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ORIGINAL ARTICLE

Comparison of computed tomography imaging analyses for evaluation after chemotherapy in patients with colorectal cancer: a retrospective pooled analysis of six phase II clinical trials

Kosuke Hirose[1] · Eiji Oki[1] · Takayuki Shimose[2] · Sanae Sakamoto[3] · Shun Sasaki[1] · Tomoko Jogo[1] · Qingjiang Hu[1] · Yasuo Tsuda[1] · Koji Ando[1] · Yuichiro Nakashima[1] · Hiroshi Saeki[1] · Masaki Mori[1]

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Abstract

Background There are several methods for analyzing computed tomography (CT) images to evaluate chemotherapy efficacy in clinical studies. However, the optimal analysis method for each drug is still under debate. We conducted a pooled analysis using data from six phase II studies to evaluate four analysis methods in colorectal cancers (CRCs): morphological responses (MRs), early tumor shrinkage (ETS), depth of response (DpR), and response evaluation criteria in solid tumors (RECIST) ver.1.1.

Methods We included 249 patients in this analysis. Pretreatments and findings of subsequent CT imaging were analyzed based on the MR, ETS, DpR, and RECIST ver.1.1. Differences in overall survival (OS) between the responders and non-responders according to each method were evaluated using survival analysis.

Results The responders had significantly better hazard ratios (HRs) for OS, in terms of DpR (≥ median), ETS, objective response rate (ORR) [complete response (CR) + partial response (PR)], and disease control rate [CR + PR + stable disease (SD)]. Patients with right-sided colon cancers showed better HRs for DpR, but not for ETS and ORR. Contrastingly, patients with left-sided CRCs had better HRs for ETS, DpR, and ORR. MR was not associated with outcomes in this study, even in cases where bevacizumab was used. In patients with liver metastasis, ETS, DpR, and ORR showed better HRs, but not in those with lung metastasis.

Conclusion Early tumor shrinkage and DpR might be predictive markers only in left-sided CRCs with liver metastasis. Each imaging analysis has a different value based on the primary and metastatic sites.

Keywords Colorectal cancer · Early tumor shrinkage · Morphologic response · Deepness of response · Primary location · Clinical trial

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide [1]. Advances in treatment with new drugs, including bevacizumab and cetuximab, have increased the median survival time from 12 up to 30 months for metastatic CRC (mCRC) [2–4]. Globally, various clinical studies have been carried out with the goal of further prolonging survival in patients with mCRC. Tumor response to chemotherapy in these studies was generally evaluated based on changes in tumor size as per the response evaluation criteria in solid tumors (RECIST) and its modified version 1.1 [5]. However, recent findings suggest that evaluation of tumor size may have its limitations in monitoring the response to drugs and predicting overall survival (OS),

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✉ Eiji Oki
okieiji@surg2.med.kyushu-u.ac.jp

[1] Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-0054, Fukuoka, Japan

[2] Clinical Research Support Center Kyushu (CReS Kyushu), 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-0054, Fukuoka, Japan

[3] Kyushu Study Group of Clinical Cancer (KSCC), 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-0054, Fukuoka, Japan

especially with antiangiogenic therapies [6]. Therefore, some evaluation criteria based on computed tomography (CT) imaging have been proposed.

While treating mCRC with bevacizumab, morphologic response (MR) criteria, which are based on changes in tumor densities of liver metastases, are believed to be superior to RECIST in predicting OS and pathological response [7]. Further, early tumor shrinkage (ETS), which is marked by a decrease in the diameter of the targeted tumor in the first 6 weeks [8], has also been shown to be a good prognostic marker for the effectiveness of angiogenesis and epidermal growth factor receptor inhibitors [9, 10]. The depth of response (DpR), which is the percentage of shrinkage measured at the tumor's nadir size, has been reported to reflect long-term outcomes with cetuximab [11, 12].

Furthermore, the importance of the primary tumor site in CRCs, as well as differences in the clinical and molecular characteristics between right- and left-sided CRCs have been recently reported [13–16].

Using CT images from different subgroups of CRCs, this study analyzes the differences among the four methods for evaluating CT images.

Patients and methods

Study design

We performed an ad hoc analysis of CT images using ETS, DpR, MR criteria and RECIST ver.1.1. from patients with advanced and unresectable CRCs to determine the effects of chemotherapeutic agents used, to identify primary tumor locations, to identify metastatic organs, and to determine which evaluation method was the most suitable for each CRC subgroup. Patients included in this study were selected from six multi-institutional phase II randomized trials [KSCC (Kyushu Study group of Clinical Cancer) 0701, 0801, 0802, 0902, 1002, 1101] [17–22] that evaluated the effects of first-line chemotherapies in patients with advanced and unresectable CRCs. The characteristics of each trial are summarized in Table 1. The characteristics of the full analysis set (FAS) are shown in Online Resource Supplementary Table 1. The registration and follow-up period were defined as reported previously [17–22]. OS was defined as the period from the date of enrollment to the date of death due to any reason. The median follow-up period for each trial is shown

