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Integrating ^{18}F-FDG PET/CT with lung dose-volume for assessing lung inflammatory changes after arc-based radiotherapy for esophageal cancer: A pilot study

Chen-Xiong Hsu[1,2†] | Kuan-Heng Lin[1,2,3†] | Pei-Wei Shueng[2,4†] | Yen-Wen Wu[4,5] | Wei-Ta Tsai[1] | Chiu-Han Chang[2] | Hui-Ju Tien[2] | Shan-Ying Wang[1,5‡] | Tung-Hsin Wu[6‡] | Greta S. P. Mok[7]

[1]Department of Biomedical Imaging and Radiological Sciences, National Yang Ming Chiao Tung University, Taipei City, Taiwan

[2]Division of Radiation Oncology, Far Eastern Memorial Hospital, Taipei City, Taiwan

[3]Industrial Ph.D. Program of Biomedical Science and Engineering, National Yang Ming Chiao Tung University, Taipei City, Taiwan

[4]Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei City, Taiwan

[5]Department of Nuclear Medicine, Division of Cardiology, Cardiovascular Medical Center, Far Eastern Memorial Hospital, Taipei City, Taiwan

[6]National Yang Ming Chiao Tung University, Taipei City, Taiwan

[7]Department of Electrical and Computer Engineering, Faculty of Science and Technology, University of Macau, Zhuhai, China

Correspondence
Shan-Ying Wang and Tung-Hsin Wu, National Yang Ming Chiao Tung University, Taipei, Taiwan.
Email: sywang201@gmail.com; tung@ym.edu.tw

Abstract

Objective: The incidence of radiation pneumonitis (RP) has a highly linear relationship with low-dose lung volume. We previously established a volume-based algorithm (VBA) method to improve low-dose lung volume in radiotherapy (RT). This study assessed lung inflammatory changes by integrating fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) with VBA for esophageal cancer patients undergoing arc-based RT.

Methods: Thirty esophageal cancer patients received ^{18}F-FDG PET/CT imaging pre-RT and post-RT were included in a retrospective pilot study. We fused lung doses and parameters of PET/CT in RT planning. Based on VBA, we used the 5Gy isodose curve to define high-dose (HD) and low-dose (LD) regions in the lung volume. We divided patients into non-RP (nRP) and RP groups. The maximum, mean standardized uptake value (SUVmax, SUVmean), global lung glycolysis (GLG), mean lung dose (MLD) and V_{5-30} in lungs were analyzed. Area under the curve values were utilized to identify optimal cut-off values for RP.

Results: Eleven patients in the nRP group and 19 patients in the RP group were identified. In 30 RP lungs, post-RT SUVmax, SUVmean and GLG of HD regions showed significant increases compared to values for pre-RT lungs. There were no significant differences in values of 22 nRP lungs. Post-RT SUVmax and SUVmean of HD regions, MLD, and lung V_5 and V_{10} in RP lungs were significantly higher than in nRP lungs. For detecting RP, the optimal cut-off values were post-RT SUVmax > 2.28 and lung V_5 > 47.14%.

Conclusion: This study successfully integrated ^{18}F-FDG PET/CT with VBA to assess RP in esophageal cancer patients undergoing RT. Post-RT SUVmax > 2.28 and lung V_5 > 47.14% might be potential indicators of RP.

KEYWORDS
esophageal cancer, lung dose, lung inflammatory, PET/CT

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† Chen-Xiong Hsu, Kuan-Heng Lin and Pei-Wei Shueng contributed equally.

‡ Shan-Ying Wang and Tung-Hsin Wu corresponding authors contributed equally.

INTRODUCTION

Esophageal cancer is a common malignancy and concurrent chemoradiotherapy (CCRT) is an essential treatment for it. Radiation pneumonitis (RP), that is, radiation-induced inflammation in the lung tissues, is one of the most common side effects after radiotherapy (RT) for esophageal cancer.[1,2] Several studies have indicated that the incidence of RP has a highly linear relationship with low-dose lung volume.[3–5] Pinnix et al.[6] showed that lung $V_5 > 55\%$ could be used as a predictor for RP. Wang et al.[7] demonstrated that when lung $V_5 \leq 42\%$ the incidence of RP could drop to 3%. The lung V_5 is a crucial predictor of RP.

Functional and metabolic imaging with fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been widely utilized to detect malignant tumor cells[8] and also to quantify the inflammation based on the metabolism of normal tissues.[9,10] Volume-based semiquantitative parameters such as standardized uptake values, metabolic tumor volume, and total lesion glycolysis could guide cancer diagnosis, staging, metastasis detection, and interpretation of treatment responses for esophageal cancer.[11–13]

Castillo et al.[14] and Hart et al.[15] indicated that the quantitative parameters of ^{18}F-FDG PET/CT could be used as indicators for detecting RP for esophageal cancer patients. Abdulla et al.[16] combined the mean standardized uptake value (SUVmean) with the lung tissue volume to calculate the global lung glycolysis (GLG). They pointed out that GLG is a potential biomarker for detecting RP. Previously we proposed the volume-based algorithm (VBA) method to reduce lung V_5 by improving the arc angle in dynamic arc-based RT.[17] We demonstrated that

the percentage of irradiated lung volume in whole lung volume is highly correlated with lung V_5. Additionally, only a few studies using ^{18}F-FDG PET have been reported to evaluate and quantify the inflammation in different radiation dose volumes of the lung.[4,18,19] This study therefore aimed to assess lung inflammatory changes by integrating ^{18}F-FDG PET/CT with VBA before and after arc-based RT for esophageal cancer.

