Response Assessment to Cancer Therapy

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Contents

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Learning Objectives

By the end of the chapter the reader will

- Be able to choose the best imaging technique for cancer assessment.
- Have learned the basic concepts of radiological assessment criteria for cancer.
- Be able to apply the knowledge in daily clinical practice.

15.1 Diagnostic Criteria

15.1.1 RECIST

RECIST (Response Evaluation *Criteria* in Solid Tumours) is a guide to daily clinical practice for cancer management in patients.

The first version of RECIST was published in 2000 [1] and later revised in 2009 [2].

The latest version of RECIST criteria was published in 2009 (RECIST 1.1) [2].

This version was named RECIST 1.1 rather than RECIST 2.0 because the fundamental approach to cancer assessment remains the same, based on an anatomical assessment of the disease as opposed to a functional one.

The major changes between RECIST 1.0 and 1.1 are:

- The number of lesions to be assessed.
- The evaluation of pathological lymph nodes.
- Disease progression definition is clarified.

RECIST define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

The first important classification introduced by RECIST is in "measurable" and "non-measurable" lesions.

It is very important to classify as "measurable" or "non-measurable" baseline lesions.

"Measurable" lesions are defined as being at least 1 cm at CT scan (with a CT scan slice thickness no greater than 5 mm); 1 cm caliper measurement by clinical exam and 2 cm at chest X-ray.

Malignant lymph nodes are considered "pathologically enlarged" and measurable when the short axis is greater than 1.5 cm (Fig. 15.1).

Whereas all other pathological nodes (having a short axis between 10 and 15 mm) are identified as non-target lesions.

On the other hand, they do not need to be recorded or followed when the short axis is <10 mm because they are considered nonpathological.

Its important to underline that RECIST criteria consider only the lymph nodes' short axis both in the diagnosis and the follow-up phase.

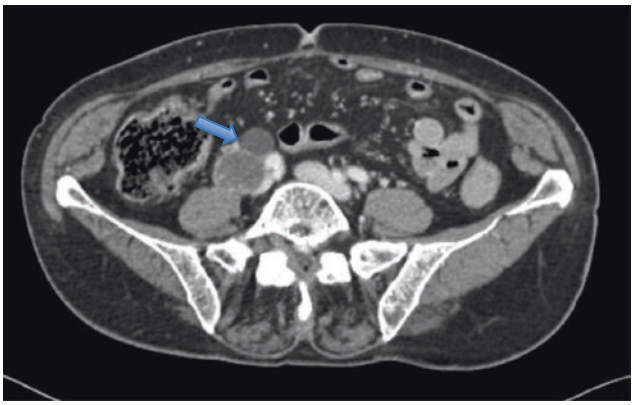

Fig. 15.1 The CT shows a pathologic iliac lymph node (arrow) in a patient with bladder cancer

By the way, we think that in radiological daily practice and not in research reporting, it could be useful for radiological and oncological follow-up to report nodes of short axis <10 mm.

On the other side "non-measurable" lesions are those where the longest diameter is inferior to 1 cm and pathological lymph nodes with a short axis between 1 cm and 1.5 cm.

Lesions which cannot be measured are always considered non-measurable.

Among "non-measurable" lesions authors list leptomeningeal disease, ascites, pleural and pericardial effusion, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly which can only be identified by means of a physical exam and not by reproducible imaging techniques.

Another important point is the definition of "target" and "non-target" lesions.

The radiologist tags lesions as "target" or "non-target" during the baseline examination; lesions should be representative and reproducible.

When more than one measurable lesion is present, all lesions up to a maximum of five (and a maximum of two per organ) should be chosen, recorded, and measured as "target" lesions, at baseline.

Particular consideration is reserved to the bone, cystic, and previously treated lesions. In particular:

- Blastic lesions are considered "non-measurable."
- Lesions with lytic and mixed lytic-blastic components are considered measurable only when the soft tissue component meets the criteria of a measurable lesion.
- Simple cysts are not considered malignant lesions (Fig. 15.2).
- Cystic lesions may be metastases, and when non cystic lesions are present in the same patient, cystic ones are not selected as target lesions.

