Assessing response to therapy allows for prospective end point evaluation in clinical trials and serves as a guide to clinicians for making decisions. Recent prospective and randomized trials suggest the development of imaging techniques and introduction of new anti-cancer drugs. However, the revision of methods, or proposal of new methods to evaluate chemotherapeutic response, is not enough. This paper discusses the characteristics of the Response Evaluation Criteria In Solid Tumor (RECIST) version 1.1 suggested in 2009 and used widely by experts. It also contains information about possible dilemmas arising from the application of response assessment by the latest version of the response evaluation method, or recently introduced chemotherapeutic agents. Further data reveals the problems and limitations caused by applying the existing RECIST criteria to anti-cancer immune therapy, and the application of a new technique, immune related response criteria, for the response assessment of immune therapy. Lastly, the paper includes a newly developing response evaluation method and suggests its developmental direction.

Keywords: Evaluation Studies as Topic; Drug Therapy; Lung Neoplasms

**Introduction**

Anti-cancer drugs effect could be measured by assessing alternation in tumor size. Response evaluation of chemotherapy is clinical trials prospective end point which is a significant guideline of decision making for clinicians. Recently, there had been much development of imaging modality of new anti-cancer drug; however, the development of chemotherapies response evaluations is not. Thus, this review article will contain response evaluation methods that had been used after lung cancer patient’s chemotherapy, limitation of Response Evaluation Criteria In Solid Tumor (RECIST) version 1.1, and introduction of new methods.

**Timeline of Response Evaluation of Chemotherapy for Cancer**

In 1979, World Health Organization (WHO) tried to invent standardize criteria of response assessment and early 1980s, WHO had published the first international standard criteria and had applied tumor response evaluating method to chemotherapy. Fundamentally, cytotoxic agents have a process on the basis of the amount of tumor shrinkage so that assessment to effect of chemotherapy has been investigated. Tumor size was traditionally assessed with bi-dimensional measurement which falls in to WHO guideline (the product of the longest diameter and its longest perpendicular diameter for each tumor). Measurability was defined as result that was recorded in metric notation using calipers or ruler. Response evaluation (applied WHO criteria) was performed and subjections were proposed. First, is about real measuring in bi-dimensional and afterwards products calculations were too complicated containing risk factors cause of theoretical variations of diameter were more correlated to the death cell’s fixed proportion of standard dose of chemotherapy rather than bi-dimensional product variations. Second, is weakness of reproducibility be-
between invested individual, group, or institution because there were no clear technique for measuring methods and selection of target lesions, in WHO guideline. Third, is new methodology was needed because of new imaging technique and new classes of anti-cancer agents. Thus, many paper and experts’ announcements brought up the WHO criteria’s modification. In response to these problems, the RECIST was reviewed by international task force (European Organization for Research and Treatment of Cancer [EORTC], National Cancer Institute [NCI], National Cancer Institute of Canada Clinical Trials Group, etc.). The international task force had reviewed RECIST with the 4,000 patients’ chemotherapy response. After the review, criteria were published in 2000 through Journal of the National Cancer Institute. This criteria is used in phase II clinical trial and made with results of solid tumor response assessment after chemotherapy, however, it was actually used for response assessment in all phases. Original RECIST’s main features are: definitions of minimum size of measurable lesion (conventional method ≥20 mm, spiral computed tomography [CT] ≥100); instructions on how many lesions to follow (up to 10; a maximum 5 per organ site); use of unidimensional rather than bi-dimensional; measure for overall evaluation of tumor burden. Definition of objective response is more strictly than WHO criteria and the evaluation rate are different: partial response (PR), at least 50% decrease to 30% and progressive disease (PD), 25% increase to 20%. Therefore, in same patients group, there had been 33% higher threshold meet to PD. Afterwards, RECIST working group made up with clinicians, experts from academic research organizations, imaging specialists, government, was formed. The group had meetings periodically, and found response evaluation limitations of original RECIST criteria by researching on new chemotherapy and developing imaging technique. After RECIST published at 2000, many investigators performed phase III clinical trials and prospective analyses. In 2004, the International Cancer Imaging Society (ICIS) published a consensus statement about the evaluation of the response to treatment of solid tumors, including a number of issues related to the implementation of RECIST. Including this paper, many research papers projected concerns, questions, and issues about RECIST’s further clarity and merit answer. Those are “Is it okay to ignore if there are less than 10 lesions objectied?”, “Is it okay to apply RECIST to randomized phase II trial even if the diseases of all patients do not have measurability form RECIST and, progressed or not response?”, “How to use new imaging techniques such as fluorodeoxyglucose–positron emission tomography (FDG-PET) and magnetic resonance imaging?”, “How to handle assessment of lymph node (should be measured in the short axis)?”, “Is it okay to ignore bone or cystic lesions; changes in tumor consistency (calcification, necrosis, etc.)?”, “Could targeted non-cytotoxic agent’s clinical trial applied to RECIST?”. These efforts toward questions and concerns helped to update the RECIST guideline and revision.

