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ORIGINAL RESEARCH

^{18}F-fluorodeoxyglucose positron emission tomography predicts lymph node responses to definitive chemoradiotherapy in esophageal squamous cell carcinoma patients

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Purpose: To evaluate the capability of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) to predict the clinical response of metastatic lymph node (mLN) to definitive chemoradiotherapy (dCRT) and guide personalized radiation dose in esophageal squamous cell carcinoma (ESCC) patients.

Patients and methods: One hundred and forty-three mLNs from 59 patients with ESCC treated with dCRT and who had undergone a pretreatment ^{18}F-FDG-PET/CT scan were included in the study. All defined mLNs were contoured by nuclear medicine radiologists. Response was evaluated by contrast-enhanced computed tomography and ^{18}F-FDG-PET/CT.

Results: Sixty-nine mLNs showed complete response (CR), and 74 mLNs showed non-complete response. The 143 mLNs were divided into 4 groups (Groups 1–4) based on the quartiles of maximum standardized uptake value (SUVmax-G1, SUVmax-G2, SUVmax-G3, and SUVmax-G4) and metabolic tumor volume (MTV-G1, MTV-G2, MTV-G3, and MTV-G4). The CR rate of SUVmax-G2 was significantly higher than the other 3 groups. The escalated radiation dose improved the CR rate of lymph nodes in SUVmax-G3 (55 Gy) and SUVmax-G4 (61 Gy). The lowest CR rate was found in MTV-G4 (the group with the largest MTV). The escalated radiation dose (59.7 Gy) improved the CR rate of lymph node in MTV-Groups 3 and 4.

Conclusion: Pretreatment metabolic parameters can predict the response of mLNs to dCRT for patients with ESCC. The parameters could also be used to guide personalized dose to mLNs.

Keywords: ^{18}F-FDG-PET/CT, esophageal squamous cell carcinoma, radiotherapy, lymph node, response, radiation dose, personalized radiation dose

Introduction

Esophageal cancer (EC) is one of the common malignancies and causes of cancer deaths worldwide.[1] Esophageal squamous cell carcinoma (ESCC) is the predominant histological type of EC worldwide, especially in Asia.[2]

At present, the standard care for the locally advanced unresectable ESCC is definitive chemoradiotherapy (dCRT).[3,4] According to the results of the RTOG 90-12 study and INT0123 trial, dose escalation from 50.4 to 64.8 Gy did not improve the overall survival (OS) and pathological complete response (pCR), but increased the toxicity. The National Comprehensive Cancer Network guidelines recommended a radiation dose of 50.4 Gy to patients with ESCC for dCRT.[5–7]

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Previous studies have suggested that response of lesions (primary tumor and metastatic lymph nodes [mLNs]) is a major determinant of recurrence and survival for patients with ESCC.[8–10] Lin et al found the pCR can predict OS (48.2 vs 19.7 months) and disease-free survival (31.1 vs 6.1 months) in patients treated with dCRT.[11]

Most of the studies on ESCC have focused on the primary tumor and indicated that escalated dose failed to improve local control (LC) or survival.[5,6,12] However, only little attention has been paid to mLN, although recent studies have indicated response of mLN is a novel prognostic factor for ESCC.[13] For nodal lesions, a higher radiation dose may lead to a better response compared with the standard dose of 50.4 Gy based on the theory of radiation biology, which may confer a better prognosis.[14] In addition, the advanced radiotherapy technologies, such as simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) techniques, allow selectively increasing the dose to partial lesions, while sparing the normal tissues and subclinical lesions.[15,16]

The challenge is to correctly identify the involved node which can gain a better response from the escalated dose before dCRT. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) parameters including maximum standardized uptake value (SUVmax) and metabolic tumor volume (MTV) may be promising biomarkers to predict the response of lesions and prognosis in patients with ESCC.[17–19]

The major aim of the present study is to evaluate the relationship between ^{18}F-fluorodeoxyglucose (FDG) metabolic level and response of mLNs that received different irradiation doses. Our study may guide personalized radiation dose to mLN for a better outcome. To our knowledge, this has not been studied previously.

