Metabolic Tumor Volume of [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Predicts Short-Term Outcome to Radiotherapy With or Without Chemotherapy in Pharyngeal Cancer

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Abstract

Purpose: This study aimed to investigate whether metabolic tumor volume (MTV) measured from [^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) predicts short-term outcome to radiotherapy with or without chemotherapy and disease-free survival (DFS) in patients with pharyngeal cancers.

Experimental Design: The MTVs of primary sites with or without neck nodes were measured in 82 patients. Short-term outcome was assessed using the treatment response evaluation by the Response Evaluation Criteria in Solid Tumors and recurrence events during follow-up (complete response/no recurrence or residual disease/recurrence).

Results: A total of 64 patients had complete response/no recurrence as of the last follow-up. A cutoff of 40 mL for the MTV was the best discriminative value for predicting treatment response. By univariate analyses, patients with MTV >40 mL showed a significantly lower number of complete response/no recurrence than did patients with MTV ≤40 mL [68.2% versus 87.8%; hazard ratio (HR), 3.34; 95% confidence interval (95% CI), 1.09-10.08; $P = 0.03$], as is the same in tumor-node-metastasis stage (87.5% for I-II versus 90% for III versus 63.8% for IV; $P = 0.02$). However, MTV was only a significant predictor of short-term outcome by multivariate analyses (HR, 4.09; 95% CI, 1.02-16.43; $P = 0.04$). MTV >40 mL indicated a significantly worse DFS than MTV ≤40 mL (HR, 3.42; 95% CI, 1.04-11.26;$P = 0.04$). The standardized uptake value for the primary tumor did not show any correlation with treatment outcome or DFS.

Conclusion: MTV has a potential value in predicting short-term outcome and DFS in patients with pharyngeal cancers. (Clin Cancer Res 2009;15(18):5861–8)

The tumor-node-metasis (TNM) stage (1) defines the T stage as the extent of primary tumor in terms of size in the greatest dimension and invasion to adjacent structure; it defines the N stage in terms of the size and multiplicity of involved lymph nodes. As stage is considered the most important prognostic factor, it is reasonable to assume that an advanced stage reflects tumor burden in the whole body of a patient more accurately than does an early tumor stage. Tumor burdens or tumor volumes, however, do not exactly correlate with tumor stage (2), because the size of the tumor in its greatest dimensions is not representative of the three-dimensional tumor volume. Although the two-dimensional parameter of a tumor is an important factor in surgical treatment, tumor burden, usually three-dimensional volumetric data, has become another important factor to be considered in radiotherapy or chemotherapy. Therefore, more reliable prognostic factors are needed for malignancies, for which the treatment of choice is nonsurgical.

Standardized uptake value (SUV), a semiquantitative parameter in [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) or fused [^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), is known to be a significant factor for prognosis and treatment guidance in many malignancies (3–8). Metabolic tumor volume (MTV), defined as the volume of tumor tissues with increased FDG uptake, is a novel index in FDG-PET and is the least studied factor so far. FDG target volume in previous studies was calculated mostly by visual delineation of tumor edge or

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Received 12/20/08; revised 5/11/09; accepted 5/27/09; published OnlineFirst 9/8/09.

Grant support: This work was supported by the Samsung Biomedical Research Institute (#SBRI C-A8-214-2).

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doi:10.1158/1078-0432.CCR-08-3290

Translational Relevance

Metabolic tumor volume (MTV) represents tumor tissues showing active [^{18}F]-fluorodeoxyglucose (FDG) uptake. It incorporates the dual characteristics of three-dimensional volumetric data and the metabolic activity of tumor. We hypothesized that MTV could be a good candidate for a new prognostic factor. In this study, we investigated whether MTV measured from pretreatment FDG positron emission tomography/computed tomography could be a predictor for short-term outcome in patients with pharyngeal cancer treated with radiatiotherapy or chemoradiation. As a result, we showed that MTV was a predictor for early outcome and recurrence. Although a further validation study with a larger number of patients in a longer period of follow-up is needed, this is the first study to present the clinical usefulness of MTV in pharyngeal cancer.

side-by-side analysis with contrast-enhanced CT scan. On the other hand, MTV in this study was semiquantitatively measured from attenuation-corrected PET/CT images by using a contouring program, which renders the volume measurement more feasible.

Because MTV represents the dual characteristics of tumor volume and the extent of FDG uptake by tumor tissues, we hypothesized that MTV may play a role as a prognostic factor in malignancies.

