CANCER DIAGNOSIS & PROGNOSIS
4: 1-8 (2024) doi: 10.21873/cdp.10278

Review

Assessing Radiological Response to Immunotherapy in Lung Cancer: An Evolving Arena

KATHRINE S. RALLIS[1,2], SHANIA MAKKER[1,3], ARUNI GHOSE[4,5,6] and MICHAIL SIDERIS[7,8]

[1]*Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, U.K.;*
[2]*Barts Cancer Institute, Queen Mary University of London, London, U.K.;*
[3]*University College London Cancer Institute, London, U.K.;*
[4]*Department of Medical Oncology, Barts Cancer Centre, St Bartholomew's Hospital, Barts Health NHS Trust, London, U.K.;*
[5]*Department of Medical Oncology, Mount Vernon Cancer Centre, East and North Hertfordshire NHS Trust, Northwood, U.K.;*
[6]*Department of Medical Oncology, Medway NHS Foundation Trust, Immuno-Oncology Clinical Network, Kent, U.K.;*
[7]*Wolfson Institute of Population Health, Cancer Research UK Barts Centre, Queen Mary University of London, London, U.K.;*
[8]*Department of Gynaecological Oncology, Barts Health NHS Trust, Royal London Hospital, London, U.K.*

Abstract. *In the past decade, immune checkpoint inhibitors (ICIs) have entered the treatment landscape of non-small-cell lung cancer, signalling a paradigm shift within the field characterized by significant survival benefits for patients with advanced and metastatic disease, and especially those with non-targetable genetic oncogenic driver mutations. However, the shift towards immune-based treatments has created new challenges in oncology. Atypical immunotherapy response patterns, including pseudo-progression and hyperprogressive disease, as well as immune-related adverse events have generated the need for new methods to predict patient response to treatment. Hence, new versions of the traditional Response Evaluation Criteria for Solid Tumors (RECIST) have emerged to help characterise with better accuracy radiological findings concerning patient response classification to immunotherapy. This review discusses response evaluation criteria relevant to unique radiological findings observed in patients treated with immunotherapy for non-small-cell lung cancer.*

Correspondence to: Kathrine S. Rallis, MBBS, MSc, Barts and The London School of Medicine and Dentistry, Turner Street, Whitechapel, London E1 2AD, U.K. Tel: +44 7526272233, e-mail: k.s.rallis@smd16.qmul.ac.uk

Key Words: Immunotherapy, immune checkpoint inhibitors, ICI, Response Evaluation Criteria for Solid Tumors, RECIST, non-small-cell lung cancer, NSCLC, review.

Lung cancer accounts for the highest proportion of cancer-associated deaths worldwide, more than prostate, breast and colorectal cancer, the most common cancers in men and women excluding skin cancer. Approximately one in four cancer-associated deaths are attributed to small-cell lung cancer and non-small-cell lung cancer (NSCLC), with the latter accounting for 85% of these cases (1, 2). Lung cancer remains the second-leading cause of cancer in men and women despite the decrease in incidence and age-adjusted lung cancer-related mortality observed for both sexes in recent decades, consistent with declining tobacco use (3-5).

Until the past decade, conventional surgical, chemotherapeutic and radiation treatments have been the only options available to patients with lung cancer, known to present late with advanced disease and to have poor 5-year survival rates (6, 7). However, advances in the molecular characterization of the disease have allowed for the emergence of novel therapeutic targets, including immunotherapies, as effective treatment strategies. Nevertheless, refractory, relapsing and progressive disease are still common amongst patients (6).

Immunotherapy in Lung Cancer

Normally, the immune system detects cancer cells via tumour antigens and mediates their elimination. However, cancer cells avoid immune surveillance and destruction (8). Immunotherapies work by increasing the immune response to target cancer cells. Although various immunotherapy types have been developed, in terms of lung cancer, the most promising and widely used immunotherapies to date are immunomodulatory monoclonal antibodies known as immune checkpoint inhibitors.

Checkpoint inhibitors are an active immunotherapy as they interact with the host's immune system to elicit a humoral or cell-mediated immune response. Checkpoint inhibitors modulate T-cell activity by interacting with specific cell surface receptors or ligands which are critical in cell-mediated adaptive immunity (9). T-cell activation is dependent on receptor-ligand interactions, known as immune checkpoints, as well as co-stimulatory and inhibitor signals (10, 11).

