Cancer Imaging in Immunotherapy

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Abstract

Immune therapeutics are revolutionizing cancer treatments. In tandem, new and confounding imaging characteristics have appeared that are distinct from those typically seen with conventional cytotoxic therapies. In fact, only 10% of patients on immunotherapy may show tumor shrinkage, typical of positive responses on conventional therapy. Conversely, those on immune therapies may initially demonstrate a delayed response, transient enlargement followed by tumor shrinkage, stable size, or the appearance of new lesions. New imaging response criteria, such as the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) and immune-related Response Criteria (irRC), are being implemented in many trials. However, FDA approval of emerging therapies, including immunotherapies, still relies on the current RECIST criteria. In this chapter, we review the traditional and new imaging response criteria for evaluation of solid tumors and briefly touch on some of the more commonly associated immunotherapy-induced adverse events.

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Introduction

Cancer immunotherapy has caused a plethora of new and important radiographic features that are imperative to understand when assessing tumor response and immune-related adverse events [1–3]. Immunotherapy, which is an approach to treat cancer by augmenting or generating an immune response against cancer cells, causes radiographic responses distinct from conventional cytotoxic chemotherapies [2, 3].

Objective imaging response criteria as measured by the World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST) criteria were originally created to assess the effects of cytotoxic chemotherapy and are dependent on tumor shrinkage and absence of new lesions; however, these criteria do not perform well in assessing the effects of drugs with other mechanisms of action, such as antiangiogenic therapies or immune therapies [1–4]. Evaluation of tumor response to cytotoxic chemotherapy depends on tumor shrinkage within a few weeks of initiating treatment. In fact, in addition to the appearance of new lesions and increased tumor size, stable disease was at

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one point considered a treatment failure [4]. On the other hand, new tumor therapies with recombinant cytokines, cancer vaccines, and immunomodulatory monoclonal antibodies may demonstrate a delayed response, transient enlargement (transit flair-up phase) followed by tumor shrinkage, stable size, or the appearance of new lesions [4] . Unique challenges associated with immunotherapy reflect delays in response and therapy-induced inflammation. Cancers after immunotherapy demonstrate confounding radiographic appearances with only 10% showing regression [4]. Typically, these tumors initially demonstrate a delay in response, including none or slow decrease in tumor size, increase in tumor size, and/or the appearance of new lesions, which over time become stable, decrease, or resolve without further treatment (Fig. 18.1). Over the years, there have been many modifications to the different assessment criteria by combining changes in size and inclusion of metabolic features of specific tumors to overcome the limitations of the traditional criteria [5]. However, these modifications have caused difficulties in assessing treatment efficacy since standardization of response assessments among those clinical trials lacks. It is critical to distinguish as early as possible between patients who are responding to a particular treatment and those who are not in order to maximize the effectiveness of patient care [5]. In addition, it is important to understand immunotherapy-induced side effects as in some cases treatment might be changed or halted. In this chapter, we discuss the use of a variety of traditional and new immunotherapy criteria for the evaluation of tumor response in patients who are undergoing immunotherapy. We also briefly discuss some of the immunotherapyinduced adverse events.

Conventional Imaging Response Criteria (Table 18.1)

The WHO and the RECIST criteria were the first criteria developed to assess tumor responses to traditional cancer treatment, which included cytotoxic chemotherapy, radiation therapy, or surgical resection. These criteria depend on changes in tumor size and do not take into consideration

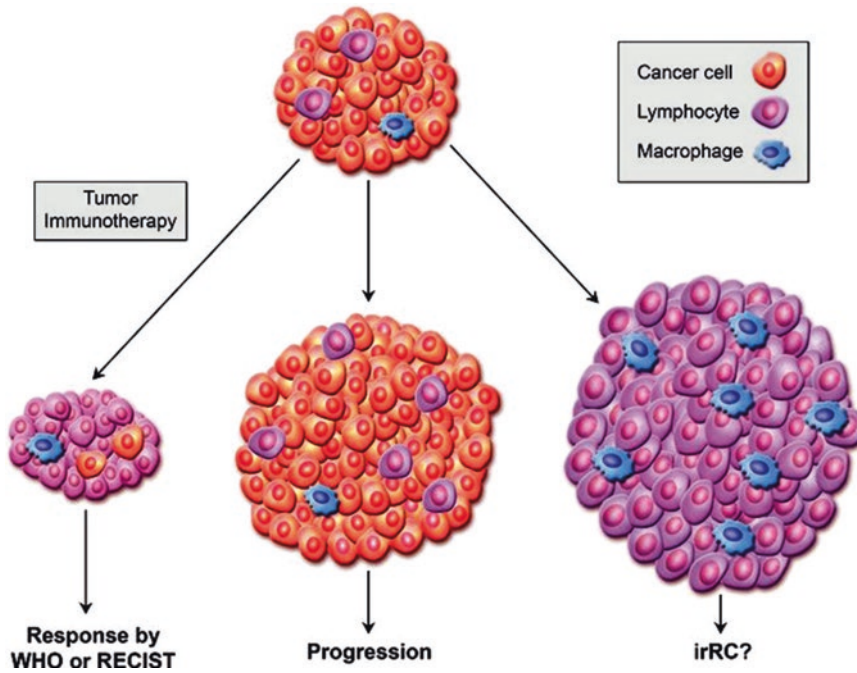

Fig. 18.1 Cancer imaging in immunotherapy

Table 18.1 Comparison between the basis of WHO, RECIST 1.0, RECIST 1.1, irRC, and irRECIST criteria [1, 2, 4]