MATERIALS AND METHODS

Study population

The flowchart for the study population selection is shown in Figure 1. Patients with esophageal cancer who underwent CCRT in our hospital between 2014 and 2018 were retrospectively reviewed. The ^{18}F-FDG PET/CT scans were acquired 1 week before RT (pre-RT) and 1–3 months after RT (post-RT). Patients with stage I to III according to the 7th American Joint Committee on Cancer (AJCC) staging systems for esophageal cancer were included.[20] Exclusion criteria were as follows: esophageal cancer stage IV, synchronous cancer, previous thoracic surgery, patients did not receive pre- or post-CCRT PET/CT, interval time between CCRT and post-CCRT PET/CT >3 months.

Thirty esophageal cancer patients treated with CCRT between 2014 and 2018 were eligible for analysis. According to Common Terminology Criteria for Adverse Events version 4.0, patients were divided into a nonradiation pneumonitis (nRP) group (grade 0) and and RP group (≥ grade 1). The study was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital (FEMH-IRB No.: 108069-E).
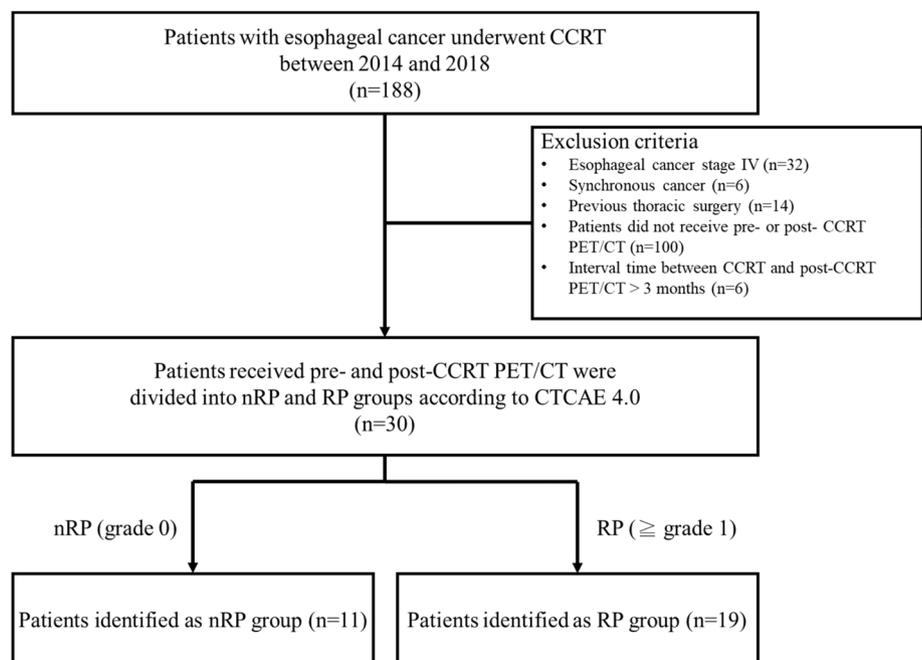
FIGURE 1 Flowchart of esophageal cancer patient selection
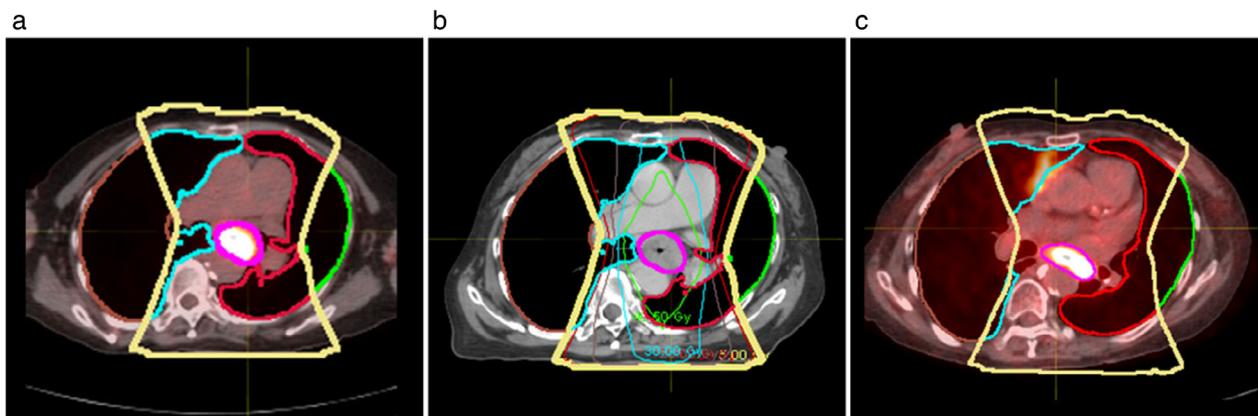
FIGURE 2 (a) Pre-RT PET/CT image fused with 5 Gy isodose curve, (b) simulation CT with isodose curves (5–50 Gy), and (c) post-RT PET/CT image fused with 5 Gy isodose curve. The yellow line is the 5 Gy isodose curve. The blue line is the right HD region. The red line is the left HD region. The brown line is the right LD region. The green line is the left LD region. The pink line is the GTV. The SUVmean, SUVmax, and GLG of the HD and LD regions in the lungs were quantified in the pre- and post-RT PET/CT, respectively

