A radiologist’s guide to the modified Response Evaluation Criteria in Solid Tumours (mRECIST) assessment of therapy for hepatocellular carcinoma

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Learning objectives

Fig.

References: - London/UK

1. To familiarise radiologists with the modified RECIST assessment of therapy for hepatocellular carcinoma.

2. To explain the rationale behind the introduction of the modified criteria and the advantages over standard RECIST.

3. To describe the practical application of the criteria and the challenges that occur with the heterogeneous nature of hepatocellular carcinoma.
Background

The original criteria used to assess tumour response were those published by the World Health Organisation (WHO) in 1979. These measured the product of the long and short axis measurements of target lesions as its fundamental parameter. As technology progressed, different groups modified the WHO criteria, with resulting divergence and confusion when comparing efficacy of agents in clinical trials.

To address this issue and to standardise assessment, as well as better correlate radiological outcomes with patient survival outcomes, the Response Evaluation Criteria in Solid Tumours (RECIST) were developed in 2000. RECIST encompassed strict definitions to the number and minimum sizes of target lesions, a change to unidimensional measurement of lesions, and precise definitions for objective response and progression [1].

RECIST have been widely adopted by clinicians, academics and the pharmaceutical industry for trials in which the primary endpoint is objective response. In 2008 RECIST was revised (to version 1.1) and several issues were simplified and clarified based on the evidence from over 6500 patients [2].

The aim of this exhibit is not to discuss RECIST in detail, as this has been done elsewhere [3, 4], but to highlight their limitations with regard to the evaluation of tumour response in hepatocellular carcinoma (HCC) treated with locoregional therapies and new targeted chemotherapy agents.

*Note: Objective response is strictly defined as either complete response, partial response or stable disease.*

The fundamental basis of RECIST is the sum of the unidimensional measurements of the largest tumour diameter, for up to five target lesions. This reliance on absolute size is sufficient for the evaluation of tumours which shrink upon treatment with cytotoxic agents. However certain tumours and cytostatic agents do not respond primarily with a reduction in size, and therefore using RECIST in these cases underestimates patients who are benefitting from treatment and instead defines them as having stable disease.

For example, for gastrointestinal stromal tumours (GIST) treated with the tyrosine kinase inhibitor imatinib (*Gleevec*) a reduction in tumour density (as measured by Hounsfield unit on CT) was shown to be a good indicator of tumour response but small reductions in size did not qualify for response according to RECIST. These findings led to the development
of the *Choi criteria for GIST* which encompass not only size changes but also *tumour density* [5].

For advanced hepatocellular carcinoma, RECIST were found to be a poor correlate for the clinical benefit demonstrated in the SHARP trial for sorafeninb (*Nexavar*, a multikinase inhibitor of the vascular endothelial growth factor and platelet derived growth factor receptors) [6]. Similar findings were seen after locoregional therapies for HCC such as radiofrequency ablation and chemoembolisation [7].

These therapies reduce the vascularity of the tumour, producing necrosis without necessarily causing a change in overall tumour size.

To provide a common framework for the design of clinical trials in HCC the American Association for the Study of Liver Diseases has proposed *modified criteria (mRECIST)*, which quantify only the *viable portions of the tumour* to provide an improved endpoint for assessment [8, 9].

*This exhibit aims to raise awareness of mRECIST amongst radiologists and describe how to apply the modified criteria in routine practice.*
The concept of measuring viable tumour is not new. At the same time as the introduction of RECIST in 2000, the European Association for the Study of the Liver (EASL) amended the WHO criteria to take into account intratumoral necrosis. These EASL criteria were based on a bidimensional product of viable tumour - defined by the uptake of contrast agent in the arterial phase on CT or MR imaging [10]. The modified RECIST criteria are a updated framework of previous AALSD guidelines which supported the EASL viable tumour concept [11].

Therefore RECIST is to mRECIST what WHO was to EASL! Both amendments incorporate viable tumour measurements.

Problems with assessing hepatocellular carcinoma

1. HCC is a heterogeneous disease.

A typical HCC is a hypervascular single nodule which shows washout of contrast in the portal venous or delayed phase. As tumours enlarge however they show intranodular variability in their enhancement pattern.
Fig.: Large hypervascular HCC with washout on the portal venous phase. Note internal structure is heterogeneous.
**Fig.**: Typical small homogeneously hypervascular HCC nodule with washout on the portal venous phase.

**References:** - London/UK

Other appearances for HCC may be multifocal, non-arterialised or infiltrative.
**Fig.**: Multifocal HCC can be measurable or ill defined and non-measurable.

