DIAGNOSTIC STRATEGIES AIMED TO MONITOR CANCER PATIENTS TREATED WITH NEW MOLECULAR THERAPIES

ESTRATEGIAS DIAGNÓSTICAS DIRIGIDAS AL SEGUIMIENTO DE LOS PACIENTES CON CÁNCER TRATADOS CON NUEVAS TERAPIAS MOLECULARES

SUMMARY

It is very important to have an objective evaluation of the response to cancer therapy. The standardization and use of a common language is essential in order to make a comparison of different therapies in different settings. It can be said that there was a direct relationship between tumor size and tumor response, comment derived from the WHO criteria, since 1979. Due to the limitations of these criteria, the RECIST criteria were created in 2000, where it is recognized that diagnostic images are the key point when monitoring cancer patients. However, with the emergence of new technologies, RECIST has evolved into new criteria such as RECIST 1.1 and PERCIST, once the limitations of the criteria created in 2000 were recognized. Meanwhile, new anti-cancer therapies are designed with mechanisms of action at the molecular level, which has shown that the current anatomical evaluation is not the only parameter and must be correlated with functional and perfusion techniques, such as Doppler, Magnetic Resonance or CT and the inclusion of new following criteria by PET (PERCIST). The main objective of this review article is to recognize the current standards in terms of RECIST criteria, RECIST practical implementation, and current limitations in a sufficient manner, so that the reader can recognize how radiologists are progressing in the evaluation of tumors according to their biological behavior and the specific therapy being received by the patient.

RESUMEN

La evaluación objetiva de la respuesta a la terapia anticáncer es muy importante. La estandarización y la utilización de un lenguaje común es fundamental para poder comparar las terapias en diferentes escenarios. Se puede afirmar que existía una relación directa entre tamaño tumoral y la respuesta, axioma derivado de los criterios de la OMS desde 1979. Debido a las limitaciones de estos criterios, los criterios RECIST fueron creados en el 2000; ahora se reconoce que las imágenes diagnósticas son el pilar en el seguimiento de los pacientes con cáncer. Sin embargo, con la aparición de nuevas tecnologías ha llevado a nuevos criterios, como los RECIST 1.1 y los PERCIST, una vez se reconoció la deficiencia de aquellos creados en el 2000. Mientras tanto, se han diseñado nuevas terapias anticáncer con mecanismos de acción molecular, lo cual ha demostrado que la evaluación anatómica no es actualmente el único parámetro y se debe correlacionar con técnicas de perfusión y de función.
como Doppler, resonancia magnética o TAC y la inclusión de nuevos criterios de seguimiento por PET (PERCIST). El principal objetivo de este artículo de revisión es reconocer de manera suficiente los estándares actuales en términos de criterios RECIST, su aplicación práctica, las limitaciones actuales y cómo los radiólogos oncológos están progresando en la evaluación de los tumores según su comportamiento biológico y la terapia que el paciente esté recibiendo.

**Introduction**

Consistent image response criteria, which are highly reproducible and objective, have been developed throughout recent oncological history, and respond to the need to have a universal language to evaluate multiple therapies in a current scenario in which new medications in the fight against cancer are developed. This assertion has greater validity when comparing new treatments with therapies that have been used for each type of cancer. Even more importantly: The standardization of criteria is fundamental when two therapies are simultaneously administered and the effect is isolated in each one of the treatments. For this reason, despite the time that is invested in creating new medications, a universal system is required to monitor the patients in an objective manner.

The radiological evaluation of cancer and its response to treatment has been intensely developed during the past 25 years. Initially, the World Health Organization (WHO) introduced response criteria in 1979 without taking into account specific radiological protocols. This was the starting point. Afterwards, multiple modifications were suggested, which led to chaos and anarchy in radiology.

In order to avoid those confusions, and especially to allow criteria to be universal, the response evaluation criteria in solid tumors was born in 2000 (RECIST, which stands for *Response Evaluation Criteria in Solid Tumors*) due to a mandate of the European Organization for the Research and Treatment of Cancer (5), the National Cancer Institute of the United States and the National Cancer Institute of Canada.

These criteria, widely known as RECIST, are very useful due to the fact that they met their main objective: to standardize and make sure that the oncological and the radiological world speak the same language. Nowadays, it is undeniable that diagnostic images are considered key for patients who are undergoing cancer treatment. However, it is clear that even as technology has evolved and diagnostic images have a tendency to be less anatomical and more functional, RECIST criteria has faults and its practical application is increasingly difficult.

