Imaging Criteria for Tumor Treatment Response Evaluation

2

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The evaluation of the tumor response to therapy represents a significant and continuously expanding part of the radiological practice, especially in services with oncological departments. The modern imaging modalities are valuable tools for objective quantitative assessment of the result of new antineoplastic therapeutic schemes. The standardization of criteria provides common endpoints for clinical trials, permits comparisons between different studies, facilitates the formation of more effective therapies and accelerates the procedure of approval of new drugs by the authorized organizations. The most widely used imaging criterion of a successful therapy is the shrinkage of the neoplastic lesions in a certain patient. It represents the typical endpoint in phase II trials, targeted to the preliminary evaluation of the effectiveness of new antineoplastic drugs in order to decide if these have to be further tested in wider clinical studies. Also, the objective criterion of "tumor shrinkage" and the duration of "progression free survival " (PFS) represent the commonest endpoints for phase III clinical trials, aiming to assess the benefit of applying one or more therapeutic schemes in specific patient populations.

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In parallel, the degree of shrinkage of the total tumor burden is widely used in the routine oncological practice in order to assess the therapeutic result in every patient and guide decisions for further clinical management. However, it has to be noted that the most important proof of an effective antineoplastic therapy is the improvement of clinical symptoms and overall survival.

2.1 The Response Evaluation Criteria of the World Health Organization

The first organized attempt for introducing standardized criteria for assessing tumor response, mostly for use in phase II trials, appeared in 1981 through a working group of experts under the auspices of the World Health Organization (WHO). According to the methodology proposed by the "WHO guidelines", in a patient with neoplastic disease the maximum diameter and the greater diameter perpendicular to the previous had to be measured on each neoplastic lesion, providing a numeric product. The sum of the products of all the neoplastic lesions represents the objective criterion of the measurable tumor burden, and its changes during and at the end of therapy permit the assessment of tumor response [1].

During the following two decades, the WHO criteria were adopted by many research groups and pharmaceutical companies and used in

A. D. Gouliamos et al. (eds.), *Imaging in Clinical Oncology*,
DOI: 10.1007/978-88-470-5385-4_2,

numerous phase II and III trials. However, the remarks that arose from their use and the wide application of new imaging modalities imposed the need for modifications, in order to overcome some imperfections and ambiguities of the initial guidelines. An international working group of experts was constituted in 1994, in order to reevaluate and modify the WHO criteria.

2.2 The Response Evaluation Criteria in Solid Tumors

Based on the proposals of the previously mentioned working group, finally the WHO, the National Cancer Institute of USA and the European Organization for the Research and Therapy of Cancer (EORTC), adopted in 2000 new guidelines, named Response Evaluation Criteria In Solid Tumors (RECIST) [2]. They incorporated the use of new imaging technologies that have appeared, matured, and gained wide clinical application, such as spiral computed tomography (CT) and Magnetic Resonance Imaging (MRI).

With RECIST, the terms of "measurable" and "non-measurable" disease were more clearly defined. Also, the procedure for selecting the most representative neoplastic lesions that have to be measured and followed ("target lesions") was better described. Specifically, it was defined that the "target lesions" must be selected among the largest, be representative of all the organs affected by the neoplasia and should not be more than ten (10) in total and five (5) per organ. The measurement of the size of "target lesions" was simplified, by taking into account only the greater transverse diameter of each lesion and not the product of two perpendicular diameters as with WHO criteria. Additionally, the term of "non target lesions" was introduced and the way of evaluating their changes was described. Finally, the methodology of assessing the "overall response" to therapy was more clearly defined.

The RECIST has been widely adopted by academic institutions, medical research groups, and pharmaceutical companies and were applied in trials where the main endpoints were the "objective response to therapy" or the "time-to-progression" of the disease. The simplification of the measurement methodology did not seem to influence the reliability of RECIST, compared to WHO criteria. However, together with the wider acceptance and application of RECIST, problems and imperfections were noted regarding their use for evaluation of specific neoplasms, such as pleural mesothelioma and tumors of childhood. Also, the decrease of the number of target lesions, the evaluation of abnormally enlarged lymph nodes, the substitution of unidimensional by three-dimensional (3D) measurement, and the incorporation of newer imaging modalities (providing molecular and "functional" imaging), were proposed.

In order to address all these issues, a new RECIST working group was constituted, including clinical doctors experienced in the development and evaluation of new drugs, representing academic sites, state health organizations, and the pharmaceutical industry, together with imaging specialists and statisticians. The group evaluated the database of EORTC, including more than 6,500 patients with more than 18,000 target lesions, and its work resulted in the first revision of RECIST 1.1, published in 2009.

2.3 The Revision 1.1 of RECIST [3]

2.3.1 Aim of Guideline RECIST 1.1

It was defined as the introduction of a new standardized procedure of measuring the extent of solid tumors and a methodology of objective evaluation of its changes, for use in clinical trials concerning neoplasias both of adulthood and childhood. It was, also, stated that it may be applied in trials for brain gliomas, although there are other criteria in wider use [4] (see Sect. III-CNS Tumors). Additionally, it was clarified that this guideline is not proposed for use in trials assessing the response of malignant lymphomas, where other widely accepted guidelines are considered to be more appropriate [5] (see section VI-Lymphoma).

