



Comparison of the Response Evaluation Criteria in Solid Tumors with Volumetric Measurement for Evaluation of Response and Overall Survival with Liver Metastases from Colorectal Cancer

대장암 간전이 환자에서 반응평가와 생존율 예측 연구:
종양 부피 측정과 RECIST 기준의 비교

In Seon Lee, MD¹ , Seung Joon Choi, MD^{1*} ,
Cho Rong Seo, MD¹, Jun Seong Kim, MD²

¹Department of Radiology, Gil Medical Center, Gachon University College of Medicine, Incheon, Korea

²Gachon University Graduate School of Medicine, Incheon, Korea

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*Corresponding author

Seung Joon Choi, MD
Department of Radiology,
Gil Medical Center,
Gachon University
College of Medicine,
14 Namdong-daero 774beon-gil,
Namdong-gu, Incheon 21565,
Korea.

Tel 82-32-460-3059

Fax 82-32-460-3045

E-mail sjchoi1118@gmail.com

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ORCID iDs

Seung Joon Choi

[https://](https://orcid.org/0000-0003-3861-7682)

orcid.org/0000-0003-3861-7682

In Seon Lee

[https://](https://orcid.org/0000-0001-5263-8661)

orcid.org/0000-0001-5263-8661

Purpose The aim of this study was to compare the measurements of diameter and volume of hepatic metastases from CT images with the overall survival and tumor response, in patients with unresectable liver metastases of colorectal cancer treated with a targeted agent.

Materials and Methods We recruited 43 patients with unresectable liver metastases of colorectal cancer, in whom targeted therapy was used as the first-line treatment. Three-dimensional quantification of the volume of hepatic metastases was performed for each patient. An independent survival analysis using the Response Evaluation Criteria in Solid Tumors guidelines was performed and compared to the volumetric measurement. Overall survival was evaluated using the Kaplan-Meier analysis and compared to the Cox proportional hazard ratios (HRs) following univariate and multivariate analyses.

Results In patients classified as non-progressing and progressing by the volumetric criteria, the median overall survival time was 21 months [95% confidence interval (CI): 491.25–768.75] and 11 months (95% CI: 0–949.42), respectively ($p = 0.001$). Using a multivariate analysis, we found that volumetric response (HR: 3.467; $p = 0.002$) was a significant factor affecting the overall survival in patients with liver metastases of colorectal cancer.

Conclusion Volumetric assessment of liver metastases could be an alternative predictor of the overall survival of patients with liver metastases of colorectal cancer treated with a targeted agent.

Index terms Colorectal Neoplasm; Neoplasm Metastasis; Chemotherapy; Outcomes Assessment

INTRODUCTION

Liver metastases occur in 30% of all patients with colorectal cancer (CRC), and are responsible for death in at least two thirds of CRC patients. Approximately 80% of patients with colorectal liver metastasis (CLM) present with unresectable disease at initial diagnosis (1, 2). Profound improvements in CLM outcome seem to be associated with advancements in medical therapy, and the increased use of hepatic resection (3). Additionally, a disease-free interval longer than 5 years can now be achieved in 16% of patients with initially unresectable CLM, resected after downsizing chemotherapy. Therefore, the importance of CLM tumor response evaluation following chemotherapy has gradually increased (4).

Therefore, an imaging test is necessary for the prognostic prediction of the response of hepatic metastasis to chemotherapy, in order to identify patients likely to respond poorly to a chemotherapeutic regimen. This may allow for changes to the treatment plan that avoid unnecessary drug toxicity and maximize chances of tumor regression.