**Evolution 1: From WHO to RECIST criteria**

In 1979, WHO suggested standardized universal criteria for the monitoring of solid tumors. This was done so that the report could be universalized in accordance with the response to treatment, the recurrence and the disease-free interval. The criteria were also suggested to grade the sub-acute and acute toxicity that appears after medical treatment (3).

OMS criteria were based on bi-dimensional parameters of tumor masses, given the fact that it was not possible to carry out a volumetry of the tumor with available technology. Therefore, it was assumed that the tumors were spherical, which did not necessarily reflect the presentation of the tumors (6,7). This being so, the different oncological societies accepted the following criteria as universal, even if great problems were recognized:

1. The minimum size of the tumor lesions for inclusion was not mentioned.
2. The actions that must be taken when a patient has several lesions were not clear.
3. The monitoring image type that must be carried out was not considered.
4. The progression of the disease, initially defined as a 25% increase of the mass diameter products was referred to by some groups as an increase in the sum of all the visualized lesions, and by other groups, as an increase in one of the lesions (4).
5. Measurement errors. In addition to measuring both diameters, it cannot always be reproduced, as it could needlessly condition patient treatment to be more aggressive, especially in small lesions.
6. By potentially considering the two diameters of the masses, it could overestimate the size of the tumor (8).

Taking into account the above mentioned serious limitations, the different organizations against cancer around the world, with the European Organization for the Research and Treatment of Cancer, the National Cancer Institute of the United States and other organizations such as the National Cancer Institute of Canada at the helm, decided in 2000 to create new monitoring criteria, called RECIST. The following were its objectives (5):

1. Unify the different versions regarding OMS criteria, in such a way that the different clinical studies can be compared.
2. Categorize the patients by response, in such a way that therapeutic decisions are made in favor of them: complete response, partial response, stable disease and progression of the disease.
3. Maintain stable disease criteria in such a way that the studies carried out with OMS methodology remain valid and performed with new criteria.
4. Be more aggressive regarding the concept of the progression of the disease, in such a way that it allows talking decisions in an early manner.

The following are the most important differences between the OMS and RECIST criteria:

1. A one-dimensional measurement is adopted, that is to say, the greater diameter of the lesion. This allows the measurement of more lesions without it becoming tedious.
2. Stipulate which diagnostic images can be used for monitoring.
3. Choose which tumors can be selected for one of the suggested categories, in accordance with the criteria.
4. Only a specific number of lesions can be evaluated, not all the lesions.
5. The cut-off point for the progression of the disease is re-defined, which is lessened.

One of the changes that RECIST introduced was that the concept of progression of the disease refers to a 20% increase in the sum of the greater diameters of the index lesions (table 1 and figure 1). In accordance with the old OMS criteria, an increase which is greater than 25% can be considered as a progression. It is important to recognize that the increase in one of the diameters corresponds to a 73% increase in spherical volume; and an increase in the product of both diameters to one of 40% in the spherical volume of the tumor (6).
Table 1. Main differences between the monitoring criteria established by OMS and the RECIST criteria established in 2000

<table>
<thead>
<tr>
<th>Criteria</th>
<th>OMS</th>
<th>RECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image Modality</td>
<td>Not Stipulated</td>
<td>CAT Scan, RT and chest x-rays</td>
</tr>
<tr>
<td>Measurable Lesion</td>
<td>Lesion which can be measured in a bi-dimensional diameter without taking into account the minimum size</td>
<td>Measurable lesion in the greater diameter, over 20 mm in a helical CAT machine or in the chest x-rays and over 10 mm in the multi-detecting CAT machine.</td>
</tr>
<tr>
<td>Measurement method</td>
<td>Product of the bi-dimensional diameters.</td>
<td>Greater diameter in the axial plane.</td>
</tr>
<tr>
<td>Response evaluation by lesions</td>
<td>Does not stipulate number of injuries.</td>
<td>Five lesions per organ, ten total lesions.</td>
</tr>
<tr>
<td>Partial response</td>
<td>Reduction greater than 50% in the target lesions, without an increase greater than 25% in any lesion.</td>
<td>Reduction of 30% of the sum of the greater diameters of the target lesions related to the base test.</td>
</tr>
<tr>
<td>Progression of the disease</td>
<td>25% increase in one of the target lesions, visualization of new lesions.</td>
<td>20% increase of the sum of the greater diameters taking as reference the lesser diameter obtained during the monitoring studies or visualization of new lesions.</td>
</tr>
</tbody>
</table>

