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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 systemic 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 RECIST1.1 (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 objective response (k=0.499) and perfect for progressive disease (k=0.901), calculated from 8 studies including 372 patients. OS was significantly longer in response group than non-response group according to mRECIST (HR 0.56, 95% CI 0.41 to 0.78, p=0.0004) calculated from 7 studies including 566 patients, however, the RECIST1.1 could not distinguish the OS well (HR 0.68, 95% CI 0.44 to 1.05, p=0.08). Subgroup analusis by type of treatment was conducted.

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.

PROSPERO registration number CRD42020200895.

Ethics approval Ethics approval is not required in this meta-analysis.

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.[4] 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,[5] 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.[6 7] Nevertheless, they have been proven to correlate poorly with survival outcomes in HCC patients and provide insufficient guidance on treatment options.[8–10] 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,[11] 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.[8]

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.[3 12] However, National Comprehensive Cancer Network guideline indicated that validated criterion to evaluate tumour response to molecular targeted therapies between the two criteria is needed.[13] 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.[14 15] On the contrary, another study observed both methods provided correlation with OS equally.[16] Which set of criteria is better to assess 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.[17] 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

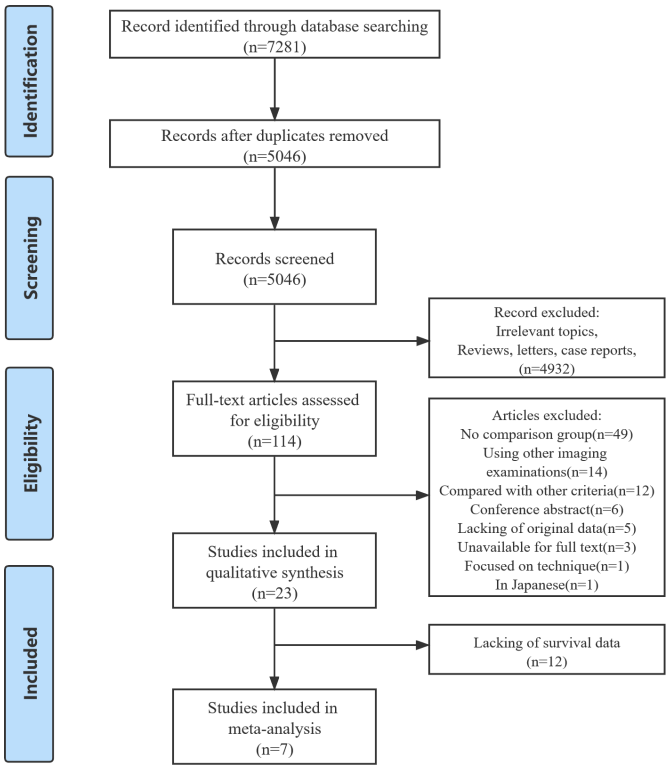

Figure 1 Flow diagram of study selection.

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 I^2 statistic. A fixed-effects model was used to analyse the results if the $I^2 \leq 50\%$, whereas the random effects model is applied if the $I^2 > 50\%$ 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 included[14–16 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] 379 patients treated with regorafenib[29] 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 studies[14 15 21 23 27 34] included 526 patients treated with sorafenib and 1 study[30] 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*[20]	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*[19]	2011	Japan	27	Sorafenib	1 (3.7%)	63	NR	A: 23 B: 4	NR	NR	NR
Edeline *et al*[16]	2012	France	53	Sorafenib	5 (9.4%)	NR	0: 29 1: 24	A: 41 B: 12	B: 22 C: 31	NR	NR
Moschouris *et al*[22]	2012	UK	21	Sorafenib	2 (9.5%)	66.8±8.5‡	NR	A: 10 B: 11	B: 9 C: 12	Solitary: 9 Multifocal: 12	NR
Kawaoka *et al*[21]	2012	Japan	66 (49)	Sorafenib	8 (12.1%)	63 (35–80)†	NR	A: 58 B: 8	0: 2 A: 1 B: 14 C: 49	1–2: 16 />3: 50	50 (8.3–194)†
Arizumi *et al*[23]	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	NR
Bargellini *et al*[24]	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*[14]	2014	France	64	Sorafenib	8 (12.5%)	62 (37–77)†	NR	A: 51 B: 13	B: 20 C: 44	NR	NR
Salvaggio *et al*[25]	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	NR
McNamara *et al*[26]	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*[15]	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: 95	NR	NR
Gavanier *et al*[27]	2016	France	60	Sorafenib	6 (10.0%)	67 (39–79)†	NR	A: 42 B: 13 C: 5	B: 12 C: 48	NR	NR
Ikeda *et al*[28]	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	NR
Pelosof *et al*[29]	2018	USA	379	Regorafenib	46 (12.1%)	64 (19–85)†	0: 251 1: 128	A: 373 B: 5 C: 1	A: 1 B: 53 C: 325	NR	NR
Kaneko *et al*[30]	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*[31]	2020	Japan	51	Lenvatinib	16 (31.4%)	74 (45–91)†	0: 48 1: 3	A:51	A: 5 B: 23 C: 23	NR	31.8 (11.0–112.7)†

