Original Article

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대한영상의학회지

Comparison of CT Volumetry and RECIST to Predict the Treatment Response and Overall Survival in Gastric Cancer Liver Metastases

위암 간전이 환자의 반응평가와 생존율 예측을 위한 종양 부피 측정과 RECIST 기준의 비교 연구

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Purpose The aim of this study was to compare the diameter and volume of liver metastases on CT images in relation to overall survival and tumor response in patients with gastric cancer liver metastases (GCLM) treated with chemotherapy.

Materials and Methods We recruited 43 patients with GCLM who underwent chemotherapy as a first-line treatment. We performed a three-dimensional quantification of the metastases for each patient. An independent survival analysis using the Response Evaluation Criteria in Solid Tumors (RECIST) was performed and compared to volumetric measurements. Overall survival was evaluated using Kaplan-Meier analysis and compared using Cox proportional hazard ratios following univariate analyses.

Results When patients were classified as responders or non-responders based on volumetric criteria, the median overall survival was 23.6 months [95% confidence interval (CI), 8.63–38.57] and 7.6 months (95% CI, 3.78–11.42), respectively (p = 0.039). The volumetric analysis and RECIST of the non-progressing and progressing groups showed similar results based on the Kaplan-Meier method (p = 0.006) and the Cox proportional hazard model (p = 0.008).

Conclusion Volumetric assessment of liver metastases could be an alternative predictor of overall survival for patients with GCLM treated with chemotherapy.

Index terms Gastric Cancer; Liver Neoplasm; Chemotherapy; Survival

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INTRODUCTION

Gastric cancer is the most common malignancy and the fourth most common cause of cancer-related deaths in South Korea (1). At the time of diagnosis, 35% of patients have evidence of distant metastases, and 4–14% have liver metastases (2, 3). The prognosis of gastric cancer with liver metastases is very poor, with a 5-year survival rate of < 30% (4). Systemic chemotherapy is the standard treatment recommended for metastatic gastric cancer by the National Comprehensive Cancer Network and Korean Guidelines (5, 6). Reports on resections of gastric cancer liver metastases (GCLM) are rare, and their effectiveness is controversial (7).

Many palliative chemotherapeutic agents, often as combination regimens, have been recommended for advanced gastric cancer. Effective cytotoxic agents used to treat metastatic gastric cancer are platinum/fluoropyrimidine combination chemotherapy. In a meta-analysis, the overall survival benefits of chemotherapy versus best supportive care showed an increased survival of approximately 6 months with chemotherapy (8).

The valid assessment of chemotherapeutic effects after treatment is essential not only for monitoring disease progression in advanced disease but also for selecting patients who would benefit from surgery after neoadjuvant systemic therapy. Accurate imaging tests are necessary to identify patients likely to respond poorly to a chemotherapeutic regimen and may allow for treatment plans that avoid unnecessary drug toxicities and maximize the chances of tumor regression.

The Response Evaluation Criteria in Solid Tumors (RECIST), which has become the most frequently used response criterion for solid tumors, measures changes in the tumors' longest diameters. However, these unidimensional measurements may not represent the entire volume of irregularly shaped or vertically growing tumors. In addition, biological target therapies have increasingly been used in patients with advanced cancer, and standard tumor response evaluation methods are of limited value for the assessment of treatment modality efficacy. Due to their varying mechanisms of action, the response patterns with targeted therapies differ from those seen with cytotoxic treatments. According to a previous clinical trial, RECIST often underestimates the effect of targeted therapies since necrosis or hemorrhaging frequently occurs without any change in the size of renal cell carcinoma (9, 10). Hence, it is unknown whether these one-dimensional criteria can sufficiently reflect treatment responses to combined targeted biological therapies.

In some previous studies, volumetric analysis has been preferred to RECIST in predicting tumor progression (11, 12). Volumetric analyses can account for three dimensions, as opposed to RECIST, which only analyzes a single axial. Therefore, we hypothesized that volumetric evaluations could be a potentially superior alternative to RECIST for determining changes in these tumors due to its ability to analyze three dimensions as opposed to a single axial dimension. The aim of this study was to compare the response of GCLMs to first-line chemotherapy using both RECIST and volumetric criteria and to determine which was a better prognostic indicator for predicting tumor progression.