Criterion	WHO	RECIST 1.0	RECIST 1.1	irRC	irRECIST
Method of measurement	SPD	Longest diameter	Longest diameter (except in lymph nodes)	SPD	Single longest diameter (except in lymph nodes)
Measurable lesions	Should be measurable in two dimensions, no minimum lesion size	Minimum size = 10 mm at spiral Computed tomography (CT), 20 mm at conventional CT	Minimum size = 10 mm at CT	Minimum size of the lesion is 5 mm × 5 mm	Minimum size = 10
Number of lesions measured	No assessment	Ten lesions (≤5 in any one organ)	Five lesions (≤2 in any one organ)	Ten lesions (≤5 in any organ)	Five lesions (≤2 in any one organ)
Progressive disease	≥25% increase in SPD	20% increase in SLD or new lesions, unequivocal progression considered to indicate progressive disease	>20% increase in SLD, ≥5-mm increase in size, new lesions, detailed description of unequivocal progression	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart
Lymph nodes	Unspecified	Unspecified	Short axis: target lesions ≥15 mm, nontarget lesions = 10–15 mm, nonpathologic lesions <10 mm	Unspecified	Short axis: target lesions ≥15 mm, nontarget lesions = 10–15 mm, nonpathologic lesions <10 mm
New lesions	No assessment	No assessment	Provides guidance as to when a lesion is considered new (i.e., representative of progressive disease)	Does not constitute progressive disease in itself, but is rather added to the SPD and contributes to progression	Does not constitute progressive disease in itself, but is rather added to the sum of longest diameter and contributes to progression
Guidance for imaging studies	No assessment	CT, MRI, chest radiography	CT, MRI, FDG PET	CT, MRI, chest radiography, FDG PET	CT, MRI, chest radiography, FDG PET

appearance of new lesions when evaluating responses that may be related to treatment [4].

WHO Criteria

In 1981, the WHO published the first tumor response criteria, thus establishing a standard assessment metric and nomenclature to evaluate treatment response [6]. The WHO criteria introduced the concept of assessing tumor burden using the sum of the products of diameters (SPD) (i.e., longest overall tumor diameter and longest diameter perpendicular to the longest overall diameter) and determining response to therapy by evaluating the changes from baseline during

treatment [6]. These criteria were categorized into four tumor response groups: complete response (tumor not detected for at least 4 weeks), partial response (≥50% reduction in the SPD from baseline, also confirmed at 4 weeks), progressive disease (≥25% increase in tumor size in one or more lesions), and no change (stable) in disease (neither partial response, complete response, nor progressive disease) (Table 18.1) [7] . However, the WHO has a few major pitfalls (discussed below), in particular, because tumor measurements are based on SPD, small increases in tumor size may result in a sufficiently overall increase in tumor size (≥25% increase) to consider it as progressive disease [5].

RECIST 1.0, 1.1, and mRECIST Criteria

RECIST 1.0

In 2000, the RECIST 1.0 criteria was established and addressed some of the pitfalls of the WHO criteria. Of these, the key features of RECIST 1.0 included a clear definition of measurable disease, number of lesions to be assessed, and the use of unidimensional (i.e., longest dimension) rather than bidimensional tumor measurements (Table 18.1) [6].

RECIST 1.1

In 2009, RECIST 1.1 was developed. RECIST 1.1 addressed multiple questions regarding the assessment of lymph nodes, number of lesions to be assessed, and use of new imaging modalities, such as multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) [8]. In RECIST 1.1, the number of target lesions is reduced; target lesions can reach a maximum of five lesions (up to two lesions in any one organ) and must be measured in their longest dimension (should be at least 10 mm in the longest diameter to be considered measurable), except for lymph nodes, which use the shortest diameter (must be at least 15 mm in the short axis to be considered pathological). In coalescing lesions (nonnodal lesions), its portions should be added together (as lesions coalesce) and its longest dimensions measured [8]. Furthermore, if a lesion cannot be reliably measured, the next largest lesion that can be reproducibly measured should be selected. In addition, if any target lesions (including lymph nodes) become too small to be measured, these should also be recorded and taken in assessment of response and reassessed in the follow-up examination to determine if they represent a new lesion [5] (Table 18.1).

Modified RECIST (mRECIST)

Modified RECIST (mRECIST) was created to measure the response rate in hepatocellular carcinoma (HCC). Similar to RECIST 1.0 and 1.1, mRECIST uses tumor size as an index of tumor response; however, in contrast, mRECIST takes into account treatment-induced tumor necrosis, and changes in size are determined by assessing for viable tumor, referred to an uptake of contrast agent in the arterial phase on CT or MRI [9, 10]. For example, a complete tumor response is defined as the disappearance of arterial phase enhancement in all target lesions which should be classified as a measurable lesion according to the RECIST criteria [5]. Tumors in malignant portal vein thrombosis are considered as nonmeasurable disease since the bland thrombus formed during the course of treatment can obscure the tumor.