Table 1 Baseline characteristics of the trials

Factors	*N*	Trial number performed in KSCC						Total
		0701	0801	0802	0902	1002	1101	
		20 (%)	44 (%)	37 (%)	43 (%)	31 (%)	33 (%)	208
Age	Median (range)	66.50 (48–74)	59.00 (37–75)	63.00 (37–74)	69.00 (45–81)	63.00 (48–83)	64.00 (44–80)	64.00 (37–83)
Gender	Male	16 (80.0)	27 (61.4)	28 (75.7)	26 (60.5)	19 (61.3)	21 (63.6)	137 (65.9)
	Female	4 (20.0)	17 (38.6)	9 (24.3)	17 (39.5)	12 (38.7)	12 (36.4)	71 (34.1)
BMI	Mean ± SD	22.34 ± 3.73	21.89 ± 3.82	22.13 ± 3.49	21.71 ± 2.28	21.89 ± 3.58	21.33 ± 3.33	21.85 ± 3.34
cStage	I	N.I.	N.I.	N.I.	0 (0.0)	1 (3.2)	0 (0.0)	–
	II–III	N.I.	N.I.	N.I.	20 (46.5)	2 (6.5)	7 (21.2)	–
	IV	N.I.	N.I.	N.I.	23(53.5)	28 (90.3)	26 (78.8)	–
ECOG PS	0	16 (80.0)	41 (93.2)	35 (94.6)	37 (86.0)	25 (80.6)	28 (84.8)	182
	1	4 (20.0)	3 (6.8)	2 (5.4)	5 (11.6)	6 (19.4)	5 (15.2)	25
	2	0	0	0	1 (2.4)	0	0	1
Location	Right-sided	4 (57.1)	16 (36.4)	N.I.	12 (27.9)	7 (22.6)	10 (30.3)	–
	Left-sided	3 (42.9)	28 (63.6)	N.I.	31 (72.1)	24 (77.4)	23 (69.7)	–
Metastatic organ	Liver	15 (75.0)	32 (72.7)	37 (100)	36 (83.7)	31 (100)	23 (69.7)	174
	Lung	7 (35.0)	16 (36.4)	0	8 (18.6)	0	18 (54.5)	49
	Lymph node	6 (30.0)	9 (20.5)	0	9 (20.9)	0	6 (18.2)	30
	Others	2 (10.0)	5 (11.4)	0	8 (18.6)	0	5 (15.2)	20
Key drug	Irinotecan	20	44	0	0	0	33	97
	Oxaliplatin	20	44	37	43	31	0	175
Molecularly targeted drug	Bevacizumab	0	44	37	43	0	33	157
	Cetuximab	0	0	0	0	31	0	31
	None	20	0	0	0	0	0	20

KSCC Kyushu Study group of Clinical Cancer, *BMI* body mass index, *SD* standard deviation, *PS* performance status, *N.I.* no information

in Online Resource Supplementary Table 1. While right-sided colon cancer was defined as that occurring between the cecum and transverse colon, left-sided CRC was defined as that which arose between the splenic flexure and rectum.

Patient selection

Among the 249 patients who participated in the six distinct phase II clinical trials, a total of 208 patients were selected based on the following criteria: (1) both pre- and post-therapeutic CT images were available, (2) date of CT imaging was clear, and (3) tumor diameter was measurable. Furthermore, contrast CT images were necessary to evaluate the morphological responses.

Image analysis

To evaluate the target lesions, multi-detector row CT was performed as part of the protocol for each study. A triphasic or single-phase technique was employed to perform contrast CT for the evaluation of liver metastases. The reports of CT images were reviewed by radiologists from each institution and by the authors of this manuscript. The 25 cases, which did not have reports, were evaluated by the authors, who were blinded to the clinical data.

Using previously defined morphological criteria [23], the tumors were categorized into three groups: homogenous low attenuation with a thin sharply defined tumor liver border (group 1), heterogeneous attenuation with a thick ambiguously defined tumor liver border (group 3), and the cohort that could not be sorted into group 1 or 3 (group 2). Representative images from each cohort are displayed in Fig. 1. Patients with tumors whose morphology changed from group 2 or 3 to group 1 were assessed as the optimal MR group. Patients with changes in morphology from group 3 to group 2 were included in the incomplete MR group. The no-response group included patients who showed no change or worsening of the condition [7]. In patients with multiple liver metastases, MR was assigned based on outcomes of the majority of other metastatic evaluations [23]. We performed the comparison in two ways: (1) optimal MR group vs. incomplete MR or no-response group and (2) optimal or incomplete MR groups vs. no-response group.

ETS is defined as the percent decrease in diameter of the target lesion at the time of follow-up compared to that at the start of treatment [8, 24]. Although the cutoff point and follow-up intervals were different from those in the past studies [25–27], in this study, follow-up CT imaging was performed 5–10 weeks after initiation of chemotherapy and various cutoff points (10%, 20%, 30%) were applied.