**References**: - London/UK
**Fig.**: These HCC nodules show no enhancement in the arterial or portal venous phase.

**References**: - London/UK
**Fig.**: In this case the HCC has invaded the right posterior portal vein branch (arrow) resulting in arterialisation of segment VII. The precise borders of the tumour are unclear and this is therefore a non-measurable or non-target lesion.

**References:** - London/UK

2. *Chronic liver disease*

HCC usually occurs in the context of chronic liver disease which in itself provides for a heterogeneous appearance and enhancement pattern of the liver parenchyma.

Regenerative and dysplastic nodules and parenchymal perfusional abnormalities can mimic HCC nodules, and new arterialised lesions appearing and disappearing during treatment may not be a neoplastic phenomenon.

3. *Image acquisition factors*
The visualisation of viable tumour requires adequate opacification during the arterial phase. Standard protocols for baseline and follow up imaging should always therefore include this, as well as at least a portal venous phase. Changes in the timing of the imaging acquisition on different occasions may influence the enhancement characteristics.

Ideally the same machine and same image acquisition parameters should be used, especially with MR imaging. Different vendor software may produce different enhancement appearances. MR artefacts may interfere with image evaluation.

**Fig.** This patient was reported as having progressed between April (image not shown) and May when imaged with scanner A, due to the increased signal within the HCC in the right lobe. However at the next follow up in July, he was imaged on scanner B, upon which all other assessments had been made, and the signal characteristics were stable since baseline.

**References:** - London/UK
4. The natural history of HCC

The natural history of hepatocellular carcinoma is progression with eventual death due to direct effects of the primary tumour and its metastases, or the effects of predisposing liver disease and liver failure. Often the two cannot be separated.

Treatment of advanced disease is palliative, and therefore complete response is almost unheard of, stable disease with eventual progression is the norm, and the focus of phase II trials is to identify anti-tumoral activity by detecting a partial response or delay progression by maintaining stable disease. The primary endpoint in such phase II trials is a time to event surrogate endpoint such as time to progression, and in phase III trials is survival. Therefore the maintenance of stable disease should be considered to be a response to therapy.

The differences between RECIST and mRECIST

1. Measurement at baseline:
### Difference between RECIST and mRECIST in the measurement of tumour burden at baseline

#### Non-measurable (non-target) lesions for mRECIST:

- infiltrative lesions with ill defined borders
- non-hypervascular lesions
- malignant portal vein thrombus
- porta hepatis nodes if > 20mm short axis (because reactive nodes are common in cirrhosis)
- lesions previously treated with locoregional therapy or systemic therapy (unless they display well defined arterial enhancement > 1 cm in size)
- new or worsening pleural effusion or ascites to define progression only if measurable tumour meets CR, PR or SD, and malignancy must be confirmed by cytological examination.

#### Definition of objective response and progression

<table>
<thead>
<tr>
<th></th>
<th>RECIST v1.1</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurable disease</strong></td>
<td>Lesion able to be accurately measured in at least one dimension &gt;1cm and suitable for repeat measurement</td>
<td>Lesion able to be accurately measured in at least one dimension &gt;1cm and suitable for repeat measurement and lesion shows intratumoral arterial enhancement</td>
</tr>
<tr>
<td><strong>Non-measurable disease</strong></td>
<td>All other lesions (&lt;1cm lesions and truly non-measurable lesions)</td>
<td>All other lesions (&lt;1cm lesions and truly non-measurable lesions) and specific lesions (see text)</td>
</tr>
<tr>
<td><strong>Number of lesions</strong></td>
<td>Up to 5 (2 per organ)</td>
<td>Up to 5 (2 per organ)</td>
</tr>
<tr>
<td><strong>Measurement</strong></td>
<td>Sum of longest diameters of individual lesions</td>
<td>Sum of longest diameters of individual lesions showing arterial enhancement</td>
</tr>
</tbody>
</table>
As with RECIST, overall patient response for mRECIST is a combined assessment of target lesions, non-target lesions and new lesions.

