeutic response
- CR, PR, or SD can occur after an initial increase in tumor burden considered PD by WHO/RECIST
- Increase in tumor burden preceding response may reflect tumor growth until sufficient immune response occurs or a transient immune-cell infiltrate ± edema
- Patients who ultimately respond to therapy can also develop new lesions after initiation of therapy

Immune-Related Response Criteria (irRC) Clinical Guidelines

- Sum of the products of largest perpendicular diameters of index lesions (5 lesions/organ, up to 10 visceral lesions and 5 cutaneous index lesions) calculated
- At subsequent tumor assessment, index lesions and new measurable lesions calculated
- Overall response:
  - irCR: complete disappearance of all lesions
  - irPR: tumor burden (tb) ≥50% relative to baseline
  - irSD: not meeting criteria for irCR or irPR or irPD
  - irPD: tb ≥25% relative to minimum recorded tb

Assessing Tumor Response

• Radiologic criteria for evaluating response are based on $\Delta$ in serial measurements of size (WHO, RECIST 1.1)

• Inherent limitations with anatomic response criteria

• Assessment complicated by therapy that targets tumor cell biology, proliferation and angiogenesis

• Anti-tumor effect of many of these new regimens is cytostatic and may not lead to regression in tumor size
• PET using 18F-2-deoxy-D-glucose (FDG) may have an important role in the assessment of response

• FDG-uptake is a function of proliferative activity as well as viable tumor cell number
Assessing Tumor Response
FDG-PET

- 60 patients with stage IIIA/IIIB NSCLC induction chemotherapy and concurrent chemoradiation
- 19 patients had pathologic CR of primary tumor
- Post induction primary tumor SUV=0.4-12 (mean, 2.9)
- SUV=0.4-9.8 (mean, 3) in tumors no viable malignancy
- CR in 44% of tumors with SUV > 2.5, large residual size

• To quantify a lesion’s metabolism, maximum standardized uptake value (SUVmax) is widely used in clinical practice

• SUVmax is a single voxel value that may not represent total tumor metabolism
<table>
<thead>
<tr>
<th>Factors</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Body composition</td>
<td>Overestimates SUV in obese patients</td>
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<tr>
<td>Uptake period</td>
<td>Increase of SUV over time in malignant tissues</td>
</tr>
<tr>
<td>Respiratory motion</td>
<td>Reduction of SUVmax up to 7-159%</td>
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<tr>
<td>Attenuation correction and</td>
<td>Underestimation of SUV with highly smoothed reconstruction by approx 20%</td>
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<tr>
<td>reconstruction methods</td>
<td></td>
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<tr>
<td>Partial volume effect (PVE)</td>
<td>Underestimates SUV in lesions with diameters &lt; 2-3 times spatial resolution of scanner</td>
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Metabolic Tumor Volume

- Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) may be more reliable markers of tumor burden and aggressiveness and better prognostic markers in NSCLC
- The tumor is delineated by a specific threshold SUV or other methods
- MTV = the volume of the delineated tumor
- TLG = MTV x SUVmean
- Commercial tools enable rapid measurement of these indices
- MTV/TLG are being used for risk stratification in NSCLC
Metabolic Tumor Volume

• Meta-analysis, 13 eligible studies, 1581 patients

• Patients with high MTV had a worse prognosis - HR 2.71 (95 % CI 1.82-4.02, p<0.001) for adverse events and HR of 2.31 (95 % CI 1.54-3.47, p<0.001) for death

• High TLG also showed a similar worse prognosis - HR 2.35 for adverse events, 2.43 for death

• Prognostic value of MTV and TLG remained significant in a subgroup analysis according to TNM stage

PERCIST Guidelines for Assessment

- SULpeak in up to 5 lesions with greatest FDG uptake
- Tumor size optimally $\geq 2$ cm
- Response is expressed as % change in SULpeak (or sum of tumor SULs) between examinations
- Because overall SUL is calculated, the lesions measured on separate examinations can differ

<table>
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<tr>
<th>Response Category</th>
<th>Criteria</th>
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<td>Complete metabolic response</td>
<td>SUL normalization of all lesions to less than the mean liver SUV and equal to normal surrounding tissue</td>
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| Partial metabolic response     | ≥30% decrease in the SUL peak  
Verification with follow-up study if anatomic criteria indicate disease progression |
| Progressive metabolic disease | >30% increase in the SUL peak  
75% increase in TLG of the 5 most active lesions  
Visible increase in extent of FDG uptake  
New lesions  
Verification with follow up study if anatomic criteria indicate complete or partial response |
| Stable metabolic disease       | Neither partial nor progressive disease                                   |

SUVpeak

- SUVmax is the highest single-voxel within the ROI and is adversely affected by noise.
- SUVpeak = mean SUV within a small region of interest (ROI) centered on the high-uptake part of the tumor.
- Because of its larger volume, SUVpeak is less affected by image noise than SUVmax.
- However, altering the size, or location of ROIpeak can potentially significantly affect SUVpeak.