SUVmax of ^{18}F-FDG PET/CT correlates to expression of major chemotherapy-related tumor markers and serum tumor markers in gastric adenocarcinoma patients

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Abstract. The expression of P53 was previously found by us significantly correlated with maximal standardized uptake value (SUVmax) in non-small cell lung cancer (NSCLC) patients. Hence, the aim of this study was to clarify the relationship between SUVmax and the status of the chemotherapy-related tumor marker expression or serum tumor markers in gastric adenocarcinoma patients. Sixty-four gastric adenocarcinoma patients who underwent ^{18}F-FDG PET/CT prior to treatment were enrolled in this study. Immunohistochemistry was performed to detect changes of Her-2, P53 and Survivin in lesions, and electrochemiluminescence (ECL) method was used to quantify expression of serum CA72-4, CA19-9 and CEA of these patients. Then, the relationships between these parameters above were assessed by Spearman correlation analysis. Also, receiver-operating characteristic (ROC) curve was performed to determine the best cut-off value of SUVmax for suggesting chemotherapy resistant tumor markers. Besides, we identified a linear correlation to estimate the equations between SUVmax and the serum tumor markers. Our results showed that higher SUVmax was detected in patients with positive expression of Her-2 and P53, compared with negative groups. The Spearman correlation analysis showed that SUVmax was associated with Her-2 or P53 with the moderate relevant Pearson correlation coefficient. ROC curve analysis showed that the sensitivity and specificity of SUVmax for suggesting Her-2 or P53-positive, when the cut-off value of SUVmax was set at 3.25 or 5.45, respectively. Moreover, the relationship between SUVmax and serum tumor markers were analyzed by linear correlation analysis, and serum CA72-4 and CA19-9 could be used as independent parameters to establish an equation for SUVmax by the linear regression models. These results suggested that SUVmax of ^{18}F-FDG PET/CT could be used to predict and evaluate Her-2 or P53 related chemotherapy resistance of gastric adenocarcinoma patients. However, before PET/CT scanning, serum tumor markers could be used to calculate the SUVmax approximately.

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Abbreviations: ^{18}F-FDG, ^{18}F-fludrodeoxyglucose; PET/CT, positron emission tomography/computed tomography; SUVmax, maximal measuring standardized uptake value; NSCLC, non-small cell lung cancer; Her-2, human epidermal growth factor receptor-2

Key words: gastric adenocarcinoma, ^{18}F-FDG PET/CT, SUVmax, chemotherapy-related tumor markers, serum tumor markers

Introduction

Gastric cancer, the third leading cause of cancer death worldwide, is very common in Eastern Asia, and most are gastric adenocarcinoma (1-3). The 5-year survival rate for gastric adenocarcinoma has increased, possibly due to surgical resection and normalized combined chemotherapy (4-6). However, a large population remains resistant to chemotherapy, this suggests that there is still significant room for improvement of diagnosis and therapy in gastric adenocarcinoma patients (7,8). To our knowledge, it is clear that some patients who are positive of human epidermal growth factor receptor-2 (Her-2), P53 and Survivin will indicate poor prognosis due to chemotherapy resistance (9-14). Therefore, the relationships between these chemotherapy-related biomarkers and the SUVmax of ^{18}F-FDG PET/CT are needed, to predict the occurrence of chemotherapy resistance and create personalized therapeutic regimens of gastric adenocarcinoma patients before chemotherapy treatment.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been used as a non-invasive efficient tool for diagnosing, staging, monitoring the response to chemotherapy and identifying the recurrence following treatment in various types of tumors (14,15). Recent studies have demonstrated that there are some significant correlation between specific tumor markers and

SUVmax in pancreatic cancer and non-small cell lung cancer (NSCLC), in which EGFR and P53 mutations are associated with tumor progression or chemotherapy resistance (16,17). Besides, several studies have reported the relationship between the SUVmax and some serum tumor biomarker levels in many kinds of cancers, such as CA19-9, CA72-4, and CEA (18-20).

In a previous study, we investigated the predictive significance of the SUVmax measured by ^{18}F-FDG PET/CT in NSCLC patients, and found that SUVmax was significantly correlated with P53 expression, and PET/CT could be considered as a simple and effective non-invasive method for predicting P53-related chemotherapy resistance at the cut-off value of 5.15 (17). However, the relationship between SUVmax and chemotherapy resistance tumor markers in gastric adenocarcinoma patients, including Her-2, P53 and Survivin, has not been studied.