^{18}F-FDG PET/CT scans, quantification analysis, and evaluation of RP

PET/CT scans were acquired on a GE Discovery VCT PET/CT scanner (GE Medical Systems). Patients were required to fast for 6 h before the PET/CT scan to achieve a blood glucose level of <140 mg/dl. Patients were intravenously injected with ^{18}F-FDG according to their body weight (4 MBq/kg) and then rested for 60 min before image acquisition. CT images were acquired with the following parameters: tube voltage 120 kVp, tube current with automatic exposure control from 10 to 300 mA, slice thickness 3.75 mm, pitch of 1, and matrix size 512 × 512. The scan range was from the top of the head to mid-thigh. Three-dimensional PET images were acquired with a z axis field-of-view (FOV) of 15 cm for 3 min at each bed position. PET images were reconstructed using the Ordered Subset Expectation Maximization (OS-EM) algorithm, corrected for normalization, attenuation, random, and scattered coincidences.

The standardized uptake value (SUV) is a semiquantitative evaluation method used in PET. It mainly evaluates the ^{18}F-FDG uptake in tissues, organs, tumors, or regions of interest (ROI). The calculation method is as follows:

$$SUV = \frac{\text{tissue concentration (MBq/mL)}}{\text{injected activity (mCi)/body weight (kg)}}$$

Tissue concentration represents the tissue radioactivity per unit volume obtained after quantitative PET image reconstruction in the target FOV.

The maximum SUV (SUVmax) is defined as the maximum voxel value within the ROI and SUVmean is the average SUV value in all pixels within the ROI. The GLG

TABLE 1 Patient characteristics

Characteristics	No. of patients ($n = 30$)
Sex	
Male	20
Female	10
Age (years)	
Median	56
Range	43–78
Staging	
I	3
II	9
III	18
Chemotherapy	
Yes	30
No	0
RT technique	
VMAT	13
Tomotherapy	17
Prescription dose	
Median (Gy)	45
Range (Gy)	41–50.4
Interval time between RT and post-PET/CT	
Median (days)	37
Range (days)	21–89
nRP lungs	22
RP lungs (≥ grade 1)	30
Right lungs	14
Left lungs	16
Both right and left lungs	11

Abbreviations: nRP, nonradiation pneumonitis; PET/CT, positron emission tomography/computed tomography; RP, radiation pneumonitis; RT, radiotherapy; VMAT, volumetric modulated arc therapy.

TABLE 2 Comparison of the inflammatory changes in lungs between pre-RT and post-RT

Parameter	Pre-RT	Post-RT	Absolute change (Δ)	Relative change	Pre-RT versus post-RT p value
Right lungs ($n = 30$)					
HD region					
SUVmax	2.04 ± 0.53	2.35 ± 0.72	0.30 ± 0.71	15%	0.024*
SUVmean	0.50 ± 0.10	0.56 ± 0.17	0.07 ± 0.14	13%	0.034*
GLG (ml)	300.79 ± 138.59	375.12 ± 181.42	77.47 ± 146.91	28%	0.010*
LD region					
SUVmax	1.89 ± 0.47	1.89 ± 0.38	0.02 ± 0.40	1%	0.918
SUVmean	0.44 ± 0.09	0.47 ± 0.13	0.04 ± 0.11	8%	0.136
GLG (ml)	450.19 ± 185.51	457.23 ± 185.13	10.24 ± 153.65	2%	0.806
Left lungs ($n = 30$)					
HD region					
SUVmax	2.02 ± 0.39	2.41 ± 0.50	0.39 ± 0.49	20%	0.000*
SUVmean	0.52 ± 0.11	0.59 ± 0.17	0.07 ± 0.13	12%	0.013*
GLG (ml)	317.39 ± 117.87	401.40 ± 184.85	85.02 ± 136.48	28%	0.002*
LD region					
SUVmax	1.79 ± 0.48	1.96 ± 0.48	0.17 ± 0.57	10%	0.119
SUVmean	0.44 ± 0.09	0.47 ± 0.14	0.04 ± 0.11	9%	0.082
GLG (ml)	282.42 ± 130.87	283.36 ± 141.29	2.06 ± 89.51	1%	0.955

Note: Values are presented as mean $\pm$ SD.
Abbreviations: GLG, global lung glycolysis; HD, high dose; LD, low dose; RT, radiotherapy; SUV, standard uptake value.
*$p < 0.05$.

is obtained by multiplying the SUVmean and lung volume. It is a derivative of total lesion glycolysis (TLG). TLG is a parameter for evaluating tumor activity and a prognostic factor of the tumor. TLG is focused on a lesion. In contrast, GLG is focused on the lung. Several studies have used GLG to detect normal tissue inflammation.[16,21]

The calculation method is as follows:

$$GLG\ (cm^3) = SUVmean \times volume\ (cm^3)$$

CT grading of radiation pneumonitis

According to the Common Terminology Criteria for Adverse Events version 4.0,[22] RP was identified through clinical symptoms and the radiographic changes on the CT images in the pre- and post-RT PET/CT scans. RP ($\geq$ grade 1) was interpreted by two senior physicians (C.X. Hsu and S.Y. Wang) at our institution.

