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A Radiologist's Guide to Response Evaluation Criteria in Solid Tumors

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Response Evaluation Criteria in Solid Tumors (RECIST), including version 1.0 and 1.1, has been universally accepted as the standard response assessment criteria for conventional chemotherapies. Increasing use of immunotherapy led to the need and development of immune-related RECIST. Imaging plays a crucial role in response assessment for solid tumors in guiding patient management as well as in clinical trials. Familiarity to different response criteria will help radiologists to optimally identify, select, and measure tumor lesions per the criteria and assess response to therapy. This article provides a comprehensive review of published RECIST criteria.

Introduction

Objective and standardized tumor measurements are essential to determine patient response and therapeutic efficacy of drugs for clinical trials that rely on an imaging endpoint. In 1981, World Health Organization (WHO) proposed criteria to address the need for standardized imaging-based objective assessment of tumor burden, as well as to facilitate comparison between studies.[1] In 2000, the International Working Group (IWG), comprising of members from European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of United States, and NCI of Canada Clinical Trial Groups introduced the Response Evaluation Criteria in Solid Tumors (RECIST 1.0), to further simplify the WHO criteria and provide a standard criteria for solid tumor assessment across clinical trials.[2] Following continuous testing and validation, a revised and updated RECIST version 1.1 was introduced in 2009 by the RECIST Working Group.[3] RECIST 1.1 is the most commonly used objective assessment criteria for tumor response.[4–7] Both WHO and RECIST criteria have been validated on patients treated with standard cytotoxic chemotherapeutics.

Immunotherapy is a new class of anticancer therapy and drugs within this class may modulate the immune pathways to enhance tumor recognition and cell death. These immuno-oncology (IO) agents may initially cause tumoral inflammation and therefore may not show a decrease in tumor size as early as traditional cytotoxic therapies. This unusual tumor response of tumor "flare" may be more pronounced in some patients or cancers and is labeled as “pseudoprogression.”[8–12] Recognition of this early tumoral inflammation led to the introduction of immune-related response criteria (irRC) in 2009, a modified WHO criteria tailored to better assess the response pattern observed in this patient population.[13] The irRC was based on bidimensional lesion measurements, as opposed to the widely accepted unidimensional RECIST criteria. In 2013, Nishino *et al.* proposed modification to irRC using unidimensional measurements to align with RECIST in assessing tumor response to immunotherapy.[14] In 2014, Bohnsack *et al.*, presented an abstract modifying irRC to further align with RECIST 1.1 and incorporating proposed changes from Nishino *et al.*, and named it irRECIST.[15] Recently in 2017, the RECIST Working Group published the consensus response criteria—“immune” RECIST (iRECIST), to address necessary modification to RECIST 1.1 for cancer immunotherapy trials. Their proposal aims to employ consistent framework in design and data collection for clinical trial database that can be used for validation of the guidelines, with no intention to define or guide clinical or treatment decisions.[11] Given the various available response criteria, the importance of understanding the mechanism of action of chemotherapy (cytotoxic versus immune mediated) when determining the criteria for the trials cannot be overemphasized.

RECIST (1.0)[2]: The RECIST 1.0 criteria were developed to standardize treatment response monitoring in solid tumors treated with cytotoxic and cytostatic cancer therapeutics.[2] While the criteria perform best with CT and MRI, it can be used in chest radiographs for clearly defined measurable lesions, as well as measurable cutaneous lesions. Per the guideline, ultrasound may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, thyroid nodules, and subcutaneous lesions. At baseline, tumor lesions are categorized as[2]: “measurable lesions” – lesions that can be accurately (and reproducibly) measured at least in their longest diameter (≥10 mm on axial spiral CT or MRI, and ≥20 mm on conventional chest radiographs), and “nonmeasurable lesions” – that includes all other tumoral lesions that are truly nonmeasurable, as well as measurable small lesions (≤10 mm with spiral CT or MRI and ≤20 mm on

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FIG 1. Axial contrast enhanced CT (CECT) of the abdomen in a 55-year-old male with cholangiocarcinoma (arrow), multiple hepatic metastasis (calipers), and portocaval lymph node (arrowhead). RECIST 1.0 uses unidimensional, long axis ≥10 mm measurable target lesion; ≤5 targets lesion per organ; maximum 10 lesions (lymph node not defined; however, ≥10 mm long axis considered measurable lesion). Tumor burden calculated as sum of longest diameters (SLD): 18.9 + 15.9 + 15.1 + 88.4 + 16.6 + 38.2 = 193.1 mm. RECIST 1.1 and irRECIST uses unidimensional ≥10 mm longest dimension, ≤2 target lesion per organ, lymph node >15 mm short axis. Tumor burden: 18.9 + 88.4 + 25.2 = 132.5 mm (SLD = Sum of Longest diameter for target lesions and short axis for lymph nodes).

conventional chest radiographs). Truly nonmeasurable lesions include the following: ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, leptomeningeal disease, inflammatory breast disease, bone lesions, cystic lesions, and abdominal masses not confirmed or followed by imaging technique. On CT, minimum measurable lesion is set at longest diameter of 10 mm for spiral CT with a maximum of 5 mm contiguous slice thickness (based on the principle that minimum lesion size should be no less than double the slice thickness).

For baseline disease burden documentation, all measurable lesions (based on their longest diameter and suitability for repeated measurements) up to maximum of five lesions per organ and total 10 lesions of all involved organs are identified as "target lesions". The sum of the longest diameters of these lesions is used for objective assessment of tumor response (Fig 1). All other measurable or nonmeasurable lesions, or sites of disease should be identified as "nontarget lesions", and documented qualitatively at baseline, and noted for presence or absence throughout follow-up (Tables 1 and 2).

Assigned objective tumor response categories for *target lesions* per RECIST 1.0 are[2]: *complete response (CR):* disappearance of all target lesions; *partial response (PR):* at least 30% decrease in sum of the longest diameters of target lesions taking as reference the sum of the longest diameters at baseline**;** *progressive disease (PD):* at least 20% increase in sum of the longest diameters of target lesions taking as reference the smallest sum of the longest diameters recorded since treatment started (nadir), or the appearance of one or more new lesions; and *stable disease (SD):* neither PR nor PD (Table 3).

