13 Evaluation and Assessment of the Radio-Peptide Treatment Efficacy

Georgios S. Limouris and Athanasios G. Zafeirakis

13.1 Introduction/Historical Corner

An early attempt to define the objective response of a tumor was made in the 1960s [1]. However, more systematically defined response assessment criteria were made by WHO in 1979, which resulted in the WHO handbook for reporting results of cancer treatments [2, 3]. Though the distinction of solid tumor was apparent, the response pattern within solid tumors was not obvious. In 1994, several organizations involved in clinical research proposed guidelines with the term RECIST 1.0 [4]; however, their applicability in different neoplasms was less than optimal [5]. With the development of newer imaging modalities (PET scan, MRI, nuclear imaging, etc.), it became clear that response assessment estimation does not fit for all solid tumors since RECIST criteria, apart from size, do not take into account changes in various tumor characteristics like tumor viability, metabolic activity, and tumor density characteristics directly associated with tumor response.

This resulted in various specialized groups to define more suitable and specific tumor response criteria (Table 13.1) according to corresponding necessities.

Table 13.1 Main response assessment criteria

a/a	Criteria	References
1	WHO [World Health Organization]	[2, 3]
2	RECIST 1.0 [Response Evaluation Criteria In Solid Tumors]	[4]
3	RECIST 1.1 [Response Evaluation Criteria In Solid Tumors]	[6]
4	mRECIST [modified Response Evaluation Criteria In Solid Tumors]	[7]
5	PERCIST [PET Response Criteria in Solid Tumors]	[8]
6	irRC [immune-related Response Criteria]	[9]
7	Choi [Choi Criteria]	[10]
8	EASL [European Association for the Study of the Liver]	[11]
9	MDA [MD Anderson Criteria]	[12]
10	SWOG [Southwestern Oncology Group]	[13]
11	MacDonald [MacDonald Criteria]	[14]
12	RANO [Response Assessment in Neuro-Oncology]	[15]
13	EORTC [European Organization for Research and Treatment of Cancer]	[16]
14	RECICL [Response Evaluation Criteria in Cancer of the Liver]	[17]

G. S. Limouris (✉)
Nuclear Medicine, Medical School, National and Kapodistrian University of Athens, Athens, Greece
e-mail: glimouris@med.uoa.gr

A. G. Zafeirakis
Nuclear Medicine Department, Army Share Fund Hospital of Athens, Athens, Greece

G. S. Limouris (ed.), *Liver Intra-arterial PRRT with ^{111}In-Octreotide*,
https://doi.org/10.1007/978-3-030-70773-6_13

13.2 Response Assessment

13.2.1 WHO Criteria

The WHO criteria aim to standardize the response assessment mainly in prospective randomized cancer clinical trials [2, 3]. According to them, the lesions are classified into two groups as *measurable* and *non-measurable*. The size of the lesion derives as a two-dimensional measure by multiplying the longest diameter by its perpendicular (vertical one) one. Complete response (CR), partial response (PR), no change (NC), and progressive disease (PD) are defined separately for measurable and non-measurable disease and bone metastases. The rules for determining overall response (OR) and the concept of duration of response (RD) and disease-free interval (DFI) are described.

However, the inadequate description of details of measurement rules and handling of exceptions lead to development of many modifications to WHO criteria in various trials and often to loss of comparability. As a sequence, WHO criteria are widely replaced by RECIST one (Table 13.2).

Table 13.2 Major differences between WHO and RECIST or RECIST 1.0 criteria

Parameter	WHO	RECIST or RECIST 1.0
CR (complete response)	Complete disappearance of all targeted lesions	Disappearance of all target lesions (up to 5 measurable liver lesions)
PR (partial response)	At least 50% decrease in tumor size	30% decrease of the sum of the greatest diameter of target lesions
SD (stable disease)	Meets neither PR nor PD criteria	Meets neither PR nor PD criteria
PD (progressive disease)	>25% increase of at least one lesion or a new lesion	20% increase of the sum of the greatest diameter of target lesions

13.2.2 RECIST Criteria

In late 1994, a new concept was presented as RECIST 1.0 guidelines [4] which subsequently after revision was released in 2009 as version 1.1 [6]. Table 13.3 provides at a glance the important features and major changes of RECIST 1.0 to RECIST 1.1. They later gained popularity and nowadays are accepted by the majority of investigation authorities in the assessment of treatment outcomes in solid tumor.

