Early Prediction by ^{18}F-FDG PET/CT for Progression-Free Survival and Overall Survival in Patients With Metastatic Colorectal Cancer Receiving Third-Line Cetuximab-Based Therapy

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Objective: In metastatic colorectal cancer (mCRC) with wild-type K-*ras*, cetuximab-based regimen is an option for third-line therapy. The objective of this study was to assess if early response evaluation by ^{18}F-FDG PET/CT can predict progression-free survival (PFS) and overall survival (OS) in these patients.

Patients and Methods: Patients with mCRC going to receive third-line cetuximab-based therapy were enrolled. ^{18}F-FDG PET/CT studies were arranged at baseline and at the ends of the first and fourth weeks of therapy. Treatment response was evaluated with 2 methods: method 1 based on PET response criteria in solid tumors 1.0 and method 2 based on the assumption that an increase in peak tumor metabolism implies nonresponse. Progression-free survival was counted to tumor progression based on the Response Evaluation Criteria in Solid Tumors 1.1 or death. The predictive powers for PFS and OS were analyzed using the Kaplan-Meier method and the log-rank test.

Results: Twenty-seven patients were eligible with a median PFS of 5.8 months and a median OS of 9.1 months. Method 2 predicts PFS ($P = 0.001$) and OS ($P < 0.001$) at the end of the first week, whereas method 1 does not. Both methods predict PFS and OS at the end of the fourth week.

Conclusions: Early response evaluation by ^{18}F-FDG PET/CT predicts PFS and OS in patients with mCRC receiving third-line cetuximab-based therapy. Early therapeutic change may be possible for nonresponsive patients after 1 week of treatment.

Key Words: metastatic colorectal cancer, cetuximab, ^{18}F-FDG PET/CT, response evaluation, survival prediction

(*Clin Nucl Med* 2015;40: 200–205)

Colorectal cancer was the third most common cancer in men and the second in women in 2012.[1] Approximately 20% to 25% of these patients have metastases at the time of diagnosis, and about one half of the remainder will develop metastases sometime after treatment.[2] The overall prognosis of patients with metastatic colorectal cancer (mCRC) is poor, with 5-year survival in the 5% to 8% range. However, recent chemotherapeutic regimens combined with targeted agents have significantly improved their 2-year survival.[3]

For patients with noncurable mCRC, combination chemotherapy including oxaliplatin-based and irinotecan-based regimens remains the standard backbone for first-line and second-line therapies.[4] For patients with wild-type K-*ras* tumors, cetuximab, an epidermal growth factor receptor inhibitor, is a common option for third-line therapy.[3] Treatment with cetuximab as compared with supportive care alone improved the median survival from 4.8 to 9.5 months.[5] However, the observed response rate according to the Response Evaluation Criteria in Solid Tumors (RECIST) was only 12.8%. The response rate remains limited even in patients receiving cetuximab plus irinotecan-based therapy.[6] Limitations of RECIST in targeted therapies have been noticed.[7,8] More accurate response evaluation during early course of treatment will be valuable for nonresponsive patients to receive alternative therapies as soon as possible.

PET/CT using ^{18}F-FDG is a powerful tool for imaging tumors as well as to assess changes in tumor metabolism during therapy.[9] Assessment of glucose metabolism using SUV is widely adopted. A correlation between SUV changes and patient outcome is observed in many cancers including the colorectal cancer.[10,11] However, response evaluation in patients with mCRC receiving targeted therapy has been rarely studied. For advanced gastrointestinal stromal tumors, Stroobants et al[12] have demonstrated that ^{18}F-FDG PET, performed before and 8 days after the start of imatinib treatment, is a sensitive method for response evaluation. It is possible that ^{18}F-FDG PET/CT can evaluate tumor response early in the course of cetuximab-based therapy and predict patient outcome.

The objective of this prospective study was to assess if tumor response evaluation by ^{18}F-FDG PET/CT at baseline and at the ends of the first and fourth weeks of therapy can predict progression-free survival (PFS) and overall survival (OS) of patients with mCRC and wild-type K-*ras* receiving third-line cetuximab and irinotecan-based therapy.