Accurate evaluation of therapeutic responses to treatment could have considerable clinical benefit for patients who receive chemotherapy. Although target therapies are increasingly being used in patients with advanced cancer, it is clear that standard tumor response evaluation methods are of limited value for assessment of treatment modality efficacy. Because of their varying mechanisms of action, it follows that the response patterns with target therapies differ from those seen with cytotoxic treatment. According to a previous renal cell carcinoma trial, the Response Evaluation Criteria in Solid Tumors (RECIST) often underestimate the effect of targeted therapy, because necrosis or hemorrhage frequently occur without any change in size (5, 6). In addition, it remains to be determined whether these one-dimensional criteria can sufficiently reflect treatment responses to combined targeted biological therapy, although RECIST criteria is widely used for the evaluation of responses to cytotoxic chemotherapy (7, 8).

In previous studies, volumetric measurement has been preferred over RECIST criteria, to predict tumor progression (9, 10). Volumetric analysis has the ability to account for three dimensions, as opposed to RECIST criteria, in which only a single axial dimension is analyzed. Therefore, we hypothesized that volumetric analysis would be superior to RECIST criteria, for the evaluation of tumor response after targeted therapy. The aim of this study was to compare RECIST and volumetric measurements of tumor response and outcome in CLM treated with a targeted agent plus folinic acid, fluorouracil, and irinotecan (FOLFIRI).

MATERIALS AND METHODS

PATIENTS POPULATION

This retrospective, single institutional analysis was approved by our Institutional Review Board (GAIRB2017-354), and requirement for informed consent was waived. CRC patients with unresectable liver metastases, treated with targeted therapy as first-line chemotherapy, were identified between January 2014 and January 2016, we identified CRC patients. Study inclusion was based on the unresectability of liver metastases, evaluated by a local multidisciplinary team. Patients that met ≥ 1 of the following criteria were included: 1) impossible

R0 resection of all hepatic lesions; 2) < 30% estimated residual liver volume after tumorectomy or hepatectomy; and 3) invasion of major vessels of remnant liver. Exclusion criteria included inadequate CT imaging (no contrast agent applied, outside CT scan). Based on these criteria, 43 patients were included in our study.

CT EXAMINATIONS

All patients underwent contrast-enhanced multi-detector CT scans, including triple, double (arterial and portal venous phases), and single-phase CT (portal venous phase), before and after chemotherapy, with 64- or 128-detector CT scanners (Somatom Definition 64, and Somatom Definition Flash, Siemens Medical Solutions, Erlangen, Germany). Arterial and portal venous phase images were obtained with delays of 18 and 50 seconds, respectively, due to the 100 Hounsfield unit (HU) enhancement of the descending aorta using a bolus tracking method. Scans were obtained with a fixed delay of three minutes following the start of the contrast agent administration. For single phase CT, portal venous imaging was obtained one minute after achieving 50 HU enhancement of the descending aorta. The contrast media was injected at a volume of 2 mL/kg of body weight (maximum 150 mL) of nonionic contrast agent (Iohexol, Bonorex 300, Central Medical System, Seoul, Korea; Iopamidol, Pamiray, Dongkook Pharmaceutical, Seoul, Korea; or Iopromide, Ultravist 300, Schering, Berlin, Germany) via 18-gauge peripheral venous access at a flow rate of 4 mL/s using an automatic power injector (OptiVantage, Liebel-Flarsheim; Mallinckrodt, Neustadt, Germany). The mean time between baseline CT imaging and first cycle of chemotherapy was 11.8 days (standard deviation, 9.3 days; range, 1–43 days), and the mean time between the first cycle of chemotherapy and follow-up CT imaging was 44.8 days (standard deviation, 10.3 days; range, 24–69 days).

IMAGE ANALYSIS

Images were interpreted by two radiologists, (S.J.C. has 7 years of abdominal imaging experience, and C.R.S. has 4 years of training as a radiology resident), blinded to patient demographics, clinical information, and official CT report. Tumor diameter and volume of the liver metastases, were measured from the baseline and first follow-up CT scans. Baseline CT scans were performed within 4 weeks prior to the start of treatment, and the first follow-up CT scan was performed after three cycles of chemotherapy. For each patient, two target lesions were selected for analysis (11). Target lesions were determined as the largest, most reproducible, and dominant lesions, treated during chemotherapy. Tumor volumes were measured by both radiologists and mean values were recorded. For tumor margin segmentation, regions of interest (ROIs) were manually drawn on two or three slices showing a well-delineated tumor. The entire tumor volume was calculated automatically on the basis of the attenuation of the drawn ROI by HUs. If needed, the reviewers manually adjusted the boundary of the tumor, between the tumor and normal liver, on each image. Percent change in volumetric tumor at the follow-up CT was compared to baseline values. Three-dimensional volumetric image analysis was performed using a commercially available software prototype (TeraRecon, iNtuition, San Mateo, CA, USA).

