Detectability of T-Measurable Diseases in Advanced Gastric Cancer on FDG PET-CT

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Abstract

Purpose Usefulness of FDG PET-CT in monitoring response in locally advanced gastric cancer has been reported. The purpose of this study was to evaluate the related factors to detect measurable diseases in advanced gastric cancer on FDG PET-CT.

Methods We retrospectively reviewed 38 patients diagnosed as having advanced gastric cancer. We defined the measurable diseases when there was visualized tumor of which maximum standardized uptake value (SUVmax) was higher than $1.35 \times \text{SUVmax of liver} + 2 \times \text{SD of liver SUV}$. We evaluated what kinds of factors from the clinicopathologic features were related to identifying measurable diseases.

Results Of 38 patients with advanced gastric cancer, 18 (50 %) had measurable tumors on FDG PET-CT. Measurable tumors were significantly more frequent in well or moderately differentiated adenocarcinoma (70.5 % vs 35.3 %, $p < 0.05$), in the tumors located at antrum or angle (66.7 % vs 29.4 %, $p < 0.05$) and in the elderly group (age of 55 years old or more, 72.0 % vs 8.3 %, $p < 0.001$) than the others, respectively. By multivariate analysis, age at diagnosis was the only independent predictor for the measurable disease on FDG PET-CT.

Conclusion We found that age at diagnosis, as well as histologic types and location of tumors, were the affecting factors to detect measurable disease on FDG PET-CT in patients with advanced gastric cancer. Our study suggests that elderly patients of age of 55 years old or more can

frequently have T-measurable disease on FDG PET-CT in advanced gastric cancer and FDG PET-CT will be helpful to monitor measurable disease.

Keywords Advanced gastric cancer · Measurable disease · FDG PET-CT · Age at diagnosis · Affecting factor

Introduction

Usefulness of FDG PET-CT in monitoring response to neoadjuvant chemotherapy in patients with locally advanced gastric cancer has been reported from other studies [1–7]. However, reliable measurement of therapy response cannot be feasible if the initial tumor uptake is too low. Its utility in response monitoring of chemotherapy is restricted only to the cases of which tumors have sufficient contrast to background on FDG PET-CT.

Detection rate of the advanced gastric cancer on preoperative FDG PET-CT has been reported to be 60 to 98 % [7–12]. As gastric cancer is known, however, to show variable FDG uptake of the primary tumor sites on PET scans because of its geometry as well as its tumor metabolism [13], the diagnosis of gastric cancer depends on the endoscopic findings and biopsy results, thoroughly. Even though the tumor was visualized on baseline FDG PET-CT, some lesions were not enough to be measured for monitoring the response to chemotherapy because of their insufficient contrasts to background, that is, partly due to the insufficient thickness of tumors as well as the tumor's metabolic characteristics. Therefore, it seems to be important to find the factors determining the detection of T-measurable diseases on FDG PET-CT, especially in patients with advanced gastric cancer.

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Ingestion of water before PET scanning causes distension of the gastric wall, so this might be helpful to visualize the primary tumor lesions for the measurable diseases. Yun et al. reported that water distention before FDG PET-CT scans could lead to higher diagnostic accuracy to detect recurrent tumors from the remnant stomach tissue [14]. We can postulate that the metabolic imaging with FDG PET-CT after water gastric distension may also be helpful for detecting the measurable diseases of locally advanced gastric cancer. The main purpose of this study was to evaluate what kinds of endoscopic and clinicopathologic factors could affect the detection of the T-measurable disease in patients with T2 advanced gastric cancer on FDG PET-CT, scanned after gastric water distention.

Patients and Methods

Patients

Fifty-seven patients who were newly diagnosed with gastric cancer on endoscopic biopsies from August 2007 to January 2009 at our institute were retrospectively enrolled. We did not include the patients who had evidence of distant metastasis and/or were not candidates for surgical resection at initial staging work-up. All patients underwent gastrofiberscopy with endoscopic biopsy and FDG PET-CT scans before the surgical resection (total or subtotal gastrectomy), and then pathologic diagnosis was confirmed on the basis of permanent specimen. The location, morphology, and differentiation of tumors were determined through endoscopic findings with biopsy. Of 57 patients, we excluded 18 patients whose endoscopic findings were early gastric cancer and one patient with a T4 tumor on pathologic specimen after surgical resection. Finally, 38 patients with advanced gastric cancer on endoscopy and pathologically-proven T2 tumors were included in this study. We performed this study following the ethical guidelines of our institutional clinical research committee.