Choi Response Criteria

The Choi criteria was initially proposed for assessment of gastrointestinal stromal tumors (GIST) on imatinib, a tyrosine kinase receptor inhibitor. This study found that GISTs on treatment may initially increase in size due to internal hemorrhage, necrosis, or myxoid degeneration. Some may show a minimal decrease in tumor size but not sufficient enough to be classified as having a positive response to therapy according to RECIST criteria [11]. The Choi criteria focuses on changes in density (Hounsfield units on CT) rather than tumor shrinkage to assess response. A decrease in tumor density on CT is often seen in these tumors responding to imatinib and is related to tumor necrosis or myxoid degeneration. There are two main limitations of the Choi criteria: it

cannot be applied to MRI and there is lack of sufficient validation in other tumors.

EORTC

The European Organization for Research and Treatment of Cancer (EORTC) criteria has formalized the concept of assessing tumor response via quantifying the changes in fluorodeoxyglucose (FDG) uptake. Criteria standardization and rules were proposed on patient preparation, timing of [18F]-FDG positron emission tomography (PET) scans, attenuation correction and dose of [18F]-FDG, methods to measure [18F]-FDG uptake, tumor sampling, reproducibility, and definition of [18F]-FDG tumor response [12, 13].

The criteria follows the model of RECIST in terms of defining four response categories with similar names as RECIST. Complete metabolic response (CMR) would be the complete resolution of [18F]-FDG uptake within the tumor volume so that it is indistinguishable from surrounding normal tissue. Partial metabolic response (PMR) would be classified as a reduction of a minimum of 15–25% in tumor [18F]-FDG SUV after one cycle of chemotherapy, and greater than 25% after more than one treatment cycle. Stable metabolic disease (SMD) would be classified as an increase in tumor [18F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [18F]-FDG tumor uptake (20% in the longest dimension). Progressive metabolic disease (PMD) would be classified as an increase in [18F]-FDG tumor SUV of greater than 25% within the tumor region defined on the baseline scan, visible increase in the extent of [18F]-FDG tumor uptake (20% in the longest dimension) or the appearance of new [18F]-FDG uptake in metastatic lesions [12, 13].

PERCIST Criteria

Based on the premise that newer cancer therapies are more cytostatic than cytocidal, tumor response can manifest with a decrease in metabolism without a notable tumor size reduction [14]. In 2009, the PET response criteria for solid tumors (PERCIST) was proposed and is based mainly on FDG uptake to evaluate tumor response [15]. PERCIST focuses on the percentage of change in metabolic activity from baseline and the number of weeks from initiation therapy. The standardized uptake value (SUV) corrected for lean body mass (SUL) is used for the assessment of tumor response. The SUL peak is measured within a spherical region of interest of 1.2 cm in diameter (or 1 cm^3 for volume) within the area of highest uptake in the tumor [5]. PERCIST defines four metabolic response categories. In brief, according to these criteria, complete response means disappearance of all metabolically active tumors while partial metabolic response is defined as a 0.8-unit (>30%) decline in SUL peak between the most intense lesion before treatment and the most intense lesion after treatment. Of note, the lesion at follow-up may be a different lesion than previously measured since the most active lesion needs to be followed. Progressive disease is defined as an increase (>30%) in SUL peak or the appearance of a new metabolically active lesion [5]. It is likely that PERCIST will replace the EORTC criteria in the same way that RECIST has replaced the WHO criteria [12].

RANO Criteria

The Revised Assessment in Neuro-Oncology (RANO) criteria was proposed to overcome the significant limitations in the Macdonald criteria for response assessment in high-grade gliomas. The Macdonald criteria didn't take into account, for example, pseudoprogression, pseudoresponse observed with antiangiogenic agents, and the inability to capture recurrence in the nonenhancing component of the lesion, due to using only the contrast-enhancing component of the tumor in it [13].

Similar to the Macdonald criteria, the RANO criteria uses two-dimensional tumor measurements; however, the RANO criteria also accounts for changes in the nonenhancing T2/FLAIR signal abnormality. Measurable disease is defined

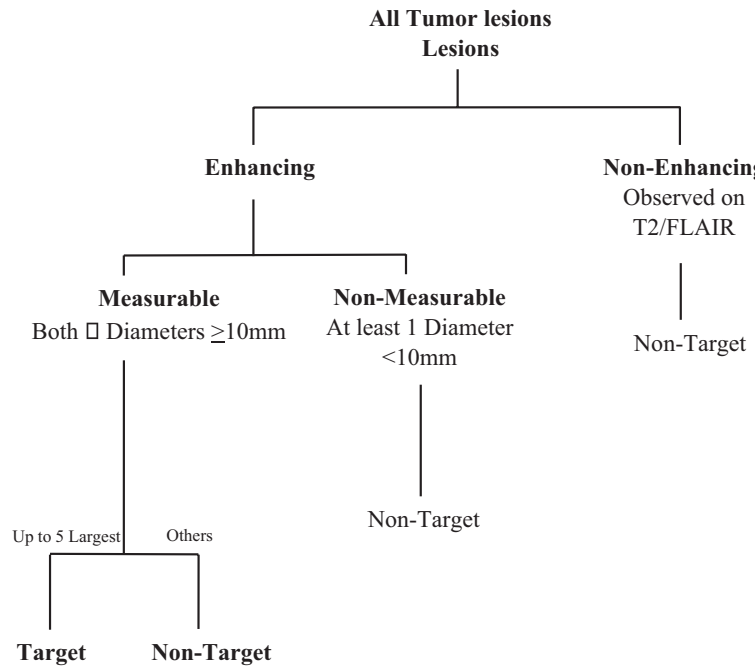

Fig. 18.2 Algorithm for identifying measurable and target lesions [16]