RESPONSE ASSESSMENT

Overall treatment response was classified as complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD), according to both RECIST 1.1, and volumetric criteria. Treatment response calculated using the mean of two times the tumor diameter, was used for classification according to RECIST 1.1 criteria: 1) CR: Disappearance of all target lesions; 2) PR: At least a 30% reduction in the sum of target lesion diameters; 3) SD: absence of PR or PD; 4) PD: At least a 20% increase in the sum of target lesion diameters, or the appearance of new lesions (11).

Volumetric criteria of liver metastasis treatment response were as follows: 1) CR: Disappearance of all target lesions; 2) PR: At least a 65% reduction in the total volume of target lesions; 3) SD: Absence of PR or PD; 4) PD: At least a 73% increase in the total volume of target lesions, or the appearance of new lesions.

These classifications were used to further assign patients to either the responder group (CR or PR), or the non-responder group (SD or PD), in addition to a non-progressing group (CR, PR, or SD), or a progressing group (PD) (Fig. 1).

STATISTICAL ANALYSIS

Categorical data, presented as percentages, frequencies, and differences in proportion,

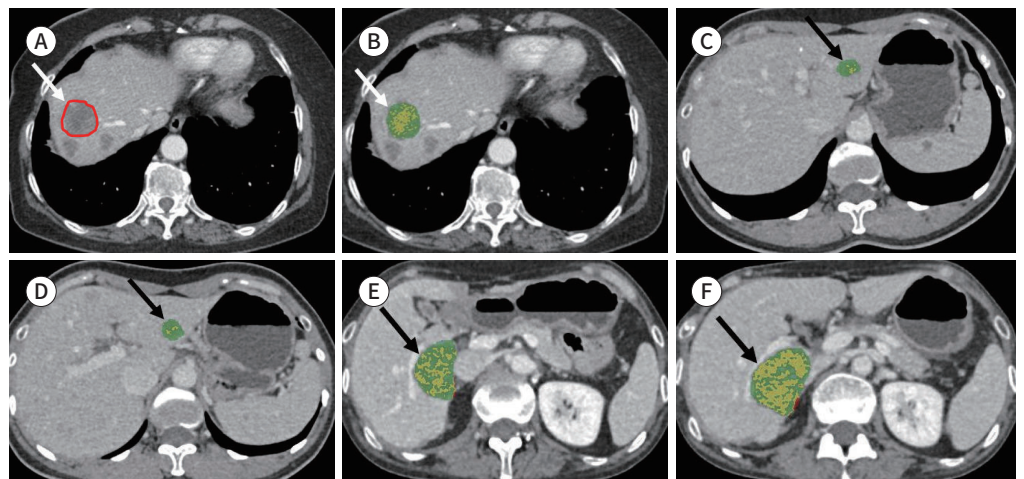
Fig. 1. Example images of the volumetric measurement of liver metastases using the semiautomated quantification technique.

A, B. For tumor margin segmentation, ROIs were manually drawn on two or three slices showing a well-delineated tumor (arrow at **A**). The entire tumor volume was calculated automatically (arrow at **B**) based on the attenuation of the drawn ROI in Hounsfield units.