MATERIALS AND METHODS

PATIENT POPULATION

This retrospective, single institutional analysis was approved by our Institutional Review Board (IRB No. GAIRB2017-369), and the requirement for informed consent was waived. GCLM patients treated with chemotherapy were identified between January 2014 and January 2016. Study inclusion was based on the presence of liver metastases, evaluated by either CT. Patients with an outside CT, whose software prototype was difficult to apply, were excluded. In addition, we excluded patients who received immune-based therapy such as trastuzumab. Based on these criteria, 43 patients were included in our study.

CT EXAMINATIONS

The patients underwent contrast-enhanced multi-detector CT scans, including triple, double (arterial and portal venous phases), and single-phase CTs (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. The delayed phase was obtained with a fixed delay of three min following the start of contrast agent administration. For single-phase CTs, portal venous imaging was obtained one min after achieving a 50 HU enhancement of the descending aorta. A nonionic contrast agent (Iohexol, Bonorex 300, Central Medical Services, Seoul, Korea; Iopamidol, Pamiray, Dongkook Pharmaceutical, Seoul, Korea; or Iopromide, Ultravist 300, Bayer Healthcare, Berlin, Germany) was injected at a volume of 2 mL/kg of body weight (maximum 150 mL) through 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 slice thickness of the transverse images was 5 mm.

IMAGE ANALYSIS

Images were interpreted by two radiologists (S.J.C., who had 9 years of abdominal imaging experience and I.L., who had 4 years of training as a radiology resident) blinded to patient demographics and CT reports. The axial diameter and volume of the liver metastases were measured using the baseline and first follow-up CTs. Baseline CTs were defined as those taken when the liver metastases first appeared and within 4 weeks of starting chemotherapy to treat them. The first follow-up CT was performed after three cycles of chemotherapy. For each patient, two target lesions were selected for analysis (13). The target lesions were the largest, most reproducible, and most dominant lesions treated during chemotherapy. Tumor volumes were measured by both radiologists, and the mean values were recorded. For tumor margin segmentation, regions of interest were manually drawn on more than three slices showing a well-delineated tumor. The entire volume was measured automatically based on the attenuation of the drawn regions of interest using HUs. If necessary, the reviewers manually adjusted the tumor margin, delineating the target tumor and normal liver parenchyma on each image.

The percent change in tumor volume from baseline to the follow-up CT was compared. Three-dimensional volumetric image assessments were performed automatically using a commercially available software prototype (TeraRecon, iNtuition, San Mateo, CA, USA) (Fig. 1).

RESPONSE ASSESSMENT

Treatment response was classified as a complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD) according to both RECIST version 1.1 and volumetric criteria. Treatment response was assessed using the mean of two times the tumor diameter according to the RECIST 1.1 classification: a) CR: disappearance of all target lesions; b) PR: at least a 30% reduction in the sum of the target lesion diameters; c) SD: absence of PR or PD; and d) PD: at least a 20% increase in the sum of the target lesion diameters or the appearance of new lesions (13).

The volumetric criteria for hepatic metastasis treatment response were classified as follows: a) CR, disappearance of all target lesions; b) PR, at least a 65% reduction in the total volume of the target lesions; c) SD: absence of PR or PD; and d) PD: at least a 73% increase in the total volume of the target lesions or the appearance of new lesions (12).

These classifications were assigned to either the responder (CR or PR) or the non-responder group (SD or PD), in addition to the non-progression (CR, PR, or SD) or progression group (PD).

STATISTICAL ANALYSIS

Categorical data, presented as percentages, frequencies, and differences in proportion, were compared using the χ^2 or Fischer's exact test. Continuous data with significantly skewed distributions were 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 method, and differences in survival between the 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 univariate analysis were used as input variables for logistic regression analysis. Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

PATIENT DEMOGRAPHICS

The GCLM demographic results are shown in Table 1. Of these patients, 36 (84%) had two or more liver metastases and 79 target lesions were examined. On baseline CT, liver metastases had a maximum diameter of more than 3 cm in 27 patients (63%) and the average volume of the liver metastases was 13.6 cm^3 (range, 1.1–215 cm^3; standard deviation, 29.3). Tumor markers were classified into two groups based on 50 ng/mL of carcinoembryonic antigen and 40 U/mL of CA19-9 (14, 15).