In 2009, consequently, updated RECIST criteria was published. This revised guideline was focused on anatomical rather than functional assessment, so it was named RECIST 1.1 not 2.0.

**RECIST Version 1.1 (Revised RECIST) Is Perfect?**

The changes in RECIST version 1.1 compared to version 1.0 are showed on Table 1. RECIST version 1.1’s changed features are five categories: number of target lesions, assessment of pathologic lymph node, clarification of disease progression, clarification or baseline documentation of unequivocal progression of non-target lesions, inclusion of $^{18}$F-FDG-PET in the detection of new lesions. Response criteria is divided into target and non-target lesion, and each evaluation are more specific than before. Revised RECIST criteria suggested standardized framework that can evaluate and analysis efficacy of cancer treatment. However, there are some limitations that evaluated certain organs (e.g., bone or liver) and some therapeutic options. In addition, in response criteria, ideas of “30% decrease for a response” and “20% increase for a progression” are selected arbitrarily without enough evidence. And, the idea was applied to patient outcome such as overall survival which is problematic. For example, anti–vascular endothelial growth factor (VEGF), target therapeutic agent, decreased naive tumor’s size change which is lower than 30%, but significantly increased patient survival. In addition, there is some variation between patient outcome and response evaluation that became large sized scar to patients having image-guided therapy such as radiofrequency ablation or chemoembolization.

In 2011, Lee et al. reported that lung cancer is generally measured on lung window from chest CT and included ground glass opacity (GGO) and solid components in part-solid lung cancer. However, GGO within part-solid lung cancer generally does not vary profoundly with cancer chemotherapy. Size change in only solid component of part-solid peripheral lung cancer, may be more accurate reflection of the actual tumor response to cancer for chemotherapy. Therefore, the article implied argument of RECIST measurement and RECIST solid measurement should be classified and applied to response criteria. In addition to patients with non-small cell lung cancer, lung image after chemotherapy show internal cavity formation due to necrosis of tumor. Cavitation within tumor caused by hampered angiogenesis, should be treated with platinum based chemotherapy and VGEF receptor blocker inhibitor for better response recoverd from damaged angiogenesis. Tumor necrosis may constitute a type of tumor response, but RECIST does not reflect this alternation. In 2007, Choi et al. reported that lung cancer patients whom had chemotherapy had no alternation in tumor diamete
evaluated from contrast chest CT, heterogeneously decreased attenuation. These alternation effected patient’s survival rate. Therefore, alternation in attenuation implied tumor has shrunk and internal cavity formation, suggesting tumor necrosis. At this point, Choi response criteria was proposed. This criteria included that tumor attenuation which is Hounsfield Unit alternation of tumor attenuation.

Beyond RECIST Version 1.1

Evaluation of treatment response of solid tumor applied tumor size based RECIST, is widely applied and well accepted. However, as mentioned before, in new therapeutic modalities such as angiogenesis inhibitors and anti-vascular therapies, without size change, alternation such as attenuation, necrosis and cavitation, could be induced, underestimate could be a result in case of RECIST. For example, using sorafenib and bevacizumab as metastatic renal cell cancer, clinicians could evaluate the disease as progressive state based on RECIST criteria: however, patient’s condition was in of significantly approved and increased in progression-free survival. After applying imatinib in gastrointestinal stromal tumor patient, clinician could observe significant alternation in standardized uptake values using by \(^{18}\)F-FDG-PET. In addition, clinicians could observe anatomical change by using CT several weeks later. There are limitations using CT which is bi-dimensional evaluative tool as the only evaluative method. Recently, many studies introduced the idea of ‘changes can precede volume changes’ and insisted metabolic changes could be detected by different molecular and functional imaging techniques.

