Imaging response assessment for oncology: An algorithmic approach

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ABSTRACT

Treatment response assessment by imaging plays a vital role in evaluating changes in solid tumors during oncology therapeutic clinical trials. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 is the reference standard imaging response criteria and provides details regarding image acquisition, image interpretation and categorical response classification. While RECIST 1.1 is applied for the majority of clinical trials in solid tumors, other criteria and modifications have been introduced when RECIST 1.1 outcomes may be incomplete. Available criteria beyond RECIST 1.1 can be explored in an algorithmic fashion dependent on imaging modality, tumor type and method of treatment. Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) is available for use with PET/CT. Modifications to RECIST 1.1 can be tumor specific, including mRECIST for hepatocellular carcinoma and mesothelioma. Choi criteria for gastrointestinal stromal tumors incorporate tumor density with alterations to categorical response thresholds. Prostate Cancer Working Group 3 (PCWG3) imaging criteria combine RECIST 1.1 findings with those of bone scans. In addition, multiple response criteria have been created to address atypical imaging responses in immunotherapy.

1. Introduction to imaging treatment response

In cancer care, evaluating changes in tumor size has become a well-accepted objective metric of treatment response in oncology therapeutic clinical trials. Using changes in size in sites of disease to determine treatment response of promising therapies continues to play an increasingly important role for drug discovery. One of the initial attempts to formalize this concept was an evaluation of simulated tumor size reproducibility by oncologists in 1976 and the effect of measurement variation on defining an objective response rate amongst patients in therapeutic clinical trials [1,2]. The World Health Organization (WHO) furthered this initiative with proposing a standardized response classification of treatment response differentiated by thresholds of change in tumor size, which included the categories: complete response, partial response, no change and progressive disease; as evaluated on clinical exam or radiograph [3]. Since then, use of cross-sectional imaging emerged as a standard method to detail anatomic distribution of tumor, quantitative measurements and changes in tumor size. Response Evaluation Criteria in Solid Tumors (RECIST) was introduced to modernize and provide further clarifications for more uniform reporting of clinical trial results [4]. With further modifications, RECIST 1.1 has become the reference standard for imaging treatment response assessment [5]. However, over time, with emerging new classes of cancer treatments and improved understanding of cancer biology on imaging, additional treatment or tumor specific response criteria have also been adopted. These response criteria can be used in place of RECIST 1.1, or
often as a supplemental method in addition to RECIST 1.1 to capture treatment/tumor specific predictive and prognostic information. Determining which response criteria to apply can be considered in an algorithmic fashion, predicated on imaging modality, tumor type, and method of treatment (Fig. 1).

2. Response criteria for solid tumors (RECIST) 1.1

The most commonly used response assessment criteria for solid tumors is RECIST 1.1 [5]. This criteria provides a standardized structure to the acquisition, review, measurement and reporting of imaging in oncology clinical trials [5]. By RECIST 1.1, baseline imaging is performed just prior (ideally within 4 weeks) to initiating therapy. Up to five tumors (two per organ system) are selected, measured and then followed over time. These target lesions must meet a minimum size threshold of 10 mm longest diameter for solid tumors and 15 mm short axis for lymph nodes. The relevant measurement of each tumor is added together to form the “sum of diameters”, a numerical representation of tumor burden from which future imaging time points will be compared [5]. Any additional lesions beyond these target lesions are deemed non-target lesions and are qualitative assessed, similar to additional sites of truly non-measurable disease such as ascites, pleural or pericardial effusion, sclerotic bone metastases, lymphangitic carcinomatosis (circle) and malignant ascites.

