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ORIGINAL ARTICLE

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Development and validation of an [^{18}F]FDG-PET/CT radiomic model for predicting progression-free survival for patients with stage II – III thoracic esophageal squamous cell carcinoma who are treated with definitive chemoradiotherapy

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ABSTRACT

Background: Radiomics is a method for extracting a large amount of information from images and used to predict treatment outcomes, side effects and diagnosis. In this study, we developed and validated a radiomic model of [^{18}F]FDG-PET/CT for predicting progression-free survival (PFS) of definitive chemoradiotherapy (dCRT) for patients with esophageal cancer.

Material and Methods: Patients with stage II – III esophageal cancer who underwent [^{18}F]FDG-PET/CT within 45 days before dCRT between 2005 and 2017 were included. Patients were randomly assigned to a training set (85 patients) and a validation set (45 patients). Radiomic parameters inside the area of standard uptake value ≥ 3 were calculated. The open-source software 3D slicer and Pyradiomics were used for segmentation and calculating radiomic parameters, respectively. Eight hundred sixty radiomic parameters and general information were investigated.

Material and Methods: In the training set, a radiomic model for PFS was made from the LASSO Cox regression model and Rad-score was calculated. In the validation set, the model was applied to Kaplan-Meier curves. The median value of Rad-score in the training set was used as a cutoff value in the validation set. JMP was used for statistical analysis. RStudio was used for the LASSO Cox regression model. $p < 0.05$ was defined as significant.

Results: The median follow-up periods were 21.9 months for all patients and 63.4 months for survivors. The 5-year PFS rate was 24.0%. In the training set, the LASSO Cox regression model selects 6 parameters and made a model. The low Rad-score group had significantly better PFS than that the high Rad-score group ($p = 0.019$). In the validation set, the low Rad-score group had significantly better PFS than that the high Rad-score group ($p = 0.040$).

Conclusions: The [^{18}F]FDG-PET/CT radiomic model could predict PFS for patients with esophageal cancer who received dCRT.

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PET; radiomics; esophageal cancer; radiation therapy; LASSO cox regression model

Backgrounds

Esophageal cancer occurs in more than 450,000 people worldwide every year [1]. Neoadjuvant therapy followed by surgery improves overall survival (OS) for esophageal cancer patients compared with the outcome of surgery alone [2,3]. However, esophagectomy is associated with a high rate of perioperative mortality. It has been reported that 3%−9.8% of patients died within 30 days after esophagectomy [2,4]. Definitive chemoradiotherapy (dCRT) is a curative treatment without surgery [5]. However, the results of dCRT have not been satisfactory and there is a high rate of local recurrence [6]. If the treatment results can be predicted beforehand, patients who have a high risk of recurrence could receive more powerful treatment such as another chemotherapy regimen or a higher dose of radiotherapy. For the realization of tailor-made medicine, research on prognosis is needed.

2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET)/x-ray computed tomography (CT) is a widely accepted method for staging esophageal cancer [7]. Several parameters including SUV_{max}, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been reported [8–10]. However, it is controversial whether such [^{18}F]FDG-PET/CT parameters are predictors of outcomes.

Recently, research of radiomics has attracted attention and the number of radiomic studies has been increasing [11–13]. Radiomics is a method for extracting a large amount of mathematical information from images and there are several types of information based on shape-based features, first-order statistics and texture features [14]. Research has

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been conducted on texture analysis in the field of technology [15]. Tixier et al. reported that texture features of [^{18}F]FDG-PET/CT distinguished good responders and non-responders for esophageal cancer treated with CRT [16]. Nakajo et al. performed texture analysis of [^{18}F]FDG-PET/CT for patients with esophageal cancer [17]. Two texture features became significant predictors of OS and progression-free survival (PFS) in univariate analysis, but no texture feature became a significant predictor in multivariate analysis. Beukinga et al. compared 12 models made from clinical features and radiomic parameters and predicted pathological complete response (pCR) for patients with esophageal cancer who were treated with chemoradiotherapy followed by surgery [11]. Du et al. used a nomogram made from radiomic features extracted from cone-beam CT to predict radiation pneumonitis [12]. Luo et al. showed that a model made from CT-based radiomic features predicted local progression-free survival for patients with esophageal cancer who were treated with dCRT [13]. Radiomic studies have been performed for patients with esophageal cancer and there have been a few PET radiomic studies for patients with esophageal cancer who are treated with definitive chemoradiotherapy. Further research is needed because there have been few studies on texture analysis that have focuses on esophageal cancer.