In 2016, there was a session of adjustment of functional or mixed functional and anatomical tumor response assessment at European Congression of Radiology (ECR) using newly introduced imaging modalities (Table 2). This meeting insisted response evaluation using new metabolic or functional imaging techniques, still acquired evaluation’s end point for treatment efficacy as new targeted agents turned into main stream of cancer treatment even if it is in phase I or II trials. Also, these imaging modalities have idealistic merits: non-invasive, validated, and reproducible. Therefore, those imaging modalities introduced as new paradigm for tumor response evaluation.

Table 1. Key features comparison of RECIST 1.0 and RECIST 1.1

|                        | RECIST 1.0 (2000 criteria) | RECIST 1.1 (2009 criteria) |
|------------------------|---------------------------|---------------------------|
| Assessment lymph node  | Not recommended           | Recommended               |
| Assessment of tumor burden | Five targets            | Ten targets               |
|                        | Two per organ             | Five per organ            |
| Measuring lymph node   | Short axis                | Long axis as for other organs |
| Finding of a new lesion| Not specifically defined  | Should be unequivocal     |
| Patient response to treatment | Initial response to treatment must be confirmed within 4 weeks | Need not be confirmed in randomized trials when the primary end point is disease progression |
| Imaging of non-target lesions | Not specifically addressed | Not necessary at every protocol-specified for declaration of PR or SD |
| Lesions too small to measurement | Not specifically defined | Default value of 5 mm |
| New imaging techniques | No specific recommendation | FDG-PET applied to incorporate as CT scanning assessment |
| Definition of progressive disease | >20% increase in sum of longest diameters form nadir | >20% increase in sum of diameters from nadir, absolute increase of >5 mm |

RECIST: Response Evaluation Criteria In Solid Tumor; PR: partial response; SD: stable disease; FDG-PET: fluorodeoxyglucose–positron emission tomography; CT: computed tomography.

Immunotherapy Response Evaluation Methods

In cytotoxic agents, early increase in tumor growth and/or appearance of new lesions analyzed as progressive disease which means treatment failure. However, there need different comprehension for noncytotoxic agent which is immunotherapeutic agent. From mid 2000s, there had been active researches on immunotherapeutic agent and response evaluation. Table 3 is arranged immunotherapy methods that
Response evaluation of chemotherapy

approached to lung cancer and malignant mesothelioma, up to date. There were four kinds of response from melanoma patients whom had ipilimumab: two conventional response, response after tumor burden increase, and response in the presence of new lesion. Last two responses are was PD aspect of conventional response criteria but patients actually reacted to PR or stable disease. Delayed action mechanism of immunotherapy progresses T-cell expansion driving in first then T cell could expand which appears as tumor burden, or make cell edema from infiltration with tumor cell which could lead to radiography misinterpretation (a version of the "tumor flare reaction").

To supplement this error, about 200 oncologists, immunotherapists, and regulatory experts shared experiences of immunotherapeutic agents of cancer patients in 2004 to 2005, and concluded with following: the appearance of measurable anti-tumor activity may take longer for immune therapies than for cytotoxic therapies; responses to immune therapies may occur after conventional PD; discontinuation of immune therapy may not be appropriate in some cases, unless PD is confirmed (as is usually done for response); allowance for "clinical insignificant" PD (e.g., small new lesions in the presence of other responsive lesions) is recommended; and durable stable disease may represent anti-tumor activity. With this basis of conclusion, novel activity criteria for immunotherapeutic agents were introduced at Clinical Cancer Research in 2009. Comparing with conventional WHO criteria, its significant features are defined as following: new measurable lesion defined as incorporated into tumor burden, new non-measurable lesion do not define progression, sum of measurements defined as sum of uni-dimensional measurements of all target lesion and any new lesion. In immune related response criteria, immune related progressive disease defined as increase in tumor volume ≥20% from nadir, immune related stable disease as not meeting criteria for CR or PR, immune related partial response defined as decrease in tumor volume ≥30% relative to baseline, and immune related complete response defined as complete disappearance of all lesions and new measurable lesions. New lesion's definition was altered as presence of new lesions alone does not define progression and measurement of new lesions included in sum of measurement was included. Many retrospective studies applied new guideline, were proceeded until now, and in 2014, immune related RECIST was suggested at European Society for Medical Oncology. Thus, future prospective randomized study requires supplements and fixation by having more clinical trials, and researches on survival.