In addition, rather than only considering one lesion, RECIST considers the sum of the diameters greater than the larger diameters of the several lesions (which is incomplete), which allows for a true evaluation of the tumor mass. In spite of these differences, several studies have shown good concordance between the OMS and the RECIST criteria (5,6,9,10). However, the following is one of the strongest criticisms to RECIST: It has shown that it requires more time to determine a progression and it requires a greater increase of lesions in order to detect progression (4,11,12).

Evolution 2: from RECIST to RECIST 1.1

Since 2000, several concerns where heard around the world and from several medical specialists (5,13). Radiologists and clinical oncologists had several questions:

1. Is it necessary to take into account target lesions?
2. Is a histological confirmation of the lesions really necessary in order to categorize them as part of a tumor?
3. Several clinical studies seek to establish progression parameters for the disease but: How must the criteria be established if the disease is not measurable, such as pleural effusion or bone metastatic disease?
4. How must the lymph nodes be treated if a clear parameter of malignancy is not present? Is architecture really considered? Size? The greater or lesser diameter?
5. What must be done with the new molecular and functional radiological techniques? Must tomography be included by positron emission? What about the Doppler test?

Many of these questions will be left unanswered. However, a new consensus in 2009 sought to solve these problems, and new concepts were redefined. As such, RECIST 1.1 was born.

What did not change in RECIST 1.1?

Several concepts adopted by RECIST in 2000 remained the same; unidirectional diameter remains the main measure to calculate the volume and tumor burden in accordance with the sum of the greater diameters of the selected lesions.

The response categories remained stable and a complete response was once again defined, as well as a partial response (understood as a 30% decrease of the sum of the index lesion diameters), a stable disease and the progression of the disease (understood as a 20% increase of the sum of the greater diameters of the lesions).

What changed in RECIST 1.1?

The first key concept which changed was the measurement of the tumor burden or the tumor volume.

- A minimum diameter of lesions that can be objectively measured and that do not correspond to lymph nodes was established.
- A maximum of five lesions, and two lesions per organ was considered.

The correct evaluation of the lymph nodes was considered as another victory by the oncological world, and was defined as follows:

- Always measure the lesser axis.
• A target lesion is considered if it has a minor diameter greater than 15 mm.
• A lesion is considered suspicious if its size is between 10 to 15 mm. However, it is not considered a target lesion.
• Normal nodes are those which have a diameter lesser than 10 mm.
• This lesser diameter is part of the sum of the target injuries and therefore, it serves as a criteria to determine the progression of the disease. This implies that lesions under 10 mm are considered as a non-measurable disease, even if the masses were previously larger.

There was also an important effort being made in order to redefine the concept of progression of a disease (14). A fundamental problem in this revision was that the percentage of variability (20% in the sum of the greater diameter) was considered as the only monitoring criteria, given that 3 mm variations often represented the progression of the disease. In addition to the percentage criteria, a minimum increase of 5 mm in the target lesion is considered in order to determine significant changes (15,16).

Similarly, the concept of progression of the disease was enlarged, as the expression unequivocal progression was introduced, which applies for a non-measurable disease (pleural effusion, for example). This expression means that an unequivocal visual increase of the disease must be present (for example, pleural diffusion which only affects the lower third of the hemithorax and currently, the entire hemithorax) (17).

A debate which was solved was the discussion regarding histological confirmation of the lesions that are observed. This is only required in case the main outcome is a complete response (18). If a complete response criteria is still not met, no histological confirmation is needed (19).

Finally, a concept that RECIST 1.1 clearly introduced was interpretation of new injuries. A new lesion is one that cannot be attributed to a difference in image acquisition techniques. If doubts arise due to this difference, the study must be repeated. At this point, emphasis is placed in using Positrons Emissions Tomography (PET) (20) while evaluating these lesions of dubious malignant potential, as well as giving importance to functional images. The following are the significant differences between the RECIST version published in 2000 and the current version (table 2).

