RECISt 1.1 versus mRECISt for assessment of tumour response to molecular targeted therapies and disease outcomes in patients with hepatocellular carcinoma: a systematic review and meta-analysis

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ABSTRACT

Objectives Response Evaluation Criteria in Solid Tumours version 1.1 (RECISt 1.1) and modified RECISt (mRECISt) are commonly used to assess tumour response. Which one is better to evaluate efficacy after molecular targeted therapies in hepatocellular carcinoma (HCC) patients is still controversial. A systematic review was performed to compare the objective response rate (ORR) and disease control rate (DCR) and a meta-analysis was conducted to compare the correlation between objective response and overall survival (OS).

Design Systematic review and meta-analysis using the Grading of Recommendations Assessment, Development and Evaluation approach.

Data sources EMBASE, PubMed, Web of Science and Cochrane Library were searched through 31 December 2021.

Eligibility criteria We included studies assessing the efficacy of molecular targeted therapy for HCC according to both RECISt 1.1 and mRECISt.

Data extraction and synthesis Two investigators extracted data independently. The consistency between RECISt 1.1 vs mRECISt is measured by the k coefficient. HRs with corresponding 95% CIs were used for meta-analysis.

Results 23 studies comprising 2574 patients were included in systematic review. The ORR according to mRECISt is higher than RECISt 1.1 (15.9% vs 7.8%, p<0.001). The DCR is similar (68.4% vs 67.2%, p=0.5). The agreement of tumour response is moderate for both criteria.

Conclusions mRECISt may be more accurate than RECISt 1.1 in assessing ORR after molecular targeted therapies in HCC patients and can better assess the prognosis. However, the performance of both criteria in assessing disease progression is identical.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Quantitative analysis of Response Evaluation Criteria in Solid Tumours version 1.1 (RECISt1.1) and modified RECISt to assess the relationship between tumour response and overall survival after molecular targeted therapies in patients with hepatocellular carcinoma.

⇒ Reliable methodological and statistical procedures were applied.

⇒ This study is limited by a small number of papers after screening according to inclusion and exclusion criteria.

⇒ The variable intervals between follow-up imaging results could be a source of heterogeneity.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth-leading cause of cancer-related mortality worldwide.1 There have been significant advances in treatment for HCC over the past decade. Available treatment options include surgical resection, liver transplantation, ablative techniques, transarterial chemoembolisation, transarterial radioembolisation, radiotherapy and molecular targeted therapies.2 Molecular targeted therapies are indicated for patients with advanced tumours or earlier stage unsuitable for surgical resection or locoregional therapies.3 It has already been confirmed that molecular targeted therapies can improve survival in patients with HCC due to their
unique antiproliferative and antiangiogenic function. The accurate assessment of therapeutic efficacy of molecular targeted therapies is essential for routine anti-cancer treatment as well as clinical trials.

Radiological evaluation of tumour response is a well-recognised surrogate endpoint in the assessment of therapeutic efficacy of molecular targeted therapies in patients with HCC, which is crucial to help identify potentially resistant patients, avoiding unnecessary toxicities. Tumour response was initially measured according to the WHO criteria and Response Evaluation Criteria in Solid Tumours version 1.0 (RECIST 1.0) guideline. Nevertheless, they have been proven to correlate poorly with survival outcomes in HCC patients and provide insufficient guidance on treatment options. Nowadays, the RECIST 1.1 and modified RECIST (mRECIST) criteria are the most commonly used criteria to assess tumour response. The major changes in RECIST 1.1 include the reduction in the number of target lesions and the augmented definition of disease progression, which relies on the change in the sum of the greatest diameters. The mRECIST has been developed which differ from RECIST 1.1 in that the target lesion measured is not the whole lesion but only the viable tumour, defined as the contrast-enhanced portion of the tumour on hepatic arterial phase images. European Association for the Study of the Liver (EASL) and European Society for Medical Oncology guidelines suggested applying mRECIST or RECIST 1.1 in patients with HCC treated with molecular targeted therapies. However, National Comprehensive Cancer Network guideline indicated that validated criterion to evaluate tumour response to molecular targeted therapies between the two criteria is needed. Besides, several studies demonstrated that overall survival (OS) can be predicted more accurately by mRECIST than RECIST 1.1, since the latter is not capable of assessing therapy induced intratumoural necrosis. On the contrary, another study observed both methods provided correlation with OS equally. Which set of criteria is better to evaluate response to molecular targeted therapies remains controversial. We perform this systematic review to compare the efficacy of RECIST1.1 and mRECIST in assessing tumour response after molecular targeted therapies in patients with HCC and to quantitatively determine which criterion correlates better with prognosis.