Table 2. Beyond RECIST 1.1: new response criteria developed by clinical trials and new imaging modalities

| Authors          | Published journal       | Name                      | Clinical trials                                      | Assessment changes                                      | Alternative imaging modalities                  |
|------------------|-------------------------|---------------------------|------------------------------------------------------|---------------------------------------------------------|-------------------------------------------------|
| Choi et al.⁵⁶    | J Clin Oncol (2007)     | Choi criteria             | Target therapy for GIST                              | Size and attenuation at CT                              | Perfusion CT, dual energy CT                     |
| Wahl et al.³⁵    | J Nucl Med (2009)       | PERCIST                   | FDG-PET                                              | FDG uptake (SUVmax)                                     | PET (metabolism, oxygenation, other tracers)     |
| Lencioni and Llovet³⁵ | Semin Liver Dis (2010)   | Lencioni criteria or modified RECIST | Ablation therapy for hepatocellular carcinoma       | Size and arterial-phase Based enhancement at CT, MRL or CEUS (contrast enhanced US) | Perfusion MRI, diffusion-weighted MRI, perfusion US |
| Smith et al.¹⁶   | AJR Am J Roentgenol (2010) | MASS criteria             | Target therapy for metastatic renal carcinoma       | Size and attenuation at CT                              | Perfusion CT, dual energy CT                     |
| Lee et al.¹⁴     | Lung Cancer (2011)      | New response criteria (NRC)| Target therapy for NSCLC                             | Size and attenuation (solid portion) at CT              | Perfusion CT, dual energy CT                     |
| Chung et al.³⁷   | AJR Am J Roentgenol (2012) | Modified CT criteria     | Chemotherapy for colorectal cancer liver metastasis | Size and attenuation at CT                              | Perfusion CT, dual energy CT                     |
| Nanni et al.³⁸   | Eur J Nucl Med Mol Imaging (2016) | Italian Myeloma criteria for PET Use (IMPeTUs) | Chemotherapy for multiple myeloma                    | FDG uptake (baseline, induction, and end of treatment) | FDG-PET/CT                                       |

RECIST: Response Evaluation Criteria In Solid Tumor; GIST: gastrointestinal stromal tumor; CT: computed tomography; PERCIST: Positron Emission Tomography Response Criteria in Solid Tumors; FDG-PET: fluorodeoxyglucose–positron emission tomography; SUVmax: maximum standardized uptake value; MRL: magnetic resonance imaging; CEUS: contrast-enhanced ultrasonography; US: ultrasonography; MASS: Morphology, Attenuation, Size, and Structure; NSCLC: non-small cell lung carcinoma.
Conclusion

Even with the rapid development and variation of cancer therapeutic agents and imaging modalities, evaluation of chemotherapy is not sufficient. Therefore, evaluating new treatment options and imaging modalities applying WHO, RECIST version 1.0, or RECIST version 1.1, the evaluation end point (progression-free survival or overall survival) does not reflect satisfactorily. In addition, for global implementation of such novel treatment evaluation methods, multicenter or multi-institution research should not use original response criteria that could cause limitations for reproducibility.

Before appearance of new response criteria, many studies and discussion had conclusion of subjection toward original criteria and development of it. Thus, researchers, clinicians, and experts should have further studies and discussions for new response evaluating method appearance by acknowledge necessity of new method and developing new treatment and imaging modalities.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.
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