The Feasibility of ^{18}F -Fluorothymidine PET for Prediction of Tumor Response after Induction Chemotherapy Followed by Chemoradiotherapy with S-1/Oxaliplatin in Patients with Resectable Esophageal Cancer

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Abstract

Purpose The aim of this study was to determine whether ^{18}F -fluorothymidine (FLT) PET is feasible for the early prediction of tumor response to induction chemotherapy followed by concurrent chemoradiotherapy in patients with esophageal cancer.

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Methods This study was prospectively performed as a collateral study of “randomized phase II study of preoperative concurrent chemoradiotherapy with or without induction chemotherapy with S-1/oxaliplatin in patients with resectable esophageal cancer”. ^{18}F -FLT positron emission tomography (PET) images were obtained before and after two cycles of induction chemotherapy, and the percent change of maximum standardized uptake value (SUVmax) was calculated. All patients underwent esophagography, gastrofiberscopy, endoscopic ultrasonography (EUS), computed tomography (CT) and ^{18}F -fluorodeoxyglucose (FDG) PET at baseline and 3–4 weeks after completion of concurrent chemoradiotherapy. Final tumor response was determined by both clinical and pathologic tumor responses after surgery.

Results The 13 patients for induction chemotherapy group were enrolled until interim analysis. In a primary tumor visual analysis, the tumor detection rates of baseline ^{18}F -FLT and ^{18}F -FDG PET were 85% and 100%, respectively. The tumor uptakes on ^{18}F -FLT PET were lower than those of ^{18}F -FDG PET. Among nine patients who completed second ^{18}F -FLT PET, eight patients were responders and one patient was a non-responder in the assessment of final tumor response. The percent change of SUVmax in responders ranged from 41.2% to 79.2% (median 57.1%), whereas it was 10.2% in one non-responder.

Conclusion The percent change of tumor uptake in ^{18}F -FLT PET after induction chemotherapy might be feasible for early prediction of tumor response after induction chemotherapy and concurrent chemoradiotherapy in patients with esophageal cancer.

Keywords ^{18}F -FLT · PET · Esophageal cancer · Induction chemotherapy · Tumor response

Introduction

Esophageal cancer has been reported to have a relatively poor prognosis with only a 20–30% 2-year survival rate [1]. Because the pathologic complete response after pre-operative therapy in esophageal cancer is an important prognostic factor associated with survival outcomes, the multimodality therapy using the combination of surgery, pre/post-operative chemotherapy and/or radiotherapy is recently preferred to increase the pathologic response and the overall survival rate [1, 2]. Several bodies of literature reported that the benefits of neo-adjuvant chemoradiotherapy in esophageal cancer are pathologic down-staging and improving survival rate. More recently, some reports demonstrated that the induction chemotherapy followed by neo-adjuvant chemoradiotherapy improves tumor response and survival rate even more, compared to routine neoadjuvant chemoradiotherapy [2, 3]. However, those benefits of the induction chemotherapy or neoadjuvant chemoradiotherapy are only present in responders. Non-responders not only show no improvement but may also present with toxic side effects and tumor progression [1]. For this reason, early detection of tumor response to induction chemotherapy or neoadjuvant chemoradiotherapy is important to individualize treatment strategies and to prevent non-responders from receiving unnecessary treatment or delaying surgery.

Conventional imaging modalities, such as computed tomography (CT), have several limitations for evaluating tumor response to pre-operative therapy (such as chemotherapy or radiotherapy), which are the difficulty in distinguishing a viable tumor from a treatment-induced necrosis and the delayed evaluation of tumor response due to slow anatomical changes [1]. On the other hand, the metabolic change of the tumor usually precedes anatomic alteration. Recently, the use of metabolic imaging modalities such as positron emission tomography (PET) for early detection of tumor response is increasing.