In lung cancer, monoclonal antibodies targeting programmed cell death-1 (PD1) and its ligand (PD-L1) have become standard treatment, gradually replacing traditional chemotherapeutic agents as they confer notable survival benefit, especially in the setting of NSCLC and for tumours expressing PD-L1 and displaying high tumour mutational burden (12, 13). Immune checkpoint inhibitors currently approved by the US Food and Drug Administration for the treatment of NSCLC in specific settings include nivolumab, pembrolizumab, and cemiplimab, all anti-PD-1 agents; atezolizumab and durvalumab, both antibodies to PD-L1; and ipilimumab, an antibody to cytotoxic T-lymphocyte associated protein 4 (14).

The Use of Imaging to Evaluate Immunotherapy Response

As treatment options evolve, radiological response has become increasingly heterogeneous and challenging to assess, particularly for patients treated with immunotherapies which demonstrate a well-documented unique response pattern, featuring pseudo-progression (PP) and hyperprogressive disease (15), that cannot be adequately evaluated with traditional tumour size-based response criteria, such as Response Evaluation Criteria in Solid Tumours (RECIST) (16) and World Health Organization (WHO) (17). Reliable response evaluation for such treatments remains crucial in experiments and clinical practice. Hence, various modified criteria for response evaluation have been proposed and utilised, including immune-related response criteria (irRC), immune-related RECIST (irRECIST), immune RECIST (iRECIST), and immune modified RECIST (imRECIST) (18). Furthermore, immunotherapies necessitate additional guidance for imaging immune-related adverse events (irAEs) experienced by patients (6). Several studies outline novel imaging techniques with promising monitoring and response-prediction value and thus potential stratification benefit in neoadjuvant and palliative settings (19). These include ^{18}F-fluorodeoxyglucose positron-emission tomography/ computed tomography (PET/CT) (20), radiomics (21), iPERCIST (22), and artificial intelligence (AI) algorithms (19), all of which may function as non-invasive biomarkers predicting immunotherapy response.

The proposed response evaluation criteria relevant to unique radiological findings and imaging of irAEs in patients treated with immunotherapy, will be discussed in this article.

Response Evaluation Criteria for Patients Treated With Immunotherapy WHO and RECIST

The WHO criteria (originally developed in 1981) and RECIST (published in 2000) were initially the most widely used systematic response evaluation criteria to characterize chemotherapy efficacy by measuring specific changes in imaging studies within weeks of therapy. Patients are assigned one of four possible response categories defined by changes in tumour burden measured on imaging: Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). These criteria have evolved starting from WHO to RECIST 1.0 and now RECIST 1.1 (published in 2009), which is considered the gold standard (16).

However, the use of these criteria is limited in monitoring the effects of immunotherapy as they assume PD if tumour measurements increase by ≥20% or new lesions appear, thus warranting inappropriate treatment discontinuation in cases where immunotherapies may be effective (6). Furthermore, immunotherapies differ from cytotoxic chemotherapies in their longer timeframe to displaying a measurable response, and potentially prolonged SD states, which may paradoxically indicate effective drug activity (23). To address these differences, modified response evaluation criteria have been proposed.

irRC

irRC was developed in 2009 from modification of the WHO criteria to address discrepancies in immunotherapy follow-up (23). Lesion measurement methods in irRC are different from those of RECIST (Table I) (6, 23, 24). Various anatomic and functional imaging modalities can be used in irRC, with the former being necessary to evaluate treatment response. Unlike RECIST, irRC uses bidimensional measurements to estimate tumour burden defined as the sum of products of the two largest perpendicular diameters for index and new measurable lesions. Up to five index lesions, measuring at least 5×5 mm on axial images, may be selected per organ, with a maximum of 10 visceral and five cutaneous lesions.