At each subsequent imaging timepoint, target lesions are re-measured in a similar fashion and a sum of diameters is calculated. This value is compared to either the baseline or if available, nadir (best response scan) to determine if there has been a significant change in tumor size. Disease progression (PD) is defined as a relative increase in 20% or more (with an absolute increase of at least 5 mm) of the sum of diameters when compared to baseline or nadir. Development of any new malignant lesion(s) also meets criteria for disease progression. Partial response (PR) represents a decrease in sum of diameters by at least 30% from baseline. Complete response (CR) is the disappearance of all lesions. Stable disease (SD) represents an increase in tumor size less than 20% or decrease less than 30%. Non-target disease is also assessed, although qualitatively at each time point; categorized as either completely resolved, unequivocally worsened, or neither resolved nor progressed.

RECIST 1.1 has been shown to be a good evaluator of treatment response for both classic chemotherapy and targeted agents, and remains the reference standard in response assessment for solid tumors [7]. However, additional response criteria have been created when patterns of response due to certain tumor-type biology or mechanisms of action of treatment agents is not adequately captured by RECIST 1.1 (Table 1).

3. Immunotherapy

Immune checkpoint inhibitors have transformed advanced cancer care, and for numerous tumor types have resulted in significant improvements in patients’ survival and quality of life [8]. In the past 7 years over 85 new oncology indications for antibodies directed against the programmed death (PD-1) or programmed death ligand (PD-L1) pathway have been approved by the US Food and Drug Administration [9]. Immune checkpoint inhibitors mechanistically differ from other cytotoxic and cytostatic agents, with T cell regulation specific to tumor
cells resulting in an enhanced native immune response against tumors [8, 10, 11], as opposed to direct cytotoxic or cytostatic drug effects on tumors from traditional and other targeted chemotherapies. Due to this different biology, unconventional tumor response patterns can be seen, including pseudoprogression [11,12]. Pseudoprogression is defined as a treatment response which occurs after an initial increase in tumor burden or development of new lesions which would otherwise be classified as disease progression by RECIST 1.1 (Fig. 3) [13]. As such, any new lesions did not represent disease progression. Instead, the SPD of any new lesions was added to the SPD of the selected target lesions to represent a total tumor burden. Thresholds of response remained similar to those of WHO criteria, and included a >20% increase in tumor burden for partial response and a >25% decrease in tumor burden for complete response.

### Table 1

| Baseline Characteristics | Categorical Responses |
|-------------------------|-----------------------|
| No. target lesions      | CR                    |
| 5 lesions               | Disappearance of all target and non-target lesions |
| ≤2 per organ            | ≥30% decrease in sum of diameters (SOD) |
| RECIST 1.1              | PR                    |
| PERCIST                 | Nether PR nor PD      |
| Single tumor with highest SUVpeak in 1.2 cm ROI | Decrease by >30% in the target measurable tumor with a 0.8 unit decline in SUVpeak |
| irRECIST                | Unchanged or a less than 30% increase or decrease in SUVpeak |
| mRECIST                 | Nether PR nor PD      |
| Pleural disease: ≥2 locations at 3 different axial levels | ≥30% reduction in total tumor measurement |
| mRECIST mesothelioma    | Nether PR nor PD      |
| 2 liver lesions         | ≥20% increase in total tumor measurement over nadir; New lesions |
| 5 lesions total         | New lesions, Unequivocal increased non-target disease |
| mRECIST hepatocellular carcinoma | Choi criteria          |
| 5 lesions               | Soft tissue: Disappearance of all lesions |
| ≤2 per organ            | Decrease in size ≥10% OR Decrease in tumor density ≥15% |
| PCWG3                   | Nether PR nor PD      |
| RECIST 1.1: 5 lesions   | Soft tissue: ≥30% decrease in sum of diameters (SOD) |
| ≤2 per organ            | Bone scan: not specified |
| Immunotherapy           | Soft tissue:            |
| irRC                    | No minimum size lesion in 2 dimensions (Sum of the product of the diameters (SPD)) |
| Up to 10 visceral and 5 cutaneous lesions (≤5 per organ) | Disappearance of all target and non-target lesions |
| ≥50% decrease in tumor burden (SPD) |
| iirRC, imRECIST         | Soft tissue: ≥10 mm in diameter; lymph nodes ≥15 mm short axis |
| 5 lesions               | Disappearance of all target and non-target lesions |
| ≤2 per organ            | ≥30% decrease in TMTB from baseline |
| Nether iPR nor ipD      | New lesions: added to TMTB |
| iUPD:                   |               |
| RECIST 1.1 PD           |               |
| iCPD: further increased tumor: |
| ≥5 mm sum of target lesions OR new target lesions, further increase non-target or new lesions, increased number new lesions |

