



The Role of Radiology in Immunotherapy Response Evaluation

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SUMMARY

Radiology plays a crucial role in the evaluation of therapy response in solid tumors. The two initial criteria, which are the WHO and Response Evaluation Criteria in Solid Tumors (RECIST), are insufficient for the assessment of response to immunotherapy. Therefore, recently several immune response criteria, such as immune-related response criteria (irRC), immune-related RECIST (irRECIST), immune RECIST (iRECIST) and immune-modified RECIST (imRECIST), were proposed and applied in clinical trials on immunotherapies. In this review manuscript, more recently defined specific response criteria for immunotherapy, atypical patterns of response to immunotherapy and the imaging of immune-related adverse effects will be presented and discussed.

Keywords: Immunotherapy; immunotherapy management; immunotherapy response; immunotherapy treatment; role of radiology.

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Introduction

Radiology plays a crucial role in the evaluation of therapy response in solid tumors. The use of response evaluating criteria is significant to standardize and compare the radiological findings in daily practice and clinical trials. The two initial criteria were the World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST) are insufficient for the assessment of response to immunotherapy. [1,2] Therefore, recently several immune response criteria, such as immune-related response criteria (irRC), immune-related RECIST (irRECIST), immune RECIST (iRECIST) and immune-modified RECIST (imRECIST), were proposed and applied in clinical trials on immunotherapies. [1,3-5]

In this review manuscript, atypical patterns of response to immunotherapy, more recently defined specific response criteria for immunotherapy and the

imaging of immune-related adverse effects will be presented and discussed.

Atypical Response Patterns After Immunotherapy

Unlike cytotoxic treatment, different response patterns may be seen in immunotherapy (Fig. 1). The duration of the immunotherapy response can be longer than cytotoxic treatment. Moreover, the treatment response may continue to appear after stopping the immunotherapy. These atypical immunotherapy response patterns have been named as prolonged, stable and/or delayed (durable responses) (Fig. 2). [6]

The other atypical response “dissociated response” is defined as the concomitant decrease in some target lesions with increasing in other sites more often in adrenal glands (Fig. 3). This response pattern is analogous to mixed responses seen with chemotherapy and targeted therapy. [6]

Pseudo-progression (PP) is defined as an initial increase in total tumor burden with stability, decreasing

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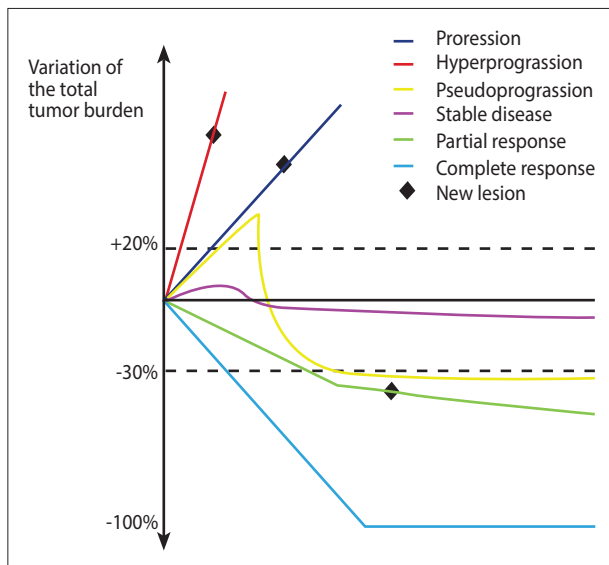


Fig. 1. Patterns of the response and progression under immunotherapy.

in size or disappearing during follow-up (Fig. 4).[7] Proposed etiologies for these morphologic changes are inflammation due to the infiltration of tumor by hyper-activated T cells or edema.[7,8]

It is very important to recognize PP from a real progression in order to avoid early cessation of effective treatment and delay in transition to a new treatment line. Immunotherapy should not be discontinued until the progressive disease (PD) is confirmed at least four weeks later follow-up (Fig. 5).