MATERIAL AND METHODS

Patient and public involvement
Patients and the public were not involved in this meta-analysis.

Search strategy
A comprehensive search of PubMed, EMBASE, Web of Science and the Cochrane Library from inception through 31 December 2021 was performed. The following Mesh terms and text words were confined to the title or abstract: “RECIST”, “mRECIST”, “Response Evaluation Criteria in Solid Tumors”, “liver cancer” and “hepatocellular carcinoma”. The detailed search strategy is included in online supplemental material table S1. The reference lists of relevant articles were also searched for other eligible studies.

Selection of studies
Two reviewers (YB and HY) independently assessed articles for eligibility, and discrepancies were resolved by a consensus and confirmed by another author YY. To be eligible for inclusion, studies had to meet the following criteria: (1) the diagnosis of HCC was based on pathology or radiological findings, in accordance with the criteria of practice guidelines; (2) patients with HCC must be treated with molecular targeted therapies; (3) response assessment after molecular targeted therapies was evaluated according to both RECIST 1.1 and mRECIST criteria; (4) available data about OS and k coefficient or sufficient information to calculate it. General exclusion criteria were: (1) presence of an additional primary malignancy in other organ; (2) patients with HCC received other therapies; (3) case analysis, letters, reviews and expert opinions; (4) studies with incomplete data; (5) published in languages other than English with no translation.

Quality assessment
The Newcastle-Ottawa scale (NOS) was used to assess the quality of the studies, this scale consists of three factors: the selection of patients, comparability of the study groups and assessment of outcome. The maximum total score on this scale is 9 and studies with scores ≥6 were defined as high-quality studies.

Data extraction
Two investigators (YY and HY) assessed and extracted data from all eligible studies independently, and discrepancies were resolved by a consensus and confirmed by another author YB. By reading the full texts of the selected studies, two investigators extracted the following data: name of all authors, year of publication, number of enrolled patients, age, sex, Eastern Cooperative Oncology Group performance status, Child-Pugh score, BCLC stage, tumour number, tumour size, type of treatment, reported HR for OS according to mRECIST and RECIST 1.1 criteria and k coefficient of concordance in each study.

Tumour response assessment
Evaluation of tumour response according to the RECIST 1.1 was defined as follows: complete response (CR) is the disappearance of all target lesions; partial response (PR) is at least a 30% decrease in the sum of the diameters of the target lesions; progressive disease (PD) is at least a 20% increase in the sum of the longest diameters of target lesions or the appearance of one or more new lesions; stable disease (SD) is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. According to mRECIST, CR is defined as the disappearance of any
intratumoural arterial enhancement in all target lesions; PR is at least a 30% decrease in the sum of diameters of viable target lesions, taking as reference the baseline sum of the diameters of target lesions; PD is an increase of at least 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded since the treatment started; SD is any cases that do not qualify for either PR or PD. Objective response (OR) included both CR and PR, and disease control included CR, PR and SD.8

Statistical analysis
Intermethod agreement between similar categorical items of the two criteria was measured using the k coefficient. The agreement was interpreted as poor (k<0), slight (k=0 to 0.20), fair (k=0.21 to 0.40), moderate (k=0.41 to 0.60), substantial (k=0.61 to 0.80) and almost perfect (k>0.80).18 The OR rate (ORR) and disease control rate (DCR) between the two criteria were compared by the chi-square tests with the significance at p<0.05. HRs with corresponding 95% CIs were performed to estimate the relationship between the ORR and OS of patients with HCC. The HRs were extracted from the text or from the K-M curves by the software Engauge Digitizer. The heterogeneity was quantified using the I² statistic. A fixed-effects model was used to analyse the results if the I²≤50%, whereas the random effects model is applied if the I²>50% among the included studies, funnel plots and Egger’s test were used to grossly exclude publication bias. All extracted data analyses were performed with Review Manager V.5.4.1 and STATA V.15.1 and SPSS V.24 software.