Hence, we examined Her-2, P53 and Survivin status using immunohistochemical staining, and found the correlation between these markers and SUVmax. Subsequently, we designed the linear correlation analysis to detect the relationships between SUVmax and serum tumor markers (CA19-9, CA72-4, and CEA), and to establish an equation of SUVmax with CA19-9 and CA125 as independent variables. Thus, based on the above data, we could establish an equation, which could provide the quantitative relation between serum tumor markers and chemotherapy-related tumor markers. According to these quantitative relations, SUVmax could be equation-generated before PET/CT scanning, and this method might screen the high-risk patients for examination, besides, combining the relationship between SUVmax and chemotherapy-related tumor markers, ^{18}F-FDG PET/CT would give us more clinical information on gastric adenocarcinoma patients.

Materials and methods

Study population. Sixty-four gastric adenocarcinoma patients who underwent preoperative ^{18}F-FDG PET/CT and were naive to chemotherapy from January 1, 2014 to December 31, 2015 were enrolled in this study at Cancer Center of the First Affiliated Hospital of Xi' an Jiaotong University. This study was approved by the Institutional Ethics Committee of Xi'an Jiaotong University, including the patients' written informed consent.

^{18}F-FDG PET/CT imaging. All patients were instructed to fast at least 6 h before the ^{18}F-FDG PET/CT scans (Gemini 64TF, Philips, Cleveland, OH, USA). Furthermore, they were also requested to drink at least 500 ml water in order to distend the stomach before scanning. Emission scans were initiated 1 h following nearly simultaneous intravenous administration of FDG (3.7 MBq/kg).

All of the PET/CT images were evaluated by two experienced physicians, and the measuring of SUVmax referred to previous described standard methods. The image results of the patients were visually evaluated and were classified as positive or negative according to ^{18}F-FDG uptake of the cancer lesions. A positive ^{18}F-FDG uptake was considered as increased ^{18}F-FDG uptake of lesions exceeded the uptake of the surrounding normal stomach wall or corresponded with cancer lesions which were diagnosed by contrast-enhanced CT or gastroduodenoscopy. Conversely, a negative ^{18}F-FDG uptake was considered as no visible increased ^{18}F-FDG uptake compared with the surrounding normal stomach wall. Additionally, focally increased ^{18}F-FDG, which did not correspond with cancer lesions diagnosing by contrast-enhanced CT or gastroduodenoscopy and histopathological findings, were excluded (21,22). Region of interest (ROI) were drawn exactly with outline of the primary tumor on the transaxial slices, and the calculation of SUV was performen by the following equation: SUV = Tumor activity concentration/(Injected dose/Body weight) (23).

Table I. Patients and tumor characteristics.

	No. of patients (%)
Sex	
Male	33
Female	31
Age	
<60	22
≥60	42
Clinical stage	
I	10
II	13
III	20
IV	21
Her-2 status	
Positive	28
Negative	36
P53 status	
Positive	30
Negative	34
Survivin status	
Positive	37
Negative	27

Her-2, human epidermal growth factor receptor-2.

Immunohistochemistry staining. Her-2 was detected by using a mouse monoclonal antibody (ab8054, Abcam, Cambridge, MA, USA), P53 was detected by using a mouse monoclonal antibody (ZM-0408, Thermo Fisher Scientific, Waltham, MA, USA), and Survivin was detected with a mouse monoclonal antibody (ab93274, Abcam). The sections were independently evaluated by two pathologists.

For P53 and Survivin, the positive expression was considered with nucleus and/or cytoplasm staining, and Her-2 expression was considered positive when cell membrane staining was observed. Decision criteria for P53 and Survivin were the following: intensity of staining was scored as 0 (no staining), + (weak staining), ++ (intermediate staining), +++ (strong staining). The percentage of positive cells was scored as 0 (0%), 1 (1-9%), 2 (10-49%), and 3 (50-100%). The staining intensity and percentage of positive cells defined as the immunohistochemistry (IHC) score from 0 to 9. When the IHC