Table 18.2 RANO criteria for response assessment in high-grade gliomas [16, 17]

Criterion	CR	PR	SD	PD
T1-Gd + (bidimensional product)	None	≥50% ↓	<50% ↓ to <25% ↑	>25% ↑[a]
Estimated volumetric change	100% decrease	≥65% decrease	<65% decrease to <40% increase	≥40% increase
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or↓	↑[a]
New lesion	None	None	None	Present[a]
Corticosteroids	None	Stable or ↓	Stable or ↓	NA[b]
Clinical status	Stable or ↑	Stable or↑	Stable or↑	↓[a]
Requirement for response	All	All	All	Any[b]

[a]Progression occurs when this criterion is met

[b]Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

as two perpendicular diameters of at least 10 mm (visible on two or more axial slices being preferably not more than 5 mm apart with 0 mm skip) and allows selection of a total of five target lesions (Fig. 18.2). RANO criteria addressed pseudoprogression and pseudoresponse. The RANO criteria for high-grade glioma are summarized in Table 18.2 [16, 17].

In RANO, the postradiation examination as the baseline for response assessment instead of the postsurgical MRI scan can be used. Progressive disease is defined by at least two sequential scans separated by at least 4 weeks, both showing >25% increase in the sum of products of perpendicular diameters or > 40% increase in total volume of enhancing lesions. If the follow-up scan exhibits SD or PR/CR, then the first scan that showed "preliminary PD" is noted at pseudoprogression. Pseudoprogression is also considered if imaging showed PD and the follow-up scan >4 weeks apart showed SD, CR, PR or the lesions became nonmeasurable; if the latter, the scan that showed "preliminary PD" is noted as "pseudoprogression" [16]. On the other hand,

if imaging demonstrated preliminary PR/CR and the follow-up scans exhibited PD with respect to the "preliminary CR/PR" scan, then the response isn't sustained and is noted as pseudoresponse. Pseudoresponse can also be noted in tumors that show regression in size of their enhancing component whilst their nonenhancing component show progression [16].

RANO-BM

The Response Assessment in Neuro-Oncology Brain Metastases working group initially convened in 2011 and proposed response assessment on the basis of literature review and consensus opinion [18]. RANO-BM adopted features from RECIST and RANO-HGG to be able to meet the specific needs of patients with brain metastases, where response assessment in RANO-BM is being based on the sum diameter of one-dimensional measurements, corticosteroid dosing and clinical status (Table 18.3) [17].

Cheson Response Criteria for Malignant Lymphomas

Tumor assessment criteria have been developed specifically for lymphoma. In lymphoma, masses often don't regress in size completely after therapy because of the presence of residual fibrosis and necrotic debris; thus, reporting whether the tumor is viable or not viable does not depend solely on the stability of the tumor's size. The Cheson response criteria analyzes the size and the metabolic activity of the tumor during the course of treatment. The revised version of the Cheson criteria in 2007 replaced gallium scintigraphy with PET and included the evaluation of flow cytometry and immunohistochemistry as mentioned in Tirkes et al. (Table 18.4) [5].

Immunotherapy Imaging Response Criteria

Evaluating tumor responses during immune therapy in solid cancers remains a challenge [5, 20]. The mechanism of action in immunotherapy differs substantially from cytotoxic agents; thus a well-tailored set of criteria to capture accurate and exact response to this new line of therapeutic agents is needed [4, 5, 20]. To this end, Wolchok et al. presented a set of criteria to evaluate immune-related responses, adopting a bidimensional approach similar to the WHO criteria and measuring a maximum number of five lesions per organ (Table 18.5) [4]. Although these criteria were widely accepted, it still harbors some

Table 18.3 RANO-BM criteria for response assessment in brain metastases [17]

Criterion	CR	PR	SD	PD
Target lesions	None	≥30% decrease in sum LD relative to baseline	<30% decrease relative to baseline, but <20% increase in sum LD relative to nadir	≥20% increase in sum LD relative to nadir[a]
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal PD[a]
New lesion(s)[b]	None	None	None	Present[a]
Corticosteroids	None	Stable or decreased	Stable or decreased	NA[c]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse[a]
Requirement for response	All	All	All	Any[c]

LD longest dimension
[a]Progression occurs when this criterion is met
[b]New lesion = New lesion not present in previous studies and visualized in at least two projections
[c]Increase in corticosteroids dose alone will not be considered to determine progression in the absence of persistent clinical deterioration

Table 18.4 Cheson response criteria definitions [19]

Table response definitions for clinical trials				
Response	Definition	Nodal masses	Spleen, liver	Bone marrow
CR	Disappearance of all evidenceof disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new site	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: *CR* complete remission, *FDG* [18F] fluorodeoxyglucose, *PET* positron emission tomography, *CT* computed tomography, *PR* partial remission, *SPD* sum of the product of the diameters, *SD* stable disease, *PD* progressive disease

Table 18.5 Summary of immune-related response criteria (irRC) [4]

