Use of Pre-treatment ^{18}F-FAMT PET to Predict Patient Survival in Squamous Cell Carcinoma of the Esophagus Treated by Curative Surgery

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Abstract. *Background: [^{18}F]-3-fluoro-alpha-methyl tyrosine (^{18}F-FAMT) as an amino acid tracer in positron emission tomography (PET) has been widely investigated in several tumor types. Herein we investigated the clinical significance of ^{18}F-FAMT PET uptake as a prognostic marker together in our updated data of patients with esophageal cancer. Patients and Methods: We retrospectively assessed the treatment outcomes of 42 patients with histologically-confirmed esophageal cancer. The survival rate was analyzed using the median peak standardized uptake value (SUV) with 2.2 as the cut-off value. Results: FAMT uptakes were significantly correlated with factors reflecting tumor progression. Moreover, a significant correlation was observed between FAMT uptake and disease-free survival (p=0.023). Moreover, on evaluation of individual lymph node groups, the specificity and positive predictive value were significantly higher for ^{18}F-FAMT-PET than for ^{18}F-FDG-PET and computed tomography (CT). Conclusion: ^{18}F-FAMT is an important pre-treatment diagnostic modality and its accumulation is a good predictor of disease-free survival (DFS) in patients with operable esophageal cancer.*

Esophageal cancer is among the leading causes of cancer-related deaths worldwide and is often characterized by lymph node metastasis throughout the cervical, mediastinal, and abdominal regions. Furthermore, the status of lymph node metastasis has been recognized as a key factor in the outcome of esophageal cancer surgery (1). Accurate tumor staging, particularly with regard to tumor invasion depth, lymph node involvement, and distant metastasis, is essential to achieve optimal treatment selection and treatment delivery to facilitate individually-tailored patient management (2). Although it is important to ascertain metastasis of esophageal carcinoma to the lymph nodes at the time of surgery in each patient, it is more important to know the extent of regional spread. To optimize radiological imaging of esophageal cancer, lymph node status should be determined using a multimodal approach, which includes data from endoscopic ultrasonography (EUS), computed tomography (CT), and positron-emission tomography (PET)/CT. EUS with ultrasonography-guided biopsy is superior to both CT and PET/CT for assessing locoregional nodes and is the primary modality used in this regard and its sensitivity, specificity, and accuracy are 89%, 75%, and 84%, respectively (3). Davis *et al*. recently reported that disease duration and the associated EUS lymph node metastasis count should be incorporated into routine esophageal cancer radiological staging to optimize stage-directed treatment outcomes (4).

The role and potential value of PET as a non-invasive imaging modality have been widely investigated (5-8), and in recent years, CT along with ^{18}F-flourodeoxyglucose (^{18}F-FDG)-PET has become a common procedure for assessing glucose metabolism as well as the details of various anatomical structures in patients with cancer. Our previous reports described the utility of ^{18}F-FAMT PET in the diagnosis of lymph node metastasis in patients with operable esophageal squamous cell carcinoma (SCC) because the specificity of ^{18}F-FAMT-PET was significantly higher compared with that of ^{18}F-FDG-PET and CT (9). Furthermore, we previously reported that ^{18}F-FAMT uptake revealed a significant correlation with invasion depth, lymph node metastasis, pathological stage, and lymphatic invasion.

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With regard to preoperative work-up, as compared with ^{18}F-FDG-PET, an important merit of ^{18}F-FAMT-PET in diagnosis is the high specificity and positive predictive value (PPV) of the procedure based on the lack of uptake in inflammation. However, our previous report enrolled an insufficient number of patients; therefore, we updated our ^{18}F-FAMT-PET data in the present report. Moreover, a limited number of reports exist in the literature regarding the correlation between ^{18}F-FAMT uptake and prediction of survival, although comparatively more reports are available for ^{18}F-FDG-PET in this regard, Kato *et al*. reported that pre-treatment with ^{18}F-FDG-PET could be used to diagnose the extent of disease efficiently, as well as to predict patient survival after esophageal cancer resection. On the contrary, Brown *et al*. reported that the maximum standardized uptake value (SUV_{max}) on pre-treatment PET scans was a useful prognostic tool in esophageal cancer, particularly in patients who underwent neoadjuvant therapy (10). Furthermore, Kaira *et al*. reported that a high SUV_{max} of ^{18}F-FAMT PET and positive L-type amino-acid transporter 1 (LAT1) expression were significant predictive factors of poor outcome in non-small cell lung cancer (11). However, as far as we are aware of, no previous study has reported a correlation between ^{18}F-FAMT-PET and survival in patients with esophageal cancer.