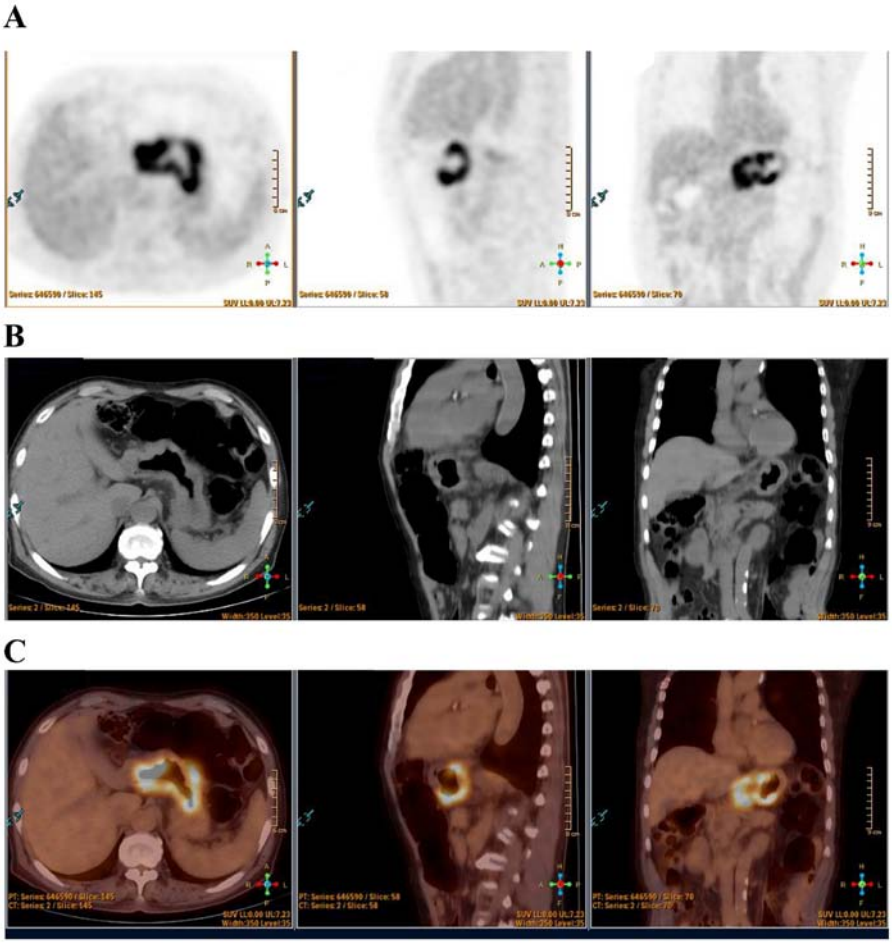

Figure 1. Representative images of PET-CT for gastric adenocarcinoma patients. Transaxial images of (A) FDG-PET, (B) diagnostic CT and (C) fusion of PET and CT images.

score was ≥1, the marker expression was judged as positive expression (24,25). For Her-2, the IHC score was defined as: no staining or <10% tumor cell positive staining as 0; faintly or barely perceptible staining on ≥10% tumor cell membrane as +; weak to moderate positive staining on ≥10% tumor cell membrane as ++; and cohesive moderate to strong staining on ≥10% tumor cell membrane as +++. In this study, we classified IHC +++ as Her 2-positive (26,27).

Serum assays for tumor markers. Serum samples for CA19-9, CA72-4, and CEA (accessories of E170 analyzer, Roche Diagnostics, Rotkreuz, Switzerland) levels were measured when the patients never had any kind of therapy including operation and chemotherapy. Serum levels of CA19-9, CA72-4, and CEA were assayed with electrochemiluminescence (ECL) method (E170 analyzer, Roche Diagnostics). The cut-off values were 6.7 U/ml, 37.0 U/ml and 5.0 ng/ml for CA19-9, CA72-4, and CEA, which were all based on the the manufacturer's instructions (28). When the marker serum levels were higher than the cut-off value, they were judged as positive expression.

