Clinical Cancer Research

The Predictive and Prognostic Value of Early Metabolic Response Assessed by Positron Emission Tomography in Advanced Gastric Cancer Treated with Chemotherapy

Chenchen Wang[1,2], Weijian Guo[1,2], Min Zhou[2,3], Xiaodong Zhu[1,2], Dongmei Ji[1,2], Wenhua Li[1,2], Xin Liu[1,2], Zhonghua Tao[1,2], Xiaowei Zhang[1,2], Yingjian Zhang[2,3], and Jin Li[1,2]

Abstract

Purpose: To evaluate the feasibility of early metabolic change assessed by PET in predicting clinical response to chemotherapy and investigate its prognostic value in patients with advanced gastric cancer.

Experimental Design: A total of 64 patients with advanced gastric cancer were prospectively enrolled and examined by PET with ^{18}F-fluorodeoxyglucose (FDG) and ^{18}F-fluoro-3′-deoxy-3′-L-fluorothymidine (FLT) at baseline and 14 days after treatment initiation. PET findings were analyzed for the correlation with best clinical response of patients, disease control status, and survival after identifying the threshold of metabolic change percentage by ROC analysis.

Results: For FDG-PET, the total uptake value reduction percentage (δ-SUV) of 40% was the cut-off point with the maximum of sensitivity (70%) and specificity (83%) to predict clinical responding and that of prediction for disease control status was 30%, with the highest sensitivity (58%) and specificity (100%). The δ-SUV of FLT-PET played no predictive role for clinical response (AUC = 0.62; P = 0.134) and disease control (AUC = 0.66; P = 0.157). The univariate Cox regression analysis revealed no significant prognostic impact. FDG uptake reduction in liver metastases could predict both clinical response (P = 0.010) and disease control status (P = 0.002) at thresholds of 35% and 15%, respectively. Those with greater FDG uptake reduction in liver lesions had a longer overall survival (P = 0.004).

Conclusions: Early metabolic change in FDG-PET might be a predictive marker for response and disease control in advanced gastric cancer. Early FDG uptake change in liver metastases might be a useful prognostic factor and needs further exploration.
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Introduction

As one of the most common malignancies and cancer-related deaths worldwide, advanced gastric cancer has a poor prognosis, with the overall survival (OS) being less than 12 months (1). Research has established the role of first-line palliative chemotherapy in advanced gastric cancer, especially combination regimens, by improving survival and relieving symptoms compared with best supportive care. However, the objective response (OR) rates of first-line chemotherapy in unresectable advanced (local advanced or metastatic) gastric cancer from a series of large clinical trials still lingers at an unsatisfactory level (25%–55%), with the median progression-free survival (PFS) being 4 to 7 months and the OS 9 to 14 months (2–7). Even with the addition of the targeted drug trastuzumab, the response rate is no more than 50% with a PFS of less than 7 months and OS of less than 14 months (8). Currently, there is still no established standard regimen for second-line therapy, and the PFS is only around 2 to 3 months (9). Patients tend to progress rapidly to end-stage disease after failure of first-line therapy. For patients with metastatic gastric cancer, the response rate and PFS with the first-line treatment is key to determining their final outcome. Thus, it is important to find out whether patients will respond to first-line treatment early in the course to avoid further use of ineffective regimens with associated adverse effects and unnecessary costs, and save time by finding the optimal regimen. More importantly, for patients with locally advanced gastric cancer receiving neoadjuvant or preoperative chemotherapy, early detection of efficacy could avoid losing the chance of curative gastrectomy.

The conventional radiologic technologies, such as CT and MRI, have been widely used to evaluate the responses of patients to chemotherapy. Commonly, patients receive a scan after every two cycles of medication at a time interval of 6 to 8 weeks. If a response marker could be found much earlier after the start of treatment, patients who will not benefit from the ongoing regimen could be identified. As a metabolic imaging system, PET has been assessed by several studies as a potentially effective noninvasive tool to predict response to chemotherapy early in the treatment course for gastric cancer in the neoadjuvant and palliative settings (10–12). The results have shown that when a certain quantitative threshold

[1]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China. [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China. [3]Department of Nuclear Medicine, Fudan University Shanghai Cancer Center, Shanghai, China.

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C. Wang and W. Guo contributed equally to this article.