In this study, we assessed the ability of MTV measured in pretreatment FDG-PET/CT to predict the short-term outcome in patients with pharyngeal cancers treated by radiotherapy alone or with concurrent chemoradiation. The role of MTV as a prognostic factor was also investigated using the correlation between MTV and disease-free survival (DFS).

Patients and Methods

Patients. This study was approved by the institutional review board at our institution. Informed consent was waived due to the retrospective design of the study. From the cancer registry at Samsung Medical Center, we retrieved and analyzed the records of 147 patients with pharyngeal cancers who had been treated from 2002 to 2008. The eligibility criteria included a histologic diagnosis of squamous cell carcinoma of the pharynx, including undifferentiated carcinoma in the nasopharynx. The initial curative treatment of radiotherapy alone or concurrent chemoradiation was done after FDG-PET/CT for staging workup. A minimum follow-up period was set to be >1 year from the completion of treatment to the last follow-up. Among 147 patients, 65 patients were excluded because of different pathologic diagnoses, history of previous treatments, or inadequacy of FDG-PET/CT data. Finally, 82 patients were determined to be eligible for this study (Table 1); distribution of the primary tumor sites was 63 nasopharynx (76.8%), 13 oropharynx (15.8%), and 6 hypopharynx (7.4%). The patient ages ranged from 11 to 70 y (mean, 53.8 y). The clinical TNM stage (1) distribution was 4 patients with stage I (4.8%), 12 with stage II (14.6%), 30 with stage III (36.5%), and 36 with stage IV (44.1%).

The treatment modalities were determined after discussion among the surgical, medical, and radiation oncologists on the head and neck tumor board at our institution. Eight patients (9.7%) underwent radiotherapy alone due to early TNM stage, old age, or poor performance

Table 1. Demographic data (N = 82)

Characteristics	No. (%)
Age (y)	
Range	11-70
Mean	53.8
Gender	
Male	69 (84.1)
Female	13 (15.9)
Site	
Nasopharynx	63 (76.8)
Oropharynx	13 (15.8)
Hypopharynx	6 (7.4)
cT stage	
T_1	22 (26.8)
T_2	25 (30.4)
T_3	17 (20.7)
T_4	18 (22.1)
cN stage	
N_0	10 (12.2)
N_1	22 (26.8)
N_2	43 (52.4)
N_3	7 (8.6)
TNM stage (ref. 1)	
I	4 (4.8)
II	12 (14.6)
III	30 (36.5)
IV	36 (44.1)
Histologic grade*	
G_1	26 (31.7)
G_2	23 (28.0)
G_3	33 (40.3)
Treatment modality	
Radiotherapy alone	8 (9.7)
Chemoradiation	
Cisplatin	14 (17.0)
Cisplatin + 5-FU	41 (50.0)
Cispaltin + docetaxel	15 (18.5)
Other	4 (4.8)
Treatment response†	
Complete response	77 (93.9)
Partial response	4 (4.8)
Stable disease	0 (0)
Progressive disease	1 (1.3)
Recurrence after complete response	13/77 (16.8)
Time after treatment (mo)	
≤12	9 (69.3)
>12	4 (30.7)
Site	
Local	0 (0)
Regional	5/13 (38.4)
Regional + Distant	2/13 (15.4)
Distant	6/13 (46.2)
Follow-up duration (mo)	
Range	12-64
Mean	34.8

Abbreviation: 5-FU, 5-fluorouracil.
*G_1, well-differentiated or keratinizing squamous cell carcinoma; G_2, moderately differentiated or nonkeratinizing squamous cell carcinoma; G_3, poorly differentiated squamous cell carcinoma or undifferentiated carcinoma.
†RECIST (ref. 11). Complete response, disappearance of all lesions, confirmed at ≥4 wk; partial response, >30% decrease from baseline, confirmed at 4 wk; stable disease, neither criteria of partial response nor of progressive disease met; progressive disease: ≥20% increased over smallest sum, or appearance of new lesions.

status, and 74 patients (90.3%) underwent cisplatin-based concurrent chemoradiation according to case-specific modification to select the most effective regimen (single-agent treatments with cisplatin in 14 patients, combination treatments with cisplatin and fluorouracil in 41 patients, cipslatin and docetaxel in 15 patients, and cipslatin and fluorouracil and bleomycin or docetaxel in 4 patients). Cisplatin and fluorouracil were administered for three cycles at every 3 wk during radiotherapy alone and an additional three cycles at 14 days after radiotherapy alone. Cisplatin and docetaxel were administered for three cycles at every 3 wk during radiotherapy alone. The total dose of radiation was 72 Gy in the radiotherapy alone group, and 34 to 72Gy in the concurrent chemoradiation group, with adjustments according to the treatment toxicity and patient's compliance.