C, D. Example of the non-progressing group based on the volumetric criteria. CLM in a 43-year-old man is shown, with the baseline and first follow-up CT images obtained in the portal venous phase in a patient with CLM treated with bevacizumab plus FOLFIRI. At the baseline, the tumor volume was 2.7 cm³ in the left lobe of the liver (arrow at **C**). After the treatment, the tumor volume slightly decreased and was 2.0 cm³ (26% reduction in the total volume of the target lesion arrow at **D**).

E, F. Example of the progressing group based on the volumetric criteria. CLM in a 47-year-old woman is shown, with the baseline and first follow-up CT images obtained in the portal venous phase in a patient with CLM treated with bevacizumab plus FOLFIRI. At the baseline, the tumor volume was 22 cm³ in the right posterior section of the liver (arrow at **E**). After the treatment, the tumor volume increased and was 47 cm³ (113% increase in the total volume of the target lesion; arrow at **F**).

CLM = colorectal liver metastasis, FOLFIRI = folinic acid, fluorouracil, and irinotecan, ROI = region of interest



were compared using the chi-square test, or Fischer's exact test, as appropriate. Continuous data with significantly skewed distributions are expressed as medians, and compared using the Mann-Whitney U-test. Mean values of continuous variables with normal distributions were compared using unpaired student's *t*-tests. Cumulative survival analysis was performed using the Kaplan-Meier (KM) method, and differences in survival between groups were assessed using the log-rank test. Potential prognostic factors of survival were evaluated using the Cox proportional hazard model. Univariate analyses were performed to identify significant predictors of survival. Characteristics determined to be statistically significant ($p < 0.1$) by the univariate analysis were used as input variables in a multivariate logistic regression analysis. Statistical analyses were performed using SPSS/PC version 20.0 (IBM Corp., Armonk, NY, USA). p -value < 0.05 , were considered statistically significant.

RESULTS

PATIENTS DEMOGRAPHICS

CRC demographics and liver mass results are shown in Table 1. Of the 43 patients, 27 (63%) had colon cancer, and 16 (37%) had rectal cancer. Of these, 34 (79%) had more than three liver metastases and a total of 61 target lesions were examined. Baseline liver metastases were greater than 3 cm in diameter in 30 patients (70%), with an average volume of 56.7 cm³ (range, 1.1–328 cm³; standard deviation, 81.9). In addition to FOLFIRI, 31 patients (72%) received bevacizumab, and 12 (28%) received cetuximab.

COMPARISON OF RECIST VS. VOLUMETRIC CRITERIA

Table 2 summarizes response assessment results based on RECIST and volumetric criteria. According to RECIST criteria, 5 patients (12%), were assigned to the responding group (CR and PR), and 9 patients (21%) were assigned to the responding group based on volumetric criteria. The non-responding group (SD and PD), consisted of 38 patients (88%) based on RECIST criteria, and 34 patients (79%) based on volumetric criteria. In patients classified as responding or non-responding by RECIST, the median overall survival was 26.8 months [95% confidence interval (CI), 532.59–1075.41], and 17 months (95% CI, 337.83–682.17), respectively ($p = 0.298$, Log-rank test).

In patients classified as responding or non-responding by the volumetric criteria, the median overall survival was 21 months (95% CI, 396.26–863.74), and 17 months (95% CI, 271.43–748.57), respectively ($p = 0.399$, Log-rank test).

The non-progressing group (CR, PR, and SD), consisted of 37 patients (86%) when based on RECIST criteria, and 34 patients (79%), when based on volumetric criteria. The progressing group (PD) included 6 patients (14%) based on RECIST criteria, and 9 patients (21%) based on volumetric criteria.

In patients classified as non-progressing or progressing by RECIST, the median overall survival was 19.5 months (95% CI, 422.56–747.44), and 12.4 months (95% CI, 305.79–440.21), respectively ($p = 0.096$, Log-rank test).