Although there were proposals of incorporating the use of 3D volumetric measurements of the neoplastic lesions and of functional techniques (such as ^{18}F-FDG-PET, dynamic contrast-enhanced CT, dynamic, and functional MRI techniques), it was judged that there is still not efficient standardization nor wide availability of these modalities in order to be adopted into the frame of a general official guideline. However, ^{18}F-FDG-PET has been officially accepted as a complementary method of assessing the extent and progression of some specific neoplasias, in terms of special therapeutic protocols (see Sects. I, IV, VI, IX, XII).

2.3.2 Assessment of Measurable Tumor Burden

A neoplastic disease affecting a specific patient is defined as "measurable" if it includes at least one "measurable lesion". To consider a lesion as measurable, it must be possible to define with accuracy its greatest diameter and this should be at least 10 mm on the transverse CT or MRI slices (given that the slice thickness is $\leq$5 mm) (Fig. 2.1a, b). Although conventional radiographs are nowadays very rarely used for therapy assessment (e.g., in lung tumors), RECIST guideline implies that a measurable lesion on them has to be $\geq$20 mm. Regarding the lymph nodes (its measurement was first introduced in the RECIST 1.1 edition), in order to be characterized as abnormally enlarged and "measurable", their short axis diameter must be $\geq$15 mm on transverse CT slices (given the slice thickness is $\leq$5 mm). It has to be noted that only the short axis diameter of the affected lymph nodes has to measured, since it has been shown that it offers more reproducible measurements than the long axis (Fig. 2.1c).

All measurements should be performed using the "metric system", in centimeters (cm) or millimeters (mm), and on the transverse plane, with the exception of some neoplasias where, due to their growth pattern, the measurement is more representative when performed on the sagittal or coronal plane (as in cases of paraspinal tumors). In any case, repeat measurements during follow-up studies should always be performed on the same imaging plane.

As "non-measurable" are considered all the remaining lesions, including those with a maximum long axis transverse diameter <10 mm, enlarged lymph nodes with a short axis diameter $\geq$10 mm but <15 mm and, also, all the tiny and difficult-to-be-measured foci. The latter include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, carcinomatous lymphangitis of the lung or skin, abdominal masses which are clinically detectable but not amenable to reproducible measurements with the currently recommended imaging techniques (Fig. 2.1d).

According to the RECIST 1.1 guidelines, secondary deposits to the bones cannot be reliably measured by means of bone scanning, ^{18}F-FDG-PET or radiographs. However, it is estimated that these imaging modalities can be used to assess the presence or elimination of the bone lesions. It is, also, clarified that secondary deposits to the bones of lytic or mixed type which are accompanied by CT or MRI detectable soft tissue masses, may be considered as "measurable" lesions if the accompanying soft tissue mass fulfills the definition described above (Fig. 2.1e). Sclerotic bone lesions are by definition "non-measurable".

Neoplastic lesions previously treated (e.g., with radiotherapy), may be considered as measurable, only if the presence of active disease in them was previously established with biopsy or cytology.

2.3.3 Evaluation of Response to Therapy [3, 6–8]

During the first (baseline) examination, which has to be performed within 4 weeks before starting therapy, it is imperative to assess accurately the total tumor burden, in order to have a reference of comparison for the new measurements during follow-up.

After assessing the presence of "measurable disease" (as defined previously) in a certain patient, the next step is to define "target" and