^{18}F -Fluoro-2-deoxy-D-glucose (^{18}F -FDG) reflects glucose metabolism of tumor and is well-established in tumor detection and response evaluation for esophageal cancer [4]. Several studies demonstrated that the changes in tumor ^{18}F -FDG uptake after neo-adjuvant therapy show correlation with the outcomes in esophageal cancer [5, 6]. However, ^{18}F -FDG has several drawbacks. ^{18}F -FDG is not a tumor-specific tracer and ^{18}F -FDG PET after chemoradiotherapy may give false-positive findings, since ^{18}F -FDG is accumulated in macrophages and granulation tissues due to post-treatment inflammation as well as tumor cells [7]. Non-specific ^{18}F -FDG uptake could be increased around the primary tumor because of the radiation-induced inflammation and might lead to misinterpretations of tumor response [8]. For this reason, many studies have been conducted to

find the novel radiopharmaceuticals overcoming these drawbacks of ^{18}F -FDG, and reflecting tumor proliferation to a greater extent.

^{18}F -fluoro-3'-deoxy-3'-L-fluorothymidine (^{18}F -FLT) is a PET tracer for in vivo evaluation of cell proliferation. ^{18}F -FLT, a pyrimidine analogue, is phosphorylated by thymidine kinase-1 and is sequentially trapped in the cells. The expression of thymidine kinase 1 increases more than tenfold during the S phase of the cell cycle. Therefore, the tumor uptake of ^{18}F -FLT supposedly reflects cell proliferation [9]. Several studies have reported that ^{18}F -FLT tumor uptake can be shown in a variety of tumors and is relatively well-correlated with the proliferation index such as Ki-67, than that of ^{18}F -FDG [10, 11]. Chao et al. [12] demonstrated that ^{18}F -FLT PET detected an early response of esophageal cancer to chemoradiotherapy before the changes in tumor volume in in vitro and in vivo tumor models. However, the human study for predicting the tumor response of esophageal cancer in chemotherapy or chemoradiotherapy has not been reported yet.

To investigate the impact of induction chemotherapy before concurrent chemoradiotherapy in resectable esophageal cancer, we planned a randomized phase II study of preoperative concurrent chemoradiotherapy with or without induction chemotherapy, which consisted of S-1/oxaliplatin. Because these benefits of the induction chemotherapy were expected only in the responders to chemotherapy, we planned to perform an interim analysis in 13 patients who were initially enrolled as induction group in the phase II study. We conducted a prospective study to assess whether ^{18}F -FLT PET is feasible for early prediction of tumor response to induction chemotherapy in patients with esophageal cancer.

Materials and Methods

Study Design

This study was performed as a collateral investigation of “the randomized phase II study of preoperative concurrent chemotherapy with or without induction chemotherapy with S-1/oxaliplatin in patients with esophageal cancer”. The study scheme was as follows (Fig. 1).

The patients with resectable esophageal cancer were randomly divided into non-induction and induction groups. The non-induction group received only concurrent chemoradiotherapy without induction therapy. Radiotherapy was performed with a dose of 4,600 cGy in 23 fractions over 5 weeks. Concurrent chemotherapy consisted of oxaliplatin and S-1. Oxaliplatin, 130 mg/m², was administered intravenously on days 1 and 22 of radiotherapy administration. S-1 30 mg/m² was administered orally, twice daily, for

Fig. 1 The scheme of the feasibility study of ^{18}F -FLT PET for prediction of tumor response after randomized phase II study of preoperative concurrent chemotherapy with or without induction chemotherapy with S-1/oxaliplatin in patients with resectable esophageal cancer

5 days per week during the radiotherapy administration. The induction group received two cycles of additional induction chemotherapy before concurrent chemoradiotherapy. Induction chemoradiotherapy of a 3-week course also consisted of oxaliplatin and S-1. Oxaliplatin 130 mg/m^2 was administered intravenously on day 1 of each cycle. S-1 40 mg/m^2 was administered orally, twice daily, from days 1 to 14. After a rest period of 1 week, the same cycle was repeated once more. After two cycles of the induction chemotherapy, this group received concurrent chemoradiotherapy like the non-induction group. Finally, all patients underwent surgery within 6–8 weeks after concurrent chemoradiotherapy completion except for those with newly detected metastasis or inoperable status.

This feasibility study with ^{18}F -FLT PET was conducted only in the induction chemotherapy group arm which is a part of the randomized phase II trial until interim analysis.