### Target lesion response definitions

<table>
<thead>
<tr>
<th></th>
<th>RECIST v1.1</th>
<th>mRECIST</th>
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<tbody>
<tr>
<td><strong>Complete response (CR)</strong></td>
<td>Disappearance of all target lesions</td>
<td>Disappearance of any intratumoral arterial enhancement in all target lesions</td>
</tr>
<tr>
<td><strong>Partial response (PR)</strong></td>
<td>≥30% decrease in sum of the longest diameters of target lesions compared with baseline</td>
<td>≥30% decrease in sum of the longest diameters of viable (arterially enhancing) target lesions compared with baseline</td>
</tr>
<tr>
<td><strong>Progressive disease (PD)</strong></td>
<td>≥20% increase in sum of the longest diameters of target lesions compared with the smallest sum of longest diameters recorded (nadir).</td>
<td>≥20% increase in sum of the longest diameters of viable (arterially enhancing) target lesions compared with the smallest sum of longest diameters recorded (nadir).</td>
</tr>
<tr>
<td><strong>Stable disease (SD)</strong></td>
<td>Neither PR or PD</td>
<td>Neither PR or PD</td>
</tr>
</tbody>
</table>

**Fig.** Differences between RECIST and mRECIST for the response of target lesions.  
**References:** - London/UK
### Non-target lesion response definitions

<table>
<thead>
<tr>
<th></th>
<th>RECIST v1.1</th>
<th>mRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response (CR)</strong></td>
<td>Disappearance of all non-target lesions</td>
<td>Disappearance of any intratumoral arterial enhancement in all non-target lesions</td>
</tr>
<tr>
<td><strong>Progressive disease (PD)</strong></td>
<td>Unequivocal increase in size of non-target lesions, or new lesions</td>
<td>Unequivocal increase in size of non-target lesions, or new lesions meeting specific criteria (see text)</td>
</tr>
<tr>
<td><strong>Incomplete response or Stable disease (IR/SD)</strong></td>
<td>Persistence of one or more non-target lesions</td>
<td>Persistence of arterial enhancement in one or more non-target lesions</td>
</tr>
</tbody>
</table>

**Fig.**: Differences between RECIST and mRECIST for the response of non-target lesions.

**References:** - London/UK

With mRECIST new HCC lesions are diagnosed when:

- Size >1 cm
- Typical hypervascularity with washout
- Or size >1 cm without typical enhancement if growth of >= 1 cm on subsequent scans
- Any new liver lesion not meeting these criteria is considered equivocal and is not considered progressive disease, because overcalling equivocal lesions as PD has a major influence on clinical trial endpoints.

**Schematic diagrams demonstrating objective response and progressive disease between RECIST and mRECIST**
Fig.: Schematic diagram showing variable mRECIST objective response, with stable disease by RECIST

References: - London/UK
Fig.: Schematic diagram showing methods of defining progressive disease with mRECIST and RECIST

References: - London/UK

How to measure the viable HCC tumour burden and response to therapy

The published criteria state that the longest dimension of arterially enhancing tumour should be taken, when the contrast between viable tumour and non-viable necrosis is greatest. In some cases where all of the nodule enhances the measurements for mRECIST and RECIST will be identical.
However this statement is far from being as simple as it stands.

In some cases the contrast between the viable tumour and necrosis is greatest in the portal venous phase, as there is poor arterial enhancement. There is *a priori* viable tumour present but if the strict mRECIST were followed these would be non-target lesions.
Fig.: This lesion demonstrates increased conspicuity of vascularised and necrotic tumour in the portal venous phase. It also shows the difficulty in deciding which axis of measurement for mRECIST is representative and reliable. In such cases the largest radial diameter is the best measure.

References: - London/UK

If a lesion has central necrosis, then the true representative dimension of tumour burden is the longest radial measurement (or thickness of enhancing peripheral tumour rind).
Fig.: It is easy to define the viable tumour in this large HCC with central well defined necrosis.

References: - London/UK

If, as is more common, the intratumoral necrosis is irregular in shape, or eccentric, then it may be difficult to determine which is the most representative axis of viable tumour to measure.

Or a large lesion may become centrally necrotic to leave multiple viable but now separate tumours. The axis chosen for measurement should not include significant intervening areas of necrosis.
**Fig.**: This patient has residual tumour following chemoembolisation. At baseline the target lesion was already necrotic. RECIST includes the embolised portion with stable overall size but mRECIST defines progression of viable tumour after sorafenib therapy. 

*References:* - London/UK

It may be more reliable to measure the maximal diameter of necrosis and subtract that from the overall diameter, than to directly measure the viable tumour. At least one group of investigators has used this approach [12].
Fig.: It seems easier and more reproducible to measure the central area of necrosis rather than the viable tumour rind of irregular width.

References: - London/UK

Other limitations of mRECIST

*Pre-existing high density or high signal within a lesion*

Transarterial chemoembolisation with lipiodol and chemotherapeutic agents results in iodine staining of the treated tumour which appears as high density on unenhanced CT images. Any residual arterially enhancing viable tumour blush may be disguised by the lipiodol. Therefore these tumours should not be regarded as target lesions.
There is no enhancement seen in the previously embolised HCC.

