Efficacy of PET-CT in the Diagnosis and Treatment of Recurrence After Esophageal Cancer Surgery

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Abstract. *Aim* The present study aimed to retrospectively investigate the utility of positron-emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (PET-CT) in regular follow-ups after esophageal cancer surgery. *Patients and Methods:* Clinical outcomes were retrospectively analyzed for 61 patients who were diagnosed with postoperative recurrence using PET-CT. *Results:* A univariate analysis revealed that single recurrence, a low cytokeratin 19 fragment (CYFRA) value, chemoradiotherapy against recurrence, and recurrence over 6 months after surgery were significant prognostic factors. A low CYFRA level and single recurrence tended to be good prognostic factors in the multivariate analysis. The prognosis of cases with single recurrent tumor of size less than 10 mm was significantly better than those with tumors of 10 mm or more. PET-CT revealed small recurrent tumors, and contributed to the early detection of recurrence outside the body trunk. *Conclusion:* PET-CT contributes to the detection of single small recurrent tumors and those outside the body trunk. This follow-up method using PET-CT should be considered for patients after esophageal cancer surgery.

Esophageal cancer (EC) is the eighth most common cancer worldwide, with an estimated 456,000 new cases in 2012 (3.2% of all cases), and the sixth most common cause of death from cancer, with an estimated 400,000 deaths (4.9% of all deaths)

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(1). Although several diagnostic modalities and multimodal therapies have been developed in recent years, the prognosis of patients with EC remains poor even when curative surgery is performed. Postoperative recurrence occurs in 78% of patients who undergo curative surgery for EC (2, 3). Recurrence of EC is regarded as a grave prognostic sign after curative surgery, with most patients dying due to the progression of their cancer. However, a few patients with postoperative recurrence have achieved long-term survival (4, 5). The development of more effective therapies or examinations is presumed to have improved the clinical outcomes of patients with recurrent EC. In order to achieve further improvements in the prognosis of these patients, the characteristics of recurrent cases that survive long-term, and prognostic factors for recurrent EC need to be elucidated in more detail.

Positron-emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose, an analog of glucose, integrated with computed tomography (PET-CT) is a functional imaging technique based on increased glucose uptake and glycolysis by cancer cells. In Japan, EC was approved as an indication for the use of PET-CT under health insurance coverage in April 2006. PET-CT is now widely used and provides a sensitive and specific examination for the staging or diagnosis of recurrent lesions in various types of cancer (6-8). Furthermore, a previous study showed that PET-CT was useful for the early detection of recurrence after esophagostomy, and contributed to a good prognosis through early detection of single recurrent tumors (5). Although the utility of PET-CT in EC has been reported, an appropriate method for applying PET-CT to follow-up after curative surgery for EC has not yet been established. In order to provide EC patients the best medical care, it is necessary to clarify the utility of PET-CT in postoperative follow-up.

PET-CT was implemented at our Institution in March 2007. We have been conducting imaging observations for regular follow-up of patients who underwent curative surgery for EC in our Division using PET-CT since January 2008. The present study aimed to retrospectively investigate the

utility of PET-CT in regular follow-up of patients after curative surgery for EC.

Patients and Methods

Patients. Between January 2008 and December 2014, 235 patients underwent curative surgery for squamous cell carcinoma of the esophagus at the Division of Digestive Surgery of Kyoto Prefectural University of Medicine. Patients who underwent preoperative therapies, *e.g.* neoadjuvant chemoradiotherapy (CRT) or preoperative definitive CRT, which are not standard therapies by the Japanese EC guidelines (9), or whose tumor invaded surrounding tissues (pT4) were excluded. Recurrence was detected in 63 out of the 198 remaining patients. Follow-up was not possible in two out of the 63 patients, and thus, they were excluded. We retrospectively analyzed data for the remaining 61 patients. The clinical and pathological classifications of EC were diagnosed based on the Japan Classification System by physicians and the pathologist at our hospital (10).

Surgery. Transthoracic esophagectomy was performed on 36 out of 61 patients (59.0%) whose data were analyzed in the present study. Video-assisted thoracic esophagostomy was performed on 14 of these patients (22.9%). Eleven patients (18.0%) underwent esophagectomy with a laparoscopic transhiatal approach. All patients underwent two-field (thoracic and abdominal) or three-field (cervical, thoracic, and abdominal) lymphadenectomy.