As the first immune-specific criteria to be formulated, irRC was adopted from the WHO criteria [12]. As such, irRC allowed for measurement of the sum of product diameters (SPD) of up to 10 visceral lesions (5 lesions per organ) and 5 cutaneous lesions. For treatment assessment, new lesions did not represent disease progression. Instead, the SPD of any new lesions was added to the SPD of the selected target lesions to represent a total tumor burden. Thresholds of response remained similar to those of WHO criteria, and included a >25% increase in tumor burden for partial response and a >−50% decrease in tumor burden for complete response.
tumor burden for disease progression [12].

However, use of bidimensional measurements by irRC limited direct comparisons to clinical trials in which unidimensional assessments by RECIST 1.1 were used. Bidimensional measurements were also shown to result in higher variability in measurement [11]. Therefore, irRECIST was introduced as a merging of concepts specific for immunotherapy from irRC with conventional RECIST. Measurable disease was unified with RECIST 1.1 and defined as lesions ≥10 mm longest diameter. RECIST 1.1 categorical thresholds were also utilized, with ≥30% decrease for partial response and ≥20% increase for progressive disease. However, aspects of irRC were also included. For treatment assessment, both the target disease and any new lesion(s) were summed together to be the numerical representation of total tumor burden and from which categorical response is calculated. Disease progression also required confirmation by two consecutive observations at least 4 weeks apart [14].

irRECIST definitions had been created as a construct to compare reproducibility of bidimensional versus unidimensional measurements in irRC. Therefore, imRECIST was introduced to provide further details necessary for criteria implementation and analysis of image based outcome measures such as progression free survival (PFS) and best overall survival [15]. Again relying on the constructs of RECIST 1.1, imRECIST defines target lesions by unidimensional measurements with target lesion criteria including number and measurability per RECIST 1.1. Categorical thresholds of at least 20% increase in size for disease progression from baseline/nadir and at least 30% decrease in size from baseline for partial response are also inherited by imRECIST. Like irRECIST, new lesions do not constitute disease progression but when measurable are incorporated into the total tumor burden. When new lesions are nonmeasurable they do not result in disease progression. Unlike RECIST 1.1, worsening of non-target disease does not contribute to progressive disease, but can contribute to complete response if all non-target lesions disappear. Therefore, disease progression is only determined by the measurable disease. However imRECIST progression is not considered progression for progression free survival assessment if the subsequent confirmatory study has a categorical response of SD, PR or CR [15].

The RECIST working group introduced iRECIST in 2017 as a method to standardize data collection from immunotherapy clinical trials [16]. With iRECIST the main principles of RECIST 1.1 hold true, except for assessment of disease progression. Initial disease progression is the same for both iRECIST and RECIST 1.1, and is defined as an ≥20% increase in sum of diameters (absolute 5 mm increase) from baseline/nadir, development of new lesions or unequivocal worsening of non-target disease. For iRECIST, new lesions should be differentiated into new measurable and new non-measurable lesions, with a maximum of 5 new lesions (2 per organ). This initial disease progression is defined as unconfirmed progressive disease (iUPD) in iRECIST. A follow up imaging timepoint 4-8 weeks later is recommended if the patient is clinically stable. If there is a further increase (≥5 mm) of the target sum, further worsening of non-target disease and/or increase in the new measurable or nonmeasurable lesions either in number or size (sum ≥ 5 mm) then progressive disease is confirmed (iCPD) [16,17].