Objective tumor response categories for *nontarget lesions* per RECIST 1.0 are[2]: *CR:* disappearance of all nontarget lesions and normalization of tumor markers levels (based on cancer type); *incomplete response(IR)/SD:* persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker levels above the normal limits; and *PD:* appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

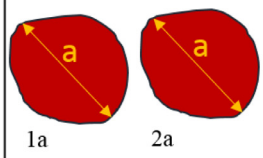
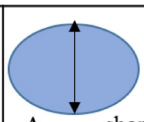
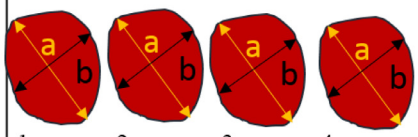
RECIST 1.1[3]: The RECIST 1.1 was introduced in 2009 by the RECIST Working Group, following review of a large database consisting of >6500 patient and >18,000 target lesions.[3,16-19] The revised version had the following major modifications[3]: number of target lesions, criteria for assessment of pathologic lymph nodes, inclusion of fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT for detection of new lesion(s), and improved definition for PD (Table 1).

The definition of measureable and nonmeasurable lesions remains the same as RECIST 1.0, except the new addition of lymph node criteria.[3] In contrast to longest dimension used for measurable target lesions, lymph nodes with short axis ≥15 mm are considered

TABLE 1
Definition of target and non-target lesion on different response criteria

	Target/Index Lesion (Measurable + Reproducible)	Non-Target Lesion (Non-measurable)
RECIST v1.0	Unidimensional (*Longest diameter* ≥10 mm) Max 10 index lesions (≤5 in any one organ) *(Lymph node assessment not further described)*	Lesions <10 mm, pleural/pericardial effusion, ascites, lymphangitis cutis/pulmonis, cystic lesions, leptomeningeal disease, inflammatory breast disease, bone lesions without soft tissue
RECIST v1.1 **irRECIST** **iRECIST**	Unidimensional (*Longest diameter* ≥10 mm) Max 5 index lesions (≤2 in any one organ) Lymph nodes: ≥15 mm short axis	Lymph nodes ≥10 to <15 mm short axis, lesions <10 mm, pleural/pericardial effusion, ascites, lymphangitis cutis/pulmonis, cystic lesions, leptomeningeal disease, inflammatory breast disease, bone lesions without soft tissue, organomegaly by physical exam
irRC **WHO***	Bidimensional (*Product of longest diameter and greatest perpendicular diameter*) Max 10 visceral + 5 cutaneous index lesions (≤5 in any one organ) [* No details on maximum number of target lesions]	Malignant disease evident on physical or radiographic exam but cannot be measured by calipers, lymphangitic cutaneous and pulmonary metastases, leptomeningeal disease, cutaneous lesions, etc.

TABLE 2
Measurable lesions and tumor burden assessment on different criteria

	Target/Index Lesion		Tumor Burden
RECIST 1.1, irRECIST, iRECIST	 Unidimensional Long axis ≥10mm ≤2 in any one organ Max. 5 lesions	 A Lymph node short axis ≥ 15mm	Sum of longest diameters (SLD) and short axis of lymph nodes = 1a +2a + A
WHO irRC	 Perpendicular bidimensional ≤5 in any one organ Max. 15 lesions (10 visceral + 5 cutaneous) Lymph node assessment not further described		Sum of products of perpendicular diameters (SPD) = 1 (a x b) + 2 (a x b) + 3 (a x b) + 4 (a x b)

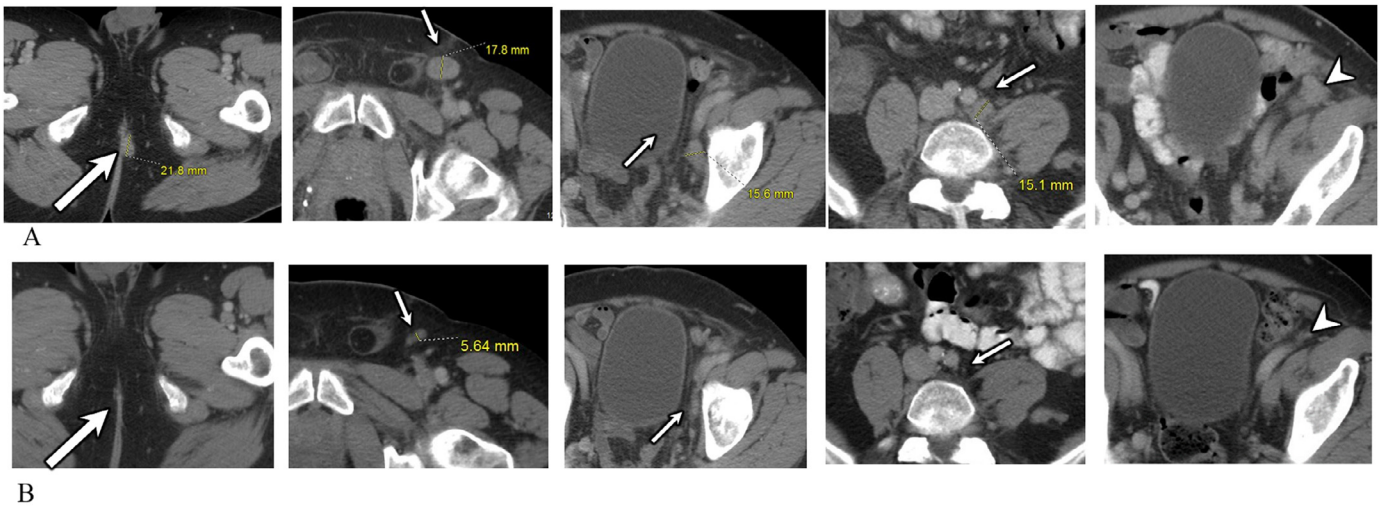
measurable and the short-axis measurement of these lymph nodes should be included in the sum of target lesions. Here, we will refer to this combination of summed long (for target lesions) and short axis measurements (for lymph nodes) in the total tumor burden as the sum of target lesion diameters instead of sum of longest diameters. Lymph nodes with short axis measurement between 10 mm and up to 15 mm are considered nontarget lesions. Lymph nodes with short axis <10 mm are defined as "nonpathologic." The change in lymph node criteria also has implication in tumor response, that is, complete response by RECIST 1.1 requires decrease in short axis measurement of lymph nodes to <10 mm (target and nontarget) in addition to the disappearance of all target and non-target lesions.[3,6] Additionally, osteolytic or mixed lytic-blastic osseous lesions with measurable soft tissue component ≥10 mm can be used as target lesions (Tables 1 and 2).[15]

For baseline evaluation, "target lesions" are measured similarly using their longest dimension as v1.0 but the number of target lesion are reduced from five to two per organ with a maximum total of 5 (compared to 10 in v1.0) lesions. All measurements should be recorded in metric notation (Fig 1). The baseline evaluations should be performed no more than four weeks before the start of treatment.[3]