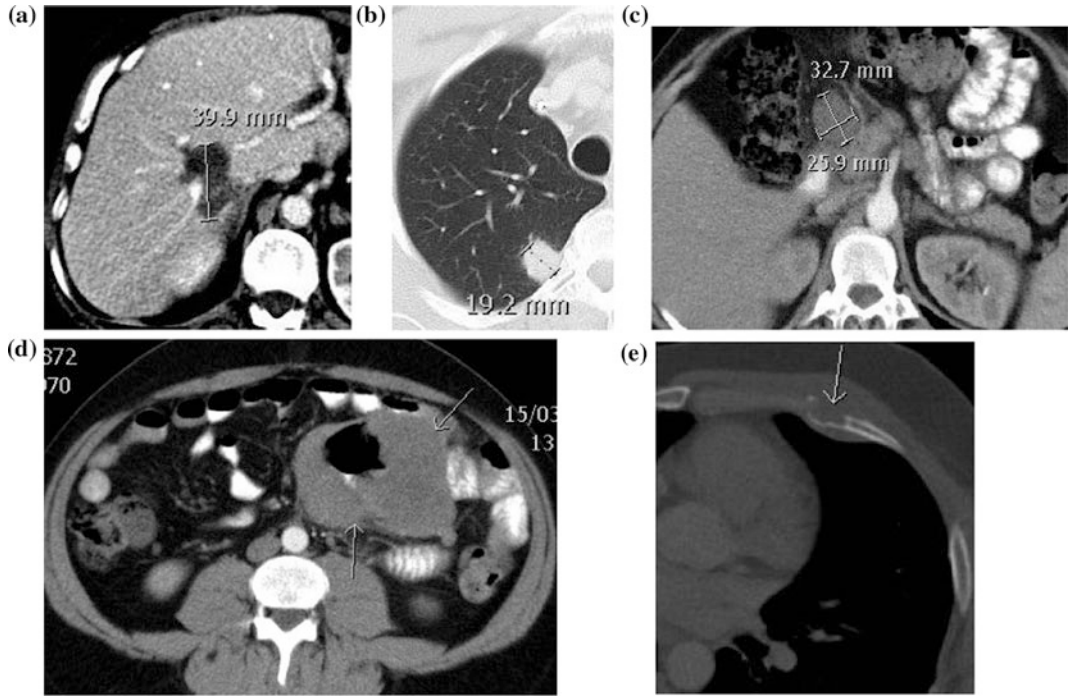

Fig. 2.1 Measurable disease: "target" and "non-target" lesions. Selected images from a CT scan of thorax and abdomen, performed in terms of the baseline examination of a patient with metastatic melanoma of the skin, before the initiation of chemotherapy. Two secondary deposits at the *right* hepatic lobe (**a**) and *right* upper pulmonary lobe (**b**) are shown, which have a maximum transverse diameter >1 cm and, hence, they fulfill the criteria to be defined as "measurable lesions" and be selected as "target lesions". The maximum diameters of these two lesions (4 cm and 1.9 cm, respectively) will be incorporated in the "total sum of diameters" of all target lesions. Also, an abnormally enlarged lymph node is depicted in the abdomen (**c**) which has a short axis transverse diameter of 2.6 cm (>1.5 cm); consequently, it can also be selected as a "target-lesion". In the "total sum of diameters" of target lesions, the short axis diameter of 2.6 cm (not the long axis diameter of 3.3 cm!) of the lymph node must be encountered. On image (**d**), the largest secondary deposit in this patient is shown, located in the small bowel wall. However, despite its large size, this lesion is not recommended to be selected as "target-lesion", since its location on the bowel wall makes its appearance on transverse slices unstable and, hence, the corresponding measurements of its diameter during the follow-up studies will lack reproducibility. On the image (**e**), a small lytic secondary deposit in the anterior part of a left rib is depicted (*arrow*), with a small accompanying soft tissue mass <1 cm, which is considered as a "non-measurable" lesion

"non-target" lesions. According to RECIST 1.1 guidelines, as "target lesions" are selected up to five measurable lesions per patient (while in the initial RECIST guideline they could be up to 10). These must be selected in order to be representative of all the organs affected by the neoplasia and, generally, should not exceed two lesions per organ (while in the initial RECIST, they could be selected up to five target lesions per organ). The selection criteria of target lesions are their size (the larger lesions in each organ should be chosen) and their suitability for reproducible repetitive measurements (Fig. 2.1a, b, d). It is advised to prefer non-cystic lesions, instead of cystic or necrotic. Also, they have to be representative of all organs affected by the tumor. In each follow-up (CT or MRI) examination, the longest diameter of each target lesion has to be measured on the transverse slice and with the direction that reflects better its size (Fig. 2.1a, b). If a target lesion separates during follow-up into more than one fragments, the sum of the longest diameters of these fragments has to be measured (Fig. 2.2). In the case that two

adjacent target lesions coalesce (without leaving a plane of normal tissue between them), then the longest diameter of the new lesion has to be measured (Fig. 2.3). If a target lesion becomes, during follow-up, too small to be measured accurately, its diameter that will be added to the sum is advised to be, by default, 5 mm.

Enlarged lymph nodes with a short axis diameter ≥15 mm can also be selected as target lesions (Fig. 2.1c). On follow-up studies, if the maximum short-axis diameter of a "target nodal lesion" reduces below 10 mm, this is no longer considered pathologic but it still has to be measured on future studies in order to assess a possible progression.

After selecting and recording the target lesions, the sum of the largest long axis diameters of all the non-nodal lesions and the short axis diameters of the selected lymph nodes, has to be calculated. During follow-up, the changes of this "sum of diameters" provide the measure for assessing the objective response of the neoplastic disease to therapy. It is important that the same target lesions (initially selected on the baseline examination) have to be measured on every follow-up examination. For all the remaining measurable lesions, which were not selected as target lesions (including, also, all the enlarged lymph nodes with a short-axis diameter 10–15 mm), there is no need to measure their diameters during follow-up, but simply to record on each examination their presence or absence or any "unequivocal increase of their extent". Based on these changes, the response of the "non-target" lesions is assumed. The final judgment concerning the "overall response" must take into account both the "target" and "non-target" lesions and, also, the appearance or not of new lesions during follow-up. It has to be noted that, in order to categorize a patient case as "stable disease" (SD) or "progressive disease" (PD), one must not use as reference the measurements of the baseline examination but, instead, the measurements of the examination where the smallest "sum of diameters" was encountered (occasionally, this examination could be the baseline one).