Method of assessment of lesion	The largest bidimensional diameters are used to evaluate each lesion.
Total tumor burden evaluation	The total tumor burden is the sum of the products of diameters (SPD) of target lesions and new lesions.
New target lesions	If the new lesions fulfill the criteria of target lesion assessment, the two diameters are determined and the product of these diameters is incorporated into the SPD and contributed to the evaluation of total tumor burden.
New nontarget lesions	If the new lesions fail to fulfill the criteria of target lesions, they do not contribute to total tumor burden. However, complete remission of such lesions is essential for establishing a complete response.
Imaging modalities	Almost all current imaging modalities could be used to assess tumors in a longitudinal manner. These include CT, MRI, and PET-CT.
Target lesions criteria	Target lesions should measure at least 5 × 5 mm. A maximum of five cutaneous lesions and 10 visceral lesions could be selected. No more than five lesions could be selected per organ.
Time-point response assessment	The growth kinetics of target and new lesions are determined. Percentage change of tumor growth is then calculated referencing baseline assessment as well as the smallest reported tumor burden (nadir).
Types of overall response	Complete response (irCR), partial response (irPR), stable disease (irSD), and progressive disease (irPD)
Complete response (irCR)	irRC requires for complete response the total (100%) remission of all target, nontarget, and new lesions for two consecutive evaluations at least 4 weeks apart.
Partial response (irPR)	irRC requires for partial response a decrease of at least 50% of the tumor burden compared to the baseline. This percentage change must be confirmed by a consecutive scan after no less than 4 weeks
Progressive disease (irPD)	irRC requires a total increase of tumor burden of at least 25% from the smallest reported tumor burden (nadir). However, irRC advice against the evaluation of progressive disease after just one cycle of immunotherapy as immune response requires more duration to establish a true and measurable antitumor effect. Also, immune response might mimic tumor flare and exaggerate the target lesion diameters, thus enhancing the percentage Increase.
Stable disease (irSD)	If percentage change shows an increase less than 25% from the smallest -recorded tumor burden (nadir) or a decrease less than 50% from baseline, patient status is recorded as stable disease and patient is usually followed for several cycles.
Limitations	No specific description on how to assess nodal disease. Bidimensional assessment reproducibility is lower than unidimensional assessments.

challenges. For instance, assessing a relatively large number of lesions per organ could be relatively time-consuming in cases of extreme tumor burdens [2, 21]. Furthermore, evaluation of excessive number of lesions impacts the reproducibility of the results [2, 21]. As such, Nishino et al. proposed a modification to the immune-related response criteria (irRC) in the light of RECIST 1.1 guidelines [2, 8, 21]. With regard to brain tumors, the Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria is a set to tumor metrics to assess brain tumors in patients undergoing immune therapies.

Immune-Related Response Criteria

Arising from the heightened awareness by national and international communities as to the unique radiographic response patterns seen with vaccines and immunotherapeutics, modifications were made to the WHO and RECIST criteria in 2004 and 2005. In 2009, the immune-related Response Criteria (irRC) was published by Wolchok et al., based on the observed patterns in treatment response from phase II clinical trials in advanced melanoma patients who were receiving ipilimumab, a human monoclonal antibody that blocks cytotoxic T lymphocyte antigen–4 (CTLA-4). In this study [4], four patterns of treatment responses were recognized: (1) a decrease in the size of the lesion and without new tumors, similar to what is seen after conventional cytotoxic therapy; (2) stable disease after completion of treatment; (3) a delay in tumor response to therapy after an initial increase in total tumor burden; (4) the appearance of new lesions that precede tumor shrinkage.

In contrast to the WHO and RECIST criteria, irRC takes into account both the index and new measurable lesions to assess the "total tumor burden," a new concept from prior criteria, and compare to the baseline scan [4]. The irRC was derived from the WHO criteria and, therefore, the thresholds of response remain the similar. However, the irRC response categories have been modified from those of the WHO criteria [4]. According to the irRC, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated at the baseline. At every time point, the index lesions and any new measurable lesions are added together to accurately measure the total tumor burden (TTB) [(TTB = SPDindex lesions + SPDnew, measurable lesions)]. This is a major difference from the WHO criteria, which considers all new measurable lesions as progressive disease [5]. Further, a confirmatory examination at least 4 weeks from the initial scan documenting progression is required by the irRC prior to declaring progressive disease, as there can be a delay in response in patients on immunotherapy. In addition, decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The overall response according to the irRC is derived from time-point response assessments based on tumor burden, as described in Table 18.5.

The irRC does not mention the use of specific imaging modalities in the assessment of tumor response, although CT and MRI are typically used. However, research on novel PET radiotracers that incorporate amino acids, nucleotides, choline, and s-receptor to detect cell proliferation or cell death is being carried out [22]. Further, immune-related adverse effect can be sometimes identified with FDG-PET/CT and metabolic changes can be noted before the clinical symptoms to allow early change of the immunotherapy [1].

Immune-Related RECIST Criteria

The newly proposed irRECIST (Table 18.6) and adopted irRC [4] set thresholds for determining different possible responses, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [2, 21]. Nishino et al. demonstrated that such changes did not result in any statistically significant variation of the response evaluation in melanoma patients receiving immunotherapy [2, 21]. They also demonstrated that irRECIST measurements were relatively more reproducible than the more involved bidimensional irRC measure-

ments [2, 21]. In 2017, the RECIST working group published the immune-RECIST (iRECIST) based on RECIST 1.1, where the definition of pseudoprogression was introduced. It is noteworthy, iRECIST criteria was used for response assessment to immunotherapy in trials for patients with brain metastases, by discerning between intra- and extracranial responses [24]. The criteria are summarized in Table 18.7 [25].