PET-CT. ¹⁸F-FDG was purchased from Nihon Medi-Physics (Tokyo, Japan). Patients were instructed to fast for at least 4 h before PET-CT imaging. Whole-body PET-CT images were acquired 1 h after the intravenous injection of 185 MBq of ¹⁸F-FDG, and emission scans were obtained from the head to thigh for 120 s/bed per field of view with the use of an integrated PET/CT system with 16 slice CT (Aquiduo, Toshiba, Tokyo, Japan). Normal CT scans were performed with the use of 64 or 128 helical CT. The diameters of tumors were evaluated based on RECIST 1.1 (11).

Postoperative follow-up. An imaging examination for the postoperative follow-up was performed using whole-body PET-CT, performed every 4-6 months after curative surgery depending on the pathological findings of the resected specimens. The tumor markers squamous cell carcinoma antigen (SCC) and cytokeratin 19 fragment (CYFRA) were assayed every 3 months after surgery. Upper gastrointestinal endoscopy was performed at least once every year after surgery. Seven patients were diagnosed with postoperative recurrence based on CT findings; six of these patients intentionally underwent CT for a detailed examination of symptoms that indicated recurrence, *e.g.* swelling of the neck lymph nodes detected during a physical examination, the remaining patient underwent CT for a detailed examination of postoperative complications and recurrence was incidentally detected.

Response evaluation of treatments against recurrence. A response evaluation of treatments against recurrence was also performed 3 months after the end of treatment using PET-CT. Although treatment responses were basically assessed by measuring tumor diameters in plain-CT images based on RECIST 1.1, the disappearance of the abnormal uptake of FDG in recurrent regions was added to the requirements for a complete response (CR). Patients who achieved CR were regularly followed-up postoperatively using PET-CT.

Statistical analysis. Survival curves were estimated by the Kaplan-Meier method, and differences in survival were examined using the log-rank test. Cox's proportional hazard model was used to identify independent prognostic factors. *p*-Values of less than 0.05 were regarded as significant.

Results

Patient characteristics. The characteristics of 61 patients with squamous cell carcinoma of the esophagus are summarized in Table I. The median follow-up time was 705 days (range=164-2,759 days). Fifty-five patients received neoadjuvant chemotherapy with 5-fluorouracil and cisplatin. The pathological stages of resected specimens were T2/T3 in the majority of cases (47/61, 77.0%). Lymph node metastasis was detected in 45 patients (73.7%).

Clinical findings of eligible patients at and after recurrence. Table II shows clinical findings at the detection of initial recurrence and treatment outcomes after recurrence. Recurrence was detected in 31 patients (50.8%) less than 6 months after surgery. SCC values were higher than the standard value in 30 patients, while those of CYFRA were higher in 12 patients at recurrence. Recurrence was single in 32 patients (52.4%) at initial recurrence and located in a lymph node in most of these cases (26/32 patients, 81.3%). The remaining patients had multiple recurrent tumors at the detection of initial recurrence. The initial treatment against recurrent tumors was chemotherapy with/without radiotherapy in most patients (53/61 patients 86.9%). CR was achieved by 17 patients (27.8%). The mean survival time after recurrence was 515.7 days (range=71-1925 days).

Prognostic factors in recurrent case. Table III shows the results of the univariate and multivariate analyses of prognostic factors in recurrent cases. Survival after the detection of initial recurrence (SAR) was compared according to different variables. In the univariate analysis, no significant differences were observed in differentiation, tumor size, pathological invasion depth, lymph node metastasis, lymphatic invasion, venous invasion, the value of SCC at the detection of initial recurrence, or CR to the initial treatment. On the other hand, the 2-year SAR of cases with single recurrence was significantly better than those with multiple recurrent tumors (49.5% *vs.* 19.0%, *p*=0.015). The SAR of patients with high CYFRA values was significantly worse than that of cases with low CYFRA values (8.3% *vs.* 45.3%, *p*<0.001). The SAR of patients who received CRT for recurrent tumors was significantly better than patients who received other treatments (49.9 *vs.* 27.6%, *p*=0.028), and the SAR of patients who developed recurrence less than 6 months after surgery was significantly worse than those developing recurrence 6 months or more after surgery (22.1% *vs.* 57.2%, *p*=0.032). A multivariable analysis was

Table I. Background of eligible patients with postoperative recurrence of esophageal cancer (n=61).