DpR was defined as the percentage of maximum tumor shrinkage compared to the baseline. Its value is 100% when all target tumor lesions have disappeared and it assumes a negative value when they increase in size [26]. Time to response (TTR) was defined as the period between the treatment start and nadir, which corresponded to the point of

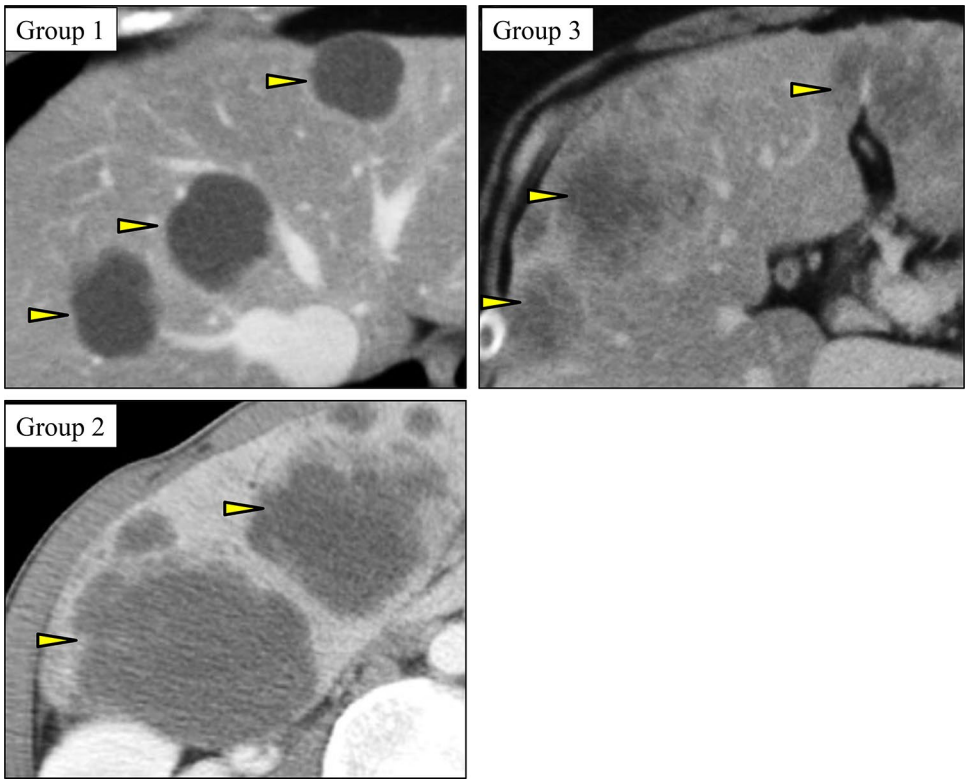

Fig. 1 Classification of CT imaging based on morphologic response criteria. Group 1: homogenous lesions with low attenuation and thin, sharply defined tumor liver borders. Group 3: lesions with heterogeneous attenuation and thick, ambiguously defined tumor liver borders. Group 2: cohort that could not be sorted into Groups 1 or 3. Arrow heads denote the liver metastases

maximum target lesion shrinkage. The schema of ETS, DpR, and TTR are shown in Fig. 2.

RECIST was applied to evaluate the efficacy of chemotherapies in all patients. If a study used the old version of RECIST [19], all cases in that study were re-evaluated with RECIST version 1.1 [28]. While the objective response rate (ORR) included the complete response (CR) and partial response (PR), the disease control rate (DCR) included the ORR and stable disease (SD). CR was defined as the disappearance of all known lesions and the absence of new lesions. PR was defined as the absence of new lesions and a reduction of 30% or more in the sum of the maximum tumor lengths for up to five known lesions. SD was defined as the absence of new lesions and a reduction of < 30% or an increase of < 20% in the sum of the maximum tumor lengths for up to five known lesions.

Statistical analysis

We performed stratified log-rank analysis and used the Cox regression model with each trial as the stratified factor to evaluate the differences in OS between responders and non-responders judged by each method. All statistical analyses were performed using the Statistical Analysis System (SAS) software, SAS 9.3 for Windows (SAS Institute, Cary, NC, USA), by an independent statistician.

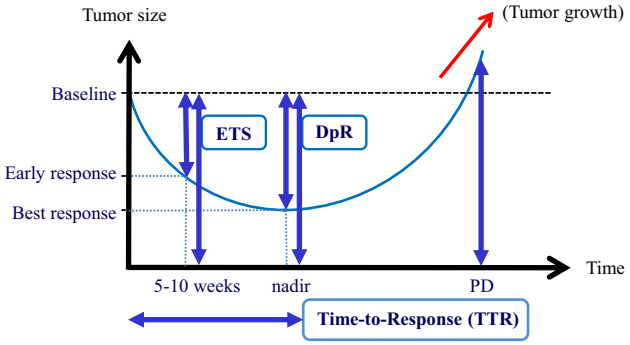

Fig. 2 Schema of ETS, DpR, and TTR showing the general time-course of malignant tumors treated with chemotherapies with each evaluation. *ETS* early tumor shrinkage, *DpR* depth of response, *TTR* time to response, *PD* progression of disease

Results

Patient characteristics

Of the 249 patients who participated in the six phase II clinical trials, 41 were not eligible for our study because the dates for all CT images of these patients were not available (Fig. 3). The remaining 208 patients were evaluated by the RECIST ver.1.1, and 141 of them were evaluated by the MR criteria. DpR and TTR were applicable for 77 patients. ETS evaluations were performed for 177 patients 5–10 weeks after initiation of chemotherapies, and MR criteria were applied in 139 patients (Fig. 3). Baseline characteristics of the final cohorts are summarized in Table 1. As for molecularly targeted drugs, 157 patients received bevacizumab, 31 received cetuximab, and 20 received none.