Table 13.3 Major differences between RECIST 1.0 and RECIST 1.1 criteria

Parameter	RECIST or RECIST 1.0	RECIST 1.1
Minimum size of the measurable lesion	CT: 10 mm spiral, 20 mm non-spiral; clinical, 20 mm; lymph nodes, not mentioned	CT: 10 mm spiral; clinical, 10 mm; lymph nodes, ≥15 mm
Overall tumor burden	Up to 10 target lesions, maximum 5 per organ	Up to 5 target lesions, maximum 2 per organ
Complete response (CR)	Disappearance of all target lesions (up to 5 measurable liver lesions)	Disappearance of all target lesions (up to 2 measurable liver lesions); CR lymph nodes must be <10 mm short axis
Partial response (PR)	30% decrease of the sum of the greatest diameter of target lesions	At least 30% decrease of the sum of the greatest unidimensional diameters of target lesions, compared to baseline
Stable disease (SD)	Meets neither PR nor PD criteria	Meets neither PR nor PD criteria
Progressive disease (PD)	20% increase of the sum of the greatest diameter of target lesions	At least 20% increase of the sum of the diameters of target lesions, compared to baseline

13.2.3 MD Anderson Cancer Center Criteria for Bone Metastases

According to WHO and RECIST criteria, bone metastases were initially considered non-measurable lesions, because metastases located in irregularly shaped bones are difficult to be measured. Since NETs do not or rarely metastasize in bone, it is clinically important to appropriately manage the osseous spread of the neuroendocrine disease. Thus, in 2004 Hamaoka et al. [12] proposed new response assessment criteria for response assessment of bone metastasis, known as the MD Anderson (MDA) criteria. These allow the use of various radiologic techniques with baseline images obtained by x-ray (XR), CT, MRI, or by some other modalities. The recommended duration for follow-up imaging is 2–6 months (Table 13.4).

Vassiliou and Andreopoulos suggested MDA criteria may be improved by becoming more objective and accurate [18]. The implementation of CT to assess bone metastases would be very useful if the bone density in metastatic regions is measured in Hounsfield units (HU) after delineation of affected bone areas [18, 19].

Table 13.4 MD Anderson Cancer Center criteria

Parameter	MD Anderson Cancer Center criteria
Complete response (CR)	Complete fill-in or sclerosis of a lytic lesion on x-ray and CT; disappearance of hot spots or tumor signal on SPECT/CT, CT, or MRI; normalization of osteoblastic lesion on x-ray and CT
Partial response (PR)	Sclerotic rim about initially lytic lesion or sclerosis of previously undetected lesion on x-ray or CT; partial fill-in or sclerosis of lytic lesion on x-ray or CT; regression of measurable lesion on x-ray, CT, or MRI; regression of lesion on SPECT/CT; decrease of blastic lesion on x-ray or CT
Stable disease (SD)	No change in measurable lesion on x-ray, CT, or MRI; no change in blastic/lytic lesion on x-ray, CT, or MRI; no new lesion on x-ray, SPECT/CT, CT, or MRI
Progressive disease (PD)	Increase in size of any existing measurable lesions on x-ray, CT, or MRI; new lesion on x-ray, SPECT/CT (excluding flares), CT, or MRI; increase in activity on SPECT/CT (excluding flares) or blastic/lytic lesion on x-ray or CT

13.2.4 Choi Criteria for Gastrointestinal Stromal Tumors (GISTs)

Choi et al. [10] in 2007 indicated that the RECIST 1.0 criteria underestimated the tumor response to imatinib in patients with metastatic GISTs; he aimed to develop criteria using CT scan as imaging modality as well as various tumor characteristics for the quantitative response evaluation in GISTs, beyond size measurement. In the meantime, EORTC criteria were available for response assessment using PET scan, but often the glucose uptake before treatment did not sufficiently detect them by FDG-PET (Table 13.5).

Choi criteria have been validated using time to progression endpoint. They are also used in assessing response in metastatic renal cell carcinoma [20], high-grade soft tissue sarcoma, solitary fibrous tumor [21], and hepatocellular carcinoma [22].

