Cancer Imaging in Immunotherapy

Murat Ak, Yousra Eleneen, Mira Ayoub, and Rivka R. Colen

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. Response Evaluation Criteria in Solid Tumors (RECIST) or WHO criteria, developed to identify early effects of cytotoxic agents, may not provide a complete evaluation of new emerging treatment response pattern of immunotherapeutic agents. Therefore, new imaging response criteria, such as the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), immune Response Evaluation Criteria in Solid Tumors (iRECIST), and immune-related Response Criteria (irRC), are proposed. 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.

Keywords

Immunotherapy · Imaging · Responses criteria

1 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]. An approach to treating cancer by augmenting or generating an immune response against cancer cells, immunotherapy 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

M. Ak · Y. Eleneen · M. Ayoub · R. R. Colen (□)
Department of Radiology, University of Pittsburgh, Pittsburgh, PA, USA

Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: colenrr@upmc.edu

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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 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, and patients receiving 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. 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 is lacking. 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 response criteria for the evaluation of tumor response in patients who are undergoing immunotherapy. We will also briefly discuss some of the immunotherapy-induced adverse events.

2 Conventional Imaging Response Criteria

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 [6, 7]. These criteria depend on reduction in tumor size and do not take in consideration appearance of new lesions when evaluating responses that may be related to treatment (Table 1) [6, 7].

2.1 WHO Criteria

In 1981, the WHO published the first tumor response criteria, thus establishing a standard assessment metric and nomenclature to evaluate treatment response [7]. The WHO criteria introduced the concept of assessing tumor burden using the sum of 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 [7]. 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 1). 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, 7].

2.2 RECIST 1.0 and 1.1

2.2.1 RECIST 1.0

In 2000, the RECIST criteria were established and addressed some of the pitfalls of the WHO

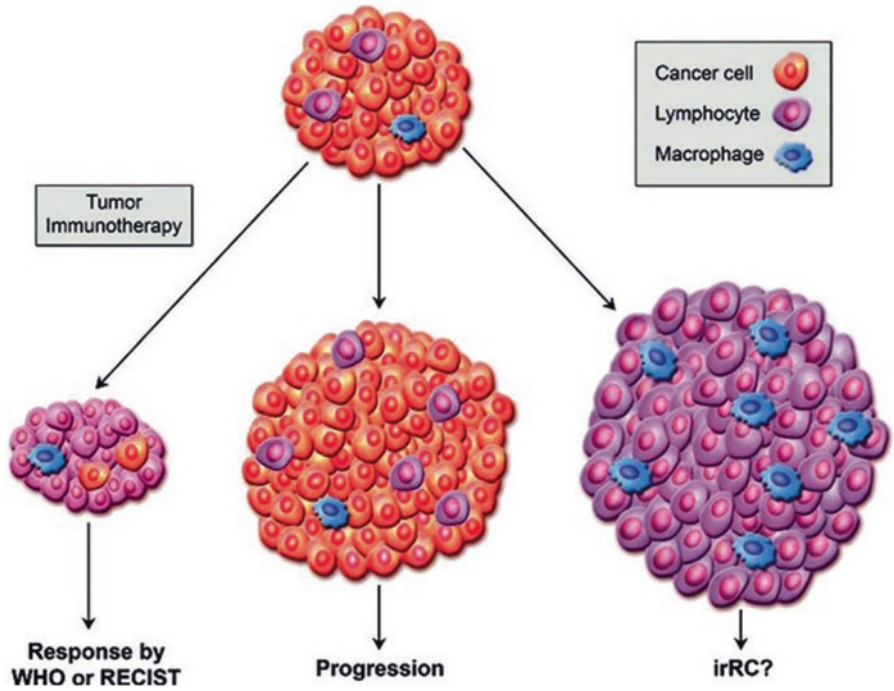

Fig. 1 Cancer imaging in immunotherapy

criteria [6]. Of these, the key features of RECIST 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 1) [6].

2.2.2 RECIST 1.1

In 2009, the RECIST 1.1 was developed to address multiple questions regarding the assessment of lymph nodes, number of lesions to be assessed, and use of new imaging modalities such as multidetector CT (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 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 (non-nodal lesions), its portions should be added together (as lesions coalesce) and measure its longest dimensions [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 it must be reassessed in follow-up examination to determine if it represents a new lesion (Table 2) [5]. Table 1 shows a brief comparison of WHO, RECIST 1.0, RECIST 1.1, irRC, and irRECIST criteria.