FDGPET-CT Acquisition

Images were obtained with PET-CT scanner (Gemini TF, Philips Medical Systems, Cleveland, OH). All patients fasted at least 6 hours before undergoing PET-CT. Blood glucose level was measured and confirmed to be less than 180 mg/dL before the administration of F-18 FDG. Approximately 50 minutes after intravenous injection of 370–480 MBq (10–13 mCi) of F-18 FDG according to the body weight, emission PET scan was acquired from the level of skull base to the thigh at 1 min per a bed position. All patients drank more than 500 ml of water for gastric distention just before acquiring the scans. The PET unit has an axial field of view

of 18 cm and a spatial resolution of 4.4 mm. A low-dose CT scan was obtained for attenuation correction and for localization, with a 16-slice multidetector helical CT unit, using the following parameters: 120 kVp; 50 mA; 0.75-s rotation time; 0.75-mm slice collimation; 4-mm scan reconstruction, with a reconstruction index of 4 mm; 60-cm field of view; and 512×512 matrix. PET data were reconstructed iteratively using a three dimensional Row Action Maximum Likelihood Algorithm (RAMLA) with low-dose CT datasets for attenuation correction. Maximum intensity projection (MIP) and cross sectional views and fusion images were generated and reviewed.

Image Interpretation and Analysis

We considered the hypermetabolic lesions distinguished from diffuse uptake of gastric wall as visualized tumors. Volume of interest (VOI) was drawn covering the lesion of stomach on the co-registered FDG PET-CT images, and the maximum standardized uptake value (SUVmax) of each lesion was recorded.

We regarded measurable diseases as the tumors showing higher SUVmax than $1.35 \times \text{SUVmax of liver} + 2 \times \text{standard deviation of liver SUV}$ (Figs. 1–3), following the reported studies [1, 3, 4]. This definition was chosen to ensure that a decrease in tumor FDG uptake by 35 % could be reliably measured on the PET scan in evaluation of response to neo-adjuvant chemotherapy. We evaluated what kinds of factors from endoscopic and clinicopathologic features could affect the identification of the measurable disease on FDG PET-CT.

Clinical Staging

Endoscopy (for localization of the tumor and assessment of the macroscopic growth type) with biopsy and computed tomography of the abdomen were performed in each patient. In subsequent histopathological evaluation of the biopsies, the Lauren classification (microscopic growth type) was applied. In this study a simplified Lauren classification was used, in accordance with routine practice at our institution. This classification only differentiates between intestinal and non-intestinal tumors. The categories “diffuse type” (diffuse tumor infiltration with no or little gland formation), “mixed type” and “non-classifiable” in the extended Lauren classification are included within the non-intestinal type. In addition to the Lauren type, differentiation grading and histopathological subtype were determined.

Statistical Analysis

Relationship between tumor measurability and the affecting clinicopathologic factors were evaluated by chi-square test. Student T test was applied for the comparison with the continuous variables. To evaluate the predictability of measurable

disease, we performed the multivariate logistic regression analysis with the significant parameters. All of the analyses were performed with the significance of $p < 0.05$ using SPSS version 12.

Results

Patients' Characteristics

Patients' characteristics are summarized in Table 1. Median age was 59.1 (range: 43 to 75) years old, and 68.4 % of

Table 1 Patients' characteristics

Characteristics	No of patients (%)
Age in years (mean + SD)	59.1±8.7
Gender	
Male	26 (68.4)
Female	12 (31.6)
Tumor size in cm (mean ± SD)	5.7±3.2
SUVmax of primary tumor (mean ± SD)*	6.5±5.1
Depth of invasion	
T2	38 (100)
LN metastasis	
N0	12 (31.6)
N1	7 (18.4)
N2	5 (13.2)
N3	14 (36.8)
Stage	
IB	12 (31.6)
II	12 (31.6)
III	14 (36.8)
Histologic type	
Well differentiated	7 (18.4)
Moderately differentiated	10 (26.3)
Poorly differentiated	17 (44.7)
Signet ring cell	4 (10.5)
Lauren	
Intestinal	16 (42.1)
Non-intestinal (diffuse)	22 (57.9)
Location	
Cardia	3 (7.9)
Body	14 (36.8)
Angle	8 (21.1)
Antrum	13 (34.2)
Borrmann type	
I	1 (2.6)
II	2 (5.3)
III	30 (78.9)
IV	5 (13.2)