Corresponding Author: Jin Li, Department of Medical Oncology, Fudan University Cancer Center, Shanghai Medical College, Shanghai 200032, China. E-mail: fudanlijin@163.com

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Translational Relevance

This study comprised clinical research that explored the value of two types of PET in predicting the best clinical response early after the start of first-line chemotherapy in patients with advanced gastric cancer. On the basis of the results, the response of a patient might be predicted prior to conventional radiologic evaluation so that the decision could be made early in the treatment course as to whether any change of chemotherapy regimen was necessary for the next cycle.

for metabolic response is identified, PET scan could probably distinguish a responding tumor from a nonresponding tumor early in the course of treatment. The MUNICON (Metabolic response evalUatioN for Individualisation of neoadjuvant Chemotherapy in Esophageal and esophagogastric adenocarcinoma) trial (12) prospectively confirmed the feasibility of ^{18}F-fluordeoxyglucose (FDG)-PET–guided metabolic response assessment only 2 weeks after the initiation of neoadjuvant therapy in 119 patients with locally advanced adenocarcinoma of the esophagogastric junction. Conversely, both Ott and colleagues (13) and Vallböhmer and colleagues (14) failed to find a significant correlation between change of metabolic uptake of PET scan and clinical response or prognosis in the neoadjuvant setting for locally advanced gastric cancer. Besides these controversial conclusions, the role of PET in response prediction has been trialed mainly for preoperative chemotherapy of locally advanced gastric cancer, focusing on patients with potentially resectable tumors.

In the palliative setting of metastatic disease, which is a large part of gastric cancer treatment with a much poorer outcome, the role of PET scan in response prediction for first-line treatment is rarely explored. Di Fabio and colleagues (10) explored the predictive role of FDG-PET in a first-line palliative setting in 22 patients with metastatic disease and demonstrated that a decrease in percentage in standardized uptake value (SUV) of FDG-PET from baseline to 2 weeks after initiation of treatment was significantly associated with and predictive of clinical response according to the RECIST criteria. However, this conclusion is limited by the small size of study such that the value of PET scan, mostly FDG-PET, in predicting the response to palliative therapy is still not clear.

The metabolic tracer ^{18}F-fluoro-3′-deoxy-3′-L-fluorothymidine (FLT) offers noninvasive assessment of tumor proliferative activity, which represents a key feature of malignancy (15). The FLT tracer may, to some extent, serve as a complement in gastric cancer without or with low FDG uptake, presenting a high sensitivity of more than 95% (16, 17). Current data show limited but encouraging results of the potential role of FLT as an early predictor of response to therapy and a prognostic indicator (15). Nevertheless, the relatively low tumor FLT uptake and the physiologically high FLT uptake in liver and bone marrow limited its utilization in clinical practice. The current status of FLT-PET from early evaluation of response to palliative treatment in metastatic gastric cancer still needs to be validated.

In previous studies, the predictive value of early uptake change in FDG- or FLT-PET scanning was explored in only one kind of tracer. So far, no study has evaluated the role of FDG- and FLT-PET simultaneously in early response prediction for palliative treatment in gastric cancer.

The aim of this exploratory study was to prospectively evaluate whether the early change of metabolic activity in FLT-PET and FDG-PET could predict the OR and prognosis in patients with advanced gastric cancer treated with the same first-line chemotherapy regimen. The patients were enrolled in a prospective phase II clinical trial, with the primary endpoint of predictive value for best objective clinical response to first-line chemotherapy. The prognostic role of early metabolic uptake change for PFS and OS was the secondary endpoint.

Patients and Methods

Patient population

This study was part of a prospective phase II clinical trial (ClinicalTrials.gov Identifier: NCT00767377), which was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (Shanghai, China). From February 2011 to October 2012, 64 consecutive patients with histologically proven, unresectable gastric cancer who were enrolled in the trial of advanced gastric cancer and metastatic gastric cancer treated with the 5-fluorouracil (5-FU) combined with epirubicin and oxaliplatin (EOF) regimen as first-line treatment were simultaneously incorporated into this PET imaging study. The eligibility criteria of the study were as follows: (i) age 18 to 75 years; (ii) histologically confirmed inoperable advanced or metastatic gastric adenocarcinoma; (iii) Karnofsky performance status higher than 60, with estimated life expectancy more than 12 weeks; (iv) at least one measurable lesion (larger than 10 mm in diameter by spiral CT scan); and (v) adequate bone marrow, renal, and hepatic function [platelets $>80 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, serum creatinine ≤ 1.5 mg/dL, total bilirubin level within 1.5× the upper limit of normal (ULN), and serum transaminase $\leq 2.5\times$ ULN]. The FDG-PET and FLT-PET imaging were performed as part of this trial and all patients provided written informed consent for the trial, including consent for all PET scan examinations.

Treatment regimen

Patients received the first-line chemotherapy of EOF regimen. Intravenous epirubicin 50 mg/m^2 was given on day 1, plus oxaliplatin 130 mg/m^2 i.v., and followed by 5-FU 2.0 g/m^2 i.v. continuous infusion for 120 hours every 3 weeks for a maximum of 6 cycles, until disease progression, occurence of unacceptable toxicity, or treatment withdrawal by patient or decision of the doctor. The maintenance therapy with either oral tegafur or observation was allowed in patients without disease progression.

