Chapter 7
Cancer Imaging in Immunotherapy

Yousra Eleneen 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. 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 review, 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 Cancer imaging • irRC • Immune imaging criteria • irRECIST • Immunotherapy

7.1 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

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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 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 overtime become stable, decrease, or resolve without further treatment (Fig. 7.1). 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

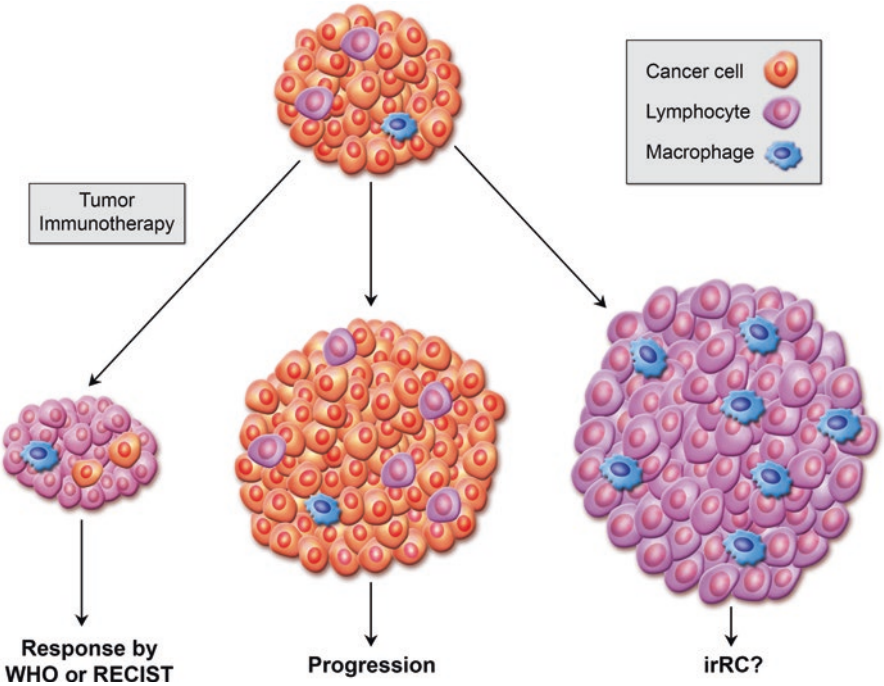

Fig. 7.1 Cancer imaging in immunotherapy

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 review, 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 will also briefly discuss some of the immunotherapy-induced adverse events.

7.2 Conventional Imaging Response Criteria (Table 7.1)

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 reduction in tumor size and do not take in consideration appearance of new lesions when evaluating responses that may be related to treatment [4].

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 [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 7.1) [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].

7.2.2 RECIST 1.0, 1.1 and mRECIST Criteria

7.2.2.1 RECIST 1.0

In 2000, the RECIST criteria were established and addressed some of the pitfalls of the WHO criteria. 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 7.1) [6].

Table 7.1 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 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

7.2.2.2 RECIST 1.1

In 2009, the RECIST 1.1 were 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 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 uses 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 [5] (Table 7.1).

7.2.2.3 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 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.

7.2.3 Choi Response Criteria

The Choi criteria were initially proposed for assessment of GIST tumors 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; these cannot be applied to MRI and there is lack of sufficient validation in other tumors.

7.2.4 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 [12]. In 2009, the PERCIST criteria were proposed and is based mainly on FDG uptake to evaluate tumor response [13]. 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].

7.3 Immunotherapy Imaging Response Criteria

Evaluating tumor responses during immune therapy in solid cancers remains a challenge [5, 14]. 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, 14]. 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 7.2) [4]. Although these criteria were widely accepted, it still harbors some challenges. For instance, assessing a relatively large number of lesions per organ could be relatively time consuming in cases of extreme tumor burdens [2, 15]. Furthermore, evaluation of excessive number of lesions impacts

Table 7.2 Summary of immune-related response criteria (irRC) [4]

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

(continued)

Table 7.2 (continued)

Summary of immune-related response criteria (irRC)	
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. 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
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

the reproducibility of the results [2, 15]. 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, 15]. With regard to brain tumors, the Immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria are a set to tumor metrics to assess brain tumors in patients undergoing immune therapies.

7.3.1 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 2005. In 2009, the immune-related Response Criteria (irRC) published by Wolchok et al. were based on 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 compared to the baseline scan [4]. The irRC was derived from WHO criteria and, therefore, the thresholds of response remain the 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 10 visceral lesions and five cutaneous index lesions). At every time point, the index lesions and any new measurable lesions are added together to accurately measure the total tumor burden (TTB) [$(\text{TTB} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}})$]. 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 7.2.