Table 1. Baseline Patient Characteristics

Parameter	No. of Patients (*n* = 43)
Age (years), mean (range)	67.5 (35–86)
Sex, male/female	40/3
Liver metastases (*n*)	
≥ 10	14
< 10	29
Tumor size (cm)	
≥ 3	27
< 3	16
Hepatic lobe involvement	
1	9
2	34
Chemotherapy regimen	
Capecitabine + cisplatin	19
Docetaxel + cisplatin + 5-FU	10
TS-1 + cisplatin	9
Capacitabine	1
Capacitabine + oxaliplatin	1
5-FU	1
Epirubicin + oxaliplatin + TS-1	1
Cisplatin + etoposide	1
Tumor marker (ng/mL)	
CEA*	
≥ 50	3
< 50	40
CA19-9*	
≥ 40	5
< 40	38

*At the time of initial gastric cancer liver metastases diagnosis.
CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, TS-1 = tegafur/gimeracil/oteracil, 5-FU = fluorouracil

COMPARISON OF VOLUMETRIC CRITERIA VS. RECIST

Table 2 summarizes the response results based on both the RECIST and volumetric criteria. According to RECIST, 7 patients (16%) were assigned to the responder group (CR and PR), while 8 patients (18%) were assigned to the responder group based on volumetric analysis. Thirty-six patients (84%) were assigned to the non-responding group (SD and PD) based on RECIST, while 35 patients (81%) were assigned based on volumetric criteria. For patients classified as responders or non-responders according to RECIST, the median overall survival was 14.4 months [95% confidence interval (CI), 8.03–20.83] and 9.4 months (95% CI, 5.39–13.41), respectively, ($p = 0.659$, log-rank test) (Fig. 2).

For patients classified as responding or non-responding, based on volumetric criteria, the median overall survival duration was 23.6 months (95% CI, 8.63–38.57) and 7.6 months (95%

Table 2. Cross Tabulation of Response to Treatment Using Volumetric and RECIST 1.1

n = 43	RECIST 1.1				
	CR	PR	SD	PD	Total
Volumetric criteria					
CR	0	0	0	0	0
PR	0	5	3	0	8
SD	0	2	13	0	15
PD	0	0	0	20	20
Total	0	7	16	20	43

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

Table 3. Prognostic Factors of Survival Based on Univariate Analyses

Variables	Univariate Analysis	
	HR (95% CI)	*p*-Value
Age	1.006 (0.970–1.043)	0.767
Number of hepatic metastases	1.038 (0.541–1.990)	0.911
Size of hepatic metastases	1.280 (0.682–2.405)	0.442
CEA	0.946 (0.334–2.685)	0.917
CA19-9	0.556 (0.215–1.436)	0.225
RECIST	2.437 (1.257–4.723)	0.008
Volumetric response	2.437 (1.257–4.723)	0.008

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

CI, 3.78–11.42), respectively ($p = 0.039$, log-rank test).

The non-progressing group (CR, PR, and SD) consisted of 23 patients (53%) according to RECIST and 23 patients (53%) according to volumetric criteria (Fig. 2). The progressing group (PD) included 20 patients (47%) based on RECIST and 20 patients (47%) based on volumetric criteria. The results of the volumetric and RECIST analyses of the non-progressing and progressing groups were equal. The median overall survival duration of the non-progressing group (16.2 months) was longer than that of the progressing group (6.6 months) based on volumetry and RECIST 1.1, respectively ($p = 0.006$) (Fig. 2).

UNIVARIATE ANALYSES

Univariate analyses based on the Cox proportional hazard model were performed to identify important predictors of overall survival (Table 3). The results of the volumetric and RECIST analyses (HR: 2.437, $p = 0.008$) were equal in the non-progressing and progressing groups.

DISCUSSION

Our study results showed that volumetric analysis could be used as a response criterion to predict overall survival in patients with GCLM treated with chemotherapy.

We found that the volumetric analysis, based on the Kaplan-Meier method for categorizing