FDG-PET/CT protocol. All patients fasted for ≥6 h prior to the FDG-PET/CT scans, which were done using a GE Discovery LS scanner (General Electric). Whole-body CT scans were done using a continuous spiral technique and an 8-slice helical CT with a gantry rotation speed of 0.8 s. CT scan data were collected using the following parameters: 40 to 80 mAs, 140 KeV, a section width of 5 mm, and a table feed of 5 mm/rotation. No i.v. or oral contrast agents were used. Following the CT scans, and after the i.v. injection of 370 MBq FDG, an emission scan was done from thigh to head at 5 min/frame for a total of 45 min. CT attenuation-corrected FDG-PET images were reconstructed using an ordered subset expectation maximization algorithm (28 subsets, 2 iterations). Images were displayed in a 128 × 128 matrix (pixel size 4.29 × 4.29 mm, slice thickness 4.25 mm). CT and FDG-PET scan data were accurately coregistered using commercial software (eNTEGRA, Elgems).

FDG-PET/CT images were reviewed by nuclear medicine physicians and a radiologist who had no knowledge of the clinical information. Target lesions were determined to be primary tumors with or without neck nodes based on FDG uptake and anatomical location.

Measurement of MTV. MTVs were measured from attenuation-corrected FDG-PET images using a SUV-based automated contouring program (Advantage Workstation VolumeShare version 2, GE Health). Initially, FDG-PET data were transferred into the workstation in DICOM format. Images were reviewed with a SUV intensity range from 0 to 5 in order to localize the hypermetabolic, target lesions in the head and neck area, which were confirmed in previous readings from FDG-PET/CT. Then, the boundaries were drawn large enough to incorporate each target lesion in the axial, coronal, and sagittal FDG-PET images. To define the contouring margins around the tumor and neck nodes, SUV 2.5 was used as previously reported (9). The contour around the target lesions inside the boundaries was automatically produced and the voxels presenting SUV intensity >2.5 within the contouring margin were incorporated to define the tumor volumes. MTV was defined as the sum of metabolic volumes of the primary tumors and neck nodes, if present.

In our study, the MTVs ranged from 1.9 to 231.9 mL (median, 39 mL). The cutoff for MTV was determined using Youden's method of cross-validated predicted probabilities (10) with the treatment response as the gold standard. The sensitivity and specificity of each MTV in predicting the gold standard were calculated, and the cutoff point showing the maximal sum of sensitivity and specificity was determined to be the significant cutoff. As a result, a cutoff of 40 mL was determined to be significant for MTV, with a sensitivity of 78.6% and a specificity of 55.9% (logistic model, $P = 0.01$).

To validate the determined cutoff for MTV, we analyzed the discriminative power in terms of the prediction for treatment response and DFS (Fig. 1). When dichotomization analysis was applied, a significantly discriminative P value was obtained for 40 mL of MTV (treatment response prediction, $P = 0.037$ in Fisher's exact test; DFS, $P = 0.025$ in the log-rank test). Therefore, 40 mL was confirmed and used as the cutoff MTV in our statistical analyses.

Measurement of SUV. The SUVs were acquired using attenuation-corrected images, amount of FDG injected, patient body weight, and cross-calibration factors between FDG-PET and the dose calibrator.

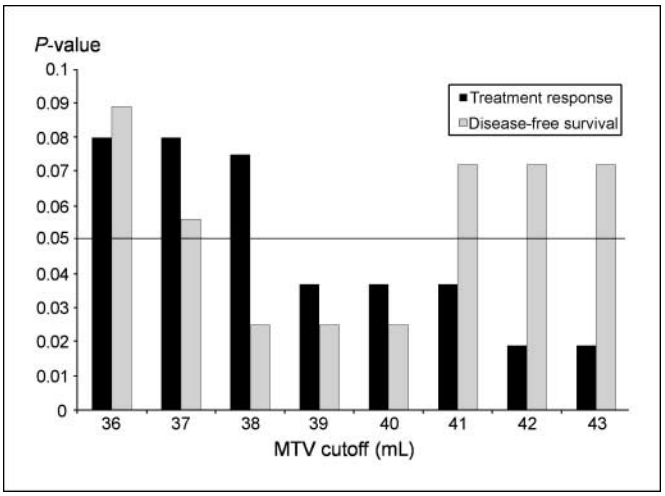

Fig. 1. Analysis of the discriminative power of various cutoffs of MTVs in the context of predicting treatment response and disease-free survival (DFS). The most significantly discriminative P value was identified at 40 mL of MTV for both the treatment response and DFS (Fisher's exact test in treatment response, log-rank test for DFS).