PET imaging

The attenuation-corrected whole-body FLT- and FDG-PET/CT imaging was performed on two consecutive days within 1 week preceding chemotherapy. Patients were included only if PET scanning showed sufficient uptake contrast between tumor lesions and surrounding tissues. The PET was repeated 14 days after the initiation of first-line chemotherapy (Supplementary Fig. S1).

^{18}F was produced by the cyclotron [Eclipse ST (40 μA × 11 MeV); Siemens] in our center. FDG was synthesized using the Explora FDG4 module (Siemens). FLT was synthesized as previously described by Wang and colleagues (^{18}). Radiochemical purity was over 95% for both types of tracers. PET/CT with two types of radiotracer were both performed using a PET/CT scanner (Biograph 16 HR; Siemens). The detailed imaging techniques and

procedures of FDG-PET and FLT-PET were identical to our recent published study (19). Before performing FDG-PET/CT imaging, the patients were instructed to fast for at least 4 hours. Peripheral blood glucose level was ensured to be less than 7 mmol/L. Sixty minutes after an intravenous injection of 7.4 MBq/kg tracer, a whole-body scan was obtained from the skull base to the proximal thighs, with 2 minutes per bed position for emission scanning. Just before scanning, the patient was instructed to drink 300 to 500 mL of water to expand the stomach, unless the patient was incapable of consuming liquids. The patient was asked to remain quiet after tracer administration to avoid muscle radioactivity uptake.

FLT-PET/CT imaging was performed under the same conditions as those used for FDG-PET/CT imaging, except that control of blood glucose and restriction of movement were not required.

Reconstruction and attenuation correction of PET images were performed using the same technique and work station. The slice thickness of both transmission and emission reconstruction images was 5 mm. Transmission data were used to perform attenuation correction of PET images. PET and CT images were transmitted to a Wizard work station to obtain fusion images automatically.

PET data analysis

All PET scans were reviewed and interpreted by two experienced nuclear medicine physicians (Min Zhou & Silong Hu) who were blinded to the clinical information and results of other imaging. If the interpretations were different between the images, the results were discussed until a consensus was reached. In the follow-up PET scan, the regions of measurement were placed in the same positions as in the baseline scans, referring to anatomic landmarks. For semiquantitative analysis of metabolic uptake using circular regions of interest, the maximal standardized uptake value (SUV_{max}) was calculated for each scan (20, 21). The SUV_{max} on the follow-up scan was set to 0 if there was no lesion visible. SUV_{max} was measured for each malignant target lesion, including the primary tumor (stomach) and metastatic sites and was added together as a total SUV_{max} value. The decrease percentage of total SUV_{max} values of all target lesions (δ-SUV) from baseline (total SUV1) to day 14 PET scan (total SUV2) was calculated as metabolic response and was compared with clinical response and disease control status.

Clinical response evaluation

The OR of patients to first-line chemotherapy was clinically evaluated every two cycles by enhanced CT or MRI scan until disease progression or one year after initiation of treatment, according to the RECIST criteria, version 1.1 (22). Complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) were included in the criteria. CR and PR were identified as clinical response, whereas SD and PD as nonresponse. Responses judged to be CR, PR, or SD were defined as disease control status. The minimum time frame for assessment by CT/MRI was 6 weeks in our study. Each response recorded for every patient in this study was best response, which was the best of all clinical evaluation results during the treatment.

Statistical analysis

The primary analysis was prospectively designed and preplanned in this article. The subgroup analysis was unplanned before patient recruitment. All quantitative data were expressed in the form of medians. PFS was measured from the start of the treatment until disease progression or death from any cause. Patients with no evidence of PD were censored at the date of the last follow-up. OS was measured from the start of the treatment until death from any cause. Patients who were alive at the time of the last follow-up were censored on that date. Survival curves were estimated according to the Kaplan–Meier method to determine prognostic factors. All the survival data were calculated on the basis of an intention-to-treat (ITT) analysis. Univariate analysis of survival within different groups of patients was performed using the log-rank test. Those variates with a P value no more than 0.1 would be further tested in multivariate model by Cox proportional hazard regression to identify independent prognostic factors.

The ROC analysis was performed, and corresponding AUC values were calculated. To separate metabolic responders from nonresponders, the criterion for selection of cut-off point was the maximum of Youden index, which was defined as $\max_c [Sen(c) + Spe(c) - 1]$, where c is the cut point ([23]). At the cut-off point, the sensitivity, specificity, as well as positive and negative predictive values of the metabolic response in FLT-PET and FDG-PET for the best clinical response (CR + PR) and disease control status (CR + PR + stable disease), along with 95% confidence intervals (CI) for these parameters, were calculated separately. All tests were two-sided, and a P value < 0.05 was chosen as statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 16.0 (SPSS, Inc.).