2.3 Modified RECIST (mRECIST)

Modified RECIST (mRECIST) was created to measure the response rate in hepatocellular carcinoma (HCC) [9]. 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

Table 1 Comparison between the basis of WHO, RECIST 1.0, RECIST 1.1, irRC, and irRECIST criteria

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 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 mm
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)
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
Complete response (CR)	Complete resolution of lesions at two consecutive scans >4 weeks apart	Disappearance of all nontarget lesions and normalization of tumor marker level	Complete resolution of all target lesions, nodes must regress to <10 mm in short axis	Complete resolution of all lesions including non- index lesions at two consecutive scans >4 weeks apart. No new measurable lesions. Referred to as irCR	Disappearance of all target and nontarget lesions, no new lesions
Partial response (PR)	≥50% decrease in SPD of all lesions (confirmed at 4 weeks)	≥ 30% decrease in tumor burden. No need to confirmation	≥30% decrease in tumor burden. Confirmation required	≥50% decrease in tumor burden. (Confirmed at 4 weeks). Referred to as irPR	Decrease of ≥30% in tumor burden relative to baseline Non-unequivocal progression of nontarget lesions No new lesions
Stable disease (SD)	Doesn't meet criteria of CR, PR, or PD	Doesn't meet criteria of CR, PR, or PD	Doesn't meet criteria of CR, PR, or PD	Doesn't meet criteria of irCR, irPR, or irPD Referred to as irSD	Doesn't meet criteria of CR, PR, or PD

(continued)

Table 1 (continued)

Criterion	WHO	RECIST 1.0	RECIST 1.1	irRC	irRECIST
Progressive disease (PD)	≥25% increase in SPD relative to nadir or appearance of new lesions	Appearance of one or more new lesions, increase in size of one or more nontarget lesions	≥20% +5 mm absolute increase in tumor burden compared with nadir, appearance of new lesions or progression of nontarget lesions	≥25% increase in tumor burden, at 4 weeks. Referred to as irPD	**iUPD**: – Increase ≥20% of the sum of longest diameters compared with nadir or progression of nontarget lesions or new lesions – Confirmation is required 4–8 weeks later the first iUPD assessment **iCPD**: – Increased size of target or nontarget lesions – Increase in the sum of new target lesions >5 mm – Appearance of another new lesion

irCR immune-related complete response, *irPR* immune-related partial response, *irSD* immune-related stable disease, *irPD* immune- related progressive disease, *iUPD* immune-unconfirmed progressive disease, *iCPD* immune-confirmed progressive disease

agent in the arterial phase on CT or MRI [10, 11]. 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 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.

2.4 Choi Response Criteria

The Choi criteria were initially proposed for assessment of GIST tumors on imatinib, a tyrosine kinase receptor inhibitor [12]. 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 [13]. The Choi criteria focus 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; these cannot be applied to MRI, and there is lack of sufficient validation in other tumors.

2.5 EORTC

The European Organisation for Research and Treatment of Cancer (EORTC) criteria have 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 def-

Table 2 Summary of immune-related RECIST 1.1

Method of assessment of lesion	The single longest diameter is measured except for nodal lesion where shortest diameter is considered for assessment
Total tumor burden evaluation	Sum of single longest diameters of all target lesions is measured and sum of shortest diameters of nodal lesions
New target lesions	If the new lesions fulfill the criteria of target lesion assessment, the single longest diameter is determined and incorporated into 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
Target lesion criteria	Target lesions should measure at least 10 × 10 mm, and nodal lesions must measure at least 15 mm in shortest diameter. A maximum of five target lesions could be selected. No more than two 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)
Complete response	irRECIST 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	irRECIST 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	irRECIST requires a total increase of tumor burden of at least 25% from the smallest reported tumor burden (nadir). However, irRECIST advice against 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	If percentage change shows an increase less than 25% from 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	Requires further testing to ensure reproducibility and accuracy of unidimensional assessment for capturing immune-related antitumor effect

inition of [18F]-FDG tumor response [14, 15]. The criteria follow 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 the 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, a 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 [14, 15].

