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ORIGINAL ARTICLE

Prognostic Value of Volume-Based Metabolic Parameters Measured by ^{18}F-FDG PET/CT of Pancreatic Neuroendocrine Tumors

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Abstract
Purpose To date, the prognostic value of ^{18}F-FDG PET/CT for patients with pancreatic neuroendocrine tumors (PNETs) has not been well characterized. We investigated the prognostic value of volumetric parameters using ^{18}F-FDG PET/CT in this patient population.
Methods We retrospectively reviewed 20 cases of pathologically proven PNET in patients who had undergone pretherapeutic ^{18}F-FDG PET/CT. PET parameters including maximum and average standardized uptake values (SUV_{max}, SUV_{ave}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the primary tumor were measured using a threshold SUV to determine the boundaries of the tumors. Univariate and multivariate survival analyses were performed with adjustments for PET parameters and other clinical values.
Results The median clinical follow-up was 22.3 (range, 1.2–95.4) months. Cancer-related death occurred in 5 of 20 patients (25 %). Patients had clinical or pathological stages of I in seven patients, II in six patients, III in three patient, and IV in four patients. According to the WHO histological classification of subtypes, 3 patients exhibited well-differentiated PNETs, 13 patients had well-differentiated endocrine carcinomas, and 4 had poorly differentiatedendocrine carcinomas. Univariate analysis showed that tumor size (p=0.028), AJCC stage (p=0.009), T stage (p=0.028), M stage (p=0.029), treatment modality (p=0.045), MTV (p=0.003) and TLG (p=0.027) were significant predictors of overall survival. On multivariate analysis, MTV (HR=10.859, p=0.031) was a significant independent predictor of overall survival along with the AJCC stage (HR=11.556, p=0.027).
Conclusion In patients with PNETs, the MTV of the primary tumor as measured by ^{18}F-FDG PET/CT along with the AJCC stage may be a significant independent prognostic factor for overall survival.

Keywords ^{18}F-FDG PET/CT · Pancreatic neuroendocrine tumor · Metabolic tumor volume · Total lesion glycolysis · Prognosis

Introduction

Pancreatic neuroendocrine tumors (PNETs) are the second most common primary pancreatic malignancy and account for 1.3 % of newly diagnosed pancreatic tumors each year. The incidence of PNETs may be >1 % in the general population, although the vast majority are indolent relative to pancreatic adenocarcinoma and thus lack clinical relevance [1, 2]. Over the past decade, there have been remarkable advances in the diagnosis and treatment of PNETs. There has not been a comparable progression in the ability to accurately predict prognosis, however, which is critical for clinical decision

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making. There have been some reports that have suggested prognostic factors for predicting survival and disease progression of PNETs, including tumor size, differentiation, distant metastases, and treatment modality, though these studies have been largely inconclusive [3, 4].

Positron emission tomography/computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has been shown to be valuable for initial staging and for detecting recurrent disease in many tumor types including PNETs.^{18}F-FDG PET/CT is a non-invasive imaging technique that is based on the principle of specific tissue metabolism [5, 6]. ^{18}F-FDG PET is useful not only for diagnosis and staging, but also for evaluating the proliferative activity and malignancy grades of tumors that may also reflect prognosis in many tumors including PNET. A recent study reported that the rate of positive ^{18}F-FDG uptake increased as the malignant potential increased according to the WHO criteria in PNETs [7]. The maximum standardized uptake value (SUV_{max}) has been well evaluated as an important prognostic factor for several cancers including PNETs. However, SUV_{max} reflects the value of a single voxel and thus does not account for the metabolism of the entire tumor. Recently, volumetric parameters measured by ^{18}F-FDG PET such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have emerged as new prognostic factors in several types of cancer [8–14]. However, the prognostic value of volumetic metabolic parameters for PNETs has not yet been evaluated. In this study, we investigated the prognostic value of volumetric metabolic PET parameters compared with other clinical variables in PNETs.

Materials and Methods

Patients

We retrospectively reviewed data from 23 consecutive patients with pathologically proven PNETs who underwent ^{18}F-FDG PET/CT scans for initial staging between January 2004 and January 2011. Among these patients, three were lost to follow-up or did not receive any treatment. Therefore, they were excluded from this study. A total of 20 patients were enrolled in this study. This study protocol was reviewed and approved by the ethics committee at our institution.