Comparison of each analysis method for OS in the total population

In the total population, as per the RECIST ver.1.1, hazard ratio (HR) for the responders was 0.40 [95% confidence interval (CI) 0.27–0.59] (Fig. 4). Based on the MR criteria, comparison of the optimal group with the incomplete or no-response group showed an HR of 1.30 (95% CI 0.54–3.12), while, that of the optimal or incomplete group with the no-response group showed an HR of 0.96 (95% CI 0.56–1.65). At a 20% cutoff value, HR of the ETS response group for OS was 0.43 (95% CI 0.29–0.65). The HR for patients with DpR ≥ median DpR of all patients was 0.15 (95% CI 0.08–0.31) and that for patients with TTR ≥ median period

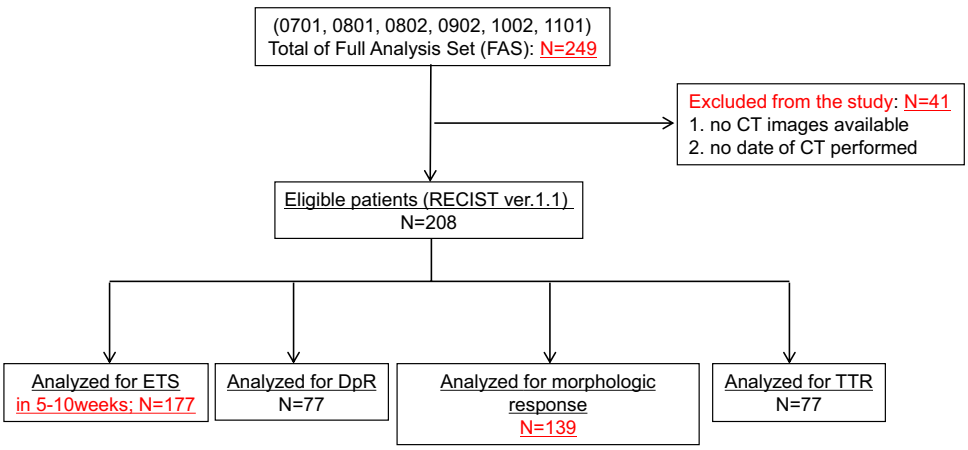

Fig. 3 Flowchart showing patient selection for each subgroup

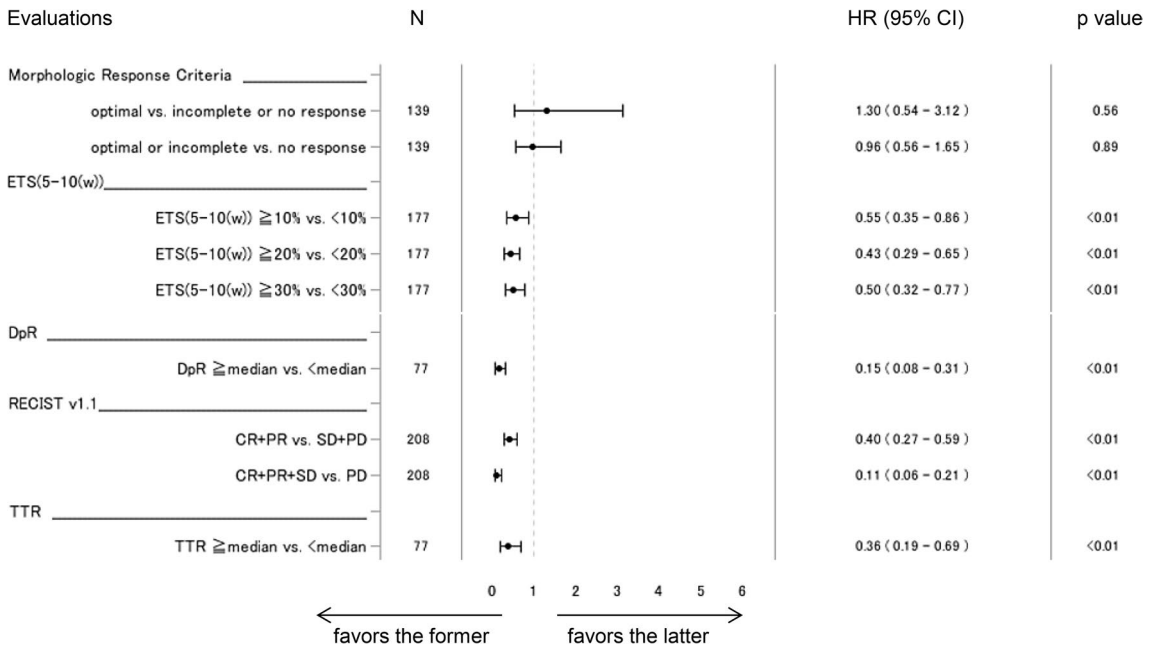

Fig. 4 Forest plots showing hazard ratios (HRs) for overall survival (OS) comparing each evaluation method in the total population. *ETS* early tumor shrinkage, *DpR* depth of response, *TTR* time to response, *CI* confidence interval