CT simulation and radiation treatment planning

The CT simulation images were input into the Pinnacle treatment planning system (version 9.8; Philips Medical

Systems North America) to design the RT plan. The clinical tumor volume (CTV) was designed to cover a region with subclinical disease from gross tumor volume (GTV) by expanding 4 cm superiorly and inferiorly, and 0.5 cm laterally on both sides, anteriorly and posteriorly. To define the planning target volume (PTV), organ movements caused by breathing, swallowing, and position uncertainty in each therapy were considered. The normal organs such as the heart, lungs, and spinal cord were defined. According to the size and shape of the tumor, different gantry arc angles were designed by medical physicists. The prescribed dose to the PTV and the dose constraints of organs at risk were based on the International Commission on Radiation Units and Measurements Report 50 (ICRP 50), and esophageal and esophagogastric junction cancers, version 1.2015, NCCN Clinical Practice Guidelines in Oncology.[23] The mean lung dose (MLD), V_5, V_{10}, V_{15}, V_{20}, V_{25}, and V_{30} in the lungs were collected. A dose-volume histogram parameter of Vx was defined as the percentage of the organ volume exceeding a radiation dose of x (Gy).

Image fusion and the high- and low-dose regions segmentation

The PET images and the simulation CT images were fused using the MIM vista treatment planning system (version 6.8.4, MIM Software Inc.). The images were adjusted and aligned based on the myocardium and spine. The

TABLE 3 Comparison of the inflammatory changes in RP and nRP lungs between pre-RT and post-RT

	Pre-RT	Post-RT	*p* value
RP lungs (*n* = 30)			
Right lungs (*n* = 14)			
HD region			
SUVmax	2.10 ± 0.60	2.83 ± 0.79	0.002*
SUVmean	0.52 ± 0.12	0.64 ± 0.21	0.040*
GLG (ml)	314.98 ± 151.93	394.29 ± 206.68	0.044*
LD region			
SUVmax	2.01 ± 0.60	2.06 ± 0.44	0.721
SUVmean	0.43 ± 0.10	0.51 ± 0.16	0.049*
GLG (ml)	452.58 ± 202.19	500.59 ± 178.43	0.222
Left lungs (*n* = 16)			
HD region			
SUVmax	2.05 ± 0.38	2.68 ± 0.52	0.000*
SUVmean	0.51 ± 0.12	0.65 ± 0.20	0.001*
GLG (ml)	348.26 ± 115.15	451.61 ± 207.45	0.020*
LD region			
SUVmax	1.77 ± 0.59	1.95 ± 0.55	0.319
SUVmean	0.42 ± 0.11	0.51 ± 0.15	0.007*
GLG (ml)	245.36 ± 131.97	289.99 ± 159.11	0.016*
nRP lungs (*n* = 22)			
Right lungs (*n* = 11)			
HD region			
SUVmax	2.06 ± 0.47	2.02 ± 0.25	0.786
SUVmean	0.51 ± 0.08	0.51 ± 0.10	0.921
GLG (ml)	278.58 ± 123.79	344.58 ± 173.13	0.282
LD region			
SUVmax	1.79 ± 0.17	1.72 ± 0.20	0.451
UVmean	0.45 ± 0.07	0.44 ± 0.09	0.269
GLG (ml)	483.64 ± 181.87	415.91 ± 188.39	0.206
Left lungs (*n* = 11)			
HD region			
SUVmax	2.04 ± 0.44	2.12 ± 0.29	0.639
SUVmean	0.55 ± 0.10	0.53 ± 0.10	0.246
GLG (ml)	266.64 ± 113.65	327.81 ± 141.17	0.115
LD region			
SUVmax	1.77 ± 0.30	1.97 ± 0.41	0.203
SUVmean	0.45 ± 0.08	0.45 ± 0.10	0.759
GLG (ml)	332.18 ± 113.09	279.59 ± 118.74	0.118

Note: Values are presented as mean ± SD.
Abbreviations: GLG, global lung glycolysis; HD, high dose region; LD, low dose region; nRP, non-radiation pneumonitis; RP, radiation pneumonitis; RT, radiotherapy; SUV, standard uptake value.
*p < 0.05.