Lesions located in a treated area are considered non-measurable unless a clear progression is shown.

Radiological evaluation should never be performed before 4 weeks from the beginning of treatment.

Analysis should always be performed using the same technique, and CT is acknowledged as being the best available and reproducible method to measure lesions selected for response assessment, and, as previously said, it is recommended to be applied to a slice thickness below 5 millimeters.

Another crucial point established from RECIST criteria is the definition of the four categories of response:

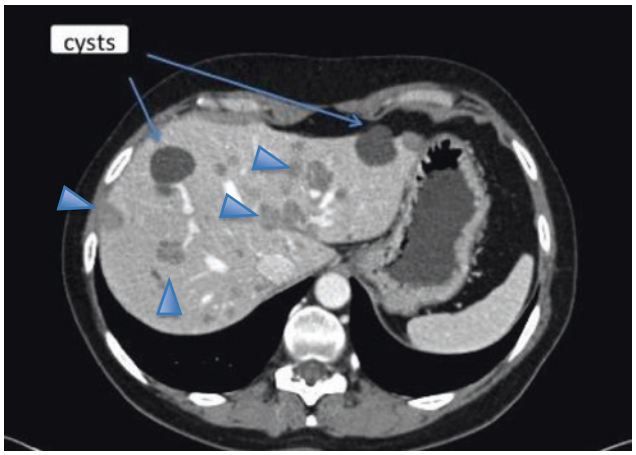

Fig. 15.2 Patient with liver metastases (arrowheads) and hepatic cysts (arrows)

- Complete response (CR): all target lesions disappear, and all pathological lymph nodes are reduced to a <10 mm short axis.
- Partial response (PR): there is at least a 30% reduction in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Stable disease (SD): shrinkage is not sufficient to define a partial response nor as progression because the increase is neither sufficient to define a progressive disease.
- Progressive disease (PD): the sum of diameters of target lesions shows at least a 20% increase and absolutely at least 5 mm.

There is also disease progression when one or more new lesions are found [2] (Figs. 15.3 and 15.4).

RECIST 1.1 recommends to analyze up to five lesions for lesion analysis, whereas the remaining lesions and sites of disease, including pathological lymph nodes, should be identified as "non-target lesions" [2].

FDG-PET scanning is sometimes considered reasonable in the assessment of disease progression.

There are, however, certain limitations in RECIST criteria due to differences in size measurements performed by different readers and in different moments by the same reader.

Margin irregularity may also be the cause of issue in the analysis of lesions [3] (Fig. 15.5).