Statistical analysis. All data were presented as mean ± standard error mean (SEM). Student's t-test was used to determine the Her-2, P53 and Survivin positivity dependent differences. Receiver operating characteristics (ROC) curve analysis was performed to assess a cut-off value for SUVmax with the most appropriate sensitivity and specificity. Spearman correlation analysis was used to evaluate the relationships between different serum markers and chemotherapy-resistance related markers, and the value of R was considered as follows: 0.8-1.0, highly strong correlation; 0.6-0.8, strong correlation; 0.4-0.6, moderate correlation; 0.2-0.4 weak correlation; 0.0-0.2, no correlation. The equations for SUVmax with serum CA72-4, CA19-9 parameters were established by the linear regression models. All calculations and statistical analyses were performed using SPSS software (version 20.0, IBM Corp., Armonk, NY, USA). $p<0.05$ was considered as a statistically significant difference.

Results

Clinical characteristics of patients. The demographic and clinical characteristics of the patients are summarized in Table I. The ages of the patients ranged from 42 to 82 years (average age, 63.0 years), There were 33 male (average age, 62.4 years), and 31 female (average age, 63.7 years). All the patients who were naive to chemotherapy were diagnosed as gastric adenocarcinoma by biopsy or operation at the cancer center of our hospital from January 1, 2014 to December 31, 2015. ^{18}F-FDG PET/CT examination and serum test were performed within one week before biopsy or operation. The representative ^{18}F-FDG PET/CT images of the patient are shown in Fig. 1,

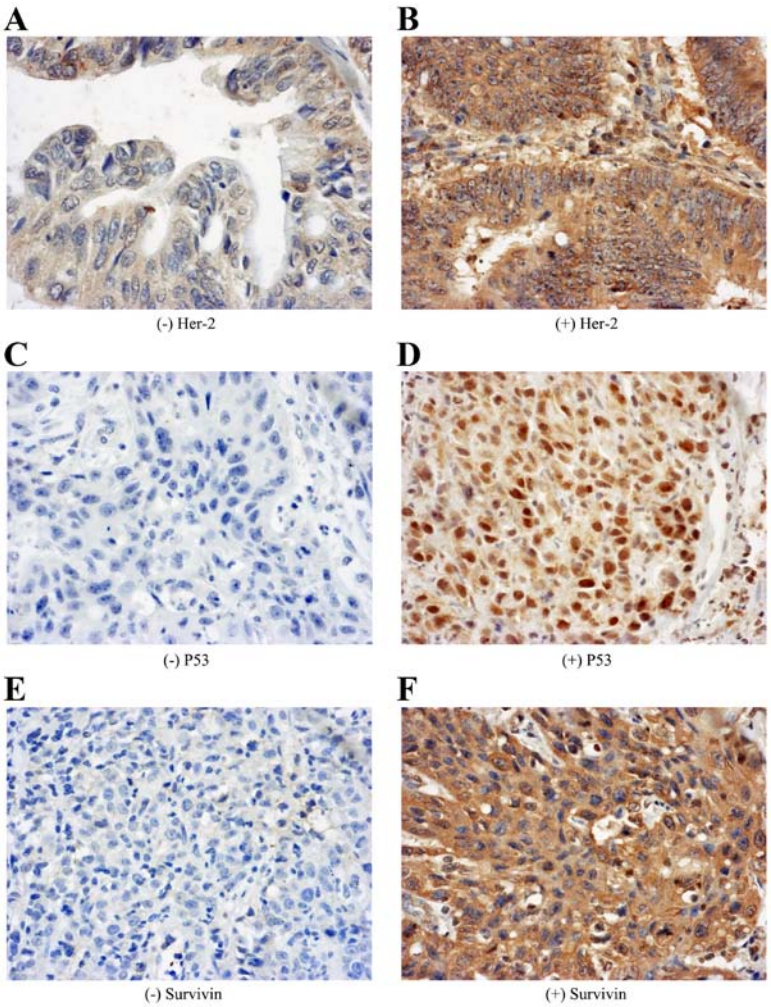

Figure 2. Immunohistochemical staining for Her-2, P53 and Survivin in pathological sections. Her-2 (A) vs (B) was considered positive expression when cell membrane staining was observed, and the positive expression of P53 (C) vs (D) and Survivin (E) vs (F) was considered with nucleus and/or cytoplasm staining (magnification, x400). Her-2, human epidermal growth factor receptor-2.

and the positive expression of Her-2, P53 and Survivin were 43.8, 46.9 and 57.8% in gastric adenocarcinoma patients, respectively (Fig. 2).