Table I. *Comparison of lesion measurement in immune-related response criteria (irRC) versus Response Evaluation Criteria for Solid Tumors (RECIST) 1.1, immune-related RECIST (irRECIST) and immune RECIST (iRECIST). Adapted and reproduced from (6).*

	RECIST 1.1, irRECIST, iRECIST	irRC
Imaging modality	CT, MRI, CXR, FDG PET	Not specified
No. of index lesions	Per organ: 2, 5 in total	Per organ: 5, ≤10 visceral, ≤5 cutaneous
Measurable lesions	Long axis measurement: ≥10 mm	≥5×5 mm
Lymph-node assessment	Short-axis measurements used:	
	≥15 mm target	
	≥10 mm and <15 mm non-target	
	<10 mm non-pathological	Same as RECIST 1.1
Measurement parameters	Unidimensional	Bidimensional
Tumour burden	Sum of longest diameter of target lesions	Sum of products of the two largest perpendicular diameters for index and new measurable lesions

CT: Computed tomography; CXR: chest X-ray; FDG PET: fluorodeoxyglucose positron-emission tomography; MRI: magnetic resonance imaging.

Response categories are defined differently in irRC compared to RECIST (Table II) (6, 15). Importantly, irRC recommends using two consecutive imaging studies at least 4 weeks apart for confirmation of PD, with follow-up imaging for new or continuously enlarging lesions to signify confirmed PD. Higher thresholds are used to define PD and PR, while SD is considered clinically significant especially for patients with a slow decrease in tumour burden of 25% or more which does not meet the ≥50% threshold for PR. Non-target lesions do not signify PD but do exclude CR.

The use of irRC, originally applied in melanoma immunotherapy, demonstrated a 14% decrease in premature treatment termination and a survival benefit for patients who continued treatment after being assessed as PD under RECIST but not irRC (24). These findings were quickly generalized to other malignancies; however, a study of irRC in a small number of patients with NSCLC showed lower rates of PP (4.9%) and similar overall response rates by RECIST 1.1 and irRC, indicating that irRC may not be as useful in NSCLC, although results may have been limited by the small sample size (25). Another disadvantage of irRC is the poor reproducibility in response assessment due to bidimensional measurements, hence the need for a new set of criteria (26-28).

irRECIST

irRECIST was formed in 2013 by combining irRC and RECIST criteria, requiring PD confirmation and using unidimensional measurements. irRECIST demonstrated less variability in response measurement than irRC (29). Methods of lesion measurement in irRECIST are very similar to those of RECIST 1.1 (Table I) (6). Response categories in irRECIST also have similar thresholds to those of RECIST 1.1, however, irRECIST incorporates new lesions differently and recommends confirmation of PD at 4 weeks, especially in the first 12 weeks of treatment (Table II) (1, 12).

Yet many immunotherapy trials have continued using RECIST 1.1, rendering it difficult to compare data of trials using different criteria (30-32). Discrepancies in the consistent application of irRECIST recommendations in different clinical trials generated the need for a consistent framework for clinical trial data collection to reduce variability in interpretation and analysis. Consequently, iRECIST was established in 2017 (33).

iRECIST

iRECIST is very similar to RECIST 1.1 and irRECIST in terms of methods for lesion measurement (Table I) (6). The response categories in iRECIST differ by the addition of 'unconfirmed progressive disease' (iUPD) and 'confirmed progressive disease' (iCPD) (Table II) (6, 15, 33). iUPD is any progressive disease defined by RECIST 1.1 while iCPD requires either a) presentation of additional new lesions subsequently to previous iUPD, or b) an increase of new lesion size of 5 mm or more for target lesions and any increase in non-target lesions. iUPD and iCPD allow for better description of atypical immunotherapy response patterns including PP and delayed response.

Many clinical trials employ the use of both RECIST 1.1 and iRECIST (34). RECIST 1.1 should be used for primary endpoints including best response, progression-free survival and overall survival, while iRECIST is recommended in exploratory analyses. Sole use of iRECIST may be appropriate for early-phase clinical trials (28). The criteria used in primary and exploratory outcomes should be explicitly stated in the clinical trial protocol (33).