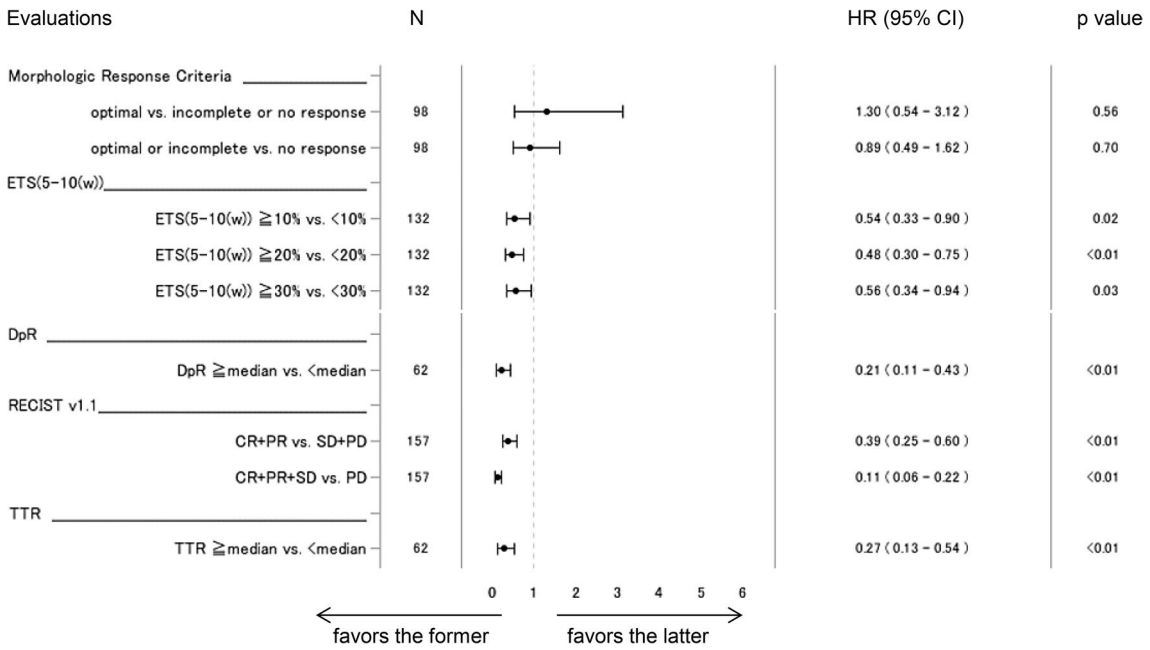

Fig. 5 Forest plots showing hazard ratios (HRs) for overall survival comparing each evaluation method in the bevacizumab-treated subgroup

from start of treatment to maximum shrinkage was 0.36 (95% CI 0.19–0.69).

Comparison of OS with each analysis method according to subgroups

When treated with bevacizumab (Fig. 5), HR for the group with ORR and DCR based on the RECIST ver.1.1 was 0.39 (95% CI 0.25–0.60) and 0.11 (95% CI 0.06–0.22), respectively. HR for the ETS response group (≥ 20%) for OS was 0.48 (95% CI 0.30–0.75). Based on the MR criteria, the HR for OS was 1.30 (95% CI 0.54–3.12) on comparing the optimal group with the incomplete or no-response group and 0.89 (95% CI 0.49–1.62) on comparing the optimal or incomplete group with the no-response group. The HR for patients with DpR ≥ median DpR of all patients was 0.21

