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Original Article

Texture Indices of ^{18}F-FDG PET/CT for Differentiating Squamous Cell Carcinoma and Non-Hodgkin's Lymphoma of the Oropharynx

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We assessed the role of ^{18}F-FDG PET/CT texture indices for the differentiation of squamous cell carcinoma (SCC) and non-Hodgkin's lymphoma (NHL) in the oropharynx. ^{18}F-FDG PET/CT data for 27 patients with SCC and 25 patients with NHL in the oropharynx were investigated. The maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and six texture indices (homogeneity, entropy, short-run emphasis, long-run emphasis, low gray-level zone emphasis [LGZE], and high gray-level zone emphasis [HGZE]) were derived from PET images. PET/CT parameters of the SCC patients were compared with those of the NHL patients. The diagnostic accuracy of the indices for differentiating SCC from NHL was calculated by a receiver operating characteristic curve analysis. ^{18}F-FDG uptake in the oropharynx was observed in all of the patients. The SUVmax, MTV, and TLG did not differ significantly between the SCC and NHL groups, but two of the six texture indices (LGZE [$p = 0.004$] and HGZE [$p = 0.03$]) showed significant differences between the groups. LGZE was the best discriminative index for the differentiation of SCC and NHL (55.6% sensitivity, 88.0% specificity). The LGZE and HGZE texture indices derived from ^{18}F-FDG PET/CT images may be useful in differentiating SCC and NHL in the oropharynx.

Key words: ^{18}F-FDG, PET/CT, oropharyngeal squamous cell carcinoma, malignant lymphoma, texture

The pharyngeal mucosal space is a common primary region for both head and neck squamous cell carcinoma (SCC) and extranodal malignant lymphoma [1]. These 2 tumors tend to occur at the same regions, such as the tonsil and tongue base, and show similar imaging findings [1]. The high density of lymphoid tissue in the tonsils predisposes these regions to the development of malignant lymphoma [2]. A large malignant lymphoma of the oropharynx may infiltrate the deep structures and mimic advanced SCC. Since the treatments of malignant lymphoma and SCC differ considerably, their pretreatment imaging evaluation is of critical importance.

Positron emission tomography (PET) with 2-deoxy-2-^{18}F-fluoro-D-glucose (^{18}F-FDG) is a useful functional tool for the diagnosis and surveillance of SCC and malignant lymphoma in the head and neck region [3]. The most commonly used PET semiquantitative parameter is the maximum standardized uptake value (SUVmax). Kato *et al.* found no significant difference in the SUVmax between SCC and non-Hodgkin's lymphoma (NHL) in the naso- or oropharynx [2]. Both SCC and malignant lymphoma in the head and neck region show intense ^{18}F-FDG uptake, making it difficult

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to differentiate them by only ^{18}F-FDG SUV analysis. Accordingly, increasing attention is being turned to measurements of tumor heterogeneity [4]. Although several investigators have focused on the textural features of ^{18}F-FDG PET in patients with head and neck SCC, these features are not sufficient [5-8].

To the best of our knowledge, no published report has focused on the use of PET texture analysis to differentiate between SCC and malignant lymphoma of the oropharynx. Here, we assessed the usefulness of ^{18}F-FDG PET/CT texture indices for this purpose.

Patients and Methods

Patients. We retrospectively reviewed the ^{18}F-FDG PET/CT findings obtained in 60 patients with SCC (n = 35) or NHL (n = 25) of the oropharynx before therapy who were examined during the period from March 2013 to April 2020 at our hospital. Eight of the patients with SCC were excluded because they did not exhibit sufficient ^{18}F-FDG tumor uptake for the textural analysis. Finally, the cases of 27 patients with SCC and 25 with NHL in the oropharynx were available for ^{18}F-FDG PET/CT studies. Their clinical data are summarized in Table 1.

This study was approved by our institutional ethics review committee, and the requirement for informed consent was waived due to its retrospective nature.