PATIENTS AND METHODS

Study Design

Time-to-progression (TTP) curves by Cunningham et al[13] and Sobrero et al[14] were referenced for sample size estimation. PET/CT studies were assumed to discriminate patients with TTP exceeding 4 months or not with an accuracy of 75%. The median PFS of patients with TTP exceeding 4 months or not was set to 7.0 and 1.5 months, respectively. The sample size to achieve a significant P value (<0.05) for the primary objective of PFS discrimination was estimated using the Kaplan-Meier method and the log-rank test. A sample size of 20 was found to be a minimum.

Patients with mCRC going to receive third-line cetuximab and irinotecan-based therapy were considered eligible. Patients with tumor specimen determined to have mutated K-*ras*, without measurable lesion as defined by RECIST, younger than the age of 18 years, being pregnant or lactating, with Eastern Cooperative Oncology Group performance status of grade 2 or above, with a history of other malignancy except nonmelanoma skin cancer, or with prior treatment of cetuximab or panitumumab were excluded.

This prospective study was approved by the institutional review board and registered in the Australian New Zealand Clinical Trials Registry (ACTRN12612000052831). Patients were well informed and had to sign the informed consent before enrollment.

Cetuximab and Irinotecan-Based Therapy

The schedules for therapy and ^{18}F-FDG PET/CT imaging were arranged after enrollment. The first administration of cetuximab was scheduled at least 4 weeks apart from the most recent major surgery

Received for publication June 30, 2014; revision accepted November 17, 2014.

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Conflicts of interest and sources of funding: Supported by grants CMRPG680321 and CMRPG680322 from the Chang Gung Memorial Hospital Research Fund.

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ISSN: 0363-9762/15/4003–0200

or radiotherapy. Cetuximab was given by IV infusion once weekly, with an initial loading dose of 400 mg/m^2 and a weekly maintenance dose of 250 mg/m^2. Chemotherapy with a modified irinotecan, fluorouracil, and leucovorin regimen was given after cetuximab: IV infusion of irinotecan (125 mg/m^2) with bolus 5-fluorouracil (500 mg/m^2) and leucovorin (20 mg/m^2) on days 1, 8, and 15 in a 4-week cycle. Drug doses might be adjusted by the attending oncologist if severe adverse effects occurred. Therapy was continued until disease progression, occurrence of unacceptable toxic effects, or completion of 6 cycles of therapy.

^{18}F-FDG PET/CT Imaging

^{18}F-FDG PET/CT studies were performed before the first administration and at the ends of the first and fourth weeks of therapy. All data were acquired on a combined PET/CT system (Discovery ST16; GE Health Systems, Milwaukee, Wis). The patients were instructed to fast for 6 hours before examinations. The scan was started at 50 minutes after IV injection of 370 MBq (10 mCi) of ^{18}F-FDG. A CT scan from the head to the thigh was acquired first, and then the PET scan was acquired in 2-dimensional mode with an acquisition time of 3 minutes per bed position. The CT data were used for attenuation correction, and the PET images were reconstructed with an ordered subset expectation maximization algorithm with 10 subsets and 4 iterations into 128 by 128 matrices.

Image Review and Parametric Quantification

Image review and parametric quantification were performed on the Syngo MI Workplace software platform (Siemens Healthcare, Forchheim, Germany). SUV normalized to lean body mass (SUL) was defined as the decay-corrected tissue concentration (MBq/mL) of the tracer divided by the injected dose per lean body mass (MBq/g).[15] The maximum SUL in the volume of interest (VOI) was designated as SUL_{max}, and SUL_{peak} was defined as the average SUL within the 1.2-cm-diameter spheric VOI centered on the pixel with SUL_{max}. Volumes of interest encompassing the malignant lesions were drawn on the workstation manually. One VOI may encompass multiple lesions in the same organ such as the liver or the same lymph node region. SUL_{max} and SUL_{peak} were obtained for all VOIs, but VOIs with SUL_{peak} less than 2.0 were discarded because of low metabolic level and vulnerability to interstudy variability. Corresponding VOIs in subsequent PET/CT studies were also manually created with SUL_{max} and SUL_{peak} recorded. The baseline study was designated as S0, and the studies at the ends of the first and fourth weeks were designated as S1 and S4, respectively. For each set of corresponding VOIs, D1 and D4 were designated to represent the percentage difference of SUL_{peak} from S0 to S1 and S4, respectively: Di = (SUL_{peak} in Si - SUL_{peak} in S0)/(SUL_{peak} in S0), wherein i is equal to 1 or 4.