In patients classified as non-progressing or progressing by volumetric criteria, the median overall survival was 21 months (95% CI, 491.25–768.75), and 11 months (95% CI, 0–949.42), re-

Table 1. Baseline Patient Characteristics

| Parameter | No. of Patients (n = 43) |
|--------------------------|--------------------------|
| Age, years, mean (range) | 60.2 (44–80) |
| Sex, male/female | 29/14 |
| Primary tumor | |
| Size, cm | |
| ≥ 7 | 19 |
| < 7 | 24 |
| Location | |
| Rectum | 16 |
| Colon | 27 |
| Liver metastases | |
| Number | |
| ≥ 3 | 34 |
| < 3 | 9 |
| Size, cm | |
| ≥ 3 | 30 |
| < 3 | 13 |
| Hepatic lobe involvement | |
| 1 | 9 |
| 2 | 34 |
| Chemotherapy regimen | |
| Bevacizumab plus FOLFIRI | 31 |
| Cetuximab plus FOLFIRI | 12 |
| Tumor marker | |
| CEA | |
| ≥ 100 | 14 |
| < 100 | 29 |
| CA19-9 | |
| ≥ 100 | 18 |
| < 100 | 25 |

CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, FOLFIRI = folinic acid, fluorouracil, and irinotecan

Table 2. Cross-Tabulation of RECIST and Volumetric Criteria Response to Treatment

| Volumetric Criteria (n = 43) | RECIST Criteria | | | | |
|---------------------------------|-----------------|----|----|----|-------|
| | CR | PR | SD | PD | Total |
| CR | 0 | 0 | 0 | 0 | 0 |
| PR | 0 | 4 | 5 | 0 | 9 |
| SD | 0 | 1 | 24 | 0 | 25 |
| PD | 0 | 0 | 3 | 6 | 9 |
| Total | 0 | 5 | 32 | 6 | 43 |

CR = complete response, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease

spectively ($p = 0.001$, Log-rank test) (Fig. 2).

UNIVARIATE AND MULTIVARIATE ANALYSIS

Univariate analyses based on a Cox proportional hazard model were performed to identify significant predictors of overall survival (Table 3). We found that age [Hazard ratios (HR): 1.038, $p = 0.037$], CA 19-9 (HR: 1.917, $p = 0.055$), and volumetric response (HR: 3.460, $p = 0.002$), were significant factors affecting overall survival (p -values less than 0.1). Multivariate

Fig. 2. Kaplan–Meier analyses with the log-rank test to compare the overall survival in (A) the progressing and non-progressing groups based on the volumetric criteria and (B) based on the RECIST version 1.1, and in (C) the responder and non-responder groups based on the volumetric criteria and (D) based on the RECIST version 1.1. The median overall survival in the non-progressing group (21 months) based on the volumetric criteria was longer than that in the progressing group (11 months; $p = 0.001$; Log-rank test). There were no statistically significant differences in the overall survival between the progressing and non-progressing groups according to the RECIST 1.1 or between the responder and non-responder groups according to the volumetric criteria and RECIST 1.1.