Continued

Table 1 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*[32]	2020	Japan	10	Ramucirumab	5 (50.0%)	76 (42–89)†	0: 7 1: 3	A: 9 B: 1	B: 6 C: 4	<4: 2>4: 8	<30: 8>30: 2
Maruta *et al*[33]	2020	Japan	152 (131)	Lenvatinib	24 (15.8%)	>73:74 (49%)	≤1: 142 >1: 10	A: 132 B: 20	C: 99	>7: 70	>50: 51
Yamamichi *et al*[34]	2020	Japan	22	Sorafenib	2 (9.1%)	76 (50–86)†	0: 19 1: 3	A:22	C: 22	NR	NR
He *et al*[35]	2021	China	86	Lenvatinib	6 (10.5)	>50: 44 (51.2%)	0: 22 1: 64	A: 86	C: 86	1-3:9 >3:77	≤10:40 >10:46
Nair *et al*[36]	2021	USA	LEN 478/ SOR 476	Lenvatinib/ Sorafenib	LEN 73 (15.3) SOR 75 (15.7)	LEN <65: 56% SOR <65: 60%	LEN 0: 301 1: 177 SOR 0: 299 1: 177	LEN A: 475 B: 3 SOR A: 471 B: 5	LEN B: 104 C: 374 SOR B: 92 C: 384	LEN 1: 207 2: 167 3: 103 SOR 1: 207 2: 183 3: 86	NR
Salem *et al*[37]	2021	USA	165(158)	Sorafenib	28 (17.0)	64.4±10.9	NR	A: 165	NR	NR	NR
Yamashige *et al*[38]	2021	Japan	11	Lenvatinib	3 (27.3)	67 (59-83)	NR	A: 11	B: 6 C: 5	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.

