RECIST 1.1 v. iRECIST

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Dec 8, 2022

BSTA 663

I. Introduction

Cancer is one of the world's leading causes of illness and death. Standard healthcare practices surrounding cancer focus on dealing with one of the main aspects: lesions or, more specifically, malignant tumors. Mainstream treatments involve the usage of surgery, chemotherapy, radiation therapy, and immunotherapy, amongst others, to shrink or remove tumors. Despite the many treatments available, in 2022, over 1.9 million Americans will be diagnosed with cancer, and 610,000 will die as a result. Even with decades of research, modern science has yet to develop a cure for cancer, partly due to the many causes and types.

As a result, thousands of clinical trials examining anti-cancer treatments are taking place every year in the search for a pharmaceutical cure. Unfortunately, one of the difficulties of trialing cancer treatments is that time (and therefore money) is a factor since cancer can take months or years to progress and eventually lead to the patient's demise. Thus, during clinical trials, one of the primary ways scientists and oncologists determine how well a patient responds to various cancer treatments is to use surrogate endpoints, such as the size of a tumor and how it progresses or shrinks throughout the treatment. The primary purpose of this paper is to investigate, compare, and contrast two methods of determining how well a cancer patient responds to their treatment: RECIST 1.1 and iRECIST.

Some of the earliest attempts to determine and quantify how tumors respond to cancer treatments began in the 1960s, with the World Health Organization (WHO) eventually publishing criteria guidelines in 1979. Unfortunately, the guidelines proved problematic as the methods and definitions used ended up varying between research organizations, resulting in non-comparable response criteria and conclusions. In response, in 1994, various organizations such as the National Cancer Institute, the European Organization for Research and Treatment of Cancer, and

the National Cancer Institute of Canada Clinical Trials Group collaborated to create a unified set of tumor response criteria; in February 2000, this working group would publish the Response Evaluation Criteria In Solid Tumors, otherwise known as RECIST, for use in clinical trials. RECIST would be updated to RECIST 1.1 in January 2009.

II. RECIST 1.1

RECIST 1.1 is the standard method of assessing tumor response to treatment when using chemotherapy; assessment of the tumors is done using X-rays, CT scans, or MRI scans, while there must be at least one measurable tumor. Depending on the examination method, the minimum length of the lesion is 10mm by CT scan, 10mm by caliper during a clinical exam, and 20mm by X-ray. In addition, lymph node lesions must be at least 15mm on their short axis. If there is more than one measurable lesion present, a maximum of the five most significant lesions shall be selected, measured, and recorded as the "overall tumor burden at baseline", with no more than two lesions from a single organ; these lesions are designated as the target lesions. Most importantly, these lesions must be able to "lend themselves to reproducible repeated measurements". Once selected, the sum of the diameters of all target lesions is recorded as the baseline sum diameters. All non-target lesions should be recorded at baseline, but measurements are unnecessary. Finally, measurements of the target lesions are taken at protocol-specified time points, where the response of the lesions is evaluated.

The evaluation of the target lesions is as follows: Complete Response (CR) is the disappearance of all target lesions, Partial Response (PR) is at least a 30% decrease in the sum of diameters of the target lesions (using the baseline sum diameters), Progressive Disease (PD) is minimum 20% increase in the sum of diameters of the target lesions (compared to the smallest

sum, baseline or not) or the appearance of new lesions, and Stable Disease (SD) is either a decrease less than 30% or increase less than 20% (using the smallest sum diameters). Non-target lesions are evaluated as follows: CR for the disappearance of all non-target lesions, Non-CR/Non-PD for the persistence of non-target lesions, and PD for the progression of non-target lesions or appearance of new non-target lesions. The frequency of lesion assessment is protocol-specific, but generally, a period of 6-8 weeks is recommended. Once all data has been collected, the best overall response for a patient is determined by comparing the time-point responses. However, should a patient ever have a lesion evaluation of PD, they are given an overall response of PD regardless of non-target lesions or new lesions.

III. iRECIST

iRECIST (immune-based therapeutics modified RECIST 1.1) is a modification of RECIST 1.1, developed for cancer immunotherapy trials, as tumors respond differently enough compared to traditional chemotherapy drugs that RECIST 1.1 evaluations may be questionable when used in such trials. Specifically, the novel mechanisms of immunotherapy agents that act on pathways such as Cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1) lead to unusual responses in tumors. As these agents cause immune and T cell activation, tumors may show "pseudoprogression" (PSPD), where the tumors "flare up," leading to an increase in the sum of diameters, the appearance of new lesions, and an unequivocal increase in non-target lesions. This flare-up would cause the mistaken assignment of Progressive Disease when using RECIST 1.1, resulting in the termination of therapy, even if the patient would later show a lesion evaluation of SD, PR, or CR.