*The SUVmax was obtained only in the visualized cases (n=31)

patients were male. The median tumor size was 5.7 cm (range: 2–16.8 cm) on the surgical specimen. Based on the revised AJCC staging system, 12 patients (31.6 %) had Stage IB tumors, 12 (31.6 %) had Stage II tumors, and 14 (36.8 %) had Stage III tumors. Especially in the T-staging, all 38 tumors were T2 tumors.

Affecting Factors to T-Measurable Diseases

Of 38 patients, 31 (81.6 %) tumors were visualized on FDG PET-CT. Only in 18 (50 %) patients could the tumor be reliably measurable by our definition mentioned in methods.

Of 38 patients, 13, 8, 14, and 3 tumors were located at antrum, angle, body, and cardia on gastrofiberoscopy, respectively. Among 13 patients whose lesions were located in antrum, 10 (76.9 %) were measurable on FDG PET-CT. Also, four (50 %) out of eight tumors located at angle were measurable. However, only four (28.6 %) out of 14 tumors which were located at body and one (33.3 %) of three cardiac lesions were measurable, respectively. Measurability of the tumor on FDG PET-CT was significant higher in the group of tumors located at distal stomach (antrum or angle) than in that of tumors above the angle (cardia or body) (66.7 % vs. 29.4 %, $p < 0.05$).

As regards the Borrmann classification, Borrmann type I, II, III and IV were 1, 2, 31, and 5, respectively. Analysis between Borrmann classification couldn't be performed because most of the tumors were Borrmann type III.

Four tumors were signet ring cell carcinoma. Of these, only one tumor was measurable (25 %). Among 34 adenocarcinoma cases other than signet ring cell type, the number of well differentiated, moderately differentiated, and poorly differentiated adenocarcinoma were 7, 10, and 17, respectively. Among these, 5 (71.4 %) out of 7, 7 (70 %) out of 10, 6 (35.3 %) out of 17 were measurable tumors, respectively. The proportion of the measurable diseases was significantly higher in well or moderately differentiated adenocarcinoma than in poorly differentiated or signet ring cell carcinoma (70.6 % vs 33.3 %, $p < 0.05$). Regarding Lauren type, 16 were intestinal type and 23 were diffuse type. Of 16 intestinal types, 11 (68.9 %) were measurable, while only 9 (39.1 %) out of 23 were measurable in non-intestinal type ($p = 0.05$).

The age of patients who had the T-measurable diseases was significantly higher than that of non-measurable disease (63.6 ± 6.4 years vs 54.7 ± 8.6 years, $p < 0.005$). With an optimal cut-off value of 55 years old (Table 4), Only one (8.3 %) out of 13 tumors were measurable on FDG PET-CT in the group with age less than 55 years old, while 18 (72.0 %) out of 25 tumors were measurable in the group with age of 55 years old or more ($p < 0.001$).

There was no statistically significant difference between the groups of measurable disease and non-measurable disease in proportion of gender, size of primary tumor, clinical stage, and nodal metastasis state (Table 2).

Logistic Regression Analysis for the Factors to Detect T-Measurable Disease

After univariate analysis, we selected the three valuable factors, that is, age at diagnosis, differentiation (well or moderately differentiated adenocarcinoma vs poorly differentiated adenocarcinoma or signet ring cell carcinoma), and location (above angle vs angle and antrum). We evaluated

Table 2 Clinicopathologic features of gastric carcinoma in measurable and non-measurable disease

Characteristics	Measurable disease	Non-measurable disease	P value
Age in years (mean $\pm$ SD)	63.58 $\pm$ 6.37	54.68 $\pm$ 8.58	<0.005*
<55	1	12	<0.001†
>55	18	7	
Gender			
Male	14	12	NS†
Female	5	7	
Tumor size in cm (mean)	5.911 $\pm$ 2.164	5.463 $\pm$ 4.010	NS*
LN metastasis			
N0	4	8	NS†
N1	3	4	
N2	5	0	
N3	7	7	
Stage			NS†
IB	4	8	
II	8	4	
III	7	7	
Histologic type			
Well differentiated	5	2	<0.05†
Moderately differentiated	7	3	
Poorly differentiated	6	11	
Signet ring cell	1	3	
Lauren			<0.05†
Intestinal	11	5	
Non-intestinal	8	14	
Location			
Cardia	1	2	<0.05†
Body	4	10	
Angle	4	4	
Antrum	10	3	
Borrmann type			
I	1	0	NS†
II	1	1	
III	16	14	
IV	1	4	