In the current study, we assessed the clinical significance of ^{18}F-FAMT PET uptake as a prognostic marker together with the application of our updated data from patients with esophageal cancer.

Patients and Methods

Eligibility criteria and patients. In the present study, we retrospectively assessed the treatment outcomes of 42 patients (37 males and 5 females; mean (±SD) age=65.9±7.5 years; range=43-80 years) with primary esophageal SCC who underwent radical esophagectomy at the Department of General Surgical Science, Graduate School of Medicine, Gunma University (Maebashi City, Japan) between April 2001 and December 2011. All the patients submitted their written, informed consent for participation in this study. None of the patients received prior treatment, and all patients underwent pretreatment CT, ^{18}F-FDG-PET, and ^{18}F-FAMT-PET for tumor staging at our institution. Tumor stage and disease grade were assigned according to the sixth edition of the Tumor, Lymph Node, Metastasis classification guidelines of the Union for International Cancer Control (12). Resectability was determined using conventional staging methods (CT, ^{18}F-FDG-PET, EUS, and esophagography).

All the eligible patients underwent standard esophagectomy according to the McKeown method, and three-field lymph node dissection was also performed, if indicated. In some patients; Ivor Lewis esophagectomy was performed for two-field (thoracoabdominal) lymph node dissection. In one patient, transhiatal dissection of the esophagus was performed. Following surgery, the lymph nodes were separated from the resected esophagus and the adjacent tissues and then numbered to indicate lymph node origin in accordance with the guidelines of the Japanese Society for Esophageal Disease (JSED) (13).

PET-CT studies. Both ^{18}F-FAMT and 18F-FDG were produced at our cyclotron facility using the methods developed by Tomiyoshi *et al*. and modified according to the methods of Hamacher *et al*. (14, 15). PET images were obtained using PET/CT scanners (Discovery STE; GE Healthcare, USA. Biograph 16; Siemens Medical Solutions USA, Inc., Madison, WI, USA). The imaging procedure and details of ^{18}F-FAMT or ^{18}F-FDG were performed as previously reported (9). All the patients provided informed consent before undergoing any examination. Regional lymph nodes were assigned specific numbers to indicate localization in accordance with the JSED classification guidelines. To compare the pathological findings with the PET images, we classified lymph node localization according to the anatomical region, *i.e*. the cervical, upper thoracic, middle thoracic, lower thoracic, and abdominal regions. A faint uptake of both ^{18}F-FAMT and ^{18}F-FDG was defined as a positive result, whereas no visualized uptake was defined as a negative result, and the SUV was assigned a value of 0 according to our previous report (9).

CT analysis. All the patients underwent preoperative CT from the neck to the abdomen for staging at initial diagnosis; for this, 5-mm continuous scans were obtained from the neck to the bottom of the liver as previously reported (9). Lymph nodes were considered positive for metastasis if the short axis was >1 cm. All the positive lymph nodes were numbered to indicate origin in accordance with the JSED guidelines.

Statistical analysis. The correlation between SUVs of 18F-FAMT and the clinicopathological features was assessed using analysis of variance (ANOVA). The sensitivity, specificity, accuracy, PPV, and negative predictive value (NPV) of CT and PET/CT were calculated using standard definitions. A probability value of less than 0.05 was considered statistically significant.

Results

Patients' characteristics. Characteristics of the 42 patients with SCC are summarized in Table I. The tumors were located in the upper esophagus in four patients, the middle esophagus in 22, and the lower esophagus in 16. The pathological tumor stages were stage I in 19 patients, stage II in 7, stage III in 15, and stage IV in 1. Thirty-five patients underwent McKeown esophagectomy, 6 underwent Ivor Lewis esophagectomy, and 1 underwent transhiatal dissection of the esophagus.