The aim of this study was to develop and validate a radiomic nomogram of ^{18}F-FDG PET/CT for predicting PFS for patients with esophageal cancer who were treated with definitive chemoradiotherapy.

Material and methods

Patients

Our institutional review board approved this retrospective study (2021-1-558). Patients with stage II or III thoracic esophageal SCC who received dCRT in our institution between January 2005 and March 2017 were reviewed from a clinical database. The patients were staged according to the International Union against Cancer TNM classification of malignant tumors 7th edition. To minimize the change in SUV caused by a difference in PET timing, only patients who underwent [^{18}F]FDG-PET/CT within 45 days before the first day of radiation were included. Patients were randomly divided into two groups at a 2:1 population. There were 130 patients and 85 patients were assigned to a training set and 45 patients were assigned to a validation set (Table 1).

Treatments

The initial radiation field covered the primary tumor and lymph node area including celiac, mediastinal and supraclavicular lymph nodes, but the supraclavicular area was omitted in 3 patients. Forty-five patients received 40 Gy per 20 fractions and one patient received 39.6 Gy per 22 fractions to the field. The boost radiation field covered the primary and lymph node lesions and received 20–30 Gy per 10–15 fractions. All patients received concurrent platinum-based chemotherapy using cisplatin or nedaplatin with fluorouracil.

[^{18}F]FDG-PET/CT acquisition

[^{18}F]FDG-PET/CT imaging was performed with two scanners (Biograph Duo LSO and Biograph 40; Siemens Medical Solution, Erlangen, Germany). The median period between [^{18}F]FDG-PET/CT and the first day of radiation was 15 days (range, 1–45 days) in all patients. All patients fasted for 4 or more hours, and a blood glucose level $<$ 200 mg/dL was required before [^{18}F]FDG injection. Patients were injected with 3.7 MBq [^{18}F]FDG/kg. Scanning began 60 min after [^{18}F]FDG injection. A spiral CT scan was performed, followed by a collection of PET emission images from the distal femur to the top of the skull. The PET scanning time was 2 min per bed position with increments of 16.2 cm (3-dimensional mode); all patients were scanned in 8-bed positions. Our institution conforms to two sets of Japanese guidelines for the data acquisition protocol of oncology fluoro-D-glucose-positron emission tomography (FDG-PET)/computed tomography (CT) scans that established by the joint task force of the Japanese Society of Nuclear Medicine Technology and the Japanese Society of Nuclear Medicine. These guidelines aim to standardize PET image quality among facilities and different PET/CT scanner models. The details of the protocol for FDG-PET/CT image acquisition including reconstruction methods are shown in Supplementary 1. Moreover, based on the prior phantom experiment, the difference in the SUV of the same spherical target that was 2 cm or larger in diameter between the two PET/CT scanners was within 10%.

Image analysis

It had been reported that PET parameters and radiomic features are influenced by delineation [18]. Therefore, to reduce the potential bias of delineation, an automatic PET segmentation method was used. The area of FDG standard uptake value $\geq$ 3 was automatically segmented and radiomic parameters inside the area were calculated. The open-source software 3D slicer v.4.10.2 was used for segmentation and Pyradiomics v.2.2.0 was used for calculating radiomic parameters [19,20]. Pyradiomics could calculate 851 radiomic parameters as default parameters and we added 9 TLG of each processing method. The details of radiomic parameters are shown in Supplementary 2 and on a Pyradiomics website [20]. Also, general information (age, gender, T stage, N stage, performance status, blood albumin level, geriatric nutritional risk index, tumor location, total radiation dose and the number of concurrent chemotherapy cycles) was investigated.

