

Dynamic whole-body positron emission tomography/computed tomography for predicting treatment response to chemoradiotherapy in patients with esophageal cancer

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Abstract. Most positron emission tomography/computed tomography (PET/CT) studies are based on static whole-body images; however, dynamic whole-body PET/CT (DW-PET/CT) enables quantification of tissue glucose metabolism dynamics. The aim of the present study was to investigate whether DW-PET/CT can predict treatment response in patients with esophageal squamous cell carcinoma (ESCC) treated with chemoradiotherapy (CRT). A total of 56 patients with ESCC who underwent pretreatment DW-PET/CT were evaluated. DW-PET/CT parameters of the main tumor, including the Patlak slope (PS, absolute rate of tracer consumption) and Patlak intercept (PI, degree of tracer perfusion in the tumor), were calculated using four DW-PET/CT image series acquired every 5 min starting 60 min after injection of

¹⁸F-fluorodeoxyglucose. The maximum standardized uptake value (SUVmax) of the tumor was also measured 60 min after tracer injection. The relationships of these PET-derived parameters with treatment response were analyzed using area under the receiver operating characteristic curve (AUC) analyses. The treatment responder group included 38 patients, whereas there were 18 non-responders according to the Response Evaluation Criteria in Solid Tumors. Tumors of responders showed significantly higher SUVmax, PS and PI than those of non-responders ($P=0.04$, 0.0012 and 0.0018 , respectively). PS and PI demonstrated good performance in predicting treatment response with AUC values of 0.71 and 0.76 , respectively, whereas the SUVmax showed a poor performance with an AUC value of 0.67 . The tumor contraction rate during CRT was significantly and positively correlated with PS and PI ($R=0.60$, $P=0.0061$ and $R=0.54$, $P=0.0265$, respectively). In conclusion, DW-PET/CT may enable pretreatment prediction of the CRT treatment response in patients with ESCC.

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Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the receiver operating characteristic curve; CF, cisplatin and 5-fluorouracil; CR, complete response; CRT, chemoradiotherapy; CT, computed tomography; DCF, cisplatin and 5-fluorouracil plus docetaxel; DW-PET/CT, dynamic whole-body positron emission tomography-computed tomography; ESCC, esophageal squamous cell carcinoma; FDG, ¹⁸F-fluorodeoxyglucose; FDG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography; FOLFOX, 5-fluorouracil, oxaliplatin, and leucovorin; LSO, lutetium oxyorthosilicate; MRI, magnetic resonance imaging; pCR, pathological complete response; PD, progressive disease; PET/CT, positron emission tomography-computed tomography; PI, Patlak intercept; PR, partial response; PS, Patlak slope; SD, stable disease; SUVmax, maximum standardized uptake value; VOI, volume of interest

Key words: esophageal cancer, PET, CT, CRT, responder

Introduction

Esophageal squamous cell carcinoma (ESCC) has a poor prognosis, ranking 11th in overall mortality, 7th among men and 17th among women, worldwide (1). Treatment options include surgery, endoscopic submucosal dissection, chemotherapy, chemoradiotherapy (CRT), and heavy ion therapy.

Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil (CF) plus docetaxel (DCF) had a better prognosis than neoadjuvant CRT in patients with locally advanced, resectable ESCC (2). One of the reasons for the worse prognosis of neoadjuvant CRT might be the side effects due to CRT, despite CRT having a high pathological complete response (pCR) rate and few local recurrences (2). Therefore, methods to predict the CRT treatment response prior to treatment in ESCC need to be developed, would be clinically useful, and could be effective in planning personalized treatments for ESCC patients.

¹⁸F-fluorodeoxyglucose (FDG) uptake is elevated in malignant tumor cells. Therefore, FDG-positron emission tomography/computed tomography (FDG-PET/CT), which can visualize FDG accumulation, has been used to identify

malignant tumors. In clinical practice, FDG-PET/CT is used to assess the presence and location of distant metastases. The most commonly used FDG-PET/CT parameter is the maximum standardized uptake value (SUVmax), which represents tissue metabolism. Moreover, SUVmax has been used to determine treatment response. Previous studies reported that post-treatment PET parameters can predict patients who will respond to treatment. Murakami *et al* (3) reported that comparing post-treatment PET parameters with pre-treatment PET parameters contributes to confirming the prognosis of patients with ESCC treated with neoadjuvant chemotherapy. Swisher *et al* (4) reported that post-treatment SUVmax was an independent predictor of survival in patients with ESCC treated with CRT. To the best of our knowledge, pretreatment PET parameters have not been able to predict the prognosis or treatment response of patients with ESCC.

Recently, whole-body continuous imaging using flow motion has become possible allowing for the measurement of FDG dynamics. To the best of our knowledge, there are no reports on the use of dynamic whole-body PET/CT (DW-PET/CT) for esophageal cancer imaging. In this study, we enrolled ESCC patients who underwent CRT and investigated the relationship between pretreatment DW-PET/CT-derived parameters, such as the Patlak slope (PS) and Patlak intercept (PI), and treatment response.

Highly proliferative cells exhibit greater radiosensitivity (5). Additionally, in malignant tumors, cells proliferate rapidly, metabolic activity is heightened, and glycolysis is upregulated (6,7). Under such conditions, the PS, which reflects the metabolic rate, is expected to be elevated. Since the PS reflects active cell division, we hypothesized that a higher PS may indicate patients more likely to have favorable response to CRT. In addition, the PI is considered a parameter reflecting perfusion (8). During CRT resistance, reduced blood perfusion within the tumor leads to hypoxia, low pH, and decreased drug delivery, all of which contribute to treatment resistance (9,10). Thus, we hypothesize that a high PI would indicate stable perfusion and potentially reduce treatment resistance and improve CRT efficacy.