In general, PP incidence does not exceed 10% of the patients treated with immune checkpoint inhibitors[8]. PP has been reported for anti-PD-1, anti-PD-L1, and anti-CTLA-4 agents not only in lung cancer but also in other cancers, such as melanoma, renal cell carcinoma, and bladder cancer. This response pattern may occur in the lymph nodes but is more commonly described in non-nodal sites, such as the kidneys, liver, lungs, peritoneum, adrenal gland, and chest and abdominal wall.[9]

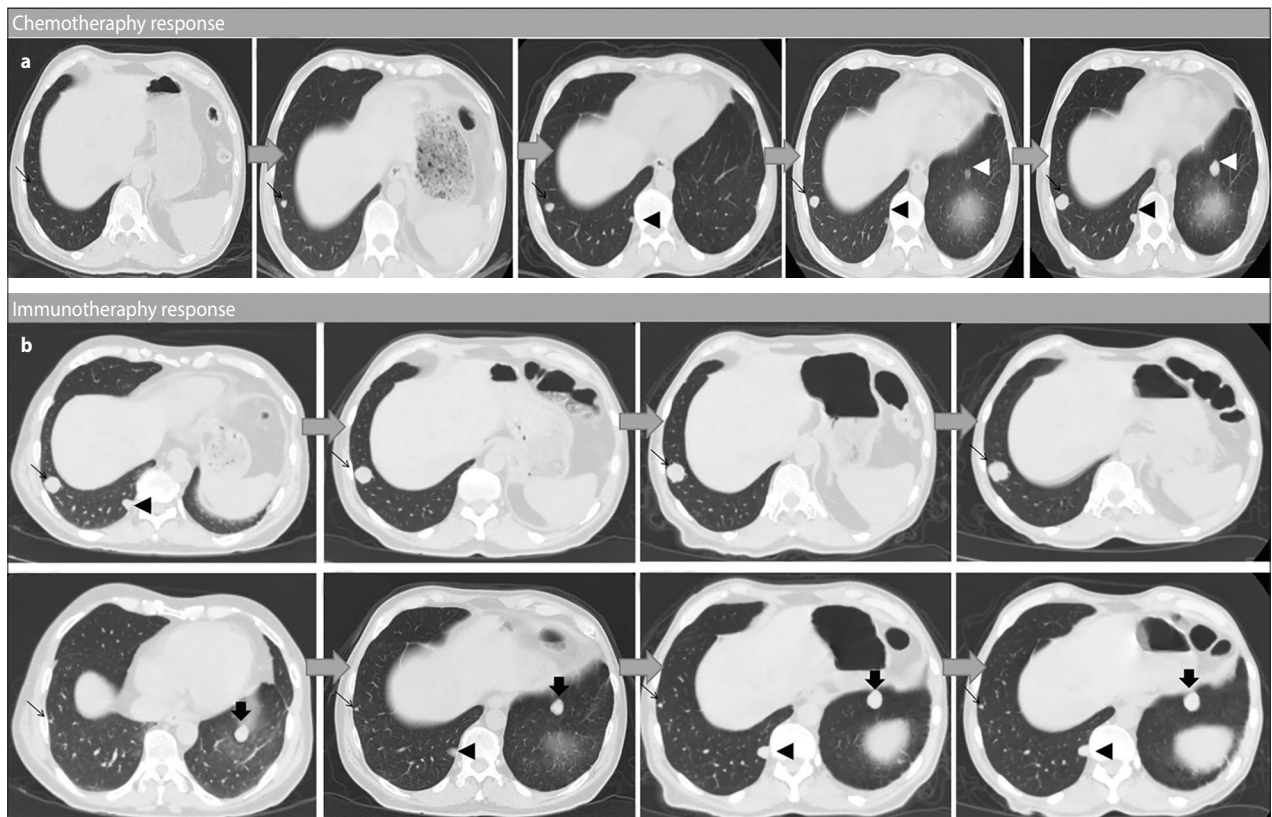


Fig. 2. Stable disease after immunotherapy in a 66-year-old male patient with metastatic clear cell renal carcinoma. (a) Before the start of immunotherapy, serial thoracic CT images show the progression of lung metastases with increasing size (arrows) and number (arrowheads) of metastatic nodules at about two years follow up examination. (b) Serial CT images during immunotherapy show bilateral stable lung metastases after four cycles of Nivolumab treatment at one year follow up.