Table II. *Response assessment in Response Evaluation Criteria for Solid Tumors (RECIST) 1.1, immune-related response criteria (irRC), immune-related RECIST (irRECIST) and immune RECIST (iRECIST). Adapted and reproduced from (6, 18, 35).*

	RECIST 1.1 (2009)	irRC (2009)	irRECIST (2013)	iRECIST (2017)
Complete response (CR)	Resolution of all lesions, confirmed after ≥4 weeks	Complete disappearance of all measurable and non-measurable lesions and lymph nodes; confirmation is not mandatory		
Partial response (PR)	≥30% Decrease in tumour burden *vs*. baseline, in the absence of any new lesion or progression of nontarget lesion	≥50% Decrease in tumour burden *vs*. baseline, confirmation after 4 weeks	Same as RECIST 1.1	
Stable disease (SD)	Neither PR nor PD	Neither PR nor PD		
Progressive disease (PD)	≥20% Increase in tumour burden from nadir (minimum of 5 mm), PD of nontarget lesions, or new lesions	≥25% Increase in tumour burden from nadir, confirmation after 4 weeks.	≥20% Increase in tumour burden from nadir (minimum of 5 mm), or PD for nontarget lesions or new non-measurable lesions, recommended confirmation ≥4 weeks	Differentiation between iUPD and iCPD. iUPD can imply CR or PR
New measurable lesions	PD	Incorporated into tumour burden	Incorporated into tumour burden	iUPD or iCPD
New non-measurable lesions	PD on FDG PET	Does not define PD	Does not define PD	iUPD or iCPD

FDG PET: Fluorodeoxyglucose positron-emission tomography; iCPD: 'immune' response (by iRECIST) confirmed progressive disease; iUPD: 'immune' response (by iRECIST) unconfirmed progressive disease.

Imaging irAEs

When evaluating immunotherapies in clinical trials, radiologists must be able to distinguish irAEs from recurrent or metastatic disease. irAEs are attributed to autoimmunity induction or a proinflammatory state, usually resolving after treatment cessation. Importantly, irAEs correlate to immunotherapy efficacy and strongly predict survival in patients with NSCLC treated with nivolumab (35). Highest risk of irAEs is observed with ipilimumab monotherapy and combination immunotherapy (36). PET/CT is superior to CT for imaging irAEs, allowing earlier detection and treatment. Dermatological toxicity, colitis, hepatitis, pneumonitis, and endocrine toxicities are the most common presentations (37). Pneumonitis is the commonest irAE in the thorax. Radiologists should be aware of the presentation of nodular pneumonitis, which closely resembles recurrent disease. Colitis is the commonest irAE in the abdomen and carries the highest irAE-related mortality due to delayed diagnosis and treatment. Immune-related colitis features ascites, pericolonic fat infiltration, segmental or diffuse wall thickening, mucosal enhancement, submucosal oedema, and air-fluid levels which should be identified by a radiologist on imaging (38, 39).

Future Prospects

Opportunities. Several studies outline novel imaging techniques with promising monitoring and response-prediction value and thus potential stratification benefit in neoadjuvant and palliative setting (19). These include ^{18}F-fluorodeoxyglucose PET/CT (20), radiomics (21), iPERCIST (22), and artificial intelligence (AI) algorithms (19). In a radiomics project based at St. Bartholomew's Hospital, we showed that a machine-learning (ML) algorithm was able to differentiate between renal cell carcinoma lesions that are likely to metastasize and those that are unlikely to metastasize after surgery, which is currently not possible with existing clinicopathological tools (40). In a similar manner, ML algorithms may also be applied to assess response to immunotherapy in lung cancer by classifying patients'

follow-up staging scans as indicative not only of SD, PD, PR and CR but even hyperprogressive disease or PP. In January 2021, researchers based at New York University and Vanderbilt University published a ground-breaking study on the utility of ML algorithms to predict immunotherapy response in patients with advanced melanoma using histology specimens and clinicodemographic features (41). Although the predictive value performance was moderate (area under the curve=0.800) and the area under the curve can be criticised as misleading due to cohort class imbalance (*i.e.*, fewer responders than non-responders), this study was still an important proof of concept. Other possible avenues for AI research include lesion-tracking software to provide increased reproducibility and rapid turnaround of scans supplemented by graphical plotting to allow visual assessment of the disease status and response; automated standard uptake value and functional information; and CT and magnetic resonance imaging spectral data for additional parameters of disease evaluation.