Materials and methods

Patient population. This retrospective study included patients with pathologically proven ESCC who underwent pretreatment DW-PET/CT followed by CRT between August 2021 and May 2024. We identified fifty-nine ESCC patients who received CRT after DW-PET/CT at our institute during the study period (Table I). Three patients were excluded because their tumors were too small to identify on PET/CT images. Finally, 56 patients were eligible for this study. The subjects included 44 men and 12 women with a mean age of 73.0 years (range 28-90 years). The clinical stage was determined by gastrointestinal endoscopy, barium esophagography, chest and abdominal computed tomography (CT) scans, magnetic resonance imaging (MRI), and ^{18}F -FDG-PET, based on the 12th Edition of the Japanese Classification of Esophageal Cancer (4,11). Clinicopathological data including age, sex, clinical TNM stage, and pathological findings were collected from electronic medical records. This study was approved by

the Institutional Review Board at Chiba University Hospital (IRB reference number: HK202302-10; Chiba, Japan). Written informed consent was obtained for all examinations and treatments, including DW-PET/CT. However, with regard to consent for participation in this study, the opt-out approach was used because of the retrospective design. The study details were made publicly available on websites or at locations accessible to potential participants, and all participants were given the freedom to opt out of the study.

Treatment plan and response evaluation. CRT consisted of two cycles of CF [800 mg/m² 5-fluorouracil (5-FU) in a continuous infusion for 5 days and 80 mg/m² cisplatin on day 1] or two cycles of FOLFOX (400 mg/m² 5-FU, 85 mg/m² oxaliplatin, and 200 mg/m² levofofolinate on day 1, followed by 1,600 mg/m² 5-FU in a continuous infusion for 2 days). All patients received 2 Gy x 15-30 fractions of radiation therapy. Re-evaluation of the primary tumor was performed by CT, endoscopy, and gastrography 3 to 4 weeks after the completion of CRT. Endoscopic ultrasound and PET were not always used for response evaluation. The treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (11). Complete response (CR) was defined as the disappearance of the target lesion and as the disappearance of endoscopically suggestive neoplastic lesions and the absence of histological evidence of cancer on biopsy. Partial response (PR) was a reduction in the target lesion by 30% or more, progressive disease (PD) was an increase in the target lesion by 20% or more, and stable disease (SD) was defined as no reduction equivalent to PR and no increase equivalent to PD. We calculated the response of the target lesion according to the thickness of the tumor. We targeted the main lesion because we wanted to examine the effects of CRT on the main lesion. In this study, patients who showed a response, CR or PR, were categorized as clinical responders. The remaining patients with either SD or PD were categorized as clinical non-responders. We also calculated the contraction rate of the main tumor during CRT. The equation for this contraction rate is as follows: Tumor contraction rate (%) = (Tumor thickness before treatment - Tumor thickness after treatment) / Tumor thickness before treatment x 100.

DW-PET/CT protocol. The study participants were scanned on a Siemens Biograph mCT Flow (Siemens Medical Solutions) with a 221-cm axial field of view. The crista was a lutetium oxyorthosilicate (LSO), the gantry opening diameter was 78 mm, the bismuth germanate detectors were set for 300 sec, the LSO for 40 ns, and the semiconductor for 214 ps. Patients were asked not to eat for 6 h before imaging, and their blood glucose levels were measured immediately before scanning. The blood sugar levels of all patients were below 150 mg/dl at the time of the PET study. FDG was administered with an auto-dispensing injector (UG-05; Universal GIKEN). First, the static whole-body images were acquired 60 min after the injection of FDG (3.7 MBq/kg [max 370 MBq]). DW-PET/CT image series were acquired every 5 min starting 60 min after the injection of FDG (65, 70, 75, and 80 min) using continuous-bed-motion technique (Flow motion technique) (12,13).

Table I. Characteristics of patients treated with chemoradiotherapy (n=56).

Characteristic	Value
Median age, years (range)	73 (28-90)
Sex, Male/Female	44/12
Tumor location, Ce/Ut/Mt/Lt	12/9/18/17
Clinical T status, T1/T2/T3/T4	6/4/12/34
Clinical N status, N-/N+	13/43
Clinical M status, M0/M1	46/10
Clinical stage, I/II/III/IV	5/6/11/34
Surgery, +/-	13/43
SCC histology	56
Median neutrophil/lymphocyte ratio (range)	3.1 (1.3-11.3)
Median prognostic nutritional index (range)	48.1 (33.6-57.9)
CEA, ≤ 5.0 / > 5.0	44/12
SCC-associated antigen, ≤ 1.5 / > 1.5	26/30
CYFRA, ≤ 3.5 / > 3.5 /not available	50/5/1
Serum p53 antibodies, ≤ 10 / > 10 /not available	46/8/2
Chemotherapy, CF/FOLFOX	52/4
Therapeutic response, Responder/Non-Responder	38/18
Median tumor length, mm (range)	50.5 (15-110)
Median tumor contraction rate, % (range)	33.33 (-14-70)

Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower third of esophagus; CF, cisplatin and 5-fluorouracil; FOLFOX, 5-fluorouracil, oxaliplatin, and levofolinate; SCC, SCC, squamous cell carcinoma.