The relationships between SUVmax and chemotherapy-related markers. Furthermore, Student's t-test was used to clarify the relationships between SUVmax and expression levels of chemotherapy-related tumor markers. We found significantly higher SUVmax in Her-2-positive (SUVmax: 9.225±1.260) or P53-positive (SUVmax: 7.600±0.859) group of gastric adenocarcinoma patients, compared to Her-2-negative (SUVmax: 5.075±0.412) or P53-negative (SUVmax: 5.020±0.877) group ($p<0.05$), but there was no SUVmax difference between Survivin-positive group (SUVmax: 6.855±0.633) and Survivin-negative (SUVmax: 5.223±0.909) group ($p>0.05$) (Fig. 3A). Moreover, the Spearman correlation analysis showed that high SUVmax was associated with higher expression level of Her-2 or P53, based on the moderate relevant Pearson correlation coefficient (R=5.27 or R=0.440, respectively), but for Survivin expression, the relevant Pearson correlation coefficient was small (R=0.304) (Fig. 3B-D). Next, ROC curve analysis revealed that the area under the curve for predicting Her-2-positivity was 0.737 with the 95% confidence interval (CI) ranging from 0.617 to 0.857, and for predicting P53-positive, the area under the curve was 0.778 with 95% CI between 0.667 and 0.890. When the optimized cut-off value of SUVmax was set at 3.25, the sensitivity and specificity of SUVmax showed Her 2-positive were 96.4 and 44.4%, respectively. For predicting P53-positivity, the sensitivity and specificity of SUVmax were 73.3 and 67.6%, when we set the optimized cut-off value of SUVmax at 5.45 (Fig. 4). We suggested that the higher SUVmax was related to the positive expression level of Her-2 or P53. Hence, we cautiously showed a hypothesis that the abnormal expression of Her-2 and P53 caused aberrant metabolic activity in tumor cells, and this process ultimately resulted in aberrant glycometabolism, which could be detect by ^{18}F-FDG PET/CT scanning in gastric adenocarcinoma patients.

The relationships between SUVmax and serum tumor markers. Serum CA72-4, CA19-9 and CEA were measured preoperatively, and the mean values were 60.3±6.8, 28.2±2.5 and 4.6±0.9 ng/ml in enrolled gastric adenocarcinoma patients, respectively. Interestingly, based on the cut-off values mentioned in methods above for these serum tumor makers, the mean values of serum CA72-4 significantly increased,