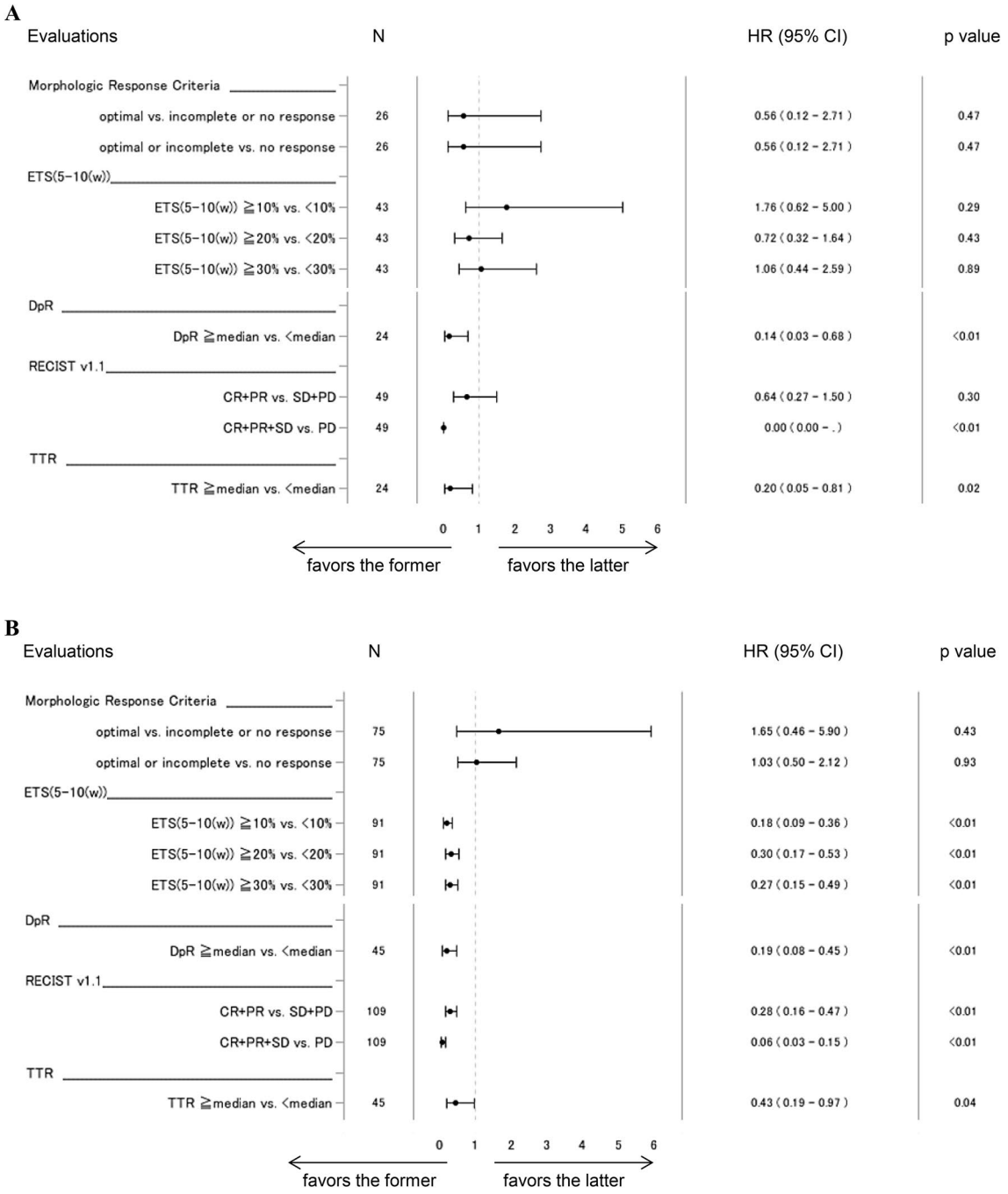

Fig. 6 Forest plots showing the hazard ratios (HRs) for overall survival comparing each evaluation method in **a** right-sided and **b** left-sided CRCs. *CRC* colorectal cancer

(95% CI 0.11–0.43) and that of those with TTR ≥ median period from start of treatment to maximum shrinkage was 0.27 (95% CI 0.13–0.54). Similar results were seen in patients who were treated with cetuximab (Online Resource Supplementary Figure 1).

Among patients with right-sided CRCs (Fig. 6a), the HR for the group that showed ORRs based on the RECIST ver.1.1 was 0.64 (95% CI 0.27–1.50), while that for the ETS response group for OS was 0.72 (95% CI 0.32–1.64). On the other hand, the HR for patients with DpR ≥ median DpR of all patients was 0.14 (95% CI 0.03–0.68) and that for patients with TTR ≥ median period from start of treatment to maximum shrinkage was 0.20 (95% CI 0.05–0.81). The HR for responders based on the MR criteria was 0.56 (95% CI 0.12–2.71) for both the comparisons.

Patients with left-sided CRCs showed different results (Fig. 6b). At a cutoff value of 10%, the HR for patients who showed ORRs based on the RECIST ver.1.1 was 0.28 (95% CI 0.16–0.47) while that for the ETS response group was 0.18 (95% CI 0.09–0.36), which was most the sensitive group. The HR for patients with DpR ≥ median DpR of all patients was 0.19 (95% CI 0.08–0.45) and that for patients with TTR ≥ median period from start of treatment to maximum shrinkage was 0.43 (95% CI 0.19–0.97). Based on the MR criteria, the HR on comparing the optimal or incomplete group with the no-response group was 1.03 (95% CI 0.50–2.12) while that on comparing the optimal group with the incomplete or no-response group was 1.65 (95% CI 0.46–5.90).

In patients with liver metastases, the HR for those showing ORRs based on the RECIST ver.1.1 was 0.35 (95% CI 0.22–0.55) (Online Resource Supplementary Figure 2), and that for the ETS response group for OS was 0.33 (95% CI 0.21–0.51). The HR for patients with DpR ≥ median DpR of all patients was 0.17 (95% CI 0.08–0.40) and that for patients with TTR ≥ median period from start of treatment to maximum shrinkage was 0.45 (95% CI 0.22–0.93). Based on the MR criteria, the HR was 0.96 (95% CI 0.56–1.65) on comparing the optimal or incomplete group with the no-response group, which was more sensitive than the other groups. However, the results were different in the presence of lung metastases (Online Resource Supplementary Figure 3).

Discussion

The prognostic capabilities of new imaging analysis methods such as MR, DpR, and ETS in patients receiving biological therapies have been controversial. In this study, we clarified the role of different analytical methods using data from six cohorts of phase II clinical studies performed by the KSCC, summarized in Table 2.

We found that regardless of the biological drugs used, ETS and DpR were candidate surrogate markers in addition to the RECIST criteria. A previous study [29] that used cytotoxic chemotherapies plus bevacizumab showed that tumor shrinkage might not be an important factor for evaluating the efficacy of bevacizumab. Our analysis revealed that in patients treated with bevacizumab or cetuximab, DpR and ETS showed an association with OS that was as high or higher than associations found using RECIST ver.1.1; however, the MR criteria were not associated with OS. Cetuximab was reported to significantly reduce tumor volume [30], and bevacizumab was shown to have less of an impact on tumor response rates when compared to cetuximab [31]. In this report, evaluations including ETS, DpR, and RECIST were found to be useful predictors of favorable OS when bevacizumab or cetuximab were used despite apparent differences in drug-related tumor reduction effects. TTR was not a reliable predictor of OS in this study for cases that used cetuximab. However, the TTR findings require careful interpretation since there were a low number of cases in the group receiving cetuximab.