RESULTS

Eligible studies for analysis
A total of 7281 studies were retrieved from the electronic database search. After removing duplicates, 5046 titles and abstracts were further examined. A total of 114 publications underwent full text review to determine their eligibility for the meta-analysis and 91 were excluded. Forty-nine studies were excluded because they applied only the mRECIST or RECIST1.1 criteria alone. Fourteen studies were excluded because using other imaging examinations or other evaluative methods, such as positron emission tomography imaging, contrast-enhanced ultrasonography and RECIST 1.0. Twelve studies compared with other methods, such as Choi and EASL criteria, etc. Six studies were excluded because they were all conference abstracts. Three studies were excluded for unavailable for full text. Five studies were excluded for lacking of original data and had insufficient data for extraction. One study focused on manual and automatically extracted measurements. One research was written in Japanese.

Finally, 23 studies including 2563 patients comparing tumour response between the RECIST 1.1 and mRECIST criteria were included14–16 19–38 (figure 1).

Summary of baseline characteristics
A total of 2574 patients form 23 studies were included in qualitative analysis (table 1). A total of 1325 patients treated with sorafenib,14–16 19–25 27 34 36 37  21 patients treated with axitinib,26 839 patients treated with lenvatinib,28 30 31 33 35 36 38 37 91 patients treated with regorafenib29 and 10 patients treated with ramucirumab.32 Most studies included Child-Pugh class A and a minority of Child-Pugh class B patients, only two studies included a small percentage of Child-Pugh class C patients.27 29

Due to lacking of survival data, 7 studies including 566 patients were finally included in this meta-analysis. Six of the studies14 15 21 23 27 34 included 526 patients treated with sorafenib and 1 study30 included 40 patients treated with lenvatinib.

Evaluation of tumour response was performed according to the RECIST 1.1 and mRECIST criteria and assessment of response was carried out by contrast-enhanced spiral CT or gadolinium-enhanced MRI after 4–8 weeks from treatment, depending on each study (table 2).

Risk of bias within studies
All of 23 studies had good quality. The quality of included studies assessed by NOS was 6–8.

Comparison of tumour response between the RECIST 1.1 and mRECIST criteria
Table 3 shows the tumour response assessed by RECIST 1.1 and mRECIST after molecular targeted therapies in the 23 considered studies. The ORR according to mRECIST was significantly higher than RECIST1.1 (15.9% vs 7.8%, p<0.001). For DCR, four study was considered not eligible for its incomplete data.29 36–38 The DCR was similar
Table 1  Baseline characteristics of include studies