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].

7.3.2 Immune-Related RECIST Criteria

The newly proposed irRECIST 1.1 (Table 7.3) 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, 15]. Nishino et al. demonstrated that such changes did not result in any statistically significant variation of the response evaluation in patient with melanoma receiving

Table 7.3 Summary of immune-related RECIST 1.1 [2]

Summary of immune-related RECIST1.1 (irRECIST)	
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 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 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)
Types of overall response	Complete response (CR), partial response (pr), stable disease (SD), and progressive disease (PD)
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

immunotherapy [2, 15]. They also demonstrated that irRECIST 1.1 measurements were relatively more reproducible than the more involved bidimensional irRC measurements [2, 15]. However, those studies were performed on relatively small cohorts of patients and better evaluation of irRECIST 1.1 is still required.

7.3.3 *Immunotherapy Response Assessment for Neuro-Oncology Criteria*

The iRANO criteria are used to assess brain lesions in patients undergoing immunotherapy [3]. In order that misclassification of patient 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 were 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 7.4). 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 [17].

Table 7.4 Summary of immune therapy Response Assessment in Neuro-Oncology (iRANO) [3]

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 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)

(continued)

Table 7.4 (continued)

Summary of immune therapy response assessment in neuro-oncology (iRANO)	
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
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

7.4 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 [4]. Plans for improving imaging response criteria include volumetric (3D) imaging, dynamic contrast imaging, and functional (molecular) imaging. More recently, radiomics is a more recent developing field within imaging that can help in more precise tumor assessments that are un-related to tumor size or burden. Further, radiogenomics, the linkage between imaging phenotypes and tumor genomics, might help develop more robust stratification and end-point imaging biomarkers for molecular targeted clinical trials.

7.5 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 [18]. 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 [18]. Because 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 complicated by colonic bowel perforation [18]. 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 as metastatic disease [1]. There are also many other events which can occur with immunotherapy for example autoimmune hepatitis, pneumonitis, thyroiditis, myocarditis, pericarditis, temporal arteritis, conjunctivitis, sarcoid-like reaction such as lymphocytic vasculitis, organizing pneumonia, and fasciitis [19, 20]. Endocrinopathies such as autoimmune hypophysitis and thyroiditis can also be seen. A recent study by our group demonstrated that specific radiomic imaging features were able to predict those patients that will subsequently develop pneumonitis (Fig. 7.2).[21] This study highlights the ability of imaging to identify those patients that might be most susceptible to irAE before the irAE even occurs.

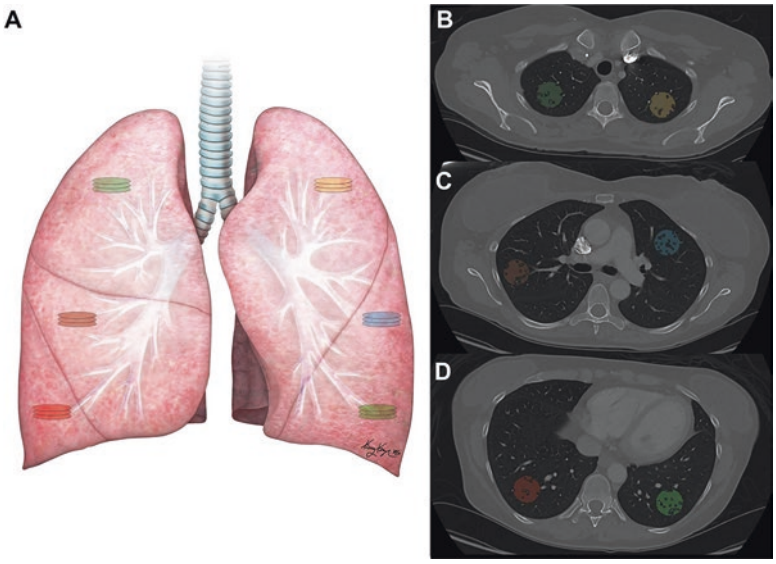

Fig. 7.2 (**a**) An illustration of the outlined ROIs in the lungs. An ROI containing three consecutive slices, taken in each lobe in the right lung and ROIs outlined in the left lung correspond to the same level as the right lung ROIs. Post-contrast lung CT images depicting the segmented ROIs in upper (**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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