Aside from imaging-based modalities to monitor treatment response, the increasing availability of next-generation sequencing technologies have laid the ground for serial circulating tumour DNA (ctDNA) monitoring as a potential strategy for assessing tumour response. The relative ease and rapid turnaround of liquid biopsies employing peripheral blood sample analysis to detect tumour-derived material in the patients' circulation make ctDNA an increasingly popular modality in oncology (42, 43). One study of 67 patients with NSCLC showed the feasibility of employing a 74-gene next-generation sequencing panel on blood samples obtained at baseline and at 9 weeks to predict patient response; molecular responders were characterised as those with a >50% decrease in mean variant allele fraction (44). A significant negative correlation was observed between molecular response values and an objective radiological response, as determined by RECIST 1.1 criteria, with lower molecular response values in patients with objective radiological response (log mean 1.25% *vs*. 27.7%, $p<0.001$). Individuals who achieved a durable clinical benefit had significantly lower molecular response values compared to those with no durable benefit (log mean 3.5% *vs*. 49.4%, $p<0.001$), while molecular responders also exhibited longer progression-free survival (hazard ratio=0.25, 95% confidence interval=0.13-0.50) and overall survival (hazard ratio=0.27, 95% confidence interval=0.12-0.64) compared to molecular non-responders (44). Yet the utility of ctDNA remains to be validated in large prospective trials, whilst the precise classification system to define molecular response categories requires further examination (43).

Challenges. Immunotherapy is steadily evolving into one of the most promising treatment options for a wide variety of cancer types and its use is expected to increase in standard clinical practice outside of the clinical trial setting. An increasing number of patients are becoming eligible for immunotherapies and therefore a robust set of radiological response criteria is paramount to ensure appropriate clinical decision-making. The translation of new immunotherapy modalities into clinical practice, such as personalised cancer vaccines for disease treatment and novel adoptive cell therapies, such as chimeric antigen receptor T-cells or natural killer T-cells, will likely bring about new challenges in radiological response interpretation in the future (34). Therapy approaches which utilise immunotherapy in conjunction with radiotherapy, chemotherapy, targeted agents, or other immune-based treatment modalities are an advancing field of research, at relative infancy, with the potential to transform cancer management (35). However, such combination therapies may also pose challenges to assessment of radiological response due to the complex ways in which these different treatments interact (34). In terms of challenges encountered in the clinical trial setting, one must not forget that details of trial drugs under investigation are often not shared with the reporting radiologists due to blinding protocols to minimise risk of bias. Under such circumstances, errors in radiological evaluation are more likely to occur as compared to when radiologists are informed of the type of immune therapy under investigation. Although AI and ML algorithms offer hope for a more accurate, time-efficient, cost-effective, reproducible, and less resource-intensive method to predict response to immunotherapy, most of these methods still remain at the 'proof-of-concept' stage and require a significant amount of further investigation before they can be translated into routine clinical practice. Moreover, AI and ML technologies will likely require close supervision and quality control from expert clinicians if they are to be applied in clinical settings, despite significant progress in AI/ML applications in modelling highly complex biological systems (45).

Conclusion

With an increasing number of clinical trials on immunotherapies, there is a necessity for a standardized set of criteria that incorporate the unique response patterns observed under such treatments, particularly PP, which may be misinterpreted as PD resulting in inappropriate treatment discontinuation. Currently, a combination of RECIST 1.1 and iRECIST is advised for primary and exploratory trial endpoints, respectively. It is important to remember that PP is rare, thus treatment continuation should be carefully considered first. Accurate radiological identification of irAEs facilitates their early treatment, improving patient outcomes, while irAEs also correlate with treatment efficacy and improved survival. New challenges are to be expected as more novel immunotherapies and combination treatments are translated into clinical practice. Identification of predictive markers to identify response, progression or hyperprogression remains a

crucial field of research. Important breakthroughs are being achieved with AI and ML algorithms, which will likely transform the way we evaluate cancer response to treatment in the future, with some of these algorithms not relying on imaging but solely on histology and clinicodemographic variables to predict response. Nevertheless, radiologists and clinicians will remain integral in ensuring the safe application of these technologies in clinical practice. Thus, radiologists and clinicians should proactively seek out involvement in AI and ML projects to help develop and translate such novel technologies into routine clinical practice.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

K.S.R.: conceptualization, reviewing the literature, drafting, and revising the article, supervision, and final approval of the version to be published. S.M., A.G., M.S.: reviewing the literature, revising the article, and final approval of the version to be published.

Acknowledgements

The Author would like to thank Dr. Anju Sahdev for her expert comments and feedback on the article and Mr. Aaditya Tiwari for reviewing an initial draft of the work.

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Received July 26, 2023
Revised November 23, 2023
Accepted December 1, 2023