Results

Study population and response evaluation

All 64 patients underwent at least one type of PET (FDG- or FLT-PET) scan at baseline before the start of the treatment and were analyzed at the end of the study. Twelve patients were still alive at the last follow-up (August 5, 2013), with a median follow-up time of 15.1 months (range, 7.7–23.3 months). The clinical characteristics of patients are summarized in Table 1.

Two patients dropped out of the study due to unacceptable toxicity after only one cycle of chemotherapy, thus the clinical response was evaluated in 62 patients. Twenty-seven of the 62 (43.5%) patients were judged to have a clinical response, including 2 (3.2%) with a best OR of CR and the other 25 (40.3%) with PR. Twenty-six patients (41.9%) had SD, and 8 (12.9%) had PD.

For 58 patients with metastatic disease, nearly half (27/58; 46.6%) had liver metastases. The second most common metastatic site was distant lymph nodes (14/58; 24.1%), followed by ovary (10/58; 17.2%).

The estimated median PFS for all (ITT population, $n = 64$) was 5.9 months (95% CI, 5.4–6.3 months). The estimated median OS for all (ITT population, $n = 64$) was 8.9 months (95% CI, 7.8–9.9 months). For patients with locally advanced gastric cancer and those with metastatic disease, there was no significant difference in PFS (5.4 vs. 5.9 months; $P = 0.871$) and OS (9.7 vs. 8.7 months; $P = 0.957$). The clinical responders (CR + PR) had a significantly better OS than nonresponders (11.1 vs. 7.3 months; $P = 0.035$), whereas only a trend favoring clinical responders for PFS was observed (6.2 vs. 4.8 months; $P = 0.084$). For patients with disease progression ($n = 8$), poorer survival was found for both PFS (1.4 versus 7.1 months; $P < 0.001$) and OS (4.7 months vs. 11.6 months; $P < 0.001$) compared with those with disease control

Table 1. Clinical characteristics of patients ($N = 64$)

Characteristics	Number of patients	Percent (%)
Age (years)		
Median	56	
Range	24–73	
Sex		
Male	37	57.8
Female	27	42.2
ECOG performance status		
0	20	31.2
1	44	68.8
Tumor location		
Cardia	12	18.7
Non-cardia	52	81.3
Resection of primary lesion		
Yes	14	21.9
No	50	78.1
Tumor stage status		
Locally advanced (M0)	6	9.4
Metastatic (M1)	58	90.6
Involved metastases ($n = 58$)		
Distant lymph node	14	24.1
Liver	27	46.6
Lung	5	8.6
Ovary	10	17.2
Bone	2	3.4
Pelvic peritoneum	8	13.8
Adrenal gland	2	3.4
Completion of PET scanning		
FDG baseline	64	100
FLT baseline	61	95.3
FDG after 2 weeks	58	90.6
FLT after 2 weeks	54	84.4
Clinical response ($n = 62$)		
CR/PR	27	43.5
SD	26	41.9
PD	8	12.9

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

(CR + PR + SD). In the subset of 58 patients with metastatic disease, the clinical responders (CR + PR) had a significantly better PFS (6.2 vs. 4.7 months; $P = 0.032$) and OS (11.2 vs. 6.8 months; $P = 0.013$) than clinical nonresponders.

PET findings

FDG uptake of PET scan. All of the 64 patients (100%) underwent FDG-PET at baseline before chemotherapy. The initial FDG-PET uptake was positive in 60 (93.8%) patients. At baseline, the mean SUV_{max} of FDG uptake was 8.7 (median 8.4, range 1.0–25.3) in primary tumor lesion, 10.5 (median 10.7, range 2–16.6) in liver metastases, 11.1 (median 11.9, range 6.8–14.7) in distant lymph nodes metastases, and 5.6 (median 5.3, range 3.1–12.2) in ovary metastases. Those with FDG non-avid tumors at baseline would not receive FDG-PET rescanning 2 weeks after the start of the treatment. Two patients whose tumor was FDG-avid initially refused the day 14 FDG-PET scanning. Thus, a total of 58 patients fulfilling both two FDG-PET scanning were evaluable for following day 14 FDG-PET analysis, with mean SUV_{max} of FDG uptake decreasing to 5.8 (median 5.4, range 0–21.7) in primary tumor lesion, 7.3 (median 7.1, range 0–15.7) in liver metastases, 8.7 (median 7.8, range 0–16.7) in distant lymph nodes metastases, and 4.2 (median 3.0, range 2.3–9.4) in ovary metastases.

The decrease of total SUV_{max} values (δ-SUV) was stronger for radiologic responders than for nonresponders (45.1% vs. 18.2%; $P = 0.001$).