Table 13.5 Choi criteria for the evaluation of treatment response in GISTs

Parameter	Choi criteria
Complete response (CR)	Disappearance of all lesions; no new lesions
Partial response (PR)	Decrease in size (sum of longest diameter as defined by RECIST criteria) of ≥10% or a decrease in tumor density ≥15% on CT; no new lesions, no obvious progression of non-measurable disease
Stable disease (SD)	No symptomatic deterioration attributes to tumor progression
Progressive disease (PD)	Increase in tumor size of ≥10%; on CT, new lesions, new intra-tumoral nodules or increase in the size of the existing intra-tumoral nodules

13.2.5 MacDonald and RANO Criteria for High-Grade Gliomas

In 1990, MacDonald et al. [14] published criteria for response assessment in high-grade gliomas, based primarily on contrast-enhanced computed tomography (CT) and the two-dimensional WHO oncology response criteria using enhancing tumor area including the use of corticosteroids and changes in the neurologic status of the patient.

However, it is obvious that there are significant limitations using only contrast-enhancing component of the tumor. Therefore, Wen et al. proposed new response criteria, commonly known as revised assessment in neuro-oncology (RANO) criteria [15].

RANO criteria provide (a) definitions and rules for standardization of imaging definitions, (b) number of lesions, and (c) definition of radiographic response. The sum of products of diameters (SPD) is calculated as products of maximal diameters, further adding them together. The responses are categorized as (a) contrast-enhancing lesions, (b) non-enhancing lesions, and (c) new lesions, based on thresholds defined in WHO criteria. The overall response (OR) is defined using response in enhancing lesions, non-enhancing lesions, new lesions, use of corticosteroids, and clinical status of the patient.

13.2.6 Response Assessment Criteria for Hepatocellular Carcinoma (HCC): EASL, mRECIST, and RECICL

The European Association for the Study of Liver (EASL) criteria is based on WHO criteria incorporating the concept of viable tumor tissue [11], quantifying the amount of enhancing (viable) tissue (Table 13.6).

Similarly, the American Association for the Study of Liver Disease (AASLD) developed a set of guidelines named as modifying RECIST criteria (mRECIST) [7] and aimed to accommodate the concept of viable tumor tissue, too (Table 13.6).

Table 13.6 Major differences between EASL and mRECIST criteria

Parameter	EASL	mRECIST
Complete response (CR)	Disappearance of any intra-tumoral enhancement in all lesions	Disappearance of any intra-tumoral enhancement in all target lesions (up to two measurable liver lesion)
Partial response (PR)	At least 50% decrease in the sum of the product of bidimensional diameters of viable (arterially enhancing) target lesions	At least a 30% decrease in the sum of unidimensional diameters of viable (arterially enhancing) target lesion, compared to baseline
Stable disease (SD)	Meets neither PR nor PD criteria	Meets neither PR nor PD criteria
Progressive disease (PD)	An increase of at least 25% in the sum of the diameters of viable (enhancing) target lesion	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions compared to baseline

In 2009, the Liver Cancer Study Group of Japan proposed revisions to Response Evaluation Criteria in Cancer of the Liver (RECICL) [17]. The criteria consider the tumor necrosis as a direct effect of treatment, whereas the dense accumulation of lipiodol is regarded as necrosis, too. Tumors are measured in two dimensions.

Furthermore, in 2009 alpha-fetoprotein (AFP) and AFP-L3 and des-gamma-carboxyl protein (DCP) were added for the overall treatment response [17, 23].

13.2.7 PET Response Criteria in Solid Tumors (PERCIST)

In PERCIST criteria [8], response to therapy is expressed as percentage change in the sum of lesions (SULs) between the pre- and posttreatment positron emission tomography (PET) scans. A complete metabolic response (CmR) is considered as a visual disappearance of all metabolically active tumors (Table 13.7). A partial

Table 13.7 Major differences between RECIST 1.1 and PERCIST criteria

Parameter	RECIST 1.1	PERCIST
Complete response (CR)	Complete resolution of FDG uptake in all lesions	Complete resolution of FDG uptake in all lesions
Partial response (PR)	≥25% reduction in the sum of SUV max after more than one cycle of treatment	≥30% reduction of the UL peak of the FDG uptake and an absolute drop of 0.8 SUL peak units
Stable disease (SD)	Meets neither PR nor PD criteria	Meets neither PR nor PD criteria
Progressive disease (PD)	≥25% increase in the sum of SUV max or appearance of FDG-avid new lesions	≥30% increase in the SUL peak of the FDG uptake and an absolute increase of 0.8 SUL peak or appearance of FDG-avid new lesions