Radiotracer synthesis and PET/CT imaging. ^{18}F-FDG was produced using an automated synthesis system with an HM-18 cyclotron (QUPID; Sumitomo Heavy Industries, Tokyo).

All acquisitions were performed using a Biograph mCT 64-slice PET/CT scanner (Siemens Medical Solutions USA, Knoxville, TN, USA), which has a 21.6-cm axial field of view.

The patients were instructed to fast for at least 5 h before the ^{18}F-FDG administration. A normal glucose level in the peripheral blood was confirmed before the injection. PET emission scanning (2 min per bed position) was performed 90 min after an intravenous injection of ^{18}F-FDG (3.7 MBq/kg) from the midcranium to the proximal thighs, and co-registered with an unenhanced CT examination of the same region (Quality Reference mAs: 100 mAs [using CARE Dose4D]; reconstructed slice thickness: 5 mm). The PET data were reconstructed with a baseline ordered-subset expectation maximization (OSEM) algorithm, incorporating correction with a point-spread function and time-of-flight model (two iterations, 21 subsets). A Gaussian filter with a full-width at half-maximum of 5 mm was used as a post-smoothing filter.

Image analyses. A board-certified nuclear medicine physician (K.M.) performed the PET/CT image analyses. The texture and SUV parameter extraction of the oropharyngeal tumors was performed using the LIFEx package [9]. After the volume of interest (VOI) of the oropharyngeal primary tumor was selected using a threshold of 40% of the SUVmax, the metabolic tumor volume (MTV) was calculated. In the same VOI, the SUVmax was calculated using the following formula: $SUV = c_{dc}/(d_i/w)$, where c_{dc} is the decay-corrected tracer tissue concentration (Bq/g), d_i is the injected dose (Bq), and w is the patient's body weight (g). Total lesion glycolysis (TLG) was defined as the product of the MTV and the mean SUV.

Texture indices were deduced from three texture matrices—the co-occurrence matrix, the gray-level run length matrix, and the gray-level zone length matrix—according to the report of Orlhac *et al.* [10]. Six texture indices were calculated: homogeneity, entropy, short-run emphasis (SRE), long-run emphasis (LRE), low gray-level zone emphasis (LGZE), and high gray-level zone emphasis (HGZE). These indices have been found to be the most robust indices with respect to the segmentation method in each texture correlation group [11].

Table 1 The patient' clinical characteristics

Characteristic		SCC (n = 27)	NHL (n = 25)
Age (years)	Mean	67.1	74.4
	Range	44–87	44–98
Sex (n)	Male	21	15
	Female	6	10
Lesion site (n)	Tonsil	22	20
	Base of tongue	3	5
	Soft palate	1	
	Posterior pharyngeal wall	1	
Histological subtype (n)			
Well differentiated SCC		8	
Moderately differentiated SCC		12	
Poorly differentiated SCC		7	
Diffuse large B cell lymphoma			23
Follicular lymphoma			1
Mantle cell lymphoma			1

SCC, squamous cell carcinoma; NHL, non-Hodgkin's lymphoma.

Statistical analyses. All statistical analyses were performed using the SPSS Statistics software package ver. 26 (IBM). Data were analyzed for statistical significance using the Mann-Whitney *U*-test. Differences in PET/CT parameters among histological subtypes in the patients with SCCs were compared with an analysis of variance (ANOVA). Receiver operating curve (ROC) analyses providing area-under-the-curve (AUC) values were performed to evaluate the diagnostic ability of the ^{18}F-FDG PET/CT parameters to differentiate between SCC and NHL of the oropharynx. Differences were considered statistically significant at p-values < 0.05.

Results

Oropharyngeal primary tumors were detected in all SCC and NHL patients on ^{18}F-FDG PET/CT images. Typical PET/CT images from SCC and NHL patients are shown in Fig. 1 and 2, respectively.