PET/CT Imaging

All patients fasted for at least 6 h before the PET/CT study. The serum glucose level needed to be less than 180 mg/dl before ^{18}F-FDG administration. PET/CT was done using two kinds of PET/CT scanners (Discovery LS or Discovery STe, GE Healthcare, Milwaukee, WI, USA). In the Discovery LS scanner, whole body CT scans (140 KeV, 40–120 mAs, 5 mm section width) were obtained 45 min after injection of ~370 MBq ^{18}F-FDG. Emission scans from the thigh to head were subsequently obtained at 4 min per frame in two-dimensional mode. PET images were reconstructed by an ordered-subset expectation maximization algorithm (OSEM) (28 subsets, 2 iterations, voxel size=4.3×4.3×3.9 mm). In the Discovery STe scanner, whole-body CT scans (140 KeV, 30–170 mAs, 3.75 mm section width) were obtained 60 min after injection of ^{18}F-FDG (5.5 MBq/kg). Emission scans from the thigh to head were then obtained at 2.5 min per frame in three-dimensional mode. PET images were reconstructed by a three-dimensional OSEM algorithm (20 subsets, 2 iterations, voxel size=3.9×3.9×3.3 mm). Standardized uptake values (SUV) were derived from the injected dose of ^{18}F-FDG and the patient's body weight. Commercial software (Advantage Workstation version 4.4, GE Healthcare) was used to accurately co-register the separate CT and PET scan data.

Image Analysis

The GE Advantage Workstation 4.4 volume viewer was used for semiquantitative and volumetric analyses of the primary tumors. The software provided an automatic method of delineating the volume of interest (VOI) based on the threshold SUV. The maximum SUV (SUV_{max}), average SUV (SUV_{avg}), and metabolic tumor volume (MTV) of the primary tumor were automatically calculated by placed delineated VOI over the primary pancreatic lesion. A VOI (5×5×1 voxels) was manually drawn at the aortic arch. The SUV_{avg} plus two standard deviations (SD) of the VOI was adopted as a threshold SUV for determination of the tumor boundaries. TLG was determined as a product of SUV_{avg} and MTV.

Statistical Analysis

Overall survival was measured from the date of diagnosis to the date of death or final clinical follow-up visit. In this study, we defined events for prognostic evaluation as cancer or treatment related. Overall survival analysis was performed using the Kaplan-Meier method for PET parameters and other clinical variables including age, sex, symptoms, tumor location, tumor size, histological differentiation, AJCC stage, T stage, N stage, M stage, treatment modality, SUV_{max}, SUV_{avg}, MTV, and TLG. Univariate analysis of prognostic factors was used by the log-rank test. To determine the optimal cutoffs for survival curves, maximal log-rank statistics were used. Cox proportional hazards regression analysis was used to assess the potential independent effects of the PET parameters after adjusting for the effects of other significant univariate factors. Estimated hazard ratios (HR) with 95 % confidence intervals (CI) were also calculated. Statistical analyses were performed using commercial software (SPSS Statistics 19, IBM Inc., New York, NY, USA). A p-value <0.05 was considered to be statistically significant. Numeric data are expressed as the mean ± SD.

Results

Clinical and PET characteristics are shown in Table 1. The mean age was 61.9±12.8 years, with a range of 36 to 79 years. Among the 20 patients included in this study, 13 were male (65.0 %) and 7 female (35.0 %). Eleven patients had symptoms (55 %). The most common symptom was abdominal discomfort or pain (90.1 %). One patient (0.09 %) had hypoglycemia. One patient was found to have MEN-I syndrome including PNETs, a parathyroid tumor, and a pituitary gland tumor. The mean SUV_{max}, MTV, and TLG of the primary tumors were 8.9±8.9 (range, 3.1–42.9), 83.8±141.0 cm^3 (range, 5.2–498.0), and 286.0±640.8 (range, 15.2–2,241), respectively. All primary tumors were PET positive by visual analysis. The clinical or pathological stage was I in seven patients, II in six patients, III in three patient, and IV in four patients. According to the WHO histological classification subtypes, 3 patients (15 %) had well-differentiated PNETs (WHO 1), 13 (65 %) had well-differentiated neuroendocrine carcinomas (WHO 2), and 4 (20 %) had poorly differentiated neuroendocrine carcinomas (WHO 3). The mean SUV_{max} for well-differentiated PNETs was 5.4±1.2, that of well-differentiated neuroendocrine carcinoma was 7.4±4.4, and that of poorly differentiated neuroendocrine carcinoma was 15.1±19.3. There were no significant differences in SUV_{max} between WHO histological types (p=0.757).