*The averages of continuous variables were compared between the measurable disease group and non-measurable disease group using student T-test. †Comparison between measurable disease and non-measurable disease using chi-square test

the predictability for T-measurable disease on FDG PET-CT with the valuable factors and other clinicopathologic parameters. In multivariate logistic regression analysis, the age at diagnosis was the only independent factor to predict measurable disease on FDG PET-CT (Table 3).

Discussion

It is of importance to differentiate chemotherapeutic responders from non-responders in order to avoid therapy-related morbidity with co-existing tumor growth. It has been reported that FDG PET-CT could be useful for monitoring response to neoadjuvant chemotherapy in patients with gastric cancer [1–6]. Unlike morphological imaging modalities, FDG-PET reflects the metabolic rate of glycolysis in tumors, and thus, it is believed that FDG-PET should be more accurate for assessing treatment response, because it can more correctly identify viable tumors. However, evaluation of therapeutic response is only available for disease presenting sufficient FDG uptake which is reliably measured on FDG PET-CT.

Ott et al. [3] reported the usefulness of FDG PET-CT to discriminate between chemotherapy responders and non-responders in advanced gastric cancer in 2003. In their report, 80 % of cases were measurable. In our study, however, 82 % were visualized on FDG PET CT and only 50 % of the cases were measurable among the 38 patients with T2 gastric cancer. A different population of patients could be a reason for a different proportion of measurable disease. In their report, 94 % of the patients were in clinical stage III or IV, whereas only 37 % of our patients were in stage III and none in stage IV in our data.

Degree of tumor differentiation was the significant factor affecting the measurability of primary tumor. Well or moderately differentiated adenocarcinomas were significantly more measurable on FDG PET-CT than poorly differentiated adenocarcinoma or signet ring cell type. This result of our study is consistent with the previous studies reporting that the well or

Table 3 Multivariate logistic regression analysis for the measurable disease on FDG PET-CT using clinicopathologic parameters

Parameters	Exp (B)	95 % C.I.		P value
		Lower	Upper	
Age in years (continuous variable)	1.163	1.021	1.324	0.023
Gender (male vs female)	0.653	0.099	4.304	0.658
Location (above angle* vs. angle or below†)	3.830	0.688	21.314	0.125
Differentiation (WM‡ vs PS§)	0.297	0.057	1.548	0.149
LN state (positive vs. negative)	1.146	0.198	6.637	0.879

* Body or cardia, † Angle and antrum, ‡ Well or moderately differentiated adenocarcinoma, § Poorly differentiated adenocarcinoma or signet ring cell carcinoma

moderately differentiated gastric carcinomas accumulated FDG more intensely than did poorly differentiated tumors [11]. Regarding Lauren type, the intestinal type of gastric carcinoma tended to be more measurable on FDG PET-CT than the non-intestinal type, although there was no statistical significance. And it also well correlated with previous studies [11, 15].

The location of tumor was another factor influencing the measurability of gastric cancer on FDG PET-CT in our study. In previous studies, Mochiki et al. and Mukai et al. reported that there was no significant relationship between tumor location and detectability of gastric cancer on FDG PET-CT [9, 10]. Only one study reported by Stahl et al. [11] found tumors in the proximal one-third of the stomach were more frequently detected than those of the distal two-thirds. In our study, however, the portion of measurable disease was significantly higher in the group of tumors located in the distal gastric part including antrum and angle than those of body or cardia. It seems opposite to a previous study. However, the previous study compared the detection rate of tumors located in the proximal one-third including cardia and fundus with those of the distal two-thirds, body and antrum, while our study compared the tumors located at cardia with those at body and antrum. Moreover, in the previous study, most of the proximal one-third tumors were located at the cardia and distal two-thirds tumors were at the body, while most of the tumors were located at body or antrum in our study. Therefore, it is