Variable	Value
Age, years	
Mean±SD (range)	65.4±7.9 (48-83)
Gender, n (%)	
Male	47 (77.0)
Female	14 (22.9%)
Location of primary tumor, n (%)	
Ce	1 (1.6%)
Ut	4 (6.6%)
Mt	34 (55.7%)
Lt	21 (34.4%)
Ae	1 (1.6%)
Tumor differentiation, n (%)	
Well	11 (18.0%)
Moderate	35 (57.3%)
Poor	15 (24.6%)
Pathological invasion depth, n (%)	
T1	14 (22.9%)
T2	13 (21.3%)
T3	34 (55.7%)
Pathological lymph node metastasis, n (%)	
Positive	45 (73.7%)
Lymphatic invasion, n (%)	
Positive	33 (54.1%)
Venous invasion, n (%)	
Positive	24 (39.3%)
Neoadjuvant therapy, n (%)	
FP	55 (9.8%)
None	6 (9.1)
Pathological response to chemotherapy, n (%)	
Grade 0	2 (3.2%)
Grade 1a	31 (50.8%)
Grade 1b	9 (14.7%)
Grade 2	2 (3.2%)

Ce: Cervical esophagus; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; Ae: abdominal esophagus; FP: 5-fluorouracil and cisplatin; SD: standard deviation.

performed on these significant variables, namely multiplicity of recurrence, CYFRA level, and the duration from surgery to recurrence, using Cox's proportional hazard model. Although a significant variable in univariate analysis, treatment of recurrence was excluded from this multivariate analysis because it strongly confounded multiplicity of recurrence. As a result, it was not possible to detect significant independent prognostic factors. However, single recurrence and low CYFRA values appeared to be good prognostic factors ($p=0.065$ and $p=0.070$, respectively).

Evaluation of cases with single recurrence with small metastasis. Our present results on prognostic factors for recurrent cases showed that the prognosis of those with single recurrent tumor appeared to be good. A previous study

Table II. Clinical findings of eligible patients at and after recurrence of esophageal cancer (n=61).

Variable	Value
SCC at recurrence, n (%)	
<1.5 ng/ml	31 (50.8%)
≥1.5 ng/ml	30 (49.1%)
CYFRA at recurrence, n (%)	
<3.5 ng/ml	49 (80.3%)
≥3.5 ng/ml	12 (19.6%)
Location of recurrence, n (%)	
Single	
Local	2 (3.2%)
Lymph node	26 (42.6%)
Distant metastasis	
Liver	1 (1.6%)
Brain	1 (1.6%)
Other	2 (3.2%)
Multiple	29 (47.5%)
Tumor diameter (n=80), mm	
Mean±SD (range)	14.4±9.8 (3-63)
Treatment for recurrence, n (%)	
CRT	29 (47.5%)
RT	5 (8.1%)
Chemotherapy	24 (39.3%)
Surgery	1 (1.6%)
Other	2 (3.2%)
Complete response to treatment for recurrence, n (%)	17 (27.8%)
Duration from surgery to recurrence, days	
Mean±SD (range)	349.1±362.4 (52-1791)
Survival after recurrence, days	
Mean±SD (range)	515.7±406.3 (71-1925)

SCC: Squamous cell carcinoma antigen; CYFRA: cytokeratin 19 fragment; CRT: chemoradiotherapy; RT: radiotherapy; SD: standard deviation.

reported that small lymph node metastases are detectable using PET-CT (12). Based on our results and these findings, we investigated whether PET-CT contributes to improvements in the prognoses of patients with recurrence after curative surgery through the early detection of single small recurrent tumors. We analyzed 26 cases of single recurrence diagnosed using PET-CT. Table IV shows the characteristics of these cases. Recurrent regions were a lymph node in the majority of cases (20/26, 70.6%). PET-CT had the ability to reveal small tumors, the size of which was less than 10 mm, at a high rate (in 11 patients, 42.3%). Figure 1A and B show plain CT and PET-CT findings for a patient with a small metastasis. Although CT was unable to detect metastatic tumors, metabolic information on the uptake of FDG provided by PET-CT revealed these tumors. Sixteen patients received CRT, while the remaining patients underwent radiotherapy, chemotherapy, or gamma knife therapy. We divided these patients based on tumor size into

Table III. Univariate and multivariate analyses of prognostic factors for patients with recurrent esophageal cancer.