FLT uptake of PET scan. Sixty-one (95.3%) patients underwent the initial FLT-PET scan, five of whom (8.2%) had negative uptake of FLT so did not undergo FLT-PET examination at day 14. In patients with positive FLT uptake, the average value of FLT uptake in baseline FLT-PET was 5.9 (median 5.4, range 2.1–13.0) in primary tumor lesion, 6.6 (median 6.2, range 4.9–13.3) in distant lymph nodes metastases, and 4.3 (median 4.0, range 2.5–6.6) in ovary metastases. Finally, 54 patients who received the day 14 FLT-PET scan were interpretable, with mean FLT uptake value 3.6 (median 3.2, range 0–9.8) in primary tumor lesion, 5.2 (median 4.6, range 0–10.2) in distant lymph nodes metastases, and 3.1 (median 2.3, range 0–7.6) in ovary metastases. In 26 patients with liver metastases who had baseline FLT-PET scans, only 6 (23.1%) showed positive uptake, with average SUV_{max} value 6.7 (median 7.2, range 3.4–9.7) and that of day 14 FLT-PET was 5.8 (median 5.0, range 3.9–7.8).

For clinical responders, total FLT SUV_{max} value decreased more than that for clinical nonresponders, but the statistical significance was not reached (δ-SUV, 43.5% vs. 32.7%; $P = 0.078$).

A total of 54 patients had taken all the serial FDG-PET and FLT-PET (Supplementary Fig. S2).

Predictive role of PET for clinical response and disease control. Fifty-three patients who had taken all the serial FDG-PET and FLT-PET were also available for the clinical response evaluation. Thus, the ROC analysis was performed using data from these patients. In evaluable population, the δ-SUV of FDG-PET was positively predictive of clinical response (AUC = 0.759; 95% CI, 0.622–0.897; $P = 0.001$; Fig. 1A). Analysis showed that the cut-off point of δ-SUV with the highest Youden index for predicting clinical response was 40%. The sensitivity and specificity was 69.6% (16/23; 95% CI, 49.1%–84.4%) and 83.3% (25/30; 95% CI, 66.4%–92.7%), respectively. The predictive accuracy was 78.1% (41/53; 95% CI, 58.5%–81.6%), with the positive and negative predictive value 76.2% (16/21; 95% CI, 54.9%–89.4%) and 78.1% (25/32; 95% CI, 61.2%–89.0%), respectively (Table 2). By the similar analyzing methods, the δ-SUV for FDG also showed a statistically significant capability to predict the disease control status (AUC = 0.794; 95% CI, 0.663–0.926; $P = 0.008$), with a cut-off point of 30% (Fig. 1B). The sensitivity and specificity was 57.8% (26/45; 95% CI, 41.2%–69.1%) and 100% (8/8; 95% CI, 67.6%–100%), respectively. The predictive accuracy was 64.2% (34/53; 95% CI, 50.7%–75.7%), with the positive and negative predictive value 100% (26/26; 95% CI, 87.1%–100%) and 29.6% (8/27; 95% CI, 15.9%–48.5%), respectively (Table 2).

ROC analysis for FLT-PET revealed that δ-SUV of FLT-uptake played predictive role for neither clinical response (AUC = 0.621; 95% CI, 0.469–0.773; $P = 0.134$; Fig. 1C), nor disease control status in evaluable patients (AUC = 0.658; 95% CI, 0.453–0.864; $P = 0.157$; Fig. 1D).

Prognostic value for survival. The impact of FDG metabolic response on clinical outcome, as measured by PFS and OS, was calculated. After getting two cut-off points for FDG-PET in predicting clinical response and disease control status, respectively, patients could be divided into three groups: those with FDG total SUV_{max} reduction < 30% (n = 27), those with reduction between 30% and 40% ($n = 5$), and those with reduction > 40% ($n = 22$). The Kaplan–Meier curve showed no survival difference within these three groups, both for PFS (5.4 vs. 6.3 vs. 5.9 months; $P = 0.201$) and OS (6.8 vs. 9.1 vs. 8.7 months; $P = 0.649$; Fig. 2).