Immunotherapy Response Assessment for Neuro-oncology Criteria

The iRANO criteria is used to assess brain lesions in patients undergoing immunotherapy [3]. In order that misclassification of patients with stable or increasing tumor size and new lesions as progressive disease does not occur when the therapy is actually effective and the patient is receiving clinical benefit, the iRANO criteria was published. In brief, the iRANO follow the same guidelines as the RANO criteria. However, in those cases of appearance of disease in the absence of clinical deterioration within 6 months of immunotherapy, continuation of immunotherapy and repeat assessment in 3 months is recommended (Table 18.8). As with all current imaging assessment criteria, the iRANO guidelines will require future amendments, including the possible incorporation of volumetrics, advanced imaging sequences, and other types of imaging analytics. A recent study by our group demonstrated that radiomics can discriminate between patients who have pseudoprogression versus true tumor progression with high sensitivity (97%), specificity (79%), and accuracy (95%) in patients with glioblastoma [26]. The iRANO criteria also added specific guidance for the determination of progressive disease in patients with brain metastases undergoing immunotherapy. The criteria for iRANO-BM is summarized in Table 18.9 [3].

It's crucial for clinicians to indicate and conclude an underlying tumor progression during the course of immunotherapy. It has been shown that early radiographic progression in patients who ultimately derive clinical benefit actually stabilize or even improve within 3 months. The

Table 18.6 irRECIST response criteria [23]

Complete response (CR)	Complete resolution of nonnodal lesions and < 10 mm short-axis for lymph nodes. No confirmation necessary
Partial response (PR)	≥30% decrease in tumour burden
Stable disease (SD)	Does not meet criteria for irCR/irPR/irPD
Progressive disease (PD)	≥20% increase in tumor burden relative to nadir and a minimum absolute increase of 5 mm; new lesions Confirmation of PD via a subsequent scan ≥4 weeks later to detect delayed responses is required

Table 18.7 iRECIST response criteria [25]

Type of response	Definition
Complete response (iCR)	Total remission of all target and nontarget lesions, including the lack of appearance of new lesions, confirmed by a consecutive imaging evaluation performed ≥4 weeks after the first one
Partial response (iPR)	A decrease of at least 50% in the total tumor burden compared to baseline, confirmed by a consecutive investigation performed after ≥4 weeks
Stable disease (iSD)	The change of the total tumor burden is reduced to less than 50% when compared with baseline, or increased to less than 20% when compared with nadir.
Unconfirmed progressive disease (iUPD)	Increase in the total tumor burden of at least 20% compared to nadir.
	The term "unconfirmed" refers to the initial dimensional increase that can be detected after 1 cycle of immunotherapy; further confirmation at imaging is needed.
Confirmed progressive disease (iCPD)	Increase in the total tumor burden of at least 20% when compared to nadir. A further increase in the tumor burden (≥5 mm) or a further increase of nontarget lesions or the appearance of new target or nontarget lesions must be noted in the next assessment after the examination in order to confirm disease progression.

Nadir: The smallest value of the sum of the longest diameters of target lesions recorded during therapy

Table 18.8 Summary of Immunotherapy Response Assessment in Neuro-Oncology (iRANO) [3]

Method of assessment of lesion	Bidimensional assessment of the longest perpendicular diameters of all enhancing lesions.
Total tumor burden evaluation	Sum of product of the longest diameters of all target lesions
New target lesions (appearing more than 6 months after initiation of immune therapy)	Target lesions appearing more than 6 months after the initiation of therapy are considered a sign of true tumor progression.
New target lesions (appearing less than 6 months after initiation of immune therapy)	Target lesions appearing less than 6 months with no associated tumor-related clinical decline of patient should be followed for at least 3 more months taking in reference the time point at which progression was initially reported.
Imaging modalities	MRI is the gold standard in evaluation of intracranial neoplasms; however, the criteria could be also used to evaluate CT scan with relative restrictions.
Target lesions criteria	Target lesions should measure at least 10 × 10 mm. A maximum of five target lesions could be selected.
Time-point response assessment	The growth kinetics of target and new lesions are determined. Percentage change of tumor growth is then calculated referencing baseline assessment as well as the smallest reported tumor burden (nadir).
Types of overall response	Complete response (CR), partial response (PR), minor response (MR), stable disease (SD), and progressive disease (PD).
Complete response	Requires 100% decrease in tumor burden, including total remission of all enhancing and nonenhancing lesions for two consecutive scans at least 4 weeks apart. With no new lesions, no clinical decline and no more than the physiological dose of steroids.
Partial response	Requires a decrease of at least 50% or more in tumor burden of enhancing lesion, with stable nonenhancing lesions and T2FLAIR lesions for two consecutive scans at least 4 weeks apart. With no new lesions, no clinical decline and a stable or decreased dose of steroids.
Minor response	Only considered in assessment of low grade gliomas, requires 25–49% decrease in the sum of the product of bi-perpendicular diameters of T2FLAIR lesions. With no new lesions, no clinical decline and stable or decreased dose of steroids.
Progressive disease	In case of malignant and low grade gliomas at least a 25% increase in the tumor burden putting in reference the smallest recorded tumor burden (nadir) while in case of brain metastases at least a 20% increase in the tumor burden, putting in reference the smallest recorded tumor burden (nadir). Also, appearance of new lesions after 6 months of start of immune therapy, remarkable clinical decline, or remarkable worsening of T2FLAIR lesions.