Table 1 Clinical and PET characteristics of subjects

No.	Sex	Age (years)	Size (cm)	Stage	WHO classification	SUV_{max}	MTV	TLG
1	M	36	10	IV	WHO 3	13.2	445.0	2047.0
2	F	78	3.5	III	WHO 3	5.2	8.4	15.2
3	M	51	3.3	IV	WHO 2	6.7	5.2	16.6
4	F	74	5.5	II	WHO 2	6.9	20.3	52.8
5	M	60	1.8	II	WHO 3	42.9	15.9	25.4
6	F	65	3.1	I	WHO 1b	5.5	30.3	60.6
7	M	49	1.5	I	WHO 1a	4.2	22.0	30.8
8	M	78	6.0	II	WHO 1b	6.6	149.9	209.9
9	M	51	2.8	III	WHO 2	5.0	38.6	69.5
10	M	64	5.0	II	WHO 2	9.1	164.0	229.6
11	F	72	3.1	II	WHO 2	16.7	25.6	122.6
12	M	47	2.1	I	WHO 2	15.7	15.3	58.1
13	M	56	7.0	IV	WHO 2	10.2	498.0	2241.0
14	F	74	2.5	I	WHO 3	3.9	9.7	21.3
15	M	48	2.0	I	WHO 2	4.8	26.8	59.2
16	M	68	2.6	IV	WHO 2	4.0	5.6	15.2
17	F	60	5.3	II	WHO 2	4.9	124.7	286.8
18	F	79	3.0	III	WHO 2	4.8	29.9	77.9
19	M	51	2.8	I	WHO 2	5.0	23.9	52.7
20	M	77	2.0	I	WHO 2	3.1	16.0	27.2

WHO 1a well-differentiated neuroendocrine tumor, benign behavior; *WHO 1b* well-differentiated neuroendocrine tumor, uncertain behavior; *WHO 2* well-differentiated neuroendocrine carcinoma; *WHO 3* poorly differentiated neuroendocrine carcinoma

Results of the univariate analysis are shown in Table 2. The median clinical follow-up was 22.3 (range, 1.2–95.4) months. Cancer-related death occurred in 5 of 20 patients (25 %). The optimal cutoff values were age of 64 years, tumor size of 3.2 cm, SUV_{max} of 6.6, SUV_{ave} of 2.2, MTV of 27 cm^3, and TLG of 166. Tumor size (p=0.028), AJCC stage (p=0.009), T-stage (0.028), M stage (p=0.029), treatment modalitiy (p=0.045), MTV (p=0.003), and TLG (p=0.027) were identified as significant predictors of overall survival, indicating that a large tumor, advanced stage, distant metastases, palliative therapy, and higher MTV and TLG were associated with poor overall survival (Fig. 1). On multivariate analysis, MTV (HR=10.859, 95 % CI=1.239–95.200, p=0.031) was a significant independent predictor of overall survival along with the AJCC stage (HR=11.556, 95 % CI=1.312–101.804, p=0.027). Patients with a higher MTV exhibited significantly shorter overall survival (Fig. 2). Multivariate analysis showed that the only independent predictor of survival was MTV.

Discussion

To our knowledge, this is the first clinical study to evaluate the prognostic value of volume-based parameters of PET in patients with PNETs. This study demonstrated that MTV, a volumetric parameter of ^{18}F-FDG PET/CT, is an important independent prognostic factor for overall survival. Although PNETs are often slow growing, survival outcomes for patients with these tumors have not improved in recent decades. However, non-surgical therapeutic advances have been made for patients with advanced PNETs with the use of sunitinib and everolimus [2, 15, 16]. Therefore, in patients who would benefit from more aggressive treatment, validated prognostic factors may play an important role. Our results suggested that MTV may be validated as a prognostic factor for PNETs and may help to select patients who are candidates for more aggressive treatment.