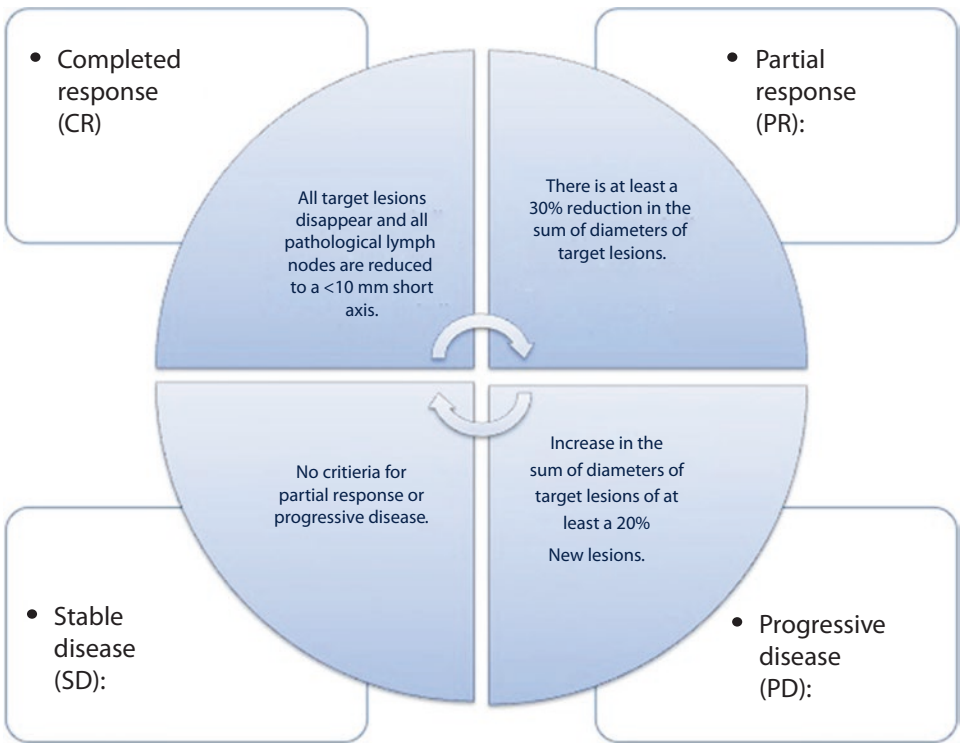

Fig. 15.3 RECIST criteria flowchart

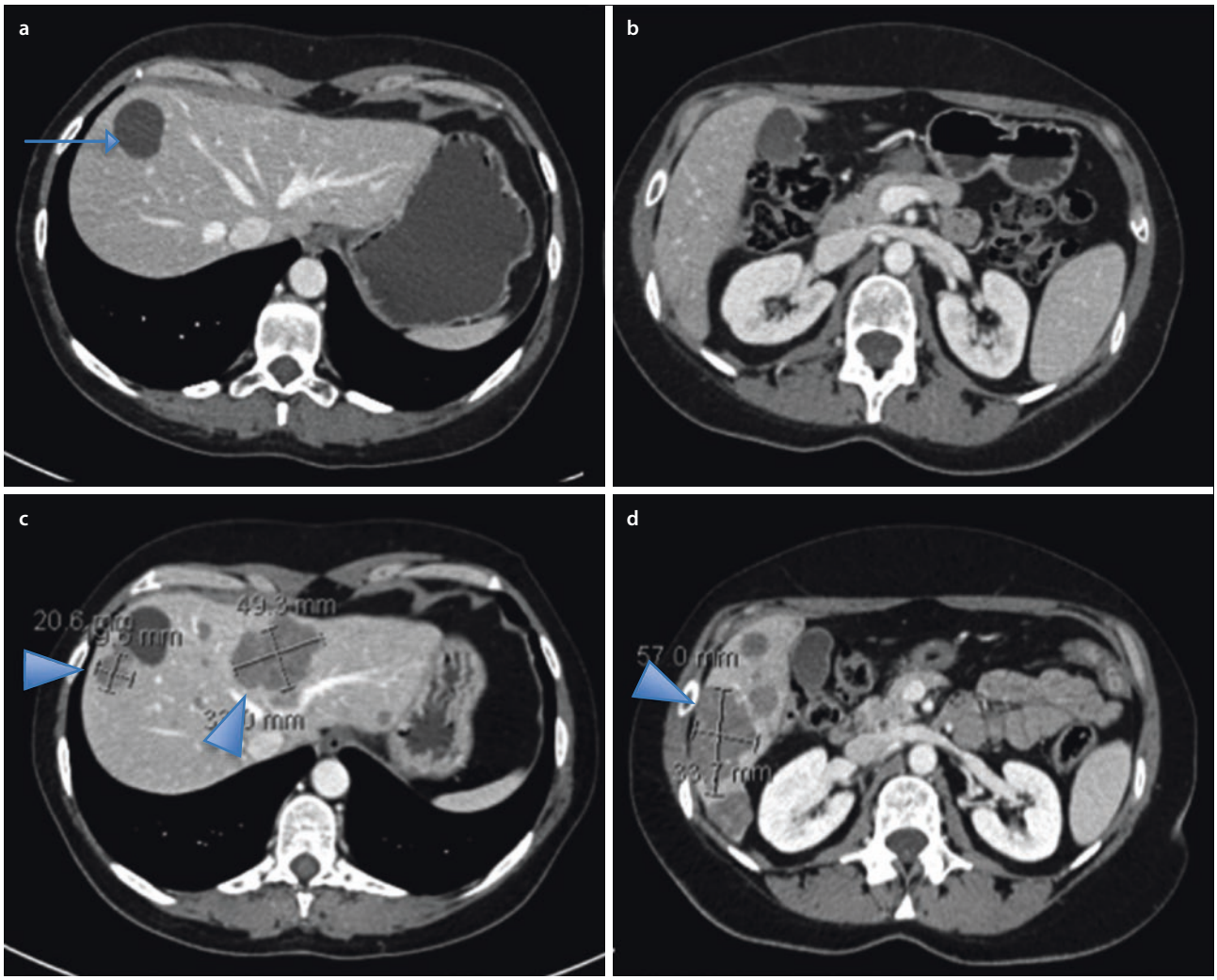

Fig. 15.4 A young woman with breast cancer and progressive disease according to RECIST criteria. The first CT scan showed only hepatic cysts (arrow in **a**). Appearance of liver metastases in the same patient after a few months (arrowheads in **c**–**d**)

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Recent findings show that limiting the evaluation to morphological criteria may determine a limitation in cancer assessment.

Metabolic tumor responses are assessed either with the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) or the European Organization for Research and Treatment of Cancer (EORTC) criteria.

The concordance of tumor responses between the morphologic criteria (RECIST) and metabolic criteria (EORTC and PERCIST) has been shown to be not excellent in a pooled analysis.

When adopting the metabolic criteria instead of the RECIST, overall response rates were significantly increased [4].

It is recommended to adapt frequency of tumor re-evaluation to the type and schedule of treatment.

Beyond RECIST criteria also tumor volume assessment could be useful.

Some findings have shown that volume measurement is more reproducible than size measurement in lung tumors [5, 6].

Zhao et al. demonstrated that volumetric tumor measurement is better than that of unidimensional and during gefitinib treatment it could be used to distinguish tumors with a sensitizing mutation from those without one [7].

Advances in CT technology have enabled vascular and perfusion assessment of lung lesions by using dynamic contrast-enhanced CT (DCE CT) [8].

Furthermore, tumor CT perfusion assessment in lung cancer has been shown to reflect tumor vascularity at histologic examinations [8].

In particular, several recent findings have evaluated changes in CT tumor perfusion by correlating perfusion parameters with RECIST response during treatment and survival.