Table 2 Time interval and imaging examinations

Included trials	Exam	Time interval	Response considered
Spira *et al*[20]	MRI	At baseline and follow-up every 8 weeks (range, 2–19 weeks; mean, 7.6 weeks).	Target response
Edeline *et al*[16]	CT	1 CT scan in the first and second months and every 2 months thereafter.	Target response
Moschouris *et al*[22]	CT/MRI	1–5 days prior to the initiation of antiangiogenetic treatment; follow-up studies were performed approximately every 2 months (range: 7–10 weeks) after the first dose of the drug.	Target response
Kawaoka *et al*[21]	CT/MRI	At 8 weeks from the date of administration of sorafenib.	Overall response
Arizumi *et al*[23]	CT/MRI	Every 4–6 weeks during and after treatment.	Overall response
Bargellini *et al*[24]	CT	4±2 weeks before and 8±2 weeks after initiation of sorafenib treatment.	Overall response
Ronot *et al*[14]	CT	6 weeks before sorafenib and had the first tumour evaluation with a second CT scan within 1–3 months after sorafenib initiation.	Overall response
Salvaggio *et al*[25]	CT/MRI	Baseline examinations were performed at a median of 30 days (range 28–36 days) before the start of treatment. Follow-up imaging study available was performed after a median of 103 days (range 55–617 days).	Target response
McNamara *et al*[26]	CT	Tumour response was assessed every 8 weeks via CT.	Overall response
Takada *et al*[15]	CT	Within 1 month of commencing treatment and every 1–2 months during treatment.	Overall response
Gavanier *et al*[27]	CT	Within 6 weeks before sorafenib administration; and Imaging available during sorafenib therapy (>4 weeks after initiation).	Overall response
Ikeda *et al*[28]	CT/MRI	Tumour response was evaluated every 8 weeks.	Overall response
Pelosof *et al*[29]	CT/MRI	Tumour assessments were performed every 6 weeks for the first eight cycles, then every 12 weeks thereafter.	Overall response
Kaneko *et al*[30]	CT	CT was performed at baseline and every 4–8 weeks after LEN administration.	Overall response
Kawamura *et al*[31]	CT	We assessed the best tumour response during 2–12 weeks.	Overall response
Kuzuya *et al*[32]	CT	CT examination was performed with a predetermined schedule at baseline and at 6 weeks after ramucirumab initiation.	Overall response
Maruta *et al*[33]	CT/MRI	Every 1–2 months after starting treatment for the evaluation of tumour response.	Overall response
Yamamichi *et al*[34]	CT	CT was performed at baseline (before initiation of treatment) and at every 2–3 months afterward.	Overall response
Murakami *et al*[19]	CT	CT was performed at baseline (before initiation of treatment) and at every 2–3 months afterward.	Overall response
He *et al*[35]	CT/MRI	Upper abdomen-enhanced CT (or MRI) was performed at baseline and every 6 weeks (±1 week).	Overall response
Nair *et al*[36]	CT/MRI	Enhanced CT or MRI was performed at baseline and every 8 weeks.	Overall response
Salem *et al*[37]	CT/MRI	Enhanced CT or MRI was performe at baseline and every 6 weeks.	Target response
Yamashige *et al*[38]	CT	Enhanced CT was performed at baseline and every 2–12 weeks.	Target response

LEN, Lenvatinib.

according to mRECIST and RECIST1.1 (68.4% vs 67.2%, p=0.5).

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 studies[15 16 20–22 25] including 340 patients receiving sorafenib, 1 study[38] with 11 patients treated with lenvatinib and 1 study[26] with 21 patients treated with axitinib. Limited by the sample size, we only performed an analysis of concordance in the sorafenib group. For

Table 3 Response assessment according to RECIST 1.1 and mRECIST criteria

Study	N	Criterion	CR	PR	SD	PD
Spira *et al*[20]	25	RECIST1.1	1	0	18	6
		mRECIST	1	11	9	4
Edeline *et al*[16]	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*[26]	21	RECIST1.1	0	2	19	0
		mRECIST	1	6	14	0
Takada *et al*[15]	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*[28]	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*[34]	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	RECIST1.1	19		459	
		mRECIST	41		437	
	SOR: 476	RECIST1.1	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.

Table 4 Intermethod agreement between RECIST 1.1 and mRECIST criteria

Tumour response by RECIST 1.1	Tumour response by mRECIST				
	CR	PR	SD	PD	Total
CR	6	0	0	0	6
PR	5	21	0	0	26
SD	4	41	168	5	218
PD	1	4	6	111	122
Total	16	66	174	116	372

CR, complete response; mRECIST, modified RECIST; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease.

OR, the agreement of tumour response between the two criteria was moderate (k=0.446). For disease control, the agreement of tumour response between the two criteria was almost perfect (k=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.[14 15 21 23 27 30 34] 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 (I^2=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 ((I^2=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[14 15 21 23 27 34] including 526 patients receiving sorafenib and 1 study[30] 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 criticalin the management of cancer. It serves as a guide to clinical practice and asa surrogate endpoint for evaluating efficacy in clinical studies.[39 40] 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

