The Laryngoscope

Tumor Heterogeneity Measured on F-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Combined With Plasma Epstein-Barr Virus Load Predicts Prognosis in Patients With Primary Nasopharyngeal Carcinoma

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Objectives/Hypothesis: Plasma Epstein-Barr virus (EBV) DNA concentrations predict prognosis in patients with nasopharyngeal carcinoma (NPC). Recent evidence also indicates that intratumor heterogeneity on F-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scans is predictive of treatment outcomes in different solid malignancies. Here, we sought to investigate the prognostic value of heterogeneity parameters in patients with primary NPC.

Study Design: Retrospective cohort study.

Methods: We examined 101 patients with primary NPC who underwent pretreatment ^{18}F-FDG PET/computed tomography. Circulating levels of EBV DNA were measured in all participants. The following PET heterogeneity parameters were collected: histogram-based heterogeneity parameters, second-order texture features (uniformity, contrast, entropy, homogeneity, dissimilarity, inverse difference moment), and higher-order (coarseness, contrast, busyness, complexity, strength) texture features.

Results: The median follow-up time was 5.14 years. Total lesion glycolysis (TLG), tumor heterogeneity measured by histogram-based parameter skewness, and the majority of second-order or higher-order texture features were significantly associated with overall survival (OS) and/or recurrence-free survival (RFS). In multivariate analysis, age (P =.005), EBV DNA load (P = .0002), and uniformity (P = .001) independently predicted OS. Only skewness retained the independent prognostic significance for RFS. Tumor stage, standardized uptake value, or TLG did not show an independent association with survival endpoints. The combination of uniformity, EBV DNA load, and age resulted in a more reliable prognostic stratification ($P < .001$).

Conclusions: Tumor heterogeneity is superior to traditional PET parameters for predicting outcomes in primary NPC. The combination of uniformity with EBV DNA load can improve prognostic stratification in this clinical entity.

Key Words: Nasopharyngeal carcinoma, positron emission tomography, F-18 fluorodeoxyglucose, Epstein-Barr virus, heterogeneity, texture features, prognosis, risk stratification.

Level of Evidence: 4

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a distinct type of head and neck cancer occurring at high frequency in southeastern Asia, Alaska, Northern Africa, and certain parts of the Mediterranean basin.[1,2] Over the last few decades, advances in radiotherapy and chemoradiotherapy (CRT) have significantly improved clinical outcomes in NPC patients. However, disease recurrences and management of treatment failures continue to pose significant clinical challenges. For example, the 5-year overall survival (OS) and recurrence-free survival (RFS) rates of NPC patients remain ~70% despite the use of state-of-the-art CRT.[3,4] In this scenario, new and reliable prognostic stratification systems can help optimize follow-up regimens, possibly resulting in better clinical outcomes.

The tumor, node, and metastases (TNM) stage is traditionally considered the most significant prognostic factor in NPC patients. Evidence also indicates that circulating Epstein-Barr virus (EBV) DNA loads can predict prognosis and treatment outcomes in this clinical

entity.[5,6] In recent years, positron emission tomography (PET) with F-18 fluorodeoxyglucose (^{18}F-FDG) is increasingly being used in the pre- and post-treatment evaluation of patients with solid malignancies. Metabolic parameters derived from pretreatment PET, including standardized uptake value (SUV) and total lesion glycolysis (TLG), have prognostic significance in NPC.[7–11] However, SUV and TLG are unable to capture the distribution changes in FDG metabolism. This shortcoming is not negligible because most solid neoplasms are characterized by a markedly heterogeneous FDG uptake. In general, tumors characterized by a high intrinsic heterogeneity have an aggressive nature and are treatment resistant, ultimately portending a poor prognosis.[12,13]

Measures of spatial heterogeneity on ^{18}F-FDG PET scans have been shown to predict prognosis in certain solid malignancies.[14–16] However, the question as to whether they can improve the prognostic stratification of NPC patients remains open. We therefore designed the current study to assess the prognostic significance of ^{18}F-FDG PET heterogeneity parameters for the prediction of OS and RFS in patients with primary NPC. We also investigated whether heterogeneity parameters can improve the prognostic value of EBV DNA load and traditional clinicopathological variables.