Maximal SUVs of the primary tumors in our cohort ranged from 1.9 to 43.3 (median, 9.9). The cutoff for SUV was also determined using the same statistical method as for MTV. As a result, SUV 10 was determined to be the cutoff and was used in the all analyses (sensitivity and specificity 50.0%, logistic model $P = 0.56$).

Statistical analysis. Response Evaluation Criteria in Solid Tumors (RECIST; ref. 11) was used to assess the treatment response at >4 wk after the completion of treatment, and the responses were classified as complete response, partial response, progressive disease, or stable disease. An imaging study (chest X-ray, CT or magnetic resonance imaging scan) and clinical examination with endoscopic evaluation were used as measurement methods for the tumors.

Short-term outcome was assessed using both the treatment response evaluation by RECIST and recurrence event during the follow-up. As a result, treatment outcome was categorized into complete response by RECIST and no recurrence at the last follow-up (complete response/no recurrence group) and partial response, stable disease, or progressive disease by RECIST or recurrence during follow-up (residual disease/recurrence group). DFS was defined as the time between the completion of treatment and the first recurrence of the disease (local, regional, and distant recurrence).

Fisher's exact test was used to compare the equality of the measures of treatment response according to each variable. Binary logistic regression was used to assess the multivariate analysis. Age was dichotomized with the median value of 53 y. The Kaplan-Meier estimates and the log-rank test were done to assess the equality of the survival functions across variables in the DFS analysis. The Cox proportional hazard model was used in the multivariate comparisons and an estimated hazard ratio (HR) with 95% confidence interval (95% CI) was presented. A P value of ≤0.05 was considered statistically significant. Data were analyzed using PASW 17.0 (SPSS, Inc.)

Results

Treatment response evaluation. After the completion of treatment, complete response was achieved in 77 patients (93.9%), partial response in 4 patients (4.8%), and progressive disease in 1 patient (1.3%), with no case of stable disease. Among patients with complete response, 13 patients had recurrences (recurrence rate, 16.8%), which were at regional sites in 5 patients,

Table 2. Prediction of short-term outcome to radiotherapy with or without chemotherapy in pharyngeal cancer: univariate and multivariate analyses (N = 82)

	No. of CR/no recurrence* (%)	HR	95% CI	$P^{\dagger}$
Univariate analyses				
Age (y)				
≤53	31/38 (81.5)	1.47	0.52-4.17	0.47
>53	33/44 (75.0)			
Gender				
Female	11/13 (84.6)	1.66	0.33-8.28	0.72
Male	53/69 (76.8)			
ECOG[†]				
0	6/7 (85.7)	4.50 (0 vs. 2)	0.42-42.01	0.19[§]
1	54/68 (79.4)	1.55 (0 vs. 1)	0.22-10.45	
2	4/7 (71.4)	2.89 (1 vs. 2)	0.64-13.12	
Histologic grade[‖]				
G_1	18/26 (69.2)	0.31 (G_1 vs. G_3)	0.08-1.12	0.08[§]
G_2	17/23 (73.9)	0.79 (G_1 vs. G_2)	0.23-2.68	
G_3	29/33 (87.8)	0.39 (G_2 vs. G_3)	0.10-1.49	
cT stage				
T_{1-2}	40/47 (85.1)	2.61	0.91-7.46	0.07
T_{3-4}	24/35 (68.5)			
cN stage				
N_{0-1}	26/32 (74.2)	1.36	0.46-3.97	0.57
N_{2-3}	38/50 (76.0)			
TNM stage (ref. 1)				
I-II	14/16 (87.5)	3.95 (I-II vs. IV)	0.85-17.76	0.02[§]
III	27/30 (90.0)	0.77 (I-II vs. III)	0.13-4.35	
IV	23/36 (63.8)	5.08 (III vs. IV)	1.36-18.61	
Treatment modality				
RT	7/8 (87.5)	2.08 (RT vs. CCRT)	0.30-13.70	0.52[§]
CCRT				
Single agent	11/14 (78.5)			
Multiple agents	46/60 (76.6)			
SUVmax				
≤10	33/42 (78.5)	1.06	0.38-3.03	0.90
>10	31/40 (77.5)			
Metabolic tumor volume				
≤40 mL	36/41 (87.8)	3.34	1.09-10.08	0.03
>40 mL	28/41 (68.2)			
Multivariate analyses				
Histologic grade[‖]				
G_1	18/26 (69.2)	1		
G_2	17/23 (73.9)	0.45 (G_1 vs. G_2)	0.10-1.86	0.27
G_3	29/33 (87.8)	0.32 (G_1 vs. G_3)	0.07-1.41	0.13
TNM stage (ref. 1)				
I-II	14/16 (87.5)	1		
III	27/30 (90.0)	0.58 (I-II vs. III)	0.07-4.35	0.60
IV	23/36 (63.8)	9.37 (I-II vs. IV)	1.76-49.82	0.29
SUVmax				
≤10	33/42 (78.5)	1		
>10	31/40 (77.5)	0.69	0.20-2.36	0.55
Metabolic tumor volume				
≤40 mL	36/41 (87.8)	1		
>40 mL	28/41 (68.2)	4.09	1.02-16.43	0.04