metabolic response (PmR) is defined as a visual disappearance of more than a 30% (and a 0.8-unit decline) in SULs between the most intense lesion before and after treatment, not necessarily of the same lesion. A stable metabolic disease (SmD) is characterized as no substantial visual metabolic change between the pre- and posttreatment scans. A progressive metabolic disease (PmD) is classified as more than a 30% (and 0.8-unit) visual increase in SULs or new lesions between the pre- and posttreatment scans. Wahl et al. proposed another metric of progression [8] in the case of a greater than 75% increase in total lesion glycolysis.

13.2.8 The European Organization for Research and Treatment of Cancer (EORTC) Criteria in Solid Tumors

Complete metabolic Response **(CmR)** would characterize a complete resolution of [^{18}F]-FDG uptake within the tumor volume to be indistinguishable from surrounding normal tissue [16].

Partial metabolic response (PmR) would be defined as a reduction of a minimum of 15% ± 25% [^{18}F]-FDG SUV in a tumor after one cycle of chemotherapy and greater than 25% after more than one treatment cycle.

Stable metabolic disease (SmD) is considered as an increase in tumor with [^{18}F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [^{18}F]-FDG tumor uptake (20% in the longest dimension).

Progressive metabolic disease **(PmD)** is classified as an increase in [^{18}F]-FDG standardized uptake value (SUV) greater than 25% before and after treatment of the tumor defined on the baseline scan visible increase in the extent of [^{18}F]-FDG tumor uptake (20% in the longest dimension) or the appearance of new [^{18}F]-FDG uptake in metastatic lesions.

13.2.9 The Immune-Related Response Criteria (irRC) [9]

The immune-related response criteria arose out of observations that using the WHO or RECIST Criteria in immuno-oncology therapeutic schemes the delay (i.e., the time gap) between dosing (initial treatment) and the observed anti-tumor response failed to be taken into account. These observations first flagged in a key 2007 paper in the *Journal of Immunotherapy* [24], evolved into the immune-related response criteria (irRC), which was published in late 2009 in the journal *Clinical Cancer Research* [25]. The therapy results express four distinct response patterns: (a) immediate response (IR), durable stable disease (DSD), response after tumor burden increase, and response in the presence of new lesions. The first two patterns are conventional, whereas the latter two are novel and specifically recognized with immunotherapeutic agents [25].

Only measurable lesions are taken into consideration. Measures are taken bi-dimensionally

for each lesion. To calculate total tumor burden, the sum of the perpendicular diameters of lesions at baseline is added to that of the new lesions.

Response categories under irRC are defined as immune-related complete response (irCR), immune-related partial response (irPR), immune-related stable disease (irSD), and immune-related progressive disease (irPD) using the same thresholds to distinguish between categories as defined in WHO criteria (Table 13.8).

According to irRC, the appearance of new lesions alone does not constitute irPD if they do not add to the tumor burden by at least 25%. Patients with new lesions but an overall tumor burden decrease qualifying for partial response (≥50% decrease) or qualifying for stable disease (<50% decrease to >25% increase) are considered to have irPR or irSD, respectively [26].

13.3 The Southwest Oncology Group (SWOG) Criteria

In 1992, the Southwest Oncology Group (SWOG), in cooperation with the National Cancer Institute (NCI) in the USA and other major cooperative oncology groups, has participated in the development of new criteria for reporting the results of cancer clinical trial [13] (Table 13.9). Observing the three tabulated criteria and their differences, we can comprehend that a particular guideline may be useful in establishing uniformity of evaluation in a desired study population but may not be the best for that population during routine clinical practice. The comparison between them indicates that each of the guidelines has its own applicability and that no guideline can outweigh the other during routine clinical practice.