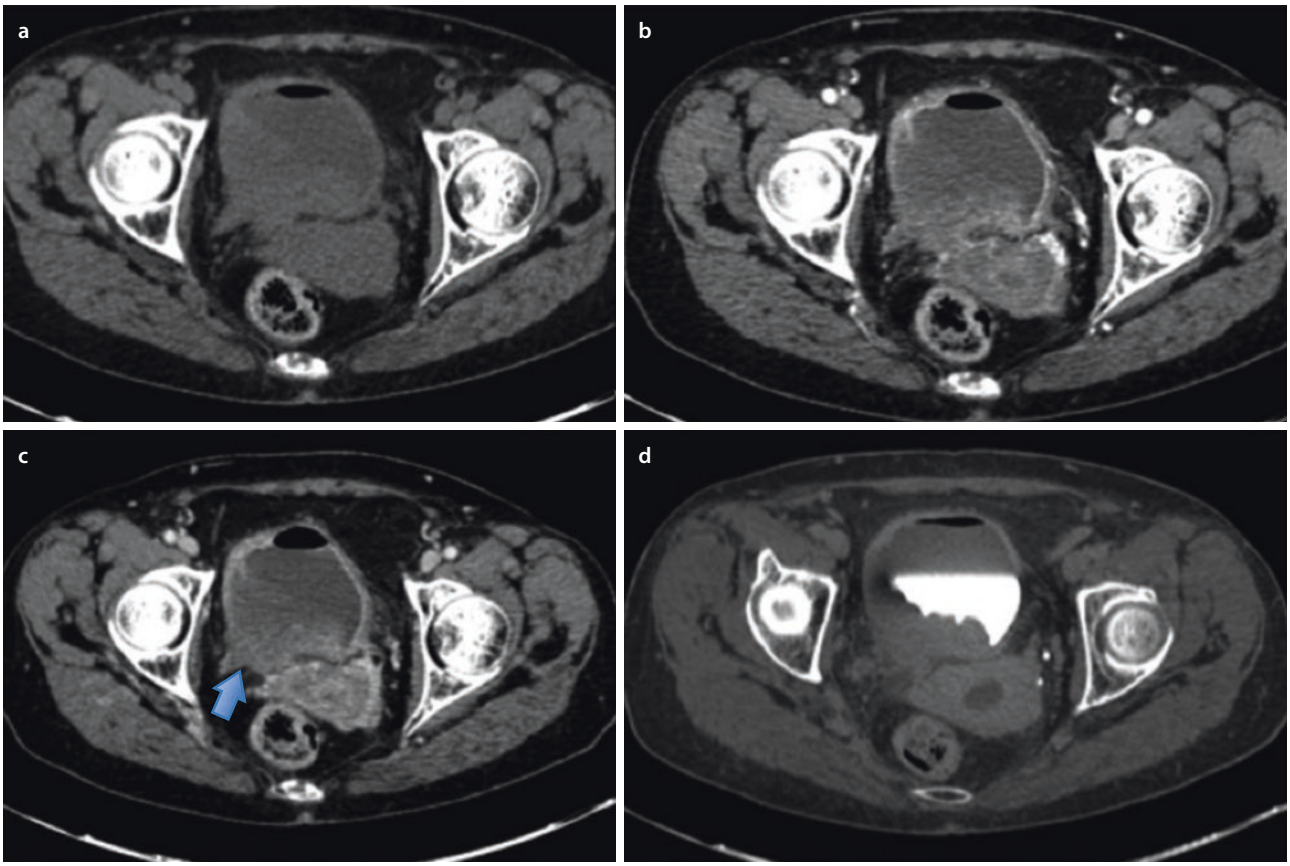

Fig. 15.5 CT examination of a patient affected by bladder cancer with irregular margins (arrow in C). **a**, pre-contrast image; **b**, arterial phase; **c**, portal venous phase; **d**, pyelographic phase

Non-small cell lung cancers with higher perfusion values are more sensitive to chemoradiation therapy than tumor with lower perfusion parameters [9].

Furthermore, authors showed that after chemoradiation therapy, findings at perfusion CT predict early tumor response and overall survival in the same cohort of patients [9].

Fraioli et al. [10] demonstrated, in a cohort of patients with unresectable lung adenocarcinoma who underwent perfusion CT before and 40 and 90 days after chemotherapy and antiangiogenetic treatment, that patients with partial response by RECIST criteria at 40-day follow-up had higher baseline blood flow and permeability compared with other patients. In conclusion perfusion CT may allow evaluation of lung cancer angiogenesis showing vascularity modifications after treatment [10].

To establish an appropriate threshold for tumor perfusion baseline and changes that may occur during the different therapies, it is necessary to introduce perfusion evaluation in daily clinical practice.

Quantitative evaluation of tumor perfusion by Dual-Energy CT could, in the near future, enter in daily clinical practice with new diagnostic criteria.

15.1.2 Targeted Therapies and CHOI Criteria

Targeted therapies arrest the growth and spread of cancer by interfering with specific molecules, the so-called molecular targets.

Usually molecular targets are involved in the growth and progression of cancer [11].

Indeed they achieve this goal by targeting specific genes or proteins found in cancer cells or in cells related to cancer growth like blood vessel cells [12].