| Study       | Year | Country | Patients, N (n)* | Treatment | Women, no (%) | Age, years | ECOG PS | Child-Pugh class | BCLC stage | Tumour no | Tumour size (mm) |
|-------------|------|---------|-----------------|-----------|----------------|------------|---------|------------------|------------|-----------|------------------|
| Spira et al  | 2011 | Germany | 25 Sorafenib    | 2 (8.0%)  | 65 (42–75)†   | 0: 6 1 or 2: 19 | A: 23  | B: 2  | NR               | NR         | NR        |
| Murakami et al | 2011 | Japan   | 27 Sorafenib    | 1 (3.7%)  | NR             | A: 23  | B: 4              | NR         | NR        | NR               |
| Edeline et al | 2012 | France  | 53 Sorafenib    | 5 (9.4%)  | NR             | 0: 29 1: 24 | A: 41  | B: 12 | B: 22             | C: 31       | NR        |
| Moschouris et al | 2012 | UK      | 21 Sorafenib    | 2 (9.5%)  | 66.8±8.5‡      | A: 10 | B: 11           | B: 9 | C: 12 | Solitary: 9 Multifocal: 12 | NR |
| Kawaoka et al | 2012 | Japan   | 66 (49) Sorafenib | 8 (12.1%) | 63 (35–80)†   | A: 58  | B: 8             | NR         | 1–2: 16  | 50 (8.3–194)† |
| Arizumi et al | 2014 | Japan   | 156 Sorafenib   | 36 (23.1%) | 73 (66–78)†   | 0: 150 1: 5 2: 1 | A: 129 | B: 27 | A: 39 | B: 36 | C: 81 | NR |
| Bargellini et al | 2014 | Italy   | 22 Sorafenib    | 4 (18.2%) | 68.3±8.2‡      | NR       | A: 22  | B: 12  | C: 10 | >3: 11 | 50±37‡ |
| Ronot et al | 2014 | France  | 64 Sorafenib    | 8 (12.5%) | 62 (37–77)†   | NR       | A: 51  | B: 13 | B: 20 | C: 44 | NR |
| Salvaggio et al | 2014 | USA     | 17 Sorafenib    | 5 (29.4%) | 69 (58–79)†   | 0: 8 1: 9 | A: 16  | B: 1  | A: 3 | B: 4 | C: 10 | NR |
| McNamara et al | 2015 | Canada  | 30 (21) Axitinib | 9 (30.0%) | 64 (18–78)†  | 0: 9 1: 21 | A: 22  | B: 8  | C: 30 | NR | NR |
| Takada et al | 2015 | Japan   | 191 (175) Sorafenib | 78 (40.8%) | 72 (34–88)† | 0: 141 1: 47 2: 3 | A: 179 | B: 12 | A: 11 | B: 85 | C: 96 | NR |
| Gavanier et al | 2016 | France  | 60 Sorafenib    | 6 (10.0%) | 67 (39–79)†   | NR       | A: 42  | B: 13 | C: 5  | B: 12 | C: 48 | NR |
| Ikeda et al | 2017 | Japan   | 46 (42) Lenvatinib | 33 (71.7%) | 66.5 (37–80)† | 0: 38 1: 8 | A: 45  | B: 1  | B: 19 | C: 27 | NR |
| Pelosof et al | 2018 | USA     | 379 Regorafenib | 46 (12.1%) | 64 (19–85)† | 0: 251 1: 128 | A: 373 | B: 5 | A: 1 | B: 53 | C: 325 | NR |
| Kaneko et al | 2020 | Japan   | 40 Lenvatinib   | 4 (10.0%) | 72 (52–87)†   | 0: 25 1: 15 | A: 38  | B: 2 | B: 12 | C: 28 | NR | NR |
| Kawamura et al | 2020 | Japan   | 51 Lenvatinib   | 16 (31.4%) | 74 (45–91)† | 0: 48 1: 3 | A: 51 | B: 23 | C: 23 | NR | 31.8 (11.0–112.7)† |

Continued
| Study               | Year | Country | Patients, N (n)* | Treatment           | Women, no (%) | Age, years | ECOG PS | Child-Pugh class | BCLC stage | Tumour no | Tumour size (mm) |
|--------------------|------|---------|-----------------|---------------------|---------------|------------|---------|------------------|------------|-----------|------------------|
| Kuzuya et al[22]   | 2020 | Japan   | 10              | Ramucirumab         | 5 (50.0%)     | 76 (42–89) | 0: 7    | A: 9            | B: 6       | <4: 2>4: 8 | <30: 8>30: 2    |
| Maruta et al[23]   | 2020 | Japan   | 152 (131)       | Lenvatinib          | 24 (15.8%)    | >73:74 (49%) | ≤1: 142 | A: 132          | C: 99      | >7: 70    | >50: 51          |
| Yamamichi et al[24]| 2020 | Japan   | 22              | Sorafenib           | 2 (9.1%)      | 76 (50–86) | 0: 19   | A: 22           | C: 22      | NR        | NR               |
| He et al[25]       | 2021 | China   | 86              | Lenvatinib          | 6 (10.5)      | >50: 44 (51.2%) | 0: 22   | A: 86           | C: 86      | 1-3:9     | ≤10:40           |
| Nair et al[26]     | 2021 | USA     | LEN 478/ SOR 476| Lenvatinib/Sorafenib| LEN 73 (15.3)| LEN <65: 56%| LEN 0: 301 B: 3| L: 104 C: 374 SOR A: 471 B: 5| LEN 1: 207 C: 384 B: 92 C: 384| NR
| Salem et al[27]    | 2021 | USA     | 165 (158)       | Sorafenib           | 28 (17.0)     | 64.4±10.9 | NR      | A: 165          | NR         | NR        | NR               |
| Yamashige et al[28]| 2021 | Japan   | 11              | Lenvatinib          | 3 (27.3)      | 67 (59-83) | NR      | A: 11           | B: 6       | NR        | NR               |