Patients

Patients were eligible if they had: (1) histologically proven resectable esophageal cancer without the evidence of invasion to trachea or aorta which is classified as clinical tumor-node-metastasis (TNM) stages II–IVa (positive celiac lymph node) according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition [13]; (2) lymph node metastasis included within a single radiation field; (3) no treatment history for esophageal cancer; (4) age between 17 and 75; (5) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (6) a treatable condition; (7) written consent to the surgical risks; (8) reasonable liver and kidney function and hematologic parameters (hemoglobin, hematocrit, erythrocytes, thrombocytes, and leukocytes); (9) the ability to undergo serial PET. All patients gave written informed consent, which was approved by our institutional review board (approval no. 2008–0485) before initiation of the study.

Treatment Response Evaluation

All patients were initially staged according to the TNM staging system of the International Union Against Cancer (IUAC) on the basis of contrast-enhanced CT, esophagography, gastrofiberscopy, endoscopic ultrasonography (EUS), and ^{18}F -FDG PET performed before induction chemotherapy, and restaged 3–4 weeks after completion of concurrent chemoradiotherapy. The clinical tumor response was evaluated using the response evaluation criteria in solid tumors (RECIST) criteria before surgery. Pathologic tumor response was determined from the microscopic examination of a surgical specimen after surgery, such as an Ivor Lewis operation. All specimens of dissected primary tumor and lymph nodes were examined according to standardized procedures and reviewed by experienced pathologists. Pathologic complete remission (pT0N0) was histopathologically defined as no residual primary tumor nor metastatic lymph node without any newly detected metastasis in the microscopic examination of surgical specimen. The final tumor response was determined according to both clinical and pathological responses.

PET Imaging

$[^{18}\text{F}] \text{F}^-$ was produced in a cyclotron (Cyclone 18/9, IBA, Belgium) using the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction. In producing ^{18}F -FLT with protic solvents (t-butanol or t-amyl alcohol), a TracerLab Mx (GE Healthcare, USA) FDG module with a disposable cassette was used [14]. The purification was achieved by high-performance liquid chromatography. The purity, the specific activity, and the yield of the ^{18}F -FLT produced were $>98 \pm 1.2\%$, $>100\text{ TBq/mmol}$, and $>60 \pm 5.2\%$, respectively. A baseline ^{18}F -FLT PET scan was performed before the initiation of induction chemotherapy and second ^{18}F -FLT PET was performed within 1 week after the completion of two cycles of induction chemotherapy. PET

scans using a PET/CT scanner (Biograph True Point 40; Siemens; Knoxville, TN) were acquired at 60 min after administration of 370 MBq of ^{18}F -FLT by scanning from the skull base to mid-thigh with 5 min per bed position. CT was done in a spiral mode at 110 mAs, 120 kV, and a slice width of 1 mm. Images were reconstructed using iterative reconstruction ordered-subsets expectation maximization and CT attenuation correction was used.

^{18}F -FDG was produced by conventional methods. ^{18}F -FDG PET was performed using one of the three integrated PET/CT scanners (Biograph Sensation 16 or True Point 40; Siemens, Knoxville, TN/ DSTe 8; GE Medical Systems, Milwaukee, WI). All patients had a fasting period of at least 6 h and blood-glucose level check before an intravenous injection of about 370 MBq ^{18}F -FDG and images were acquired after 60 min.

PET Analysis

All images were independently interpreted by two experienced nuclear medicine physicians who were unaware of clinical information using a Siemens e-soft workstation. After visual analysis, maximum standardized uptake value (SUVmax) of primary tumor normalized to the patient's body weight was measured. To evaluate tumor response by ^{18}F -FLT PET after induction chemotherapy, the percent change of SUVmax in primary tumor between baseline and second ^{18}F -FLT PET was calculated according to the equation:

$$\frac{\text{SUVmax}(\text{baseline } ^{18}\text{F-FLT PET}) - \text{SUVmax}(\text{second } ^{18}\text{F-FLT PET})}{\text{SUVmax}(\text{baseline } ^{18}\text{F-FLT PET})} \times 100$$

The patients with no visible tumor uptake above baseline ^{18}F -FLT PET were considered to have an SUVmax of 0.5, and were excluded from the analysis for the evaluation of tumor response by ^{18}F -FLT PET.