NOTE: Metabolic tumor volume is the sum of metabolic volumes of primary tumor with or without neck node.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy alone, CCRT, concurrent chemoradiation; SUVmax, maximal standardized uptake value
*CR/no recurrence (n = 64) is complete response with no recurrence.
[†]χ^2 test (univariate), Binary logistic regression (multivariate).
[‡]Performance status scale by ECOG (ref. 31). 0, fully active; 1, symptoms, but fully ambulatory; 2, requires nursing assistance >50% of waking hours.
[§]Test for trends using linear by linear association.
[‖]G_1, well-differentiated or keratinizing squamous cell carcinoma; G_2, moderately differentiated or nonkeratinizing squamous cell carcinoma; G_3, poorly differentiated squamous cell carcinoma or undifferentiated carcinoma.

regional and distant sites in 2 patients, and distant sites in 6 patients. There were 64 patients with complete response/no recurrence (78%) and 18 patients with residual disease/recurrence (22%) at the last follow-up in our study.

Prediction of short-term outcome. We examined whether the measurement of MTV could predict the short-term outcome to radiotherapy alone or concurrent chemoradiation. By univariate analyses (Table 2), the patients with MTVs >40 mL had a

significantly lower number of complete response/no recurrence than the patients with MTVs ≤40 mL (68.2% versus 87.8%; HR, 3.34; 95% CI, 1.09-10.08; $P = 0.03$). The TNM stage had a significant correlation with short-term outcome (87.5% for I-II versus 90.0% for III versus 63.8% for IV; $P = 0.02$ for trends using linear by linear association) as well. However, a SUV ≤10 for the primary tumor was not significantly associated with the number of complete response/no recurrence in comparison to a SUV >10 by univariate analyses (78.5% versus 77.5%; $P = 0.90$). Clinical T stage showed only the trend toward significance (85.1% for T_{1-2} versus 68.5% for T_{3-4}; $P = 0.07$). By multivariate analyses, MTV was the only significant predictor for short-term outcome with a MTV >40 mL associated with an increased risk of residual disease/recurrence (HR, 4.09; 95% CI, 1.02-16.43; $P = 0.04$). SUV did not show any significant correlation with short-term outcome by multivariate analyses either ($P = 0.55$).

Prediction of DFS. MTV was identified as a significant prognostic factor for DFS both by univariate (HR, 2.88; 95% CI, 1.02-8.09; $P = 0.04$) and multivariate (HR, 3.42; 95% CI, 1.04-11.26; $P = 0.04$) analyses (Table 3). A representative case (Fig. 2) with nasopharyngeal cancer presenting with a MTV >40 mL achieved complete response, but the patient showed early recurrence at a distant site 7 months after treatment. The Kaplan-Meier curve for DFS in patients with MTV >40 mL and MTV ≤40 mL is presented in Fig. 3. SUV did not show any prognostic impact on DFS.