Follow-up

The primary endpoint was PFS. PFS was calculated from the first day of radiotherapy. Gastrointestinal endoscopy, CT and medical interviews were performed 2–6 weeks after the last day of dCRT. Thereafter, gastrointestinal endoscopy, CT and medical interviews were performed every 3–6 months. PFS

Table 1. Patients' characteristics.

Characteristics	Training set ($n = 85$)	Validation set ($n = 45$)	p value
Age (years)			
Median (range)	67 years (41–79 years)	68 years (49–79 years)	0.681*
Gender			
Female	10 (11.8 %)	10 (22.2 %)	0.123
Male	75 (88.2 %)	35 (77.8 %)	
T stage			0.835*
1	7 (8.2 %)	6 (13.3 %)	
2	8 (9.4 %)	2 (4.4 %)	
3	52 (61.2 %)	28 (62.2 %)	
4	18 (21.2 %)	9 (20.0 %)	
N stage			
N+	66 (77.6 %)	38 (84.4 %)	0.349
N0	19 (22.4 %)	7 (15.6 %)	
PS			0.492*
0	24 (28.2 %)	11 (24.4 %)	
1	58 (68.2 %)	31 (68.9 %)	
≥ 2	3 (3.5 %)	3 (6.6 %)	
Blood albumin level			
Median (range)	3.7 g/dL (2.7−4.5 g/dL)	3.7 g/dL (2.3−4.8 g/dL)	0.691*
GNRI			
Median (range)	96.1 (65.1−110.6)	97.2 (75.1−122.7)	0.386*
Tumor location			0.118*
Ut	12 (14.1 %)	7 (15.6 %)	
Mt	40 (47.1 %)	28 (62.2 %)	
Lt	33 (38.8 %)	10 (22.2 %)	
Total radiation dose			
Median (range)	60 Gy (30–70 Gy)	60 Gy (56–70 Gy)	0.662*
Concurrent chemotherapy cycles			
2 cycles	71 (83.5 %)	39 (86.7 %)	0.634
1 cycle	14 (16.5 %)	6 (13.3 %)	

PS: performance status; GNRI: geriatric nutritional risk index; Ut: upper thoracic; Mt: middle thoracic; Lt: lower thoracic.
*p value was calculated from the Mann-Whitney U test. The other p value was calculated from the x^2 test.

was defined as the duration until the day on which local recurrence, distant metastasis or death occurred.

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.0.

Statistical analysis

Statistical analysis was performed by using JMP pro v.15.0.0 (SAS Institute). PFS was calculated using the Kaplan-Meier method. In the training set, general information and radiomic features were investigated by Cox's proportional hazards model for univariate analyses to predict PFS. General information and radiomic features with $p < 0.05$ in univariate analyses were included in the least absolute shrinkage and selection operator (LASSO) Cox regression model. Calculation using the LASSO Cox regression model was performed by Rstudio ver 2021.09.0 (RStudio, PBC). The LASSO Cox regression model selected features and made a rad model. In the validation set, the rad model was tested by the Kaplan-Meier method. A cutoff value of the rad model was the median value of Rad-score of the training set.

$p < 0.05$ was defined as significant.

Quality assessment of radiomics research

In order to evaluate the quality of radiomics research, Radiomics Quality Score (RQS) and the Transparent Reporting of a multivariable prediction model for the Individual Prognosis Or Diagnosis (TRIPOD) initiative were scored [21–24].

Results

Patients' outcomes

The characteristics of patients in both cohorts are summarized in Table 1. There was no significant difference between the patients' characteristics in the training and test sets. In the training set, the median follow-up periods were 21.9 (range, 4.5–195.1 months) months for all patients and 63.4 (range, 5.4–195.1 months) months for survivors. The 3-year and 5-year PFS rates were 29.5% (95% confidence interval [CI]: 20.6–40.2) and 24.0% (95% CI: 15.8–34.5), respectively. Fifty-two patients died, 54 patients had local recurrence and 25 patients had distant metastasis. There were 2 patients who were lost to follow-up within 1 year.