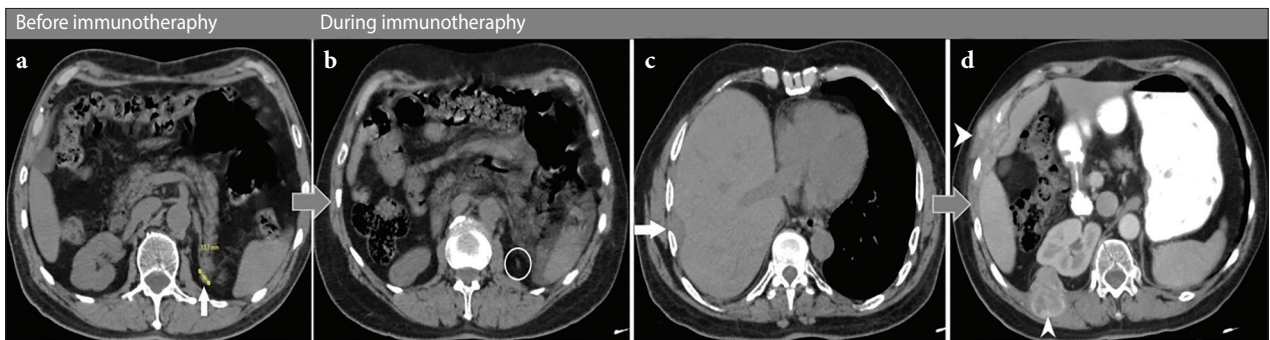


Fig. 3. Dissociated disease after immunotherapy in a 60-year-old male patient with operated renal cell carcinoma in the left kidney. (a) Before immunotherapy, abdominal CT image shows a 13 mm residual tumor in the operated left kidney region (arrows). (b, c, d) Serial CT images during immunotherapy show dissociated disease, which is a new metastatic lesion in the liver capsule (arrows) and chest wall (arrow heads) with regression in local recurrence (circle).

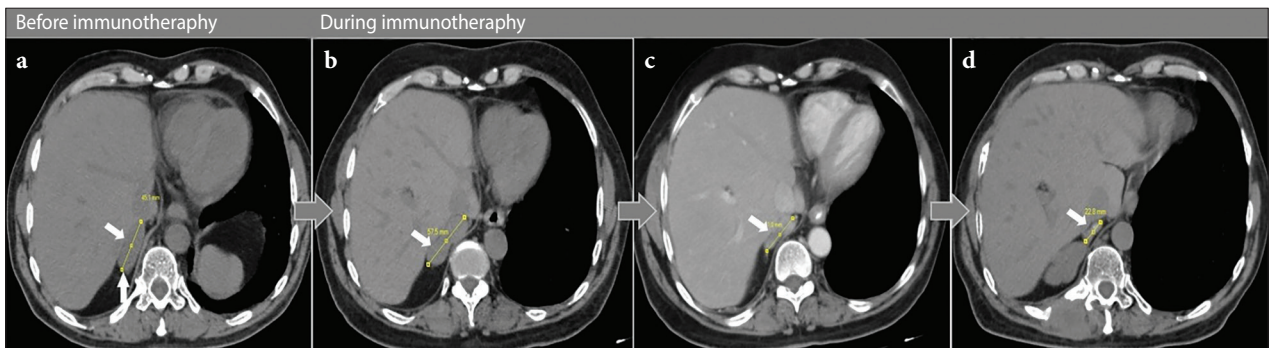


Fig. 4. Pseudoprogressive disease after immunotherapy in a 60-year-old male patient with operated renal cell carcinoma in the left kidney. (a) Abdominal CT image taken three months after the operation shows metastasis measured 45 mm in the right adrenal gland (arrow). (b, c, d) Serial CT images during immunotherapy show pseudoprogression of the adrenal lesion (arrows). Seven months after initiation of nivolumab treatment there was an increase in the size of the right adrenal gland metastasis measured 57 mm and then at the 10th and 17th months follow up scans show gradually decrease in size (57 mm to 41 and then 22 mm in diameter) of the adrenal gland metastasis (arrows).