Fig. 1. Images of volumetric measurements of liver metastases using the semiautomated quantification technique.
A-F. A case of gastric cancer liver metastases of partial response based on volumetric criteria in a 57-year-old male, with baseline and first follow-up CT images obtained in the portal venous phase. Free-hand drawn images before three-dimensional volumetric reconstruction, arrows at baseline (A) and post-treatment (B). At baseline, the tumor volume was 24 cm^3 in the right lobe of the liver (arrow, C). After treatment, the tumor volume decreased to 7 cm^3 [71% reduction in the total volume of the target lesion; arrow at (D)]. Based on the RECIST, this patient was diagnosed with stable disease [from 38 to 33 mm, a 13% reduction in the maximal diameter of the target lesion, and arrows at (E), (F)].
G-L. A progression case with gastric cancer liver metastases based on volumetric criteria in a 70-year-old female is shown, with baseline and first follow-up CT images obtained in the portal venous phase. Free-hand drawn images before three-dimensional reconstruction, arrows at baseline (G) and post-treatment (H). At baseline, the tumor volume was 6 cm^3 in the left lobe of the liver (arrow, I). After treatment, the tumor volume increased to 15 cm^3 [150% increase in the total volume of the target lesion; arrow at (J)]. Based on the RECIST, this patient was diagnosed with stable disease [from 31 to 34 mm, a 9.7 % increase in the maximal diameter of the target lesion, and arrows at (K) and (L)].
RECIST = Response Evaluation Criteria in Solid Tumors