Discussion

This study investigated the usefulness of MTV measured from FDG-PET/CT in patients with pharyngeal cancers. The most significant result of the present study was that MTV could be a potential predictor of short-term outcome and a prognostic factor for DFS in patients with pharyngeal cancers treated by radiotherapy alone or concurrent chemoradiation.

Trials to delineate or measure tumor volumes using CT scan or FDG-PET have been undertaken mostly for target volume determination in radiotherapy for lung, cervix, and head and neck cancers (12–18). Despite the promising results of previous studies on tumor volumes, the methodology used to calculate the tumor volumes, such as the visual delineation of tumor margins manually using imaging or specific protocols at each study, was neither reproducible nor feasible.

Because we used the commercial software algorithm available, the MTV measurement methods of this study can be easily adopted and applied to clinical practice. In the absence of an established SUV for the delineation of FDG-PET positive tissues for tumor volume (13), SUV 2.5 was adopted based on the results of a previous study (9). It may be argued, however, that the automated contouring method could incorporate noncancerous regions nearby or exclude necrotic portions inside tumors so that MTV would be overestimated or underestimated. Along the pharyngeal tract, there are several hypermetabolic regions such as tonsil tissues and other inflammatory mucosal lesions. Although the pharynx is not as mobile a site as the lung or the heart, we tried to reduce the possibility of inaccurate measurement of MTV as much as possible in the present study. First, image findings from radiologist and nuclear medicine physician were used to decide whether the hypermetabolic lesion was cancerous or not. Second, coronal, axial, and sagittal sections of PET images were used altogether to designate the exact region of interest around the tumors. In addition, necrotic

Table 3. Analyses of prognostic factors for disease-free survival ($N = 82$)

Variables	Test for disease-free survival	HR (95% CI)	P*
Univariate analyses			
Age	≤53 vs. >53	1.21 (0.48-3.05)	0.68
Gender	Female vs. Male	1.54 (0.35-6.70)	0.56
ECOG†	0 vs. 1	1.42 (0.18-10.84)	0.73
	0 vs. 2	2.89 (0.30-27.80)	0.35
cT stage	T_{1-2} vs. T_{3-4}	2.30 (0.89-5.94)	0.08
cN stage	N_{0-1} vs. N_{2-3}	1.36 (0.51-3.64)	0.53
TNM stage (ref. 1)	I-II vs. III	0.79 (0.13-4.74)	0.79
	I-II vs. IV	3.42 (0.77-15.1)	0.10
Histologic grade‡	G_1 vs. G_2	0.81 (0.28-2.35)	0.70
	G_1 vs. G_3	0.34 (0.10-1.13)	0.07
SUVmax	≤10 vs. >10	1.06 (0.42-2.69)	0.88
Metabolic tumor volume	≤40 mL vs. >40 mL	2.88 (1.02-8.09)	0.04
Multivariate analyses			
cN stage	N_{0-1} vs. N_{2-3}	1.26 (0.37-4.23)	0.70
TNM stage (ref. 1)	I-II vs. III	0.54 (0.06-4.33)	0.56
	I-II vs. IV	1.99 (0.33-11.85)	0.44
Histologic grade‡	G_1 vs. G_2	0.48 (0.14-1.55)	0.22
	G_1 vs. G_3	0.33 (0.09-1.16)	0.08
SUVmax	≤10 vs. >10	0.76 (0.28-2.07)	0.59
Metabolic tumor volume	≤40 mL vs. >40 mL	3.42 (1.04-11.26)	0.04

*Cox proportional hazard model.
†Performance status scale by Eastern Cooperative Oncology Group (ref. 31): 0, fully active; 1, symptoms, but fully ambulatory; 2, requires nursing assistance >50% of waking hours.
‡G_1, well-differentiated or keratinizing squamous cell carcinoma; G_2, moderately differentiated or nonkeratinizing squamous cell carcinoma; G_3, poorly differentiated squamous cell carcinoma or undifferentiated carcinoma.