The more recently defined atypical response pattern is “hyper-progression (HP)”, which is an apparent increase in total tumor burden with clinical deterioration. HP was firstly defined by Champiat et al. in 2016 as a ≥ 2 -fold increase in tumor growth rate (TGR) in patients with disease progression between baseline and first assessment by RECIST criteria at eight weeks.[10] Kato et al. defined HP as a time to treatment failure < 2 months, a 50% increase in tumor burden compared to baseline and an increase in progression pace greater than two-fold (Fig. 6).[11] Potential explanations include oncogenic signaling activation, upregulation of alternative immune checkpoints, or modulation of other protumor immune subsets.[12,13] HP incidence in patients receiving immunotherapy ranges from 4% to 29% in different studies because of variations in the definition of HP in the literature.[10,11,14,15]

HP was not associated with the degree of tumor burden, histologic tumor type, number of metastatic sites, prognostic score, number of previous lines of chemotherapy, or type of prior treatment, whether it was conventional chemotherapy, targeted therapy, or radiotherapy. It was, however, associated with older age (> 65 years old) and worsened overall survival (OS).[10]

Immunotherapy Specific Response Criteria

The comparative definitions of different immune-specific response criteria (irRC, irRECIST, iRECIST and imRECIST) with RECIST 1.1 are summarized in Tables 1 and 2.

Immune-related Response Criteria (irRC)

In 2009, immune-related response criteria (irRC) was proposed to evaluate tumor response to immunotherapy, considering the possibility of PP.[3] The main dif-