2.6 Response Assessment in Neuro-Oncology (RANO) Criteria

The Response Assessment in Neuro-Oncology (RANO) criteria was proposed to overcome the significant limitations in the McDonald criteria for response assessment in high-grade gliomas. The McDonald criteria didn't take into account,

for example, pseudoprogression, pseudoresponse observed with antiangiogenic agents, and the inability to capture recurrence in the non-enhancing component of the lesion, due to using only the contrast-enhancing component of the tumor in it [15]. Similar to the McDonald criteria, the RANO criteria uses two-dimensional tumor measurements; however, the RANO criteria also accounts for changes in the non-enhancing T2/FLAIR signal abnormality. Measurable disease is defined 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. RANO criteria addressed pseudoprogression and pseudoresponse. The RANO criteria for high-grade glioma are summarized in Table 3 [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, and PR or the lesions became nonmeasurable; if the latter, the scan that showed "preliminary PD" is noted as "pseudoprogression" [17]. 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, while their non-enhancing component shows progression [17].

2.6.1 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 4) [16].

2.7 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 analyze the size and the metabolic activity of the tumor during the course

Table 3 RANO criteria for response assessment in high-grade gliomas

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

Table 4 RANO-BM criteria for response assessment in brain metastases

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 does 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

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 by Tirkes et al. (Table 5) [19].

2.8 PERCIST Criteria

While a range of factors have been linked with FDG uptake, there appears to be a considerably strong association between FDG uptake and quantity of cancer cells in a substantial number of studies [20, 21]. Additionally, 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 [22]. Thus, metabolic response may enhance the morphologic criteria. Therefore, the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST 1.0) were proposed and are based mainly on FDG uptake to evaluate tumor response to refine and validate quantitative approaches to monitoring PET [23]. 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 [23]. 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 [23]. PERCIST defines four metabolic response categories [23]. In brief, according to these criteria, complete metabolic 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 [23]. Of note, the lesion at follow-up may be a different lesion than previously measured since the most active lesion needs to be followed. For classification as stable metabolic disease, an increase or decrease in SUL peak of less than 30% is required [23]. Progressive metabolic disease is defined as an increase (>30%) in SUL peak or the appearance of a new metabolically active lesion [23].

3 Immunotherapy Imaging Response Criteria

The emerging use of immunotherapeutic agents has led to the appearance of new treatment response patterns, and conventional response evaluation criteria might not be sufficient in evaluating immunotherapy response. One of the main differences in tumor response to immunotherapy in

Table 5 Cheson response criteria definitions

Table response definitions for clinical trials				
Response	Definition	Nodal masses	Spleen, liver	Bone marrow
CR	Disappearance of all evidence of 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 six 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 the 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

comparison to conventional therapies is a longer delay time for suitable response [24]. Another major response difference associated with immunotherapy is the enlargement of preexisting lesions and development of new lesions during the initial phase of treatment, which would necessitate classification as progressive disease (PD) with conventional criteria [24]. However, in patients on immunotherapy, therapeutic response can be observed in later follow-up scans after initial enlargement and emerging of new lesions. The initial increase in tumor burden or development of new lesions during the initial phase of treatment with immunotherapies could be due to transient flare-up and explained on a histological basis as either tumor growth until development of adequate immune response or transient immune cell infiltrate [24]. Thus, a well-tailored set of criteria to capture accurate and exact response to this new line of therapeutic agents is needed. To this end, immune-related Response Criteria (irRC), immune-related Response Evaluation Criteria in

Solid Tumors (irRECIST), immune RECIST (iRECIST), and immunotherapy Response Assessment in Neuro-Oncology (iRANO) were developed. Since their inception, immune-related evaluation criteria have been used in several clinical trials in patients receiving immunotherapies and have potentially representing improvement over conventional criteria for assessment of treatment response; however, they have their own challenges [2, 4, 25, 26]. While these criteria are the mainstay in the early-phase clinical trials, they have yet to be implemented for use in phase III trials; therefore, further prospective robust validation is warranted. Table 6 shows comparison of irRC, irRECIST, and iRECIST.