difficult to say that our result is totally opposite to the previous study. Koga H et al. [16] reported that physiologic uptake of FDG was more frequently found in the proximal portion of the stomach than the distal portion. One probable hypothesis of lower detection of measurable disease in the proximal stomach, we considered, was because the higher physiologic uptake of the gastric wall may lower the detection of the measurable tumors on FDG PET-CT. Another possibility, we can postulate, would be the immobility of the stomach angle and antrum, compared to the other location. Gastric distension using ingestion of water at pre-scan might be helpful to detect the measurable diseases on FDG PET-CT in this present study. As a view point in detection of a measurable disease, this simple method would improve the diagnostic ability in advanced gastric cancer.

Interestingly, age of the patients at diagnosis was another factor influencing the measurability of advanced gastric cancer on FDG PET-CT in our study. Gastric cancer is thought to result from a combination of environmental factors and the accumulation of generalized and specific genetic alterations, and consequently affects mainly older patients. Gastric cancer is rare below the age of 30 years; thereafter, its occurrence increases rapidly and steadily to reach the highest rates in the oldest age groups both in males and females. The intestinal type rises faster with age than the diffuse type and is more frequent in males than in females [17]. Early onset gastric cancer (EOGC) is defined as

Fig. 1 Measurable disease on FDG PET-CT. A 68-year-old woman has a Borrmann type III lesion located at gastric angle on gastrofiberoscopy. An endoscopic biopsy was used to diagnose a moderately differentiated adenocarcinoma, an intestinal type according to the Lauren classification. On enhanced CT, non-specific wall thickening is shown at antrum. The tumor is well visualized on FDG PET-CT with a SUVmax of 5.5. The metabolism of the tumor was higher than the cut-off SUVmax for the measurable disease, 4.3, calculated by formula of $1.35 * (\text{maxSUV of liver} + 2 * \text{SD of liver SUV})$ as mentioned in Methods

Fig. 2 Visualized but non-measurable disease on FDG PET-CT. Gastrofiberscopy shows a Borrmann type IV gastric lesion in the stomach body of a 63-year-old man. Gastrofiberscopic biopsy was used to diagnose a poorly differentiated adenocarcinoma, non-intestinal type. On enhanced CT, circumferential wall thickening is shown along the lesser curvature of body (above the angle). On FDG PET-CT, the SUVmax of this lesion is 4.3. The cut-off SUVmax is 4.9. Eventually, this region was regarded as a non-measurable disease by our definition, in spite of clear visualization on FDG PET-CT

gastric cancer presenting at the age of 45 years or younger. Approximately 10 % of gastric cancer patients fall into the EOGC category [18]. In our data, we had only two patients with EOGC in the category of age under 45 years old, and all of them

showed non-measurable tumors on FDG PET-CT. Regardless of the criteria of EOGC, our data showed more detectability of T-measurable disease as the age of patients at diagnosis increased (Fig. 4). In patients of age 55 years old or less, only one patient

Fig. 3 Non-visualized and non-measurable disease. Gastrofiberscopy shows a Borrmann type III lesion in cardia in a 43-year-old man. Gastroscopic biopsy confirmed that this lesion was a poorly differentiated adenocarcinoma, non-intestinal type. There is no significant wall thickening on enhanced CT. The tumor is not visualized on the FDG PET CT, so it is defined as a non-measurable disease. The SUVmax of the tumor could not be measured on this image

Fig. 4 Disease measurability in relation to age. The greater the detectability of the T-measurable disease, the older the patients are at diagnosis

had a T-measurable disease on FDG PET-CT, whereas 72 % of the others showed T-measurable disease (Table 4).

The clinicopathologic features of gastric cancer are said to differ between young and elderly patients. Young patients more frequently develop diffuse lesions which often arise in the background of histologically normal gastric mucosa. It is postulated that genetic factors may be more important in EOGC than in the older patients as they have less exposure to environmental carcinogenesis [19]. In our data, the patients with an age of less than 55 years old showed more frequency of poorly-differentiated or signet ring cell types and of diffuse type (non-intestinal) of Lauren classification than the other elderly patients. These findings correlated well with the clinicopathologic features of age of onset in advanced gastric cancer. However, there was no statistically significant difference of histologic features between the aged and less aged groups in our study (Table 5).