Many of these therapies have an effect on proteins involved in cell signaling pathways,

governing basic cellular functions and activities such as the division, movement and responses of the cells to specific external stimuli, as well as cell death [3].

These therapies differ from the mechanisms of action of traditional cytotoxic chemotherapy.

Following the introduction of these news therapies, the need of new diagnostic criteria was felt owing to the growing awareness that cancer could respond to treatment and remain of the same dimension or grow but change in density.

15.1.2.1 Choi Response Criteria

Choi et al. [13] demonstrated that small changes in tumor size or density on CT are sensitive and specific procedures of response assessment of GISTs and proposed new diagnostic criteria for the evaluation of patients with GIST treated by imatinib.

Imatinib is a kinase inhibitor used to treat tumors like chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs) [14].

In particular gastrointestinal stromal tumors (GIST) are treated with imatinib [15].

GISTs are a particular kind of neoplasms that arise from special cells found in the wall of the gastrointestinal tract called the *interstitial cells of Cajal* (ICCs) [16].

Choi criteria arise from the finding that RECIST criteria, based exclusively on anatomic information only, underestimate the initial tumor response to imatinib in patients with metastatic GIST [13, 17].

At the same time, changes in tumor density were found by the authors who demonstrated that some lesions, despite clinical and PET response, increase in size.

It is believed that responding tumors decrease in density on CT because of the development of tumor necrosis, cystic, or myxoid degeneration.

Furthermore CT examination allows tumor density quantification in an objective manner, representing a valuable technique for cancer evaluation.

Measurements can be done objectively by using an optimal venous phase during the different examinations.

Furthermore, the CT triphasic imaging technique may facilitate the detection of lesions and the evaluation of tumor vascularity [17].

So, it is mandatory to use contrast medium delay automatic synchronization systems to obtain correct phases of post-contrast CT examination.

According to CHOI criteria [13], we can identify:

- Complete response (CR): when all the lesions disappear in the absence of new lesions.
- Partial response (PR): when there is a decrease in size (measured according to RECIST criteria) ≥10% or a decrease in tumor density (HU) ≥15% on CT examination, without new lesions and without progression of non-measurable lesions.
- Stable disease (SD): In the absence of criteria for CR, PR or progression of disease in the absence of symptomatic deterioration attributed to tumor progression (Fig. 15.6).
  - Progression of disease (PD): in case of an increase in tumor size ≥10% without criteria for partial response by tumor density on CT (HU), in case of new lesions or intratumoral nodules onset or dimensional growth (Fig. 15.7).

Despite its several limitations, CT is still considered the standard method for the evaluation of therapy response in patients with GIST.

The issue of intratumoral hemorrhage, which mimics disease progression, cannot indeed be solved by the Choi criteria.

Furthermore, patients with progressive GIST may present a "nodule in a mass" and not necessarily an overall increase in tumor volume because of a focal progression within a generally responsive lesion [18].

CT morphology-oriented criteria like the Choi criteria or the iodine-related attenuation measured on Dual-Energy CT have been recently developed and are more sensitive than the RECIST criteria, showing a greater correlation to the FDG changes.

An evaluation based on both changes in morphological and functional tumor data (like FDG metabolism and tumor perfusion) is required in patients with GIST [19].

15.1.3 Immunotherapeutics and iRECIST

Immunotherapy is a new a type of cancer treatment which fights cancer by strengthening the immune system.

There are several kinds of immunotherapy:

- Monoclonal antibodies
- Adoptive cell transfer
- Cytokines
- Treatment vaccines
- Bacillus Calmette-Guérin [20].

The concept of pseudoprogression was introduced by immunotherapy and described in patients with melanoma during early trials of immune-based therapeutics.

Authors noted that some patients with a RECIST diagnosis of progression showed late but deep and durable responses [21–25].

Authors proposed the modified RECIST 1.1 for immune-based therapeutics, the so-called iRECIST.