Statistical Analysis

The differences of SUVmax between ^{18}F -FLT and ^{18}F -FDG PET images or between the baseline and the second ^{18}F -FLT PET images were compared through Wilcoxon signed-rank tests using the SPSS software (version 17.0). A p value of less than 0.05 was considered to be significant.

Results

Patient's characteristics

Between March and December 2009, 13 consecutive patients (12 men, one woman; mean age 60 years, range 48–71 years) with resectable esophageal cancer were

Table 1 Summary of patient characteristics, PET results and treatment response for the induction chemotherapy group

Patient no.	Sex	Age (years)	Histology	Initial stage	Initial TNM	Baseline FDG SUVmax	Baseline FLT SUVmax	Second FLT SUVmax	SUVmax change (%)	Clinical response	Pathologic response	Final response
1	M	59	SCC	III	T3N1	12.5	9.6	5.3	44.8	PR	pT0N0	CR
2	M	66	SCC	IIB	T2N1	6.9	6.1	2.3	62.3	CR	pT0N0	CR
3	M	69	SCC	IIB	T3N1	2.4	0.5	NA	NA	CR	pT0N0	CR
4	F	58	SCC	IIB	T2N1	14.4	12.0	2.5	79.2	PR	pT2N1	PR
5	M	50	SCC	III	T3N1	NA	12.1	5.1	57.9	PR	pT2N0	PR
6	M	61	SCC	III	T3N1	NA	8.7	3.7	57.5	CR	pT1N1	PR
7	M	64	SCC	IIA-III	T3N0-1	NA	5.3	2.3	56.6	PR	pT0N1	PR
8	M	53	SCC	IIA-III	T3N0-1	6.4	6.6	3.0	54.5	PR	pTisN0	PR
9	M	71	SCC	IIB	T3N1	2.9	3.4	2.0	41.2	PR	NA	PR
10	M	56	SCC	IIB	T2N1	3.3	0.5	NA	NA	PR	pT1N1	PR
11	M	57	SCC	III	T3N1	14.2	4.9	4.4	10.2	PR	M1	PD
12	M	69	SCC	III	T3N1	22.0	9.6	NA	NA	NA	NA	NA
13	M	48	SCC	III	T3N1	13.0	7.6	NA	NA	NA	NA	NA

M male, F female, NA not available, FDG ^{18}F -fluorodeoxyglucose, FLT ^{18}F -fluorothymidine, SUVmax maximum standardized uptake value, SCC squamous cell carcinoma, CR complete response, PR partial response, PD progressive disease

enrolled in an interim analysis (Table 1). All of patients had esophageal cancer of stage IIA to III with the squamous cell type. Two of 13 patients did not undergo a second ^{18}F -FLT PET due to withdrawal of consent (patient no. 12) and death (patient no. 13). Of the remaining 11 patients, eight underwent Ivor-Lewis operation. Among the remaining three patients, one had McKeown's operation, one had exploratory laparoscopic surgery, and one patient did not receive surgery. When analyzing the final tumor responses of the patients, complete responses were achieved in three patients and partial responses in seven patients. One patient showed progression of the disease with liver metastasis. The patients with complete response or partial response were classified as responder group (nine men, one woman; mean age 60 years, range 50–71 years), while one patient with progressive disease was put into the non-responder group (man, age 57 years).

Baseline ^{18}F -FLT PET

On ^{18}F -FLT PET, increased uptake by whole-body bone marrow and liver was visualized in all patients. Eleven of 13 (85%) primary tumors showed increased focal ^{18}F -FLT uptake, whereas all primary tumors were visualized on ^{18}F -FDG PET. The primary tumors of two patients (nos. 3 and 10) with no visibly increased uptake on ^{18}F -FLT PET showed ^{18}F -FDG tumor uptakes of 2.4 and 3.3, respectively.

After excluding three patients (nos. 5, 6 and 7) who underwent ^{18}F -FDG PET at other hospitals, the SUVmax values of primary tumors were compared between ^{18}F -FLT and ^{18}F -FDG PET. The median SUVmax values of ten patients in ^{18}F -FLT and ^{18}F -FDG PET scans were 6.4 (range 0.5–12.0) and 9.7 (range 2.4–22.0), respectively. The tumor uptake of ^{18}F -FLT was significantly lower than that of ^{18}F -FDG ($p=0.013$).

