Current Clinical Practice of Tumor Response Assessment
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Learning Objectives
- Review various response assessment criteria used in clinical trials
- Illustrate some limitations of response assessment at imaging
- Discuss how response assessment often is performed in daily clinical care

Evolving Concept of "Response"
- Cytotoxic chemotherapy
  - Response = tumor shrinkage
  - No size change = drug failure
- Targeted therapies
  - Response = no size change, or tumor shrinkage
  - No size change = drug success
- Immunotherapy
  - Response = tumor shrinkage, or initial enlargement then shrinkage, or shrinkage despite new lesion(s)
  - No size change, or shrinkage with new lesions = drug success
- Locoregional ablative techniques
  - Response = ablation zone larger than tumor
  - No size change = treatment failure
- Paradigm shift - from "curing cancer" to making cancer a "chronic disease"

Common response criteria used in clinical research trials
- General criteria
  - WHO (World Health Organization)
    - Largest tumor diameter x largest perpendicular tumor diameter
    - Measurable disease
      - CR [Complete Response] Disappearance of all known disease, observed at least 4 weeks apart
      - PR [Partial Response] >50% decrease in sum of products of perpendicular diameters; no new lesion
      - NC (SD) [No Change (Stable Disease)] Neither PR nor PD
• PD [Progressive Disease]  >25% increase in product of perpendicular diameters of lesion(s); or appearance of new lesion

- Non-measurable disease
  - CR  Disappearance of all known disease, for at least 4 weeks
  - PR  >50% estimated decrease in size
  - NC (SD)  Neither PR nor PD
  - PD  >25% estimated increase in size, or appearance of new lesion

- Overall response (measurable disease + non-measurable disease)
  - Progression anywhere = PD
  - Persistence anywhere despite substantial improvement elsewhere = PR

○ RECIST (Response Evaluation Criteria In Solid Tumors), versions 1.0, 1.1
  - Largest tumor diameter
  - In clinical trial, use the criteria version specified in the protocol; do not automatically switch from RECIST 1.0 to RECIST 1.1 for trials in progress
  - Some major changes in RECIST 1.1 (compared to RECIST 1.0) include:
    - Maximum of 5 measurable lesions per patient, up to 2 per organ
    - Minimum target lesion size (long axis) at CT or MRI is 10 mm, except 15 mm (short axis) for lymph node
    - Short axis measurement used for lymph nodes
      - Normal: <10 mm
      - Non-measurable: 10 to <15 mm
      - Measurable (Target): ≥15 mm
    - Soft tissue component of a lytic or a mixed lytic and blastic bone metastasis can be measurable disease
    - PET may be used as a complement to CT, particularly for PD

- Target lesions
  - CR  Disappearance of all target lesions. Any pathological lymph nodes must have short axis <10 mm
  - PR  >30% decrease in sum of diameters since baseline; no new lesion
  - SD  neither PR nor PD
  - PD  >20% increase in sum of diameters of target lesions since nadir AND absolute increase ≥5 mm; or appearance of new lesion

- Non-target lesions
  - CR  Disappearance of all non-target lesions. All lymph nodes <10 mm (short axis)
  - Non-CR/Non-PD  Persistence of non-target lesion(s)
• PD: Unequivocal progression of existing non-target lesions, or new lesion

  o NOTE: The WHO and RECIST articles explicitly state that the response criteria were designed for use in clinical trials, not for guiding decisions in the care of an individual patient.