Methods

Patients and mLNs selection

Retrospectively, 59 consecutive patients with biopsy-proven locally advanced ESCC treated with dCRT in the years 2011–2017 who underwent ^{18}F-FDG-PET/CT scan before treatment were included in the study. All patients gave written informed consent to participate in the study, which was approved by the Ethics Committee of the Shandong Cancer Hospital and Institute. mLNs were defined as follows: SUVmax >2.5 and short axis >0.5 cm.

Pretreatment evaluation

The extent of disease was evaluated by esophagoscopy, barium esophagography, computed tomography (CT), and ^{18}F-FDG-PET/CT in all patients. The clinical stage was defined according to the criteria of the American Joint Committee on Cancer.

dCRT

Radiotherapy (RT) was delivered as either 3-dimensional conformal RT or IMRT with high-energy linear accelerators. Radiation was given at a dose of 1.8 or 2 Gy once daily for 5 days/week up to a total dose of 50.4–68.4 Gy to lesions (primary tumor and mLNs). The primary tumor and mLNs were contoured as gross tumor volume – tumor (GTVt) and gross tumor volume – nodes (GTVn), respectively. Clinical tumor volume (CTV, including CTVt and CTVn) was defined as GTV plus a 3.0 cm margin superior and inferior to the primary tumor, and a 1.0 cm radial margin plus the regional draining lymphatics. The planning target volume included each plan with a margin of 5–8 mm. Details are shown in Figure 1.

All patients were treated with 2–3 cycles of chemotherapy concurrent with RT. The chemotherapy regimens used in this study included 5-Fu/platinum, docetaxel/platinum, paclitaxel/platinum, and others. Baseline data of patients and treatment characteristics are shown in Table 1.

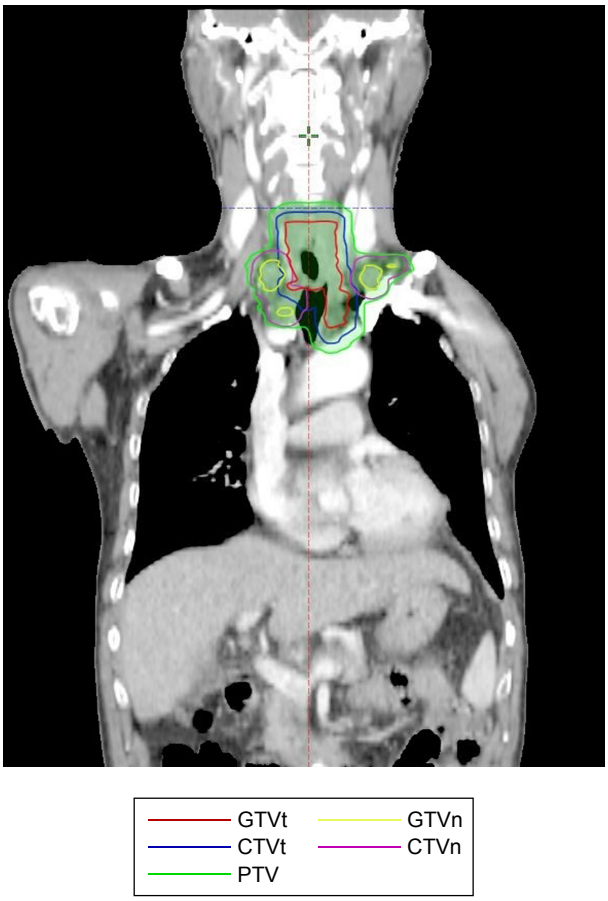

Figure 1 Target area of radiotherapy in the study.
Abbreviations: GTVt, gross tumor volume – tumor; GTVn, gross tumor volume – nodes; CTVt, clinical tumor volume – tumor; CTVn, clinical tumor volume – nodes; PTV, planning target volume.