There are not strict guidelines regarding the frequency of follow-up examinations. However, it is generally recommended to perform follow-up studies at the end of each chemotherapy cycle (usually every 6–8 weeks), at least

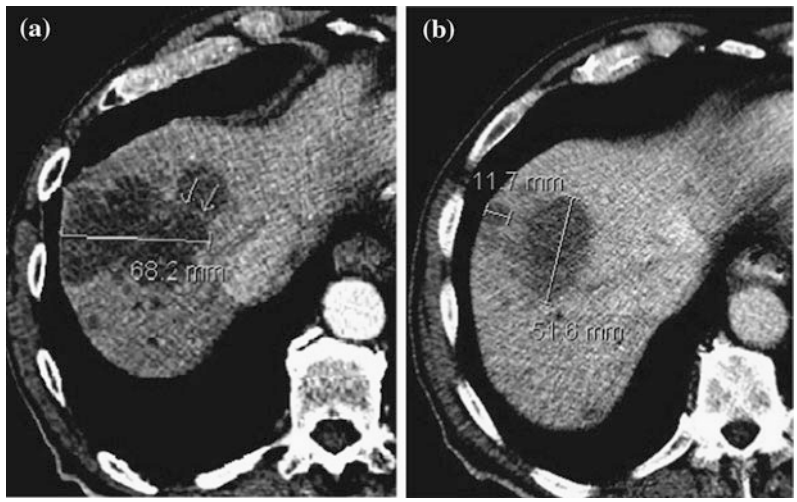

Fig. 2.2 Splitting lesions. On a CT image (**a**) a metastatic "target" lesion in the liver is shown, with a maximum diameter of 68.2 mm, which is separated from another adjacent lesion by a thin line of normal-appearing liver parenchyma (*arrows*). On follow-up CT (**b**), after effective chemotherapy, the previous lesion has split in two smaller adjacent lesions, clearly separated by normal-appearing liver tissue. Eventually, the longest transverse diameters of the two resulting lesions (51.6 and 11.7 mm) must be added in the sum of diameters of target lesions

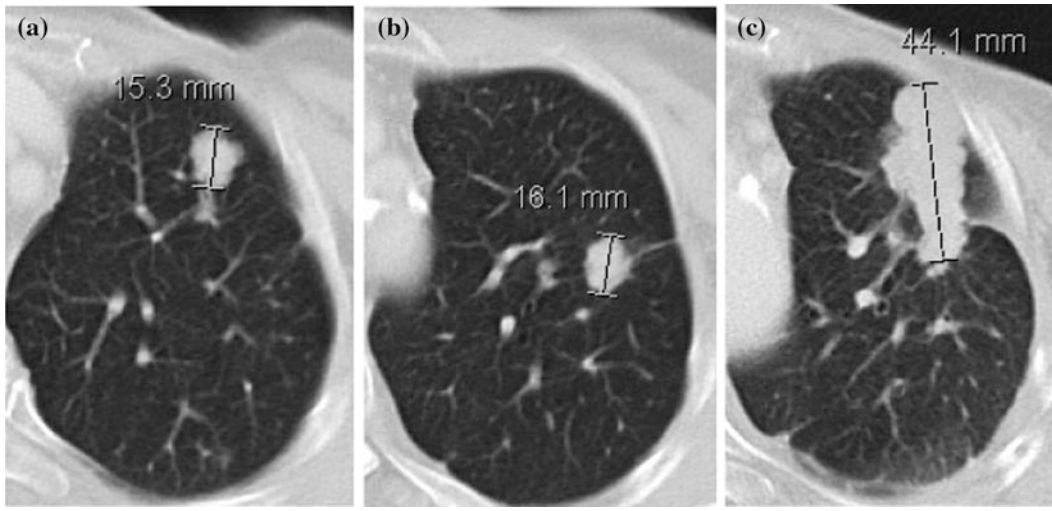

Fig. 2.3 Coalescent lesions. Two secondary deposits, selected as target lesions, in the *left upper* pulmonary lobe (**a**, **b**) have increased in size on the follow-up CT (**c**) and merged in a larger lesion. The largest transverse diameter of the latter must now be added in the sum of diameters of target lesions

in terms of phase II trials where the benefit of the therapy is unknown. The assessment of the "overall response to therapy" is performed on the results of the final examination at the end of therapy.

Evaluation of the Response of "Target-Lesions"

According to RECIST 1.1, the definitions on which the response evaluation is based are as follows:

Complete Response (CR): disappearance of all target-lesions. Additionally, every previously enlarged lymph node must have a decreased short axis diameter not exceeding 10 mm.

Partial Response (PR): decrease of the baseline "sum of diameters" of the target-lesions ≥30 %.

Progressive Disease (PD): increase of the "sum of diameters" of the target lesions of at least 20 % in comparison to the smallest value of this sum that was encountered during the whole period of the study (including the baseline sum). Additionally, the "sum of diameters of target lesions" must have shown an absolute increase of at least 5 mm (this criterion was not included in the first RECIST guideline).

Stable Disease (SD): changes of the "sum of diameters of target lesions" which do not fulfill the criteria for PR or PD (Fig. 2.4).

It must be noted that RECIST 1.1 includes detailed instructions concerning the methodology of measurement of target lesions, on the baseline and the follow-up imaging studies.

Evaluation of the Response of "Non-Target" Lesions

Non-target lesions must be evaluated only qualitatively (present, absent, or unequivocally larger), even if their diameters seem to be measurable. The corresponding criteria and definitions for response evaluation are as follows:

Complete Response (CR): disappearance of all the non-target lesions. All lymph nodes must have a short-axis diameter <10 mm. Additionally, tumor marker levels must be within normal limits.

Progressive Disease (PD): unequivocal increase of the size/extent of preexisting non-target lesions (Fig. 2.5).