• Disease-specific criteria
  o Hepatocellular carcinoma
    ▪ EASL (European Association for the Study of the Liver)
      • Response criterion: Reduction in viable tumor estimated visually as extent of contrast uptake at arterial-phase CT or MRI
    ▪ mRECIST (modified RECIST)
      • Assessment of intratumoral arterial enhancement in target lesions
      • CR: Disappearance of any intratumoral arterial enhancement in all target lesions
    ▪ RECICL (Response Evaluation Criteria In Cancer of the Liver)
      • Proposed by the Liver Cancer Study Group of Japan
      • Criteria address adequacy of ablative margins after locoregional therapies such as radiofrequency ablation and transcatheter arterial chemoembolization
  o Gastrointestinal Stromal Tumor (GIST)
    ▪ Choi
      • PR: ≥10% decrease in unidimensional size, or ≥15% decrease in CT attenuation measurement (HU)
      • PD: New or enlarging intratumoral nodules
  o Renal cell carcinoma
    ▪ SACT (Size and Attenuation CT)
      • PD if marked central fill-in of previously centrally necrotic metastasis, or new enhancement in homogeneously hypoattenuating, nonenhancing mass
      • Requires 3D analysis (proprietary)
    ▪ MASS (Morphology, Attenuation, Size, and Structure)
      • Favorable response: No new lesion, AND ≥20% decrease in tumor size, or predominantly solid enhancing lesion with marked central tumor necrosis or ≥40 HU decrease in CT attenuation
      • Indeterminate response: Neither Favorable nor Unfavorable response
      • Unfavorable response: ≥20% increase in tumor size in absence of marked central necrosis or marked decreased CT attenuation; or new metastasis; or marked central fill-in or new enhancement of previously homogeneously hypoattenuating, nonenhancing mass
- **Lymphoma**
  - **Cheson**
    - Abnormal lymph node: Long axis >1.5 cm, or long axis 1.1-1.5 cm AND short axis >1.0 cm
    - Nodes: CR if any nodal mass becomes PET negative, or if nodes initially were variably FDG-avid or PET negative but regressed to normal size on CT
    - Nodes: PR if ≥50% decrease in sum of products of diameters of up to 6 largest dominant nodal masses, with no increase in size of other nodes
    - Hepatic or splenic nodules: PR if ≥50% decrease in sum of products of diameters of nodules (for single nodule in greatest transverse diameter)

- **Bone tumors**
  - **Huvos criteria**
    - Good response: >90% necrosis in resected tumor specimen at histopathologic analysis

- **Modality-specific criteria**
  - **PET**
    - **EORTC (European Organization for Research and Treatment of Cancer)**
      - Progressive Metabolic Disease (PMD): >25% increase in \( ^{18}\text{F}\)-FDG tumor SUV relative to baseline scan; or visible increase >20% in longest dimension of tumor uptake; or new uptake
      - Stable Metabolic Disease (SMD): <25% increase or <15% decrease in \( ^{18}\text{F}\)-FDG tumor SUV; no visible increase in uptake extent
      - Partial Metabolic Response (PMR): >15-25% decrease in \( ^{18}\text{F}\)-FDG tumor SUV after 1 cycle of chemotherapy, and >25% decrease after >1 treatment cycle
      - Complete Metabolic Response (CMR): Complete resolution of \( ^{18}\text{F}\)-FDG uptake within tumor (same uptake as normal surrounding tissue)

  - **PERCIST (PET Response Criteria In Solid Tumors)**
    - Assess normal reference tissue values in a 3-cm-diameter ROI in liver
    - Use a fixed, small ROI (1.2-cm diameter [corresponding to approximately 1 cm\(^3\)]) in most active region of metabolically active tumors
    - Assess SUV lean measurements in the most metabolically active tumor focus as a continuous variable
    - Response: >30% decline in SUV
• Treatment-specific criteria
  o Immunotherapy
    ▪ Delay in appearance of radiologic changes after successful immunotherapy, due to time required for T-cell expansion and subsequent infiltration of the tumor
    ▪ irRC (immune-related Response Criteria)
      • Largest tumor diameter x largest perpendicular tumor diameter
      • Tumor burden: Sum of diameter products of all measurable lesions, including baseline and new lesions
      • Four favorable response patterns:
        - Immediate response - Rapid resolution of tumor
        - Durable stable response - Stable disease with possible continued slow decrease in tumor burden
        - Increase followed by response - Tumor initially enlarges, then decreases in size
        - Response despite new lesions - New lesions that contribute <25% to total tumor burden do not alone imply PD

Limitations in response assessment
• Intra- and inter-reader variability

• Ambiguous or absent criteria
  o Enlargement of tumor due to extensive internal hemorrhage
  o Increase in amount of solid tumor within a cystic mass, despite interval decrease in size of mass

• Which lesions to select
  o Response assessment classification in patients with renal cell carcinoma is affected by exclusion or inclusion of the primary renal tumor (which may not be resected) in the calculations
    ▪ Primary tumor is often much larger than its metastases, and thus mathematically dominates the sum of lesion diameters

• How many lesions to select
  o Selecting 6 lesions (bidimensional measurements) or 4 lesions (unidimensional measurement) results in 90% decrease in variance of summed diameters

• Technical variations
  o On repeat lung CT scans taken 15 minutes later, 84% of lung tumor measurements were ± 10% of earlier measurement
    ▪ 3% were sufficiently different that an apparent PD would be recorded
Response criteria in daily clinical practice

- Clinical signs and symptoms - e.g., decreased swelling, decreased pain
- Laboratory data - e.g., decreased serum alkaline phosphatase level
- Radiologic findings - e.g., decreased bidimensional measurements, sclerosis of lytic lesion, reduced perfusion

References


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