*N=Number of included patients; n=Number of patients evaluated by RECIST 1.1 and mRECSIT criteria.
†Data are medians, with IQR in parentheses.
‡Data are means±SD.
BCLC stage, Barcelona Clinic Liver Cancer stage; ECOG PS, Eastern Cooperative Oncology Group performance status; LEN, Lenvatinib; mRECSIT, modified Response Evaluation Criteria in Solid Tumours; NR, not reported; SOR, Sorafenib.
The agreement and disagreement of tumour response of the two criteria were described in Table 4, which could be available or calculated from 8 studies including 372 patients.15 16 20–22 25 26 38 For OR, the agreement of tumour response between the two criteria was moderate (k=0.499). Of 218 patients with SD according to RECIST 1.1, 45 patients were reclassified to OR according to mRECIST. For disease control, the agreement of tumour response between the two criteria was almost perfect (k=0.901). Of 116 patients with PD according to mRECIST, only 5 patients were reclassified to SD according to RECIST 1.1.

Subgroup analysis was performed based on therapeutic agents. Of the total of 8 studies included in the consistency test, 6 studies15 16 20–22 25 including 340 patients receiving sorafenib, 1 study38 with 11 patients treated with lenvatinib and 1 study26 with 21 patients treated with axitinib. Limited by the sample size, we only performed an analysis of concordance in the sorafenib group. For
| Study                  | N   | Criterion          | CR | PR | SD | PD |
|-----------------------|-----|--------------------|----|----|----|----|
| Spira et al[25]       | 25  | RECIST1.1          | 1  | 0  | 18 | 6  |
|                       |     | mRECIST            | 1  | 11 | 9  | 4  |
| Edeline et al[18]     | 53  | RECIST1.1          | 0  | 1  | 42 | 10 |
|                       |     | mRECIST            | 2  | 10 | 30 | 11 |
| Moschouris et al[22]  | 21  | RECIST1.1          | 0  | 1  | 16 | 4  |
|                       |     | mRECIST            | 2  | 6  | 11 | 2  |
| Kawaoka et al[21]     | 49  | RECIST1.1          | 1  | 1  | 30 | 17 |
|                       |     | mRECIST            | 2  | 4  | 26 | 17 |
| Arizumi et al[23]     | 156 | RECIST1.1          | 3  | 12 | 71 | 70 |
|                       |     | mRECIST            | 6  | 30 | 55 | 65 |
| Bargellini et al[24]  | 22  | RECIST1.1          | 0  | 1  | 5  | 16 |
|                       |     | mRECIST            | 0  | 4  | 5  | 13 |
| Ronot et al[14]       | 64  | RECIST1.1          | 2  | 43 | 19 |
|                       |     | mRECIST            | 18 | 29 | 17 |
| Salvaggio et al[25]   | 17  | RECIST1.1          | 0  | 2  | 10 | 5  |
|                       |     | mRECIST            | 0  | 3  | 10 | 4  |
| McNamara et al[18]    | 21  | RECIST1.1          | 0  | 2  | 19 | 0  |
|                       |     | mRECIST            | 1  | 6  | 14 | 0  |
| Takada et al[19]      | 175 | RECIST1.1          | 4  | 11 | 80 | 80 |
|                       |     | mRECIST            | 5  | 20 | 72 | 78 |
| Gavanier et al[27]    | 60  | RECIST1.1          | 0  | 2  | 28 | 30 |
|                       |     | mRECIST            | 0  | 4  | 27 | 29 |
| Ikeda et al[29]       | 42  | RECIST1.1          | 0  | 11 | 25 | 6  |
|                       |     | mRECIST            | 0  | 17 | 19 | 6  |
| Pelosof et al[29]     | 379 | RECIST1.1          | 0  | 25 | 354|
|                       |     | mRECIST            | 2  | 38 | 339|
| Kaneko et al[30]      | 40  | RECIST1.1          | 1  | 9  | 21 | 9  |
|                       |     | mRECIST            | 3  | 12 | 9  | 4  |
| Kawamura et al[31]    | 51  | RECIST1.1          | 0  | 26 | 21 | 4  |
|                       |     | mRECIST            | 6  | 32 | 9  | 4  |
| Kuzuya et al[32]      | 10  | RECIST1.1          | 0  | 0  | 8  | 2  |
|                       |     | mRECIST            | 0  | 1  | 7  | 2  |
| Maruta et al[33]      | 131 | RECIST1.1          | 2  | 22 | 78 | 29 |
|                       |     | mRECIST            | 3  | 59 | 42 | 27 |
| Yamamichi et al[24]   | 22  | RECIST1.1          | 1  | 1  | 12 | 8  |
|                       |     | mRECIST            | 1  | 1  | 7  | 13 |
| Murakami et al[19]    | 27  | RECIST1.1          | 0  | 0  | 16 | 11 |
|                       |     | mRECIST            | 1  | 2  | 13 | 11 |
| He et al[35]          | 86  | RECIST1.1          | 0  | 8  | 54 | 24 |
|                       |     | mRECIST            | 0  | 14 | 48 | 24 |
| Nair et al[36]        |     | LEN: 478           | 19 | 459|
|                       |     | mRECIST            | 41 | 437|
|                       |     | SOR: 476           | 7  | 469|
|                       |     | mRECIST            | 12 | 464|
| Salem et al[37]       | 158 | RECIST1.1          | 18 | 140|
|                       |     | mRECIST            | 22 | 136|
| Yamashige et al[38]   | 11  | RECIST1.1          | 6  | 5  |
|                       |     | mRECIST            | 9  | 2  |