Table 4 Age in years at diagnosis for a predicting factor of the measurable disease on FDG PET-CT

Age (years) cut-off		T-measurable tumors on FDG PET-CT		Measurability (%)	
		Measurable	Non-measurable	Over the cut-off	Under the cut-off
45	<45	0	2	52.8	0.0
	≥45	19	17		
50	<50	0	5	57.6	0.0
	≥50	19	14		
55	<55	1	12	72.0	7.7
	≥55	18	7		
60	<60	6	14	72.2	30.0
	≥60	13	5		
65	<65	10	16	75.0	38.5
	≥65	9	3		

Table 5 Difference of histologic types between less elderly and elderly groups

Parameters		Age (years)		Total	P value
		<55	≥55		
Differentiation	WM*	3	14	17	0.53
	PS†	10	11	21	
Lauren type	Intestinal	3	13	16	0.87
	Non-intestinal	10	12	22	

* Well or moderately differentiated adenocarcinoma, † Poorly differentiated adenocarcinoma or signet ring cell carcinoma

More interestingly, age factor itself, was a more powerful independent factor to predict the measurability of T2 tumors than the histologic types in multivariate logistic analysis. So, we can postulate that the age of onset could partially affect the measurability of T2 tumors on FDG PET-CT with some linkage between the two factors (age of onset and differentiation of tumors), but the linkage must be partially, not totally related.

There are some studies that have determined the factors affecting the detectability of gastric cancer on FDG PET-CT [8–11]. However, there were no studies evaluating the relationship between clinicopathologic characteristics and measurability in order for the response evaluation following neoadjuvant chemotherapy, previously, especially using FDG PET-CT with the aid of gastric distention by water intake. Our data can give information about the factors affecting tumor measurability on FDG PET-CT for patients who would possibly undergo neoadjuvant chemotherapy. Measurable disease can be more frequently found in gastric cancer in elderly patients, as can tumors with well or moderately differentiated cancer (and/or intestinal type of gastric cancer), located at the angle or below. Among the various endoscopic and clinicopathologic features, however, age at diagnosis was the only independent factor to predict T-measurable diseases on FDG PET-CT in patients with T2 gastric cancer.

Nevertheless, the present study has some inherent limitations. Firstly, it was a single-center study with a relatively small number of Korean patients. Gastric cancer shows different incidence and/or patterns according to the regions. Different etiology is assumed involving the carcinogenesis of gastric cancer. Therefore, the predictability of T-measurable disease must be validated prospectively in a larger patient population with various races and geographic regions. Secondly, the partial volume effect caused by limited spatial resolution may have caused FDG uptake underestimations in small or diffuse lesions, which would reduce SUV accuracy. For this reason, we included the T2 tumors of advanced gastric cancer to reduce the confounding factors to measure the SUV between the comparisons. It should be validated with different PET scanners having different resolutions. Thirdly, we didn't perform the molecular expression profile of gastric cancer

according to the degree of FDG uptake. Many kinds of molecular mechanisms were suspected to involve the different features in EOGC, compared to the conventional gastric cancer. Glucose metabolism can also be affected by different molecular expressions. Further studies with molecular expression profile will be helpful to understand the reason why some gastric cancers show low FDG uptake and why elderly patients show relatively good FDG uptake in gastric cancer. Lastly, we did not analyze the cost-effectiveness of FDG-PET in order to detect measurable disease in advanced gastric cancer. This should also be validated by multi-center study with a larger population.

In spite of the limitations of our study, we found several factors to predict the T-measurable disease in patients with advanced gastric cancer. And this study represents the first evaluation of the association of the presence of age factor with FDG PET findings in patients with advanced gastric cancer. Although our data indicate that FDG PET-CT will be helpful to detect T-measurable disease in elderly patients with advanced gastric cancer, it should be established through further studies.

Conclusion

We found that the location and histologic types on endoscopic findings and age at diagnosis could affect the identification of the T-measurable diseases on FDG PET-CT in patients with advanced gastric cancer. If we could predict the measurable diseases just after the endoscopy and prior to the surgical treatments, it might be helpful for the selection of patients whether to perform the FDG PET-CT in order to detect measurable tumors during the following surgical planning and tailoring therapies.

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Conflict of Interest The authors declare that they have no conflict of interest.

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