MATERIALS AND METHODS

This study is a post hoc analysis of data previously collected in a prospective investigation conducted at the Chang Gung Memorial Hospital, for which written informed consent was obtained from all participants. The institutional review board of the Chang Gung Memorial Hospital approved the current protocol.

Patients

Consecutive patients with primary NPC diagnosed by conventional work-up and ^{18}F-FDG PET/computed tomography (CT) were deemed eligible. The conventional workup consisted of head and neck magnetic resonance imaging (MRI), nasopharyngeal fiberoscopy, bone scan, chest radiograph, and abdominal ultrasound. Patients were excluded if they met the following criteria: 1) presence of metastatic disease at presentation (M1 disease), 2) concomitant malignancies in different anatomical districts, or 3) previous treatment at other institutions. Between 2006 and 2009, a total of 106 eligible patients were identified.

Definitive Treatment and Follow-up Schedule

The treatment and follow-up protocol have been previously described.[8] Briefly, all patients received definitive radiotherapy with a total cumulative dose $\geq$64.8 Gy. In keeping with our current treatment guidelines, all patients with a tumor stage of 3 or greater received additional cisplatin-based concurrent CRT. Patients were followed every week during treatment and then every 3 months for the first 2 years, every 4 months for the subsequent 2 years, and every 6 months thereafter. Flexible fiberoptic nasopharyngoscopy was performed at every visit. A conventional workup was performed 3 months after the completion of treatment and subsequently either on a yearly basis or when clinically indicated.

^{18}F-FDG PET/CT Imaging

All of the study patients fasted for at least 6 hours before ^{18}F-FDG PET/CT scans. Imaging was performed with a PET/CT system (Discovery ST 16; GE Healthcare, Milwaukee, WI) consisting of a PET scanner and a 16-section CT scanner. Before the acquisition of PET images, a standardized helical CT scan was acquired from the head to the proximal thigh using the following settings: transverse 3.0-mm collimation $\times$ 16 modes, 100 kVp, 100 mAs, 0.5-s tube rotation, 35-mm/s table speed, and 1.5 pitch. No intravenous iodinated contrast agent was used. CT data were resized from a 512 $\times$ 512 matrix to a 128 $\times$ 128 matrix to match the PET results and generate fused images and CT-based transmission maps. Emission scans (two-dimensional mode, 3 minutes per table position) were acquired from the head to the proximal thigh at 50 to 70 minutes after injection of 370 MBq of ^{18}F-FDG. PET images were reconstructed with CT for attenuation correction and an ordered-subset expectation maximization iterative reconstruction algorithm (4 iterations and 10 subsets).

Image Analysis

Tumors were segmented using the PMOD 3.2 software package (PMOD Technologies Ltd., Zurich, Switzerland). An experienced nuclear medicine physician who was blinded to clinical data drew boundaries large enough to include the primary tumor within the nasopharyngeal area in axial, coronal, and sagittal ^{18}F-FDG PET scans. To avoid the inclusion of areas with physiological FDG uptake within the regions of interest, a joint reading of both the head and neck MRI and ^{18}F-FDG PET scans was performed side by side. The volumes of interest were checked and validated by an independent senior nuclear medicine physician. An SUV threshold of 2.5 was used to define the contouring margins around the target. The contour around the target lesion inside the boundaries was automatically drawn, and the voxels presenting a SUV intensity $>$2.5 within the contouring margin were incorporated for metabolic tumor volume (MTV) determination. A computer program was used to automatically calculate SUV (maximal, mean), MTV, and TLG of the lesion as previously described.[8]