3.1. PET-CT

Multimodality imaging with $^{18}$F-FDG PET/CT can provide insight to the anatomic distribution of tumor and information on physiologic glucose metabolism [18]. PET/CT is commonly used in various clinical scenarios for initial diagnosis, staging, restaging and treatment response assessment [18]. Methods have been proposed to standardize both, the acquisition and interpretation of PET/CT for its use in clinical trials.

3.1.1. Positron emission tomography response criteria in solid tumors (PERCIST)

PERCIST 1.0 was introduced in 2009, designed to create a standardized approach to baseline selection of metabolic disease and reliable, reproducible assessment of treatment response on $^{18}$FDG PET/CT [19]. A single target lesion is selected at baseline upon finding the tumor with the highest FDG uptake and is then measured by placing a 1.2 cm diameter region of interest (ROI) over the area of highest FDG uptake [19]. For quantitative measurement, SUV should be corrected for lean
body mass (SUL) to measure tumor peak standardized uptake value corrected for lean body mass (SUL peak) [19–21].

As a reference value, mean SUL and standard deviation obtained from a 3 cm diameter spherical volume of interest in the right hepatic lobe is defined as normal background 18FDG. For a tumor to be considered measurable at baseline, its SUL peak must measure at least 1.5 times the mean SUL measured in the liver plus or minus two standard deviations [19,20].

On follow up 18FDG PET/CT, maximal SUL peak is again measured from the most metabolically active tumor, which may not necessarily be the same target at baseline [19]. The percent change in SUL peak from baseline is then calculated and reported as a continuous variable, along with the number of weeks since treatment has begun [19,20].

Categorical responses can also be reported. A complete metabolic response (CMR) is defined as a decrease in FDG uptake of all target and non-target lesions below background blood-pool. A partial metabolic response (PMR) is defined as a decrease by at least 30% and at least 0.8 unit decline in SUL peak in the most avid lesion from each timepoint (may be different lesions) with < 30% increase in SUL or size of target or nontarget lesions, and no new FDG-avid lesions in a pattern suggestive of cancer. Stable metabolic disease (SMD) represents unchanged or a less than 30% increase or decrease in SUL peak. Progressive metabolic disease (PMD) is a result of a 30% and 0.8 unit increase in SUL peak from baseline, unequivocal progression of FDG avid non-target disease or the development of new FDG avid lesions in a pattern suggestive of cancer. Visibly increased extent of tumor with a greater than 75% increase in total lesion glycolysis will also result in PMD [19,20].

3.2. Technical considerations:

Standardization of image acquisition requires well-calibrated and well-maintained PET/CT scanners. For uniform patient preparation, patients should be fasting for at least 4–6 h prior to imaging and have a serum glucose level < 200 mg/dL. The baseline PET should be obtained 50–70 min from radiotracer injection with all other subsequent imaging performed within 15 min from the baseline timing [20]. Patients should be imaged on the same PET scanner each time, using the same injected dose ± 20% of radioactivity [20]. Background liver uptake should consistently be within 0.3 SUL unit from study to study [20].