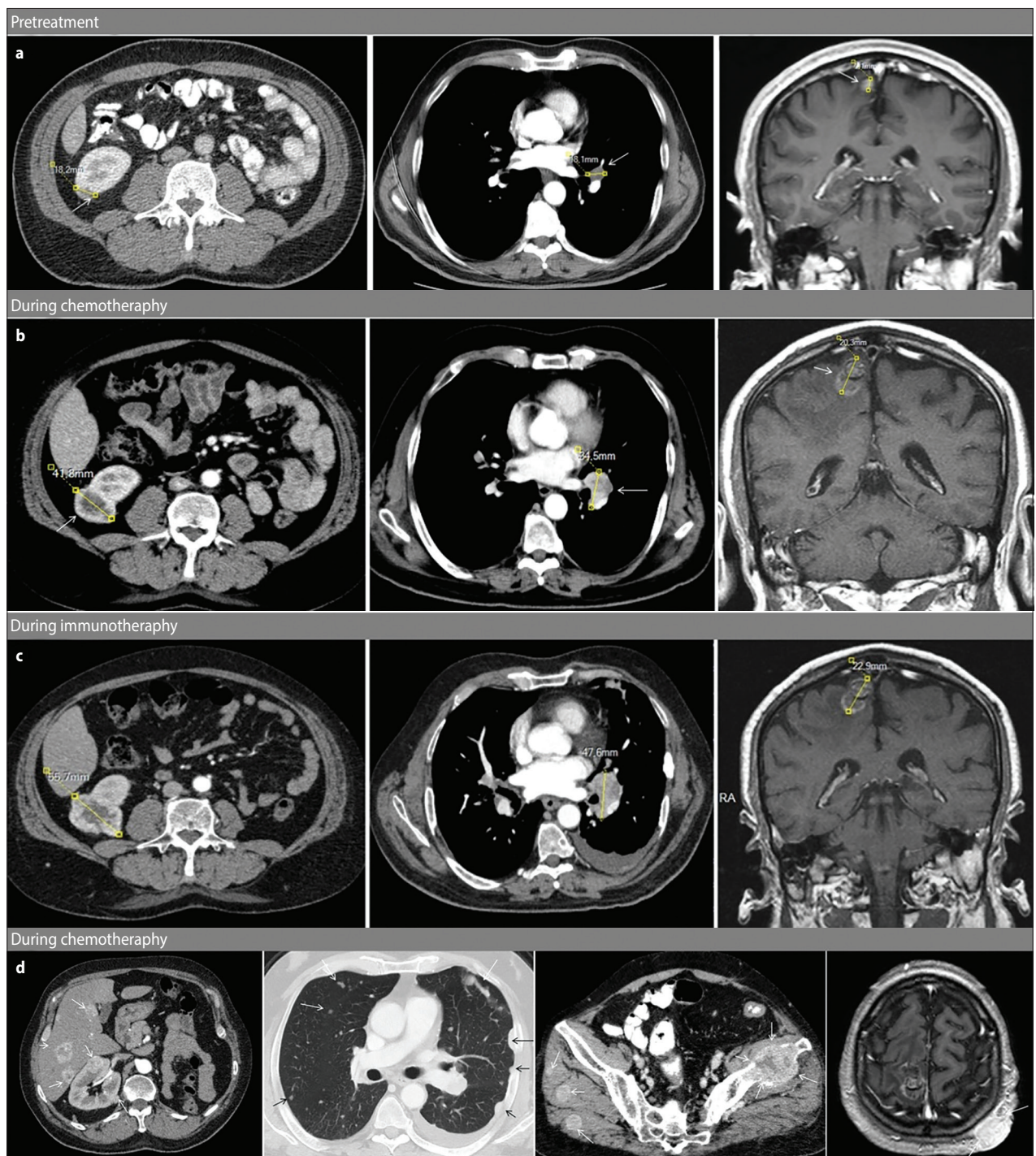


Fig. 5. Progressive disease after immunotherapy in a 52-year-old male patient with metastatic renal cell carcinoma. (a) Before the start of chemotherapy, contrast-enhanced abdominal and thoracic CT and coronal T1-weighted TSE brain MR images show the presence of the tumor in the right kidney (short arrow), left hilar metastatic lymph node (arrowhead) and brain metastasis in the right parietal lobe (long arrow). (b) The disease, which was stable six months after chemotherapy, progressed in the 18th month of treatment and thus started to immunotherapy. (c) CT and MR images taken six months after immunotherapy show progressive disease. (d) Progressive disease was confirmed by control imaging taken four weeks later. Multiple metastatic new lesions are seen in the right kidney, liver, lung, pleura, bone, subcutaneous and soft tissues (arrows).