3.1 Immune-Related Response Criteria

Arising from the heightened awareness by the national and international community as to the unique radiographic response patterns seen with vaccines and immunotherapeutics, modifications were made to the WHO and RECIST criteria in 2004 and 200. In 2009, the immune-related Response Criteria (irRC) published by Wolchok et al. [4] were based on observed patterns in treatment response from phase II clinical trials in advanced melanoma patients who were receiving ipilimumab in 2009 [4]. In this study [4], four patterns of treatment responses were recognized, and two of them were captured with conventional response criteria: (1) a decrease in the size of the lesion and without new tumors and (2) stable disease after completion of treatment; the other two response patterns were new and involve (3) a delay in tumor response after an initial increase in total tumor burden and (4) a decrease in total tumor burden during or after the emerging of new lesion at time points later than week 12.

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 compared to the baseline scan [4]. The irRC was derived from WHO criteria, and therefore, the thresholds of response remain similar. However, the irRC response categories have been modified from those of 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 ten visceral lesions and five cutaneous index lesions). At every time point, the index lesions and any new measurable lesions are added together to accu-

Table 6 Features of immune response criteria

	irRC	irRECIST	iRECIST
Model based on	WHO criteria	IrRC and RECIST 1.1	RECIST 1.1
Method of measurement	Bidimensional	Unidimensional	Unidimensional
Definition of measurable disease	Selection of five lesions (≥5 × 5 mm) per organ (up to ten visceral and five cutaneous)	Selection of maximum five lesions (two per organ) (≥10 mm in diameter, ≥15 mm for nodal lesions)	Selection of maximum five lesions (two per organ) (≥10 mm in diameter, ≥15 mm for nodal lesions)
Progressive disease definition	25% increase from the nadir	20% increase from the nadir	20% increase from the nadir; results in iUPD; confirmation is necessary for iCPD
New lesion	New lesion does not define progression; the measurements of the new lesion are included in the sum of the measurements and added to total tumor burden at follow-up	New lesion are included in the sum of target lesions to define total tumor burden at follow-up	New lesion does not indicate progression; the measurements of the new lesion are not included in the tumor burden
Confirmation	≥4 weeks later	≥4 weeks later	≥4 weeks later no longer than 8 weeks

rately measure the total tumor burden (TTB) [(TTB = $SPD_{index\ lesions}$ + $SPD_{new,\ measurable\ lesions}$)]. This is a major difference from the WHO criteria which considers all new measurable lesions as progressive disease [5, 7]. 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 7.

The irRC does not mention the use of specific imaging modalities in 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 the cell proliferation or cell death is being investigated [16]. 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]. While potentially an advancement over traditional criteria for immunotherapy, the irRC may still not evaluate or completely characterize all relevant patterns of clinical activity. For example, one drawback for the irRC is that the term "irSD" represents both for cases of minimal change in tumor burden in time and for large increases in tumor burden followed by a reduction to baseline levels [4].

3.2 Immune-Related RECIST Criteria

The newly proposed irRECIST was developed based on irRC to evaluate tumor burden in patients receiving immunotherapy [2, 24]. The irRECIST adjusted the approach of unidimensional measurement and the number of lesions according to RECIST 1.1 while adding the important new features such as approval of PD and inclusion of new lesion measurements to assess immunotherapy treatment responses (Table 1) [2, 24]. In comparison to the bidimen-

Table 7 Summary of immune-related response criteria (irRC)

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 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 contributes to the evaluation of total tumor burden
New non-target 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. This includes CT, MRI, and PET-CT
Target lesions criteria	Target lesions should measure at least 5 × 5 mm. A maximum of five cutaneous lesions and ten 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

(continued)

Table 7 (continued)

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 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 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

sional method used by irRC, unidimensional measurement is more reproducible, demonstrates fewer variability, and results in lower misclassification rates for treatment response evaluation in clinical trials [2, 24]. The irRECIST is simple and practical and provides response evaluations that can be easily compared and implemented to the results from other studies applying RECIST [2, 24].

3.3 Immune RECIST Criteria

In 2017, immune RECIST (iRECIST) was proposed by the RECIST group to assess patients treated with immunotherapy [25]. iRECIST is based on RECIST 1.1, and the response categories (PD, SD, PR, CR) are assigned a prefix of "i" to indicate "immune" *(*i.e., immune complete response (iCR)) [25]. The continued use of RECIST 1.1. is suggested to approach tumor lesions and measurements; but new lesions are evaluated and subclassified as new target and new nontarget lesions [25]. The principles applied to determine tumor response are almost unchanged from RECIST 1.1 [25]. However, iRECIST defines immune unconfirmed progression (iUPD) which requires confirmation, and assessment of iUPD will be made if there is more than 20% increase in tumor burden or appearance of new target or nontarget lesions [24, 25]. Confirmation should be done by observing either a further increase of at least 5 mm of target tumor burden or new target lesion or any increase in nontarget disease [24, 25]. If no change is determined, the response is classified as iUPD. This method allows identification of atypical responses such as delayed treatment responses seen after pseudoprogression (Table 8) [24, 25].