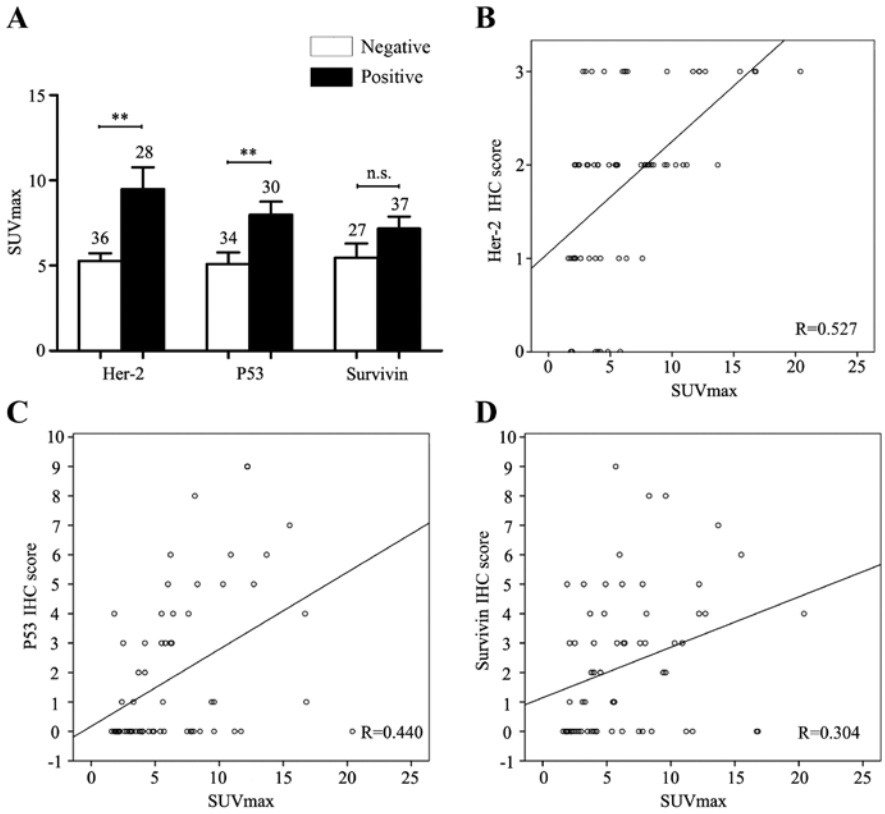

Figure 3. Correlations between SUVmax and the expression level of Her-2, P53 and Survivin. (A) There were SUVmax differences among the patients with different expression of 3 biomarkers. SUVmax was significantly correlated with Her-2 (B) and P53 (C) IHC score with moderately relevant Pearson correlation coefficients, but for Survivin (D), the coefficient was small. *p<0.05; **p<0.01. SUVmax, maximal standardized uptake value. Her-2, human epidermal growth factor receptor-2.

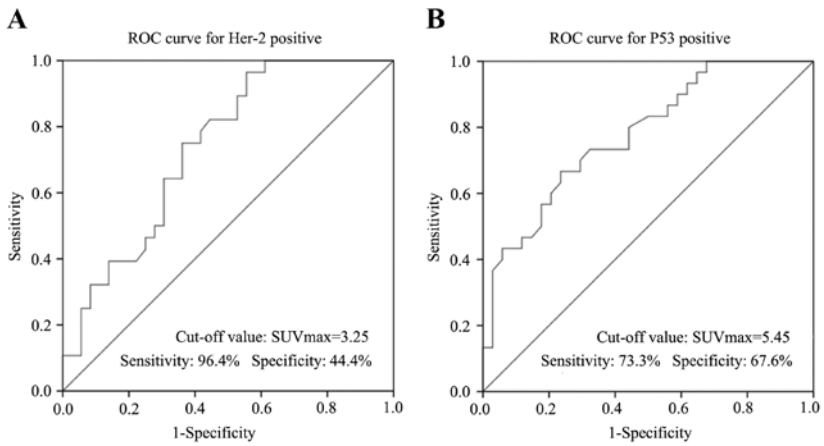

Figure 4. The receiver operating characteristics curves. The ROC curves for the optimal cut-off of SUVmax for predicting Her-2 (A) and P53-positive (B) in gastric adenocarcinoma patients. ROC, receiver operating characteristics. SUVmax, maximal standardized uptake value. Her-2, human epidermal growth factor receptor-2.

however, the increase of serum CA19-9 and CEA were not found in our study. Next, the Spearman correlation analysis was used to evaluate the linear relationships of SUVmax and serum tumor markers of gastric adenocarcinoma patients. The results showed that SUVmax was significantly linearly correlated with serum CA72-4, CA19-9 and CEA (Table II). Furthermore, we found that SUVmax was correlated with CEA with small relevant Pearson correlation coefficient (R=0.346), but SUVmax was strongly correlated with CA72-4

Table II. The correlation between SUVmax and serum CA19-9, CA72-4, and CEA.

	Pearson correlation coefficient	CA19-9	CA72-4	CEA
SUVmax	R value	0.691	0.676	0.346
	p-value	0.000	0.000	0.005

SUVmax, maximal standardized uptake value.