Peak SUV of FAMT and clinicopathological parameters. Primary tumors were detected in 31 (73.8%) out of the 42 patients by FAMT-PET imaging. The median peak SUV (2.16; range=0-5.5) was used as the cut-off value to separate the the high (n=22) and low (n=20) SUV groups. A comparison of FAMT uptake and clinicopathological characteristics revealed a significant positive correlation between the peak SUV value and each of the following factors (Table I): depth of invasion (pT) (p<0.0001), lymph

Table I. *Correlation of ^{18}F-FAMT and clinico pathological characteristics in 42 patients with esophageal squamous cell carcinoma.*

Parameter	No. of cases	^{18}F-FAMT uptake (SUV) mean±SEM	*p*-Value
Gender			
Male	37	2.20±(0.28)	0.6655
Female	5	1.84±(0.81)	
Location			
Upper	4	2.86±(1.01)	
Midthoracic	22	2.19±(0.34)	0.6218
Lower	16	1.94±(0.45)	
Differentiation			
Well	9	2.16±(0.55)	0.6273
Moderate	22	1.78±(0.35)	
Poorly	11	2.91±(0.50)	
TNM clinical classification			
PT			
Tl	19	1.02±(0.27)	<0.0001
T2	7	2.38±(0.75)	
T3	15	3.37±(0.28)	
T4	1	4.15	
pN			
N0	14	1.23±(0.42)	0.0001
Nl	28	2.62±(0.30)	
pM			
M0	37	2.07±(0.28)	0.3571
Ml	5	2.82±(0.56)	
pStage			
I	10	0.65±(0.32)	
II	14	1.82±(0.46)	0.0001
III	13	3.44±(0.30)	
IV	5	2.82±(0.56)	
Lymphatic invasion			
Negative	9	1.19±(0.09)	0.0490
Positive	33	2.42±(0.28)	
Blood vessel invasion			
Negative	12	1.53±(0.57)	0.1287
Positive	30	2.41±(0.29)	

^{18}F-FAMT: L-[3-^{18}F]-a-methyltyrosine, SEM: standard error of the mean, SUV: standardized uptake value.

node metastasis (pN; p=0.0001), pathological stage (p=0.0001), and lymphatic invasion (p=0.049). However, no significant correlation was observed between ^{18}F-FAMT uptake and other clinicopathological features.

Survival according to each clinicopathological parameter. The three-year disease-free (DFS), overall (OS), and cancer-specific (CS) survival rates were calculated using the Kaplan–Meier method. No significant correlations were observed between the three-year OS rate and each of the following factors: sex, location, histology, depth of invasion, lymph node status, lymphatic invasion, and venous invasion. A significant negative correlation was observed between the three-year OS rate and distant lymph node metastasis (pM; p=0.007).

With regard to the three-year CS rate, no significant correlation was observed between patient survival and each of the following factors: sex, histology, depth of invasion, lymphatic invasion, and venous invasion. However, significant correlations were observed between patient survival and location (p=0.032), lymph node status (pN; p=0.017), and distant lymph node metastasis (pM; p=0.002). With regard to the three-year DFS rate, no significant correlation was observed between patient survival and each of the following factors: sex, histology, and venous invasion. However, significant correlations were observed between patient survival and location (p=0.006), depth of invasion (p=0.035), lymph node status (pN; p=0.008), distant lymph node metastasis (pM; p=0.020), and lymphatic invasion (p=0.024).

Correlation of FAMT uptake to OS, CS, and DFS. A survival curve was constructed and then analyzed using a cut-off value of 2.2, which was the median peak SUV. As presented in Figure 1A and B, no significant correlations were observed between OS or CS with FAMT uptake. However, as indicated in Figure 1C, a significant negative correlation was observed between FAMT uptake and DFS (p=0.023). The three-year DFS rates of the high and low SUV groups were 49.5% and 78.4%, respectively.

Diagnosis of lymph node metastasis. Out of the 42 patients who initially underwent surgery, 28 had histopathologically-confirmed lymph node metastases. During surgery, a total of 2,914 lymph nodes were dissected from these 42 patients (average, 69.4 lymph nodes/patient). A total of 195 lymph node groups (according to the JSED classification guidelines) were identified in these 42 patients. Histopathologically, lymph node metastasis was present in 56 lymph node groups. Diagnostic sensitivity, specificity, and accuracy rates for ^{18}F-FAMT-PET, ^{18}F-FDG-PET, and CT in the detection of lymph node metastases are summarized in Table II.