Tumor Response Evaluation by ^{18}F-FDG PET/CT

Two different methods for tumor response evaluation were carried out. Method 1 is based on PET response criteria in solid tumors (PERCIST) 1.0.[8] Essentially, the percentage difference in SUL_{peak} between the lesions with maximal SUL_{peak} in the baseline and subsequent studies is assessed. The lesions with maximal SUL_{peak} at different time points need not to be in the same position or organ. Complete metabolic response (CMR) means complete resolution of lesions. Partial metabolic response (PMR) means SUL_{peak} reduction of 30% or more. Progressive metabolic disease (PMD) means SUL_{peak} increase larger than 30%. Stable metabolic disease (SMD) means situations other than CMR, PMR, and PMD. For dichotomous interpretation, CMR and PMR are categorized as responsive, whereas PMD and SMD are categorized as nonresponsive.

Method 2 is an intuitive one based on the assumption that an increase in SUL_{peak} in a single VOI implies progression, with the condition that SUL_{peak} has to be above 2.0, that is, a patient will be categorized as nonresponsive if there is any eligible VOI for which Di is positive and SUL_{peak} in Si is above 2.0. Otherwise, the patient will be categorized as responsive.

With methods 1 and 2, the predictive powers of response evaluation at the ends of the first and fourth weeks are analyzed.

Assessment of PFS and OS

CT imaging was scheduled every 3 months after the treatment initiation and with clinical or biochemical suspicion of disease progression. Assessment of tumor response based on RECIST 1.1 was reviewed independently of PET/CT results. Survival was counted from the treatment initiation, with PFS counted to tumor progression by RECIST 1.1 or death and OS counted to death.

Statistical Analysis

The comparison of mean SUL_{peak} values in serial ^{18}F-FDG PET/CT studies was performed using the Wilcoxon signed rank test. The predictive power of maximal SUL_{peak} in baseline PET/CT for PFS and OS was assessed using the Cox proportional hazards model. The predictive powers of response evaluation by ^{18}F-FDG PET/CT using methods 1 and 2 for PFS and OS were analyzed using the Kaplan-Meier method and the log-rank test. SPSS software (version 19.0; IBM Corp, New York, NY) was used for statistical analysis. All tests were 2-sided, and P values less than 0.05 were considered significant.

RESULTS

Patients and Parametric Quantification

A total of 28 patients were enrolled, with 27 patients eligible for analysis. One patient who died before the completion of PET/CT studies was excluded. Baseline characteristics of 27 patients are given in Table 1. A total of 85 VOIs were eligible for analysis. The level and distribution of SUL_{peak} in 3 consecutive PET/CT studies are illustrated in Figure 1. The change of SUL_{peak} is significant between all 3 studies ($P < 0.001$ between S0 and S1, $P = 0.023$ between S1 and S4, $P < 0.001$ between S0 and S4).

TABLE 1. Baseline Characteristics of Patients

Characteristic	n	Mean (SD)
Sex		
Male	14	
Female	13	
Primary tumor site		
Ascending colon	4	
Transverse colon	4	
Descending colon	4	
Sigmoid colon	4	
Rectum	11	
Primary tumor grade		
Well differentiated	3	
Moderately differentiated	19	
Poorly differentiated	5	
Primary stage group		
II	1	
III	10	
IV	16	
Age at primary diagnosis, y		51.2 (12.2)
Age at M1 diagnosis, y		51.8 (12.0)
Age at study enrollment, y		53.4 (12.2)

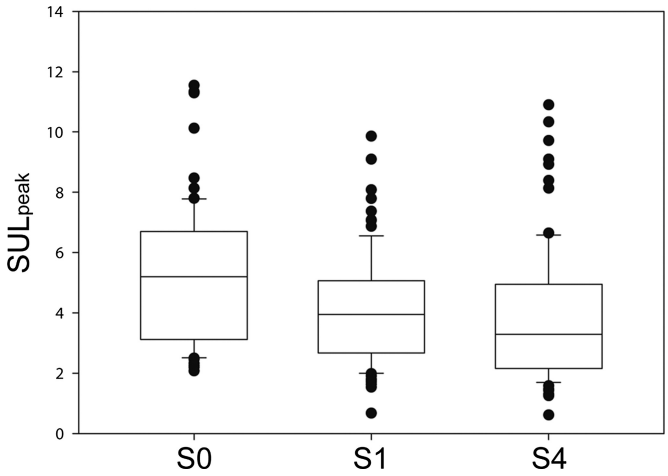

FIGURE 1. Box plot graphs illustrating the distribution of SUL_{peak} in the baseline study (S0), the study at the end of the first week (S1), and the study at the end of the fourth week (S4) from tumor VOIs in patients receiving third-line cetuximab-based therapy. The mean (SD) of SUL_{peak} is 5.19 (2.30) in S0, 4.11 (1.82) in S1, and 3.86 (2.21) in S4. The reduction of tumor metabolism is most obvious during the first week of therapy.