Evaluation of early tumor response using ^{18}F -FLT PET

Among 13 patients of the induction group, four patients were excluded because they did not undergo the second ^{18}F -FLT PET due to withdrawal of consent (no. 12) or death (no. 13), or did not show ^{18}F -FLT tumor uptake in the baseline ^{18}F -FLT PET (nos. 3, 10). Finally, nine patients were evaluated for tumor response using ^{18}F -FLT-PET. The baseline SUVmax on ^{18}F -FLT PET ranged from 3.4 to 12.1 in the responders, and it was 4.9 in one non-responder. The ^{18}F -FLT tumor uptakes in responders were significantly decreased after the induction chemotherapy from median SUVmax 7.7 to 2.8 ($p=0.012$). The percent change of SUVmax ranged from 41.2 and 79.2% (median 57.1%). In contrast, little difference of tumor ^{18}F -FLT uptake was seen in the non-responder (no. 11), with a decrease of SUVmax from 4.9 to 4.4 (10.2% change of SUVmax) (Fig. 2).

Fig. 2 The changes in SUVmax of primary tumor on ^{18}F -FLT PET before and after induction chemotherapy for responders and non-responder according to the final tumor response

Figure 3 shows two representative cases of responder and non-responder.

Discussion

In our study, the ^{18}F -FLT tumor uptake after induction chemotherapy decreased markedly in all patients of the responder group, with complete or partial responses, which were assessed by the final tumor response, while the single non-responder patient showed a minimal change of ^{18}F -FLT tumor uptake. The non-responder was assessed as a partial responder by the RECIST criteria, but metastasis to the liver was found during surgery. This pilot study suggests that the percent change in SUVmax of primary tumor in ^{18}F -FLT PET might be a good parameter for the prediction of preoperative concurrent chemoradiotherapy response.

Until now, there have been no published literature about ^{18}F -FLT PET application in the prediction of chemotherapy in patients with esophageal cancer. There have been several studies on the usefulness of ^{18}F -FDG PET in early prediction or monitoring of tumor response to pre-operative chemotherapy or chemoradiotherapy in esophageal cancer. Weber et al. [5] suggested that a decrease of more than 35% in ^{18}F -FDG tumor uptake at 14 days after the beginning of chemoradiotherapy is the optimal cut-off value, showing a correlation with tumor response after the completion of pre-operative therapy. Ott et al. [6] reported that the change of tumor FDG uptake during pre-operative chemotherapy is useful in differentiating between responders and non-responders, and may allow an early change of treatment plan in non-responders. However, the role of ^{18}F -FDG PET in early assessment of tumor response to pre-operative therapy has not been fully established yet. Each single study

Fig. 3 Two representative cases of responder and non-responder. *White arrow indicates primary tumor.* **a** In a 59-year-old man (no. 1) with lower esophageal cancer, baseline uptake on ^{18}F -FDG and ^{18}F -FLT PET were SUVmax 12.5 and 9.6, respectively. After induction chemotherapy, ^{18}F -FLT tumor uptake was decreased to SUVmax 5.3 (44.8% change of SUVmax). Final tumor response was complete response. **b** In a 57-year-old man (no. 11), baseline SUVmax on ^{18}F -FDG and ^{18}F -FLT PET were 14.2 and 4.9, respectively. After induction chemotherapy, ^{18}F -FLT tumor uptake was decreased to SUVmax 4.4 (10.2% change of SUVmax). Final tumor response was progressive disease with liver metastasis

shows heterogeneity in the study design and the cut-off value of ^{18}F -FDG tumor uptake [15]. In patients with locally advanced esophageal carcinoma who were treated with two cycles of induction chemotherapy, Klaeser et al. [16] demonstrated that ^{18}F -FDG PET was unable to predict non-responsiveness to induction chemotherapy and it did not have valid evidence to directly alter the treatment plan. Furthermore, during or after neo-adjuvant therapy including radiotherapy, the radiation-induced inflammation may lead to a false high ^{18}F -FDG uptake and the misinterpretation of tumor response [17].