Table 2 summarizes the results of the PET/CT parameters. No significant differences were noted in the SUVmax, MTV, or TLG values between the SCC and NHL groups. Two of the 6 texture indices, *i.e.*, the LGZE ($p = 0.004$) and the HGZE ($p = 0.03$), showed significant differences between the SCC and NHL groups. The values of SUVmax, MTV, TLG, homogeneity, entropy, SRE, LRE, LGZE, and HGZE in the single case of follicular lymphoma were 12.30, 4.56, 32.64,

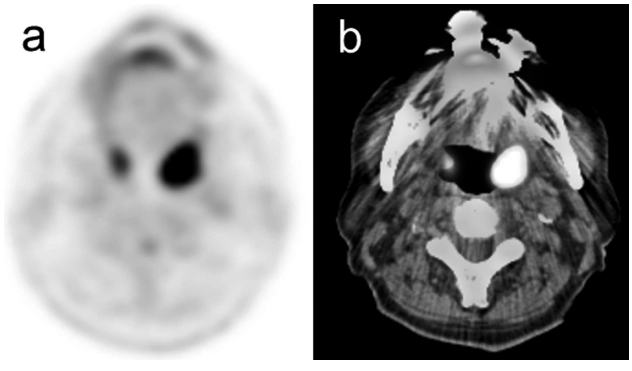

Fig. 1 PET/CT images from a 79-year-old male diagnosed with well-differentiated squamous cell carcinoma in the left palatine tonsil. The transverse ^{18}F-FDG PET image **(a)** and fused PET/CT image **(b)** show intense uptake in the tumor: SUVmax = 14.37, MTV = 6.94, TLG = 61.30, homogeneity = 0.219, entropy = 2.135, SRE = 0.975, LRE = 1.111, LGZE = 0.00155, and HGZE = 816.78.

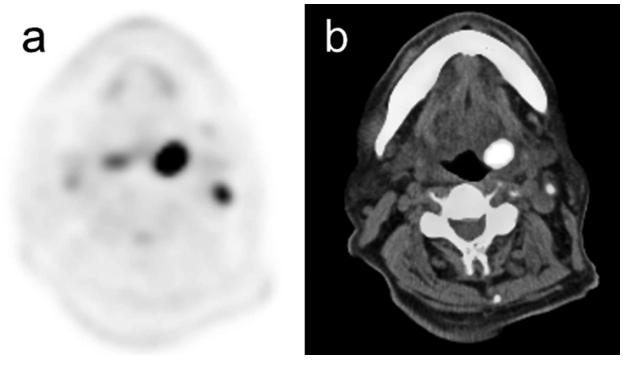

Fig. 2 PET/CT images from a 77-year-old male diagnosed with diffuse large B-cell lymphoma in the left palatine tonsil. The transverse ^{18}F-FDG PET image **(a)** and fused PET/CT image **(b)** show intense uptake in the tumor: SUVmax = 33.52, MTV = 3.95, TLG = 84.02, homogeneity = 0.512, entropy = 1.161, SRE = 0.802, LRE = 2.359, LGZE = 0.00038, and HGZE = 2758.68.

Table 2 ^{18}F-FDG PET/CT findings of the patients with oropharyngeal SCC and NHL

^{18}F-FDG PET/CT	SCC (n = 27)		NHL (n = 25)		*P* value
parameter	Mean	SD	Mean	SD	
SUVmax	18.29	8.84	20.84	6.58	0.06
MTV	13.80	11.93	12.89	13.41	0.41
TLG	152.81	128.47	176.66	194.05	0.91
Homogeneity	0.304	0.163	0.272	0.121	0.21
Entropy	2.028	0.531	2.024	0.360	0.63
SRE	0.931	0.098	0.942	0.061	0.41
LRE	1.633	1.297	1.441	0.642	0.39
LGZE	0.00179	0.00124	0.00090	0.00500	0.004
HGZE	1255.04	794.92	1710.26	724.02	0.03

SCC, squamous cell carcinoma; NHL, non-Hodgkin's lymphoma; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; SRE, short-run emphasis; LRE, long-run emphasis; LGZE, low gray-level zone emphasis; HGZE, high gray-level zone emphasis.