Table 18.9 summary of immune therapy response assessment in brain metastases (iRANO-BM) [3]

Complete response	Disappearance of all the enhancing target and nontarget lesions for ≥4 weeks; no new lesions; no steroids; clinically stable or improved
Partial response	≥30% decrease in the sum of the longest diameters of all target lesions for ≥4 weeks; no new lesions; stable or decrease steroid dose; clinically stable or improved
Minor response	NA
Stable disease	Does not qualify for complete response, partial response or progressive disease
Progressive disease	≥20% increase in the sum of the longest diameters of target lesions; or unequivocal progression of enhancing nontarget lesions; or new lesions; or substantial clinical decline

iRANO working group has come up with an algorithm to guide assessment of progressive disease in neuro-oncology patients undergoing immunotherapy to decrease the likelihood of prematurely stating progressive disease in patients with PsP or delayed response (Fig. 18.3) [3].

Future Directions for Immune Therapy Imaging Assessment

Although irRECIST and irRC represent an improvement over the conventional WHO criteria and RECIST to evaluate tumor response in immunotherapy, there remains limitations and challenges and further refinements are warranted

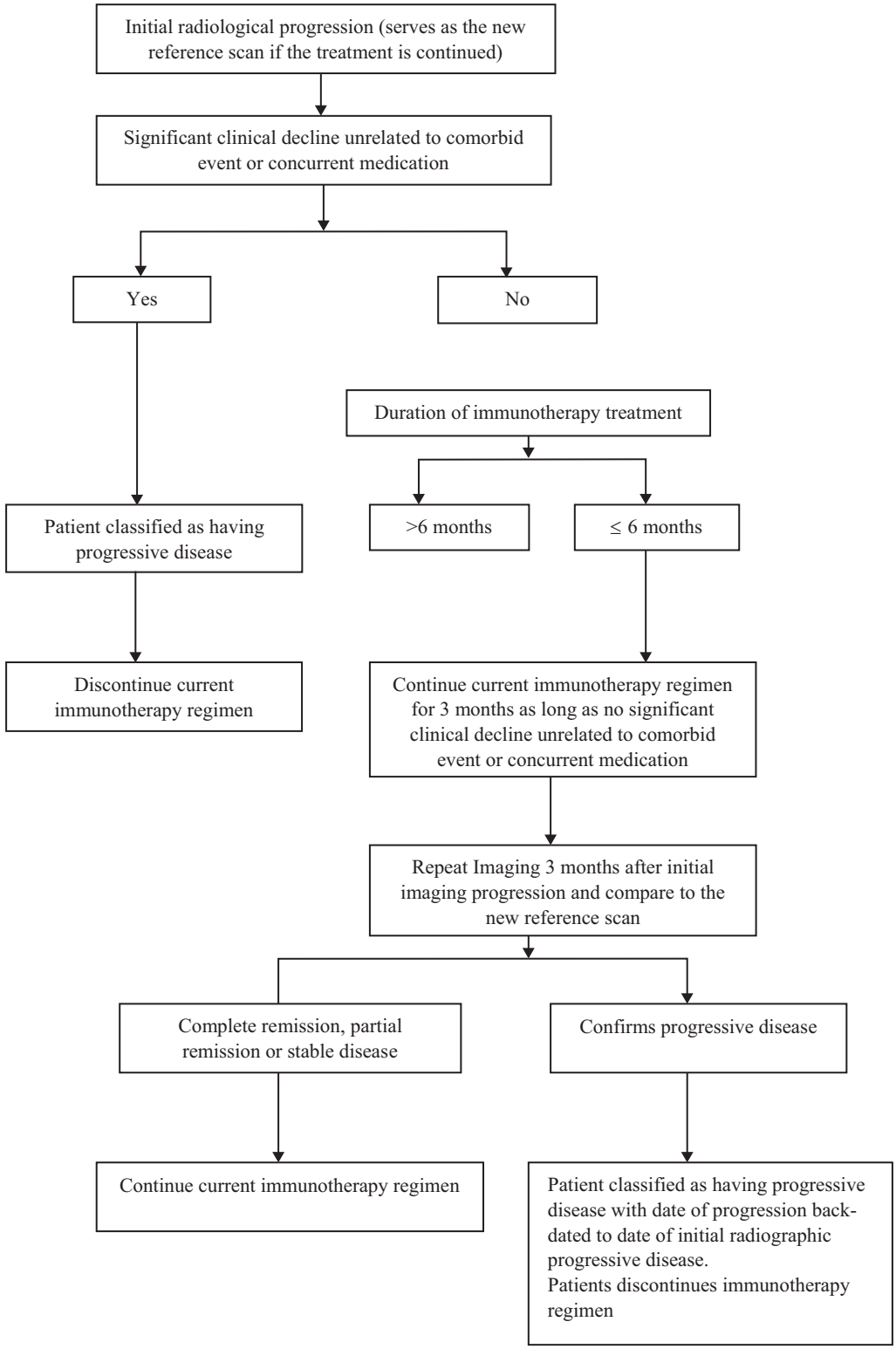

Fig. 18.3 iRANO treatment algorithm for the assessment of progressive imaging findings in neuro-oncological malignancies [3]