RECIST = Response Evaluation Criteria in Solid Tumors

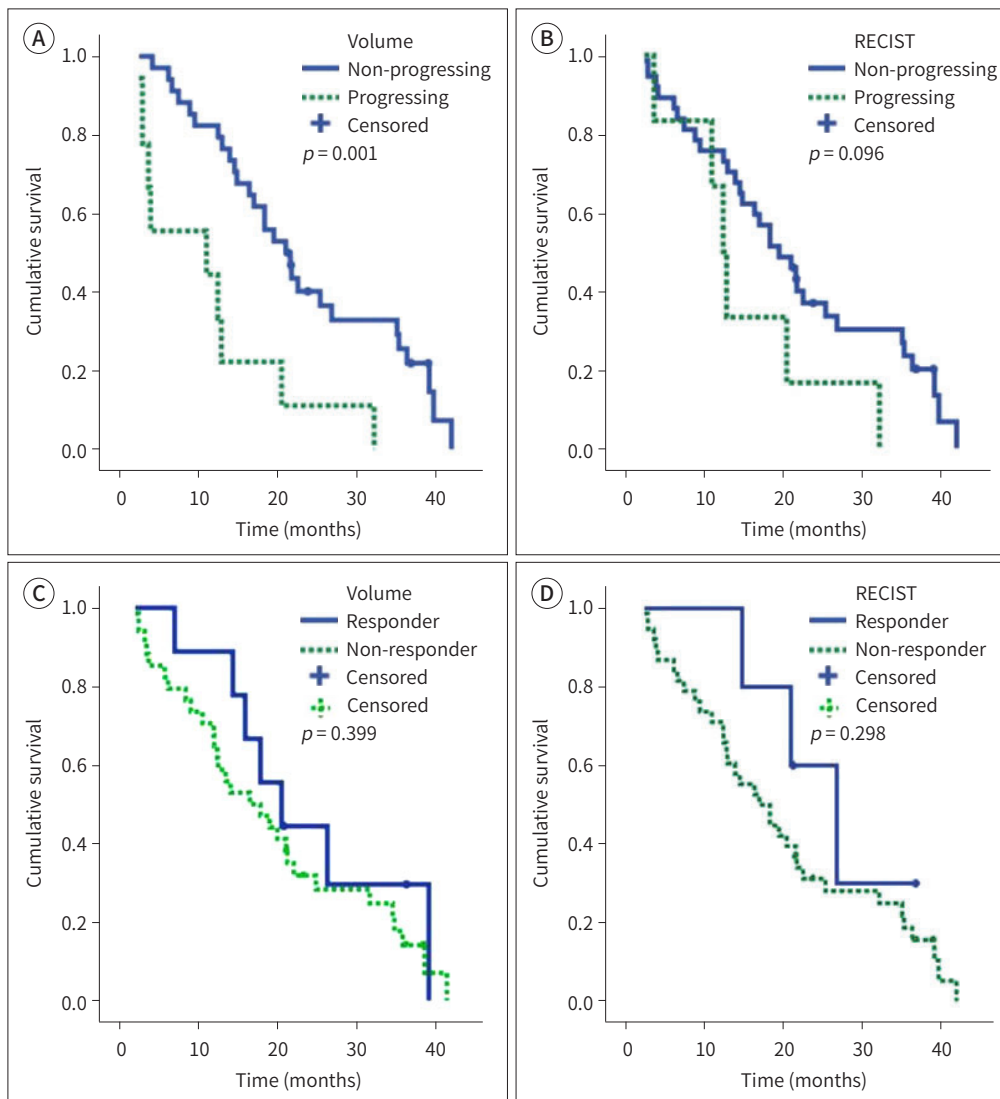


Table 3. Prognostic Factors Affecting Survival Based on Univariate Analysis

| Variable | HR | 95% CI | p-Value |
|------------------------------|-------|-------------|---------|
| Age | 1.038 | 1.002–1.074 | 0.037 |
| Location of primary tumor | 0.802 | 0.404–1.596 | 0.530 |
| Size of primary tumor | 1.746 | 0.885–3.445 | 0.108 |
| Number of hepatic metastases | 1.438 | 0.627–3.298 | 0.391 |
| Size of hepatic metastases | 1.473 | 0.687–3.161 | 0.320 |
| Chemotherapy regimen | 0.838 | 0.422–1.667 | 0.615 |
| CEA | 1.107 | 0.556–2.203 | 0.772 |
| CA19–9 | 1.917 | 0.986–3.727 | 0.055 |
| RECIST | 2.106 | 0.858–5.173 | 0.104 |
| Volumetric response | 3.460 | 1.573–7.610 | 0.002 |

CA19–9 = carbohydrate antigen 19–9, CEA = carcinoembryonic antigen, CI = confidence interval, HR = hazard ratios, RECIST = Response Evaluation Criteria in Solid Tumors

Table 4. Prognostic Factors Affecting Survival Based on Multivariate Analysis

| Variable | HR | 95% CI | p-Value |
|---------------------|-------|-------------|---------|
| Age | 1.038 | 0.999–1.079 | 0.055 |
| CA19–9 | 2.023 | 1.026–3.992 | 0.042 |
| Volumetric response | 3.467 | 1.521–7.899 | 0.003 |

CA19–9 = carbohydrate antigen 19–9, CI = confidence interval, HR = hazard ratios

analyses found that CA 19–9 (HR: 2.023, $p = 0.042$), and volumetric response (HR: 3.467, $p = 0.003$), were significant factors affecting overall survival (Table 4).