Tumor Response Evaluation by ^{18}F-FDG PET/CT

The results of tumor response evaluation are presented in Table 2. Using method 1, response rate was 37% at S1 and 52% at S4. Using method 2, response rate was 74% at S1 and 67% at S4. At S1, 10 and 20 patients were grouped as responsive by method 1 and 2, respectively. The additional 10 patients grouped as responsive by method 2 was grouped as SMD by method 1. At S4, 14 and 18 patients were grouped as responsive by method 1 and 2, respectively. The additional 4 patients grouped as responsive by method 2 were also grouped as SMD by method 1.

Using method 1, 10 patients were grouped as PMR at S1 and remained PMR at S4. Seventeen patients were grouped as SMD at S1, of whom 12 remained as SMD, 4 shifted to PMR, and 1 shifted to PMD at S4. Using method 2, 7 patients were grouped as nonresponsive at S1 and remained nonresponsive at S4. Twenty patients were grouped as responsive at S1, and 2 of them shifted to nonresponsive at S4.

The PET images of a patient grouped as responsive by method 2 both at S1 and S4 are illustrated in Figure 2. The PET images of another patient grouped as nonresponsive by method 2 both at S1 and S4 are illustrated in Figure 3.

Patient Follow-up Status and Prediction of PFS and OS

The patient follow-up status is also shown in Table 2. The minimum duration of follow-up for patients alive was 9 months. Six patients remained alive, whereas all others died. The median PFS is 5.8 months,

TABLE 2. Response Evaluation by ^{18}F-FDG PET/CT and Patient Follow-up Status

Response Evaluation at the End of the First Week		Response Evaluation at the End of the Fourth Week		Patient Follow-up		
Method 1	Method 2	Method 1	Method 2	Status	OS, mo	PFS, mo
SMD	NR	PMD	NR	DOD	9	6
SMD	R	PMR	R	AWD	>21	15
PMR	R	PMR	R	DOD	10	4
SMD	NR	SMD	NR	DOD	3	3
SMD	R	PMR	R	DOD	14	9
PMR	R	PMR	R	DOD	6	6
PMR	R	PMR	R	DOD	9	6
SMD	R	SMD	R	DOD	14	6
PMR	R	PMR	R	DOD	10	5
SMD	R	SMD	R	DOD	15	6
PMR	R	PMR	R	DOD	16	9
SMD	R	SMD	NR	DOD	5	2
SMD	NR	SMD	NR	DOD	4	2
SMD	R	SMD	R	DOD	13	6
SMD	R	SMD	NR	DOD	2	2
PMR	R	PMR	R	DOD	8	6
SMD	NR	SMD	NR	DOD	7	3
SMD	R	PMR	R	AWD	>19	12
SMD	NR	SMD	NR	DOD	3	3
PMR	R	PMR	R	AWD	>17	12
SMD	R	SMD	R	DOD	5	3
PMR	R	PMR	R	AWD	>13	11
PMR	R	PMR	R	AWD	>13	>12
PMR	R	PMR	R	DOD	5	3
SMD	NR	SMD	NR	DOD	7	3
SMD	NR	SMD	NR	DOD	5	3
SMD	R	PMR	R	AWD	>9	>9

AWD, alive with disease; DOD, died of disease; NR, nonresponsive; R, responsive.