Table 1 Baseline data of patients and tumor characteristics

Characteristics	Value	Percentage
Age (years)		
Median	59	
Range	44–80	
Sex		
Female	11	18.6
Male	48	81.4
Tumor length (cm)		
Median	4.5	
Range	1–10	
T category		
T_2	9	15.3
T_3	28	47.5
T_4	22	37.3
Lymph node category		
N_1	37	62.7
N_2	13	22.0
N_3	9	15.3
Tumor location		
Cervical	8	13.6
Upper thoracic	23	39.0
Mid-thoracic	17	28.8
Lower thoracic	11	18.6
Chemotherapy		
5-Fu/platinum	19	32.2
Paclitaxel/platinum	16	27.1
Docetaxel/platinum	13	22.0
Others	11	18.6
Radiotherapy dose (Gy)	50.4–68.4	

^{18}F-FDG PET/CT imaging

The ^{18}F-PET/CT scans were performed before dCRT with an integrated scanner (Discovery LS PET/CT System; GE Healthcare). All patients fasted and rested for at least 6 h, and the blood glucose level had to be <150 mg/dL before intravenous injection of ^{18}F-FDG at a dose of 5.5 MBq/kg body weight. Whole-body images were acquired approximately 60 min after injection. PET images were acquired from the head to the proximal thigh for 5 min per field of view, each covering 14.5 cm, at an axial sampling thickness of 4.25 mm per slice. Low-dose CT data were collected in helical acquisition mode. PET data sets were reconstructed iteratively using CT data for attenuation correction. PET, CT, and fused PET/CT images displayed as coronal, sagittal, and transaxial slices, respectively, were viewed on the Xeleris workstation (GE Healthcare, Chicago, IL, USA).

^{18}F-FDG-PET/CT analysis

PET images were transferred to the workstation in Digital Imaging and Communications in Medicine format. Using a semiautomatic gradient-based contouring algorithm (PET Edge), all visible hypermetabolic lesions were contoured for each patient by 2 experienced nuclear medicine radiologists without knowledge of the patients' history.

The SUVmax of the lesion was measured by placing a volume of interest around the visible lesion, with careful attention to avoid inclusion of ^{18}F-FDG-avid normal tissue. MTV was defined as the total volume of lesion with an SUV greater than the defined threshold of 2.5 in body in milliliters.

Lymph node response evaluation

Response of lesions to dCRT was evaluated within 4–8 weeks after dCRT using contrast-enhanced CT or ^{18}F-FDG-PET/CT, and was identified as 4 classes including progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). PD was defined as an increase of at least 20% in a lesion as measured bidimensionally, the appearance of any new lesions, or reappearance of a previously eradicated lesion. PR was defined as a decrease in the lesion, as measured bidimensionally, by at least 30% with no signs of either new lesions or progression of any existing lesions. SD was defined as a tumor response that did not fulfill the PR criteria but exceeded the PD criteria. CR was defined as the condition of disappearance of involved lymph node or no FDG-avid lesions. We define mLNs which had an outcome of PD, SD, and PR as mLNs with non-complete response (non-CR) in this article.

Statistical analysis

Statistical analyses were performed using SPSS software, version 23.0. Quantitative data for SUVmax and MTV are expressed as mean±standard deviation. mLNs were grouped based on the quartiles of metabolic parameters. Chi-square test was used to analyze the difference in CR rate among groups. Differences in parameters were analyzed by Mann–Whitney *U* test, independent-samples *t*-test, and ANOVA test. To find the effect of escalated dose in every group, receiver-operating characteristic (ROC) curve analysis was used. CR was used as the reference standard. The area under the ROC curve (AUC) provided a measure for the accuracy of response test; it ranged from 0.5 (random guessing) to 1.0 (perfect test). A *P*-value <0.05 from 2-sided tests was considered to indicate statistical significance.

Results

Patient characteristics and clinical outcomes

One hundred and forty-three mLNs of 59 patients met the inclusion criteria for the study. Baseline data of patients and

Table 2 Correlations between the CR and metabolic parameters (mean±SD)

Parameters	Total	CR	Non-CR	*P*-value
Number	173	69	74	
SUVmax	8.91±5.59	8.16±5.16	9.62±5.92	0.313
MTV	17.174±27.35	9.84±11.70	21.92±35.44	0.066

Abbreviations: CR, complete response; non-CR, non-complete response; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume.

treatment characteristics are shown in Table 1. Of the total mLNs, 69 (48.0%) had a CR and 74 (52.0%) showed non-CR. Neither SUVmax nor MTV showed a significant difference between 2 groups (P=0.313 and P=0.066, respectively). The results are summarized in Table 2.