Non-CR/non-PD: residual one or more non-target lesions and/or tumor markers measured above the normal levels.

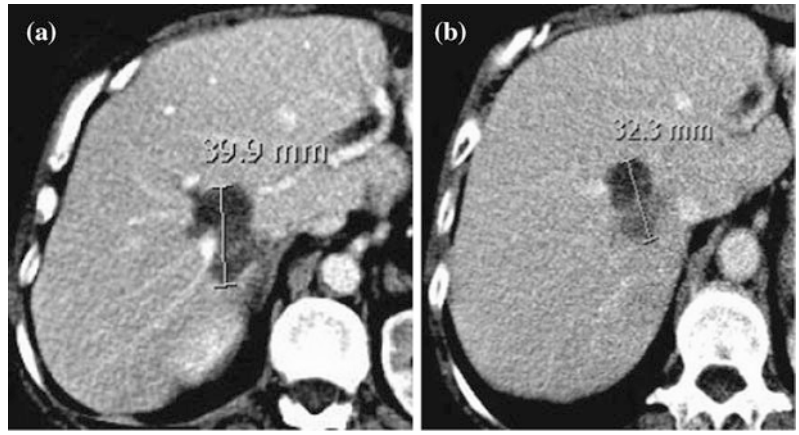

Fig. 2.4 Stable disease. Secondary deposit to the liver, from skin melanoma. On a transverse image from a baseline contrast-enhanced CT, performed before chemotherapy, the maximum diameter of the hepatic lesion is measured 4 cm (**a**). On the corresponding image of the follow-up CT study, performed after one cycle of chemotherapy (**b**), the maximum diameter of this "target lesion" is measured 3.2 cm. The 20 % decrease of the maximum diameter of the lesion does not accomplish the definition of partial response (it should be at least 30 %). Consequently, the status of this specific lesion has to be assessed as "stable disease"

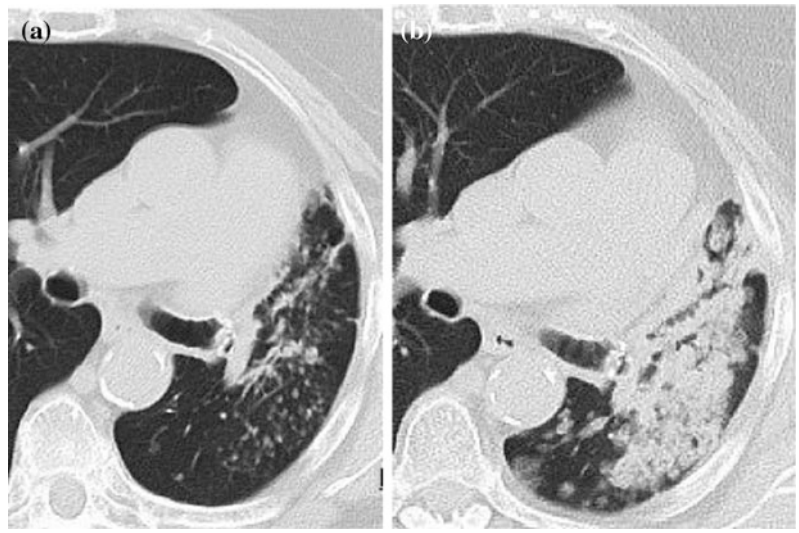

Fig. 2.5 Non-measurable disease, unequivocal progression. A slice from a thorax CT scan (**a**) of a patient with previous left upper lobectomy (due to lung cancer), shows multiple micronodular secondary deposits measuring only a few mm each, at the left lower lobe. Due to their tiny size, they are classified as "non-measurable disease". On the corresponding CT slice of the follow-up examination (**b**) a significant increase of the number and size of the lesions is observed, many of which coalesce, forming a large ill-defined mass. This change obviously represents an "unequivocal progression" of the disease

The RECIST 1.1 includes clarifications concerning the "unequivocal progression" of non-target lesions and guidelines for the methodology of evaluating response in patients with only "non-measurable" disease, since such patients may be included in the population of

phase III clinical trials. In cases where non-target lesions show unequivocal increase (PD), while target lesions show PR or SD, the overall response is assessed as PD only if the progression of non-target lesions seems to increase substantially the overall tumor burden. A mild to moderate increase of only few non-target lesions, while the other lesions (target and non-target) show SD or PR, is not considered sufficient to change the overall response assessment to PD.

Evaluation of New Lesions

The appearance of new malignant lesions indicates PD, given that these are unequivocal, meaning not depended on the imaging modality and its technique and do not represent a false diagnosis. All the previous are very important, especially when the lesions (target and non-target) of baseline examination show PR or CR.

A lesion detected during follow-up at an anatomic area that was not included in the baseline study, it has to be considered by definition as "new lesion" indicating PD. For that reason, the protocol of each trial must provide to include in the baseline study all the anatomic areas that may be potentially affected by the specific neoplasia. If it is not certain that a new lesion represents neoplasia, its nature must be clarified during the follow-up.