DW-PET/CT analysis. DW-PET/CT analysis was performed using the syngo.via software. Using this software, kinetic analysis of FDG was performed according to the compartment model. PS and PI were calculated as DW-PET/CT parameters based on four whole-body PET/CT image series acquired at every 5 min starting 60 min (65, 70, 75, and 80 min) after the injection of FDG, and DW-PET/CT images of the PS and PI were generated. PS was presumed to represent the absolute metabolic rate of FDG, while PI represented the percentage of blood concentration and represents perfusion within the tissue (14-16). A spherical volume of interest (VOI) was placed over the primary tumor with the highest glucose uptake on the trans-axial PET images acquired at 60 min after the injection of FDG, and the tumor lesion was automatically delineated by using threshold of 40% of SUVmax within the VOI (Fig. 1) (13,17). In this automatically defined tumor area, the SUVmax and mean PS and PI values were calculated. This analysis was performed by a single observer (M.I. with 3 years of experience in PET and CT interpretation) supervised by an experienced gastroenterologist (Y.K. with 10 years of experience in PET and CT interpretation).

Statistical analysis. All statistical analyses were performed using the JMP Pro software (version 17.0; SAS Institute, Inc.). Differences were considered statistically

significant at $P < 0.05$. The Mann-Whitney U test was applied for comparison of DW-PET/CT parameters between responder and non-responder groups. Correlations between DW-PET/CT parameters and tumor contraction rate during CRT was analyzed using Spearman's rank correlation coefficients. Area under the receiver operating characteristic curve (AUC) analyses were performed to assess the predictive value of DW-PET/CT parameters for predicting treatment responders. Logistic regression analysis was also performed to improve the AUC.

In addition to evaluating the predictive accuracy of the PS and PI using AUC analyses, we evaluated the characteristics of misclassified cases. Categorical variables were analyzed using Fisher's exact test; continuous variables were assessed using the Mann-Whitney U test.

Results

Relationship between DW-PET/CT-derived parameters and treatment response. We compared DW-PET/CT parameters between treatment responders and non-responders. Tumors of responders showed significantly higher SUVmax, PS, and PI than non-responders ($P=0.04$, $P=0.0012$, and $P=0.0018$, respectively; Table II). Next, we investigated the relationships between the PS, PI, and clinical parameters. A weak correlation was observed between squamous cell carcinoma-associated antigen levels and PS ($r_s=0.31$, $P=0.0193$; Fig. 2). No correlations were found between SUVmax or PI and clinical parameters. Additionally, the PS did not correlate with the neutrophil-lymphocyte ratio, prognostic nutritional index, carcinoembryonic antigen levels, cytokeratin fragment levels, or serum p53 antibodies. The PS and PI showed good performances in predicting treatment response with AUCs of 0.71 and 0.76, whereas the SUVmax showed a poor performance with an AUC of 0.67 (Fig. 3). For the PS, when the cut-off point was set at 3.26 (calculated by the Youden Index method), the sensitivity was 89.5%, specificity was 50.0%, and accuracy was 76.8% for the prediction of patients who showed good response to CRT. For the PI, when the cut-off point was set at 71.37 (calculated by Youden Index method), the sensitivity was 73.7%, specificity was 72.2%, and accuracy was 73.2% for the prediction of patients who showed good response to CRT. The tumor contraction rate during CRT showed significant positive correlations with the PS and PI ($r_s=0.60$, $P=0.0061$ and $r_s=0.54$, $P=0.0265$, respectively; Fig. 4).

To evaluate the predictive accuracy of the PS and PI using AUC analyses, we evaluated the characteristics of misclassified cases. No significant differences in clinical or imaging features were observed between the PS true-positive and false-positive groups. However, when comparing the PS true-positive and false-negative groups, the false-negative group was characterized by less advanced T and N classifications and overall stage ($P < 0.0001$, $P=0.0237$, and $P=0.0002$, respectively), as well as lower squamous cell carcinoma-associated antigen levels ($P=0.0360$). Similarly, no significant differences were found between the PI true-positive and false-positive groups. In contrast, the PI false-negative group showed significantly less advanced T classification and overall stage compared to the true-positive group ($P=0.0221$ and $P=0.0479$, respectively). These findings suggest that cases with less advanced T

Table II. Relationship between therapeutic responders and SUVmax, Patlak slope and Patlak intercept in patients with esophageal cancer treated with chemoradiotherapy.

Measured parameter	Responder (n=38)	Non-responder (n=18)	P-value
SUVmax	17.57±8.22	12.86±8.38	0.04
Patlak slope, mg/min/100 ml	5.55±2.51	4.10±3.72	0.0012
Patlak intercept, %	161.42±188.30	57.96±58.03	0.0018