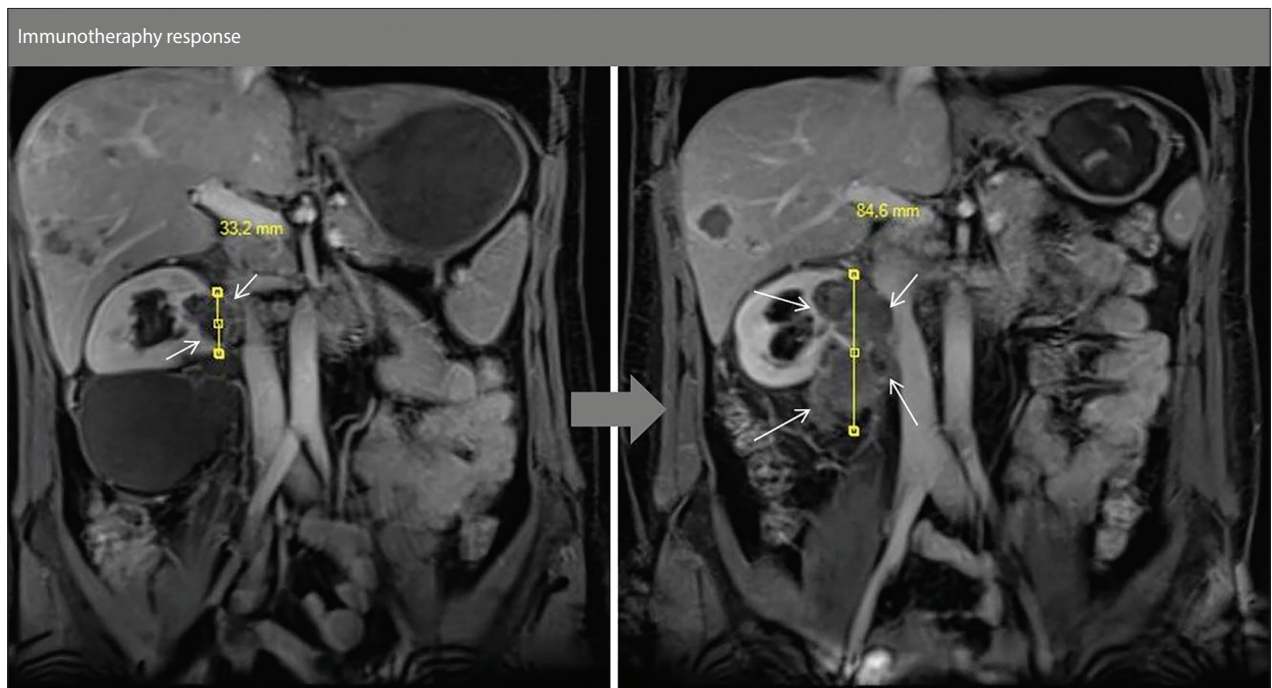


Fig. 6. Hyperprogressive disease after immunotherapy in a 30-year-old male patient with metastatic renal carcinoma. Serial coronal reformatted contrast-enhanced abdominal CT images before (a) and during (b) immunotherapy show a dramatic increase in the renal tumor size (more than twice) on surveillance imaging approximately six weeks after starting immunotherapy (arrows).

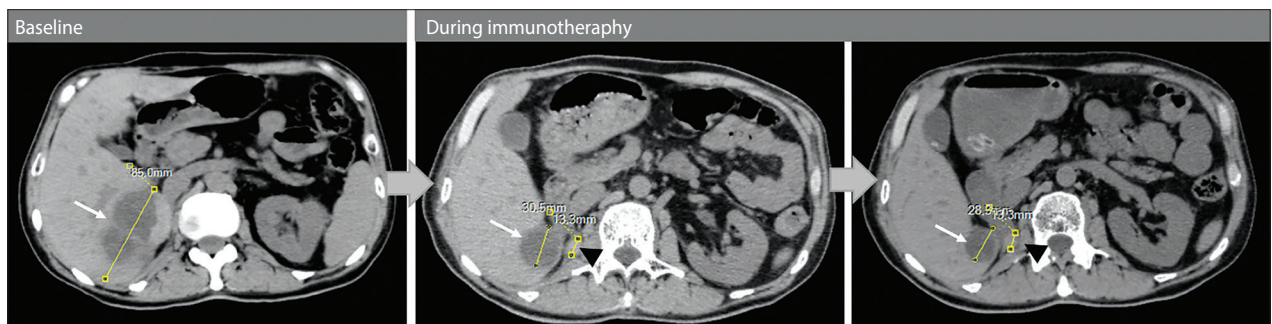


Fig. 7. iRECIST and imRECIST evaluation difference. According to IRECIST, while the new target lesion is a progressive disease, imRECIST is considered as a partial response since the new lesion (arrowheads) is included in the total tumor burden (arrow).

ferences between RECIST 1.1 and irRC are that tumor size measurement is bi-dimensional and newly measurable lesions are not automatically classified as “PD” but are added to the total diameter of the target lesions. The definition of the PD requires an increase in total tumor burden to be confirmed at two consecutive imaging studies at least four weeks apart. Furthermore, ‘partial response’ is diagnosed after 50% and not after 30% of size reduction. The number of the lesions to evaluate is higher if compared to RECIST 1.1 (up to five per organ, up to 10 visceral vs. two per organ, five in total) (Tables 1 and 2).[2,6]

Despite these described advancements, several critiques were addressed to irRC criteria. First, the reproducibility of bidimensional assessment is lower if compared with unidimensional assessment; second, large number of target lesions to be measured can be time-consuming; third, lymph nodes assessment is not clearly evaluated.[16,17]

Immune-related RECIST (irRECIST)

To obtain a more reproducible and faster reporting system, Nishino et al. are proposed the irRECIST criteria[4], a system based on unidimensional evaluation

Table 1. The definition of immune-specific response criteria of irRC, irRECIST iRECIST and imRECIST comparison with RECIST 1.1