Heterogeneity parameters and texture features were determined using histogram analysis, the normalized gray-level co-occurrence matrix (NGLCM), and the neighborhood gray-tone difference matrix (NGTDM). First, the voxel intensities were resampled within the segmented tumors to yield a limited range of values, with the ultimate goal of reducing noise and normalizing images.[16] The intensity of ^{18}F-FDG uptake in the primary tumor was resampled to 32 and 64 different values. Subsequently, the texture features were calculated as described previously.[14] An SUV histogram analysis was implemented to calculate variance, standard deviation, skewness, kurtosis, and SUV entropy. The NGLCM was applied for the calculation of second-order texture features (i.e., uniformity, contrast, entropy, homogeneity, dissimilarity, and inverse difference moment). Higher-order texture features (i.e., coarseness, contrast, busyness, and complexity) were determined from the NGTDM. All of the texture features were determined with an in-house software package (Chang-Gung Image Texture Analysis toolbox) implemented under MATLAB 2012a (MathWorks Inc., Natick, MA).

Quantification of Plasma EBV DNA Load

Before treatment, blood samples (10 mL) were collected by venipuncture in ethylenediaminetetraacetic acid–containing tubes. Samples were immediately centrifuged at 2,000*g*, and plasma aliquots were stored in polypropylene tubes at -80°C

until analysis. Only one freeze-thaw cycle was allowed. DNA extraction and quantification of plasma EBV DNA load were performed as previously described.[17]

Data Analysis

All of the patients were followed up until December 2014 or until death. OS and RFS served as the main outcome measures. OS was calculated from the date of diagnosis to the date of death or censored at the date of the last follow-up for surviving patients. RFS was defined as the time between the end of treatment and the date of recurrence or censored at the date of the last follow-up. Different cutoff points were tested for each PET parameter (i.e., TLG, MTV, and SUV), and the value showing the lowest P was selected as the cutoff for subsequent analyses. Survival curves were plotted using the Kaplan-Meier method (log-rank test). The effect of the study variables on survival outcomes was investigated using Cox regression models. The effect of each individual variable on the study outcomes was initially investigated using univariate analysis. We then constructed multivariate regression models to identify the independent predictors of survival after allowance for potential confounders. Two-tailed P values $<.05$ were considered statistically significant.

RESULTS

Table I depicts the general characteristics of the study participants. The median follow-up was 5.14 years (range, 2−110 months). Five patients were lost to follow-up. Therefore, 101 patients were included in the final analysis. Post-treatment tumor relapses were identified in 37 patients. At the time of the last follow-up, 61 patients were alive and 40 were dead.

TABLE I.
General Characteristics of the Study Participants (n = 101).

Variable	Value
Age, yr, median ± SD	50.5 ± 14
Sex, no. (%)	
Male	79 (78.2)
Female	22 (21.8)
Histology, no. (%)	
WHO type I	7 (6.9)
WHO type II	17 (16.8)
WHO type III	77 (76.2)
Overall stage, no. (%)	
I	9 (8.9)
II	19 (18.8)
III	28 (27.7)
IVa-b	45 (44.6)
T classification, no. (%)	
T1	21 (20.8)
T2	29 (28.7)
T3	21 (20.8)
T4	30 (29.7)
N classification, no. (%)	
N0	14 (13.9)
N1	36 (34.7)
N2	34 (33.7)
N3	18 (17.8)
EBV copy number (mL^{-1}), mean ± SD	3,581 ± 10,913

Data are given as counts (percentages) unless otherwise indicated.
EBV = Epstein-Barr virus; SD = standard deviation; WHO = World Health Organization.

Predictors of Survival Endpoints

In univariate analysis, the following parameters were identified as significant predictors of OS: advanced age, T3−4 tumors, stage III−IVb disease, EBV DNA load >6,800 copies/mL, TLG >55.80 g/mL × mL, high skewness or SUV entropy values, and high values of second-order or higher-order texture parameters (Table II and Supplementary Table I). Because PET heterogeneity variables showed a high degree of collinearity, each one was entered separately into multivariate Cox regression models. After adjustment for potential confounders in multivariate analysis, age (P = .005), EBV DNA load (P = .0002), and uniformity (P = .001) (Fig. 1) were identified as independent predictors of OS (Table III). The addition of uniformity to other independent risk factors (i.e., EBV DNA load and age) resulted in a more reliable prognostic stratification of OS (P <.001) (Fig. 2). T classification, tumor stage, TLG, skewness, SUV entropy, and the majority of second-order or higher-order texture features were identified as significantly associated with RFS in univariate analysis (Table II and Supplementary Table I). However, only skewness retained their independent prognostic significance for RFS in multivariate analysis (Table III, Fig. 1).