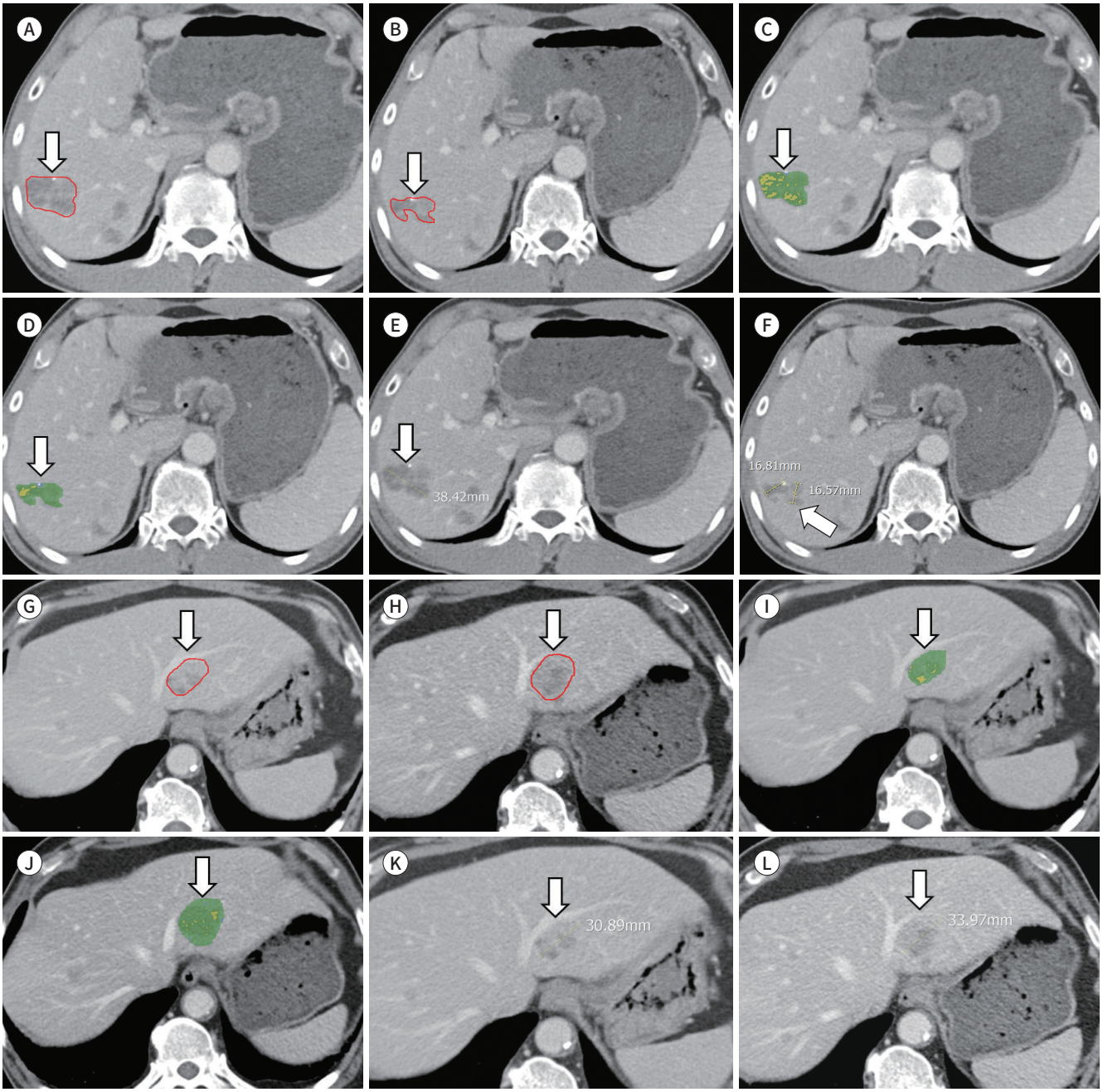
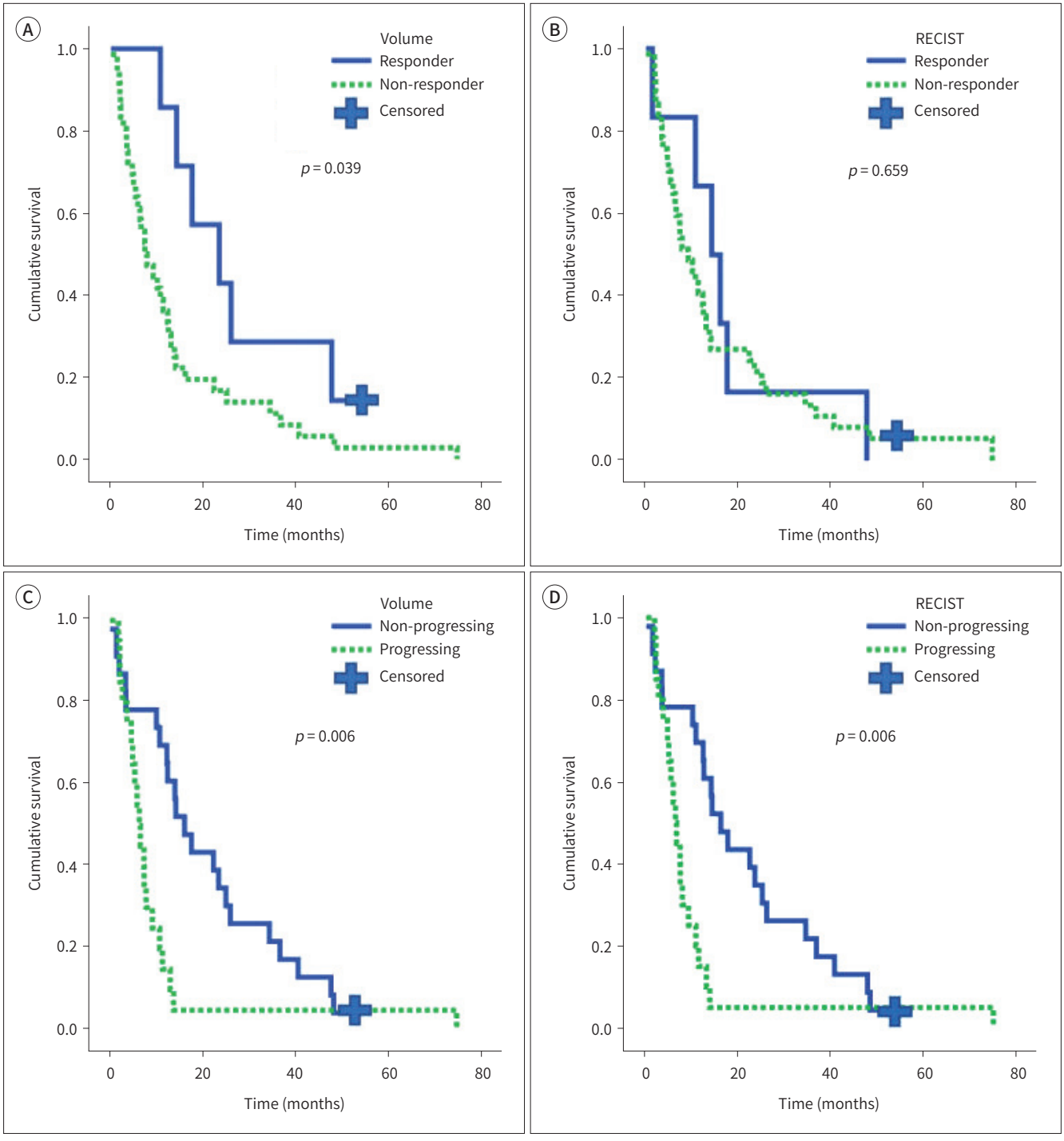