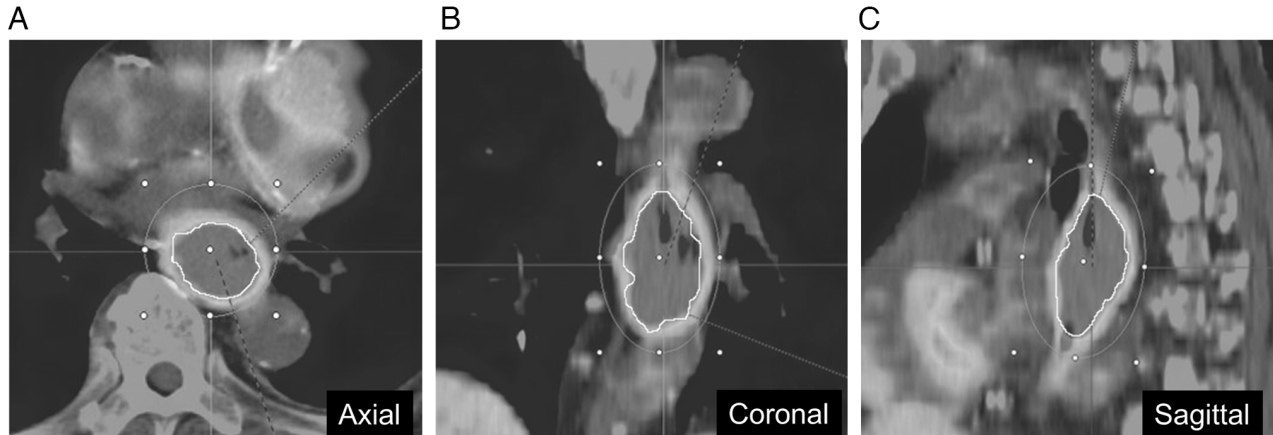


Figure 1. An example of a VOI that was generated semi-automatically. (A) Axial, (B) coronal and (C) sagittal slices. VOI, volume of interest.

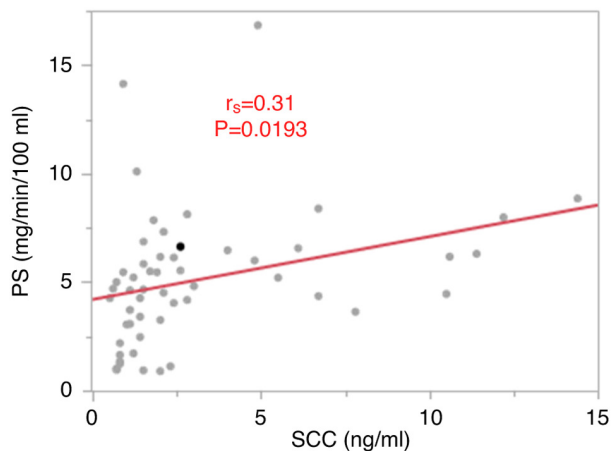


Figure 2. Relationship between SCC-associated antigen and PS. SCC, squamous cell carcinoma; PS, Patlak slope.

classification and overall disease stage are more likely to result in false-negative predictions for both PS and PI.

To improve the AUCs for PS and PI, logistic regression analysis was performed; however, the AUCs showed no improvement. Logistic regression was conducted using the following explanatory variables: $PS \geq 3.26$ vs. $PS < 3.26$ and $PI \geq 71.37$ vs. $PI < 71.37$. Individually, neither PS (OR=3.38, 95% CI: 0.63-21.00, $P=0.16$) nor PI (OR=3.73, 95% CI: 0.74-18.83, $P=0.11$) were significant indicators of the responder status. However, a combined model incorporating both PS and PI significantly distinguished responders from non-responders (log-likelihood ratio=6.37, $\chi^2=12.75$, degree of freedom=2, $P=0.0017$, $R^2=0.18$, AIC=64.04). The ROC

analysis yielded an AUC of 0.76. When PS and PI were treated as continuous variables, the overall model test yielded the following parameters: log-likelihood ratio=5.74, $\chi^2=11.48$, degree of freedom=2, $P=0.0032$, $R^2=0.16$, and AIC=65.31. The corresponding ROC curve analysis showed an AUC of 0.75.

Discussion

Patients with ESCC have a poor prognosis and are treated using a multidisciplinary approach that combines various therapies. The JCOG1109 trial (2) showed that postoperative DCF therapy has a better prognosis than CF or CRT in terms of overall survival. In contrast, the pCR rates for preoperative DCF therapy and CRT with CF therapy were 18.6 and 36.7%, respectively. DCF also carries a higher risk of adverse events such as myelosuppression and neutropenia, with 42-90% of patients developing grade 3 or higher neutropenia and 10-39% developing febrile neutropenia (18-20). These data indicate the presence of a population for which CRT is suitable. Determining which cases are suitable for CRT can be useful for treatment decision-making. The results of our study indicate that, in ESCC patients undergoing CRT, those with higher measured PS and PI had better responses. Similarly, the tumor contraction rate correlated with a higher PS. The PS measured using FDG-PET may be promising imaging biomarker for treatment selection in patients with ESCC.

Various methods have been proposed to predict CRT efficacy, including analyses of genes, RNA, proteins, metabolites, the tumor microenvironment, and the microbiome. Among

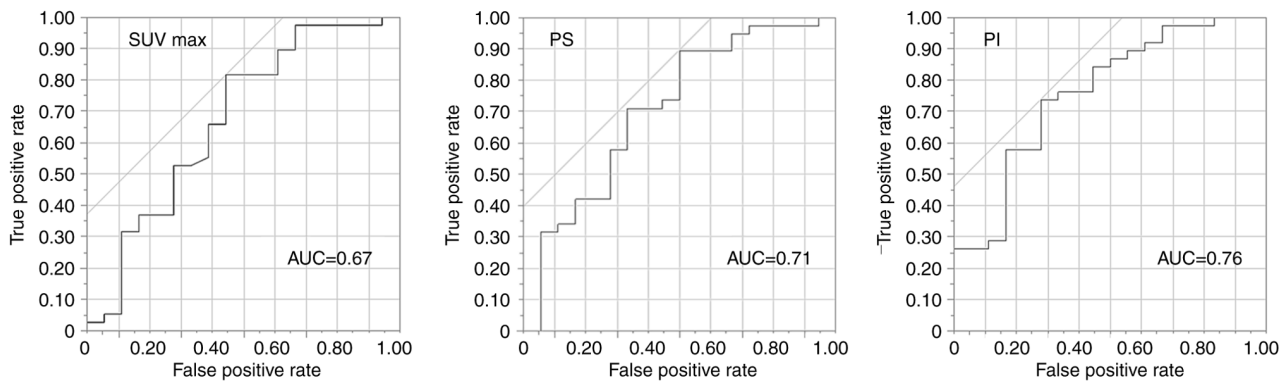


Figure 3. Relationship between treatment response, and SUVmax, PS or PI. AUC, area under the receiver operating characteristic curve; PI, Patlak intercept; PS, Patlak slope; SUVmax, maximum standardized uptake value.