We also found that in right-sided colon cancers, the traditional RECIST and ETS were not predictive for OS, but DpR and TTR were predictive. Contrastingly, in left-sided colon cancers, all the evaluations, except the MR criteria, were useful for predicting OS. Recently, biological differences in the effects of drugs based on primary tumor locations have been reported [11–14, 16]. Our findings suggest that the prognosis of right-sided colon cancer is not good

Table 2 The summarized recommendation for every method of image evaluation within each subgroup

	Tumor location (right- or left-sided)	Molecular targeted therapy (Bmab or Cmab)	Metastatic sites (liver or lung)
RECIST ver1.1	Not in right-sided	Both drugs	Not in lung
Early tumor shrinkage (ETS)	Not in right-sided	Both drugs	Both sites (*cutoff value: 20%)
Depth of response (DpR)	Both sides	Both drugs	Not in lung
Time to response (TTR)	Both sides	Bmab only	Not in lung
Morphologic response (MR)	Not recommended	Not recommended	Not recommended

Bmab bevacizumab, *Cmab* cetuximab

even if the patients showed ETS or objective response. In 2008, Grothey et al. first reported that even patients who did not achieve a response according to the RECIST criteria could benefit from chemotherapies, including bevacizumab [29]; however, the association between tumor shrinkage and prognosis for each primary location was not clarified. Right-sided colon cancers more often (a) carry *BRAF*, *KRAS* [32], and *PI3KCA* [33] mutations and (b) metastasize to the peritoneum [34] compared with left-sided colon cancers, suggesting that the shrinkage of metastatic sites may not lead to improvements in OS. On the other hand, TTR and DpR also reflected the OS in both subgroups. These results suggested that longer TTR and increased DpR, but not RECIST, could be useful in predicting favorable OS in mCRCs regardless of primary tumor location, drugs used, or metastatic sites.

Contrary to previous reports [7, 23, 35], we found that the MR criteria were not useful in predicting OS in advanced unresectable colon cancer. There are a few potential reasons for this difference. First, though there are several previous reports on MR [7, 23, 35–38], all of them were retrospective analyses, and none of them used data from clinical trials. Our study is, therefore, the first one to use and analyze data from clinical studies. Second, while previous reports described objective cohorts including patients with only liver metastases, we evaluated patients including not only liver metastases but also other metastatic sites, such as liver lesions with simultaneous involvement of the lungs or distant lymph nodes. Furthermore, differences in morphology and tumor density can sometimes be ambiguous, leading to errors.

This study had some limitations. First, since this was a pooled and retrospectively analyzed study, the effect of confounding factors could not be ruled out. For example, trial 0802 and 1002 included cases with liver metastases only, but other trials enrolled patients with various metastases. Second, since the data in this study were collected from six distinct cohorts of phase II clinical studies, there were some variations in CT imaging techniques, types of equipment used, and intervals between follow-up CTs. These factors could have influenced the measurements of densities of liver metastases. Furthermore, there was insufficient information regarding *KRAS* and *BRAF* mutations except for KSCC1002. According to a previous report, the ETS response could be dependent on KRAS status [24], and, therefore, having this genetic information would have made the results more valuable.

Conclusion

Ad hoc analysis of pooled phase II randomized trials indicated that ETS, DpR, and RECIST ver.1.1 are useful for predicting OS, especially in left-sided CRCs with liver metastases. In patients with advanced and unresectable CRCs receiving first-line chemotherapies, the usefulness of each evaluation varies with the chemotherapeutic drugs used, primary tumor locations, and metastatic organs.

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Compliance with ethical standards

Conflict of interest There are no potential conflicts of interest to disclose.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386
2. Heinemann V, Rivera F, O'Neil BH et al (2016) A study-level meta-analysis of efficacy data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in patients with RAS wild-type metastatic colorectal cancer. Eur J Cancer 67:11–20
3. Holch J, Stintzing S, Heinemann V (2016) Treatment of metastatic colorectal cancer: standard of care and future perspectives. Visc Med 32:178–183
4. Gopal S (2016) Moonshot to Malawi. N Engl J Med 374:1604–1605
5. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
6. Ratain MJ, Eckhardt SG (2004) Phase II studies of modern drugs directed against new targets: if you are fazed, too, then resist RECIST. J Clin Oncol 22:4442–4445
7. Chun YS, Kopetz S, Palavecino M et al (2009) Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA 302:2338–2344
8. Piessevaux H, Buyse M, De Roock W et al (2009) Radiological tumor size decrease at week 6 is a potent predictor of outcome in chemorefractory metastatic colorectal cancer treated with cetuximab (BOND trial). Ann Oncol 20:1375–1382
9. Van Der Veldt AAM, Meijerink MR, Van Den Eertwegh AJM et al (2010) response criteria for early prediction of clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. Br J Cancer 102:803–809
10. Krajewski KM, Franchetti Y, Nishino M et al (2014) 10% tumor diameter shrinkage on the first follow-up computed tomography predicts clinical outcome in patients with advanced renal cell carcinoma treated with angiogenesis inhibitors: a follow-up validation study. Oncologist 19:507–514