Locoregional therapies such as chemoembolisation can result in haemorrhage within the tumour. This can also happen spontaneously due to tumour outgrowth of its blood supply with haemorrhagic necrosis. Paramagnetic haemoglobin breakdown products produce high signal on both unenhanced and gadolinium enhanced T1 weighted MR sequences and may disguise or mimic true tumour vascularity.
Fig.: Haemorrhage within the HCC makes assessment of residual vascularity difficult.

References: - London/UK

Alternatives to mRECIST?

The problems associated with consistent and reliable unidimensional measurement of viable tumour burden would be overcome by the adoption of a volumetric approach to measuring viable tumour. Historically measuring volumes of tumour tissue on workstations is very time consuming, requiring manual segmentation of each tumour area on every cross sectional slice. The sum of the areas is then combined with the slice thickness to provide an overall tumour volume. With advances in software technology it is now possible to automatically segment lesions within a 2D slice and a 3D volume providing a rapid, accurate and objective measurement of tumour volume. Unfortunately such software is not yet universally available on reporting workstations, but hopefully in the future it will be.

Subtraction imaging may also provide a more objective measurement of viable tumour burden. Subtraction can be performed as part of a dynamic perfusion imaging protocol.
or by the simple subtraction of the unenhanced component of a routine arterial enhanced study. Again the software to do this is available but not universally. Dual energy CT can obviate the requirement for a dedicated unenhanced acquisition, as it can filter for the iodine absorption spectra, and therefore reduce the overall radiation dose.

Functional imaging can directly assess the tumoral metabolic activity and therefore negate the need for surrogate markers of response such as tumour size and vascularity measured by RECIST and mRECIST.
**Fig. 0:** Large hypervascular HCC with washout on the portal venous phase. Note internal structure is heterogeneous.

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Fig. 0: Typical small homogeneously hypervascular HCC nodule with washout on the portal venous phase.

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**Fig. 0:** Multifocal HCC can be measurable or ill defined and non-measurable.

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Fig. 0: These HCC nodules show no enhancement in the arterial or portal venous phase.

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**Fig. 0:** In this case the HCC has invaded the right posterior portal vein branch (arrow) resulting in arterialisation of segment VII. The precise borders of the tumour are unclear and this is therefore a non-measurable or non-target lesion.

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Fig. 0: Schematic diagram showing methods of defining progressive disease with mRECIST and RECIST

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Fig. 0: Schematic diagram showing variable mRECIST objective response, with stable disease by RECIST

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**Fig. 0:** This typical HCC shows identical mRECIST and RECIST measurements.

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**Fig. 0:** This lesion demonstrates increased conspicuity of vascularised and necrotic tumour in the portal venous phase. It also shows the difficulty in deciding which axis of measurement for mRECIST is representative and reliable. In such cases the largest radial diameter is the best measure.

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**Fig. 0:** It is easy to define the viable tumour in this large HCC with central well defined necrosis.

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Fig. 0: This patient has residual tumour following chemoembolisation. At baseline the target lesion was already necrotic. RECIST includes the embolised portion with stable overall size but mRECIST defines progression of viable tumour after sorafenib therapy.

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**Fig. 0:** It seems easier and more reproducible to measure the central area of necrosis rather than the viable tumour rind of irregular width.

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Fig. 0: There is no enhancement seen in the previously embolised HCC.

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**Fig. 0:** Haemorrhage within the HCC makes assessment of residual vascularity difficult.

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Conclusion

The modified RECIST assessment for HCC involves evaluation of the viable tumour burden. However, as described, the reliable and consistent measurement of the viable tumour can be challenging.

In the future it is expected that mRECIST will be adopted within updated guidelines for the management of HCC [9]. As radiologists gain wider experience with the modified criteria, and after pathological correlation with tumour measurements is made, mRECIST will be validated as a reliable method for assessing tumour response in current and future HCC therapeutic trials.
Personal Information

This work was performed during my time as a ESOR/ESGAR abdominal imaging exchange fellow in Autumn 2010 which took place in Professor Menu's department in Saint Antoine Hospital, Paris.

I wish to convey my deepest gratitude to Professor Menu, my supervisor Dr Ana Ruiz, all the other department staff and the ESOR/ESGAR fellowship committee for the excellent opportunity which I experienced.

Fig.: Front entrance to Saint Antoine Hospital

References: - London/UK
Dr Jeremy S Rabouhans, FRCR
Images for this section:

Fig. 0: Front entrance to Saint Antoine Hospital

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References


