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^{18}F-FAMT-PET Is Useful for Judging Clinical Complete Response in Advanced Esophageal Cancer Patients Who Have Received Definitive Chemoradiotherapy

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We developed L-[3-^{18}F]-α-methyltyrosine (^{18}F-FAMT) as an amino acid tracer for positron emission tomography (PET) imaging. In esophageal cancer, the specificity of ^{18}F-FAMT PET was significantly higher than that of fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET and computed tomography (CT) in the evaluation of individual lymph node groups. Definitive chemoradiotherapy (CRT) has been considered a potentially curative treatment for locoregional esophageal cancer and may achieve the same survival benefits as surgical resection. Clinical evaluation of complete response (CR) is important using several modalities. We evaluated 6 patients who had been diagnosed with clinical CR by FAMT-PET following definitive CRT for esophageal squamous cell carcinoma between June 2008 and July 2012. Treatment evaluation of ^{18}F-FAMT was performed following CRT and approximately 1 month later. In primary tumors, 66.7% of patients (4/6) showed FDG uptake following CRT, whereas that of FAMT was 33.3% (2/6). In lymph node metastases, 50% of patients (3/6) showed FDG uptake following CRT, whereas that of FAMT was 0% (0/6). In the present study, FAMT-PET following CRT was a useful modality to predict clinical CR in esophageal cancer. There is a limit to judging clinical CR by CT or FDG-PET following CRT, because radiation-related esophagitis and reactive

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mediastinal lymphadenopathy by FDG and wall thickness by CT still remain 1 month following CRT. FAMT-PET is the most useful modality at the present time.

Key words: 18F-FAMT PET – 18F-FDG PET – Complete response – CRT

The prognosis of esophageal cancer remains poor despite recent improvements in diagnosis and treatment (such as surgical techniques or chemotherapy/radiotherapy). In Japan, the most common histologically confirmed esophageal cancer is squamous cell carcinoma (SCC), which is considered to have high radio-sensitivity. Chemoradiotherapy (CRT) is effective in patients with stages II to III esophageal SCC with tolerable toxicities, making it a useful nonsurgical treatment option.[1] Definitive CRT is a potentially curative treatment for locoregional esophageal cancer and may achieve the same survival benefits as surgical resection.[2,3] With the development of CRT, a predictive marker of treatment efficacy has become important. If tumors are sterilized following CRT, salvage surgery, which can lead to additional postoperative mortality and morbidity, may not be necessary.[4–6] The most commonly used staging modalities for esophageal cancer are computed tomography (CT) scans of the chest, abdomen, and pelvis; endoscopic ultrasonography (EUS); and positron emission tomography with fluoro-2-deoxy-D-glucose (FDG-PET). In particular, judgment of a complete response (CR) after CRT is very important in esophageal cancer. Li *et al* showed that pretreatment maximal esophageal wall thickness is independently associated with response to CRT in patients with T3 to T4 esophageal SCC.[7] There have been several reports concerning the response prediction of FDG-PET for neoadjuvant CRT or definitive CRT. We previously reported that the Standard Uptake Value (SUV) of FDG-PET prior to CRT was an independent predictor for clinical CR in esophageal cancer.[8] Myslivecek *et al* also reported that ^{18}F-FDG-PET/CT predicted a complete histopathologic response with a sensitivity of 87%, a specificity of 88%, and an accuracy of 88%.[9] However, other reports have not shown any predictive value of FDG-PET with respect to response following neoadjuvant CRT and histopathology.[10,11] Swisher *et al* showed that after CRT, FDG-PET cannot rule out residual microscopic disease; thus, esophagectomy should remain a therapeutic option even if the post-CRT imaging modalities are normal.[10] We developed L-[3-^{18}F]-α-methyltyrosine (^{18}F-FAMT) as an amino acid tracer for PET imaging and confirmed its potential usefulness in the detection of neoplasms using experimental tumor models.[12–14] We previously reported that the specificity of ^{18}F-FAMT PET was significantly higher than that of ^{18}F-FDG PET and CT in the evaluation of individual lymph node groups in esophageal cancer.[15] Because of the high specificity ^{18}F-FAMT PET may show the clinical usefulness for evaluation of residual tumors.

In the current study, we retrospectively assessed the ability of ^{18}F-FAMT PET to predict clinical CR following definitive CRT.

Materials and Methods

Patient population

We evaluated 6 patients who had been diagnosed with clinical CR by FAMT-PET following definitive CRT for esophageal SCC at the Department of General Surgical Science, Graduate School of Medicine, Gunma University, Japan, between June 2008 and July 2012. Patients with histologically confirmed primary esophageal SCC were eligible for inclusion. Clinical data from a consecutive series of patients were retrospectively reviewed. Patients had locally advanced disease (cT4, n = 2), laryngeal functional preservation (n = 2), or patient preference (rejection of surgery, n = 2). As a result, patients with distant organ metastases and severe organ dysfunction were not included in the present study. There were no cases of salvage esophagectomy performed after CRT.