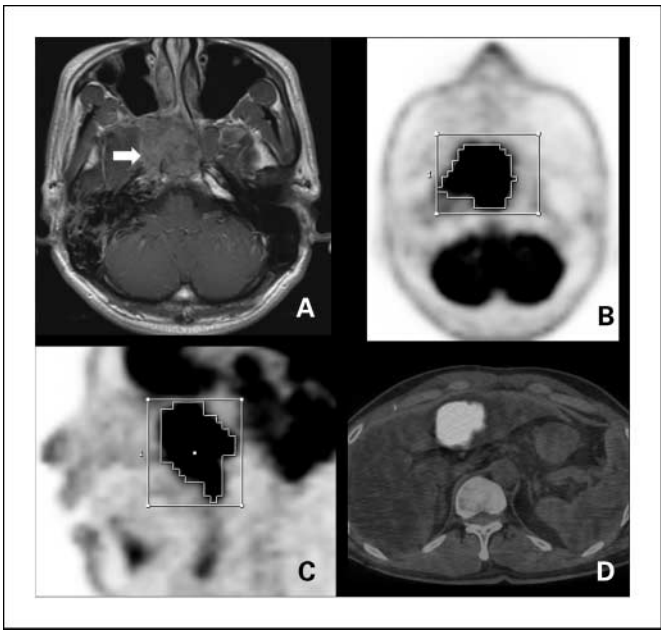

Fig. 2. *A*, pretreatment T_1-weighted, gadolinium enhanced magnetic resonance imaging of a patient with nasopharyngeal carcinoma (*arrow*) showing a large mass infiltrating the adjacent petrous apex. *B* and *C*, in axial (*B*) and sagittal (*C*) images, metabolic tumor volume measured from attenuation-corrected FDG-PET data was 104 mL for the primary lesion. There was no nodal metastasis. After concurrent chemoradiotherapy, a complete response was achieved, but at 7 mo after treatment, a distant metastasis to liver was detected (*D*).

tumor cells show decreased FDG uptake; an automated contouring algorithm does not include necrotic portions in the tumor into MTV calculation.

TNM stage, one of most widely accepted prognostic factors, showed a significant correlation with short-term outcome only by univariate analyses. It failed to retain significance by multivariate analyses, and showed no correlation with DFS.

We carried out the correlation analyses between TNM stage and MTV. First, we compared mean values of MTV of primary tumors according to *c*T stage. The mean ± SD of primary tumor MTV according to each *c*T stage were as follows: 10.98 ± 10.6 mL in cT_1 stage, 27.49 ± 20.0 mL in cT_2 stage, 43.69 ± 33.71 mL in cT_3 stage, and 74.65 ± 50.61 mL in cT_4 stage (Bonferroni corrected $P < 0.05$). By bivariate correlation analysis, a positive correlation was identified with Spearman correlation coefficient 0.621 and $P < 0.001$. With regard to cN stage, there was also a significant difference in mean values of MTV of the neck nodes between $cN_{0\text{-}1}$ and $cN_{2\text{-}3}$ (mean ± SD, 10.83 ± 21.2 mL versus 28.36 ± 28.36 mL; $P = 0.02$) and a positive correlation as well (Spearman correlation coefficient 0.417; $P = 0.001$). When we analyzed the correlation between MTV and clinical TNM stage, there was a significance difference in mean values of MTV between clinical TNM stage I-II and IV (mean ± SD, 29.58 ± 28.7 mL versus 68.1 ± 53.3 mL, Bonferroni corrected $P = 0.01$) with probable positive correlation (Spearman correlation coefficient 0.300; $P = 0.006$).

In addition, it is interesting that MTV of primary tumor showed a wide range of values even in the same *c*T stage (for example, MTVs of cT_2 stage ranged from 6.68 to 67.1 mL) as well as a positive correlation with *c*T stage. This suggests that MTV might have a different characteristic from *c*T stage possibly because it reflects the three-dimensional, volumetric parameter of primary tumor better than two-dimensional *c*T stage.

A patient (Fig. 2) with nasopharyngeal cancer presented with a MTV of 104 mL and a maximal SUV for the primary tumor of 16.4 (stage IV, $cT_4N_0M_0$). This patient showed a complete response after initial treatment, but at 7 months after treatment, a distant metastasis in the liver was detected. Among our cohort, another case with the same TNM stage cancer (stage IV, $cT_2N_2M_0$) in the oropharynx showed a MTV of 25.1 mL (2.52 mL for the primary lesion and 12.58 mL for the neck node). The maximal SUVs for the primary tumor and neck node were 11.2 and 11.1, respectively. Unlike the case in Fig. 2, this patient had complete response and no evidence of recurrence at the last follow-up. Some might argue that because the primary sites were different, the tumor biology is also different between these two cases. However, we assumed that this finding highlights the distinct feature of MTV and supports the need for further research.