Associations Between the Study Variables

Supplementary Table II summarizes the associations between the clinicopathological characteristics, EBV DNA load, conventional PET parameters (SUVmax, MTV, TLG), and heterogeneity PET parameters identified as independent prognostic factors in multivariate analysis. TLG, SUV, EBV DNA values, skewness, and uniformity were significantly associated with T classification. We also identified significant associations of MTV, TLG, texture feature uniformity, and EBV DNA load with the overall stage. Correlation analyses identified low-to-moderate associations between EBV DNA load and TLG (ρ = 0.248) or SUV (ρ = 0.168). Moreover, the EBV DNA load was found to be only mildly associated with uniformity (ρ = −0.211; Supplementary Table III).

DISCUSSION

The results of our study indicate that intratumor heterogeneity on ^{18}F-FDG PET scans is associated with OS and RFS in patients with primary NPC. Specifically, a higher heterogeneity reflected by the texture feature uniformity was an adverse prognostic factor for OS, whereas the parameter measured by the histogram-based factor skewness independently predicted a lower RFS. Interestingly, heterogeneity features were superior to conventional PET parameters as prognostic factors (Fig. 3). In addition, the combination of heterogeneity with EBV DNA load and traditional clinical variables

TABLE II.
Univariate Analysis of Clinical and Conventional PET Risk Factors in Relation to Overall Survival and Recurrence-Free Survival.

Parameter	No. of Patients (%)	OS *P* Value	RFS *P* Value
Age, yr		.0001	.192
≤50.46	60 (40.6)		
>50.46	41 (59.4)		
Sex		.181	.199
Male	79 (78.2)		
Female	22 (21.8)		
Tumor stage		.001	.029
I–II	28 (27.8)		
III–IVb	73 (72.2)		
T classification		.002	.007
T1–2	50 (49.5)		
T3–4	51(50.5)		
N classification		.260	.371
N0-1	49 (48.6)		
N2-3	52 (51.4)		
Histology		.939	.692
WHO type I	7 (6.9)		
WHO type II	17 (16.8)		
WHO type III	77 (76.3)		
EBV DNA load (copies/mL)		.008	.801
≤6,800	92 (91)		
>6,800	9 (10)		
Conventional PET parameters			
TLG (g/mL × mL)		.004	.009
≤55.80	44 (43.6)		
>55.80	57 (57.4)		
MTV (mL)		.001	.007
≤18.32	61 (60.0)		
>18.32	40 (40.0)		
maxSUVt (g/mL)		.392	.325
≤9.55	38 (37.6)		
>9.55	63 (63.4)		

EBV = Epstein-Barr virus; maxSUVt = maximum standardized uptake value of the primary tumor; MTV = metabolic tumor volume; OS = overall survival; PET = positron emission tomography; RFS = recurrence-free survival; TLG = total lesion glycolysis; WHO = World Health Organization.

significantly improved the prognostic stratification of NPC patients (Fig. 2).

NPC differs significantly from other head and neck malignancies in terms of histology, staging, and treatment strategies. Conventional PET-derived parameters, including SUV, MTV, and TLG, have been recently linked to OS and disease recurrence in NPC patients.[8,9,11,18,19] Despite these encouraging results, ^{18}F-FDG PET is still not sufficiently accurate to guide treatment decisions in NPC patients. Recently, there has been growing interest in assessing the intratumor heterogeneity of ^{18}F-FDG distribution using either intensity histogram analysis or the correspondence between voxel gray level intensities and their position within an image. Although heterogeneity parameters are not routinely used in clinical ^{18}F-FDG PET imaging, evidence on their potential usefulness for predicting treatment outcomes and personalizing treatment approaches is mounting. Intratumor heterogeneity characterized by texture features on ^{18}F-FDG PET has been evaluated in primary esophageal cancer by Tixier et al.[16] They found heterogeneity parameters, such as homogeneity and entropy, were more accurate predictors than SUV to discriminate responders from nonresponders among patients after concomitant radiochemotherapy. Cook et al. investigated the utility of ^{18}F-FDG heterogeneity in non–small cell lung cancer, and reported that heterogeneity parameters contrast and entropy were independently associated with overall survival.[15] To our knowledge, this study is the first to compare intratumor heterogeneity, conventional ^{18}F-FDG PET parameters, and plasma EBV DNA load for the prediction of long-term clinical outcomes in NPC patients.