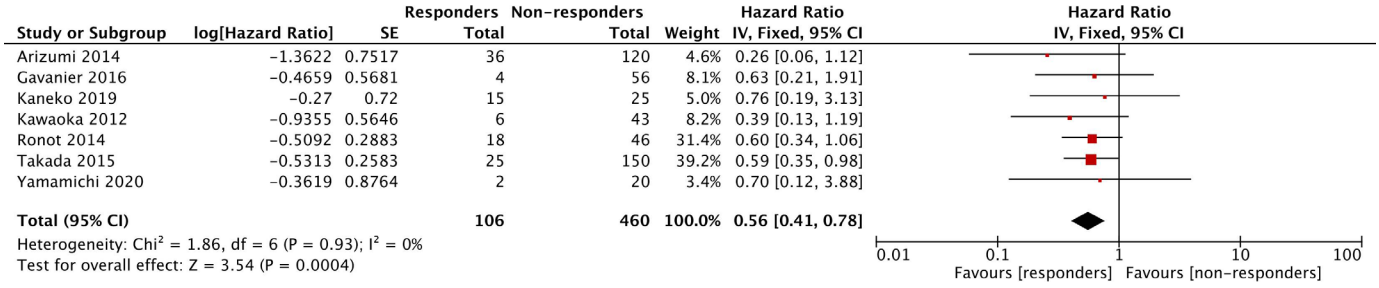

Figure 2 Forest plot for HR for overall survival (responders vs non-responders) according to mRECIST. IV, inverse variance; mRECIST, modified Response Evaluation Criteria in Solid Tumours.

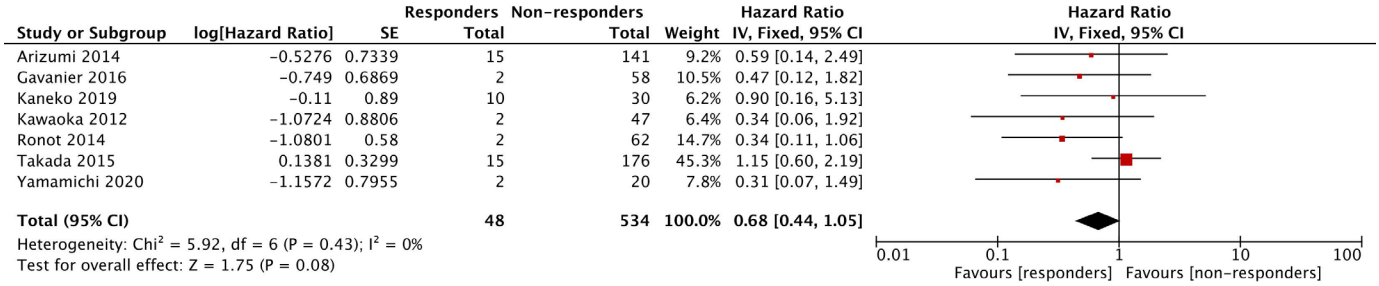

Figure 3 Forest plot for HR for overall survival (responders vs non-responders) according to RECIST1.1. IV, inverse variance; RECIST1.1, modified Response Evaluation Criteria in Solid Tumours version 1.1.

are based on the inhibition of several proangiogenic signalling pathways, which stimulating angiogenesis, are responsible of the characteristic hyper-vascular pattern of HCC lesions.[41] 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.[42] 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.[43]

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 able 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).[44]

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.[16] 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.