^{18}F -FLT, the imaging tracer of tumor proliferation, is recently drawing attention as a predictor of tumor response. The usage of ^{18}F -FLT for early evaluation of tumor response

to pre-operative therapy has been supported by several animal studies, which have demonstrated rapid reductions in ^{18}F -FLT tumor uptake after therapy [12, 18, 19]. Several pilot studies also have reported that the change of ^{18}F -FLT tumor uptake after chemotherapy in some tumors is useful in predicting tumor responses. In 14 patients with breast cancer, the change of tumor uptake on ^{18}F -FLT PET after one course of chemotherapy could predict the tumor response [20]. Another study also has demonstrated that the prediction of clinical response could be made by observing the decreases in ^{18}F -FLT tumor uptakes 1 week after chemotherapy in patients with breast cancer [21]. In a study including patients with recurrent high-grade glioma treated with bevacizumab/irinotecan, ^{18}F -FLT PET was found to be predictive of

overall survival [22]. A study has reported that ^{18}F -FLT PET may be useful in the differentiation between residual tumor and inflammation, and be eventually helpful in evaluating tumor response after radiotherapy in esophageal cancer [23]. Our study also showed the feasibility that ^{18}F -FLT may serve as an imaging tracer for early prediction of the induction chemotherapy response in patients with esophageal cancer, in concordance with previous studies. However, some studies have also reported that there is no correlation between the change of ^{18}F -FLT tumor uptake and the tumor response, contrary to the findings listed above [24, 25]. The relation between the early change of ^{18}F -FLT uptake and the tumor response has not been established yet in other various types of tumors or therapies. Larger multicenter trials should be performed to find out whether the change of ^{18}F -FLT tumor uptake during pre-operative therapy can predict tumor response, if changing the treatment strategies according to the results of ^{18}F -FLT PET increases the patients' relapse-free and overall survival rates, and whether it has cost-effectiveness in various tumors.

In order to use ^{18}F -FLT in evaluating the treatment response, the standardization of the imaging protocol and the determination of the optimal timing of second PET after the start of pre-operative therapy will be necessary. The time course between the start of chemotherapy and the second ^{18}F -FLT PET in our study was 39 days on average. Not enough studies regarding the timing of ^{18}F -FLT PET for the evaluation of tumor response have been carried out so far. Further studies are needed to determine the optimal imaging protocol, as well as the threshold of SUV change, to differentiate responders from non-responders in patients with esophageal cancer.

Our study revealed that the ^{18}F -FLT uptake of the primary tumor was lower than that of ^{18}F -FDG. ^{18}F -FLT uptake of tumors could not be distinguished from the physiologic activity of the esophagus in two patients. The tumor detection rate of ^{18}F -FLT PET for detection of esophageal cancer (85%) was lower than that of ^{18}F -FDG PET (100%). Similar to our study results, there are several reports that the ^{18}F -FLT uptake in solid tumors, including esophageal cancer, was significantly lower than that of ^{18}F -FDG [26–28]. For this reason, we think that ^{18}F -FLT PET is unsuitable for the initial staging of esophageal cancer when compared with ^{18}F -FDG PET.

This pilot study has a limitation of small sample size because only nine patients were evaluated for the change of ^{18}F -FLT tumor uptake. Although the uptake after induction chemotherapy in the non-responder showed minimal change when compared with responders, it would be difficult to apply this result generally, since there was only one non-responder in this study. For this reason, further prospective studies with larger populations are needed to evaluate the usefulness of ^{18}F -FLT PET in the early prediction of tumor

response and to define the optimal cut-off value of the change in ^{18}F -FLT uptake for differentiating between responders and non-responders. Another limitation is that the patients received additional radiotherapy after the induction chemotherapy. The tumors that were not responsive to chemotherapy may have responded to additional radiotherapy, and therefore may have been falsely regarded as 'responders' to chemotherapy.

In conclusion, the percent change of tumor uptake in ^{18}F -FLT PET after induction chemotherapy seems to be feasible for the early prediction of tumor response in esophageal cancer patients receiving induction chemotherapy followed by concurrent chemoradiotherapy. ^{18}F -FLT PET may aid in earlier modifications of treatment plans in non-responders.

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Conflicts of Interest None.

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