In a mouse model of head and neck cancer, the intratumor FDG uptake has been found to be associated with different tumor components (i.e., malignant cells, stromal tissue, and necrotic areas).[20] In this context, conventional PET factors such as SUV seem to be less suitable than heterogeneity PET parameters to capture the difference of glucose metabolism within malignancy. Because glucose metabolism is associated with tumor aggressiveness, proliferation, and metastatic potential, patients with tumors of more heterogeneous ^{18}F-FDG distribution would be prone to develop resistant clones,

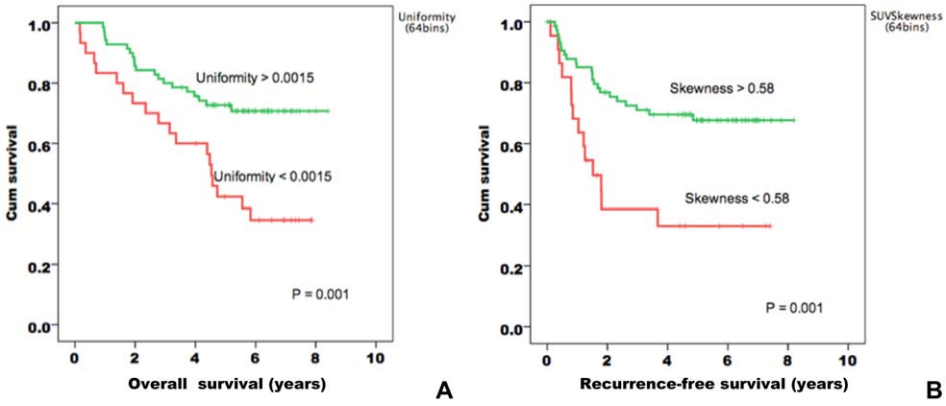

Fig. 1. Kaplan-Meier plots of patients with primary NPC stratified according to high and low ^{18}F-FDG PET uniformity (A) and skewness (B). Panel A depicts overall survival curves, whereas panel B shows recurrence-free survival plots. Cum = cumulative; NPC = nasopharyngeal carcinoma; ^{18}F-FDG PET = F-18 fluorodeoxyglucose positron emission tomography; SUV = standardized uptake value.

TABLE III.
Multivariate Analysis of Risk Factors in Relation to Overall Survival and Recurrence-Free Survival.

	OS		RFS	
Risk Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	2.668 (1.345-5.291)	.005	—	N/A
T classification	—	NS	—	NS
Tumor stage	—	NS	—	NS
EBV DNA load	6.284 (2.404-16.421)	.0002	—	N/A
TLG	—	NS	—	NS
Skewness	—	NS	0.394 (0.199-0.781)	.008
Uniformity	0.314 (0.162-0.609)	.001	—	N/A

CI = confidence interval; EBV = Epstein-Barr virus; HR = hazard ratio; N/A = not applicable; NS = non-significant; OS = overall survival; RFS = recurrence-free survival.