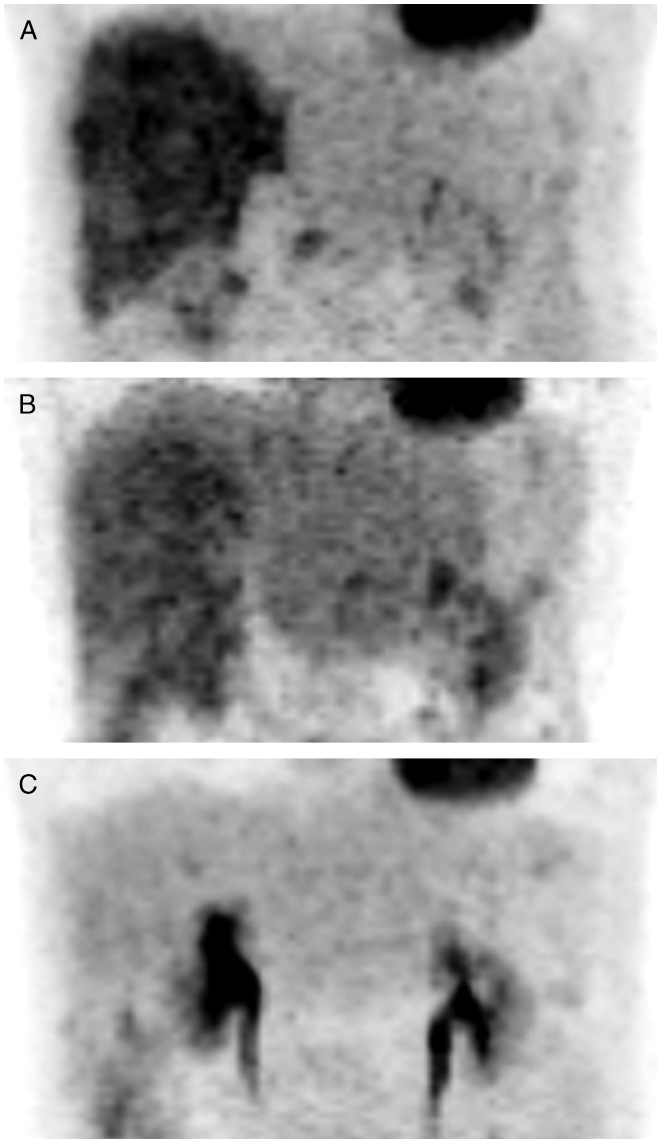

FIGURE 2. The MIP PET images in a 56-year-old male patient with multiple hepatic metastases. The liver SUL_{peak} was 5.51 in S0 (**A**), 3.94 in S1 (**B**), and 2.78 in S4 (**C**). This patient was grouped as SMD by method 1 and responsive by method 2 at the end of the first week. He had a PFS of 15 months and lived for at least 21 months.

and the median OS is 9.1 months. Maximal SUL_{peak} in the baseline PET/CT is not a significant predictor for PFS ($P = 0.279$) and OS ($P = 0.136$). With response evaluation at the end of the first week, method 1 does not predict PFS ($P = 0.316$) and OS ($P = 0.404$), whereas method 2 predicts PFS ($P = 0.001$) and OS ($P < 0.001$). Kaplan-Meier curves for PFS in patients grouped as responsive or not are illustrated in Figure 4, and those for OS are illustrated in Figure 5. With response evaluation at the end of the fourth week, both methods predicts PFS ($P < 0.001$ for both methods) and OS ($P = 0.002$ for method 1; $P < 0.001$ for method 2).

DISCUSSION

The K-*ras* genetic test is indicated before the use of cetuximab as activating mutations are detected in approximately 40% of patients with mCRC and will lead to therapeutic resistance.[16] However, not all patients with wild-type K-*ras* respond to cetuximab. Early and accurate evaluation of therapeutic response is therefore important. Response Evaluation Criteria in Solid Tumors has limitations for response evaluation with targeted therapies and newer radiologic criteria proposed still may not suit for early evaluation within weeks of therapy.[7,17,18] Wahl et al[19] found a rapid and significant decrease in tumor glucose metabolism after initiation of effective neoadjuvant therapy for breast cancer, with the reduction in metabolism antedating any decrement in tumor