TABLE 3
Response criteria as defined by different guidelines

	RECIST 1.1	irRC	irRECIST	iRECIST
Complete response (CR)	Disappearance of all lesions	irCR= Disappearance of all lesions (measurable or not, and no new lesion) Confirmation by repeat, consecutive assessment no less than 4 weeks from the date first documented	irCR= Disappearance of all measurable and nonmeasurable lesions (nodes short axis <10 mm) Confirmation of response not required	iCR= Similar to RECIST 1.1
Partial response (PR)	≥30% decrease in SLD from baseline	irPR= ≥50% decrease in SPD from baseline Confirmation by repeat, consecutive assessment at least 4 weeks after first documented	irPR= ≥30% decrease in SLD from baseline	iPR= Similar to RECIST 1.1
Stable disease (SD)	Neither CR, PR or PD	irSD= Neither CR, PR or PD	Neither irCR or irPR in the absence of irPD	iSD= Similar to RECIST 1.1
Progressive disease (PD)	≥20% increase in SLD from nadir (*and* a minimum absolute increase of 5 mm), or unequivocal increase in non-target lesions	irPD: ≥25% increase in SPD from nadir, or unequivocal increase in non-target lesions Confirmation by repeat, consecutive assessment no less than 4 weeks from the date first documented	irPD: ≥20% increase in SLD and a minimum absolute increase of 5 mm in total measurable tumor burden from nadir, or unequivocal increase in non-target lesions or new nonmeasurable lesions Confirmation on repeat scans ≥4 weeks after first irPD	**iUPD=** criteria for PD per RECIST 1.1 but requires confirmation on repeat scans (4-8 weeks) If no progression on follow-up, to be assigned iCR/iPR or iSD based on the shrinkage or stability in tumor burden **iCPD=** confirmation of progression of iUPD lesions at follow-up imaging (4-8 weeks)

iUPD, "immune" unconfirmed PD; iCPD, "immune" confirmed PD; SLD, sum of longest diameters; SPD, sum of product of diameters.
Note: Per irRECIST, irNN (non-irCR and non-irPD) is used when no target lesion is noted at baseline and follow-up fails to meet criteria for irCR or irPD.



	Lesion description	Baseline (mm)	Follow-up 10 weeks (mm)
1	Gluteal fold mass (T)	21.8	0.0
2	Left inguinal lymph node (T)	17.8	5.6
3	Left obturator lymph node (T)	15.6	0.0
4	Para aortic lymph node (NT)	15.1	0.0
5	Inguinal mass (NT)	Present	Non-CR/PD

FIG 2. Complete response per RECIST 1.1. Axial CECT of the abdomen and pelvis in a 60-year-old male with anal carcinoma. (A) At baseline, and (B) 10-weeks post treatment showing: soft tissue perianal mass (arrow), enlarged left inguinal, obturator, left para-aortic lymph nodes (short arrows) & left inguinal soft tissue mass (arrowhead) (<10 mm short axis lymph node considered resolved; T = Target lesion; NT = Nontarget lesion).

RECIST 1.1 allowed FDG-PET to be used to detect "new" disease in defining disease progression (PD). Following algorithms have been defined for defining 'new' lesions on FDG-PET[3]:

(a) Negative FDG-PET at baseline, and positive FDG-PET ("positive" defined as avid FDG uptake of the lesion greater than twice the surrounding tissue on attenuation corrected image) at follow-up suggests PD based on new lesion.

(b) No FDG-PET at baseline, with positive FDG-PET at follow-up:
- Positive FDG-PET confirmed as new site of disease by CT, suggest PD.
- Positive FDG-PET not confirmed as new site of disease on CT requires additional follow-up CT to determine if true progression does occur later at the site, and if so, date of PD will be the date of initial abnormal FDG-PET.
- Positive FDG-PET corresponds to pre-existing disease by CT that is not progressing on the basis of anatomic image is not PD.

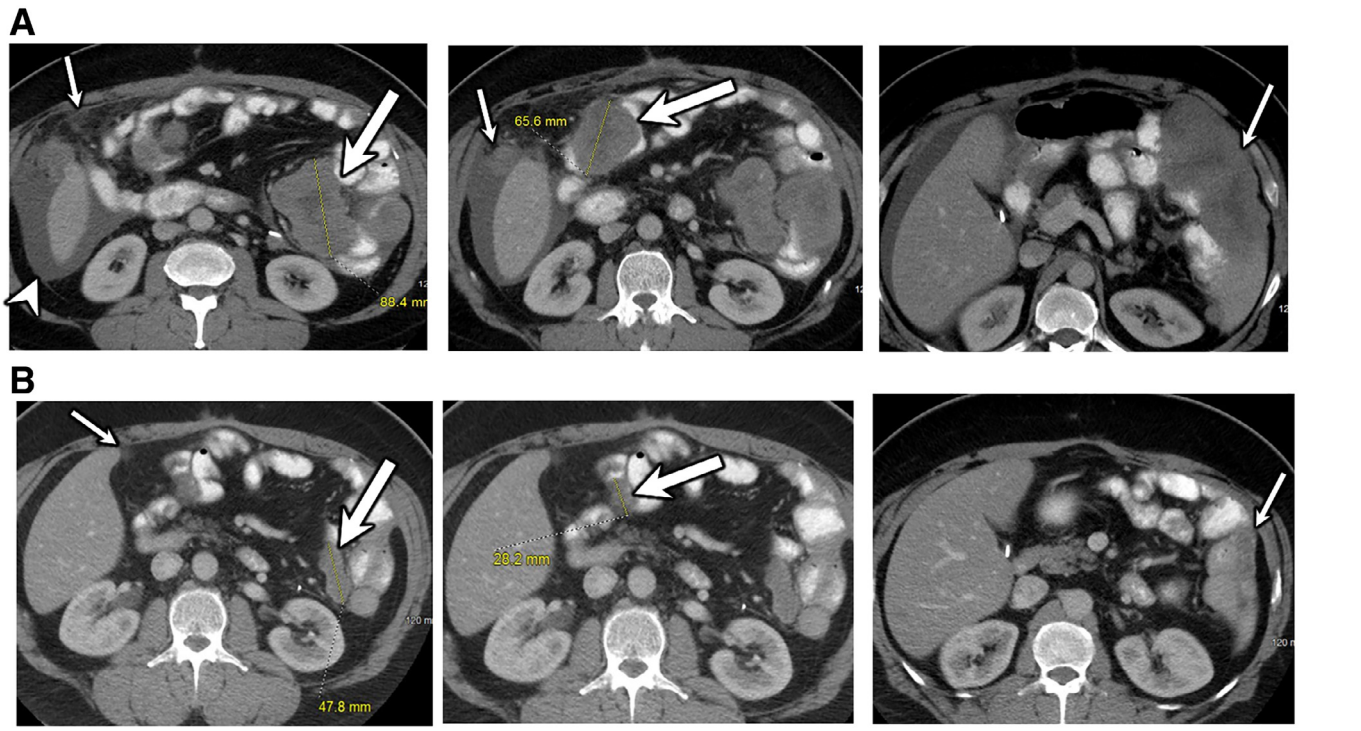
Objective response criteria per RECIST 1.1 for *target lesions* is as follows[3] (Table 3): *CR:* disappearance of all target lesions and decrease in size of pathological lymph nodes (target or nontarget) to <10 mm short axis (Fig 2); *PR:* at least a 30% decrease in sum of diameter of all target lesions from the sum of diameters at baseline (Fig 3); *PD:* requires a 5 mm absolute increase in the sum of longest (for lymph nodes, shortest) diameters of the target lesions in addition to 20% increase in sum of the diameters, taking as reference the smallest sum diameters on study, or appearance of new or more lesions (Fig 4); *SD:* neither sufficient decrease to qualify as PR or increase to qualify as PD (Fig 5).