less responsive to single treatment, and have reduced survival.[21] Here, we demonstrate that the heterogeneity PET parameters uniformity independently predicts OS and improves the prognostic stratification of NPC patients when used in combination with age and plasma EBV DNA load (Fig. 2). The model comprising the three parameters allowed the identification of distinct prognostic groups whose OS was more clearly delineated as compared with age and plasma EBV DNA load or tumor stage. Interestingly, tumor stage and conventional PET parameters did not retain their independent prognostic value in multivariate analysis. Uniformity is the sum of squares of entries in the gray-level co-occurrence matrix and is a measure of image homogeneity. Consequently, its values are high when the image is characterized by good homogeneity or when pixels are similar.[22] Cheng et al.[14] has also reported that uniformity is an independent prognostic factor in patients with locally advanced oropharyngeal carcinoma treated with CRT. In our study specifically focusing on NPC patients, uniformity improved the prognostic stratification when combined with EBV DNA load. In this scenario, we were able to identify a specific subgroup of patients who are expected to have a low-to-intermediate OS (marked by the orange line in Fig. 2B). Such cases may be ideal candidates for trials of adjuvant chemotherapy aimed at reducing the likelihood of persistent disease. Importantly, this specific patient subgroup was not identifiable using a prognostic model based on plasma EBV DNA load and age only (Fig. 2A). We therefore propose that the superior prognostic stratification provided by the addition of uniformity to traditional parameters may be clinically relevant. Currently, the identification of NPC patients at high risk of early death remains problematic,

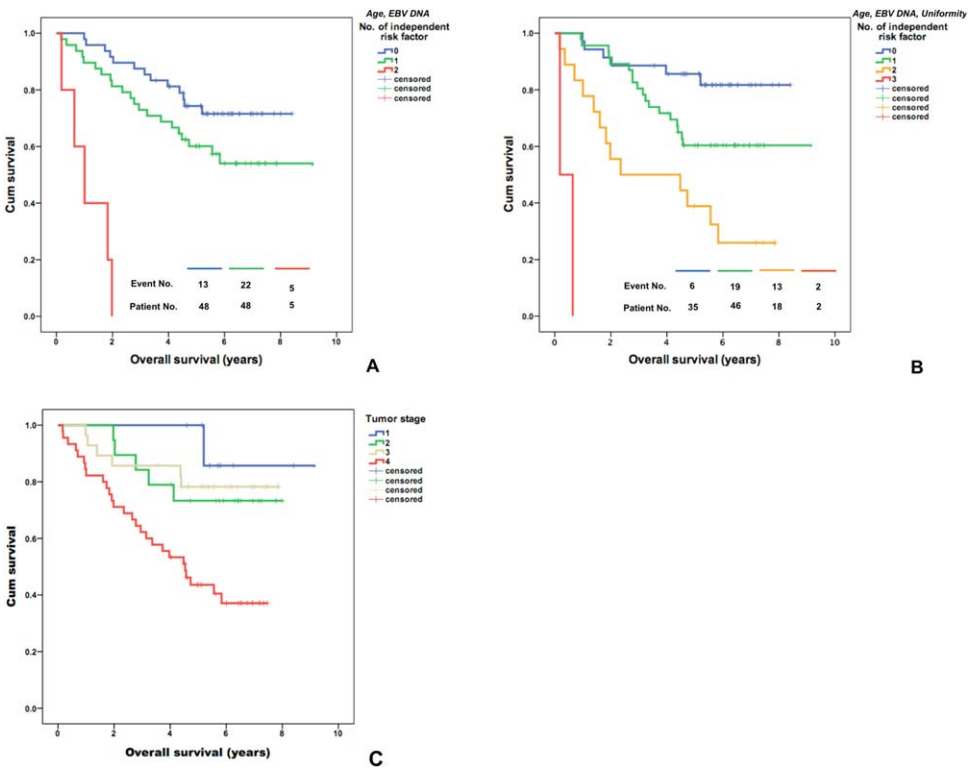

Fig. 2. Kaplan-Meier plots of overall survival in patients with primary NPC stratified according to EBV DNA load and age (A), EBV DNA load, age, and uniformity (B), or tumor stage (C). The addition of uniformity to EBV DNA load and age improved the prognostic stratification of NPC patients ($P < .001$). Accordingly, the model comprising three parameters allowed the identification of four distinct prognostic groups whose OS was more clearly delineated (B) as compared with the three groups identified by EBV DNA load and age only (A) or the four groups by tumor stage (C). Cum = cumulative; EBV = Epstein-Barr virus; NPC = nasopharyngeal carcinoma; OS = overall survival.