Treatment plan and evaluation

Four patients were treated with 2 cycles of docetaxel, cisplatin, and 5-fluorouracil–based chemotherapy and radiotherapy concurrently. However, 2 patients were treated with 1 cycle of chemotherapy due to side effects. External radiotherapy was delivered by a 2-field technique using a 10- to 15-MV photon beam at 2 Gy per fraction/day, 5 fractions/wk, to a total of 60 to 66 Gy. Clinical evaluation of the primary tumor and lymph node metastases included repeat endoscopy, esophagography, and CT scans. All patients underwent a CT scan of the neck, chest, and abdomen, with continuous scans of 5-mm slices obtained from the neck to the bottom of the liver following

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Table 1 Summary of patient characteristics

Case	Age, years	Sex	Tumor type	Location	cT	cN	cM	Stage	Cycle of CT
1	60	Male	0–Is	Ce	T1	N0	M0	S1	2
2	64	Female	0–IIa	Ce	T1	N0	M0	S1	1
3	77	Male	3	Ce	T4 (aorta)	N1	M0	S4	2
4	69	Male	0–IIc	Mt	T1	N1	M0	S4	2
5	62	Male	2	Mt	T2	N0	M0	S2	1
6	68	Male	4	Mt	T4 (aorta)	N1	M0	S4	2

cT, depth of invasion; cN, lymph node metastasis; cM distant metastasis; Ce, cervical esophageal cancer; Mt, middle thoracic esophageal cancer.

intravenous injection of contrast medium. Treatment evaluations were classified as follows: CR (complete disappearance of all clinical evidence of existing lesions beyond 4 weeks) and non-CR (all states except CR such as partial response, stable disease, and progressive disease). Treatment evaluation of ^{18}F-FAMT was performed following CRT and approximately 1 month later.

PET-CT studies

Both ^{18}F-FAMT and ^{18}F-FDG were produced at our cyclotron facility using the method developed by Tomiyoshi *et al*[16] and a modified method based on that of Hamacher *et al*.[17] PET images were obtained using PET/CT scanners (Discovery STE, GE Healthcare, Tokyo, Japan; and Biograph 16, Siemens Medical Solutions Inc, Tokyo, Japan). Imaging procedures of ^{18}F-FAMT and ^{18}F-FDG were performed as previously reported.[15] A faint uptake of both ^{18}F-FAMT and ^{18}F-FDG was defined as a positive result, and no visualized uptake was defined as a negative result. SUV was assigned as 0 according to our previous report. Furthermore, none of the patients had diabetes, and all the blood sugar levels were <120 mg/dL when undergoing the PET scan.

Table 2 Uptake of PET after CRT in CR cases

	FDG-PET		FAMT-PET		
Case	Primary tumor	Lymph node	Primary tumor	Lymph node	Survival
1	N	P	N	N	Dead
2	N	N	N	N	Alive
3	P	N	N	N	Alive
4	P	P	N	N	Alive
5	P	N	P	N	Alive
6	P	P	P	N	Alive

N, there was no uptakes of PET (negative); P, there was uptakes of PET (positive).

Results

Patient characteristics

The mean age of the 6 included patients was 66.7 ± 6.1 years. Their characteristics are shown in Table 1. Three cases of cervical esophageal cancer were included. In 2 cases, CRT was performed due to laryngeal functional preservation. Two cases [cervical esophageal cancer (Ce) and middle thoracic esophageal cancer (Mt)] of cT4 had invaded the surrounding aorta, and CRT was performed in inoperable cases. In the remaining 2 cases of middle thoracic esophageal cancer, CRT was performed due to operative rejection. Moreover, in 2 cases (33%), only 1 cycle of chemotherapy was performed due to adverse effects.

Correlation between CR and uptake of PET uptake of FDG or FAMT following CRT in CR cases

Uptake of FDG or FAMT after CRT in CR cases is shown in Table 2. In primary tumors, 66.7% of patients (4/6) showed FDG uptake following CRT, whereas that of FAMT was 33.3% (2/6). In lymph node metastases, 50% of patients (3/6) showed FDG uptake following CRT, whereas that of FAMT was 0% (0/6). As a result, all patients were retrospectively diagnosed with CR at this time. All patients were macroscopically diagnosed with incomplete response or stable disease (IR/SD) by endoscopy after CRT because of radiation esophagitis at that time; however, there were no obvious remnant cancer cells pathologically in the biopsy specimens of any patient. Afterward, local recurrences were not pathologically recognized in any patient in the follow-up period. The average follow-up period in all patients was 4.53 years (range: 0.5–7.91 years). Unfortunately, however, 1 patient who had distant lymph node metastases died due to recurrence of lymph node metastases. Additionally, 1 patient discontinued follow-up along the way at his own