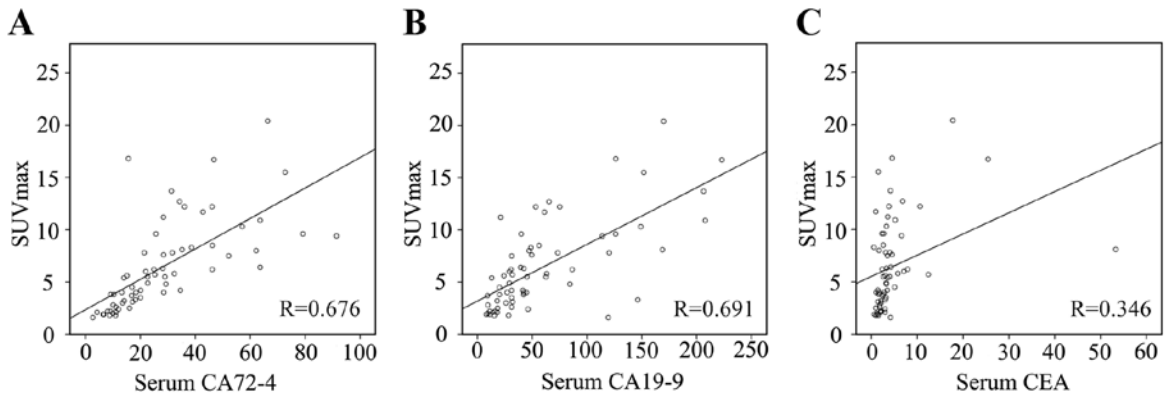

Figure 5. Correlation between SUVmax and the level of serum CA19-9, CA72-4, and CEA. SUVmax was significantly correlated with serum CA19-9 (A) and CA72-4 (B) with strong relevant Pearson correlation coefficients, but for CEA (C), the coefficient was small. $^{*}p<0.05$; $^{**}p<0.01$. SUVmax, maximal standardized uptake value.

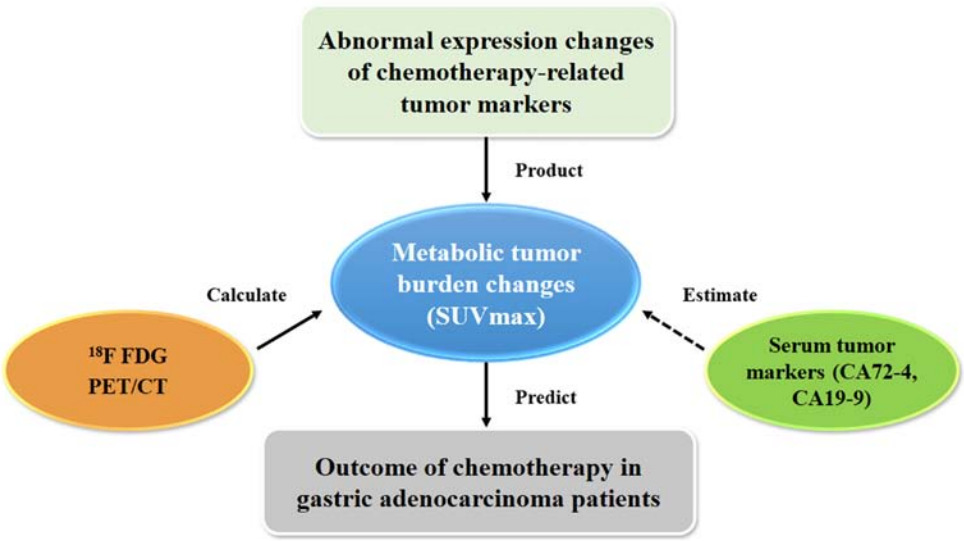

Figure 6. Schematic diagram of SUVmax in predicting outcome of gastric adenocarcinoma patients, which may be evaluated using ^{18}F-FDG PET/CT and estimated by serum tumor markers.

and CA19-9 (R=0.676 and R=0.691, respectively, Fig. 5). So we applied linear regression models to establish an equation for SUVmax using CA72-4 and CA19-9 as independent variables. SUVmax = 1.701+0.092 x CA72-4+0.033 x CA19-9.

According to this equation, we suggest that CA72-4 and CA19-9 could be used as parameters to estimate the value of SUVmax, if ^{18}F-FDG PET/CT was not available or for screening the high-risk patients.

Discussion

^{18}F-FDG PET/CT, one of the non-invasive methods, is used to detect glucose metabolism in malignant tumors and indicated by increased ^{18}F-FDG PET/CT uptake which is represented by an increased SUVmax (29). Currently, ^{18}F-FDG PET/CT scans are widely used in cancer diagnosis, assessment of treatment response, and as a prognostic marker (30-32). However, the underlying relationships between some chemotherapy resistant markers and the clinical observation of ^{18}F-FDG accumulation have not yet been elucidated. To the best of our knowledge, it has been proved that the positive expression of Her-2, P53 and Survivin is closely related with chemotherapy resistance in gastric cancer patients, but the relationships are still unknown between these positive tumor markers and the abnormal SUVmax detected by ^{18}F-FDG PET/CT scanning.