In the test set, the median follow-up periods were 30.0 (range, 3.1–179.5 months) months for all patients and 74.9 (range, 3.1–179.5 months) months for survivors. The 3-year and 5-year PFS rates were 44.9% (95% CI: 30.9–59.7) and 41.7% (95% CI: 27.8–57.0), respectively. Twenty-four patients died, 22 patients had local recurrence and 16 patients had distant metastasis. There were 2 patients who were lost to follow-up within 1 year.

Univariate analyses and a radiomic model in the training set

The results of the univariate analysis in the training set are shown in Table 2 and Supplementary 2. T stage (hazard ratio [HR]: 1.76, 95% CI: 1.25−2.55, $p = 0.001$) and concurrent chemotherapy cycles (HR: 0.43, 95% CI: 0.24−0.82, $p = 0.012$)

were significant predictors for PFS. Two hundred thirty-six radiomic features were significant predictors for PFS in univariate analysis. The features with $p < 0.05$ in univariate analysis were included in the multivariate LASSO Cox regression model. The LASSO Cox regression model selected 6 factors and calculated coefficients. Factor 1 was T stage, factor 2 was large dependence high gray level emphasis of gray level dependence matrix (GLDM) with a wavelet-LHL filter, factor 3 was the complexity of neighboring gray-tone difference matrix (NGTDM) with a wavelet-LHH filter, factor 4 was small area high gray level emphasis of gray level size zone matrix (GLSZM) with a wavelet-HLH filter, factor 5 was large dependence high gray level emphasis of GLDM with a wavelet-HHL filter and factor 6 was size zone nonuniformity of GLSZM with a wavelet-HHL filter (Figure 1). Factors 2 – 6 were all texture features. From the results of the LASSO Cox regression model, Rad-score was calculated by the following formula: Rad-score = factor $1 \times 1.325784 \times 10^{-1}$ + factor $2 \times 8.532578 \times 10^{-6}$ + factor $3 \times 3.977719 \times 10^{-2}$ + factor $4 \times 9.331339 \times 10^{-3}$ + factor $5 \times 4.386995 \times 10^{-5}$ + factor $6 \times 3.107097 \times 10^{-3}$. The median value of Rad-score was 0.75068674. The log-rank test showed that PFS was significantly better in the low Rad-score group ($p = 0.019$, Figure 2).

Table 2. Univariate analysis for PFS in general parameters.

Variables	HR	95 % CI	*p* value
Age	1.01	0.99−1.05	0.322
Gender (Male vs Female)	0.72	0.30−1.48	0.397
Tumor location	0.86	0.61−1.23	0.398
T stage	1.76	1.25−2.55	0.001
N stage (N0 vs N+)	1.30	0.74−2.44	0.375
PS	1.25	0.78−2.01	0.349
Albumin	0.83	0.46−1.53	0.550
GNRI	0.99	0.97−1.02	0.492
Total radiation dose	1.01	0.96−1.06	0.854
Concurrent chemotherapy cycles (1 cycle vs 2 cycles)	0.43	0.24−0.82	0.012

PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; PS: Performance Status; GNRI: geriatric nutritional risk index.

Kaplan–Meier curve in the test set

In order to evaluate the radiomic model, a Kaplan-Meier curve was drawn in the test set. The median value of Rad-score in the training set was used as a cutoff value in the test set. The log-rank test showed that PFS was significantly better in the low Rad-score group in the test set ($p = 0.040$, Figure 3). On the other hand, T stage was not significantly associated with PFS ($p = 0.576$, Figure 3).

Quality assessment of radiomics research

RQS was 18 and the number of TRIPOD items was 23. The details of ROS and the TRIPOD items are shown in Supplementary 3 and Supplementary 4.