Practical Definitions in RECIST 1.1 (21)

Base tumor burden measurements

The tumors and the lymph nodes must be categorized as measurable or non-measurable diseases in accordance with the following:

Measurable:
• A lesion which can be objectively measurable in its greater diameter, with a minimum size of 10 mm. If the size of the cuts in the scan is not greater than 5 mm; 10 mm in the clinical test, and 20 mm in the chest x-rays.
• Lymph nodes: 15 mm in its lesser diameter by Cat scan, if the size of the cuts in the scan is not greater than 5 mm.

Non-measurable:
• All lesions which greater diameter is lesser than 10 mm or lymph nodes with a diameter lesser than 15 mm.

1. Bone Lesions
• Bone scan, PET or simple x-rays are not considered adequate methods to measure bone injuries. They are only adequate to confirm their presence.
• Any bone lesion that goes along with a soft tissue lesion is considered a measurable disease which meets measurable disease criteria in terms of size.
• Bone lesions with a soft tissue component are considered as measurable diseases through axial radiological techniques, such as CAT scans or magnetic resonance (MR).
• Blast bone lesions are considered non-measurable.

2. Cystic Lesions:
• Simple cysts are not considered malignant.
• Cystic metastases, if they meet size criteria, are considered as a measurable disease if histological confirmation is present.
• If solid and cystic lesions coexist in the patient, then solid lesions must be measured.

3. Lesions which received local treatment
Previously irradiated lesions, or lesions which had local treatment are considered as non-measurable, unless progression of the disease can be easily demonstrated.

Considerations for adequate measuring

1. Measurement of lesions:
• All measurements must follow the metric system, as soon as the treatment starts, without exceeding a period of four weeks.
• The same radiological technique must always be used, and must overlap the clinical exam, except if the clinical exam palpatas the lesion and the lesion cannot be demonstrated by images.

2. Radiological techniques:
• A CAT scan of the chest is a preferred method instead of X-rays, especially if the outcome that is being considered is a progression of the disease, given that the CAT scan detects more lesions, which are often invisible via simple x-rays.
• The CAT scan and the RM are the most reproducible radiological techniques, especially when the cuts do not have a diameter which exceeds 5 mm.
• The ultrasound is not useful to determine the size of the tumor, as the ultrasound has characteristics which are dependent on the operator.
Currently: How is the response to the tumor categorized?

Currently, and taking into account that the RECIST 1.1 criteria must be used for a correct evaluation and for the morphological and objective monitoring of the tumor, and always under the premise that the observations and criteria are met when the studies (refer to section “Practical definitions in RECIST 1.1”) in tables 3 and 4 and in algorithm 1 are assessed, a summarized and practical way to categorize the response is presented.

Table 2. Main differences between the monitoring criteria established in 2000 (RECIST) and the RECIST 1.1 criteria introduced in 2009

<table>
<thead>
<tr>
<th>Criteria</th>
<th>RECIST</th>
<th>RECIST 1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement of Tumor Burden</td>
<td>10 lesions, 5 per organ.</td>
<td>5 lesions, maximum of 2 per organ.</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>Measurement of the greater diameter. Measurement with a normal diameter is not mentioned.</td>
<td>Short axis measurement. Define normal size (less than 10 mm).</td>
</tr>
<tr>
<td>Definition of progression</td>
<td>20% increase in the sum of the greater diameters, taking as a reference the lesser diameter obtained during the monitoring studies or visualization of new lesions.</td>
<td>20% increase in the sum of the greater diameters, taking as a reference the lesser diameter obtained during the monitoring studies or visualization of new lesions. Absolute increase in the size of a lesion greater than 5 mm.</td>
</tr>
<tr>
<td>Progression of non-measurable disease.</td>
<td>Must be unequivocal.</td>
<td>Unequivocal progression is defined, as well as the progression of lesions that are initially non-measurable, but can be categorized (i.e. bone disease, pleural effusion).</td>
</tr>
<tr>
<td>Histological confirmation of lesions</td>
<td>Required</td>
<td>Required only when the outcome is a complete response.</td>
</tr>
<tr>
<td>New lesions by functional radiological techniques</td>
<td>Are not included</td>
<td>Includes the interpretation of lesions when they are visualized by other radiological techniques (PET).</td>
</tr>
</tbody>
</table>

Table 3. Actual criteria for the categorization of tumor response according to criteria RECIST 1.1 (measurable disease)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>Disappearance of all lesions, confirmed by four weeks</td>
</tr>
<tr>
<td>Partial response</td>
<td>30% reduction of the sum of larger diameters of the target lesions with the base test as reference and a four week confirmation.</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Does not meet partial response criteria or progression of disease criteria.</td>
</tr>
<tr>
<td>Progression of the disease</td>
<td>20% increase of the sum of larger diameters with the smaller diameter obtained during the monitoring studies or visualization of new lesions as reference, unequivocal progression of non-measurable disease.</td>
</tr>
</tbody>
</table>

Table 4. Summary of current criteria in order to categorize tumor response according to RECIST 1.1 criteria.