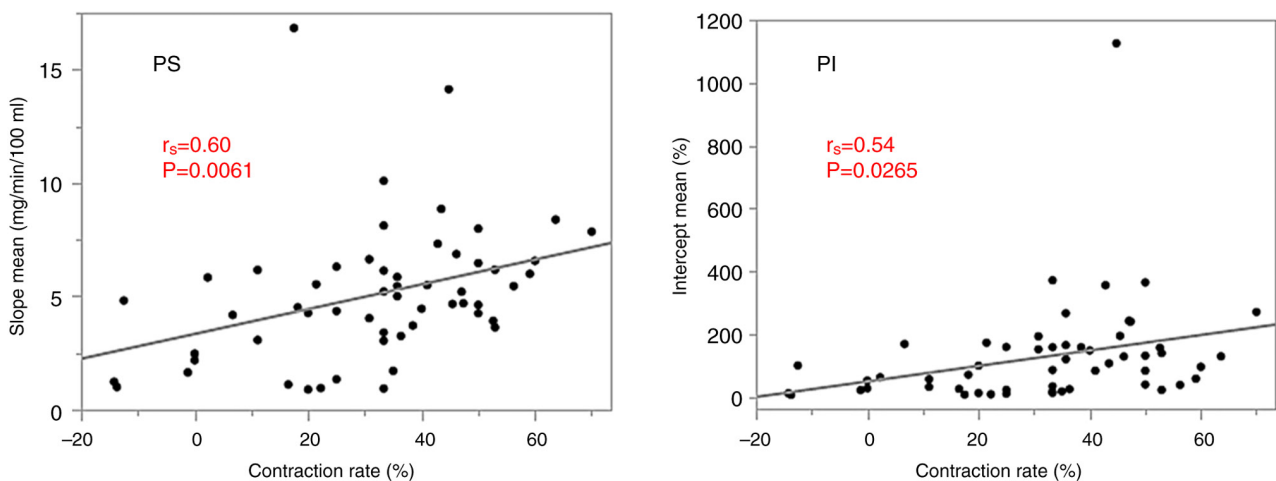


Figure 4. Correlation between the tumor contraction rate and PS or PI. PI, Patlak intercept; PS, Patlak slope.

these, imaging techniques offer the distinct advantage of being non-invasive. In this study, we focused on imaging biomarkers obtained during baseline clinical assessments.

Several studies have reported on the use of various imaging modalities, such as CT, MRI, and PET, in assessing the response of esophageal cancer to CRT. During CT perfusion imaging, blood flow has been shown to correlate with treatment response and overall survival (21,22). Other CT-derived parameters, such as tumor thickness (23) and radiomic features like LLLEnergy (24), have also been reported to be associated with treatment response and overall survival. Among MRI-derived parameters, the apparent diffusion coefficient has been reported to correlate with survival outcomes (25,26). Ktrans has been associated with pCR (27,28), and has also been shown to be useful for predicting response (29). Additionally, histogram analysis of apparent diffusion coefficient values has been reported to correlate with both pCR and recurrence-free survival (30).

The advantages of PET imaging include not needing contrast agents, its applicability in patients with metallic implants, and a lower susceptibility to motion artifacts caused by cardiac activity. van der Aa *et al* (31) reported that the SUVmax, which has been widely used in clinical practice, is not predictive of pCR. In our study, however, we demonstrated

the potential utility of alternative PET parameters, PS and PI, in predicting treatment response.

Several studies have examined dynamic PET parameters in cancers other than esophageal cancer. Many of these studies suggest that such parameters are useful in distinguishing between benign and malignant lesions including in lung cancer, liver cancer, nasopharyngeal tumors, bone lesions, post-operative gastroesophageal cancers, and colorectal lesions (13,32-36). Additionally, dynamic PET has been used to predict hormone receptor status in breast cancer (37) and to differentiate subtypes of pheochromocytoma and paraganglioma (38).

Differences in metabolic behavior have also been reported among different cancer types within the same tissue. For example, Kaneko *et al* (39) showed that MRI-FDG imaging could differentiate between intrahepatic cholangiocarcinoma, hepatocellular carcinoma, and liver metastases. Similarly, Lv *et al* (40) demonstrated that ΔKi is useful for distinguishing between primary and synchronous multiple lung cancers.

Several studies have investigated the relationship between cancer and treatment response using dynamic PET parameters. Wang *et al* (41) reported that the Patlak Ki is associated with the response to immunotherapy in non-small cell lung cancer. In addition, de Geus-Oei *et al* (42) demonstrated that MRI-FDG

correlates with overall survival and progression-free survival in colorectal cancer, while Dimitrakopoulou-Strauss *et al* (43) found that the influx rate was useful for predicting response to neoadjuvant chemotherapy in soft-tissue sarcoma. In concert, Hofheinz *et al* (44) reported an association between the Kslope and progression-free survival in non-small cell lung cancer. Dimitrakopoulou-Strauss *et al* (45) have also examined prognosis in non-small cell lung cancer and shown that k3 is related to progression-free survival in multiple myeloma. To the best of our knowledge, no studies have reported on these parameters in esophageal cancer.