An evaluation of individual lymph node groups revealed that ^{18}F-FAMT-PET exhibited 18.2% sensitivity, 100% specificity, 76.4% accuracy, 100% PPV, and 75.1% NPV, whereas ^{18}F-FDG-PET exhibited 29.1% sensitivity, 92.6% specificity, 74.3% accuracy, 61.5% PPV, and 76.4% NPV. Furthermore, CT exhibited 40.0% sensitivity, 88.2% specificity, 74.3% accuracy, 57.9% PPV, and 78.4% NPV. Moreover, with regard to the evaluation of individual lymph node groups, the following were observed: The specificity of ^{18}F-FAMT-PET was significantly higher compared with that of ^{18}F-FDG-PET (p=0.0013) and CT (p<0.0001; Figure 2A); the PPV of ^{18}F-FAMT-PET was significantly higher compared to that of ^{18}F-FDG-PET (p=0.021) and CT

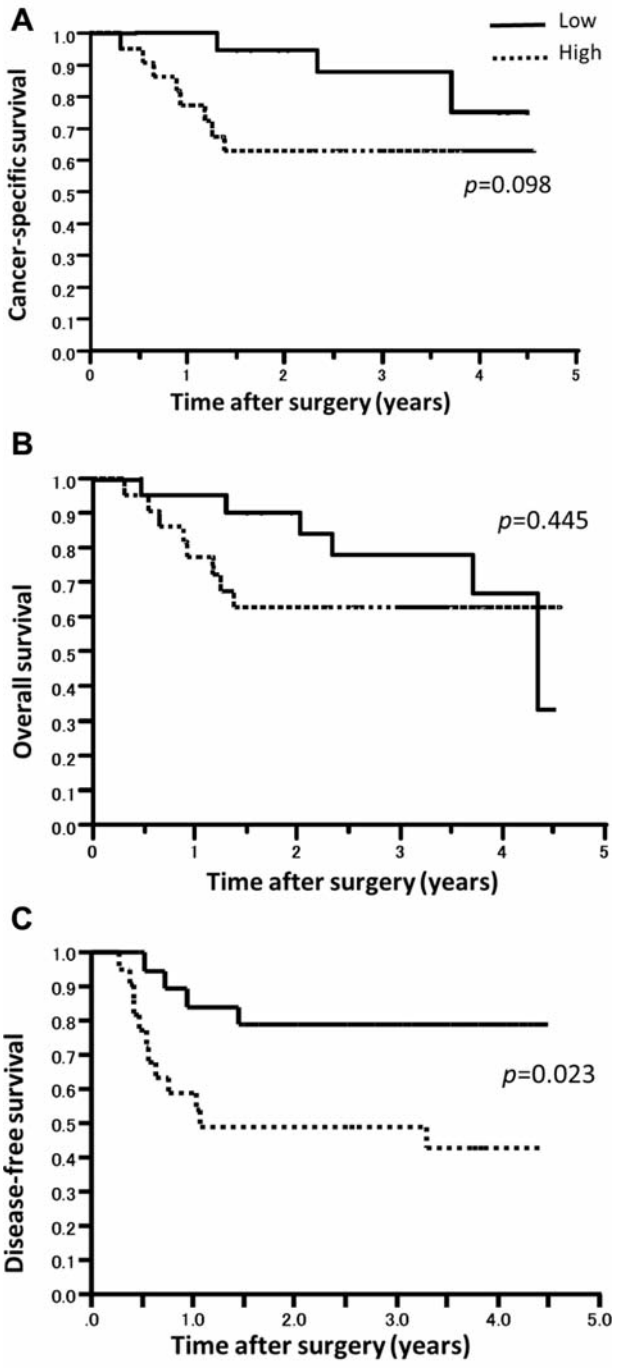

Figure 1. *A: Cancer-specific postoperative survival rates according to ^{18}F-FAMT accumulation. Patients with low ^{18}F-FAMT accumulation tended to exhibit more favorable prognoses compared to those with high ^{18}F-FAMT accumulation (3-year survival rate: low accumulation 89.6%, high accumulation 62.5%). B: Overall postoperative survival rates according to ^{18}F-FAMT accumulation. No significant correlation was observed between FAMT uptake and overall survival (p=0.445). C: Disease-free postoperative survival rates according to ^{18}F-FAMT accumulation. Patients with low ^{18}F-FAMT accumulation had significantly favorable prognoses compared with those with high ^{18}F-FAMT accumulation (3-year survival rate: low accumulation 78.4%, high accumulation 49.5%).*