<table>
<thead>
<tr>
<th>Target lesion</th>
<th>Non target lesions</th>
<th>New Lesions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>-</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>No CR / No PD</td>
<td>-</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>NE</td>
<td>-</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>No PD/NE</td>
<td>-</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>No PD/NE</td>
<td>-</td>
<td>SD</td>
</tr>
<tr>
<td>NE</td>
<td>No PD</td>
<td>-</td>
<td>UE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>+/-</td>
<td>PD</td>
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<td>Any</td>
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<td>+/-</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>+</td>
<td>PD</td>
</tr>
</tbody>
</table>


Algorithm 1: Current criteria for the categorization of tumor response according to RECIST 1.1 criteria (non-measurable disease)

In accordance with the 2000 categorization, some of the criteria that were maintained for the current RECIST 1.1 defined the following conclusions according to the observed radiological response:

1. Complete response: Disappearance of all index lesions. Any visualized lymph node must have a diameter lesser than 10 mm in its short axis.
2. Partial response: At least a 30% reduction of the sum of the larger diameters of the index lesions, using the first available radiological test as reference.
3. Progression of the Disease: a 20% increase of the sum of the diameters of the index lesions, using the study with the smaller result as reference. In addition, it is necessary to demonstrate an absolute increase in 5 mm lesions. The appearance of new lesions is considered as progression of the disease.
4. Stable disease: Disease which is not classified as a progression of disease or as a partial response.

The evaluation of non-considered target lesions and their progression must be taken into account in the following manner:
1. Complete response: Disappearance of all lesions which are considered as non-target and normalization of tumor markers. The visualized nodes must be lesser than 10 mm in their short axis.

2. Incomplete response / lack of progression of the disease: maintenance of tumor markers in pathological ranges.

3. Progression of the disease: unequivocal progression or appearance of new lesions is not considered as target.

**From RECIST to PERCIST: limitations of the anatomical analysis**

Even though the RECIST criteria have been widely used during the last eight years, and although revision 1.1 was implemented a year ago, some aspects have not been widely discussed (22):

1. Reducing the tumor response to four categories could represent a bias, as the amount of information is being reduced in order to fit it in one of the categories (23-26). For example, in a scenario of a cytostatic treatment in which the outcome seeks the stabilization of the illness, this must be considered as a successful result. Some examples of tumor behavior in this sense exist in the Gastrointestinal Stromal Tumor (GIST), where the volume of the tumor goes down very slowly, but the disease-free period increases in an exponential manner (27,28). This assertion is so important that, due to this, the Choi criteria for GIST were developed, in which a 10% reduction of the size of the tumor is established or a reduction of 15% of the attenuation coefficients of the CAT scan masses represent a partial response or a good response to treatment (29-31). In addition, in the GIST scenario, the appearance of mural nodules in a predominantly cystic neoplasia is indicative of a tumor progression and an incorrect prognosis (32,33).

2. RECIST present limitations to determine the response to anti-angiogenics, such as Sorafenib. In a recently published study, SHARP, where 602 patients with hepatocellular carcinoma had not received previous therapy, only 1% of the control group and 2% of the intervention group had a partial response in accordance with the RECIST criteria, which is a figure which could lead to the conclusion that the medication is not effective. However, the outcome of this study was not to demonstrate a non-response, but to demonstrate survival free of progression and global survival. When the study ended, an increase in the average survival of patients who received anti-angiogenics was evidenced, and the radiological progression was slower in this group of patients. These findings were associated with an anatomically stable disease (34). Due to the previous point, the criteria of the European Association for the Study of the Liver were established. These criteria take into account the highlight with the contrast material after carrying out the endovascular therapy and are superior to the RECIST criteria when determining progression (25). This type of progress is also happening in mesothelioma and in some pediatric tumors (36-39).