Although ^{18}F-FDG-PET is not included in the basic imaging modalities proposed by RECIST 1.1, it could be used in selected cases as an additional method to confirm new lesions and verify cases of PD. According to the algorithm defined by this guideline, if a ^{18}F-FDG-PET scan performed during follow-up becomes positive while a baseline ^{18}F-FDG-PET was negative, this represents PD. If there is no available baseline ^{18}F-FDG-PET scan, but such a study performed during follow-up is positive for new sites of the disease, this situation is determined as PD only in the case that the new lesions are detectable by CT either at the same time-point (but not at baseline CT) or later during the following imaging studies [3, 7].

Assessment of the Best Overall Response

Best Overall Response (BOR) is defined as the best response encountered since the beginning of the evaluated therapy, till its completion. It is influenced by the changes of target and non-target lesions and by the appearance or not of new lesions. The methodology of evaluating BOR is described in detail in RECIST 1.1 guideline. As previously stated, depending on the type of the trial and the demands of its protocol, there may be a need for confirmation of this evaluation. Specifically, confirmation of a PR or CR with new imaging studies after at least 4 weeks, is required only in non-randomized trials in which objective response is the primary endpoint. It has to be noted that, according to RECIST 1.1, lesions must show larger increase to be categorized as PD, compared to WHO and RECIST 1.0 guideline [7, 8].

2.3.4 Recommendations and Guidelines for Performing Imaging Examinations

The recent RECIST 1.1 edition includes an appendix, where basic guidelines for the standardization of performing imaging studies, mainly CT and MRI, are offered. According to these guidelines, it is preferable to use systems of latest technology (such as multi-slice CT scanners), adequate and standardized scanning technique, protocols with reduced radiation dose and appropriate contrast media at the proper dose and way of administration [3, 6].

Computed Tomography (CT)

It is defined as the basic imaging study for the follow-up of patients with most types of neoplastic disease and for the assessment of therapeutic result. Significant issues are the full coverage of the possible anatomic extent of the disease, the slice thickness, the slice gap and the proper use of contrast media.

The baseline CT examination should cover all the anatomic areas of possible spread of the specific tumor. It is noted that the maximum diameter of a target lesion must be measured only on the transverse plane. In case of using a CT scanner of spiral of multislice technology, which is the common practice nowadays, a target lesion must have a minimum transverse diameter of at least 10 mm, given that the CT slices are reconstructed with a slice thickness $\leq$5 mm and without gap. The aim of this rule is to reduce the effect of "partial volume averaging" which may lead to underestimation of the size of a lesion. All the above are applicable to most anatomic areas and specifically to thoracic, abdominal, and pelvic lesions. Regarding the anatomic areas where the typical thickness of CT slices is less than 5 mm (e.g., the neck) and, also, patients with small size and children, the smaller transverse diameter of a measurable lesion in order to be selected as "target lesion" may vary according to the rule of "twice the slice thickness".

According to RECIST 1.1, the administration of diluted contrast medium per os is recommended in all CT scans of abdomen and pelvis.

The intravenous (IV) administration of iodinated contrast medium is recommended even in types of neoplasia where the data from studies do not favor such use. However, it is also noted that the IV contrast medium (CM) can be avoided when only a specific lesion in the lung is followed. It is obvious that IV use of CM must be avoided in cases of patients with allergy to iodine or renal insufficiency. However, RECIST 1.1 does not include specific guidelines concerning the optimal dose, the way of IV administration (with power injector or manually) and the flow rate of the CM. It is simply stated that this must be performed with adequate manner. The recent RECIST 1.1 edition incorporates additional recommendations concerning the examination protocol of liver and solid viscera of the abdomen after bolus IV injection of CM. Specifically, in most neoplasias a single post-contrast scanning at portal venous phase is considered to be efficient. A triphasic study (one scan before and two scans after bolus IV injection of CM, at arterial and portal venous phase) is recommended specifically for the hepatocellular cancer and the neuroendocrine tumors. If the IV use of iodinated CM is contraindicated in a patient, usually due to allergy or renal insufficiency that were previously known or appeared during the survey, it must be decided if the follow-up studies will be performed with noncontrast-enhanced CT or, alternatively, with MRI.

Magnetic Resonance Imaging (MRI)

According to RECIST 1.1, MRI may be used as an alternative to CT for measurements in most neoplasias, excluding those involving the lungs. It is well known that the clinical applications of MRI in oncological imaging are continuously expanding since the first edition of RECIST, while it is also considered as examination of choice or first-line in some specific neoplasias, like in children and young adults. Specifically, in childhood neoplasias, MRI offers better estimation of the extent of the disease (paraspinal/intracanalicular neuroblastoma is a typical example) and it does not involve the use of potentially harmful radiation.

It has to be noted that the measurements must always be performed on the same imaging plane (preferably on the transverse) and, if possible, the serial examinations must be done in magnets of the same type and with the same or similar pulse sequences. In general, the use of magnets of different power must be avoided during follow-up studies. The recent RECIST 1.1 edition does not include detailed guidelines regarding the specific parameters of the pulse sequences. It is simply recommended to use standardized T1-W and T2-W sequences, with and without fat suppression, before and after IV injection of paramagnetic contrast medium, which have to be suitable for each anatomic area studied and also, for the type of MR system used.

The size criteria for selecting "measurable" and "target" lesions depend on the slice thickness of the images as it is previously described in detail in the section for CT.