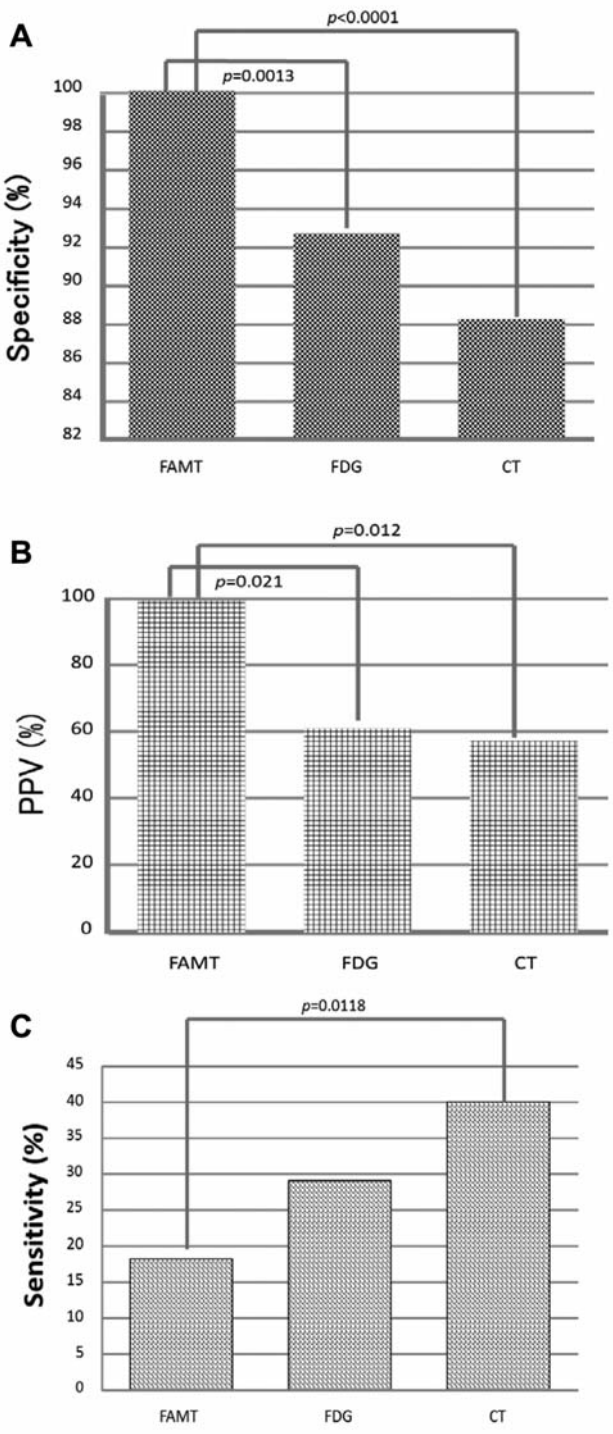

Figure 2. *A: The specificity of ^{18}F-FAMT-PET, ^{18}F-FDG-PET and CT in the evaluation of individual lymph node groups. ^{18}F-FAMT-PET exhibited a significantly higher specificity compared to that of ^{18}F-FDG-PET and CT. The PPV of ^{18}F-FAMT-PET, ^{18}F-FDG-PET and CT in the evaluation of individual lymph node groups. ^{18}F-FAMT-PET had a significantly higher PPV compared with that of ^{18}F-FDG-PET and CT. C: The sensitivity of ^{18}F-FAMT-PET, ^{18}F-FDG-PET and CT in the evaluation of individual lymph node groups. ^{18}F-FAMT-PET had significantly lower sensitivity compared with that of CT.*