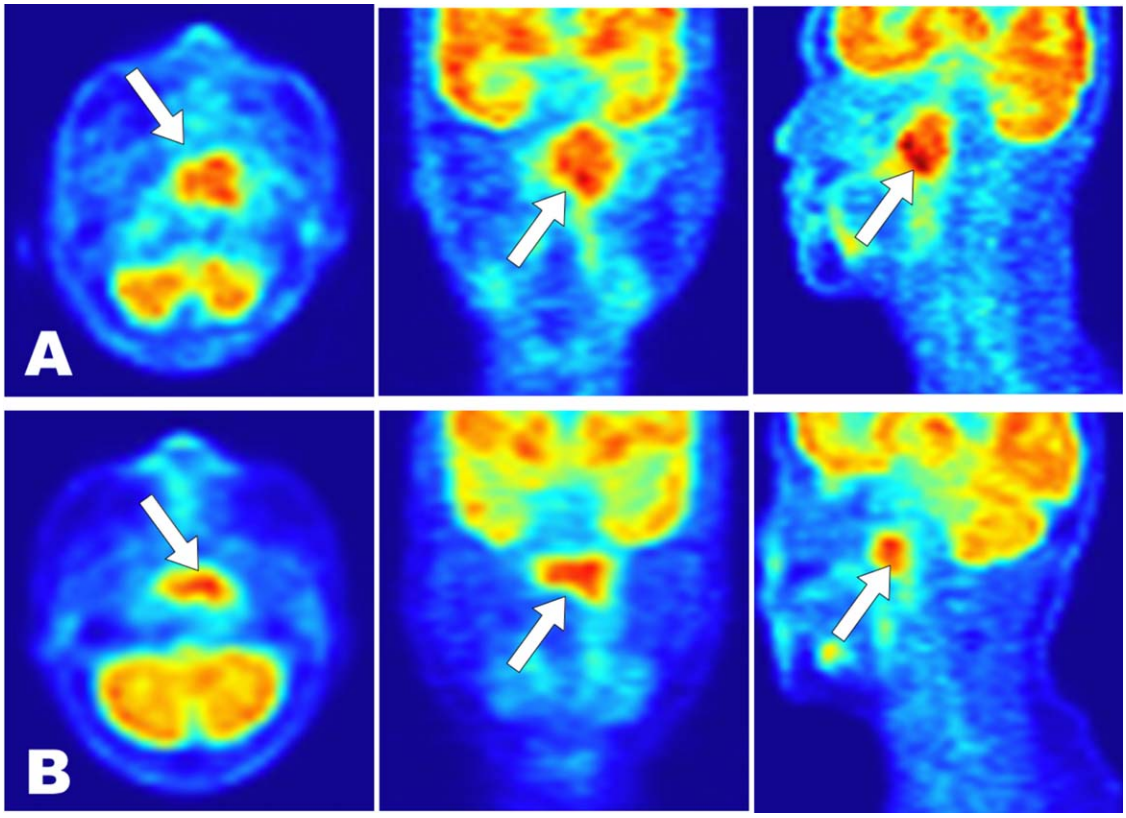

Fig. 3. Three orthogonal planar views of tumor heterogeneity obtained from ^{18}F-FDG PET scans in two patients with primary NPC. A 43-year-old male patient with stage IVa disease had a uniformity value of 0.001 in the primary nasopharyngeal tumor (EBV DNA load = 25.7 copies/mL, TLG = 110.85 g/mL × mL) (A). The patient died of distant failure 3.2 years after definitive therapy. The arrows indicate the primary nasopharyngeal tumor. A 59-year-old male patient with stage IVa disease had a uniformity value of 0.002 in the primary nasopharyngeal tumor (EBV DNA load = 98.53 copies/mL, TLG = 99.07 g/mL × mL) (B). At 6.7 years after treatment, the patient is alive and well. ^{18}F-FDG PET = F-18 fluorodeoxyglucose positron emission tomography; EBV = Epstein-Barr virus; NPC = nasopharyngeal carcinoma; TLG = total lesion glycolysis.

ultimately hampering tailored adjustments to therapies. The ability of heterogeneity parameters to improve prognostic stratification can provide an opportunity to optimize individual patient management and may allow a better case selection for clinical trials.