3.4 Immunotherapy Response Assessment for Neuro-Oncology Criteria

Immunotherapy RANO (iRANO) criteria were presented as an update to RANO criteria to evaluate patients with neuro-oncological malignancies undergoing immunotherapy [26]. During the initial phase of immunotherapy treatment, the size of the tumor might increase, and/or new inflammatory lesions appear. These temporary changes typically stabilize or subside, but they are generally difficult to differentiate from PD [27]. This PD resembling event is called pseudoprogression (PsP) [27]. To overcome this challenge, iRANO was proposed (put table). In brief, the iRANO follows the same guidelines as the RANO criteria (Table 9). 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 are recommended (Table 10). 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. Promisingly, a recent study by our group demonstrated that radiomics can discriminate between patients who have PsP and true tumor progression with high sensitivity (97%), specificity (79%), and accuracy (95%) in patients with glioblastoma [28].

Table 8 iRECIST response criteria

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 one 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

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 are summarized in Table 11 [26].

4 Future Directions for Immune Therapy Imaging Assessment

Although irRECIST, irRC, and iRECIST represent an improvement over the conventional assessment criteria to evaluate tumor response in immunotherapy, there remain limitations and challenges, and further refinements are warranted. Therefore, RECIST is still a highly validated and reproducible tool, and majority of clinical trials continue to perform RECIST 1.1 for evaluation of treatment response. Plans for

Table 9 Summary of immune therapy Response Assessment in Neuro-Oncology (iRANO)

Method of assessment of lesion	Bidimensional assessment of the longest perpendicular diameters of all enhancing lesions
Total tumor burden evaluation	Sum of product of 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 three more months taking in reference the time point at which progression was initially reported
Target lesion criteria	Target lesions should measure at least 10 × 10 mm. A maximum of five target lesions could be selected
Complete response	Requires 100% decrease in tumor burden including total remission of all enhancing and non-enhancing 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 non-enhancing 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 product of bi-perpendicular diameters of T2FLAIR lesions. With no new lesions, no clinical decline and stable or decreased dose of steroids

(continued)

Table 9 (continued)

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

improving imaging response criteria include volumetric (3D) imaging, dynamic contrast imaging, and functional (molecular) imaging. Despite these aforementioned tremendous efforts to improve the radiological criteria and guidelines in tumor response evaluation, there still lie challenges to capture the precise volume of the tumor due to a variety of elements such as its shape irregularity. In addition to that, conventional imaging failed to describe local tumor heterogeneity, as well as molecular and biological com-

Table 10 iRANO criteria for high-grade glioma, low-grade glioma, and brain metastases