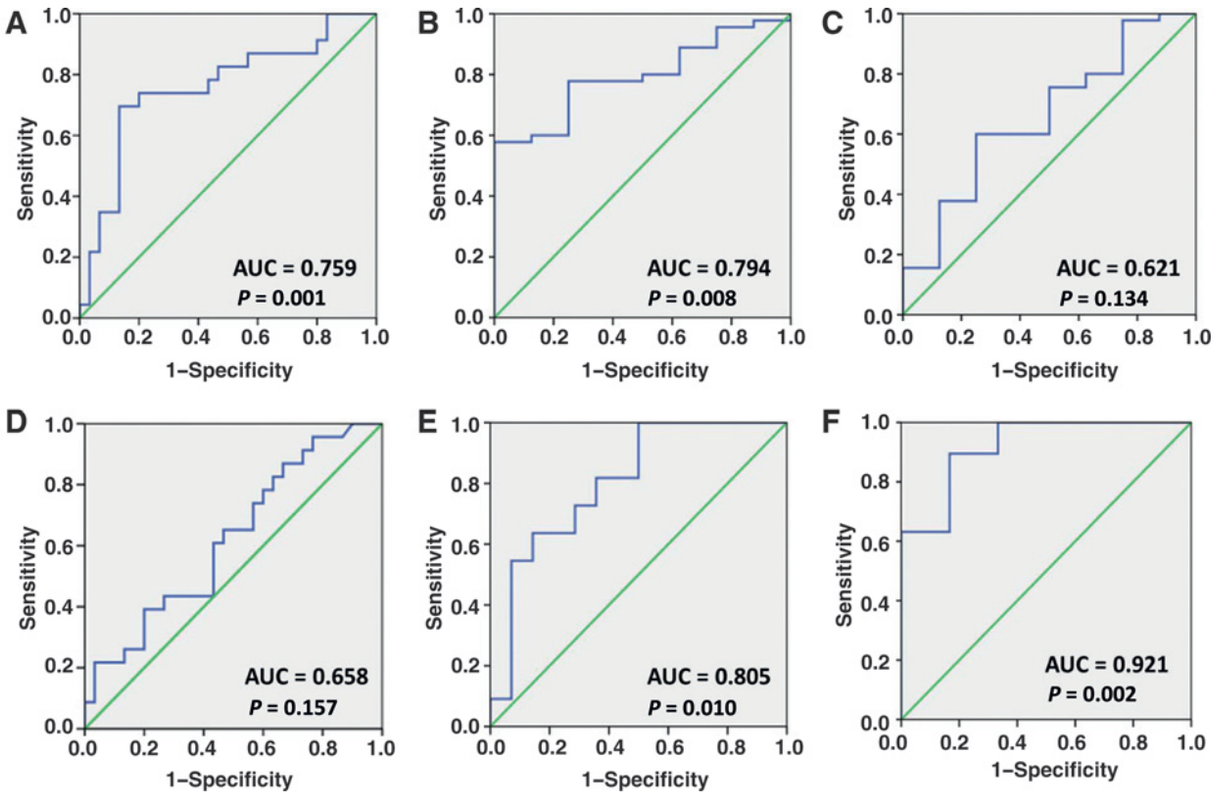

Figure 1.
ROC curve of FDG-PET predicting clinical response (A) and disease control status (B); and of FLT-PET predicting clinical response (C) and disease control status (D); and of FDG-uptake change in liver metastases predicting clinical response (E) and disease control status (F).

Univariate Cox regression analysis found that there was no prognostic impact of δ-SUV in both FDG-PET and FLT-PET on either PFS or OS (Table 3).

In the subset of 58 patients with metastatic disease, univariate Cox regression analysis found no prognostic impact of δ-SUV in both FDG-PET and FLT-PET on PFS and OS as well (Table 3).

Subgroup analysis of patients with liver metastasis

A total of 27 patients had radiologically confirmed liver metastases at the time of enrollment. In 26 patients with baseline FLT-PET scan, six (23.1%) showed increased FLT uptake so that predictive role of total uptake change could not properly evaluated in FLT-PET. As for FDG-PET, the initial uptake was positive in liver metastatic lesions in 26 patients (96.3%), and scan was repeated at day 14 in these patients.

Table 2. Early metabolic response for FDG-PET in correlation with clinical response and disease control.

	Metabolic response[a] (number of patients)	No metabolic response[b] (number of patients)	Total
Prediction for clinical response			
Clinical response (CR+PR)	16	7	23
Nonresponse (SD+PD)	5	25	30
Total	21	32	53
Prediction for disease control			
Disease control (CR+PR+SD)	26	19	45
No disease control (PD)	0	8	8
Total	26	27	53

[a]δ-SUV in prediction for clinical response > 40%; δ-SUV in prediction for disease control ≥ 30%.
[b]δ-SUV in prediction for clinical response ≤40%; δ-SUV in prediction for disease control < 30%.