[4]. Plans for improving imaging response criteria include volumetric (3D) imaging, dynamic contrast imaging, and functional (molecular) imaging. Radiomics is a more recent developing field within imaging that can help in more precise tumor assessments that are unrelated to tumor size or burden. Radiomics has the potential to be a noninvasive digital biopsy technique that is spatially guided and that can quantify T-cell infiltration of tumors and reflect the entire tumor burden by providing information on each cancer lesion, in contrast to the traditional biopsy that represents only a sample of the tumor. Quantitative imaging biomarkers can support personalized design of immunotherapy interventions and longitudinally monitor and assess immune checkpoint blockade response [27, 28]. Radiomics can be the key to help discriminate between pseudoprogression and true progression, which are significantly difficult to differentiate radiographically. Multiple studies conducted by our group demonstrated 5 texture features were able to robustly predict whether a GBM patient had pseudoprogression or true progression [29–32]. Roger Sun et al. reported on an eight-feature radiomics-based signature of CD8 cell expression, which they developed by use of CT images. The radiomics signature was also shown to be associated with clinical outcomes in patients treated with anti-PD-1 or anti-PD-L1 immunotherapy in an independent cohort [28]. Further, radiogenomics, the linkage between imaging phenotypes and tumor genomics, might help develop more robust stratification and end-point imaging biomarkers for immunotherapy and molecular targeted clinical trials.

Imaging in Immune-Related Adverse Events

Immune-related adverse events (irAE) can represent a serious complication and can be challenging for any imager. Thus, it is important to be aware and take into consideration the possibility of its occurrence so that early management is undertaken [33]. Treatment of adverse events is typically based on published guidelines and includes delaying treatment dosing, administering corticosteroids, or terminating therapy depending on the severity of the event. However, success in outcome lies heavily on correctly identifying and interpreting these complications.

Severe colitis has the highest mortality and worst outcome associated with irAE [33]. Because of the possibility of misdiagnosis of autoimmune colitis, the patient can take antibiotic therapy instead of corticosteroid therapy, which can result in a delayed diagnosis and complication by colonic bowel perforation [33]. Other common immune adverse events are sarcoid-like adenopathy and pancreatitis. It is important to recognize and accurately diagnose these events in order to avoid misdiagnosis for metastatic disease [1]. There are also many other events which can occur as a result of immunotherapy, for example, autoimmune hepatitis, pneumonitis, thyroiditis, myocarditis, pericarditis, temporal arteritis, conjunctivitis, sarcoid-like reaction such as lymphocytic vasculitis, organizing pneumonia, and fasciitis [34, 35]. Autoimmune hepatitis may be seen as periportal edema and hypoattenuation of the edematous liver parenchyma in CT. However, these finding are not specific to autoimmune hepatitis and can be seen in the setting of cancer immunotherapy [1].

Immunotherapy-induced pneumonitis is an uncommon yet potentially fatal irAE that requires clinical suspicion and early detection. A recent study by our group demonstrated that specific radiomic imaging features (extracted from baseline CT scans) were able to predict those patients that will subsequently develop pneumonitis prior to the initiation of immune therapy (Fig. 18.4). This study highlights the ability of imaging to identify those patients that might be most susceptible to irAE before the irAE even occurs [36].

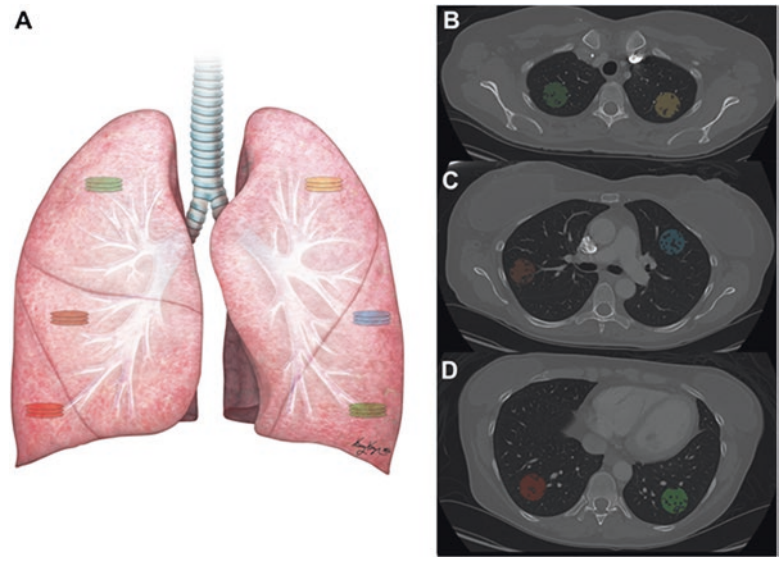

Fig. 18.4 (**a**) An illustration of the outlined regions of interest (ROIs) in the lungs. An ROI containing three consecutive slices, taken in each lobe in the right lung and ROIs outlined in the left lung correspond to the same level as the right lung ROIs. Postcontrast lung CT images depicting the segmented ROIs in upper (**b**), middle (**c**), and lower, (**d**) sections of the right and left lungs. Each ROI is outlined with a different label. Contrast-enhancing vessels from the ROIs were subtracted. Radius of the ROI ranged between 14 and 15 mm

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