Analysis of SUVmax

Based on the quartiles of SUVmax, mLNs were divided into 4 different groups: Group 1 (SUVmax-G1, 2.82–4.38), Group 2 (SUVmax-G2, 4.38–6.88), Group 3 (SUVmax-G3, 6.88–12.89), and Group 4 (SUVmax-G4, 12.89–28.41). The CR rate was 38.89%, 72.22%, 47.22%, and 34.29%, respectively (all, P=0.006). As shown in Figure 2A and Table 3A, SUVmax-G2 had the best CR rate among the 4 groups (SUVmax-G2 vs SUVmax-G1: P=0.004, SUVmax-G2 vs SUVmax-G3: P=0.031, SUVmax-G2 vs SUVmax-G4: P=0.001). In addition, there were no significant differences among the other 3 groups (all, P>0.05).

To compare the impact of radiation dose on the response of mLNs, univariate analysis was further applied to each

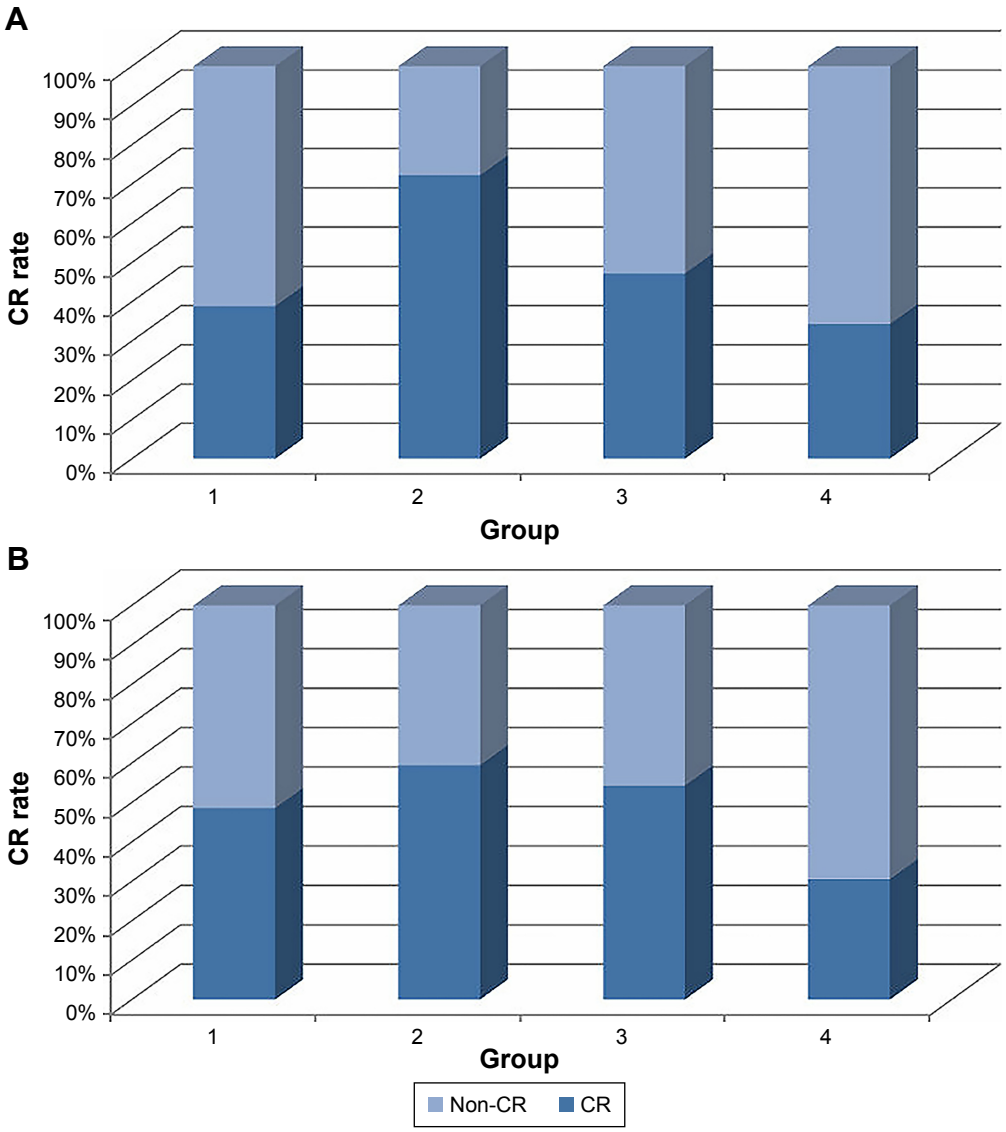

Figure 2 CR rate in groups.
Notes: (**A**) CR rate: 38.89%, 72.22%, 47.22%, and 34.29% in SUVmax groups (SUVmax-G1–SUVmax-G4). (**B**) CR rate: 48.57%, 59.46%, 54.29%, and 30.56% in MTV groups (MTV-G1–MTV-G4).
Abbreviations: CR, complete response; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; non-CR, non-complete response.

Table 3 Range of metabolic parameters in SUVmax (**A**) and MTV (**B**) groups and difference of CR rate among groups

Groups	Parameter range	CR rate (%)	Compared groups	*P*-value	*P*-value
A					
G1	2.82–4.38	38.89	G2	0.004	0.006
			G3	0.475	
			G4	0.687	
G2	4.38–6.88	72.22	G3	0.031	
			G4	0.001	
G3	6.88–12.89	47.22	G4	0.268	
G4	12.89–28.41	34.29	G1–G3	–	
B					
G1	0.256–3.114	48.57	G2	0.534	0.076
			G3	0.632	
			G4	0.120	
G2	3.114–6.229	59.46	G3	0.658	
			G4	0.013	
G3	6.229–16.336	54.29	G4	0.043	
G4	16.336–189.504	30.56	G1–G3	–	