In our study, the histogram-based factor skewness independently predicted a lower RFS. Furthermore, tumor stage did not retain its independent prognostic value. If the histogram is symmetrical about the mean, the skewness is zero or otherwise either positive or negative depending upon whether it is skewed above or below the mean. Previous studies demonstrated that skewness on contrast-enhanced CT images predicts long-term survival in colorectal cancer[23] as well as OS in patients with locally advanced squamous cell carcinoma of the head and neck treated with induction chemotherapy.[24]

Here, only low-to-moderate correlations were evident between EBV DNA load and heterogeneity parameters. These results suggest that the EBV infection status dose does not directly reflect tumor heterogeneity in patients with primary NPC. The biological features underlying heterogeneity parameters and texture features have been

TABLE IV.
Prognostic Significance of Pretreatment Plasma EBV DNA Load in Patients With Primary NPC According to the Published Literature.

Author	Patient Stage	No. of Patients	Curative Treatment	Median Follow-up Time (Years)	EBV DNA Cutoff (Copies/mL)	Association of EBV DNA With Patient Survival
Lin et al.[5]	Stage III–IVb	99	Neoadjuvant C/T + RT	2.5	1,500	OS, $P < .001$; RFS, $P = .02$
Peng et al.[29]	Stage I–IVb	584	CRT	3.2	2,010	OS, $P < .001$; RFS, $P < .001$
Chen et al.[30]	Stage III–IVb	874	CRT	3.1	6,620	OS, $P < .001$; RFS, $P < .001$
Chai et al.[31]	Stage I–IV	459	N/A	N/A	8,000	OS, $P < .001$
Leung et al.[32]	Stage I–IV	376	RT or CRT	5.8	4,000	OS, $P = .0053$
Current study	Study I–IVb	101	CRT	5.1	6,800	OS, $P = .0002$

CRT = chemoradiotherapy; C/T: systemic chemotherapy; EBV = Epstein-Barr virus; N/A = not applicable; OS = overall survival; RFS = recurrence-free survival; RT = radiotherapy.

studied in some reports. The intratumor FDG uptake has been found to be dependent on the tumor components in the animal study.[20] Moreover, a clinical study conducted in breast cancer patients demonstrated a good degree of correlation between sonographic texture heterogeneity and tumor histopathological components.[25] In head and neck cancer, heterogeneity parameters extracted from PET have been reported to provide good discrimination performance between tumor and normal tissues.[26]

Currently, there is no single widely accepted tumor-segmentation method for PET imaging, and controversy still exists on the choice of the optimal segmentation methodology.[27] In this study, an SUV of 2.5 was used for tumor contouring. This approach is in line with previous studies focusing on the analysis of PET parameters in NPC patients,[8,9,11,28] ultimately allowing a direct comparison of the current report with the published literature. However, additional longitudinal multicenter investigations are required to compare different segmentation methods and identify the optimal prognostic approach for NPC patients.

Table IV summarizes the differences between the published studies conducted in NPC patients in terms of disease stage, number of patients, curative treatment, median follow-up time, EBV DNA cutoff points, and association of EBV DNA viral load with survival. Although pretreatment plasma EBV DNA load was identified as a significant prognostic factor in different studies, the cutoff values varied markedly (from 1,500 to 8,000 copies/mL). Such differences may be at least in part explained by variations in lab conditions, inclusion criteria, treatment modality, sample size, and follow-up periods.

The main limitation of the current study lies in its retrospective design. Moreover, the association between tumor biology and PET heterogeneity parameters warrants further scrutiny.

CONCLUSION

Tumor heterogeneity appears superior to traditional PET parameters for the prediction of OS and RFS in patients with primary NPC. Its combination with EBV DNA load allowed an improved prognostic stratification in this patient group.

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