0.236, 1.936, 0.974, 1.106, 0.00215, and 611.74, respectively. The corresponding values in the single case of mantle cell lymphoma were 14.69, 9.82, 87.26, 0.230, 2.269, 0.976, 1.109, 0.00142, and 903.02, respectively. When these two cases were excluded from the analysis, the SUVmax ($p = 0.04$), LGZE ($p = 0.002$), and HGZE ($p = 0.02$) were significantly different between the SCC and NHL groups.

Table 3 summarizes the results of the PET/CT parameters of the patients with SCCs according to the histological subtype. No significant difference in any of the PET/CT parameters was noted among the histological subtypes.

The LGZE was the best discriminative index for the differentiation of SCC and NHL: AUC of 0.735, cutoff value of 0.00142, 55.6% sensitivity and 88.0% specificity. The discriminative index for the differentiation of SCC and NHL by the HGZE was as follows: AUC of 0.686, cutoff value of 895.54, 51.9% sensitivity and 88.0% specificity.

Additional findings. In the patients with SCC, ^{18}F-FDG PET/CT showed 24 nodal sites (all cervical) and two extranodal sites (all bone) suggestive of metastases. In the patients with NHL, ^{18}F-FDG PET/CT showed 28 nodal sites suggestive of involvement (21 cervical, 3 mediastinal, 2 retroperitoneal, and 2 inguinal).

Discussion

SCC and malignant lymphoma are the most common primary tumors occurring in the oropharynx, and their radiologic imaging characteristics are sometimes impossible to distinguish. The present study is the first to focus on the differentiation of these tumors using an ^{18}F-FDG PET/CT texture analysis. The results of our analyses demonstrated that two texture indices that use the gray-level zone length matrix may be of value in the differentiation of SCC and NHL of the oropharynx.

The ^{18}F-FDG SUVmax of renal lymphoma was reported by Nicolau *et al.* to be higher compared to that of renal cell carcinoma [12]. Ou *et al.* similarly documented higher ^{18}F-FDG SUVmax values of breast lymphoma compared to those of breast carcinoma [13]. In the present study, although the SUVmax values of the NHLs tended to be higher than those of the SCCs, the difference was not significant. Kato *et al.* also demonstrated no significant difference in the SUVmax between SCCs and NHLs in the naso- or oropharynx [2]. A similar result obtained by Cho *et al.* indicated that the SUVmax value was not conclusive in distinguishing between nasopharyngeal lymphoma and nasopharyngeal carcinoma [14]. However, although we observed no significant difference in ^{18}F-FDG SUVmax values between carcinoma and lymphoma in the head and neck region, additional large studies will be needed to confirm these findings.

Lv *et al.* reported that ^{18}F-FDG PET texture parameters outperformed the MTV in the differentiation of nasopharyngeal carcinoma and chronic nasopharyngitis [15]. Chen *et al.* reported that ^{18}F-FDG PET/CT texture parameters could differentiate benign from malignant solitary pulmonary nodules [16]. Most of the previous reports about texture features focused on the

Table 3 ^{18}F-FDG PET/CT findings of the patients with oropharyngeal SCC according to the histological subtype

^{18}F-FDG PET/CT	Well (n = 8)		Moderately (n = 12)		Poorly (n = 7)	
parameter	Mean	SD	Mean	SD	Mean	SD
SUVmax	18.74	10.63	19.66	9.79	15.43	4.19
MTV	13.65	10.68	11.86	10.57	17.31	16.04
TLG	134.09	79.28	152.15	146.62	175.34	154.00
Homogeneity	0.334	0.207	0.316	0.175	0.247	0.056
Entropy	1.941	0.598	1.974	0.568	2.222	0.394
SRE	0.912	0.131	0.924	0.104	0.966	0.017
LRE	1.886	1.796	1.704	1.321	1.220	0.176
LGZE	0.00174	0.00120	0.00166	0.00133	0.00206	0.00126
HGZE	1179.42	839.29	1346.16	907.41	1185.27	613.97