To date, few studies regarding prognostic factors for PNETs have been conducted. In those studies, tumor size, differentiation, distant metastases, and treatment modality were thought to be related to prognosis [3, 4]. Thus, large tumors, poorly differentiated tumors, distant metastases, and a positive resection margin of primary tumors in patients with PNETs were associated with poor survival. Our data indicated that tumor size, treatment modality, AJCC stage, and the presence of distant metastases were significant prognostic factors on univariate analysis, too.

PNETs have a spectrum of phenotypes ranging from well to poorly differentiated, which reflects both disease prognosis and the biology of the tumor itself. Well-differentiated PNETs

Table 2 Results of univariate analysis for predicting overall survival

Variable	Overall survival (months)	HR	95 % CI	*p*-value
Age (years)				
<64 (*n*=12)	32.9±7.6			
≥64 (*n*=8)	72.8±11.3	0.585	0.111–3.070	0.506
Sex				
M (*n*=13)	44.8±7.5			
F (*n*=7)	69.7±15.3	0.893	0.168–4.733	0.896
Symptoms				
No (*n*=9)	69.4±12.7			
Yes (*n*=11)	64.6±14.4	1.216	0.243–6.072	0.810
Location				
Head or uncinate process(*n*=14)	68.5±11.3			
Body or tail (*n*=6)	67.1±16.4	1.001	0.183–5.456	0.999
Tumor size (cm)				
<3.2 (*n*=12)	86.7±8.1			
≥3.2 (*n*=8)	46.0±14.8	7.628	1.485–39.170	0.028
Histological differentiation	63.0±0.0			
Well-differentiated neuroendocrine tumor (*n*=3)	62.2±10.8			
Moderate, poorly differentiated neuroendocrine carcinoma (*n*=17)		NA	NA	0.244
Stage				
I, II (*n*=13)	87.6±7.5			
III, IV (*n*=7)	18.4±5.7	9.939	1.824–54.169	0.009
T stage				
T1-T2 (*n*=11)	86.8±8.2			
T3-T4 (*n*=9)	46.0±14.8	7.628	1.485–39.170	0.028
N stage				
N0 (*n*=15)	76.4±9.8			
N1 (*n*=5)	35.7±20.1	3.391	0.503–22.857	0.110
M stage				
M0 (*n*=16)	77.7±9.2			
M1 (*n*=4)	16.0±6.9	4.946	0.582–42.013	0.029
Treatment modality				
Curative surgery±adjuvant CTx or RTx (*n*=13)	80.6±9.6			
Palliative surgery or CTx or RTx (*n*=7)	19.4±6.1	4.780	0.827–27.636	0.045
SUV_{max}				
<6.6 (*n*=11)	78.2±11.0			
≥6.6 (*n*=9)	54.7±15.1	2.681	0.532–13.512	0.235
SUV_{avg}				
<2.2 (*n*=11)	55.7±6.9			
≥2.2 (*n*=9)	55.2±13.4	4.186	0.840–20.873	0.154
MTV				
<27 cm^3 (*n*=12)	87.5±7.6			
≥27 cm^3 (*n*=8)	15.4±4.3	9.459	1.759–50.869	0.012
TLG				
<166 (*n*=14)	82.0±8.8			
≥166 (*n*=6)	37.0±17.0	5.478	0.899–33.398	0.027

HR hazard ratio, *CI* confidence interval, *RTX* radiotherapy, *CTX* chemotherapy, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis, *SUV* standized uptake value, *NA* not applicable

have high cell surface expression of somatostatin receptors (SSTR), which are G protein-coupled receptors that trigger an inhibitory signaling pathway. In poorly differentiated tumors, the cells are more aggressive, exhibiting rapid proliferation