Fig. 2. Kaplan-Meier analysis with log-rank test to compare overall survival between the responder and non-responder groups according to the volumetric criteria (A) and RECIST 1.1 (B); and between the non-progressing and progressing groups according to the volumetric criteria (C) and RECIST 1.1 (D). The median overall duration of survival of the responders (23.6 months), based on the volumetric criteria, was longer than that of the non-responders (7.6 months, p = 0.039, log-rank test). The outcomes of the volumetric and RECIST analyses were similar in the non-progressing and progressing groups. The median overall duration of survival of the non-progressing group (16.2 months) was longer than that of the progressing group (6.6 months) based on volumetry and RECIST 1.1 (p = 0.006).
RECIST = Response Evaluation Criteria in Solid Tumors



responders and non-responders, significantly affected overall survival. Neither group was significantly different based on the RECIST criteria. We also found that the results of the volumetric and RECIST analyses of the non-progressing and progressing groups, based on the Kaplan-Meier method and the Cox proportional hazard model, were equal.

Early detection and accurate diagnosis of tumor progression may constitute an effective treatment plan, resulting in improved overall survival, liver health, and decreased medical costs (16). Moreover, reliable prognostic factors may provide physicians with appropriate interventional plans and allow for optimal therapies for treatment-resistant patients.

Since the development of diverse and complex oncological therapies for advanced gastric cancer, sophisticated imaging criteria to measure treatment responses are essential (17). RECIST is a highly reproducible, widely and easily used response criterion tool that allows for rapid classification (16). However, RECIST is primarily based on the unidimensional calculation of the longest transverse diameters of the target lesions, and when the target lesions split into smaller lesions or merge to form a conglomerate mass after treatment, it is often a clinical dilemma for radiologists to determine the longest diameters (11, 18). These criteria may not reflect the actual tumor volume, since tumors tend to grow irregularly, especially after chemotherapy. Size-based criteria remain subject to differences in interpretation and do not provide a quantifiable measure of response. Moreover, RECIST may reflect tumor changes that are slower than the actual therapeutic effects (19, 20). A previous study showed that the relationship between RECIST and pathologic response is limited with colorectal liver metastases (CLM) (21, 22).

Some studies have demonstrated that volume response evaluation may be a useful tool for the preoperative staging of primary advanced gastric carcinoma, evaluation of response to neoadjuvant chemotherapy, and predicting prognosis after curative resection of gastric cancer (23-25). Lee et al. (24) reported that volume reduction rates in gastric cancer were correlated with histopathological grades of regression, where the tumor volume was reduced by 35.6% or more after neoadjuvant chemotherapy. In addition, previous studies have shown that CT volumetry demonstrated better outcome predictions, while size-based criteria were limited in assessing the response of metastatic lesions in colorectal cancer (26, 27).

Volumetric measurements may be used to detect changes within the entire tumor mass; measurement variability seems to have a relatively limited contribution to measurement changes. Kikuchi et al. (28) reported that a staging system based on volumetric measurement in continuous tissue sections by the surface rendering method could have advantages over the conventional staging systems for gastric cancer. Hallinan et al. (23) demonstrated that volumetric analysis is feasible and reproducible, which could provide useful information for the staging of gastric cancers.

However, little is known about the appropriate imaging response-predicting tool for GCLM. To better understand how chemotherapy-induced responses may be captured by CT, we need to improve our understanding of the internal tumor structure and change. Hence, in the current study, we hypothesized that CT volumetry could provide better prognostic information by quantifying the content of liver metastases.

In this study, the responder group showed improved overall survival compared with the non-responder group based on the volumetric analyses; both groups were not significantly

different based on the RECIST criteria. Additionally, the non-progressing and progressing groups were significantly different based on the volumetric and RECIST criteria. Two patients were assessed as having SD according to volumetry and PR according to RECIST, and three patients were assessed as having PR according to volumetry and SD according to RECIST.

We excluded patients who received immune-based therapy. Biologically targeted therapy often causes intratumoral bleeding, necrosis, cavitation, and peritumoral edema during treatment, which may cause an increase in tumor size despite good clinical response. Thus, the effect of biological therapy is often underestimated when using size-based RECIST. Due to the apparent increase in tumor size, SD can often be misinterpreted as PD (29-31). Targeted therapy has a different mechanism of action compared with classic cytotoxic agents for tumors. Some agents cause angiogenesis, cell growth signaling, and apoptosis, while others stop the progression (19, 32). Since biological and cytotoxic therapies show different mechanisms of action, tumors treated with biological therapies may not exhibit radiological findings similar to cancers treated with conventional cytotoxic therapies (32). Hence, axial unidimensional-based criteria may result in the inappropriate classification of therapeutic values for patients treated with biological therapies. The modified RECIST 1.1 for immune-based therapeutics (iRECIST) has been suggested for evaluating patients receiving immune-based therapy (33). At least three CT scans are required to confirm the disease progression in iRECIST. However, iRECIST could not be applied because only two CT scans (baseline CT and first follow-up CT) were analyzed in our study. In addition, the response analysis could not be conducted separately for patients treated with cytotoxic chemotherapy, due to the lack of patients treated with trastuzumab combination therapy (13 patients).