SCC, squamous cell carcinoma; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; SRE, short-run emphasis; LRE, long-run emphasis; LGZE, low gray-level zone emphasis; HGZE, high gray-level zone emphasis; Well, well differentiated SCC; Moderately, moderately differentiated SCC; Poorly, poorly differentiated SCC.

differentiation of benign and malignant lesions. Several researchers have evaluated the feasibility of using ^{18}F-FDG PET/CT texture parameters to predict cancer subtypes by analyzing the ability of these parameters to differentiate primary and metastatic lung tumors [17] or adenocarcinoma and SCC of the lung [18]. The great potential of texture parameters for the differentiation of lesions, not only between benign and malignant lesions but also among malignancy subtypes, is now being more widely recognized. However, the ability of ^{18}F-FDG texture features to reliably predict malignant lymphoma and carcinoma remains unclear.

To the best of our knowledge, the present study is the first to perform an ^{18}F-FDG PET/CT texture analysis between SCC and NHL of the oropharynx. Orlhac *et al.* observed that healthy tissue showed higher homogeneity, lower entropy, higher LGZE values, and lower HGZE values compared to tumor tissue [19]. Ou *et al.* confirmed that the HGZE values of breast lymphoma were higher than those of breast carcinoma [13], which is consistent with our present findings. They suggested that the differences in tumor cell proliferation may be a possible explanation for the different ^{18}F-FDG uptake between breast lymphoma and carcinoma [13]. Xu and colleagues also showed that ^{18}F-FDG PET texture parameters were more effective than SUV parameters in differentiating hepatocellular carcinoma from hepatic lymphoma [20].

Although the textural indices have been reported as potentially useful, the consistency of published results is difficult to assess for several reasons: the name given to a textural index does not always correspond to the same definition; many texture indices have been studied and the methods used to calculate them have not always been identical; and the optimal threshold for the tumor volume for a texture analysis is different in each study. Due to the still limited experience of ^{18}F-FDG PET texture analyses in distinguishing malignant lymphoma and carcinoma, additional studies in this area are still needed.

Chan *et al.* showed that heterogeneity on ^{18}F-FDG PET/CT was prognostically superior to traditional SUV parameters in patients with oro- or hypopharyngeal SCC [5]. Chen *et al.* also demonstrated that ^{18}F-FDG heterogeneity indices were more informative than classical SUV parameters for the prediction of prognosis in patients with pharyngeal cancer [6]. Such findings are attributable to the inability of classical PET parameters such as SUV to delineate tumor heterogeneity, which has been explained by a number of underlying factors, including cellular proliferation, cellularity, angiogenesis, necrosis, and vascularization [21]. However, the exact biological correlates of these PET heterogeneity parameters are not yet clear.

Limitations of the present study include its small sample size and retrospective design. Most of the NHLs in the present study were diffuse large B-cell lymphoma (DLBCL), accounting for 92% of the total. This may have introduced bias in comparisons of SCC and DLBCL of the oropharynx. Additional large prospective studies are needed to test and expand the present results.

Chan *et al.* found the combination of ^{18}F-FDG PET/CT heterogeneity parameters and dynamic contrast-enhanced MRI parameters to be useful in the prediction of patient prognosis in pharyngeal cancer [5]. It is anticipated that advances in hardware such as simultaneous PET/MRI will help to further facilitate imaging research in analyses of tumor heterogeneity. Few tumor heterogeneity studies have been undertaken using newer radiopharmaceuticals other than ^{18}F-FDG. Further studies are needed to investigate texture features to elucidate their potential clinical value.

In conclusion, although this preliminary study was conducted in a small patient population, its results clearly suggested that ^{18}F-FDG PET/CT texture indices using the gray-level zone length matrix may be useful in differentiating SCC and NHL in the oropharynx.

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