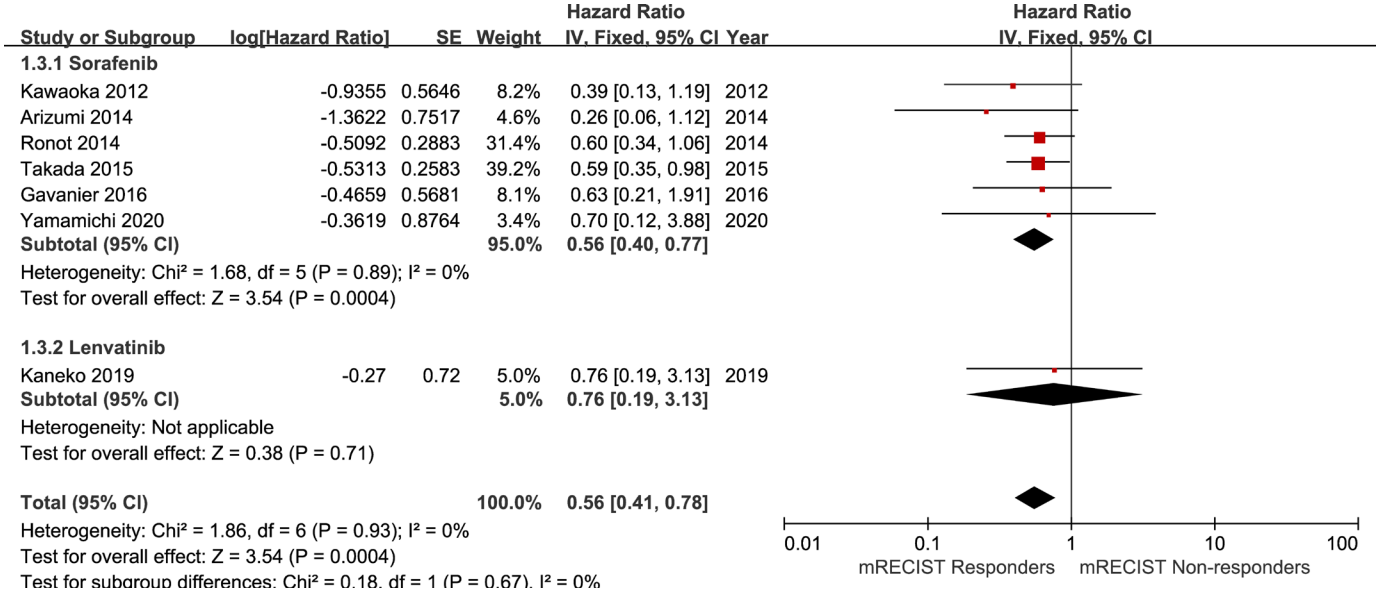

Figure 4 Subgroup analysis for the association between response and overall survival according to mRECIST. IV, inverse variance; mRECIST, modified Response Evaluation Criteria in Solid Tumours version 1.1.

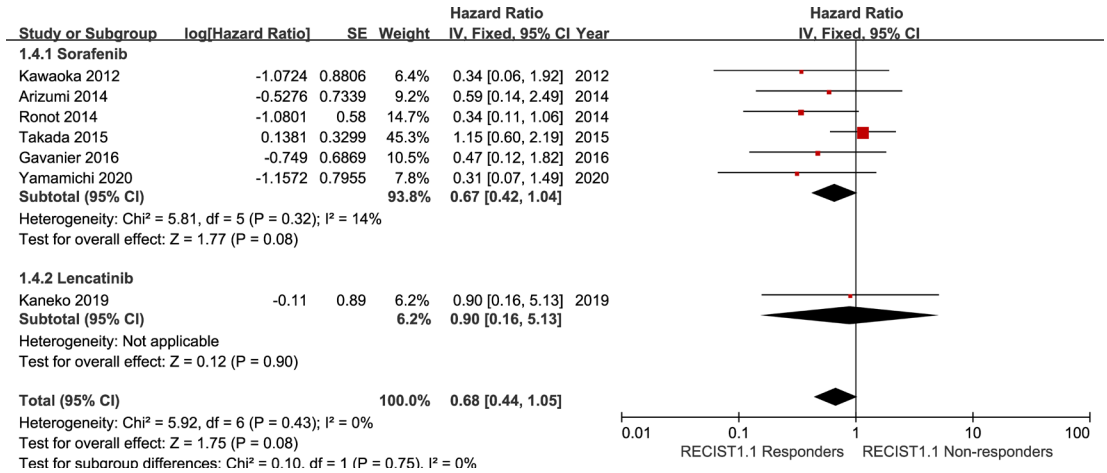

Figure 5 Subgroup analysis for the association between response and overall survival according to RECIST1.1. IV, inverse variance; RECIST, Response Evaluation Criteria in Solid Tumours.

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.[45] 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 benefiting from molecular targeted therapies in patients with HCC.

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