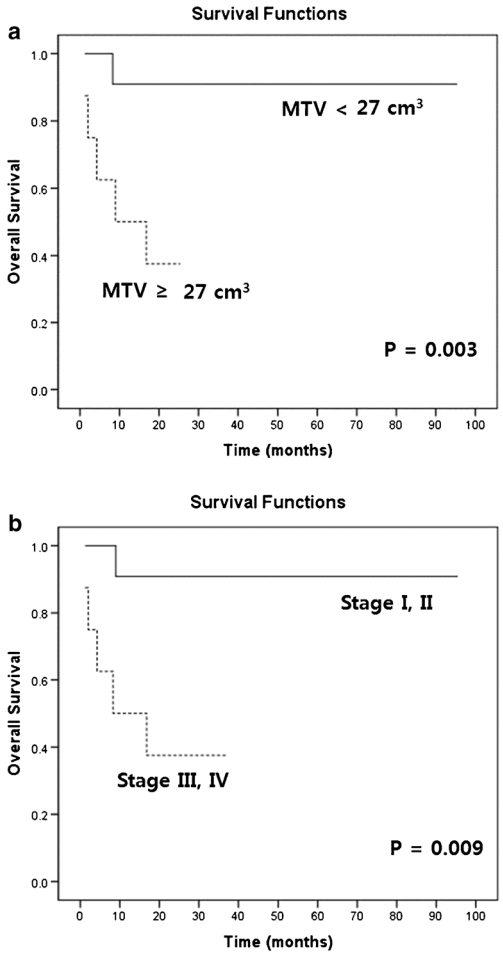

Fig. 1 Kaplan-Meier survival curves according to the MTV of the primary tumor (**a**) and stage (**b**) in patients with pancreatic neuroendocrine tumors. Both higher MTV and higher stage were significantly associated with worse prognoses

and an accelerated clinical course. ^{111}In octreotide scintigraphy and ^{68}Ga-DOTA-octreotate PET/CT were used to obtain non-invasive SSTR images, which were useful in identifying well-differentiated PNETs. Poorly differentiated PNETs, on the other hand, exhibited high ^{18}F-FDG activity [17–21]. It was reported that ^{18}F-FDG uptake of PNETs was useful for predicting tumor aggressiveness. Toshihiko et al. reported 11 out of 16 well-differentiated neuroendocrine tumors were PET negative (SUV_{max}<3.0) and 5 out of 16 well-differentiated neuroendocrine and 5 out of 5 well-differentiated neuroendocrine carcinomas were PET positive results (SUV_{max}>3.0) [7]. On the contrary, all PNETs in our study were PET positive. This might result from the difference in WHO subtypes. In our study, only 15 % of subjects belonged to the WHO 1 group, while 76 % of subjects belonged to the WHO 1 group in the previous study. Especially the WHO 1a group, which showed the highest PET-negative ratio of 43 % in the previous study, was only 5 % of patients in our study.

Recently, ^{18}F-FDG PET/CT has become a popular imaging modality for characterizing both anatomy and function. ^{18}F-FDG PET/CT has been used in a variety of malignancies such as lymphoma, esophageal, breast, colorectal, and head and neck cancers. This tool was not only useful for providing information about tumor spread but also for the evaluation of treatment response [22]. The parameters measured by ^{18}F-FDG PET/CT such as SUV, MTV, and TLG were thought to represent tumor burden and aggressiveness [12–14]. The most popular semiquantitative index for tumors on ^{18}F-FDG PET/CT was SUV_{max}. A number of studies have shown that SUV_{max} can help to determine prognoses in various types of cancers [23, 24]. However, in some recent studies, the