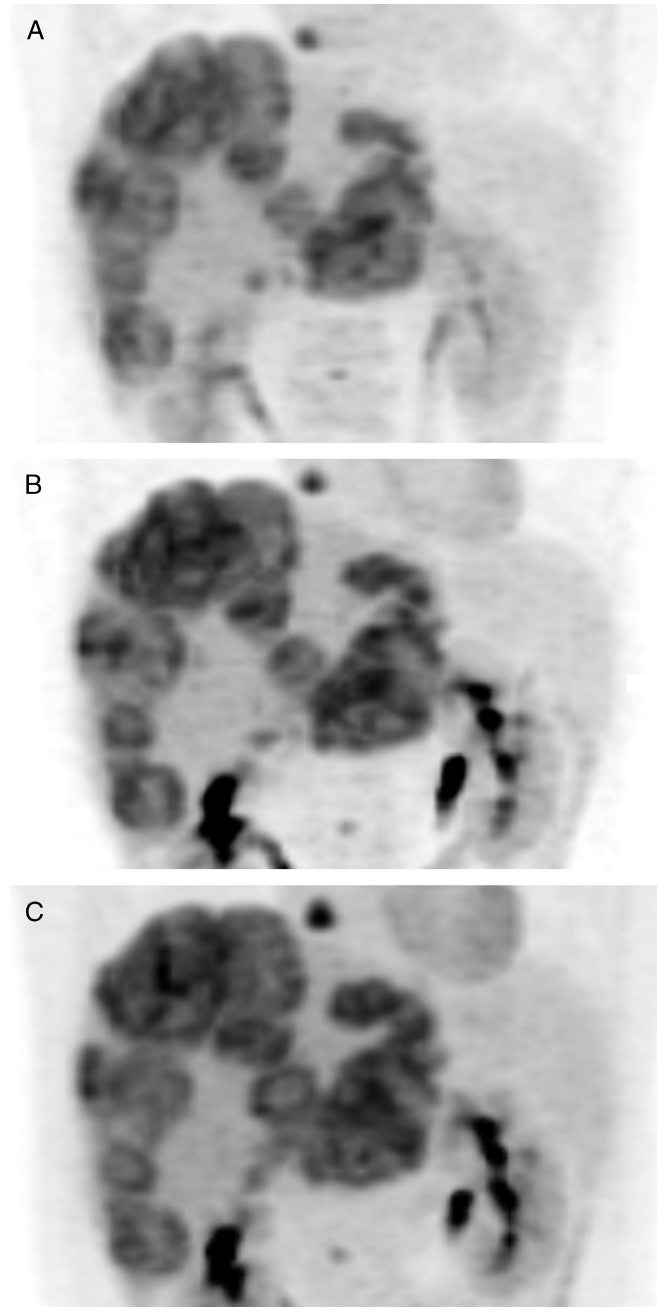

FIGURE 3. The MIP PET images in a 47-year-old male patient with multiple hepatic metastases and a T9 vertebral metastasis. The liver SUL_{peak} was 5.74 in S0 (**A**), 6.30 in S1 (**B**), and 6.50 in S4 (**C**). This patient was grouped as SMD by method 1 and nonresponsive by method 2 at the end of the first week. He had a PFS of 2 months and an OS of 7 months.