3. RECIST also requires that the observer carries out the first study, as well as the monitoring study. Various studies have identified several mistakes regarding the classification of patients by high inter-observational variability (40).

4. The size of the tumor matters. Studies prove that, if there is evidence that a tumor is rapidly decreasing in size, it is more probable that the response lasts longer. In the lymphoma scenario, a tumor which rapidly decreases in size probably requires less aggressiveness in the treatment. It is also probable that patient mortality decreases (41). However, sometimes an increase in the size of the tumor can be seen, with a diminishment in the attenuation coefficients. This finding suggests a response to the treatment (figure 2).

5. Volumetrics vs. one-dimensional diameter. Different studies have proved that tumor volumetrics could be more useful that one-dimensional evaluation of masses. However, it is important to note that the anatomical image or the volume does not always represent a histological response, as is the case with lung carcinoma and neoadjuvant therapy (42).

If the five previously mentioned comments are carefully examined, a conclusion could be made that the universalization of the RECIST criteria, conceived as an excellent alternative, currently presents problems and, due to this, it must complement the functional image in such a way that it could progressively adapt to the new medications. Given these reasons, the need to search new criteria and new radiological techniques is suggested, as follows.

**Introduction to PERCIST 1.0: What is PERCIST and when must a functional image be obtained?**

In accordance with the great quantity of available literature regarding the evaluation of solid tumors through PET and knowing the limitations of only having anatomical information, a combination of techniques under the PERCIST criteria has been suggested. PERCIST refers to Positron Emission Tomography Response Criteria in Solid Tumors. It takes into account cases where the anatomical image does not present changes, while the functional image shows new malign pathology focus points (figure 3).

The premise that is taken into account is the following: Cancer, when evaluated by PET, is a continuum which presents variables throughout time. The radiologist and the oncologist can evaluate the same patient several times with different radiological techniques and achieve the stabilization of the anatomical information. However, the consumption of glucose is considerably reduced and therefore, tumor metabolic activity is also reduced.

Findings regarding the moment when PET must be obtained during treatment still exist. It seems as if reasonable intervals suggest the acquisition of the study after the first therapy cycle, just before starting the next cycle, as almost 60-70% of collection units fall after the first cycle (43). Afterwards, the acquisition of functional images at the end of therapy seems reasonable, at least ten days afterwards, in order to avoid false negatives by the continuous effect of medications (44-46).

**Adequate taking of PET: Standard protocol**

Patients must fast for at least four to six hours and must present non-corrected concentrations of g200 mg/dl of glucose. Patients can undergo treatment with oral glucose-lowering medication, but not insulin. The base image must be obtained towards 50 to 70 minutes after the injection of Fluorodeoxyglucose, and the monitoring test must be carried out 14 minutes after the first acquisition and must be performed with the same equipment and with the same proportional dosage of radiation. The attenuation of the nuclear test must be correctly adapted, which can be achieved with a complementary CAT scan.
Generalities of the PERCIST criteria

The following are some of the criteria that must be taken into account for PET monitoring with cancer patients:

1. A measurable lesion is categorized as an area of greater capitation in the inner part of a tumor and, at the moment when the interest area is placed, its diameter cannot be greater than 1.2 centimeters.

2. Inside the tumor, the area of greater capture of the radiotracer is taken into account. The area is not necessarily the same area at the start of the treatment.

3. Measure five measurable lesions in accordance with RECIST, choosing the lesions which the radiotracer can capture the most (generally the largest tumors), without taking into account over two lesions per organ.

4. Definition of the response:
   - Complete response: absence of radiotracer, even though size abnormality persists in the anatomical information.
   - Partial response: A reduction of the capture of the radiotracer (fluorodeoxyglucose) by 30% of the capture units that are standardized by the tumor.
   - Progression of the disease: Increase in radiotracer capitation (fluorodeoxyglucose), by 30% of the capture units that are standardized by the tumor or the appearance of new lesions.
   - Stable disease: A disease which does not fall under the previous categories.

More variables exist regarding these monitoring criteria, which makes the PERCIST evaluation more complex, even though recent studies show that the functional information of the tumor seems more reliable.

New perspectives: Different strategies for the monitoring of tumors in accordance with biological therapy.