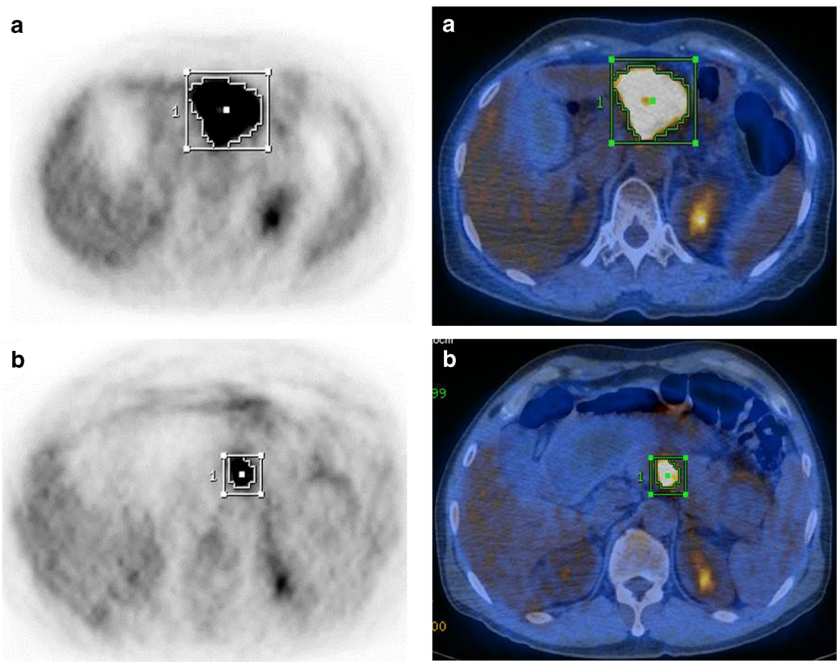

Fig. 2 Representative ^{18}F-FDG PET and PET/CT fusion images in high-MTV (**a**) and low-MTV (**b**) pancreatic neuroendocrine tumors (PNETs). **a** PET/CT of a 60-year-old male patient with a PNET that showed a high MTV (98.9 cm^3) of the primary tumor, with a poor overall prognosis (overall survival=13.6 months). **b** PET/CT of a 59-year-old male patient with a PNET that showed a low MTV (13.6 cm^3) of the primary tumor, with a good overall prognosis (overall survival=68.9 months)

SUV_{max} of the primary tumor was not an independent prognostic factor for survival based on univariate analysis. SUV_{max} is a single voxel value that cannot represent the metabolic burden of the entire tumor and may be confounded by tumor size and statistical noise [25]. In contrast, volume-based parameters such as MTV and TLG may be more effective prognostic factors in that they reflect metabolic characteristics of the whole tumor. Notably, conventional volumetric measurement performed by manually drawing the VOI had several serious disadvantages including time constraints and high inter-/intra-observer variance. In this study, we chose to use commercially available volumetric analysis tools that produce automatic VOIs with isocontour thresholds. This method showed an excellent reproducibility (nearly 100 %) and short measuring time (less than 2–3 min), which may be clinically applicable. In our study, MTV was a better independent prognostic factor in patients with PNETs than SUV. Among previous studies in other types of cancers, some showed that TLG was a significant independent prognostic factor [10, 26]. On the contrary, others reported that MTV was a significant independent prognostic factor for esophageal cancer and tongue cancer [27, 28]. In our study, there was a significant high correlation between TLG and MTV (r=0.973, p<0.001). If MTV was not included as a variable in the multivariate analysis, TLG proved to be an independent prognostic factor with marginal significance (p=0.056). Therefore, further confirmatory studies are warranted to reveal which parameter is a better prognostic indicator.

Many PNETs are associated with genetic cancer syndromes such as multiple endocrine neoplasia type I (MEN-I) and von Hippel-Lindau syndrome (VHL) [29, 30]. One patient in our study had a diagnosis of MEN-I. This patient exhibited ^{18}F-FDG uptake in the upper mediastinum and pituitary gland as well as the pancreas. After further workup, this patient was found to have PNETs, a parathyroid tumor, and a pituitary tumor. This suggests that whole-body ^{18}F-FDG PET/CT imaging may be helpful in screening for other pathological conditions associated with PNETs.

Our study had several limitations. While PNETs are relatively rare, the number of subjects enrolled was notably small. Additionally, this study was retrospective in nature. Two different types of PET scanners that utilized different protocols were used, which could have potentially influenced SUV measurements. Therefore, our study has generated a hypothesis that requires further research in a large number of patients using uniform PET protocols.

In conclusion, our data suggest that MTV as a volumetric parameter of ^{18}F-FDG PET as well as AJCC stage may be independent prognostic factors for survival in patients with pancreatic neuroendocrine tumors. Therefore, ^{18}F-FDG PET may be helpful in selecting candidates for adjuvant therapy and close follow-up after treatment.

Conflict of interest Ho Seong Kim, Joon Young Choi, Dong Wook Choi, Ho Yeong Lim, Joo Hee Lee, Sun Pyo Hong, Young Seok Cho, Kyung-Han Lee, and Byung-Tae Kim declare no conflict of interest.

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