Hounsfield unit (HU) between −950 HU and −250 HU was defined as the lung volume on CT images,[4] and the regions overlapping with the trachea and bronchus were manually removed. To avoid the ^{18}F-FDG uptake of the chest wall from affecting the calculation of inflammatory changes in the lung, the lung volume was obtained by shrinking a 1.5-mm thick slab inward from its original three-dimensional boundary in simulation CT. Spill-out artifacts appeared in the ^{18}F-FDG high uptake area of the heart, liver, and lesion, which affected the ^{18}F-FDG value in the adjacent regions,[24] therefore the regions with SUV higher than 2.5 in the thoracic cavity were subtracted.[25]

According to the VBA established by our team,[17] we proposed the VBA method to reduce lung V_5 in dynamic arc-based RT. Therefore, we integrated the irradiated lung volume in RT planning and volume-based parameters in PET/CT. We used the 5 Gy isodose curve to define the high-dose (HD) (≧5 Gy) and low-dose (LD) (<5 Gy) regions in the lung volume (Figure 2) to assess lung inflammatory changes pre- and post-RT. The SUVmean, SUVmax, and GLG of the HD and LD regions in the lungs were quantified in the pre- and post-RT PET/CT, respectively.

Statistical analysis

The SPSS software package (version 24.0; IBM Corporation) was used for statistical analysis. A two-tailed paired *t*-test was used to compare the inflammatory changes of the HD and LD regions between pre- and post-RT. An independent *t*-test was used to compare the inflammatory changes of the HD and LD regions as well as lung dose between RP and nRP lungs. A *p* < 0.05 was considered statistically significant. Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were estimated for each marker. Receiver operator characteristic (ROC) curves and area under the curves (AUCs) of lung inflammatory changes and lung dose were performed, and the optimal cut-off value was determined by the Youden index.[26]

RESULTS

Patient population

Thirty esophageal cancer patients treated with VMAT were included between 2014 and 2018. The detailed patient characteristics are shown in Table 1. The median of the prescribed dose to PTV was 45 Gy. The median interval time between pre-RT ^{18}F-FDG PET/CT and RT was 17 days (range 12–29 days). The median interval time between RT and post-RT ^{18}F-FDG PET/CT was 37 days (range 21–89 days). The median interval time between the pre- and post-RT ^{18}F-FDG PET/CT scans was 68 days (range 98–174 days). Eleven patients were identified as the nRP group and 19 patients were identified as the RP (≥ grade 1) group. Twenty-two nRP lungs and 30 RP (≥ grade 1) lungs were identified. There were 14 right lungs and 16 left lungs with RP in 30 lungs.

^{18}F-FDG PET inflammatory changes in lungs

Table 2 shows the inflammatory changes of the HD and LD regions in the right and left lungs between pre-RT and post-
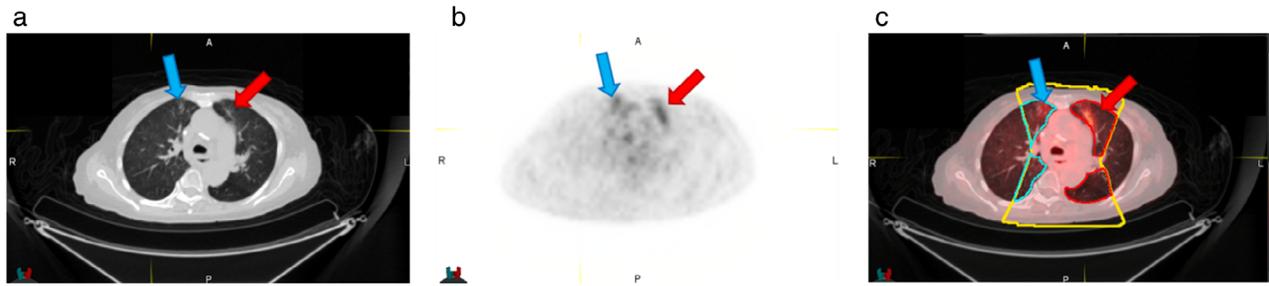
FIGURE 3   The inflammatory changes of the high-dose (HD) region in fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) after radiotherapy in one esophageal cancer patient with radiation pneumonitis (RP). (A) RP with linear infiltration changes interpreted in CT images (blue arrow and red arrow). (B) Increased ^{18}F-FDG uptake of the left lung (red arrow) and right lung (blue arrow) in PET images. (C) Integration of the lung dose-volume in RT planning and volume-based parameters in PET/CT. The yellow line is 5 Gy isodose curve. The blue line is the right HD region. The red line is the left HD region. The inflammatory changes of the HD region can be quantified in the left lung (SUVmax 2.43, SUVmean 0.73, GLG 368.27 ml) and right lung (SUVmax 2.82, SUVmean 1.13, GLG 472.9 ml). GLG, global lung glycolysis; RP, radiation pneumonitis; SUVmax, SUVmean, maximum and minimum standardized uptake values

TABLE 4   Comparison of post-RT inflammatory changes and RT dose between 30 RP and 22 nRP lungs

Parameter	RP lungs ($n = 30$)	nRP lungs ($n = 22$)	p value
Post-RT inflammatory changes in HD region			
SUVmax	2.78 ± 0.64	2.07 ± 0.27	0.000*
SUVmean	0.64 ± 0.20	0.52 ± 0.10	0.015*
GLG (ml)	422.43 ± 204.77	336.26 ± 155.18	0.104
RT dose of lung			
Mean lung dose (Gy)	10.15 ± 3.88	8.11 ± 2.83	0.041*
V_5 (%)	49.78 ± 17.69	38.07 ± 11.86	0.010*
V_{10} (%)	32.25 ± 12.20	24.71 ± 8.80	0.017*
V_{15} (%)	22.38 ± 10.01	17.43 ± 7.81	0.060
V_{20} (%)	16.32 ± 8.47	13.24 ± 6.68	0.165
V_{25} (%)	12.49 ± 7.30	10.21 ± 5.69	0.230
V_{30} (%)	9.39 ± 6.10	7.73 ± 4.78	0.293

Note: Values are presented as mean $\pm$ SD. V_x, percentage of the total organ volume exceeding a radiation dose of x (Gy).