3.2.1. Tumor specific criteria

3.2.1.1. Gastrointestinal stromal tumors. Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and most commonly arise in the stomach, small intestine, rectum, colon and esophagus [22]. In the metastatic setting, tumor deposits are most commonly seen in the liver and peritoneal cavity. Imatinib mesylate, a small-molecule tyrosine kinase inhibitor, received initial approval in 2002 for the treatment of metastatic GIST and has resulted in dramatic improvements in survival and patient outcomes [22,23]. However, it was shown that actual changes in tumor size were small and use of RECIST 1.1 can underestimate tumor response [24,25]. Instead, treatment efficacy was associated with significant changes in tumor density, enhancement of intratumoral tumor nodules and tumor vessels when evaluated with contrast enhanced CT [26]. Therefore modifications to CT response evaluation criteria to include changes in tumor size and density were proposed specifically to assess for treatment response to imatinib in patients with GIST [26], called the Choi criteria. Complete response is defined by the disappearance of all lesions. Partial response is defined by a decrease in size by at least 10% or a decrease in tumor density (Hounsfield Unit (HU)) by at least 15% on CT (Fig. 4). Progressive disease occurs with an increase in tumor size by at least 10% and does not meet criteria of partial response by tumor density (HU) on CT. New lesions, new intratumoral nodules, or increase in size of existing intratumoral nodules also defined disease progression [26]. It has been shown that use of Choi criteria better correlated with time to progression and disease-specific survival compared to RECIST [25]. However, it has also been shown that use of RECIST 1.1 could also provide prognostic information, with absence of disease progression indicating improved survival [27].

3.2.1.2. Hepatocellular carcinoma. Hepatocellular carcinoma (HCC) demonstrates characteristic imaging features on multiphasic imaging,
including arterial phase hyperenhancement with portal venous or delayed washout [28]. Modifications to RECIST (mRECIST) have been created to include an evaluation for treatment related alterations in viable tumor, as measured by arterial enhancement. Decreased or resolved arterial phase hyperenhancement is likely indicative of response evidenced by tumor necrosis and may occur regardless of changes in tumor size [29–32].

Using mRECIST, up to two liver lesions can represent target lesions if they are well delineated and demonstrate non-rim arterial enhancement measuring at least 10 mm in greatest diameter and excluding regions of tumor necrosis (Fig. 5) [31]. It is suggested to not include liver lesions which are infiltrative or not well marginated, those which have undergone prior local therapy, as well as malignant portal vein thrombosis as target lesions [30]. mRECIST criteria also increase the size threshold to 20 mm short axis for porta hepatic lymph nodes, including portocaval and gastrohepatic lymph nodes to be considered pathologic and measured as target lesions [30,31]. Any other extra-hepatic sites of disease can be accounted similar to RECIST 1.1 as target and non-target disease.

Categorical responses by mRECIST are determined in part by evaluating for the presence and greatest diameter of arterial enhancement on subsequent imaging of the target lesions. A complete response represents resolution of all intra-tumoral arterial enhancement in target and non-target liver disease as well as disappearance of any additional extraneoplastic lesions. In the setting of malignant portal vein thrombus, complete resolution of enhancement is also required for complete response [31]. A decrease in the sum of diameters of arterial hyperenhancing liver lesions and any additional extra-hepatic target lesions from baseline by at least 30% is defined as partial response. Stable disease represents a category in which neither definition of partial response nor disease progression are met. Disease progression is a result of an increase in the sum of the diameters (including arterial enhancement of liver lesions) by at least 20% (with 5 mm absolute increase). Development of new lesion(s) and/or significant worsening of non-target disease also represents disease progression. [30,31]. New liver lesions must measure at least 10 mm in size and demonstrate imaging characteristics of hepatocellular carcinoma with arterial phase enhancement with portal venous or delayed washout [29,31].

3.4. Mesothelioma

Malignant pleural mesothelioma is an uncommon neoplasm which can arise from the pleura. Unilateral rind-like nodular pleural thickening, interlobar fissural thickening and pleural effusion can commonly be seen by imaging [33]. The natural circumferential tumor growth along the pleura by mesothelioma is not well characterized by RECIST 1.1 due to the response assessment’s spherical assumptions [34]. Instead, modifications (mRECIST) have been developed to capture short axis pleural thickness perpendicular to the chest wall or mediastinum on axial imaging [34,35]. Areas of pleural thickness of at least 10 mm in short axis thickness can be measured in up to two locations at three separate axial levels along the pleura, giving preference to tumor in the upper thorax (above carina) and regions of greatest pleural thickness (Fig. 6). These pleural measurements are then summed to represent a single diameter [34,36]. Any non-pleural sites of metastases can also be accounted for as target or non-target disease per RECIST 1.1 [36]. These areas of pleural thickening are re-measured on post-baseline imaging at the same level to determine categorical response by mRECIST. A complete response represents disappearance of all target and non-target disease. Partial response results from a decrease in total tumor measurement by at least 30%. Stable disease is measured tumor burden which does not meet the threshold for either partial response nor disease progression. Disease progression results from an increase in 20% or more of total measured tumor [34].