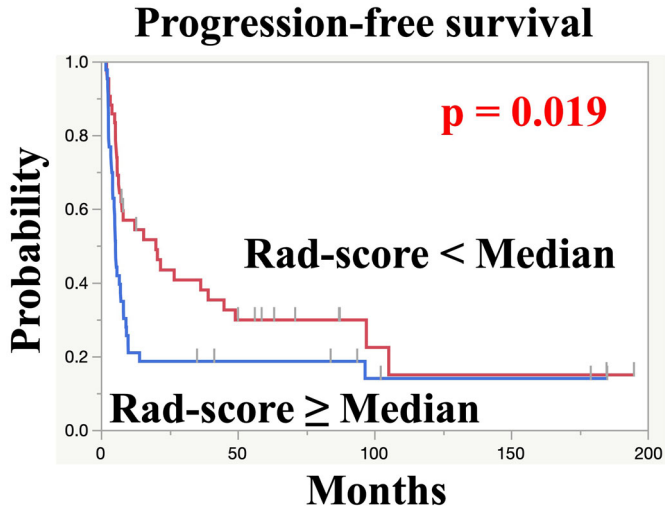

Figure 2. Results of the log-rank test for the Kaplan-Meier curve for Rad-score in the training set. The median value of Rad-score was 0.75068674. Progression-free survival was significantly better in the low Rad-score group.

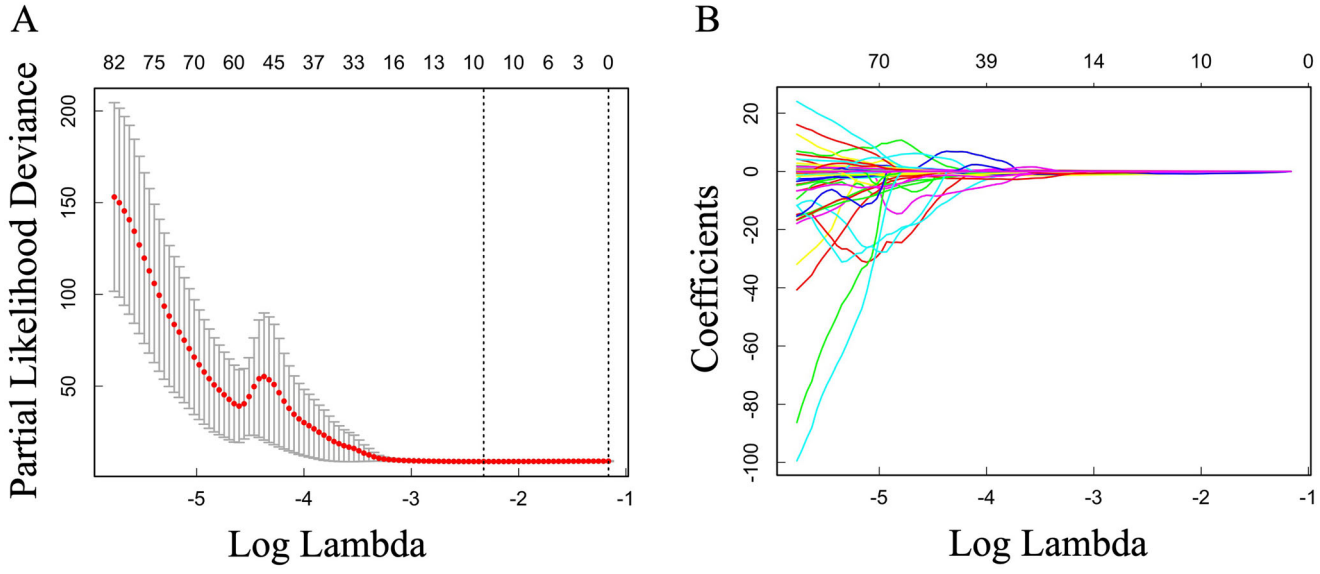

Figure 1. Radiomic feature selection using the LASSO Cox regression model. (A): Cross-validation by the LASSO Cox regression model with 10-fold cross-validation. The horizontal axis indicates log lambda and the vertical axis indicates partial likelihood deviance. (B): Coefficient profiles of radiomic features. The horizontal axis indicates log lambda and the vertical axis indicates coefficients.