Table 13.8 Major differences between WHO and iRC criteria

Parameters	WHO	iRC
New measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New non-measurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR (complete response)	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart
PR (partial response)	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 weeks apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden com-pared with baseline in two observations at least 4 weeks apart
SD (stable disease)	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD (progressive disease)	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart

Table 13.9 Major differences between WHO, RECICT 1.0, and SWOG criteria

Response	WHO	RECIST 1.0	SWOG
CR (complete response)	Complete disappearance of all targeted lesions	Disappearance of all target lesions (up to 5 measurable liver lesions)	Complete disappearance of all measurable and evaluable disease; no evidence of non-evaluable disease, including normalization of markers and other abnormal laboratory values for at least 3–6 weeks Complete disappearance of all targeted lesions including normalization of markers and other abnormal laboratory values for at least 3–6 weeks
PR (partial response)	At least 50% decrease in tumor size	30% decrease of the sum of the greatest diameter of target lesions	Sum of products of all lesions decreased by ≥50% for at least 3–6 weeks; no new lesions; no progression of evaluated lesions
SD (stable disease)	Meets neither PR nor PD criteria	Meets neither PR nor PD criteria	Sum of products of lesions decreased by <50% or increased by <50% or 10 cm^2 for at least 3–6 weeks
PD (progressive disease)	>25% increase of at least one lesion or a new lesion	20% increase of the sum of the greatest diameter of target lesions	50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over the smallest sum observed; clear worsening of any evaluable disease; appearance of a new lesion

References

1. Zubrod CG, Schneiderman SM, Frei E III, et al. Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thio-phosphamide. J Chronic Dis. 1960;11:7–33.
2. World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization; 1979.
3. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer. 1981;47:207–14.
4. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.
5. Forner A, Ayuso C, Varela M, et al. Evaluation of tumor response after loco-regional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer. 2009;115:616–23.
6. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
7. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepato-cellular carcinoma. Semin Liver Dis. 2010;30:52–60.
8. Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50:S122–50.
9. Subbiah V, Chuang HH, Gambhire D, et al. Defining clinical response criteria and early response criteria for precision oncology: current state-of-the-art and future perspectives. Diagnostics (Basel). 2017;7(1):10.
10. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol. 2007;25:1753–17597.
11. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the barcelona-2000 EASL conference. European association for the study of the liver. J Hepatol. 2001;35:421–30.
12. Hamaoka T, Madewell JE, Podoloff DA, et al. Bone imaging in metastatic breast cancer. J Clin Oncol. 2004;22:2942–53.

13. Green S, Weiss GR. Southwest oncology group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs. 1992;10:239–53.
14. Macdonald DR, Cascino TL, Schold SC Jr, et al. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol. 1990;8:1277–80.
15. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010;28:1963–72.
16. Young H, Baum R, Cremerius U, et al. European Organization for Research and Treatment of Cancer (EORTC) Pet Study Group Measurement of clinical and subclinical tumor response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. Eur J Cancer. 1999;35:1773–82.
17. Kudo M, Kubo S, Takayasu K, et al. Liver Cancer Study Group of Japan Response evaluation criteria in cancer of the liver (RECICL) proposed by the Liver Cancer Study Group of Japan (2009 revised version). Hepatol Res. 2010;40:686–92.
18. Vassiliou V, Andreopoulos D. Assessment of therapeutic response in patients with metastatic skeletal disease: suggested modifications for the MDA response classification criteria. Br J Cancer. 2010;103(6):925–6.
19. Limouris GS, Toubanakis N, Shukla SK, et al. Prostate osseous metastases: evaluation of the combined application of disodium pamidronate/^{89}Sr-chloride/^{186}Re-HEDP. In: Bergmann H, Kroiss A, Sinzinger H, editors. Radioactive isotopes in clinical medicine and research XXII. Basel: © Birkhäuser Verlag; 1997.
20. Van der Veldt AA, Meijerink MR, van den Eertwegh AJ, et al. Choi response criteria for early prediction of clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. Br J Cancer. 2010;102:803–9.
21. Stacchiotti S, Negri T, Palassini E, et al. Sunitinib malate and figitumumab in solitary fibrous tumor: patterns and molecular bases of tumor response. Mol Cancer Ther. 2010;9:1286–97.
22. Faivre S, Zappa M, Vilgrain V, et al. Changes in tumor density in patients with advanced hepatocellular carcinoma treated with sunitinib. Clin Cancer Res. 2011;17:4504–12.
23. Kudo M, Han KH, Kokudo N, et al. Liver cancer working group report. Jpn J Clin Oncol. 2010;40:i19–27.
24. Hoos A, Parmiani G, Hege K, et al. A clinical development paradigm for cancer vaccines and related biologics. J Immunother. 2007;30(1):1–15.
25. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412–20.
26. Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst. 2010;102:1388–97.