RECIST 1.1 further clarifies the use of "unequivocal progression" for nontarget lesions.[3] In the presence of measurable disease/target lesion, unequivocal progression is assigned when there is an overall substantial worsening in nontarget disease despite a PR or SD of target lesions. In the absence of measurable disease/target lesion (may be seen in some phase III trials), the increase in overall nontarget disease burden should be comparable in magnitude to an increase that would be required to declare PD in measureable disease. For example, an increase in pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread.[3,7]

RECIST 1.1 also provides response criteria for *nontarget lesions* assessed only qualitatively[3]: *CR:* disappearance of all nontarget lesions and normalization of tumor markers. All lymph nodes must be <10 mm short axis (nonpathological); *PD:* unequivocal progression of existing nontarget lesions, or appearance of one or more new lesions; *non-CR/non-PD:* persistence of one or more nontarget lesions and/or tumor marker levels above normal limit.

Immune-related response criteria (irRC)[13]: Immunotherapeutic anticancer agents work differently from conventional cytotoxic agents by inducing cancer-specific immune response and/or modifying native immune response.[8-10,12] As a result, imaging response patterns from immunotherapeutic agents may differ from cytotoxic therapies often manifesting as initial increase in tumor burden and/or appearance of new lesions, which could be mislabeled as PD per RECIST criteria.[20-22] Immunotherapeutics may have delayed response to treatment in contrast to cytotoxic chemotherapy.[23-25] Following a series of meetings and workshops to discuss the experience of immunotherapeutic agents in cancer treatment, a new set of criteria based on WHO criteria was proposed.[13] This proposed criteria, evaluated in a series of multinational studies in patients with advanced melanoma treated with immunotherapeutic agent ipilimumab, was published in 2009 by Wolchok *et al.* as irRC for the evaluation of tumor responses in patients on immunotherapy.[13]

At baseline, the tumor burden is calculated using the sum of the products of two largest perpendicular diameters (SPD) of all index lesions. Index lesions are defined as 5 measurable lesions (defined



	Lesion Description	Baseline (mm)	Follow-up 10 weeks
1	Mesenteric mass 1 (T)	65.6	28.2
2	Mesenteric mass 2 (T)	88.4	47.8
3	Ascites (NT)	NM	CR
4	Multiple peritoneal masses (NT)	NM	Non-CR/PD

	Baseline	Follow-up 10 weeks
Sum of longest diameters (SLD)	154.0	76.0
% change from baseline	BL	-50.6%
New Lesions	BL	No
Recist v1.1 Response	BL	PR

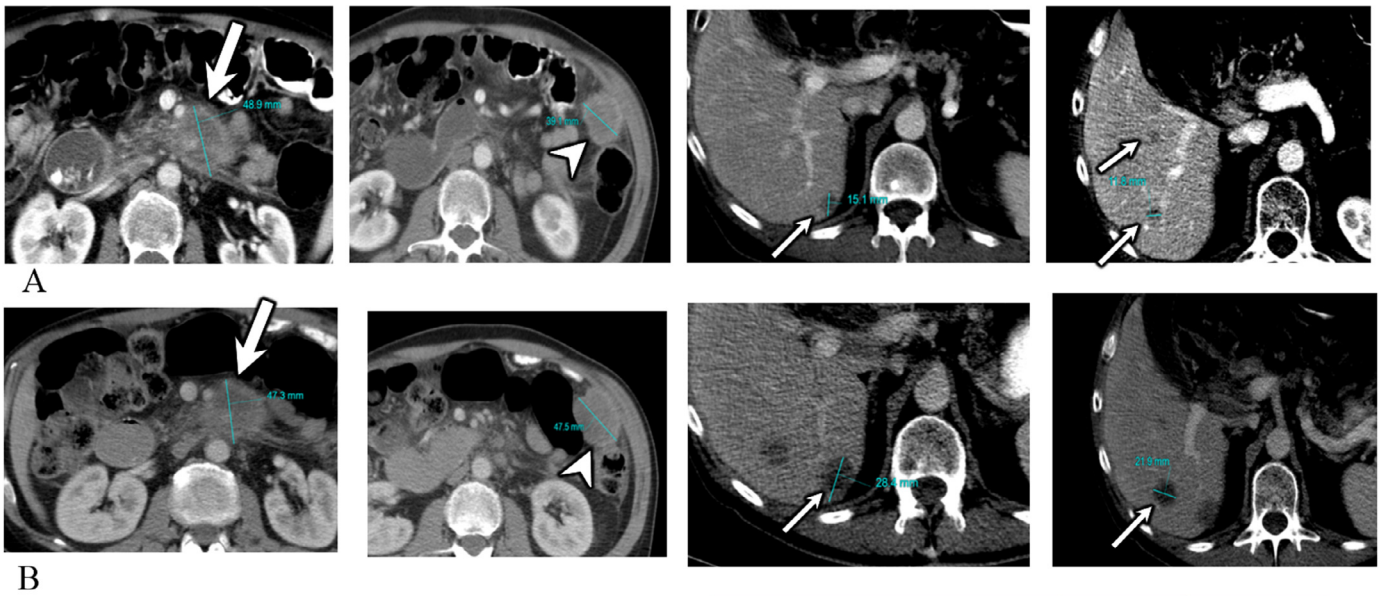
FIG 3. Partial response per RECIST 1.1. Axial CECT of the abdomen and pelvis in a 58-year-old female with peritoneal carcinoma. (A) At baseline, and (B) 10-weeks post-treatment shows: multiple mesenteric masses (thick arrows), multiple peritoneal masses (thin arrows), ascites (arrowhead). The percentage decrease in SLD from baseline is 50.6% = partial response. [T = Target lesion, NT = Nontarget lesion, NM = Nonmeasurable].

as $\geq 5 \times 5$ mm^2 lesions, per WHO criteria) per organ, up to 10 visceral lesions and 5 cutaneous lesions total (Fig 6).[13] At subsequent tumor assessment, new measurable lesions (similar to index lesions) can be added to the SPD. The SPD of index lesions, and any new lesions are added together to provide the total tumor burden. The presence of new nonmeasurable lesions ($<5 \times 5$ mm^2) does not define progression but preclude immune related complete response (Table 4).