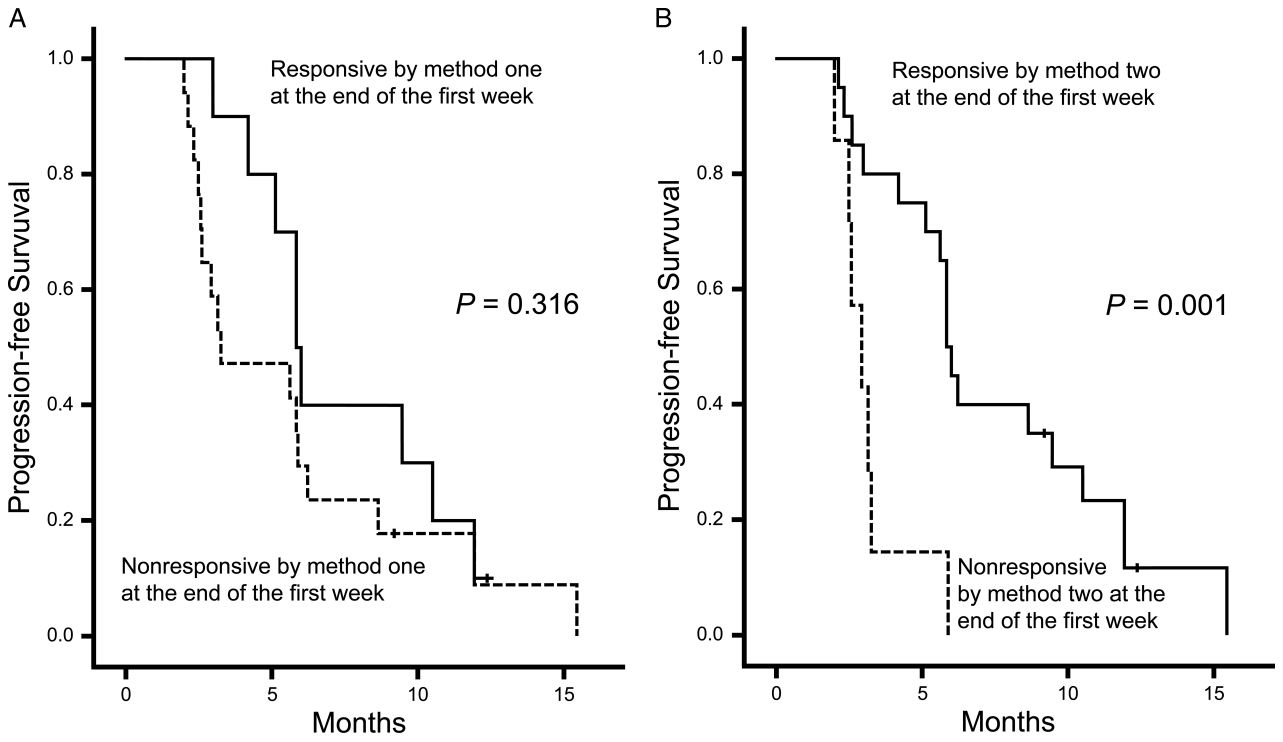

FIGURE 4. Kaplan-Meier curves for PFS in patients grouped as responsive or nonresponsive at the end of the first week by method 1 (**A**) and method 2 (**B**).

size. In patients of colorectal cancer with liver metastases, Findlay et al[20] found that ^{18}F-FDG PET performed at baseline and 4 to 5 weeks on fluorouracil treatment can discriminate response from nonresponse. The usefulness of ^{18}F-FDG studies in response evaluation and survival prediction has been evaluated in several solid tumors including colorectal cancer.[11,21] In the absence of therapeutic options, early evaluation of tumor response may not substantially change disease management. However, different therapeutic choices are available for mCRC now.

There is no universally accepted definition for tumor response in ^{18}F-FDG studies. The European Association for Research and Treatment of Cancer published preliminary criteria for the assessment of tumor response in 1999.[22] However, distinct tumor characteristics,