Several studies have used CT, MRI, and conventional FDG-PET images as biomarkers for prognosis prediction and treatment selection in patients with ESCC (46,47). A common limitation of these studies was the objectivity of the region of interests generated when the parameters were obtained from the images. To ensure objectivity, many studies have taken measurements at the site of the maximum tumor diameter when obtaining regions of interest from images, and in some cases, artificial intelligence has been employed. However, the methods evaluated only one image slice of the tumor and could not evaluate the entire tumor. The method employed in this study semi-automatically set the VOI to surround the entire tumor, allowing for evaluation of the whole tumor and ensuring objectivity. We believe that these results are superior to those of previous studies. Compared to CT and MRI, FDG-PET has drawbacks such as patient exposure to radiation and examination costs; however, if the results of these studies can be introduced into clinical practice, the test will be a useful tool for making treatment decisions and predicting prognoses.

This study included patients with cT0-1 ESCC. These patients are generally candidates for surgery or endoscopic treatment; however, CRT is often performed for elderly patients, patients with poor activities of daily living, and patients with circumferential lesions. Therefore, we decided to include such cases in our analysis.

Our study had several limitations. First, the biological investigations were not performed to confirm the parameters obtained from DW-PET/CT. Second, our study was based on single-center retrospective data and had a relatively small sample size. Thus, prospective multicenter investigations with larger populations are required to strengthen the statistical power of our results. Third, we drew the VOI semi-automatically, which is therefore objective. Fourth, this study included several types of treatment, which could be biased. Finally, we did not assess the histological tumor grade in this study.

In conclusion, our findings suggest that parameters obtained from DW-PET/CT, such as the PS and PI, can be useful predictors for treatment response in ESCC patients treated with CRT.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MI, YK, KH, GO, ToT, AH, RM, MU, TaT, YM, AN, TS, NS, TI and HM contributed to the study conception and design. Material preparation, data collection and analysis were performed by MI and KH. The first draft of the manuscript was written by MI, and YK, KH, GO, ToT, AH, RM, MU, TaT, YM, AN, TS, NS, TI and HM commented on previous versions of the manuscript. MI and YK confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Written informed consent was obtained from all participants before examinations and treatments, including DW-PET/CT. However, with regard to consent for participation in this study, the opt-out approach was used due to the retrospective design of the study. The study details were made publicly available on websites or at locations accessible to potential participants; all participants were given the freedom to opt out of the study. This retrospective study was approved by the Clinical Research Center (Institutional Review Board) of Chiba University Hospital (IRB reference number: HK202302-10).

Patient consent for publication

Consent for publication of the study was obtained via the opt-out approach.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Wagle NS and Jemal A: Cancer statistics, 2023. *CA Cancer J Clin* 73: 17-48, 2023.
2. Kato K, Machida R, Ito Y, Daiko H, Ozawa S, Ogata T, Hara H, Kojima T, Abe T, Bamba T, *et al*: Doublet chemotherapy, triplet chemotherapy, or doublet chemotherapy combined with radiotherapy as neoadjuvant treatment for locally advanced oesophageal cancer (JCOG1109 NExT): A randomised, controlled, open-label, phase 3 trial. *Lancet* 404: 55-66, 2024.
3. Murakami K, Yoshida N, Taniyama Y, Takahashi K, Toyozumi T, Uno T, Kamei T, Baba H and Matsubara H: Maximum standardized uptake value change rate before and after neoadjuvant chemotherapy can predict early recurrence in patients with locally advanced esophageal cancer: A multi-institutional cohort study of 220 patients in Japan. *Esophagus* 19: 205-213, 2022.
4. Swisher SG, Maish M, Erasmus JJ, Correa AM, Ajani JA, Bresalier R, Komaki R, Macapinlac H, Munden RF, Putnam JB, *et al*: Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. *Ann Thorac Surg* 78: 1152-1160, 2004.
5. Bergonie J and Tribondeau L: Interpretation of some results of radiotherapy and an attempt at determining a logical technique of treatment. *Radiat Res* 11: 587-588, 1959.