Criteria	RECIST 1.1	irRC	irRECIST	iRECIST	imRECIST
Measurement method	Unidimensional (longest diameter for visceral lesions, short diameter for nodal lesions)	Bidimensional longest diameter × the longest perpendicular diameter)	Unidimensional (The same with RECIST 1.1)	Unidimensional (The same with RECIST 1.1)	Unidimensional (The same with RECIST 1.1)
Target lesions	≥10 mm (≥15 mm for nodal lesions) (up to 5 lesions) (maximum 2 lesion/organ)	≥5×5 mm per organ (up to 10 visceral and 5 cutaneous ones) (maximum 5 lesion/organ)	The same with RECIST 1.1	The same with RECIST 1.1	The same with RECIST 1.1
Non-target lesions	<10 mm (<15 mm for nodal lesions)	<5×5 mm	The same with RECIST 1.1	The same with RECIST 1.1	The same with RECIST 1.1
Non-measurable lesions					
New lesions	New lesions are included in the sum of the target lesions at follow-up; result in progressive disease(PD).	New lesions are included in the sum of the target lesions at follow-up; result in pseudoprogressive (PP) disease.	New lesions are included in the sum of the target lesions at follow-up; result in pseudoprogressive (PP) disease.	New lesions are not included in the sum of the target lesions but recorded separately at follow-up, result in unconfirmed progressive disease (iUPD).	New lesions are included in the sum of the target lesions at follow-up; result in pseudoprogressive (PP) disease.

RECIST: Response evaluation criteria in solid tumors; irRC: Immune-related response criteria; irRECIST: Immune-related RECIST; iRECIST: Immune RECIST; imRECIST: Immune-modified RECIST; PD: Progressive disease; PP: Progressive disease; iUPD: Immune unconfirmed progressive disease.

and a lower number of target lesions (five total target lesions with a maximum of two per organ). IrRECIST is basically similar to RECIST 1.1; however, in irRECIST, new lesions are incorporated in the total tumor burden; differently from RECIST 1.1, new lesions do not immediately mean PD. This method allows us to not to discontinue a potentially effective therapy in case of the appearance of new lesions. Confirmatory evaluation of PD is not mandatory; however, confirmation of progression should be recommended for patients with a minimal total tumor burden increase over 20%, particularly during the first 12 weeks of treatment.[4,17]

Immune RECIST (iRECIST)

iRECIST are comparable with RECIST 1.1 and irRECIST concerning recommended imaging modalities, definitions of measurable lesions and target lesions. [1] However, in iRECIST, new lesions are not included

in the sum of the target lesions but recorded separately at follow-up, result in unconfirmed progressive disease (iUPD). The response categories of iRECIST include iCR (complete response), iSD (stable disease) and iPR (partial response) but also unconfirmed PD (iUPD) and confirmed PD (iCPD) (Tables 1,2). In iCPD, a further increase in the size of previous new lesions (5 mm for the sum of target lesions or any increase in non-target lesions) or additional new lesions appearance is required at the follow-up.

Immune-Modified RECIST (imRECIST)

Unlike iRECIST, in the imRECIST, new lesions are added to the total tumor burden along with the sum of the target lesions when measurable; when not measurable, they are not included in PD assessment (Fig. 7).[5] In addition, progression in nontarget lesions is not defined as PD.

Table 2. Overview of immune-specific related response criteria of irRC, irRECIST iRECIST and imRECIST comparative with RECIST 1.1.

	RECIST 1.1	irRC	irRECIST	iRECIST	imRECIST
Response criteria					
Complete response (CR)	Disappearance of all target and non-target lesions	Disappearance of all target and non-target lesions	Disappearance of all target and non-target lesions	Disappearance of all target and non-target lesions	Disappearance of all target and non-target lesions
Partial response (PR)	≥30% decrease in total tumor burden compared with baseline	≥50% decrease in total tumor burden compared with baseline	≥30% decrease in total tumor burden compared with baseline	≥30% decrease in total tumor burden compared with baseline	≥30% decrease in total tumor burden
Stable disease (SD)	Neither CR nor PD	Neither CR nor PD	Neither CR nor PD	No new lesions Neither CR nor PD	Neither CR nor PD
Progressive disease (iCPD)	≥20% and ≥5 mm increase in the nadir of the sum of the target lesions	≥25 increase in the nadir of the sum of the target lesions at least four weeks later	≥20% and ≥5 mm increase in the nadir of the sum of the target lesions at least four weeks after and up to 12 weeks	≥20% and ≥5 mm increase in the nadir of the sum of the target lesions or new non-target lesion at least four weeks after and up to eight weeks	≥20% and ≥5 mm increase in the nadir of the sum of the target lesions at least four weeks after
New Lesions	PD	Incorporated in the sum of measurements	Incorporated in the sum of measurements	Not incorporated in the sum of measurement (iUPD); becomes iCPD if confirmed	Incorporated in the sum of measurements

RECIST: Response evaluation criteria in solid tumors; irRC: Immune-related response criteria; irRECIST: Immune-related RECIST; iRECIST: Immune RECIST; imRECIST: Immune-modified RECIST; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; iUPD: Immune unconfirmed progressive disease; iCPD: Immune confirmed progressive disease.