The effects and tumoral changes resulting from new therapeutic modalities, such as angiogenesis inhibitors and anti-vascular therapies, are more complex. In previous studies, metastatic renal cell cancer treated with molecularly targeted agents, including sorafenib and bevacizumab, failed to achieve a significant objective response according to RECIST, but did result in a significant improvement in progression-free survival (9, 34). Biological information needs to be incorporated into future RECIST, thereby providing a realistic evaluation method for treatment response (19). Additionally, more information about tumor responses to targeted therapies is necessary. In this study, due to the lack of patients treated with trastuzumab combination therapy (23%), the evaluation of biological therapy response is limited. In order to determine biological treatment responses, further studies of those treated with a targeted agent are necessary.

Recently, the authors published a paper about the volumetric analysis of CLM (35). We included unresectable CLM patients treated with targeted therapy (bevacizumab or cetuximab). The goal of chemotherapy for unresectable CLM is to reduce the size of liver metastases to an operable status. Previous studies have shown that 12% to 33 % of patients with initially unresectable liver metastases have an objective response to conversion therapy to permit a subsequent complete resection (36, 37). The present study included GCLM patients treated with various chemotherapeutic agents, compared with CLM. Therefore, the research design was more heterogeneous and complex. As palliative resection is not recommended for GCLM in gastric cancer guidelines, valid assessments of liver metastases are essential for monitoring disease progression (38). However, few studies have evaluated the response as-

sessments of GCLM. Therefore, we believe that it is necessary to evaluate response assessment in different cancer groups to factor in the various viewpoints on follow-up and the different chemotherapy regimens used for CLM and GCLM.

Our study has several limitations. First, the study population was small. A larger study is needed to validate these results. Second, as mentioned earlier, we excluded patients who received immune-based therapy. Further research with additional CT scans and patients is needed to assess the treatment response in patients undergoing immune-based therapy.

In conclusion, volumetric assessment of liver metastases could be an alternative predictor of overall survival for patients with GCLM treated with chemotherapy.

Author Contributions

Conceptualization, C.S.J.; data curation, Y.S.H., C.S.J., N.H., L.I.S, K.S.J.; formal analysis, C.S.J.; investigation, Y.S.H., C.S.J., N.H., L.I.S., K.S.J.; methodology, C.S.J.; project administration, C.S.J.; resources, C.S.J.; software, C.S.J.; supervision, C.S.J.; validation, C.S.J.; visualization, C.S.J.; writing—original draft, all authors; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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위암 간전이 환자의 반응평가와 생존율 예측을 위한 종양 부피 측정과 RECIST 기준의 비교 연구

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목적 항암 치료를 진행하는 위암 간전이 환자에서 종양의 길이를 이용한 반응 평가와 비교하여 종양의 부피를 이용한 반응 평가가 환자의 생존율을 더 잘 예측할 수 있는지 알아보는 연구이다.

대상과 방법 항암 치료를 진행하는 위암 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 반응군(23.6개월; 95% 신뢰구간, 8.63~38.57)과 질환 비반응군(7.6개월; 95% 신뢰구간, 3.78~11.42)간 생존율에 통계학적 유의한 차이를 확인하였다($p = 0.039$). 질환 안정군과 질환 진행군을 부피를 이용한 반응 평가와 길이를 이용한 반응 평가로 구분할 경우 양군은 생존기간과 위험비에서 의미 있는 차이를 보였으나 두 반응 평가 방법 간 차이는 없었다(카플란-마이어 모형: $p = 0.006$; 콕스비례위험 모형: 위험비, 2.437, $p = 0.008$).

결론 항암 치료를 진행하는 위암 간전이 환자들에서 간전이의 부피 반응 평가는 환자들의 생존율을 예측하는 데 도움을 줄 수 있다.

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