6. Warburg O, Wind F and Negelein E: The metabolism of tumors in the body. *J Gen Physiol* 8: 519-530, 1927.
7. Vaupel P and Multhoff G: The warburg effect: Historical dogma versus current rationale. *Adv Exp Med Biol* 1269: 169-177, 2021.
8. Dimitrakopoulou-Strauss A, Hohenberger P, Pan L, Kasper B, Roumia S and Strauss LG: Dynamic PET with FDG in patients with unresectable aggressive fibromatosis: Regression-based parametric images and correlation to the FDG kinetics based on a 2-tissue compartment model. *Clin Nucl Med* 37: 943-948, 2012.
9. Carmeliet P and Jain RK: Angiogenesis in cancer and other diseases. *Nature* 407: 249-257, 2000.
10. Gatenby RA and Gillies RJ: Why do cancers have high aerobic glycolysis? *Nat Rev Cancer* 4: 891-899, 2004.
11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
12. Hu J, Panin V, Smith AM, Spottiswoode B, Shah V and von Gall CA: Design and implementation of automated clinical whole body parametric PET with continuous bed motion. *IEEE Trans Radiat Plasma Med Sci* 4: 696-707, 2020.
13. Watanabe M, Kato H, Katayama D, Soeda F, Matsunaga K, Watabe T, Tatsumi M, Shimosegawa E and Tomiyama N: Semiquantitative analysis using whole-body dynamic F-18 fluoro-2-deoxy-glucose-positron emission tomography to differentiate between benign and malignant lesions. *Ann Nucl Med* 36: 951-963, 2022.
14. Patlak CS and Blasberg RG: Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. *J Cereb Blood Flow Metab* 5: 584-590, 1985.
15. Osborne DR and Acuff S: Whole-body dynamic imaging with continuous bed motion PET/CT. *Nucl Med Commun* 37: 428-431, 2016.
16. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L and Kuhl DE: Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: Validation of method. *Ann Neurol* 6: 371-388, 1979.
17. Lemarignier C, Di Fiore F, Marre C, Hapdey S, Modzelewski R, Gouel P, Michel P, Dubray B and Vera P: Pretreatment metabolic tumour volume is predictive of disease-free survival and overall survival in patients with oesophageal squamous cell carcinoma. *Eur J Nucl Med Mol Imaging* 41: 2008-2016, 2014.
18. Yamasaki M, Miyata H, Tanaka K, Shiraishi O, Motoori M, Peng YF, Yasuda T, Yano M, Shiozaki H, Mori M and Doki Y: Multicenter phase I/II study of docetaxel, cisplatin and fluorouracil combination chemotherapy in patients with advanced or recurrent squamous cell carcinoma of the esophagus. *Oncology* 80: 307-313, 2011.
19. Umeki Y, Matsuoaka H, Fujita M, Goto A, Serizawa A, Nakamura K, Akimoto S, Nakauchi M, Tanaka T, Shibasaki S, *et al*: Docetaxel cisplatin 5-FU(DCF) therapy as a preoperative chemotherapy to advanced esophageal squamous cell carcinoma: A single-center retrospective cohort study. *Internal Medicine* 62: 319-325, 2023.
20. Katada C, Sugawara M, Hara H, Fujii H, Nakajima TE, Ando T, Kojima T, Watanabe A, Sakamoto Y, Ishikawa H, *et al*: A management of neutropenia using granulocyte colony stimulating factor support for chemotherapy consisted of docetaxel, cisplatin and 5-fluorouracil in patients with oesophageal squamous cell carcinoma. *Jpn J Clin Oncol* 51: 199-204, 2021.
21. Hayano K, Okazumi S, Shuto K, Matsubara H, Shimada H, Nabeya Y, Kazama T, Yanagawa N and Ochiai T: Perfusion CT can predict the response to chemoradiation therapy and survival in esophageal squamous cell carcinoma: Initial clinical results. *Oncol Rep* 18: 901-908, 2007.
22. Makari Y, Yasuda T, Doki Y, Miyata H, Fujiwara Y, Takiguchi S, Matsuyama J, Yamasaki M, Hirao T, Koyama MK, *et al*: Correlation between tumor blood flow assessed by perfusion CT and effect of neoadjuvant therapy in advanced esophageal cancers. *J Surg Oncol* 96: 220-229, 2007.
23. Wongwaiyut K, Ruangsri S, Laohawiriyakamol S, Leelakiatpaiboon S, Sangthawan D, Sunpaweravong P and Sunpaweravong S: Pretreatment esophageal wall thickness associated with response to chemoradiotherapy in locally advanced esophageal cancer. *J Gastrointest Cancer* 51: 947-951, 2020.
24. Kasai A, Miyoshi J, Sato Y, Okamoto K, Miyamoto H, Kawanaka T, Tonoiso C, Harada M, Goto M, Yoshida T, *et al*: A novel CT-based radiomics model for predicting response and prognosis of chemoradiotherapy in esophageal squamous cell carcinoma. *Sci Rep* 14: 2039, 2024.
25. Aoyagi T, Shuto K, Okazumi S, Shimada H, Kazama T and Matsubara H: Apparent diffusion coefficient values measured by diffusion-weighted imaging predict chemoradiotherapeutic effect for advanced esophageal cancer. *Dig Surg* 28: 252-257, 2011.
26. De Cobelli F, Giganti F, Orsenigo E, Cellina M, Esposito A, Agostini G, Albarello L, Mazza E, Ambrosi A, Socci C, *et al*: Apparent diffusion coefficient modifications in assessing gastro-oesophageal cancer response to neoadjuvant treatment: Comparison with tumour regression grade at histology. *Eur Radiol* 23: 2165-2174, 2013.
27. Sun NN, Liu C, Ge XL and Wang J: Dynamic contrast-enhanced MRI for advanced esophageal cancer response assessment after concurrent chemoradiotherapy. *Diagn Interv Radiol* 24: 195-202, 2018.
28. Lei J, Han Q, Zhu S, Shi D, Dou S, Su Z and Xu X: Assessment of esophageal carcinoma undergoing concurrent chemoradiotherapy with quantitative dynamic contrast-enhanced magnetic resonance imaging. *Oncol Lett* 10: 3607-3612, 2015.
29. Gu L, Xie X, Guo Z, Shen W, Qian P, Jiang N and Fan Y: Dynamic contrast-enhanced magnetic resonance imaging: A novel approach to assessing treatment in locally advanced esophageal cancer patients. *Niger J Clin Pract* 24: 1800-1807, 2021.
30. Hirata A, Hayano K, Ohira G, Imanishi S, Hanaoka T, Murakami K, Aoyagi T, Shuto K and Matsubara H: Volumetric histogram analysis of apparent diffusion coefficient for predicting pathological complete response and survival in esophageal cancer patients treated with chemoradiotherapy. *Am J Surg* 219: 1024-1029, 2020.
31. van der Aa DC, Gisbertz SS, Anderegg MCJ, Lagarde SM, Klaassen R, Meijer SL, van Dieren S, Hulshof M, Bergman J, Bennink RJ, *et al*: (18)F-FDG-PET/CT to detect pathological complete response after neoadjuvant treatment in patients with cancer of the esophagus or gastroesophageal junction: Accuracy and long-term implications. *J Gastrointest Cancer* 55: 270-280, 2024.
32. Weissering M, Atmanspacher M, Spengler W, Seith F, Von Beschwitz S, Dittmann H, Zender L, Smith AM, Casey ME, Nikolaou K, *et al*: Diagnostic performance of dynamic whole-body patlak [(18)F]FDG-PET/CT in patients with indeterminate lung lesions and lymph nodes. *J Clin Med* 12: 3942, 2023.
33. Wang Q, Wang RF, Zhang J and Zhou Y: Differential diagnosis of pulmonary lesions by parametric imaging in (18)F-FDG PET/CT dynamic multi-bed scanning. *J BUON* 18: 928-934, 2013.
34. Parodi D, Dighe E, Biddau G, D'Amico F, Bauckneht M, Marini C, Garbarino S, Campi C, Piana M and Sambucetti G: Localized FDG loss in lung cancer lesions. *EJNMMI Res* 14: 102, 2024.
35. Skawran S, Messerli M, Kotasidis F, Trinckauf J, Weyermann C, Kudura K, Ferraro DA, Pitteloud J, Treyer V, Maurer A, *et al*: Can dynamic whole-body FDG PET imaging differentiate between malignant and inflammatory lesions? *Life (Basel)* 12: 1350, 2022.
36. Huang X, Zhuang M, Yang S, Wang Y, Liu Q, Xu X, Xiao M, Peng Y, Jiang P, Xu W, *et al*: The valuable role of dynamic (18) F FDG PET/CT-derived kinetic parameter K(i) in patients with nasopharyngeal carcinoma prior to radiotherapy: A prospective study. *Radiother Oncol* 179: 109440, 2023.
37. Sundaraiya S, T R, Nangia S, Sirohi B and Patil S: Role of dynamic and parametric whole-body FDG PET/CT imaging in molecular characterization of primary breast cancer: A single institution experience. *Nucl Med Commun* 43: 1015-1025, 2022.
38. van Berkel A, Vriens D, Visser EP, Janssen MJR, Gotthardt M, Hermus ARMM, Geus-Oei LF and Timmers HJLM: Metabolic Subtyping of Pheochromocytoma and Paraganglioma by (18) F-FDG Pharmacokinetics Using Dynamic PET/CT Scanning. *J Nucl Med* 60: 745-751, 2019.
39. Kaneko K, Nagao M, Yamamoto A, Yano K, Honda G, Tokushige K and Sakai S: Patlak reconstruction using dynamic 18 F-FDG PET imaging for evaluation of malignant liver tumors: A comparison of HCC, ICC, and metastatic liver tumors. *Clin Nucl Med* 49: 116-123, 2024.
40. Lv W, Yang M, Zhong H, Wang X, Yang S, Bi L, Xian J, Pei X, He X, Wang Y, *et al*: Application of dynamic (18)F-FDG PET/CT for distinguishing intrapulmonary metastases from synchronous multiple primary lung cancer. *Mol Imaging* 2022: 8081299, 2022.
41. Wang D, Qiu B, Liu Q, Xia L, Liu S, Zheng C, Liu H, Mo Y, Zhang X, Hu Y, *et al*: Patlak-Ki derived from ultra-high sensitivity dynamic total body [(18)F]FDG PET/CT correlates with the response to induction immuno-chemotherapy in locally advanced non-small cell lung cancer patients. *Eur J Nucl Med Mol Imaging* 50: 3400-3413, 2023.