Abbreviations: GLG, global lung glycolysis; HD, high dose region; nRP, nonradiation pneumonitis; RP, radiation pneumonitis; RT, radiotherapy; SUV, standard uptake value.

*$p < 0.05$.

RT. There were significant increases in SUVmax, SUVmean, and GLG of the HD regions between pre-RT and post-RT. However, there were no significant differences in SUVmax, SUVmean, and GLG of the LD regions between pre-RT and post-RT.

^{18}F-FDG PET inflammatory changes in RP and nRP lungs between pre-RT and post-RT

Table 3 shows the inflammatory changes in RP and nRP lungs between pre-RT and post-RT. In RP lungs ($n = 30$) between pre-RT and post-RT SUVmax, SUVmean, and GLG of the HD regions showed significant increases (all

$p < 0.05$). However, there were no significant differences in the inflammatory changes of the HD and LD regions in nRP lungs. The inflammatory changes of HD regions in PET/CT images from one patient with RP are shown in Figure 3.

Table 4 shows the post-RT inflammatory changes and the RT dose between RP and nRP lungs. The post-RT SUVmax (2.78 vs. 2.07, $p = 0.000$) and post-RT SUVmean (0.64 vs. 0.52, $p = 0.015$) of the HD regions in RP lungs were significantly higher than those of the HD regions in nRP lungs. However, there were no significant differences in the GLG of the HD regions between RP and nRP lungs. The MLD (10.15 Gy vs. 8.11 Gy, $p = 0.041$), lung V_5 (49.78% vs. 38.07%, $p = 0.010$), and lung V_{10} (32.25% vs. 24.71%, $p = 0.017$) of the RP lungs were significantly higher than for nRP lungs.

ROC curve analysis, AUCs, and cut-off values

The sensitivity, specificity, PPV, NPV, and AUC of post-RT inflammatory changes and RT dose are presented in Table 5. In the post-RT inflammatory changes, the single most sensitive predictor was GLG (83.33%), and the most specific, best positive predictor and best negative predictor was SUVmax (specificity 86.36%, PPV 88.90%, NPV 76.00%). The AUCs of post-RT SUVmax, post-RT SUVmean, and post-RT GLG of the HD regions were 0.852 ($p = 0.000$, 95% confidence interval [CI] 0.719–0.931), 0.667 ($p = 0.025$, 95% CI 0.523–0.792), and 0.668 ($p = 0.029$, 95% CI 0.524–0.793), respectively, for discriminating the RP and nRP lungs (Figure 4). The differences of areas in the AUC between post-RT SUVmax and post-RT SUVmean, post-RT SUVmax and post-RT GLG, and post-RT SUVmean and post-RT GLG were 0.179 ($p = 0.020$), 0.179 ($p = 0.038$), and 0.0007 ($p = 0.993$), respectively. An ROC analysis of RP demonstrated that the AUC for post-RT SUVmax was greater than those for post-RT SUVmean or post-RT GLG. Thus, the optimal cut-off value of post-RT SUVmax was 2.28.

TABLE 5 Sensitivity, specificity, PPV, NPV, and AUC of post-RT inflammatory changes and RT dose used in 30 RP and 22 nRP lungs

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	AUC % (95% CI)
Post-RT inflammatory changes in HD region					
UVmax	80.00 (61.4–92.3)	86.36 (65.1–97.1)	88.9 (73.4–95.9)	76.0 (60.3–86.8)	84.6 (71.9–93.1)
SUVmean	60.00 (40.6–77.3)	72.73 (49.8–89.3)	75.0 (58.8–86.3)	57.1 (44.5–68.9)	66.7 (52.3–79.2)
GLG	83.33 (65.3–94.4)	54.55 (32.2–75.6)	71.4 (60.6–80.2)	70.6 (49.7–85.3)	66.8 (50.4–79.3)
RT dose of lung					
Mean lung dose	63.33 (43.9–80.1)	72.73 (49.8–89.3)	76.0 (60.3–86.8)	59.3 (46.0–71.3)	66.5 (52.1–79.0)
V_5	60.00 (40.6–77.3)	81.82 (59.7–94.8)	81.8 (63.9–92.0)	60.0 (48.1–70.8)	72.7 (58.6–84.1)
V_{10}	73.33 (54.1–87.7)	63.64 (40.7–82.8)	73.3 (60.3–83.3)	63.6 (47.2–77.4)	71.1 (56.9–82.9)