Responses related to iRECIST [26] method can be recognized by the "i" prefix (immune), as opposed to those related to RECIST 1.1.:

- —"Immune" complete response (iCR)
- —"Immune" partial response (iPR)
- —"Immune" unconfirmed progressive disease (iUPD)
- —"Immune" confirmed progressive disease (iCPD)
- —"Immune" stable disease (iSD)

The use of RECIST 1.1 is recommended to define measurable or non-measurable lesions, for the management

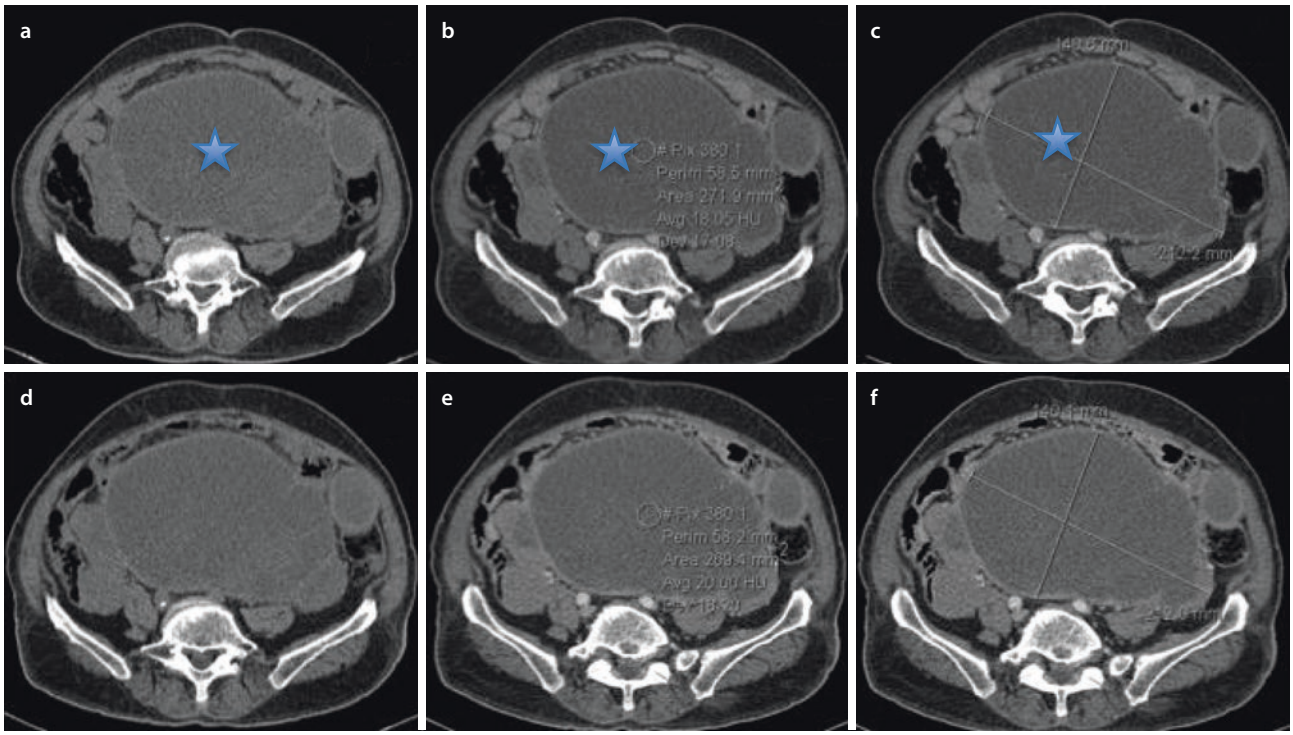

Fig. 15.6 Patient with GIST and stable disease after 1 year according to CHOI criteria. Images show stable density values and stable diameters (stars). **a**–**c** (first CT examination): **a**, non-contrast CT; **b**, **c**, post-contrast portal-venous acquisition. **d**–**f** (second CT examination): **d**, non-contrast CT; **e**, **f**, post-contrast portal-venous acquisition