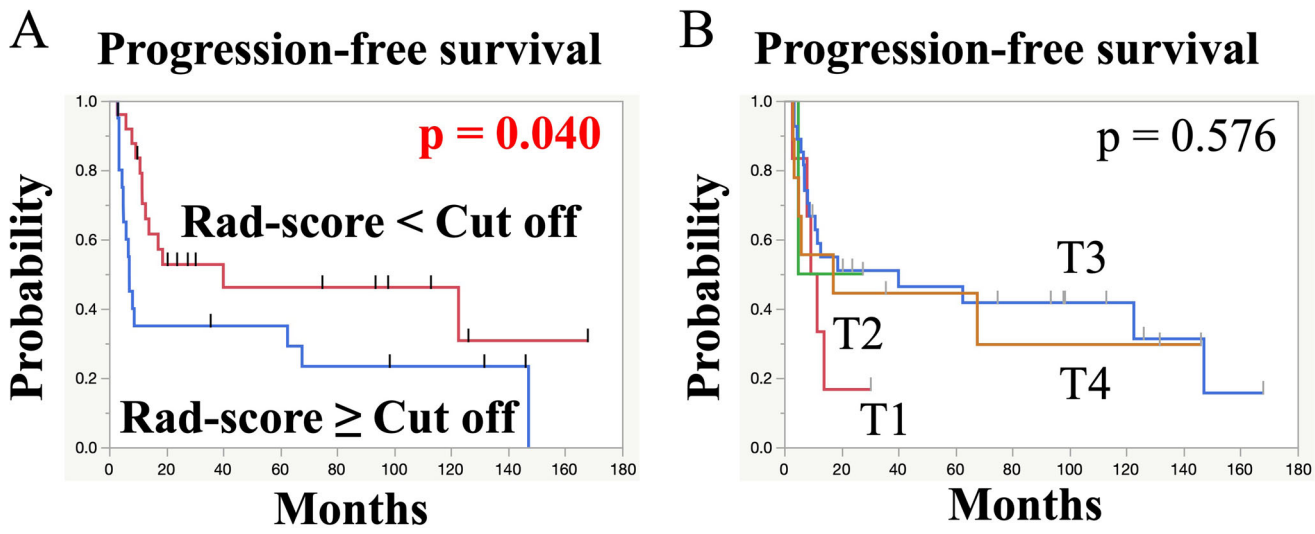

Figure 3. Results of the log-rank test for the Kaplan-Meier curve for Rad-score and T state in the test set. (A): The median value of Rad-score in the training set was used as cutoff value in the test set. Progression-free survival was significantly better in the low Rad-score group in the test set. (B): The log-rank test showed that there was no significant difference between T stage.

Discussion

The radiomic model that we made could predict PFS for patients with esophageal cancer who were treated with dCRT. If it is possible to predict outcomes of treatment beforehand, patients with a high risk of progress could receive tailor-made treatment such as another concurrent chemotherapy regimen or dose escalation of radiotherapy. Radiomics is a method for evaluating heterogeneity in images. Tumors include the area of necrosis, hypoxia and different densities. By evaluating such heterogeneities, the results of treatment could be predicted. To the best of our knowledge, this study is the first study showing that [^{18}F]FDG-PET/CT radiomics could predict PFS for patients with esophageal cancer who were treated with dCRT.

The number of radiomic studies has been increasing, but the number of radiomic studies for esophageal cancer is still small. Beukinga et al. showed that a model combining T stage and one [^{18}F]FDG-PET/CT radiomic feature named joint maximum was a good model for predicting pCR for patients with esophageal cancer who were treated with neoadjuvant chemoradiotherapy (nCRT) followed by surgery [11]. The difference between their study and our study was treatment methods and outcomes. The outcome of their study was pCR and their patients were treated with nCRT. The outcome of our study was PFS and patients were treated with dCRT. Moreover, Beukinga's study included a small patient population. It is better to divide patients into a training set and validation set in order to check the radiomic features or model. Du et al. showed that a model made form cone-beam CT radiomics could predict radiation pneumonitis for patients who received radiotherapy [12]. The difference between their study and our study was outcome. They predicted side effects of CRT by using a radiomic model. Luo et al. showed that a CT radiomic model could predict local progression-free survival for patients with esophageal cancer who were treated with dCRT [13]. The difference between their study and our study was image modality. There have been few [^{18}F]FDG-PET/CT radiomic studies for patients with esophageal cancer and further research is needed.