ROC analysis for FDG-PET showed that the percentage reduction of SUV_{max} of FDG uptake in liver metastases was significantly predictive for both clinical response (AUC = 0.805; 95% CI, 0.632–0.978; $P = 0.010$; Fig. 1E) and disease control status (AUC = 0.921; 95% CI, 0.796–1.046; $P = 0.002$; Fig. 1F) in evaluable patients. The cut-off points with the highest sensitivity and specificity for predicting clinical response and disease control status were 35% and 15%, respectively, for reduction of SUV_{max} in liver lesions. The sensitivity and specificity of FDG uptake change locally for predicting clinical response were 63.6% (7/11; 95% CI, 35.4–84.8%) and 85.7% (12/14; 95% CI, 60.1–96.0%), respectively. The sensitivity and specificity for disease control status were 89.5% (17/19; 95% CI, 68.6–97.1%) and 83.3% (5/6; 95% CI, 43.7–97.0%), respectively. After getting two cut-off points for predicting clinical response and disease control status, patients with liver metastases could be divided into three groups: those with FDG SUV_{max} reduction ≤15% ($n = 7$), those with reduction between 15% and 35% ($n = 9$), and those with reduction ≥35% ($n = 10$). The Kaplan–Meier curve showed clearly the survival difference within these three groups (median OS, 5.3 vs. 9.9 vs. 12.1 months; $P = 0.004$). Patients with greater SUV_{max} reduction of FDG-PET in liver lesions had a longer OS (Fig. 3).

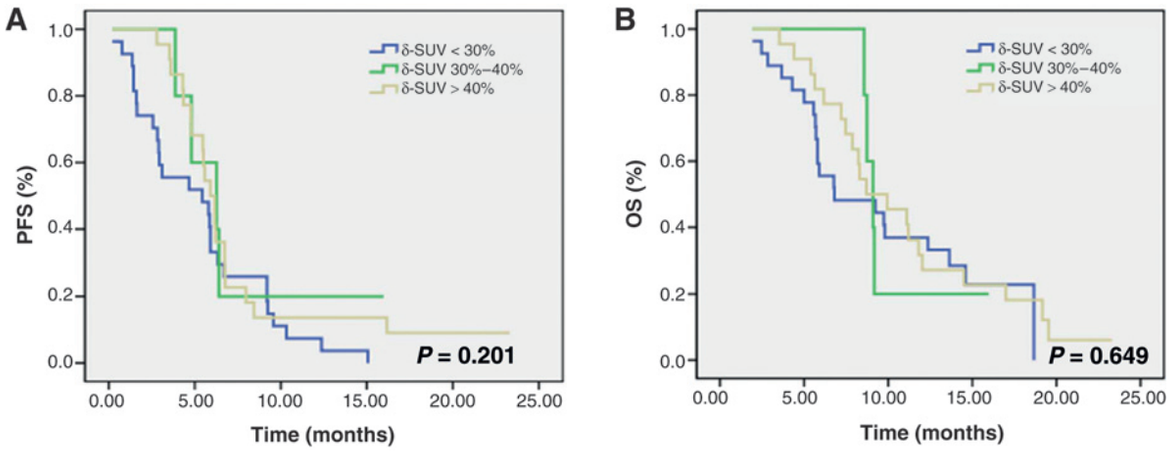

Figure 2.
Kaplan–Meier curves of PFS (A) and OS (B) for patients with different early FDG-uptake change (δ-SUV).

Subgroup analysis of patients with primary gastric lesion

Fifty patients who did not receive the resection surgery of gastric tumor at the time of enrollment had the primary tumor lesion. The primary tumor showed increased FDG uptake in 46 patients (92.0%) initially, and 45 of them took a second FDG-PET scanning 2 weeks after chemotherapy. For baseline FLT-PET, the positive uptake was shown in 40 of 47 patients (85.1%), and 39 of them received the day 14 PET scan. By the ROC analysis, uptake change in both FDG-PET and FLT-PET in primary lesion could not predict clinical response or disease control status.

Univariate Cox regression analysis within this subgroup revealed that the reduction percentage of SUV_{max} in the primary lesion for FDG-PET scan had a significant prognostic impact on PFS (HR = 0.503; 95% CI, 0.265–0.935; $P = 0.036$) as well as OS (HR = 0.390; 95% CI, 0.192–0.792; $P = 0.009$).

Discussion

Our study prospectively evaluated the predictive and prognostic value of PET/CT using two different tracers, FDG and FLT, in 64 patients with initially unresectable advanced gastric cancer. The decrease rate of total value of FDG uptake at 2 weeks after chemotherapy could positively predict not only the objective clinical response but also disease control status at a high accuracy, suggesting the clinical feasibility of early FDG-PET evaluation in identifying response of the first-line chemotherapy. However, δ-SUV of total uptake FLT-PET showed no predictive role for both clinical response and disease control. According to uptake change in FDG-PET before and after chemotherapy, we could consider at an early time whether or not to continue using the same first-line regimen for the next cycle to avoid treatment failure.