Per irRC, overall response as derived from time-point response assessment, based on tumor burden, are as follows[13]: *immune-related complete response (irCR):* complete disappearance of all lesions (measurable and nonmeasurable), and no new lesions confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented; *immune-related partial response (irPR):* decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation; *immune-related stable disease (irSD):* not meeting criteria for irCR or irPR, and in the absence of irPD (Fig 7); *immune-related progressive disease (irPD):* increase in tumor burden ≥25% relative to nadir with confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented (Table 3).

In 2013, Nishino *et al.*[14] published a study comparing response assessment by irRC using unidimensional versus bidimensional measurements in 57 advanced melanoma patients treated with ipilimumab. For unidirectional assessment, measurable lesions were defined per the RECIST criteria with measurable lesions ≥10 mm in longest diameter, response assessment was based on RECIST 1.1 (*PD*: ≥20% increase from nadir; *PR*: ≥30% decrease from baseline; *CR*: disappearance of all lesions), presence of new lesions added to the sum of measurements but does not define progression and confirmation by 2 consecutive studies at least 4 weeks apart required for CR, PR, and PD. The authors showed that irRC using unidimensional longest diameter provide higher concordance and better reproducibility relative to bidimensional measurements, and proposed the use of unidimensional irRC to assess response to immunotherapy in solid tumors[14].

irRECIST[15]: Since 2009 several proposal and recommendations has been presented incorporating RECIST into irRC to further define and streamline response to immunotherapy[15,26,27]. In 2014, Bohnsack *et al.*, presented an abstract modifying irRC to further align with RECIST 1.1 and incorporating proposed changes from Nishino *et al*, and named it irRECIST. Definition of measurable and nonmeasurable lesions is similar to RECIST 1.1. New measurable lesions have similar criteria as baseline (≥10 mm long axis for target lesion and ≥15 mm short axis for lymph nodes), and ≤2 lesions per organ, total ≤5 lesions can be recorded as new per timepoint.[15] On follow-up, longest diameters on nonnodal targets, new nonnodal measurable lesions and short axis diameters of target nodal and new nodal lesions are recorded to determine the total measured tumor burden (TMTB).



	Lesion description	Baseline (mm)	Follow-up 12 weeks (mm)
1	Right hepatic lobe 1 (T)	15.1	28.4
2	Right hepatic lobe 2 (T)	11.8	21.9
3	Duodenal mass (T)	48.9	47.3
4	Left peritoneal mass (T)	39.1	47.5
5	Liver lesions (NT)	NM	PD

	Baseline (mm)	Follow-up 12 weeks (mm)
Sum of longest diameters (SLD)	114.9	145.1
% change from baseline (BL)	BL	26.3%
% change from nadir	BL	26.3%
New lesions	BL	Yes
RECIST v 1.1 response	BL	PD

FIG 4. Progressive disease per RECIST 1.1. Axial CECT of the abdomen and pelvis in a 59-year-old male with primary duodenal carcinoma. (A) At baseline, and (B) 12-weeks post treatment showing: primary duodenal mass (arrows), left abdomen peritoneal mass (arrowheads), multiple liver metastases (thin arrows) and new lesion (short arrow). The percentage increase in SLD from baseline/nadir is 26.3% = progressive disease. [T = Target lesion, NT = Nontarget lesion, NM= Nonmeasurable].

The response criteria per irRECIST[15]: *irComplete response (irCR):* complete disappearance of all lesions (measurable, nonmeasurable and no new lesions), lymph node decrease to <10 mm; confirmation of response is not mandatory; *irPartial Response (irPR):* decrease in tumor burden ≥30% TMTB relative to baseline and no unequivocal progression of new nonmeasurable lesions; *irStable Disease (irSD)*: failure to meet criteria for irCR or irPR, in absence of irPD (Fig 7); *irProgressive Disease (irPD)*: minimum 20% increase with a minimum 5 mm absolute increase in TMTB relative to nadir, or progression of nontarget or new nonmeasurable lesions. Recommend confirmation of progression at a minimum 4 weeks following first irPD (Tables 3 and 4).

The major modifications of irRECIST relative to irRC are as follows: On follow-up, response of nontarget lesion does not affect irPR and irSD assessments but contributes to overall assessments of irCR or irNon-CR/irNon-PD (irNN = no target lesion at baseline, and follow-up fails to meet irCR or irPD); in contrast irRC uses complete disappearance of nontarget lesion on follow to define irCR. All new lesions not selected as new measurable lesions are considered nonmeasurable and followed

TABLE 4
Impact of new lesion(s) on follow-up imaging per different guidelines

New lesion(s)	RECIST 1.1	irRC	irRECIST	iRECIST
New measurable lesion(s)	(≥10 mm long axis, ≥15 mm short axis node- Results in overall disease progression (PD)	(>5 × 5 mm^2; ≤5 lesions/organ, total 10 visceral and 5 cutaneous lesions) - Incorporated into tumor burden to assign PD (≥25% increase)	(as RECIST 1.1.) Added to TMTB to define PD (≥20% increase in TMTB from nadir); confirmation at minimum 4 weeks after first irPD assessment	Recorded but not included in the tumor burden, Results in iUPD (requires confirmed 5mm increase at 4-8 weeks to assign iCPD)
New, nonmeasurable lesion(s)	Attention on follow-up If persists:PD assigned retrospectively	(<5 × 5 mm^2) Do not define PD (but *precludes* irCR)	Only unequivocal progression of new nonmeasurable lesions leads to an overall response of irPD; confirmation at minimum 4 weeks after first irPD assessment	Recorded but not included in the tumor burden, Results in iUPD (requires confirmed increase in number or size at 4-8 weeks to assign iCPD)

PD, progressive disease; TMTB, total measured tumor burden; irCR, immune related complete response; iUPD, “immune” unconfirmed PD; iCPD, “immune” confirmed PD.