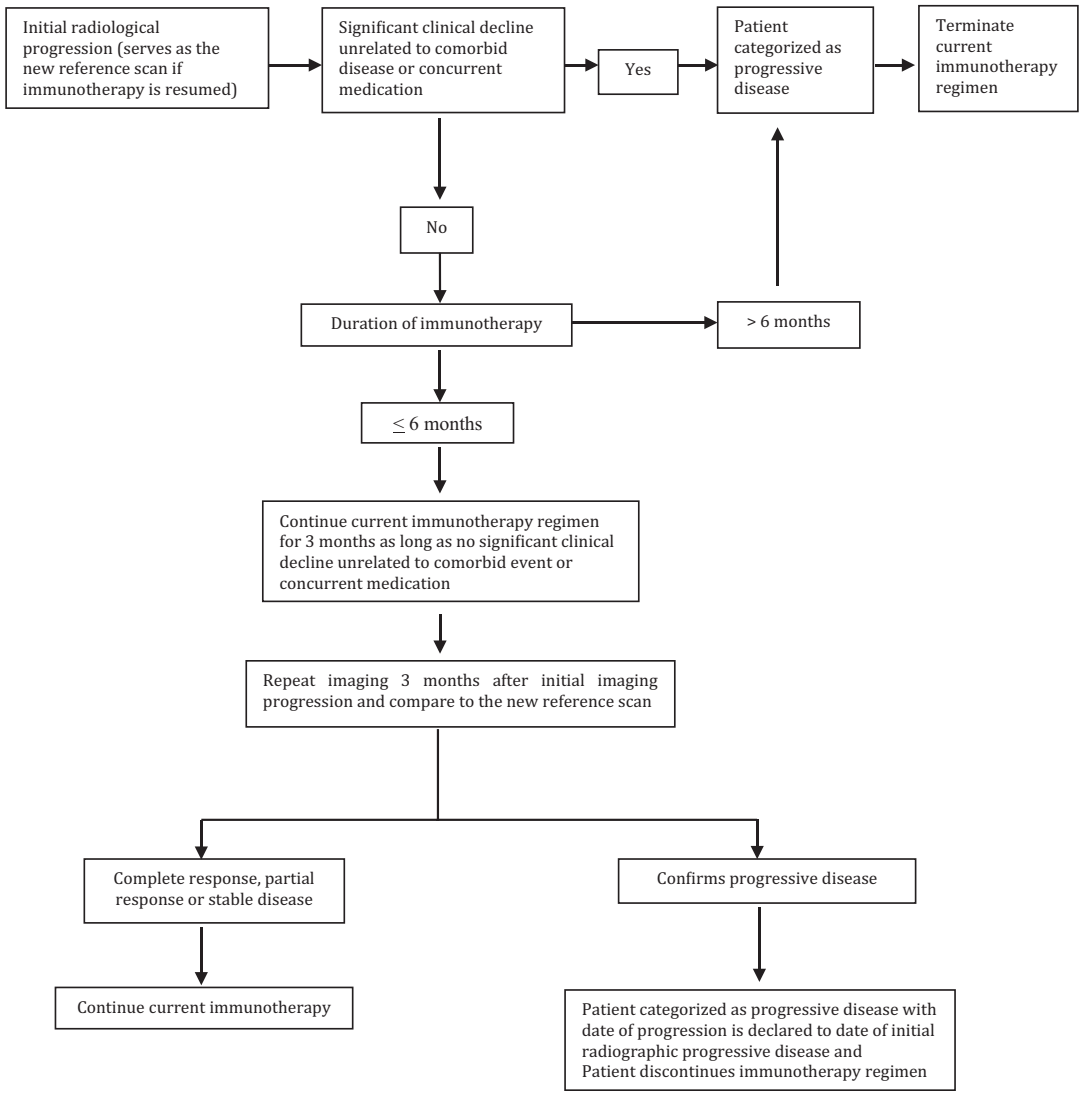

Table 11 Summary of immune therapy response assessment in brain metastases (iRANO-BM)

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

plexity of the tumor. Even with the obvious advancement in the quality of MR and CT imaging technologies, reporting is still subjective, descriptive, and nonquantitative. Additionally, despite immunotherapy have revolutionized the treatment of several malignancies, only a subset of patient derived clinical benefit as the absence of predictive biomarkers. As a promising rapidly evolving field, radiomics has potential to overcome these challenges [29]. Radiomics is a method that extracts large amount of imaging features from medical images [29]. As an extraordinary innovation in computational imaging, radiomics has led to providing significant information for personalized therapy such as tumor biology [30], genomics [31], spatial heterogeneity [31], and immune infiltration [32]. Also, radiomics has been demonstrated to predict immunotherapy response multiple cancers, including non-small cell lung cancer [33, 34], melanoma [34, 35], and advanced solid tumors [32]. These studies highlight that radiomics can potentially play a significant role in the clinical setting as an imaging biomarker to predict immunotherapy response a priori. Radiomics have many advantages; it is noninvasive, and features are extracted from standard medical images, making it ideal for clinical implementation. As a conclusion, radiology will continue to adjust the new tumor response patterns observed with the current and future immunotherapeutic agents. With the advent of molecular medicine and radiomics in the era of personalized medicine, the essential aim of research is to accommodate treatments to both the specific type of cancer and the patient.