Note: Sensitivity = TP/TP + FN, specificity = TN/TN + FP, PPV = TP/TP + FP, NPV = TN/TN + FN. V_x, percentage of the total organ volume exceeding a radiation dose of x (Gy).
Abbreviations: AUC, area under the curve; CI, confidence interval; GLG, global lung glycolysis; HD, high-dose region; NPV, negative predictive value; PPV, positive predictive value; nRP, nonradiation pneumonitis; RP, radiation pneumonitis; RT, radiotherapy; SUV, standard uptake value.
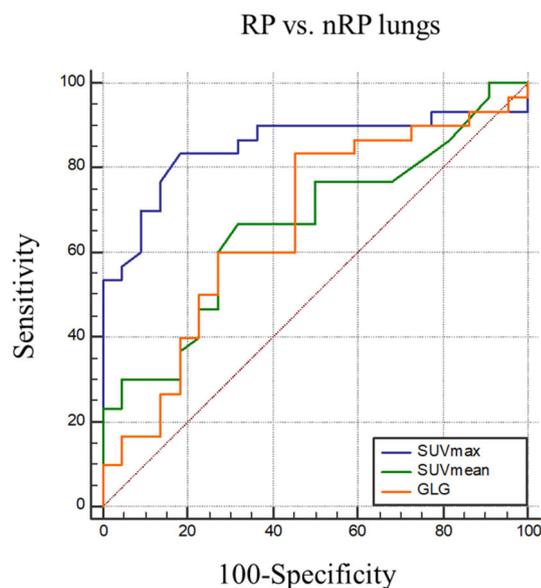
FIGURE 4 Comparison of area under the receiver operating characteristic curve of post-RT SUVmax, post-RT SUVmean, and post-RT GLG of high-dose regions for discriminating between RP and nRP lungs. GLG, global lung glycolysis; MLD, mean lung dose; nRP, nonradiation pneumonitis; RP, radiation pneumonitis; RT, radiotherapy; SUVmax, SUVmean, maximum and minimum standardized uptake values; V_x, percentage of the total organ volume exceeding a radiation dose of x (Gy)

FIGURE 5 Comparison of area under the receiver operating characteristic curve of mean lung dose (MLD), lung V_5, and lung V_{10} for discriminating between RP and nRP lungs. nRP, nonradiation pneumonitis; RP, radiation pneumonitis; V_x, percentage of the total organ volume exceeding a radiation dose of x (Gy)

In the RT dose to lung, the single most sensitive and best negative index was V_{10} (sensitivity 73.33%, NPV 63.60%), and the most specific and best positive index was V_5 (specificity 81.82%, PPV 81.80%) (Table 4). The AUCs of MLD, lung V_5, and lung V_{10} were 0.665 ($p = 0.031$, 95% CI 0.521–0.790), 0.727 ($p = 0.001$, 95% CI 0.586–0.841), and 0.711 ($p = 0.003$, 95% CI 0.569–0.829), respectively, for discriminating between the RP and nRP lungs (Figure 5). The differences of areas in the AUC between MLD and lung V_5, MLD and V_{10}, and lung V_5 and V_{10} were 0.062 ($p = 0.070$), 0.046 ($p = 0.063$), and 0.015 ($p = 0.609$), respectively. An ROC analysis of RP demonstrated that the AUC for lung V_5 was

greater than those for MLD or lung V_{10}. The optimal cut-off value of lung V_5 was 47.14%.

DISCUSSION

Increased ^{18}F-FDG uptake occurs not only in tumor cells with upregulated glucose transporter but also in the inflammatory process of normal tissue with cellular hypermetabolism.[27] In recent years, several studies have used ^{18}F-FDG PET/CT to assess and quantify the inflammation of lung tissue after RT for thoracic cancers.[21,28] Our study assessed lung inflammation between HD and LD regions by integrating ^{18}F-FDG PET/CT with VBA in esophageal cancer

patients undergoing dynamic arc-based RT. We found that the SUVmax, SUVmean, and GLG increased significantly in the HD regions of RP lungs between pre- and post-RT. The present study indicated that the post-RT SUVmax > 2.28 of HD regions lungs may be a potential indicator of RP and lung V_5 can be less than 47.14% to prevent RP.

Several studies have demonstrated that ^{18}F-FDG PET/CT could be used to evaluate RP after RT.[9,29,30] Yue et al.[24] found that the changes of SUVmax, SUVmean, and GLG in lungs could detect the severity of RP during the first 6 months after treatment. Abdulla et al.[16] indicated that SUVmean and GLG in lung parenchyma could be potential biomarkers to quantify RP after thoracic RT in lung cancer. De Ruysscher et al.[31] found that the SUVmax is highly correlated with clinical radiation-induced lung toxicity during the first week of thoracic RT. In the abovementioned studies, the analysis of the volume of interests was divided into the affected lung, the nonaffected lung, or the global lung volume to measure the inflammatory changes. However, the nonaffected lung would still receive LD radiation $\geqq$5 Gy during RT for lung cancer and esophageal cancer. Numerous studies have reported that the lung V_5 might reach as high as 40–60% in esophageal cancer, which indicates that 40–60% of the lung volume might receive absorbed doses of $\geqq$5 Gy. LD radiation could be a significant predictor of RP.[6,7,32] Based on the VBA,[17] the present study used the 5 Gy isodose curve to define the HD ($\geqq$5 Gy) and LD (<5 Gy) regions in the lung volume to assess the relationship between inflammatory changes and absorbed dose. There were statistically significant increases in the SUVmax, SUVmean, and GLG of HD regions between pre- and post-RT. Furthermore, we found that there were no statistically significant increases in the SUVmax, SUVmean, and GLG of LD regions between pre- and post-RT.