DISCUSSION

Our study demonstrates that volumetric measurement may have the potential to predict overall survival in patients with unresectable CLM treated with target therapy. Accurate and early detection of treatment response of liver metastases is important for optimal intervention planning (12). Early, reliable prognostic information may help physicians to develop proper treatment plans for individual patients, and allow for more timely attempts of alternative therapies for treatment-resistant tumors.

RECIST criteria is easy to use, allows for rapid classification, and is highly reproducible and therefore, is widely used in clinical trials and clinical practice (13). However, increases in the sophistication of imaging instrumentation has led to the development of markedly diverse and complex oncologic therapies (14). For example, volumetric image assessment allows precise three-dimensional measurement of tissue volumes (15). In this study, the non-progressing group showed longer overall survival than the progressing group based on volumetric criteria, while the RECIST criteria was not significantly different between them. Three patients were additionally assessed as PD according to volumetric criteria and SD according to RECIST criteria. We hypothesized that volumetric evaluation allowed precise mea-

surement of the geometric tumor and reflected smaller changes more than the traditional criteria (16, 17). In addition, there was no significant difference between the responder and non-responder groups according to the volumetric and RECIST criteria. Molecular targeted therapy is often associated with potential intratumoral hemorrhage and peritumoral edema; this is attributed to increasing tumor size despite good clinical response. Because of the apparent increase in lesion size, SD may often be misinterpreted as PD (18, 19).

The National Comprehensive Cancer Network and European Society for Medical Oncology guidelines (20, 21) suggest an active combination regimen doublet chemotherapy plus a targeted agent (e.g. bevacizumab or cetuximab for KRAS wild-type tumors). Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), prevents VEGF from binding to its functional receptor, leading to the inhibition of tumor vessel growth, neo-vascularization, and decreased permeability in the surviving vasculature. Cetuximab, a monoclonal antibody against epidermal growth factor receptor, inhibits downstream signaling pathways, leading to the inhibition of cell proliferation and angiogenesis (22). Targeted therapies have different mechanisms of action than cytotoxic chemotherapy. Some agents induce apoptosis, whereas other agents stop progression. Due to these differences in the mechanisms of action, tumors treated with targeted therapies may not demonstrate radiographic findings similar to that of tumors treated with conventional cytotoxic therapies (23). Therefore, traditional diameter-based criteria can lead to improper classification of treatment response for tumors treated with targeted therapies.

Our results further support the necessity for revised RECIST criteria that includes the use of volume measurements, in the response assessment of metastatic tumor burden in the liver after treatment with target agents. Similarly, another group has reported the need for revised RECIST criteria, adopting the concept of volumetry superiority over unidimensional measurements (24). Conversely, volumetric measurements are cumbersome and time consuming, and thus, are unlikely to be widely adopted in clinical practice. However, recent technological advancement in medical imaging software has promised to provide solutions for rapid, easy, and accurate volume measurements (25, 26).

Response evaluation with RECIST criteria is limited by the use of a unidimensional measurement as a surrogate marker for three-dimensional growing tumors. Conventional one- or two-dimension tumor measurements are made based on the assumption that lesion diameter is correlated to lesion volume. This assumption is due to the inaccurate belief that tumors grow and shrink in a spherical pattern. Volumetric measurements may more accurately reflect actual tumor size and shape compared to conventional measurements (8).