Notes: As G4 in (**A**) and (**B**) were compared with every group, "–" indicates *P*-value not listed. In G1 for (**A**) and (**B**), The first *P*-values was compared with 1 group and the second *P*-value was compared with all groups.

Abbreviations: SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; CR, complete response; G, group.

Table 4 Impact of radiation dose on the response of mLNs in SUVmax (**A**) and MTV (**B**) groups

Group	Response	Mean dose±SD (Gy)	*P*-value	CR rate
A				
G1	CR	60.96±1.96	0.543	48.57
	Non-CR	59.93±4.50		
G2	CR	58.89±4.16	0.556	59.46
	Non-CR	58.28±2.38		
G3	CR	59.68±3.23	0.031	54.29
	Non-CR	57.13±3.25		
G4	CR	61.98±2.51	<0.001	30.56
	Non-CR	56.99±3.94		
B				
G1	CR	60.55±2.92	0.389	48.57
	Non-CR	59.48±4.46		
G2	CR	59.07±4.34	0.500	59.46
	Non-CR	58.59±4.46		
G3	CR	60.05±3.38	0.029	54.29
	Non-CR	59.78±2.68		
G4	CR	61.15±2.08	0.001	30.56
	Non-CR	56.94±3.71		

Abbreviations: mLNs, metastatic lymph nodes; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; CR, complete response; non-CR, non-complete response; G, group.

group. The escalated dose was not found to improve the CR rate in SUVmax-G1 and SUVmax-G2 (SUVmax-G1: *P*=0.543, SUVmax-G2: *P*=0.556). However, higher radiation dose improved the CR rate of mLNs in SUVmax-G3 and SUVmax-G4 (SUVmax-G3: *P*=0.031, SUVmax-G4: *P*=0.0005). Details are shown in Table 4A.

ROC curve analysis was used to identify a dose threshold which could achieve a good response to dCRT. The doses of 55 and 61 Gy were determined as thresholds with corresponding sensitivity of 88.2% and 58.3% and specificity of 42.1% and 91.3% in SUVmax-G3 and SUVmax-G4, respectively. The AUC of radiation dose was 0.703 (*P*=0.038, 95% CI 0.532–0.874) and 0.857 (*P*=0.001, 95% CI 0.730–0.984) in the 2 groups, respectively (Figure 3A and B and Table 5A).