	Lesion description	Baseline (mm)	Follow-up 12 weeks (mm)
1	Abdominal sarcoma (T)	209.0	210.0
2	Pancreatic tail (T)	35.4	49.2
3	Mesenteric mass (T)	49.5	55.2
4	Mesenteric LN (T)	16.5	11.0
5	*Left pelvic LN (not shown)*	*NM*	*Non-CR/PD*

	Baseline (mm)	Follow-up 12 weeks (mm)
Sum of longest diameters (SLD)	310.0	325.4
% change from baseline (BL)	BL	4.8%
% change from nadir	BL	4.8%
New lesions	BL	No
RECIST1.1 response	BL	SD

FIG 5. Stable disease per RECIST 1.1. Axial CECT of the abdomen and pelvis in a 61-year-old male with sarcoma. (A) At baseline, and (B) 12-weeks post-treatment showing: mesenteric sarcoma (arrows), pancreatic tail mass (thin arrows), mesenteric lymph node (arrowhead), left mesenteric mass (double arrows) (SD = stable disease). [T = Target lesion, NT = Nontarget lesion, NM = Nonmeasurable, LN = Lymph node, BL= Baseline].

qualitatively; and only unequivocal progression of these lesions may lead to overall assessment of irPD. The threshold for irPR and irPD are similar to RECIST 1.1. The irRECIST response criteria also include immune related no disease (irND): in adjuvant setting when no disease is identified, and immune related not evaluable (irNE): exceptional cases where insufficient data exists.

iRECIST[11]: In 2015-16, the RECIST working group and the immunotherapy subcommittee reviewed the existing approaches and proposed a plan to modify RECIST 1.1 for immune-based therapeutics. As a result, a consensus criteria-termed iRECIST, was published in 2017 for the use of modified RECIST 1.1 primarily for cancer immunotherapy trials to ensure consistency in design, data collection, interpretation and analysis of immunotherapy trials.[11]

The definition of measurable and nonmeasureable lesions, as well as recommendations regarding method of measurement remains unchanged from RECIST 1.1 (Tables 1 and 2).

The response assigned using iRECIST includes *"immune" complete response (iCR), "immune" partial response (iPR), "immune" stable disease (iSD)* that are unchanged from the RECIST 1.1 (Fig 7). The major addition is *"immune" unconfirmed progressive disease (iUPD),* and *"immune" confirmed progressive disease (iCPD).* iUPD is defined on the basis of RECIST 1.1 but requires confirmation on further imaging by documenting further increase in size of the observed lesion or any other new lesion per RECIST 1.1. If progression is not confirmed, but tumor shrinkage occurs compared to baseline meeting the requirement for iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again and confirmed in the subsequent follow up study to assign iCPD (Fig. 8). This approach helps to account for the atypical response ("pseudoprogression") related to immunotherapies. iCPD (confirmed progressive disease) is defined as a further increase in sum of measures ≥5 mm in the previously identified target iUPD, or increase in nontarget iUPD at follow-up imaging no more than 4-8 weeks after the initial unconfirmed progressive disease (iUPD). New lesions identified on follow-up are recorded separately but not included in the sum of target lesions and assigned iUPD. iCPD (confirmed progressive disease) is defined as further increase in size of these lesions (≥5 mm for sum of new lesions) or additional new lesion at 4-8 weeks. Patient who are categorized as iUPD may continue with the therapy and reimaged at 4-8 weeks (Tables 3 and 4).[11]

Although iRECIST is recently introduced and not yet validated, it emphasizes the need to confirm progression in order to exclude pseudoprogression. It advocates continued use of RECIST 1.1 in existing trials to define primary outcome, and using iRECIST for new early phase clinical trials with no intent to guide treatment decisions. Recording both RECIST 1.1 and iRECIST in trials could be informative and the data can be used to validate and further refine RECIST guidelines in immunotherapeutics.

Conclusion

RECIST 1.1 is validated and standardized criteria that remains universally accepted for response assessment of solid tumors treated with cytotoxic chemotherapies. Immunotherapy in cancer may

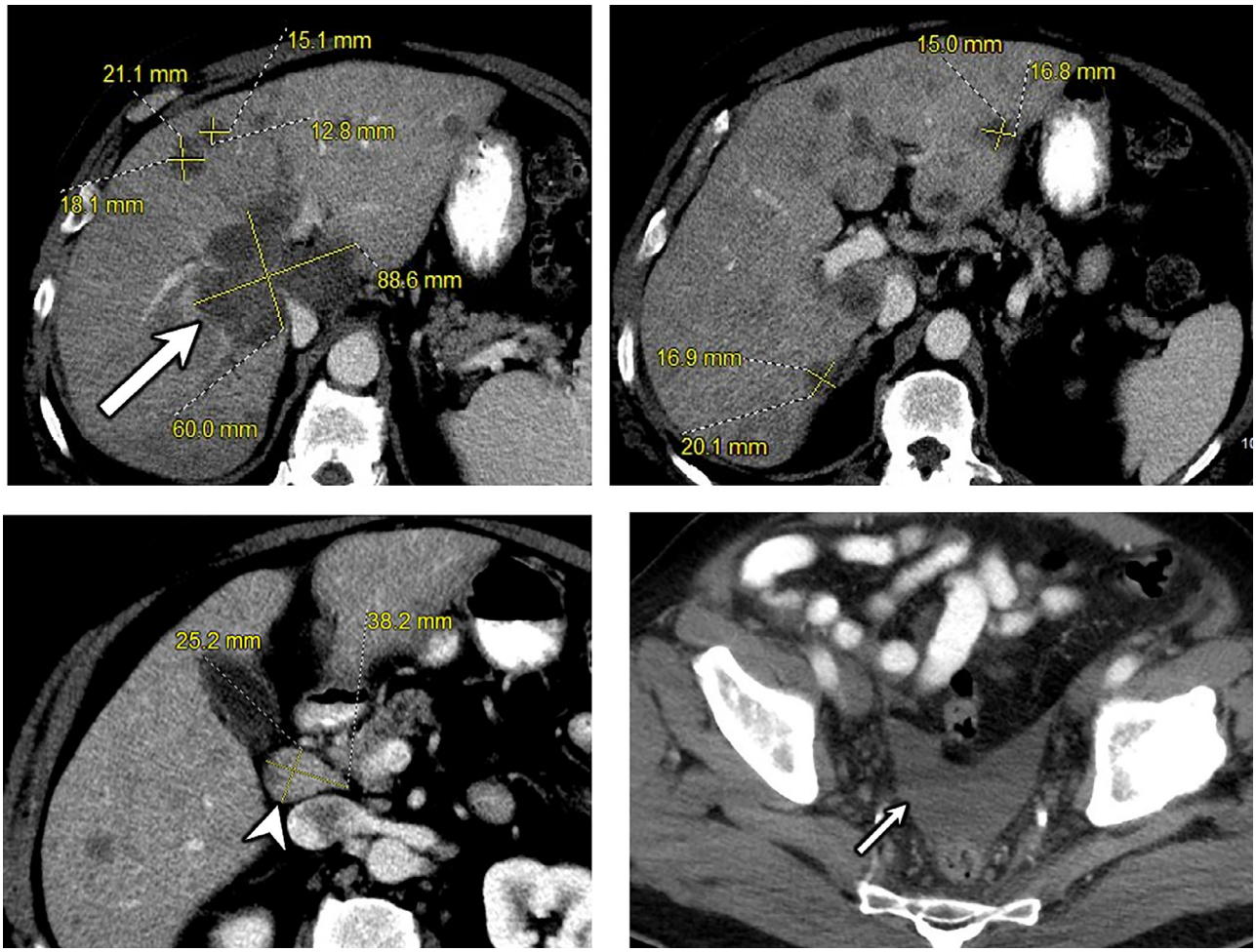
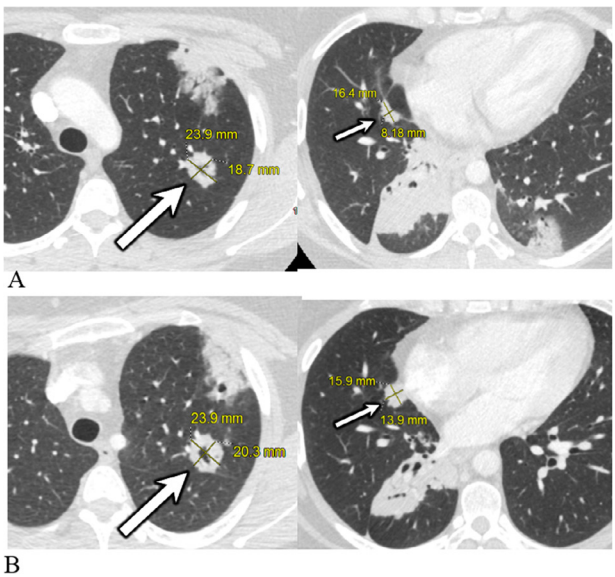