CR, complete response; LEN, Lenvatinib; mRECIST, modified RECIST; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; SOR, Sorafenib.
OR, the agreement of tumour response between the two criteria was moderate (κ = 0.446). For disease control, the agreement of tumour response between the two criteria was almost perfect (κ = 0.897).

Survival analysis according to the RECIST 1.1 and mRECIST criteria

Of the 19 articles, 12 studies were excluded due to lack of survival data. Finally, 7 studies including 566 patients were included in this meta-analysis. The ORR according to RECIST 1.1 and mRECIST criteria was 7.79% and 15.93%, respectively. According to mRECIST, OS was significantly longer in patients with response than patients with non-response (HR 0.56, 95% CI 0.41 to 0.78, p = 0.0004) (figure 2), with no significant heterogeneity among the studies (I² = 0, p = 0.93). In contrast, RECIST 1.1 could not distinguish well between the responders and the non-responders for OS (HR 0.68, 95% CI 0.44 to 1.05, p = 0.08) (figure 3), with no significant heterogeneity among the studies (I² = 0, p = 0.43). Funnel plots for both RECIST 1.1 and mRECIST did not show asymmetry (online supplemental figures 1; 2). Egger’s test also showed no clear evidence of publication bias (p = 0.052 for RECIST1.1 and p = 0.503 for mRECIST).

Subgroup analysis was performed based on therapeutic agents. Of the total of 7 studies included in the survival analysis, 6 studies including 526 patients receiving sorafenib and 1 study with 40 patients treated with lenvatinib.