5 Immune-Related Adverse Events

Immune-related adverse events (irAEs) are a unique spectrum of adverse effects of immunotherapy that resembles autoimmune responses. irAEs affect almost every organ system and are usually observed in the skin, gastrointestinal tract, lung, endocrine, and musculoskeletal system [36]. 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 [18]. Immunotherapy can generally continue in the presence of mild irAEs with close observation. However, moderate to severe irAEs may be related with severe declines in organ function and quality of life, and fatal outcomes have been reported; thus, these toxicities need early detection and proper management. 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 [36]. However, success in outcome lies heavily on correctly identifying and interpreting these complications.

In general, irAEs most experienced across the spectrum of the current immunotherapeutic agents may include but not limited to colitis, diarrhea, hepatitis, pneumonitis, thyroiditis, myocarditis, pericarditis, temporal arteritis, conjunctivitis, sarcoid-like reaction such as lymphocytic vasculitis, organizing pneumonia, fasciitis, hypophysitis, and thyroiditis [36]. A recent study by our group demonstrated that specific radiomic imaging features were able to predict those patients that will subsequently develop pneumonitis (Fig. 2) [37]. This study highlights

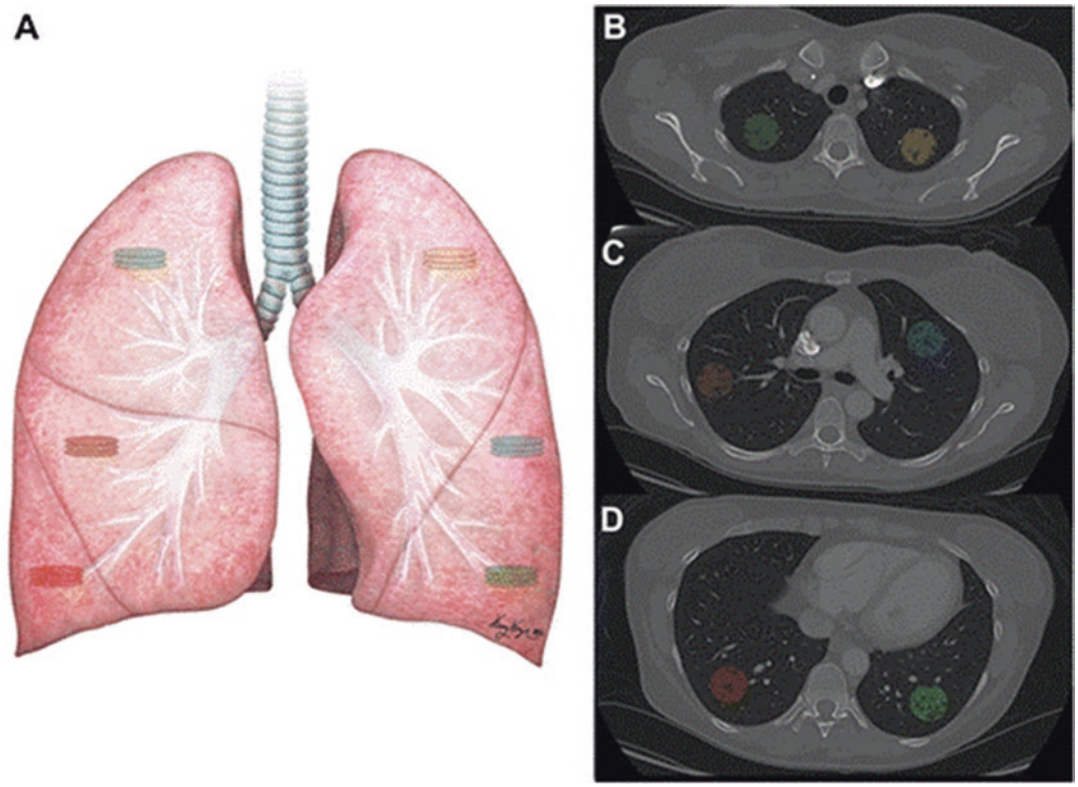

Fig. 2 (**a**) An illustration of the outlined regions of interest (ROIs) in the lungs. An ROI containing three consecutive slices, taken in each lobe in the right lung, and ROIs outlined in the left lung correspond to the same level as the right lung ROIs. Postcontrast lung CT images depicting the segmented 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

the ability of imaging to identify those patients that might be most susceptible to irAE before the irAE even occurs [38].

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