Unlike in previous reports on the correlation of SUVs with treatment response and prognoses of various malignancies (3–6, 8, 19–22), we did not find any significance between SUV for the primary tumor and short-term outcome in our cohort. A few previous studies (3, 23, 24) on the predictive value of SUVs of pharyngeal cancers have used the median value of SUVs as the cutoff for analyses. In the present study, on the other hand, Youden's method using cross-validated predicted probabilities of key variables such as SUV for the primary tumor and MTV was applied to identify the cutoff for the statistical exactness. Nevertheless, the cutoff for SUV was determined to be almost the same with the median value 9.9 in this study, and it failed to show statistical significance in subsequent analyses. Because the cutoff and median value seemed to be higher than cutoffs used in previous reports, we tested the prognostic role of SUV using the different cutoffs (SUV 4-6). However, we did not find any significance, either. Possible explanations for the discrepancy between the results of previous studies and the present study would be the relative small number of patients, heterogeneity of tumor sites, and short-term duration of follow-up. Therefore, the result of the present study on the predictive role of SUV must be interpreted with

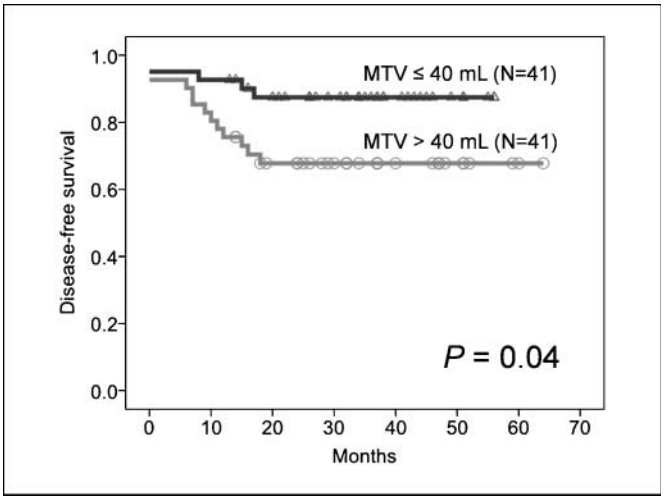

Fig. 3. Disease-free survival curve of the 82 patients according to the metabolic tumor volumes (MTV).

caution. Another explanation could be that because pharyngeal cancers originate from the mucosa, the status of the mucosa (inflammation or postbiopsy) might affect maximal SUV. Interestingly, all these findings could make us speculate that MTV might be not a simple surrogate of SUV and could be an independent factor.

We used RECIST, which lacks bidimensional measurement of target lesion, to determine the treatment response in the present study. To test the adequacy of current reporting criteria, we reevaluated treatment response with WHO criteria for cancer treatment response (25), which define partial response as a lesion showing ≥50% decrease and progressive disease as ≥25% increase in the size in multiplication of the longest diameter by greatest perpendicular diameter. As a result, there was no case of response grade change from RECIST criteria in our cohort.

The results of this study do not explain the exact pathophysiology for the correlation between MTV and treatment outcome or DFS. Although several investigators have speculated that FDG uptake correlates with cellular proliferation (26–28) or the aggressive behavior of cancer (29, 30), more studies are needed to elucidate the molecular mechanisms underlying these correlations.

There are several limitations to the present study, including the retrospective nature of the study design, uneven distribution of the primary tumor sites, and the heterogeneity of treatment modalities, which could affect the treatment outcomes and the short period of the follow-ups. Especially, the periods of follow-up of several patients in our cohort are <2 years which is a minimum period of time for analysis of treatment outcome of head and neck cancer. Therefore, the interpretation of the current study must be confined to short-term outcome which implies the limited period of follow-up. Nevertheless, this report is noteworthy because it is the first study to show the predictive value of MTV in patients with pharyngeal cancers, and our findings suggest the need for further studies on MTV.

In conclusion, MTV is a significant predictor of short-term outcome and a possible prognostic factor for DFS in patients with pharyngeal cancers treated by radiotherapy alone or concurrent chemoradiation. These results indicate that MTV could be an important factor to consider in the treatment planning and follow-up of patients with pharyngeal cancers. Analyses with larger numbers of cases and with a longer period of follow-up in prospective trials are required to validate the results of the present study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We are greatly indebted to Seonwoo Kim, PhD. (Biostatistics Unit, Samsung Biomedical Research Institute), for the statistical analyses in this study.

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