Analysis of MTV

Based on the quartiles of MTV, mLNs were also divided into 4 different groups: Group 1 (MTV-G1, 0.256–3.114), Group 2 (MTV-G2, 3.114–6.229), Group 3 (MTV-G3, 6.229–16.336), and Group 4 (MTV-G4, 12.336–189.504). MTV values of the groups were compared using ANOVA. MTV values of G1–G3 were not significantly different (*P*=0.074), but the MTV of G4 was higher than the other 3 groups (*P*<0.001). The result is shown in Table 6. The CR rate was 48.57%, 59.46%, 54.29%, and 30.56%, respectively (all, *P*=0.076). As shown in Figure 2B and Table 3B, MTV-G4 had the worst CR rate among the 4 groups (MTV-G4 vs MTV-G1: *P*=0.12, MTV-G4 vs MTV-G2: *P*=0.013, MTV-G4 vs MTV-G3: *P*=0.043). In addition, the CR rate was not significantly different for the other 3 groups (all, *P*>0.05).

Similar to SUVmax, the univariate analysis was also applied to each group. The escalated dose was not found to improve the CR rate of mLNs in MTV-G1 and MTV-G2 (MTV-G1: *P*=0.389 and MTV-G2: *P*=0.500). However, higher radiation dose improved the CR rate of mLNs in MTV-G3 and MTV-G4 (MTV-G3: *P*=0.029, MTV-G4: *P*=0.001). Details are shown in Table 4B.

ROC curve analysis was used to find an optimal dose to achieve a good response to dCRT. The dose of 59.7 Gy was

Table 5 Predictive values of SUVmax (**A**) and MTV (**B**) groups in the prediction of CR before dCRT, by ROC analysis

Groups	AUC	Se (%)	Sp (%)	95% CI		*P*-value
				Lower	Upper	
A						
G1	0.558	1.00	18.2	0.371	0.746	0.559
G2	0.562	0.731	0.4	0.359	0.764	0.572
G3	0.703	88.2	42.1	0.532	0.875	0.038
G4	0.857	58.3	91.3	0.730	0.984	0.001
B						
G1	0.589	0.765	0.5	0.389	0.778	0.400
G2	0.436	ND	ND	0.242	0.631	0.516
G3	0.711	68.4	68.7	0.539	0.882	0.034
G4	0.824	100.0	56.0	0.691	0.957	0.002

Abbreviations: SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; CR, complete response; dCRT, definitive chemoradiotherapy; ROC, receiver-operating characteristic; AUC, area under the ROC curve; Se, sensitivity; Sp, specificity; G, group; ND, no difference.