FIG 6. Axial CECT of the abdomen and pelvis in a 55-year-old male with cholangiocarcinoma (arrow), multiple hepatic metastases (calipers), and portocaval lymph node (arrowhead) and pelvic ascites (short arrow) as nonmeasurable lesion. irRC: Bidimensional, longest perpendicular dimension ≤5 target per organ (max. 10 visceral+ 5 cutaneous lesion), Nontarget ascites. Tumor burden (SPD= Sum of product of perpendicular diameters): (21.1 × 18.1) + (88.6 × 60) + (15.1 × 12.8) + (15.0 × 16.8) + (20.1 × 16.9) + (25.2 × 38.2) = 7445.3 mm^2.



	irRC		irRECIST 1.1	
Lesion description	**Baseline (mm)**	**Follow-up (mm)**	**Baseline (mm)**	**Follow-up (mm)**
Left upper lobe mass (T)	23.9 x 18.7	23.9 x 20.3	23.9	23.9
Right middle lobe mass (T)	16.4 x 8.2	15.9 x 13.9	16.4	15.9
Tumor burden	581.3	706.2	40.3	39.8
% change from baseline (BL)	BL	+21.5%	BL	-1.24
New lesion	BL	No	BL	No
Response		***irSD***		**SD**

FIG 7. Immune-related stable disease on irRC and irRECIST 1.1. Axial CT chest in a 29-year-old female with metastatic adenocarcinoma of the lung, treated with pembrolizumab. (A) At baseline, and (B) 5-weeks following treatment shows left upper lobe mass (arrow), right middle lobe mass (thin arrow) (T = target lesion, BL = baseline, irSD = immune-related stable disease, SD = stable disease).