One of the concepts that has currently revolutionized neoplastic therapy, and of course, the evaluation of its response through diagnostic images is the concept of angiogenesis. Angiogenesis is defined as the formation of capillary vases, which is a process which is essential for the growth of tumors, in such a way that it maintains a constant supply of oxygen, glucose and other nutrients (47). In the past ten years, several agents have been developed regarding angiogenesis inhibitors. The great majority of these block the tyrosine kinase activity of the Vascular Endothelial Growth Factor (VEGF). One of the signature medications of this group of new drugs, which principle is molecular therapy, is known as Sorafenib (48,49).

Several tumors such as hepatocellular carcinoma, renal cell carcinoma, solid tumors which remain refractory to treatment, as well as others show a high receptor expression to VEGF, which is why these medications have been effective in this scenario (30,50).
Taking the previous points into account, and clarifying the fact that the main effect of these medications is cytostatic, the evaluation through RECIST criteria is not applicable, given that the reduction in tumor size is not easily visualized (51,52) (algorithm 2).

**Ultrasound in the era of molecular treatment of solid tumors**

In mode B, morphological evaluation of lesions is fundamental, as long as equipment and harmonic transducers are present so that they improve sensitivity and specificity due to reduction of background noise. The ultrasound has had a fundamental role in the detection of liquid changes in the inside of tumor masses secondary to necrosis, which is a finding that could also be related to a complete response of the disease. In hyper-vascular tumor scenarios, the color Doppler and the power Doppler carry out an important role due to the diminishment of intra-tumor flow, and this determines an early response to treatment (53-56).

**Dynamic computerized axial tomography**

At times, morphological changes do not occur during therapy and they turn tomography into a tool for long-term monitoring, especially in a scenario of surveillance. Given the previous point, and taking into account that anti-angiogenic therapy seeks to reduce intra-tumor blood flow, changes in the attenuation coefficients are evident at first. That is to say, the changes in pre and post contrast attenuation allow for a credible control of the events surrounding the tumor microvasculature. (figure 4). Currently, some studies prove that perfusion by tomography is an excellent method to monitor patients who are receiving anti-angiogenics (57).

**Algorithm 2. Proposal of follow-up of tumors with treatment based on antiangiogenics drugs**

**Magnetic Resonance**

Magnetic resonance has been an established technique for diagnosis, due to its greater sensitivity to detect and characterize focal lesions in solid organs or simply for the diagnosis of masses in any part of the body.

The most important aspect to this technique, before starting treatment, are the base images, given the fact that tumors behave in a specific manner with each one of the sequences that are classically used.

It is known in this scenario that anti-angiogenics tend to produce hemorrhagic necrosis, in such a way that-in terms of magnetic resonance-changes regarding the presence of hemoglobin degrading products can be identified, especially intra and extra-cellular methemoglobin and hemosiderin. These findings become a reference point to determine response to the therapy.

Additional changes have been recently documented: An increase in the signal intensity of sequences with T1 information and fat saturation, as well as in the sequences with T2 information, which is expected between the period of 2-4 weeks of treatment. When this change occurs, signal intensity differs between patients who respond to treatment and those who do not. Similarly, if contrast material is used, there is a possibility to establish a degree of perfusion of these tumors so that it becomes a second parameter to establish a response.

It is possible to determine a response through additional sequences, such as the practice of diffusion sequences which prove that malign and high-degree treatments are made with high intensity in the diffusion, and in the ADC sequences or in coefficients of apparent diffusion which are made with low intensity. This situation reflects a restriction for diffusion (impossibility for trans-membrane movement of water-free molecules) (58). Once therapy has started, the ADC signal increases, which reflects a re-accommodation of macromolecular architecture of the tumor secondary to necrosis (59).
Conclusions
The recent demand to objectively verify the response that new medications induce in cancer treatment has translated into a greater use of medical images.

In spite of the limitations in RECIST, there is a great potential to universalize the use of this tool which allows the standardized evaluation of the response to solid tumor treatment. However, advances in medical technology are greater and due to this reason, the deficiencies in these criteria must be recognized.

By identifying these deficiencies, we must be able to include these new technologies when evaluating an oncological patient, further recognizing the role of molecular biology in cancer treatment and therefore, its role in the evaluation of the response to treatment.

Every patient must be evaluated based on current scientific evidence (RECIST), taking into account other radiological techniques that are more efficient, while objectively observing the expected tumor response and the reflection of new molecular drugs such as PET and magnetic resonance in the specific use of anti-angiogenics.

References