Her-2 related signal transduction pathway takes part in many kinds of chemotherapy-resistance mechanisms (33). In SGC7901 and BGC823 cell lines of gastric cancer, transfection of Her-2 resulted in chemotherapy-resistance for various drugs including paclitaxel, adriamycin, fluorouracil, platinum-based chemotherapy and camptothecin (34). However, the patients Her-2-positive also have some benefits. Trastuzumab, one of anti-Her-2 antibodies from human protooncogene, has the ability to inhibit the Her-2 related signal transduction pathway to elevate chemotherapy sensitivity for many patients, in order to enhance response effect and prolong survival period (35,36). In previous studies, SUVmax of Her-2-positive and Her-2-negative phenotype subgroups in breast cancer were significantly different, and this indicated that there was

a relationship between the Her-2 expression and SUVmax (37,38).

P53 plays an important role in the chemotherapy response of various gastric cancer cell lines and clinical treatment, including cisplatin, carboplatin, paclitaxel and gemcitabine (10,39). In our previous study, we found that P53 expression was significantly related to SUVmax, and SUVmax in P53-positive cases was statistically higher than that of P53-negative cases in non-small cell lung cancer (NSCLC) patients (17). Furthermore, in lung adenocarcinoma patients, the diffusivity and intensity of P53 staining had a significant relationship with the SUVmax (17). However, in one triple-negative breast cancer study, there was no association between P53 expression and SUVmax. The difference might result from the different types of tumor or pathological patterns (40). In conclusion, it was meaningful and interesting to clarify the underlying relationship between P53 expression and SUVmax, for making chemotherapy regimens in gastric cancer.

Survivin, an inhibitor of apoptosis repeat-containing 5 (BIRC5), is found in almost all human tumors (40,41). Overexpression of it mainly indicates inhibition of apoptosis and cell cycle control (42). One study found that Survivin was a positive biomarker for predicting the sensitivity of paclitaxel treatment in gastric cancer patients by western blotting method, however, overexpression of Survivin was closely related with cisplatin and 5-FU treatment sensitivity in gastric SGC7901 cancer cells, and in nude mice, and knockdown of Survivin expression by shRNA, the cisplatin and 5-FU treatment sensitivity of gastric SGC7901 cancer cells and the nude mice enhanced significantly (13,43,44).

The present study of 64 gastric adenocarcinoma patients was the first report that the SUVmax was significantly higher in the positive expression of Her-2 and P53, compared to that of negative expression in gastric cancer patients. The results suggested that SUVmax might reflect the expression level of chemotherapy resistant-related markers, such as Her-2 and P53 when the cut-off values were set at 3.25 and 5.45. Interestingly, higher SUVmax was not found in the positive Survivin expression group, and we considered SUVmax might not be suitable for determining Survivin-related chemotherapy resistance for gastric cancer patients.

In clinic, high expression of CA72-4, CA19-9 and CEA could be used to evaluate patients' prognosis and efficacy of chemotherapy, and serum examination is more convenient and affordable, compared with ^{18}F-FDG PET/CT. If certain specific quantitative relationship between SUVmax and the values of different serum tumor markers were detected, we could use the results of serum tumor markers to predict the range of SUVmax approximately. In this study, we found that CA72-4 and CA19-9 significantly linearly related to SUVmax, but not CEA. Linear regression models were used to establish equations for SUVmax using CA72-4 and CA19-9 as independent variables. Thus, CA72-4 and CA19-9 could be used as parameters to estimate the value of SUVmax. Hence, it is suitable for monitoring of treatment response in gastric adenocarcinoma patients evaluated by ^{18}F-FDG PET/CT or estimated by CA19-9 and CA72-4 (45) (Fig. 6).

However, we recognized that there were some shortcomings in our study: i) clinical cases were limited, further studies were needed to expand the number of cases. ii) The mechanism that the positive expression of Her-2 and P53 induced high metabolic tumor burden was still unclear in gastric adenocarcinoma patients. iii) We considered that the relationship between SUVmax and serum tumor markers was very complicated. In this study, only 3 types of serum tumor markers were performed. Further studies are needed to expand the types of serum tumor markers, more sufficient data provided, including more accurate equations. So the results should be accepted cautiously.

In conclusion, SUVmax is associated with the expression level of Her-2 and P53, which were closely related to chemotherapy resistance in gastric adenocarcinoma patients. SUVmax, either calculated by ^{18}F-FDG PET/CT or estimated by serum tumor markers of CA72-4 and CA19-9, could be used to predict and evaluate Her-2 or P53 related chemotherapy resistance of gastric patients.

Acknowledgements

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