Ultrasonography (US)

According to RECIST 1.1 guideline, US must not be systematically used for evaluating the response of tumors to therapy, with the exception of superficially located lesions. This guideline is based on the fact that US is not an objective examination, since it is operator-dependent. Additionally, US do not provide reproducible images, adequate for future reevaluation.

Positron Emission Tomography (PET)

Although the use of PET in some types of neoplasia (such as lymphomas, non-small cell lung cancer-NSCLC- and melanoma) is already established and continuously expanding, the expert authors of RECIST 1.1 guideline estimated that there are still no standardized criteria which can permit the full incorporation of this modality (usually performed in combination with CT, in terms of the "hybrid" examination PET/CT) in the protocols of phase II clinical trials. However, it is a fact that PET/CT is frequently used in studies evaluating the effectiveness of new antineoplastic drugs. For that reason, RECIST 1.1 authors accept the use of FDG-PET as a complementary tool for assessing PR or PD.

2.3.5 Limitations of RECIST 1.1

The measurement of the size of a neoplastic lesion is a time-consuming procedure, susceptible to systematic and statistical errors, mainly due to interobserver and intraobserver variability regarding the estimation of the lesion borders. This may be particularly difficult in cases of lesions with irregular shape and spiculated borders or in small lesions and may eventually lead to a false categorization of the response (Fig. 2.6). Although RECIST 1.1 revision has addressed many of these issues, there are still sources of discrepancies in clinical practice. In terms of phase II trials, these causes of variability and inaccuracy may be counterbalanced or even eliminated through the use of independent evaluators, who reassess the data of measurements that were performed by the radiologists of the centers included in such studies.

Single center studies have shown that 3D volumetric measurements, using semi-automated or automated software, permit more accurate and reproducible assessment of the size of neoplastic lesions and its changes, compared to unidimensional measurements of RECIST and bidimensional measurements of WHO criteria. However, due to the variety and limited availability of such software tools which preclude their wide use, they were not incorporated in the RECIST 1.1 guideline [6, 9].

Some tumors, due to their growth pattern and shape, may be practically impossible to be measured with a reproducible manner. Malignant mesothelioma of the pleura represents a typical example of a neoplasia where the previously described methodology of RECIST 1.1 is not suitable. According to relative studies, it has been shown that the particular growth pattern and anatomical extension of this neoplasia can be more accurately assessed by measuring, on the selected transverse CT slices, the maximum diameter of the pleural lesions that is perpendicular to the adjacent part of the pleura, instead of the maximum longitudinal diameter according to RECIST 1.1 (Fig. 2.7). The evaluation of the size of other measurable lesions of the mesothelioma except of pleural lesions, including infiltrated lymph nodes, is performed according to the guidelines of RECIST 1.1 and the corresponding measurements are added to the sum of diameters of pleural lesions. The total sum of these diameters is counted and its changes, during the follow-up studies and at the end of therapy, represent the criterion for evaluating the response of mesothelioma to therapy. However, there are still problems and inconsistencies regarding the standardization of the methodology of measuring the lesions of pleural mesothelioma, which impose the need for accurate description of the way of selecting and evaluating measurable and target lesions in the protocol of each study targeted on this type of neoplasia [10].

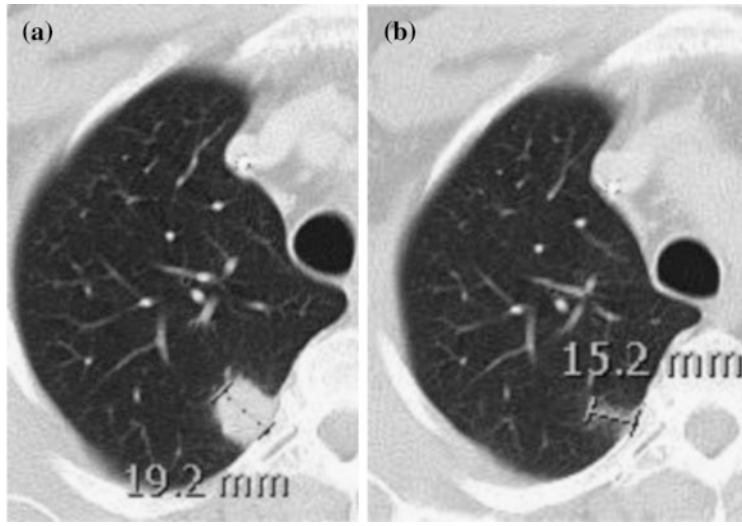

Fig. 2.6 Limitations of RECIST 1.1. CT of the thorax of a patient with metastatic melanoma at the right upper pulmonary lobe. Before initiation of the therapy (**a**) the maximum transverse diameter of this ovoid solid lesion is 19.2 mm. After completion of chemotherapy, on the corresponding CT slice the lesion shows almost complete regression, with only a faint ill-defined soft tissue lesion remaining. This has a maximum transverse diameter of 15.2 mm and could be attributed to scar tissue, not necessarily residual disease. By strictly implementing the measurement methodology of RECIST 1.1, the maximum diameter of the lesion has decreased by 21 % (from 19.2 to 15.2 mm) a change that typically corresponds to "stable disease". However, taking into account the overall appearance and 3D dimensions of the lesion, the decrease of its volume is obviously very significant, almost reaching the limits of Complete Response, especially if the absence of active disease in it could be verified