Table II. *Results of F-FAMT-PET, F-FDG-PET and CT in the assessment of lymph node metastases.*

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV(%)	NPV(%)
Lymph node group evaluation					
^{18}F-FAMT-PET	18.2 (10/55)	100 (136/136)	76.4 (146/191)	100 (10/10)	75.1 (63/90)l
^{18}F-FDG-PET	29.1 (16/55)	92.6 (126/136)	74.3 (142/191)	61.5 (16/26)	76.4 (59/84)
CT	40 (22/55)	88.2 (120/136)	74.3 (142/191)	57.9 (22/38)	78.4 (54/74)

(p=0.012; Figure 2B); and, the sensitivity of ^{18}F-FAMT-PET was significantly lower compared to that of CT (p=0.0118; Figure 2C). However, no significant differences were observed with regard to NPV or accuracy among these three modalities.

Discussion

We previously reported a correlation between FAMT uptake and progression of esophageal cancer; however, the number of patients enrolled was insufficient. Therefore, in the current study, we revisited our data and investigated the correlation between FAMT uptake and progression of esophageal cancer with a larger patient cohort and verified a negative correlation between FAMT uptake and survival of patients with esophageal cancer.

FAMT uptake revealed a significant positive correlation with depth of invasion, lymph node metastasis, pathological stage, and lymphatic invasion. Furthermore, our data indicated that FAMT uptake correlated with the malignant status of esophageal cancer. These results were similar to those in our previous report. Kaira *et al*. reported that ^{18}F-FAMT uptake by the primary tumor was associated with poor outcome in non-small cell lung cancer and observed that ^{18}F-FAMT uptake was a stronger prognostic factor compared with ^{18}F-FDG uptake (16). In accordance with these previous reports, our data suggest that ^{18}F-FAMT uptake has a potential role in the prognosis of other types of malignant tumors.

To the best of our knowledge, the correlation between baseline ^{18}F-FAMT-PET values and prognosis in patients with localized esophageal cancer has not yet been established. We reasoned that baseline ^{18}F-FAMT PET values were correlated with survival in patients with operable esophageal cancer. Therefore, we performed a retrospective study to assess whether ^{18}F-FAMT uptake (*i.e*. SUV_{max}) in a primary tumor was associated with patient survival. In the current study, the OS of the patients in the low SUV group tended to be higher compared to that of the patients of the high-SUV group, although there was no significant difference. Moreover, the DFS of patents of the low-SUV group was significantly higher compared with that of patients in the high-SUV group. Our data suggest that pre-treatment ^{18}F-FAMT uptake is a reliable predictor of DFS in patients with operable esophageal cancer.

Moreover, diagnostic potential analysis revealed that the specificity and PPV of ^{18}F-FAMT were significantly higher compared to those of other modalities. Cumulatively, our ^{18}F-FAMT data for diagnostic potential were generally in accordance with our previous data, although a significant difference in PPV was observed in the current study.

The results of the present study should improve the diagnostic accuracy of lymph node metastases in patients with esophageal cancer. Esophagectomy is an invasive procedure and involves three fields (the cervical, mediastinal, and abdominal regions) in lymph node dissection. Esophageal SCC is one of types of cancer most highly sensitive to chemotherapy and radiotherapy. Moreover, mediastinal lymph nodes tend to be swollen because of the high incidence of tobacco and alcohol use among patients with esophageal cancer. On the basis of the above-mentioned findings, high specificity and PPV are particularly important factors to distinguish true lymph node metastases from inflammatory lymph node swellings. ^{18}F-FAMT PET is an important diagnostic modality to decide the treatment strategies to combat esophageal cancer.

In the current study, we assessed the predictive value of DFS and the diagnostic importance of ^{18}F-FAMT in patients with operable esophageal cancer. ^{18}F-FAMT is an important pre-treatment diagnostic modality with high specificity, although its sensitivity is lower compared with that of ^{8}F-FDG PET and CT, and its accumulation is well-suited as a predictor of DFS in patients with operable esophageal cancer. However, additional cases will undoubtedly influence the strategic decisions in esophageal cancer management.

Conflicts of Interest

There exist no conflicts of interest for any of the Authors nor any competing financial interest with regard to this study.

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