As shown in figures 4 and 5, among patients receiving sorafenib, when mRECIST was used as an evaluation criterion, OS was significantly longer in patients who responded (HR 0.56, 95% CI 0.40 to 0.77), while using RECIST 1.1 as the evaluation criterion failed to clearly distinguish between responder and non-responder (HR 0.67, 95% CI 0.42 to 1.04). Possibly limited by sample size, tumour response assessed using mRECIST or RECIST 1.1 did not differentiate well between OS in responders and non-responders for patients receiving lenvatinib (HR 0.76, 95% CI 0.19 to 3.13 vs HR 0.90, 95% CI 0.16 to 5.13). No significant heterogeneity was found in the subgroup analysis.

DISCUSSION

Tumour response assessment is critical in the management of cancer. It serves as a guide to clinical practice and as a surrogate endpoint for evaluating efficacy in clinical studies. In particular, an increasing number of patients with HCC have been treated with molecularly targeted therapies in recent years.

Since new molecular targeted agents exert antitumoural activity by inducing tumour necrosis, with rare changes in volume shrinkage, traditional WHO and RECIST criteria do not always represent an appropriate tool for response evaluation. Anatomic imaging alone may have limitations, particularly in assessing the activity of targeted therapies which stabilise diseases. This promoted the development of the mRECIST for a response that incorporated treatment-induced tumour necrosis by dynamic imaging. In this study, we compared the effectiveness of the RECIST 1.1 and mRECIST criteria in assessing the efficacy of molecular targeted therapies in patient with HCC.

We investigated the concordance between the RECIST 1.1 and mRECIST criteria for the assessment of tumour response in patients with HCC treated with molecular targeted therapies. Our results showed that there was a considerable discrepancy in the assessment of OR between the RECIST 1.1 and mRECIST criteria. When adopting the mRECIST, the ORR was significantly higher, suggesting that mRECIST better identifies the response of HCC after molecularly targeted therapy. There are several possible reasons. First, molecular targeted therapies...
are based on the inhibition of several proangiogenic signalling pathways, which stimulating angiogenesis, are responsible of the characteristic hyper-vascular pattern of HCC lesions. The therapeutic response after molecularly targeted therapy is closely associated with structural changes, mainly including decreased vascularisation and increased tissue necrosis or cavitation, but it is not always reflected in the reduction in tumour size. Second, HCC and cirrhosis coexist in more than 80% of cases. The inherent pathogenic factors and haemodynamic changes of cirrhosis may mimic or mask intrahepatic tumours.

From a clinical perspective, clinicians need to accurately distinguish between PD and disease control, and thus make clinical decisions to switch from first-line to second-line treatment when disease progresses. We also found that there was an excellent agreement in the assessment of the disease progression between the RECIST 1.1 and mRECIST criteria, both of the criteria are equally able to discriminate progressors and non-progressors and thus equally allow to give appropriate guidance for clinical decision making, which is the most relevant parameter in clinical practice. And we presume that this consistency is due to the fact that disease progression appears to involve an increase in vascularisation, which transforms into an increase in lesion dimension. In general, it is assumed that interoperator variability can affect the interpretation of the same image, even when guided by the same evaluation criteria. In particular, evaluation based on mRECIST addresses the subjectivity of the reviewer. However, it has been shown that in the evaluation of disease control, there is still a high level of agreement between the results obtained by experts and those without specialist training in liver imaging (k=0.737±0.114).

Our results also show that mRECIST can be of help in predicting OS in patients receiving molecular targeted therapies. Those patients with OR having significantly better survival outcome compared with patients who only achieve SD or PD. However, the OS of those classified as OR by RECIST 1.1 is not significantly different from that of non-responders. Edeline et al demonstrated that in the 79.2% of patients classified as stable by RECIST 1.1, the use of mRECIST enabled the prediction of different prognostic subgroups with a significantly better median OS of 17.1 months for responding patients compared with 9.7 months for stable patients and 3.7 months in patients who had a PD. Our results suggest that mRECIST may offer a suitable alternative to RECIST in phase II clinical trials, in which detection of an efficacy signal is paramount.
However, as previously mentioned, mRECIST did not demonstrate superiority in guiding the replacement of second-line therapeutic agents.