Researchers have found that radiation-induced lung inflammation may develop after the lungs received higher radiation doses.[4,33] Radiographically evident changes are uncommon when the total radiation dose delivered is less than 30 Gy, but they are almost always seen with doses higher than 40 Gy.[34,35] Furthermore, Zhang et al.[19] showed that there was a significant difference in the SUVmean of the lungs with RP group received more than 35 Gy for nonsmall-cell lung cancer patients. It should be noted that several studies have evaluated patients with symptomatic RP ($\geq$ grade 2) and asymptomatic RP by using volume-based ^{18}F-FDG PET.[19,24] Yue et al.[24] found the cut-off values of SUVmax, SUVmean, and GLG of 4.54, 0.78, and 2295, respectively, after RT predicted later development of symptomatic RP ($\geq$ grade 2). The present study found that there were significant differences between pre- and post-RT SUVmax, SUVmean, and GLG of the HD regions in RP lungs. We found the optimal cut-off values of post-RT SUVmax, post-RT SUVmean, and post-RT GLG were 2.28, 0.56, and 287.65 for detection of RP, respectively. The cut-off values in this study were lower than those of Yue et al. The main reason for this was probably that we aimed to detect asymptomatic and symptomatic RP ($\geq$ grade 1) while they detected symptomatic RP ($\geq$ grade 2), therefore the cut-off

value might be more sensitive to detect asymptomatic RP. Our study showed that post-RT SUVmax with the highest AUC has a sensitivity of 80% and a specificity of 86.36%. Post-RT SUVmax >2.28 could be used as an early indicator for RP with grade $\geq$1.

It is common to assess the relationship between radiation absorbed dose and the risk of symptomatic RP. Graham et al.[36] indicated that the incidence of grade $\geq$2 RP was associated with the V_{20}. Tonison et al.[37] found that the lung V_{20} should be kept below 23% to decrease the incidence of symptomatic RP. Wang et al.[7] demonstrated that lung V_5 was highly related to the risk of RP, and the risks of V_5 < 42% and V_5 > 42% causing RP within 1 year were 3% and 38%, respectively. Pinnix et al.[6] noted that a lung V_5 exceeding 55% was associated with the maximum likelihood ratio for RP. Jo et al.[38] showed a statistically significant association between the development of grade 2–3 RP and pulmonary dosimetric parameters, including lung V_5, V_{10}, V_{15}, V_{20}, V_{25}, and MLD. The AUC value was highest for V_5. However, we evaluated changes of lung dose and inflammatory changes in patients with grade $\geq$1 RP versus nRP to detect the presence of RP at the earlier stage. The results of the present study revealed that there were significant differences between RP and nRP in MLD, lung V_5, and lung V_{10}. However, there were no significant differences for lung V_{15}, V_{20}, and V_{25}. Lung V_5 has the highest AUC, with a sensitivity of 60.00% and specificity of 81.82%, similar to the results of the previous study. We recommend limiting V_5 to $\leqq$47.14% to decrease the incidence of grade $\geq$1 RP. Additionally, it was possible to define the HD and LD regions to assess RP by using the 5 Gy isodose in our study.

There were some limitations in this study. First, this study was a retrospective pilot study and we only analyzed the existing clinical data. Most esophageal cancer patients did not regularly have ^{18}F-FDG PET/CT scans within 3 months after RT, which resulted in the relatively small sample size in this study. Therefore, larger prospective studies with more patients are needed to verify the optimal cut-off value for RP. Second, the interval time between completion of RT and post-RT PET/CT scans ranged from 21 to 89 days. The degree of metabolism may change in different stages of the inflammatory process. The interval time of PET/CT scans could be standardized in a future study. Third, the two PET/CT scans were performed before and after RT treatment, therefore the lung volume might change in different PET/CT scans, somehow leading to the GLG changing. Finally, the fusion and registration of simulation CT images and PET/CT images were based on the experience of the operators in this study. There might be some inconsistencies in the manual operation.

CONCLUSION

This study successfully integrated ^{18}F-FDG PET/CT with VBA to assess RP in esophageal cancer patients undergoing dynamic arc-based RT. The post-RT SUVmax and post-RT

SUVmean of HD (≥ 5 Gy) regions can be used to evaluate RP. The post-RT SUVmax > 2.28 of HD regions and lung $V_5 > 47.14\%$ might be potential indicators of RP. ^{18}F-FDG PET/CT is a promising tool to detect RP for esophageal cancer patients treated with arc-based RT.

CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The institutional review board of Far Eastern Memorial Hospital (No. 108069-E) approved this retrospective study and waived the need for written informed consent.

ORCID

Tung-Hsin Wu https://orcid.org/0000-0002-0583-7921

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