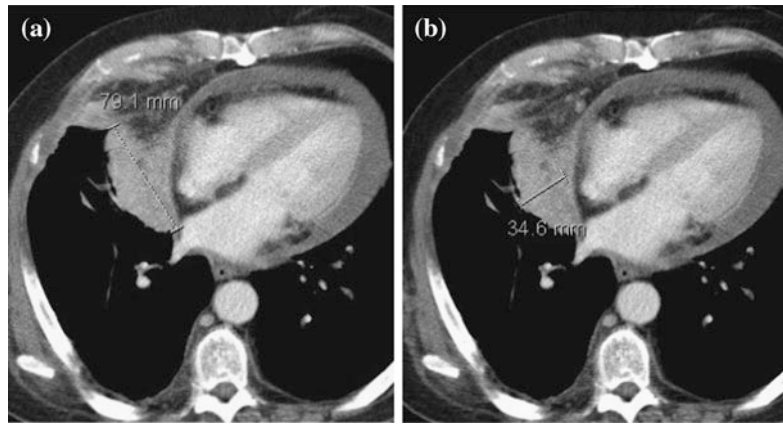

Fig. 2.7 Methodology for measuring on CT images the size of lesions of malignant mesothelioma. According to the general RECIST 1.1 guideline, on each area of pleural thickening that is selected as "target lesion" the longest transverse diameter should be measured (**a**). However, according to the modified RECIST criteria for mesothelioma (mRECIST), on each lesion the maximum diameter being perpendicular to the adjacent pleural segment has to be measured (**b**)

Another issue is the differentiation of neoplastic lesions from surrounding fibrosis or normal tissue, which in some cases may be difficult or even impossible based only on CT and MRI findings. If this differentiation is crucial for assessing CR, the ambiguous tissue must be sampled by core biopsy or fine needle aspiration and then characterized with histopathological or cytological examination, respectively. In this effort, ^{18}F-FDG-PET may be helpful in selected cases [3, 6–8]. However, both procedures have limitations regarding sensitivity and overall accuracy.

It is important to note that RECIST 1.1 are based on the assessment of the size change of neoplastic lesions, in order to evaluate the overall response of the disease to therapy. However, it is known that the shrinkage of a tumor is not always representative of the effect of therapy, especially when new antineoplastic drugs are used, which have rather a cytostatic than a cytotoxic action. Through several studies, it has been validated that, in such cases, the RECIST methodology often underestimates the objective response, while there may be clinical response and improved survival. Today, there are enough data imposing the use of modified criteria for assessing response in specific tumors and/or therapies, like hepatocellular carcinoma, gastrointestinal stromal tumors (GISTs) treated with imatinib mesylate, and hepatic metastases treated with antiangiogenic drugs. Also, the RECIST criteria are not reliable for assessing the therapeutic effect of radiofrequency ablation and cryoablation of liver lesions [6–8] (see Section I-chap. 4 and section IX).

As previously mentioned, RECIST guidelines do not incorporate the use of US for response assessment, although they accept and propose the clinical palpation, the endoscopic studies and the histopathological examination [3]. These latter cannot be considered as objective examinations since they are also highly operator-dependent. It worths consideration the fact that, in cases of patients with breast cancer, the evaluation of the size of the breast lesions by palpation is officially acceptable and recommended, while US evaluation is not. Also, US is a valuable tool in the daily practice of paediatric oncology, where the avoidance of radiation exposure is of major concern. Finally, recent studies confirm the usefulness of contrast-enhanced US in the evaluation of the therapeutic result after ablation of liver tumors or after the use of newer antiangiogenic therapies. These facts impose the need to reconsider the use of US in the aim of assessing the therapeutic result.

According to RECIST 1.1, ^{18}F-FDG-PET or PET/CT may be used selectively as a complementary tool for detecting active disease in residual masses and confirming the appearance of new neoplastic lesions [3]. Despite the validated usefulness of this modality in lymphomas and its growing use in NSCLC, breast cancer and colorectal cancer, the lack of standardization of data acquisition and evaluation criteria, precluded its incorporation in RECIST methodology. Recently, new guidelines for assessing solid tumors response to treatment, fully incorporating the use of ^{18}F-FDG-PET, have been proposed [11, 12].

New imaging techniques of dynamic contrast-enhanced CT and MRI and diffusion-weighted MRI, have shown promising results for assessing response of various tumors to new targeted therapies. However, they need further standardization and validation in order to be suitable for wider application and be incorporated in a future revision of RECIST guideline [12].

In conclusion, RECIST guidelines, including the last version 1.1 of 2009, are based on the assessment of the size changes of neoplastic lesions, in order to evaluate objectively the degree of response to therapy. Regarding the definition of different categories of response, there were not any essential changes, in comparison to the previous WHO guidelines. What has changed is the recognition of the importance of using newer imaging technologies as CT and MRI and the methodology of measuring the size of lesions (unidimensional instead of bidimensional measurements). Also, the estimation of the overall response to therapy is based on the change of all neoplastic lesions (target, measurable and non-measurable) and on the appearance or not of new lesions during follow-up. Finally, according to

RECIST 1.1, a larger increase of the total tumor burden is needed in order to categorize the case of a patient with neoplasia as "progressive disease".

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