In previous studies (10–12), a decrease of 35% in FDG uptake was given as the cut-off point for response prediction. In the MUNICON I study, a decrease of 35% in FDG–SUV_{max} was prospectively preset as a clinical threshold for guiding the following treatment regimen choice (12). In our study, 40% and 30% were the points with highest sensitivity and specificity for response and disease control prediction. According to the ROC curve, an uptake decrease of 40% in FDG-PET could separate clinical responders from nonresponders at a sensitivity of 69.6% and specificity of 83.3%. The decrease of 30% separate those with disease control and those with progressive disease. The different cut-off points between previous study and ours might be within the expected variability of SUV assessments due to different study population and relatively small sample size. However, for FDG-PET, the two cut-off points of response prediction model in our study, which could probably predict the response, could no longer significantly separate the survival of patients, indicating uptake change before and after chemotherapy might not be a good predictor for survival.

Few data about FLT-PET for prediction of response and prognosis in gastric cancer have been reported in the literature so far. Ott and colleagues (13) performed FLT-PET and FDG-PET on 45 patients with locally advanced gastric cancer before and 2 weeks after preoperative chemotherapy but failed to find a predictive value for FLT-PET for clinical response. Also, our data in this study did not show the predictive role of total FLT uptake change for response and disease control. The role of FLT-PET in response prediction was still limited so far due to these negative results.

We performed two subgroup analyses focusing on the role of local change in tracer uptake. For patients with liver metastases, the early liver uptake change for FDG-PET showed a predictive value not only for clinical response but also for disease control

Table 3. Univariate Cox regression analysis for uptake change of FDG and FLT on survival

	PFS		OS	
Continuous variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
FDG–δ-SUV	0.763 (0.426–1.366)	0.362	0.686 (0.356–1.322)	0.261
FLT–δ-SUV	0.947 (0.348–2.583)	0.916	1.001 (0.306–3.276)	0.999
In subset of patients with metastases ($n = 58$)				
FDG–δ-SUV	0.795 (0.437–1.444)	0.451	0.696 (0.354–1.374)	0.298
FLT–δ-SUV	0.912 (0.333–2.496)	0.858	0.942 (0.289–3.163)	0.942

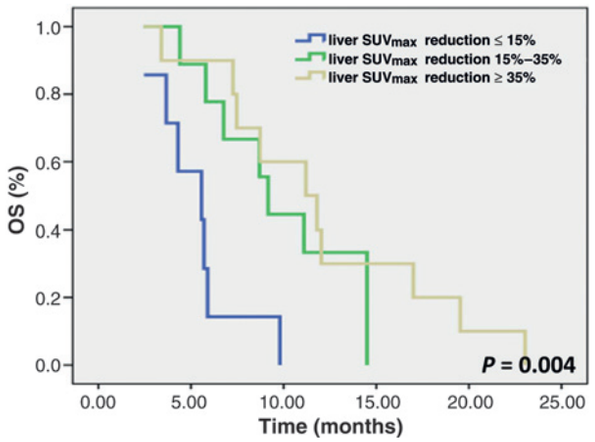

Figure 3.
Kaplan–Meier curves of OS for patients with different early FDG-uptake reduction in metastatic liver lesions.

status, which could play a prognostic role. Studies have demonstrated that the accuracy of FDG-PET for detection of liver metastases was high (24, 25). Thus, for patients with liver metastases, a local FDG uptake change could also provide key information to predict response. While FLT-PET performed as an unsatisfying tracer when judged locally in the liver, the high background hepatic uptake could interfere with lesion imaging. For patients with a primary gastric lesion, some Korean studies found high FDG uptake of primary tumor was a robust prognostic factor in patients with metastatic gastric cancer (26, 27). In our study, we also found that FDG-uptake change in primary gastric cancer showed a prognostic impact for PFS and OS. A greater reduction of FDG uptake in the primary site might convert to a better outcome. Because of the limitation of the small sample size, the predictive and prognostic role of local tracer uptake change for response and survival need to be further studied.

Conclusions

We demonstrated in our prospective study that early metabolic response evaluated by FDG-PET could predict clinical response as well as disease control status in patients with advanced gastric cancer treated by first-line chemotherapy, and metabolic uptake change of FLT-PET could predict neither response nor disease control. Both FDG and FLT uptake values at baseline and on day 14 after initiation of therapy revealed no prognostic impact on either PFS or OS. Locally, the early FDG-uptake change in liver metastases might not only predict the response to chemotherapy but also serve as a prognostic factor for survival. FDG-uptake change in the primary gastric cancer also had a significant impact on prognosis. However, our single-center study data should be interpreted with caution due to the relatively small patient population. Larger trials on this topic are urgently needed in the future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: W. Guo, J. Li
Development of methodology: C. Wang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Wang, W. Guo, M. Zhou, X. Zhu, D. Ji, W. Li, X. Liu, Z. Tao, X. Zhang, Y. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Wang
Writing, review, and/or revision of the manuscript: C. Wang, W. Guo, Z. Tao, J. Li
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Ji, W. Li, Y. Zhang, J. Li
Study supervision: J. Li

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