One of the significant changes from RECIST 1.1 is the concept of "resetting the bar" should a patient show tumor progression followed by tumor shrinkage at the next assessment. An unconfirmed assignment of PD (iUPD) must be confirmed (iCPD) at the following assessment by a further increase in tumor size or new lesions in the same category (target or non-target lesions) where PD was previously assigned. Should there be tumor shrinkage or no progression, the next time a PD is assessed, it must be confirmed at the following assessment (between 4-8 weeks) for PD to be confirmed. Multiple unconfirmed PDs can be assigned as long as it is never confirmed. This change in criteria allows for pseudoprogression responses resulting from immunotherapy and continuation of therapy rather than terminating it.

iRECIST guidelines for lymph nodes, too-small lesions, split or coalesced lesions, and the definitions of CR, PR, SD, and PD are unchanged from RECIST 1.1., but iRECIST has many unique aspects for lesion assessment. For example, therapy for a clinically stable patient can be continued even in the presence of a new lesion, new lesions are recorded and categorized, and new target and non-target lesions can cause a PD assessment should they meet the criteria. The reasoning for continuing therapy for clinically stable patients following an unconfirmed PD is that there may be a "deep response, including complete response" at the following assessment. However, continuing treatment for non-stable patients is not recommended as it can prevent the timely usage of "potentially effective salvage therapy". Interestingly, the continuation/discontinuation of therapy for non-stable patients is left up to the investigator or patient. The assessment of the best overall response follows RECIST 1.1, but the presence of PSPD requires accounting for the last time-point response or end of treatment so that a false overall response is not assigned. Overall, the significant differences between RECIST and

iRECIST are that in iRECIST, new lesions are not grouped with previous lesions and that an assessment of PD must be confirmed to account for pseudoprogression caused by tumor flares.

IV. Examples and Conclusion

The need for iRECIST can be seen in one study, Evaluation of Immune-Related Response Criteria and RECIST v1.1 in Patients With Advanced Melanoma Treated With Pembrolizumab by Hodi et al. In the study, a large proportion of patients (~15%) that had been classified with PD according to RECIST 1.1 but not by irRC (immune-related response criteria), were found to have a more prolonged overall survival compared to the patients who had been assessed as PD by both sets of criteria. In particular, one patient classed as PD per RECIST 1.1 but not by irRC showed a perfect example of pseudoprogression, when her total tumor burden increased by 35.7%, but four weeks later, the burden had decreased by 8.9% without termination of treatment. Had the study only used RECIST 1.1, the patient would have been taken off the treatment, and the study results would have failed to account for the pseudoprogression, potentially leading to different conclusions about the effectiveness of Pembrolizumab on advanced melanoma. Hodi et al. highlight that what may be excellent criteria for one type of cancer therapy may not work for a different type of therapy, thus necessitating the need for iRECIST when it comes to anti-cancer immunotherapeutic trials.

In a pooled FDA analysis study that covered 14 clinical trials, Comparison of iRECIST versus RECIST V.1.1 in patients treated with an anti-PD-1 or PD-L1 antibody: pooled FDA analysis, Mulkey et al. found that RECIST 1.1 appears to "capture most of the treatment effect based on [objective response rate]" (Mulkey et al., 2020), but that evaluating responses according to iRECIST found that 2.8% of patients had a Complete Response or a Partial

Response after a RECIST 1.1 assessment of PD. In addition, the authors note that assessing the durability of response using iRECIST led to a modest increase in duration of response of approximately one month within the overall analysis population and more significant increases within specific therapeutic categories. Cancer treatments aim to increase the duration of life if cancer proves incurable, so an extra month of life can mean a lot to people. Overall, Mulkey et al. conclude that using RECIST 1.1 may lead to the early termination of treatment for a small group of patients who display pseudoprogression. A comparative study by Tazdait et al., Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria, found that RECIST 1.1 fails to capture atypical responses (PSPD), leading to the underestimation of the benefit of immune checkpoint inhibitors in 11% of patients who had been classified as PD.

Overall, RECIST 1.1 is excellent for traditional cancer treatments such as chemotherapy but falls short when immunotherapy is concerned, providing a need for iRECIST to identify patients who display pseudoprogression when undergoing anti-cancer immunotherapy. That's not to say that iRECIST doesn't have its shortcomings, as the increased complexity in managing and interpreting data creates an extra burden on clinical trials. Additionally, many studies comparing RECIST 1.1 and iRECIST have noted that there simply isn't enough data yet concerning the effectiveness of iRECIST. In the end, it may prove best to use both RECIST 1.1 and iRECIST simultaneously to account for pseudoprogression and allow for the continuation of treatment in clinical trials involving anti-cancer immunotherapies.

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