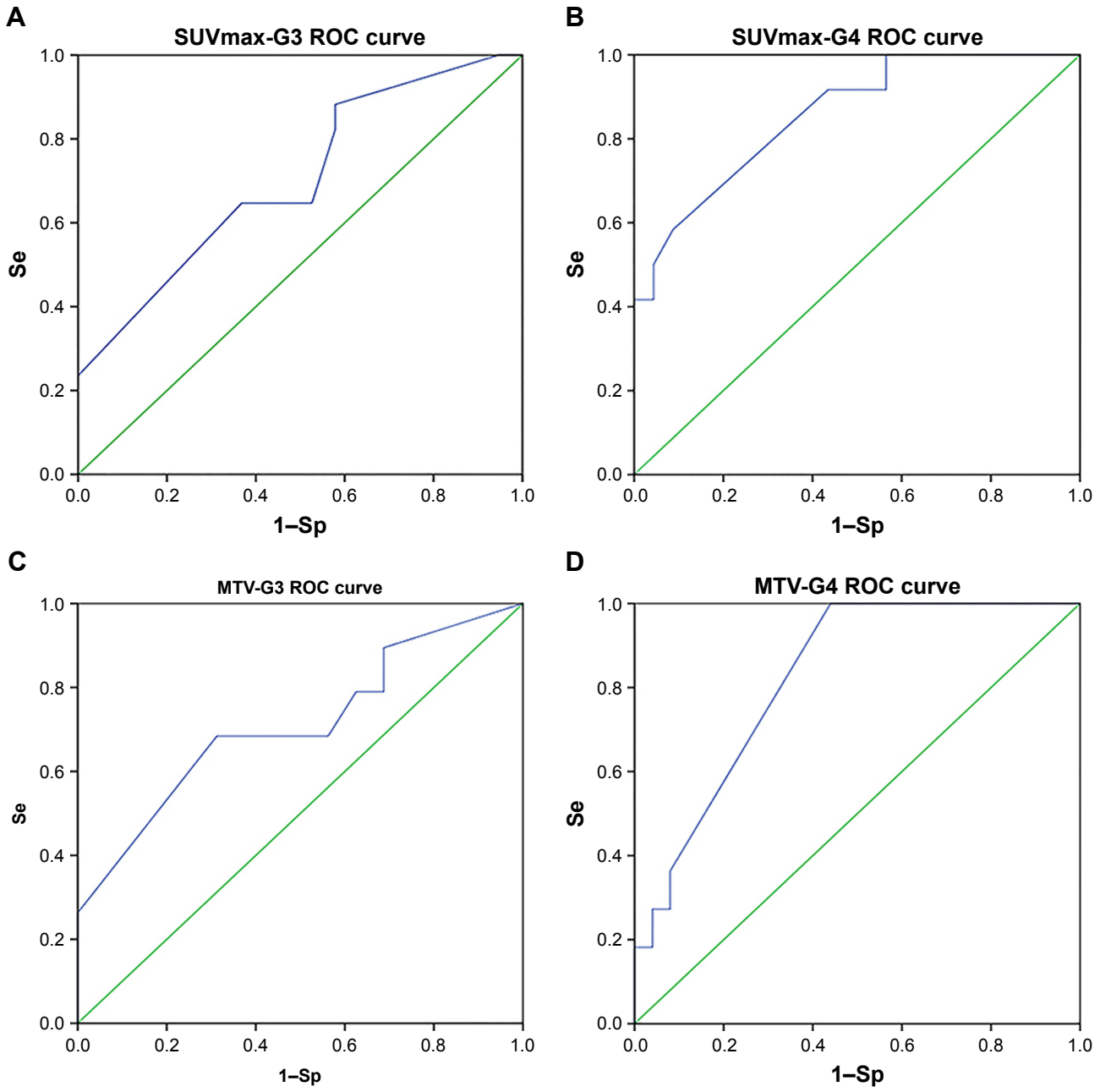

Figure 3 ROC curve in (**A**) SUVmax-G3, (**B**) SUVmax-G4, (**C**) MTV-G3, and (**D**) MTV-G4.
Notes: The green line represents reference axis. The blue line represent ROC curve radiotherapy dose.
Abbreviations: ROC, receiver-operating characteristic; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; G, group; Se, sensitivity; Sp, specificity.

Table 6 Comparison of MTV group by group

Group	Compared groups	*P*-value	*P*-value
G1	G2	0.534	<0.001
	G3	0.062	
	G4	<0.001	
G2	G3	0.202	
	G4	<0.001	
G3	G4	<0.001	
G4	G1–G3	–	

Notes: As G4 was compared with every group, "–" indicates *P*-value not listed. In G1, the first *P*-values was compared with 1 group and the second *P*-value was compared with all groups.
Abbreviations: MTV, metabolic tumor volume; G, group.

optimal with corresponding sensitivity of 68.4% and 100% and specificity of 68.7% and 56% in MTV-G3 and MTV-G4, respectively. The AUC of radiation dose was 0.711 (P=0.034, 95% CI 0.539–0.882) and 0.824 (P=0.002, 95% CI 0.691–0.957) in the 2 groups, respectively (Figure 3C and D and Table 5B).

Discussion

In the present study, we retrospectively analyzed 143 mLNs from 59 patients with ESCC treated with dCRT. Although SUVmax and MTV did not show any significant difference

between the CR group and non-CR group, we found that patients with different metabolic levels were showing different CR rates by dividing them into 4 groups. For example, the CR rate of mLNs in Group 2 with an SUVmax range of 4.38–6.88 was significantly higher than the other 3 groups. An escalated dose (eg, 55 and 61 Gy) may improve the CR rate of patients with higher SUVmax. For MTV, the lowest CR rate was found in the group with the largest MTV. An escalated dose (eg, 59.7 Gy) may improve the lymph nodal CR rate in the groups with larger MTV (Groups 3 and 4), which suggests that these parameters could be used to guide personalized radiation dose to mLNs before dCRT.