Currently, iRECIST and imRECIST are seen as the most promising criteria for applicability.[10,18,19] However, it is very difficult to draw conclusions about which of the existing criteria is superior because of limited data.[20]

Immune-Related Adverse Reactions

Immune checkpoint inhibitors are associated with a unique spectrum of adverse reactions compared with cytotoxic chemotherapy. These immune-related adverse reactions are attributed to induction of the autoimmunity or a pro-inflammatory state and increase in T-cell activation and can involve almost every organ system (Table 3).[21]

Many of these reactions do not have radiological manifestations, such as immune-related skin toxicity,

nephritis, ocular and some endocrinopathies which are diagnosed clinically. However, radiologists should be aware of the potential adverse effects, their radiological manifestations and the importance of alerting this to the clinicians who will invariably cease treatment, at least temporarily. Immune-related adverse reactions with radiological findings as follows:

Hypophysitis

Hypophysitis is inflammation of the anterior lobe of the pituitary gland, which presents with headache, fatigue, dizziness and memory impairment. It typically presents at 6–12 weeks after initiation of anti-CTLA-4 therapy. MRI findings include an enlarged pituitary gland and stalk with variable heterogeneous or homogeneous enhancement.[22]

Table 3. A table of the more common immune-related adverse reactions in each system

System	Toxicity
Skin	Rash Pruritis Vitiligo
Endocrine system	Adrenal insufficiency Hypo/hyperthyroidism Hypophysitis Type 1 diabetes mellitus
Urinary system	Nephritis
Hepatobiliary system	Hepatitis Pancreatitis
Gastrointestinal system	Diarrhoea Enterocolitis
Lung	Pneumonitis Sarcoid-like reaction
Central nerve system	Encephalitis Transverse myelitis Guillain Barre
Musculoskeletal system	Myalgia Arthralgia
Cardiac system	Pericarditis Arrhythmias Myocarditis

Pneumonitis

Pneumonitis is a focal or diffuse inflammation of the lung parenchyma. The median time to onset was 2.8 months after starting therapy. 56% had additional immune-related toxicity. Five radiological subtypes were described.[21] Cryptogenic organizing pneumonia, ground-glass opacities, interstitial, hypersensitivity and pneumonitis not otherwise specified. There are no pathognomonic radiographic features to distinguish ICI-related pneumonitis from pneumonitis of another etiology. Lung biopsies may help clarify in select cases if the underlying etiology is unclear.

Sarcoid-Like Reactions

Sarcoid-like reaction is a rare immune-related adverse event that may result in numerous small pulmonary nodules in a perilymphatic distribution (along the bronchovascular bundles and in the subpleural regions) with or without ground-glass opacities and/or mediastinal/hilar lymphadenopathy.[23]

Colitis

Typical clinical features are diarrhoea, abdominal pain and fever. Imaging can depict signs of colitis on CT, as well as its complications. Colitis is a significant clinical complication that has the highest mortality of all

immune-related adverse events, and prolonged time to diagnosis and management is associated with poor outcomes.[21,24] In the setting of an acute abdomen, it may exclude bowel perforation, obstruction and toxic megacolon.

Pancreatitis and Hepatitis

Pancreatitis and hepatitis are rare gastrointestinal complications with nonspecific CT findings.[21]

Meningitis, Encephalitis and Guillain Barre Syndrome

The incidence of neurological adverse effects is 12% to 3.8%, with less than 1% of them having headache, encephalopathy, meningitis and Guillain Barre syndrome.[21,25]

In conclusion, the role of immunotherapy in treating patients with cancer continues to expand. Therefore, it is essential that radiologists and other providers have a thorough understanding of the novel response criteria developed to evaluate these patients. In addition, because a wide variety of immune-related adverse events may affect patients who receive immunotherapy, the prompt identification and reporting of such side effects are imperative.

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