Advances in CT technology allow for the acquisition of isotropic data with accurate and reproducible tumor volumetric data (15). Semi-automated segmentation techniques use software algorithms to measure tumor volume based on ROI outlines drawn by the reader. Recently, the feasibility of volumetric tumor measurement as well as semiautomatic quantification of viable tumor (enhancing portion), has been shown for hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolization (27). Volumetric quantification of HCC necrosis has been shown to be more reproducible than quantification using EASL criteria (28). As RECIST is primarily based on one-dimensional measurements of the longest diameters of the tumors in a transverse image, it is often difficult for radiologists to determine the longest diameters

in cases in which the target lesions split into smaller tumor, or merge to form a conglomerate mass after intervention (9, 29). A previous study used RECIST to assess responses to imatinib in gastrointestinal stromal tumors, and found that the time to tumor progression did not differ between good and poor responders, suggesting that RECIST is not effective for this assessment. Similarly, Chun et al. (30) demonstrated that response assessment based on RECIST criteria was not correlated to overall survival in patients with CLM treated with target agents. Instead, interest and acceptance of volumetric evaluation as an alternative assessment method has increased (31, 32). An important theoretical advantage of volumetric evaluation is that it offers more accurate measurement and reflection of tumor burden, with less inter-observer variability, and is superior to measurements of the longest diameters from up to five target lesions per organ (15). Previous studies have also reported that pretreatment tumor volume of HCC is a potential predictor of posttransplant recurrence (33, 34).

Our study has several limitations. First, our study had a small number of patients. A larger series is needed to clinically validate our results. Second, our analysis was a retrospective assessment of dominant index lesions and non-target lesions were not included. However, several studies established that prognostic use of the dominant lesion, is sufficient to predict outcome after treatment (30, 35, 36). This access is based on the assumption that the longest tumors can reflect tumor burden and, represent the most aggressive condition of the cancer. Third, we enrolled CLM patients treated with different target agents (bevacizumab and cetuximab). However, both bevacizumab and cetuximab are now routinely used molecular target agents in metastatic CRC. Thus, this study could reflect real-time clinical practice.

In conclusion, volumetric assessment of liver metastases may become the preferred method to detect tumor progression, and predict overall survival for patients with unresectable liver metastases from CRC treated with a targeted agent.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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대장암 간전이 환자에서 반응평가와 생존율 예측 연구: 종양 부피 측정과 RECIST 기준의 비교

이인선¹ · 최승준^{1*} · 서초롱¹ · 김준성²

목적 이 연구는 표적 치료제를 사용한 절제 불가능한 대장암 간전이 환자에서 종양의 길이를 이용한 반응 평가와 비교하여 종양의 부피를 이용한 반응 평가가 환자의 생존율을 더 잘 예측할 수 있는지 알아보는 연구이다.

대상과 방법 저자들은 표적 치료제를 초치료로 사용한 절제 불가능한 대장암 간전이 환자 43명을 연구에 포함하였다. 간전이 종양의 부피를 정량적으로 계산한 기준과 Response Evaluation Criteria in Solid Tumors 기준을 비교하였다. 카플란-마이어, 콕스비례위험 모형을 사용하여 일변량분석과 다변량분석을 통해 환자 생존율 및 연관된 인자를 알아보았다.

결과 저자들은 간전이 종양의 부피를 정량적으로 계산한 기준을 이용했을 때, 질환 진행군(11개월; 95% 신뢰구간, 0~949.42)과 질환 안정군(21개월; 95% 신뢰구간, 491.25~768.75), 간 생존율에 통계학적 유의한 차이를 확인하였다($p = 0.001$). 다변량분석에서 부피를 이용한 반응 평가는 생존율을 예측하는 주요 요소로 쓰일 수 있었다(위험비, 3.467, $p = 0.002$).

결론 간전이의 부피 반응 평가는 표적 치료제를 사용하는 대장암 간전이 환자들의 생존율을 예측하는 방법으로 사용할 수 있다.

¹가천대학교 의과대학 길병원 영상의학과, ²가천대학교 의학전문대학원