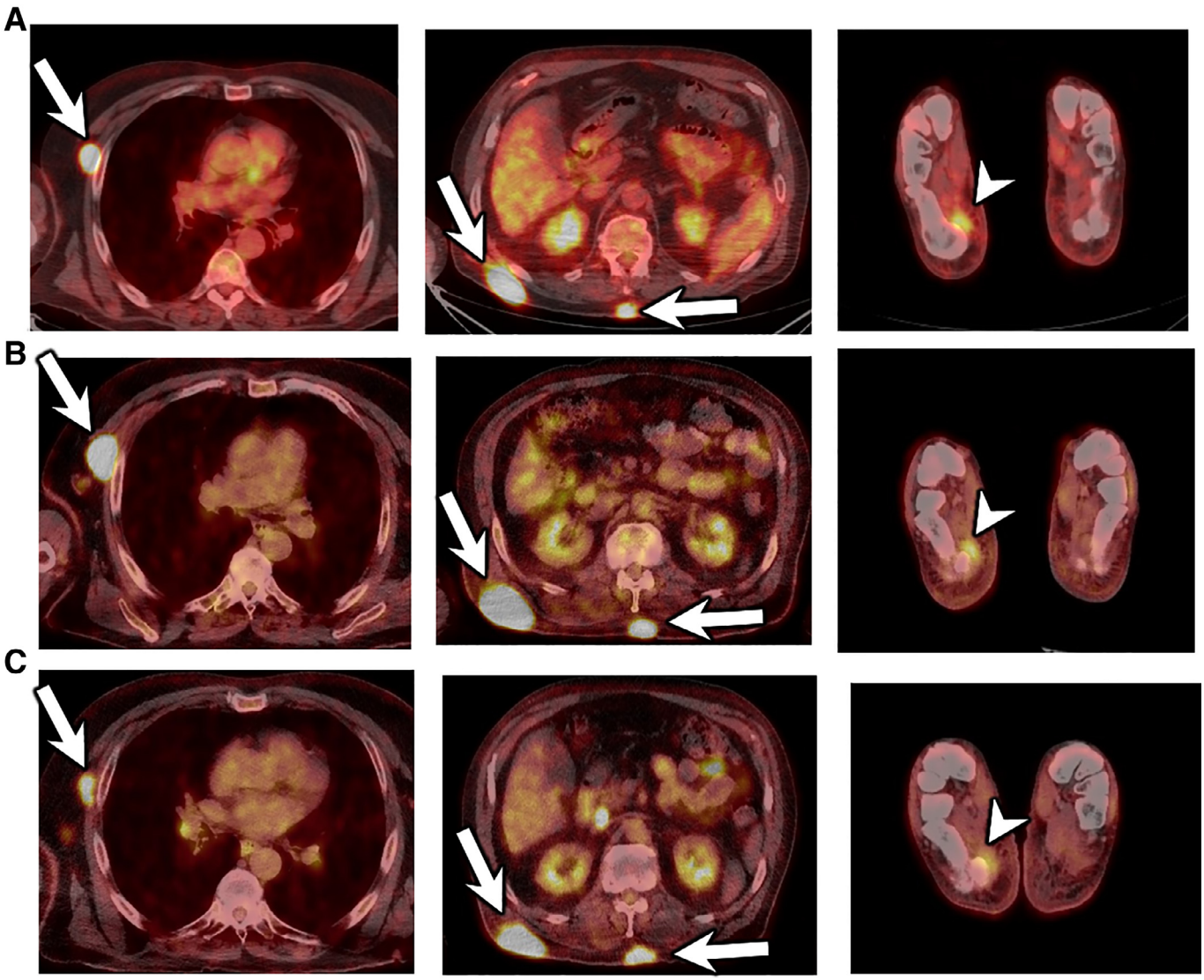


FIG8. iUPD per iRECIST. Sixty-four years old male with malignant melanoma. (A) Baseline FDG-PET scan shows multiple chest and body wall (arrows) and right foot (arrowhead) FDG-avid metastatic masses; (B) Follow-up study 5-weeks from baseline, on Ipilimumab, shows an apparent increase in size of the masses (iUnconfirmed PD)-patient continued on therapy; (C) 5-weeks follow-up from the scan (B) shows apparent decrease in size of the masses confirming partial response rather than true progression. [Note = Scan (B) shows pseudoprogression as described with immunotherapies].

manifest unconventional imaging responses, sometimes with pseudoprogression due to an inflammatory response, requiring modification to RECIST 1.1 to avoid mislabeling it as true disease progression. A few irRC have been proposed over the last several years, including irRC, irRECIST, and iRECIST. iRECIST guidelines were recently proposed by the RECIST Working Group in 2017 and include addition of new iUPD and iCPD responses with which the radiologists and oncologists need to develop familiarity for accurate response assessment. This review serves to provide a comprehensive review of these various response criteria and guidelines for the radiologists.

Declaration of Interest

All the authors have no financial relationship or conflict of interest relevant to this manuscript.

This work has not been published and is not under consideration for publication elsewhere. An education exhibit on similar theme was presented at annual meeting of Radiological Society of North America 2017 and Society of Abdominal Radiology 2018.

This review study has been approved by the Institutional Review Board.

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Manuscript drafting, revisions and editing for important intellectual content: All authors.

Images and Figures: URL, KH, VS, APW.

Approval of final version of the manuscript: All authors.

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Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1067/j.cpradiol.2018.07.016.

References

1. Miller AB, Hoogstraten B, Staquet M, *et al.* Reporting results of cancer treatment. Cancer 1981;47:207–14.
2. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
3. Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
4. Liu Y, Litiere S, de Vries EG, *et al.* The role of response evaluation criteria in solid tumour in anticancer treatment evaluation: results of a survey in the oncology community. Eur J Cancer 2014;50:260–6.
5. Schwartz LH, Litiere S, de Vries E, *et al.* RECIST 1.1-Update and clarification: from the RECIST committee. Eur J Cancer 2016;62:132–7.
6. Schwartz LH, Seymour L, Litiere S, *et al.* RECIST 1.1 - Standardisation and disease-specific adaptations: perspectives from the RECIST Working Group. Eur J Cancer 2016;62:138–45.
7. Nishino M, Jackman DM, Hatabu H, *et al.* New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for advanced non-small cell lung cancer: comparison with original RECIST and impact on assessment of tumor response to targeted therapy. AJR Am J Roentgenol 2010;195:W221–8.
8. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev 2008;224:166–82.
9. Hoos A, Parmiani G, Hege K, *et al.* A clinical development paradigm for cancer vaccines and related biologics. J Immunother 2007;30:1–15.
10. Iwai Y, Ishida M, Tanaka Y, *et al.* Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A 2002;99:12293–7.
11. Seymour L, Bogaerts J, Perrone A, *et al.* iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.
12. Tarhini AA. Tremelimumab: a review of development to date in solid tumors. Immunotherapy 2013;5:215–29.
13. Wolchok JD, Hoos A, O'Day S, *et al.* Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412–20.
14. Nishino M, Giobbie-Hurder A, Gargano M, *et al.* Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013;19:3936–43.
15. Bohnsack O, Hoos A, Ludajic K. Adaptation and modification of the immune related response criteria (IRRC): IrRECIST. J Clin Oncol 2014;32:e22121.. e22121.
16. Bogaerts J, Ford R, Sargent D, *et al.* Individual patient data analysis to assess modifications to the RECIST criteria. Eur J Cancer 2009;45:248–60.
17. Moskowitz CS, Jia X, Schwartz LH, *et al.* A simulation study to evaluate the impact of the number of lesions measured on response assessment. Eur J Cancer 2009;45:300–10.
18. Schwartz LH, Bogaerts J, Ford R, *et al.* Evaluation of lymph nodes with RECIST 1.1. Eur J Cancer 2009;45:261–7.
19. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. Eur J Cancer 2006;42:1031–9.
20. Kruit WH, van Ojik HH, Brichard VG, *et al.* Phase 1/2 study of subcutaneous and intradermal immunization with a recombinant MAGE-3 protein in patients with detectable metastatic melanoma. Int J Cancer 2005;117:596–604.
21. Little RF, Pluda JM, Wyvill KM, *et al.* Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. Blood 2006;107:4650–7.
22. van Baren N, Bonnet MC, Dreno B, *et al.* Tumoral and immunologic response after vaccination of melanoma patients with an ALVAC virus encoding MAGE antigens recognized by T cells. J Clin Oncol 2005;23:9008–21.
23. Hoos A, Wolchok JD, Humphrey RW, *et al.* CCR 20th anniversary commentary: immune-related response criteria—capturing clinical activity in immuno-oncology. Clin Cancer Res 2015;21:4989–91.
24. Kwak JJ, Tirumani SH, Van den Abbeele AD, *et al.* Cancer immunotherapy: imaging assessment of novel treatment response patterns and immune-related adverse events. Radiographics 2015;35:424–37.
25. Prieto PA, Yang JC, Sherry RM, *et al.* CTLA-4 blockade with ipilimumab: long-term follow-up of 177 patients with metastatic melanoma. Clin Cancer Res 2012;18:2039–47.
26. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. J Clin Oncol 2015;33:3541–3.
27. Hodi FS, Hwu WJ, Kefford R, *et al.* Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol 2016;34:1510–7.