11. Cremolini C, Loupakis F, Antoniotti C et al (2015) Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the gruppo oncologico del nord ovest. Ann Oncol 26:1188–1194
12. Tsuji A, Sunakawa Y, Ichikawa W et al (2016) Early tumor shrinkage and depth of response as predictors of favorable treatment outcomes in patients with metastatic colorectal cancer treated with FOLFOX plus cetuximab (JACCRO CC-05). Target Oncol 11:799–806
13. Missiaglia E, Jacobs B, D'Ario G et al (2014) Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol 25:1995–2001
14. Yamauchi M, Lochhead P, Morikawa T et al (2012) Colorectal cancer: A tale of two sides or a continuum? Gut 61:794–797
15. Yamauchi M, Morikawa T, Kuchiba A et al (2012) Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum. Gut 61:847–854
16. Carethers JM (2011) One colon lumen but two organs. Gastroenterology 141:411–412
17. Oki E, Emi Y, Akagi Y et al (2013) Phase II trial of alternating mFOLFOX6 and FOLFIRI regimens in the first-line treatment for unresectable or metastatic colorectal cancer (KSCC0701). Oncology 84:233–239
18. Miwa K, Oki E, Emi Y et al (2016) Phase II trial of an alternating regimen consisting of first-line mFOLFOX6 plus bevacizumab and FOLFIRI plus bevacizumab for patients with metastatic colorectal cancer: FIREFOX plus bevacizumab trial (KSCC0801). Int J Clin Oncol 21:110–117
19. Beppu T, Emi Y, Tokunaga S et al (2014) Liver resectability of advanced liver-limited colorectal liver metastases following mFOLFOX6 with bevacizumab (KSCC0802 Study). Anticancer Res 34:6655
20. Ogata Y, Shimokawa M, Tanaka T et al (2016) A prospective study of XELOX plus bevacizumab as first-line therapy in Japanese patients with metastatic colorectal cancer (KSCC 0902). Int J Clin Oncol 21:335–343
21. Oki E, Emi Y, Miyamoto Y et al (2015) Phase II trial of S-1 and oxaliplatin plus cetuximab for colorectal cancer patients with initially unresectable or not optimally resectable liver metastases (KSCC1002). Ann Surg Oncol 22:1067–1074
22. Ando K, Emi Y, Suenaga T et al (2017) A prospective study of XELIRI plus bevacizumab as a first-line therapy in Japanese patients with unresectable or recurrent colorectal cancer (KSCC1101). Int J Clin Oncol 22:913–920
23. Shindoh J, Loyer EM, Kopetz S et al (2012) Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. J Clin Oncol 30:4566–4572
24. De Roock W, Piessevaux H, De Schutter J et al (2008) KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 19:508–515
25. Piessevaux H, Buyse M, Schlichting M et al (2013) Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. J Clin Oncol 31:3764–3775
26. Heinemann V, Stintzing S, Modest DP et al (2015) Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). Eur J Cancer 51:1927–1936
27. Sakamaki K, Kito Y, Yamazaki K et al (2017) Exploration of time points and cut-off values for early tumour shrinkage to predict survival outcomes of patients with metastatic colorectal cancer treated with first-line chemotherapy using a biexponential model for change in tumour size. ESMO Open 2:e000275
28. Ramaiya NH, Ad A (2011) Revised RECIST Guideline Version 1.1: What oncologists want to know and what radiologists need to know. AJR Am J Roentgenol 195:281–289
29. Grothey A, Hedrick EE, Mass RD et al (2008) Response-independent survival benefit in metastatic colorectal cancer: a comparative analysis of N9741 and AVF2107. J Clin Oncol 26:183–189
30. Folprecht G, Gruenberger T, Bechstein WO et al (2010) Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 11:38–47
31. Saltz LB, Clarke S, Diaz-Rubio E et al (2019) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 26:2013–2019
32. Sinicrope FA, Mahoney MR, Yoon HH et al (2015) Analysis of molecular markers by anatomic tumor site in stage III colon carcinomas from adjuvant chemotherapy trial NCCTG N0147 (Alliance). Clin Cancer Res 21:5294–5304
33. Mouradov D, Sloggett C, Jorissen RN et al (2014) Colorectal cancer cell lines are representative models of the main molecular subtypes of primary cancer. Cancer Res 74:3238–3247
34. Missiaglia E, Jacobs B, Ario GD, Di Narzo AF et al (2014) Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncsol 25:1995–2001
35. Mazard T, Boonsirikamchai P, Overman MJ et al (2018) Comparison of early radiological predictors of outcome in patients with colorectal cancer with unresectable hepatic metastases treated with bevacizumab. Gut 67(6):1095–1102
36. Nishioka Y, Shindoh J, Yoshioka R et al (2015) Radiological morphology of colorectal liver metastases after preoperative chemotherapy predicts tumor viability and postoperative outcomes. J Gastrointest Surg 19:1653–1661
37. Shindoh J, Chun YS, Loyer EM et al (2013) Non-size-based response criteria to preoperative chemotherapy in patients with colorectal liver metastases: the morphologic response criteria. Curr Color Cancer Rep 9(2):198–202
38. Yoshita H, Hosokawa A, Ueda A et al (2014) Predictive value of optimal morphologic response to first-line chemotherapy in patients with colorectal liver metastases. Digestion 89:43–48