42. de Geus-Oei LF, van Laarhoven HW, Visser EP, Hermesen R, van Hoor BA, Kamm YJ, Krabbe PF, Corstens FH, Punt CJ and Oyen WJ: Chemotherapy response evaluation with FDG-PET in patients with colorectal cancer. *Ann Oncol* 19: 348-352, 2008.
43. Dimitrakopoulou-Strauss A, Strauss LG, Egerer G, Vasamillette J, Mechtersheimer G, Schmitt T, Lehner B, Haberkorn U, Stroebel P and Kasper B: Impact of dynamic 18F-FDG PET on the early prediction of therapy outcome in patients with high-risk soft-tissue sarcomas after neoadjuvant chemotherapy: A feasibility study. *J Nucl Med* 51: 551-558, 2010.
44. Hofheinz F, Hoff JV, Steffen IG, Lougovski A, Ego K, Amthauer H and Apostolova I: Comparative evaluation of SUV, tumor-to-blood standard uptake ratio (SUR), and dual time point measurements for assessment of the metabolic uptake rate in FDG PET. *EJNMMI Res* 6: 53, 2016.
45. Dimitrakopoulou-Strauss A, Hoffmann M, Bergner R, Uppenkamp M, Eisenhut M, Pan L, Haberkorn U and Strauss LG: Prediction of short-term survival in patients with advanced nonsmall cell lung cancer following chemotherapy based on 2-deoxy-2-[F-18]fluoro-D-glucose-positron emission tomography: A feasibility study. *Mol Imaging Biol* 9: 308-317, 2007.
46. Okazumi S, Ohira G, Hayano K, Aoyagi T, Imanishi S and Matsubara H: Novel advances in qualitative diagnostic imaging for decision making in multidisciplinary treatment for advanced esophageal cancer. *J Clin Med* 13: 632, 2024.
47. Hayano K, Ohira G, Hirata A, Aoyagi T, Imanishi S, Tochigi T, Hanaoka T, Shuto K and Matsubara H: Imaging biomarkers for the treatment of esophageal cancer. *World J Gastroenterol* 25: 3021-3029, 2019.



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