3.5. Prostate cancer

Prostate cancer is the most common cancer amongst men and is known to have high inter and intra-patient heterogeneity of disease biology [37,38]. When metastatic, tumor most commonly spreads to bones, lymph nodes, liver, and lungs [38]. Given this disease distribution, radionuclide bone scanning and conventional CT and MRI are commonly used in synergy for detection of metastases and response assessment, with assessments previously shown to be associated with overall survival [39]. While next generation imaging techniques, including whole body MRI and prostate-specific membrane antigen (PSMA) PET/CT have been shown to be more sensitive in detecting metastases, they may be used at baseline, but are not yet routinely used in all timepoints in therapeutic clinical trials [38,40,41] with continued reliance of 99mTc bone scan.

The Prostate Cancer Clinical Trials Working Group 3 (PCWG3) recommendations provide guidelines for baseline assessment and serial follow up of patients with prostate cancer in clinical trials. Taking a more holistic approach, these guidelines recommend integrating serial imaging assessments with other predictive biomarkers, including blood‐based biomarkers (eg. PSA and circulating tumor cells), patient reported outcome measures to assess health-related quality of life and/or biopsy results. Instead of focusing on evaluating for the first evidence of disease
progression, PCWG3 emphasizes data integration to better determine when patients are no longer clinically benefiting, and treatment should be discontinued [42].

For imaging response assessment, PCWG3 relies on RECIST 1.1 for extraskelatal imaging response assessment [42]. However, these guidelines also recommend collecting additional image-based information to better capture anatomic distribution and tumor heterogeneity. Similar to RECIST 1.1, lymph nodes at least 15 mm short axis can be measured as target lesions, and lymph nodes measuring 10–15 mm are considered pathologic [5,42]. Per RECIST 1.1, lymph nodes are considered an organ system, and only two target lesions can be included from the same organ system [5]. PCWG3 recommends recording up to five lymph nodes and defining them as either pelvic (locoregional) or extrapelvic (metastatic eg. retroperitoneal, mediastinal, thoracic or other) in location. A more detailed description of anatomic disease burden is also suggested by PCWG3, including recording individual sites of disease spread (eg. lung, liver, adrenal, central nervous system) separately and to include up to five lesions per organ site. With respect to progression, PCWG3 also recommends differentiating radiographic disease progression by growth of existing lesions versus development of new lesions [42].

Imaging with 99 m-Tc-methylene diphosphonate radionuclide bone scintigraphy is used for evaluating bone disease by PCWG3. Pre-treatment bone disease is recorded on baseline bone scan. In the setting of worsening bone disease, a “2 + 2” rule is used to control for potential tumor flare; defined as a paradoxical worsening of bone disease due to bone healing. By this rule, disease progression by only bone disease is defined as the appearance of 2 or more new lesions by bone scan which must be then confirmed 6 or more weeks later and with the appearance of at least 2 additional new lesions (Fig. 7) [43,44]. Enlargement of pre-existing bone lesions by bone scan does not meet criteria for disease progression [38].

4. Conclusion

Image-based outcome measures are more commonly being used as intermediate endpoints in clinical trials and for regulatory approval [45]. A fundamental understanding of imaging response assessment and available imaging response criteria is essential for patient care and trial reporting. While RECIST 1.1 remains the reference standard for evaluating solid tumors, multiple additional criteria are also available to select from when evaluating certain tumor types, assessing response to immunotherapy or incorporating PET imaging.

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