Some studies reported that lesions with low SUVmax could show higher CR rate than those with high SUVmax leading to potentially better LC and survival.[11,19–21] However, some conflicting results revealed high initial SUVmax was associated with good response.[22,23] Previous studies also revealed lesions with larger MTV always exhibited worse response.[24–26]

In view of the inconsistent outcomes, our study divided these mLNs into 4 subgroups with different metabolic levels (SUVmax and MTV) instead of the simple 2 groups (lower and higher metabolic groups) adopted in the available studies. According to our data, we found higher metabolic mLNs could show significantly bad response. However, the response of mLNs with the lowest FDG uptake was found to be worse in our study. The outcome may be consistent with previous studies comparing lower and higher metabolic groups. All of these data suggested that metabolic and biological heterogeneity of cancer was not interpreted fully by the simple 2 groups.

Some reports indicated FDG uptake was correlated with proliferative activity in various malignancies.[27–29] Based on radiobiology, the lower proliferative activity was associated with resistance to irradiation.[30] In addition, for lesions with lower metabolism, the poor response could be improved by hypofractionated irradiation.[31] However, we did not find that an escalated dose could improve the CR rate (SUVmax-G1: P=0.543, MTV-G1: P=0.389). This could be because the number of cases in the lower metabolic group was too small to reveal a statistical difference and because a higher radiation dose which the mLNs require could not be applied in our study. In addition, when tracer uptake in small tumors is measured, large biases can be introduced by the partial volume effect. This factor may also have an effect on our data.

The following could be the reasons for a worse response of higher metabolic mLNs (SUVmax-G3, SUVmax-G4 and MTV-G3, MTV-G4). First, higher FDG uptake not only entails the metabolic state of whole lesion but also could mean large lesion volume size and real lesion burden. Also, Chen et al found GTVn and GTVt were significantly associated with both OS and progression-free survival.[32] In addition, increased FDG uptake in tumors could be partly reflective of tumor hypoxia. Hypoxia is a common phenomenon in ESCC and renders cancers resistant to chemotherapy and RT.[33,34]

Based on the above theories and our data, acquiring a better response is difficult for the lesions with high FDG uptake with conventional dose. To test and verify the impact of escalated dose, we conducted an ROC analysis of radiation dose. Our results demonstrated that mLNs having higher FDG uptake (SUVmax-G3, SUVmax-G4 and MTV-G3, MTV-G4) could achieve a better response by the escalated dose. These metabolic parameters of [18]F-FDG-PET/CT could also be used to guide personalized irradiation dose.

From a histology point of view, cancerous tissue is composed of a heterogeneous cell population rather than homogeneous one, with distinct molecular and phenotypic characteristics.[35] The main reason for resistance to irradiation is suspected to be the biological heterogeneity of tumor cells and microenviroment.[36] Based on the hypothesis that FDG uptake could be a projection of underlying tumor biology, including glucose metabolism, necrosis, oxygenation, angiogenesis, and presence of inflammatory cells, FDG uptake could reflect the sensitivity of cancer to irradiation.[37] Hence, the metabolic parameters could help identify lesions which can gain a better response by an escalated dose and guide personalized dose before dCRT. In addition, escalated dose to GTV by SIB may not only reduce dose to normal tissue and subclinical lesions but also reduce the reproliferation of cancer cells.[15,16,38] Therefore, FDG metabolic parameters could be used to guide personalized dose, decrease toxicity, and improve prognosis.

Despite our efforts to ensure data reliability and adjust for confounding variables, the present study had several limitations. First, it should be noted that this study evaluated response of mLNs using the clinical method, but the current gold standard to assess disease response is direct histopathological examination. Second, the cutoff values (optimal doses which show a good response) were found by the ROC analysis in higher metabolic groups, but specificity or sensitivity was not satisfactory in the groups. The reason may be the standard defining mLN is inaccurate. Third, although we could find some differences in groups, the sample size was too small to be persuasive. Hence, our outcomes need to be validated by prospective and random

studies with larger numbers of patients. Our prospective study regarding personalized dose is ongoing.

Conclusion

Pretreatment metabolic parameters of ^{18}F-FDG-PET/CT can be used to distinguish specific mLNs with different responses to dCRT for locally advanced ESCC. The metabolic parameters could be used to identify mLNs which can gain a better response by escalated radiation dose before dCRT and guide personalized dose. However, we should also pay more attention to identifying the toxicity-causing doses in clinical practice in our future studies.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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