Variable	n	Univariate		Multivariate		
		SAR (%)	p-Value	HR	95% CI	p-Value
Tumor differentiation	Well/moderate	46	38.0	0.961		
	Poor	15	35.7			
Tumor size	≥50 mm	19	33.3	0.834		
	<50 mm	41	39.3			
Pathological invasion depth	T1/T2	27	38.3	0.783		
	T3	34	36.4			
Pathological lymph node metastasis	Negative	16	45.1	0.153		
	Positive	45	32.4			
Lymphatic invasion	Negative	28	36.0	0.957		
	Positive	33	37.6			
Venous invasion	Negative	37	46.1	0.330		
	Positive	24	23.1			
Multiplicity of recurrence	Single	37	49.5	0.015	0.534 1.00	0.268-1.042 0.065
	Multiple	24	19.0			
SCC	Low (<1.5 ng/ml)	31	35.1	0.792		
	High (≥1.5 ng/ml)	30	38.5			
CYFRA	Low (<3.5 ng/ml)	49	45.3	<0.001	0.476 1.00	0.222-1.066 0.070
	High (≥3.5 ng/ml)	12	8.3			
Treatment for recurrence	CRT	29	49.9	0.028		
	Other	32	27.6			
Response to treatment for recurrence	CR	17	49.4	0.164		
	Non-CR	44	32.4			
Duration from surgery to recurrence	≥6 Months	30	57.2	0.032	0.797 1.00	0.364-1.608 0.539
	<6 Months	31	22.1			

SAR: Two-year survival after recurrence; SCC: squamous cell carcinoma antigen; CYFRA: cytokeratin 19 fragment; CRT: chemoradiotherapy; CR: complete response.

groups with tumor of less than 10 mm diameter and 10 mm or more, and evaluated survival curves (Figure 2). The results obtained showed that the prognoses of the 11 cases small tumors were significantly better than the 15 non-cases with larger tumors ($p=0.045$).

Efficacy of PET-CT in the detection of recurrent tumors outside the body trunk. Three patients with initial recurrent tumors outside the body trunk, two with brain metastasis and one with elbow joint metastasis, were diagnosed using PET-CT. Figure 1C-F shows plain CT and PET-CT results in 2 out of these patients. Although one patient with brain metastasis and the patient with metastasis of the elbow joint exhibited some symptoms indicating the existence of these recurrent tumors, the other patient without any symptoms was incidentally diagnosed with brain metastasis. This patient was a 52-year-old woman who underwent curative subtotal esophagectomy with lymphadenectomy after neoadjuvant chemotherapy. Fifteen months after surgery, brain metastasis was detected using PET-CT (Figure 1E and F). Gamma knife therapy (total 60 Gy) was performed on this tumor, and CR was achieved. The patient is currently alive 54 months after surgery. Therefore, PET-CT may

Table IV. Clinical findings of single recurrent cases ($n=26$) with small tumors.

Variable	Value
Recurrence, n (%)	
Local	2 (7.6%)
Lymph node metastasis	20 (76.9%)
Distant metastasis	4 (15.3%)
Tumor size, mm	
Mean±SD (range)	14.8±13.5 (4.9-63.0)
≥10	15 (57.6%)
<10	11 (42.3%)
Treatment for recurrent lesions, n (%)	
CRT	16 (61.5%)
RT	4 (15.3%)
Chemotherapy	4 (15.3%)
Gamma knife	1 (3.8%)
Complete response, n (%)	8 (30.7%)

CRT: Chemoradiotherapy; RT: radiotherapy; SD: standard deviation.

contribute to the early detection of recurrent tumors outside the body trunk and lead to long-term survival after recurrence.

Figure 1. Positron-emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (PET-CT) findings of three patients with postoperative recurrence of esophageal cancer. A, B: This patient was diagnosed with postoperative recurrence using PET-CT 26 months after surgery. Although the metastasis was not detectable by plain CT, it was identified using PET-CT. C, D: This patient was diagnosed with elbow joint metastasis using PET-CT 59 months after surgery. A whole-body scan using PET-CT contributed to the detection of the recurrent tumor outside the body trunk. E, F: This patient, who did not have any symptoms at that time, was incidentally diagnosed with brain metastasis using PET-CT 15 months after surgery. Gamma knife therapy was performed on this tumor, and complete response was achieved. This patient is still alive 54 months after surgery.

Discussion

The development of effective multimodal therapies for EC has recently improved the prognosis of patients with EC. For example, neoadjuvant chemotherapy before curative surgery has been shown to improve the prognosis of patients with EC (13), and the clinical outcomes of definitive CRT are now similar to those of curative surgery (14). Furthermore, a new chemotherapeutic regimen involving 5-fluorouracil, cisplatin and docetaxel, and a new method of radiotherapy called intensity-modulated radiotherapy, are receiving increasing attention as more effective therapies against EC (15, 16). These advances in therapies directed at EC also improve the prognosis of patients with postoperative recurrence of EC. A previous study reported that salvage

radiotherapy or CRT for locoregional recurrence after surgery for EC was safe and effective (17). The effectiveness of multimodal therapies involving chemotherapy, salvage surgery, and salvage CRT against recurrent tumors has already been demonstrated (18, 19). Concurrent three-dimensional conformal radiotherapy, which is similar to intensity-modulated radiotherapy, and chemotherapy may increase local tumor control, reduce the rate of distant metastasis, and increase long-term survival rates (20, 21). These findings suggest that the postoperative recurrence of EC is no longer as incurable as it once was. Therefore, recurrent tumors need to be detected as soon as possible and treated effectively.