In addition, we find that most of included patients were classified as PD. Patients with PD always have a poor outcome. Treatment beyond radiological progression is not warranted and that patients should be actively monitored for radiological progression rather than waiting for symptomatic progression. A recent review indicated that ‘PD’ concept includes different patterns of progression leading to different prognosis. The reason for the imperfect correlation between surrogate end point and OS likely relies on the basis that not all patterns of progressions are equal in terms of prognostic implications. In a brilliant paper, Reig et al demonstrated that the appearance of new extrahepatic lesions has a far worse prognostic impact than the enlargement of pre-existing lesions or the appearance of new intrahepatic nodules. Thus, a careful evaluation of the progression pattern is indeed required in clinical practice before switching to a second line treatment.

There are several limitations in our study. First, most of the included studies were retrospective. Second, this study included heterogeneous patients with different kinds of therapeutic agents and the variable interval between follow-up imaging examinations. It is necessary to verify these results in studies with larger homogeneous patients’ cohort.

In conclusion, RECIST 1.1 has similar efficacy to mRECIST in assessing disease progression with molecularly targeted drugs, but mRECIST is better at identifying OR. And mRECIST appears more appropriate than RECIST 1.1 to identify responders with long survival benefitting from molecular targeted therapies in patients with HCC.

Figure 5

| Study or Subgroup | log(Hazard Ratio) | SE Weight | Hazard Ratio (IV, Fixed, 95% CI) Year | Hazard Ratio (IV, Fixed, 95% CI) |
|-------------------|------------------|-----------|--------------------------------------|----------------------------------|
| 1.4.1 Sorafenib   | -0.5778          | 0.7396    | 0.59 [0.14, 2.49] 2014               |                                  |
| Kawacka 2012      | -1.0724          | 0.8056    | 0.34 [0.06, 1.52] 2012               |                                  |
| Artzi 2014        | -0.5276          | 0.7339    | 0.59 [0.14, 2.49] 2014               |                                  |
| Ronot 2014        | -1.0051          | 0.58      | 0.34 [0.11, 1.06] 2014               |                                  |
| Takada 2015       | 0.1381           | 0.3299    | 1.13 [0.80, 1.59] 2015               |                                  |
| Gavant 2016       | -0.7499          | 0.6989    | 0.47 [0.12, 1.60] 2016               |                                  |
| Yamaichi 2020     | -1.1572          | 0.7955    | 0.31 [0.07, 1.49] 2020               |                                  |
| Subtotal (95% CI) | 93.8%            | 0.67      | 94.2% (1.42, 1.04)                  |                                  |

Heterogeneity: $P = 5.81$, df = 5 ($P = 0.32$); $I^2 = 14$

Test for overall effect: $Z = 1.77$ ($P = 0.08$)

1.4.2 Lencatinib

| Study or Subgroup | log(Hazard Ratio) | SE Weight | Hazard Ratio (IV, Fixed, 95% CI) Year | Hazard Ratio (IV, Fixed, 95% CI) |
|-------------------|------------------|-----------|--------------------------------------|----------------------------------|
| Kaneo 2019        | -0.11            | 0.69      | 0.90 [0.16, 5.13] 2019               |                                  |
| Subtotal (95% CI) | 6.2%             | 0.90      | 0.90 [0.16, 5.13] 2019               |                                  |

Heterogeneity: Not applicable

Test for overall effect: $Z = 0.12$ ($P = 0.90$)

Total (95% CI):

| Study or Subgroup | log(Hazard Ratio) | SE Weight | Hazard Ratio (IV, Fixed, 95% CI) Year | Hazard Ratio (IV, Fixed, 95% CI) |
|-------------------|------------------|-----------|--------------------------------------|----------------------------------|
| Kaneo 2019        | -0.11            | 0.69      | 0.90 [0.16, 5.13] 2019               |                                  |
| Subtotal (95% CI) | 6.2%             | 0.90      | 0.90 [0.16, 5.13] 2019               |                                  |

Heterogeneity: $P = 0.62$, df = 6 ($P = 0.43$); $I^2 = 0$

Test for overall effect: $Z = 1.75$ ($P = 0.08$)

Test for subgroup differences: $P = 0.10$, df = 1 ($P = 0.75$); $I^2 = 0$

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