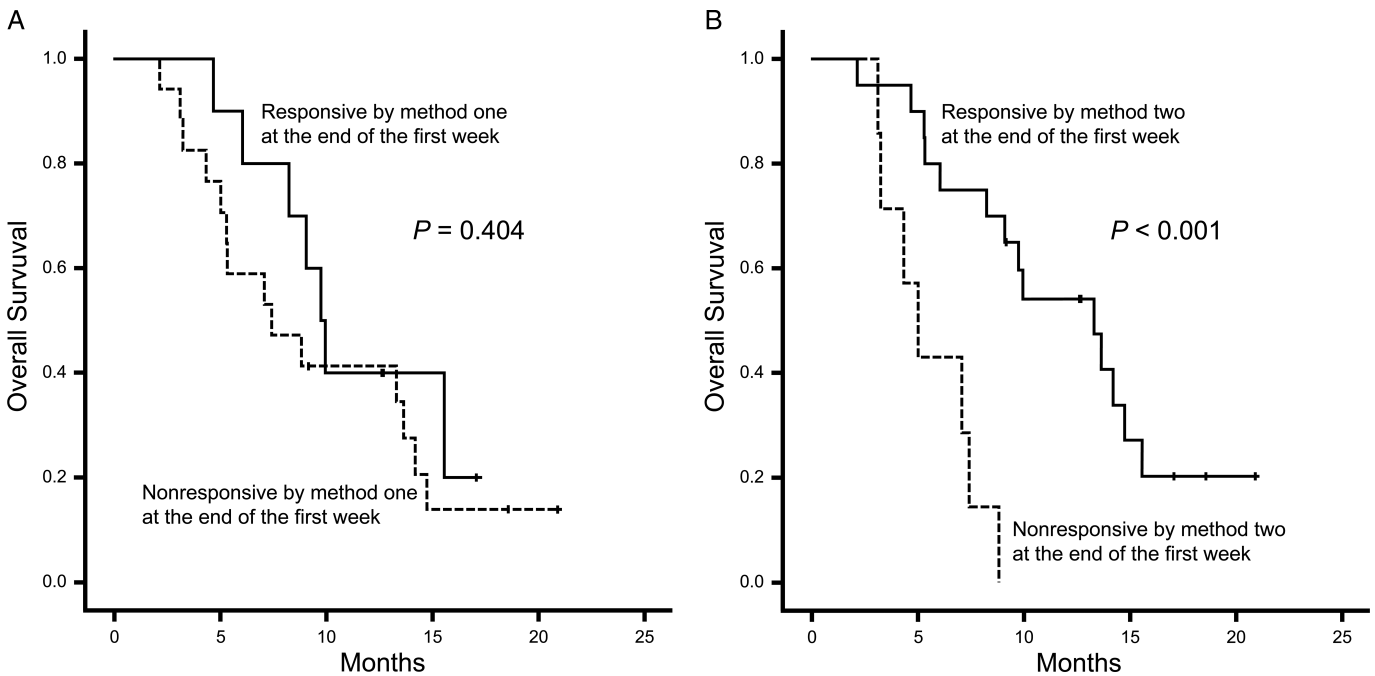

FIGURE 5. Kaplan-Meier curves for OS in patients grouped as responsive or nonresponsive at the end of the first week by method 1 (**A**) and method 2 (**B**).

different therapeutic regimens, and various evaluation time points can all confound the optimal SUV cutoff value for response. Thus, it is not surprising that different criteria for tumor response were used in studies. The PERCIST criteria have been proposed as an effort of standardization for PET/CT studies to assess treatment effect in solid tumors.[8] The use of SUL_{peak} to represent tumor ^{18}F-FDG metabolic activity has been recommended due to better consistency and reproducibility. We concur with the use of SUL_{peak} and the choice of the most active lesions for evaluation at different time points. In the palliative setting, tumor lesions can be numerous, and it is impractical to assess each lesion separately. Comparison of the most active lesions does provide a simple and reasonable way for response evaluation. A recent study of 61 mCRC patients receiving third-line irinotecan and cetuximab showed PET/CT response evaluation with the European Association for Research and Treatment of Cancer criteria, and PERCIST gave similar responses and similar significant differences in median OS between response groups.[23]

In the current study, PET/CT response evaluation with PERCIST predicts survival at the end of the fourth week but not at the end of the first week. The requirement of a 30% decrease in SUL_{peak} by PERCIST seems too demanding in the first week of therapy. The current study proposed a simple method for tumor response evaluation by ^{18}F-FDG PET/CT for cetuximab-based therapy and demonstrated its predictive value for PFS and OS as early as 1 week into treatment. The reduction of tumor metabolism is most obvious during the first week of therapy as illustrated in Figure 1. This can explain why the response evaluation for targeted therapy is possible within the first week. Early response evaluation can facilitate the shortening of ineffective treatment for nonresponding patients and a quick shift to alternative therapy. Whether earlier tumor response evaluation such as at the second day of therapy can predict survival as well is an interesting question and deserves further studies.

For mCRC patients receiving second-line or higher anti-epidermal growth factor receptor–based treatment, the pooled response rate in patients without K-*ras* mutation was around 37%.[6] The disease control rate ranged from 60% to 84% in studies with cetuximab plus chemotherapy. In the current study, the response and disease control rates using method 1 at the end of the fourth week were 52% and 96%, respectively, and seemed to be higher than optimal. Using method 2, 74% and 67% of patients were grouped as responsive at the ends of the first and fourth weeks, respectively, and were concordant with the range of disease control rates.

The current study is a single-institutional trial, and thus further validation will be needed. Proper patient preparation and quality assurance between serial ^{18}F-FDG studies are essential. For example, the image acquisition time must be fixed after tracer injection because SUVs are not stable with time.[19,24] Inconsistent protocol and poor quality control will result in assessment errors and may jeopardize the clinical benefit. The current study had followed the consensus recommendations for protocol standardization to minimize the interstudy variability.[15,25]

CONCLUSIONS

In conclusion, tumor response evaluation by ^{18}F-FDG PET/CT can predict PFS and OS in patients with mCRC and wild-type K-*ras* as early as 1 week into third-line cetuximab and irinotecan-based therapy. Early management change may become feasible for nonresponsive patients. In the era of personalized cancer medicine, early response evaluation by ^{18}F-FDG PET/CT can become a useful surrogate marker for therapeutic efficacy.

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