Previous studies investigated the utility of FDG-PET in EC (22). PET-CT is widely performed as an imaging

Figure 2. Long-term outcomes of patients with single recurrent tumors according to tumor diameter.

examination for the staging and detection of recurrent tumors. However, its utility in postoperative follow-up has not yet been established. The diagnostic superiority of metabolism-based methods, such as FDG-PET, may be most pronounced under conditions in which the non-specific sequelae of surgery, radiotherapy, or chemotherapy render conventional, anatomy-based modalities less accurate. On the other hand, CT has been widely used as an imaging examination in regular follow-up of patients after curative resection of EC. However, CT often has difficulties in detecting a postoperative recurrent lesion because it identifies abnormal lesions based on normal anatomy. For example, it is often challenging to establish whether lymph nodes less than 10 mm in size are metastatic using CT. In contrast, PET-CT often identifies their status because it provides metabolic information. In a previous study, PET-CT was shown to have the ability to detect small lymph node metastases with a minimum diameter of 0.9 mm (12). Moreover, PET and CT are regarded as reliable imaging modalities with high sensitivity and moderate specificity for detecting recurrent EC after treatments with curative intent (23). In the systematic review and meta-analysis by Goense *et al.*, the sensitivity of PET-CT ranged between 89% and 100% and the specificity between 55% and 94% for the detection of recurrent EC (23). On the other hand, previous studies reported that the sensitivity of contrast-enhanced CT

ranged between 65% and 89% and specificity between 79% and 91.2% for the detection of recurrent EC (8, 24). Although the lower specificity of PET-CT is a limitation for patients with EC, its higher sensitivity may contribute to the early start of treatments for recurrent tumors, which may, in turn, improve the prognosis of patients with recurrent EC. Therefore, PET-CT needs to be considered for use in the postoperative follow-up of patients with EC.

The evaluation of responses to treatments for recurrent tumors has also been performed using PET-CT at our Division since January 2008. Although it remains controversial whether PET-CT is appropriate as an imaging modality for evaluating responses to cancer treatments, its usefulness was previously demonstrated. It is impossible to evaluate viable tumor tissues using the other imaging modalities, CT and magnetic resonance imaging, whereas PET-CT has the ability to evaluate cancer function on the basis of information on glucose metabolism. Comparisons between cancer metabolism revealed by PET-CT before and after treatments enables evaluation of responses to treatments (6, 24, 25). Previous studies reported that decreases of standardized uptake value in tumors evaluated by PET-CT after preoperative chemoradiotherapy were associated with histopathological tumor responses (26, 27). Moreover, PET-CT performed after CRT predicted the prognoses of patients with primary or postoperative recurrent EC (28, 29). These

findings suggest that PET-CT is as effective as other imaging modalities in the evaluation of responses to cancer treatments.

Although PET-CT needs to be used in the follow-up of postoperative EC as described above, the frequency at which it needs to be performed or whether CT needs to be used concurrently has not yet been established. To the best of our knowledge, this is the first study to investigate the clinical outcomes of patients with EC, followed-up using PET-CT only. We consider PET-CT to have two advantages over CT in the postoperative follow-up of patients with EC. The first advantage is that PET-CT has the ability to reveal whether small nodes are metastatic through the uptake of FDG, which indicates cancer metabolism. The second advantage is that PET-CT routinely scans the whole body. In the present study, PET-CT revealed small tumors, the diameters of which were less than 10 mm, as well as recurrent tumors outside the body trunk, which are not detectable by CT. The patient with brain metastasis, which was incidentally diagnosed using regular follow-up PET-CT, has already survived for more than 3 years since this recurrence. Furthermore, patients with single recurrent tumors of less than 10 mm in size survived for a significantly longer time than those with tumors that were 10 mm or more in size. We consider that these results support the utility of this modality. A limitation of our study is the relatively small sample size, which may limit the statistical power. Furthermore, it was not possible to perform comparisons of clinical outcomes between follow-up by CT and that by PET-CT. More patients will be accumulated and a prospective study planned.

In conclusion, we analyzed the clinical outcomes of patients who developed postoperative recurrence and were followed-up using PET-CT. PET-CT may contribute to the early detection of small recurrent tumors and searches outside the body trunk. The method of this follow-up needs to be considered for patients after EC surgery.

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