Based on the idea that [^{18}F]FDG-PET/CT reflects the tumor nature or viability, there have been many studies using [^{18}F]FDG-PET/CT to predict treatment outcomes [8–10]. Rajendran et al. showed that SUV_{max} was associated with tumor hypoxia [25], and Calais et al. reported that a high [^{18}F]FDG uptake area in pretreatment [^{18}F]FDG-PET/CT was associated with local relapse area in esophageal cancer patients [26]. Nakajo et al. performed texture analysis of [^{18}F]FDG-PET/CT for patients with esophageal cancer and excluded patients with small tumor [17]. Intensity variability and size-zone variability based on the intensity-size-zone matrix were significant predictors of OS and PFS in univariate analysis but were not significant predictors in multivariate analysis. Texture analysis is one of the parts of radiomic features. Radiomic features consist of shape-based features, first-order statistics and texture features [14]. There are many features for radiomic research, and it is, therefore, important to increase the number of patients and divide patients into a feature training group and a validation group. The advantage of our study is that there were many patients and they were divided into a training group and a validation group.

Radiomic features, especially texture features, are affected by the method used for delineation [18]. The delineations in our study were automatically made. It might be difficult to make the same segmentation of esophageal cancer on the same CT image by different doctors. By using automatic segmentation on [^{18}F]FDG-PET/CT, it is possible to reduce errors by doctors when manually performing segmentation on CT images.

Previous studies showed that there are various clinical factors including clinical stage, tumor location, number of concurrent chemotherapy cycles and nutritional status for predicting outcomes of patients with esophageal cancer who were treated with chemoradiotherapy [5,27,28]. Only T stage among the clinical factors was selected by LASSO to make the model in our study. T stage might be a better prognostic

factor than other clinical factors for PFS, and other clinical factors might be worse prognostic factors than radiomic features for PFS. Moreover, there was no significant difference in PFS between T stage in the validation set. Beukinga et al. reported that a model combining T stage and radiomic features was the best model for predicting the pCR rate for patients with esophageal cancer who were treated with chemoradiotherapy followed by surgery [11]. Based on their results and our results, it might be better to make a prediction model not only from clinical factors or radiomic features but from a combination of clinical factors and radiomics.

RQS was 18 and the number of TRIPOD items was 23 in this study. Park et al. reported that mean RQS was 9.4 (range, 5–21) and the mean number of TRIPOD items was 18.51 (range, 11–26) in 77 studies [22]. The radiomics software Pyradiomics is based on an image biomarker standardization initiative. From the above, our study had sufficiently good quality for radiomics research.

It is often controversial whether radiomics data can be applied to other centers. Our data were obtained not by using only a single PET scanner but by using two PET scanners and the PET acquisition protocol conformed to Japanese guidelines. Moreover, we divided patients into a model training set and a model validation set. By using these methods, our data should be more applicable to other patient groups than data obtained in a study using only one PET scanner or data obtained in a study in which cases were not divided into two groups.

There are some limitations of our study. First, all of the patients in this study were patients with SCC. SCC and AC are the main types of esophageal cancer. Therefore, it is not clear whether our results can be applied to all types of esophageal cancer. Second, this study was a retrospective study. A randomized control trial including many patients would be needed to obtain strong evidence for radiomics.

Conclusion

The [^{18}F]FDG-PET/CT radiomic model could predict PFS for patients with esophageal cancer who were treated with dCRT. Radiomics has the potential for predicting outcomes of treatment. Further research is needed to apply our results to clinical settings.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [N.T.], upon reasonable request after approval from the Ethical Committee of Tohoku University.

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