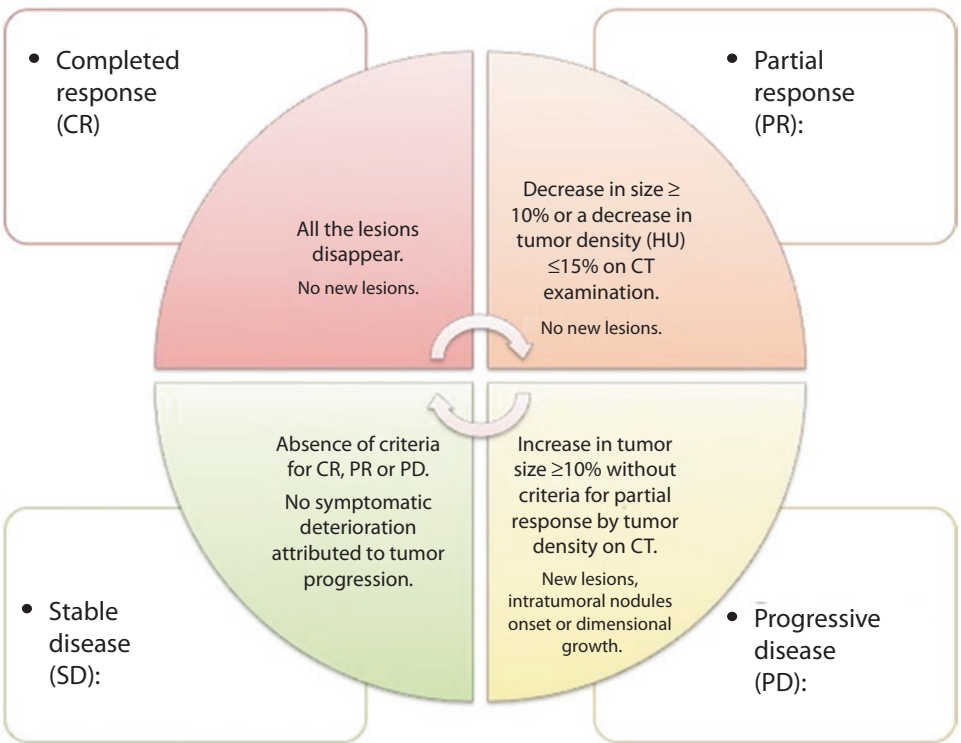

Fig. 15.7 CHOI criteria flowchart

of bone lesions, cystic lesions, and lesions with previous local treatment.

At the same time, the method of measurement was not changed by the authors.

The most important distinctive feature of iRECIST is that it resets the class of response if RECIST 1.1 progression is followed, at the next assessment, by tumor shrinkage.

In particular progression is confirmed if the next imaging assessment after unconfirmed progressive disease (4–8 weeks later) confirms a further increase in the sum of measures of target disease from iUPD of at least 5 mm [26].

15.2 Conclusion

The correct cancer assessment is crucial for the oncological patient's survival.

Radiologists must comprehend the adequate criteria for the definition of patient's response.

Development of new therapies is a challenge for radiologists.

In clinical practice, in our department, we usually make a report by using the appropriate diagnostic criteria.

At the same time, we write reports that can help clinicians in the interpretation of patient's clinical assessment.

The use of appropriate and international diagnostic criteria is important so as to share a common language between clinicians and radiologists all over the world.

Clinicians need to know the correct staging of the patient and understand changes in cancer features, also beyond the simple description of cancer dimension.

We can conclude that morphologic criteria should be used together with metabolic ones.

Key Points

- RECIST (response evaluation *criteria* in solid tumors) is a guide in daily clinical practice for cancer management; RECIST is define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.
- Choi response criteria arise from the finding that RECIST criteria, based exclusively on anatomic information only, underestimate the initial tumor response to imatinib in patients with metastatic GIST.
- iRECIST are a kind of modified RECIST 1.1 for immune-based therapeutics.

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