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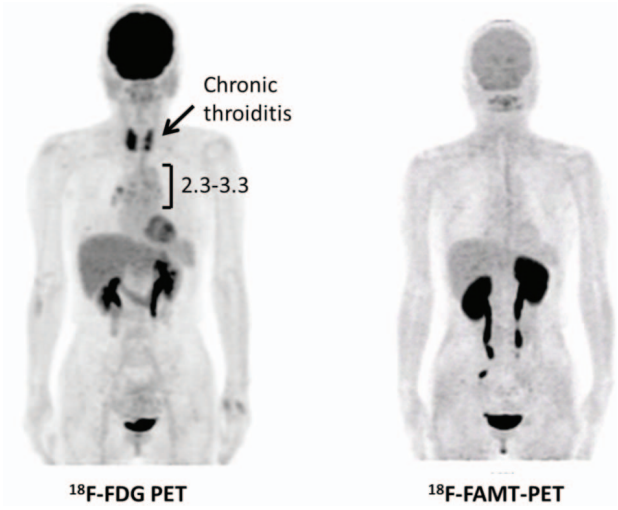

Fig. 1 ^{18}F-FDG-PET (coronal section) and ^{18}F-FAMT-PET (coronal section) of a 64-year-old woman who was judged CR following CRT. ^{18}F-FDG-PET shows an increased uptake in the bilateral thyroid, mediastinal, and hilar lymph node lymphadenopathy (range of SUV: 2.3–3.3). On the other hand, ^{18}F-FAMT-PET did not show uptake at these lesions.

request. The remaining 4 patients were alive without relapse.

Here, we present one such case. Case 2 (Table 2), a 64-year-old woman, was referred to our hospital from another clinic for treatment of esophageal cancer. She was diagnosed with operable cervical esophageal cancer. CRT was chosen because she hoped for laryngeal functional preservation. Following CRT, ^{18}F-FDG PET did not show any uptake at the primary lesion; however, mediastinal and hilar lymph node lymphadenopathy was shown. ^{18}F-FAMT-PET showed no uptake at either the primary lesion or the lymph nodes (Fig. 1). As a result, we subsequently judged this case as clinical CR.

Discussion

Conventional structure-based imaging techniques, such as CT, endoscopy, and EUS, are generally considered inaccurate in predicting response to CRT, primarily because these modalities cannot differentiate between viable tumors and inflammatory reactions, edema, and fibrosis.[18,19] In particular, esophageal wall thickness following CRT is difficult to distinguish between residual tumor and edema due to treatment by CT. Kim *et al*[20] reported that endoscopic biopsy only had a 30.4% sensitivity for detecting residual disease, whereas it had a false-negative rate for predicting residual primary tumors of 58.2%. It was also reported that disease-free endoscopic biopsy could not predict CR to preoperative CRT.[20] In our previous study, we reported that SUV of FDG-PET prior to CRT was an independent predictor for clinical CR in esophageal cancer.[8] Our data are important for predicting CR, because FDG-PET is a functional imaging technique that permits better characterization of tumor metabolism than does CT, which was shown by structure-based imaging. However, although the uptake of FDG is a marker for predicting clinical CR, many cases have shown false positives due to radiation esophagitis and reactive mediastinal lymphadenopathy. This is a weak point of FDG-PET for CR judgment after CRT. Klayton *et al* reported that there was no significant relationship between the pre- or post-CRT SUV of FDG and the presence of residual disease.[21]

In the current study targeted at CR, our FDG data show that 33.3% of cases were diagnosed as having no residual tumor in primary lesions. On the other hand, that of FAMT was 66.7%. FAMT-PET was a more accurate modality than FDG-PET for CR judgment following CRT in esophageal cancer. These data were attributed to a low accumulation of FAMT in inflammatory lesions compared with FDG. Furthermore, the most important result is a 100% diagnostic rate of FAMT-PET for no residual lymph node metastasis following CRT. CR judgment is very important following CRT when choosing a treatment strategy for esophageal cancer. If broad lymph node metastases remained, additional chemotherapy was chosen. Local uptake surrounding primary tumors in definitive CRT cases was higher than that of neoadjuvant CRT cases, because definitive CRT has high-dose radiation and chemotherapy compared with neoadjuvant CRT. Therefore, definitive CRT cases tend to have more radiation esophagitis and reactive mediastinal lymphadenopathy compared with neoadjuvant CRT cases. Our previous study demonstrated that SUV of FDG-PET prior to CRT was an independent predictor for clinical CR in esophageal cancer.[8] SUV of FDG-PET following CRT, however, did not show any predictive usefulness of clinical CR. On the other hand, FAMT-PET following CRT was useful to predict clinical CR in esophageal cancer.

An important limitation of the present study is that it included a small number of patients. Further clinical research with a higher number of patients is

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required to confirm the results and demonstrate reliability.

We hypothesize that SUV of FDG following CRT will gradually decrease according to the passage of time if the esophageal cancer is CR, and additional later evaluation of residual tumor will increase the rate of accurate clinical CR judgment. It is highly likely that radiation esophagitis and reactive mediastinal lymphadenopathy by FDG and wall thickness by CT will remain 1 month following CRT. Therefore, there is a limit to judging clinical CR by CT or FDG-PET following CRT. As a result, additional later evaluation by CT or FDG-PET will detect tumor progression if residual tumor existed, and a prompt start to treatment will be required. Based on the above understanding, FAMT-PET is the most useful modality at present.

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