

Clinical Usefulness of F-18 FDG PET/CT in Papillary Thyroid Cancer with Negative Radioiodine Scan and Elevated Thyroglobulin Level or Positive Anti-thyroglobulin Antibody

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Abstract

Purpose Elevated thyroglobulin (Tg) levels, along with a negative radioiodine scan, present a clinical problem for the diagnosis of recurrence in papillary thyroid cancer (PTC) patients. The purpose of this study was to assess (1) the usefulness of ¹⁸F-fluorodeoxyglucose (F-18 FDG) positron emission tomography (PET)/computed tomography (CT) for PTC patients with negative diagnostic radioiodine scan and elevated serum Tg level or positive anti-thyroglobulin antibody (TgAb), and (2) the effect of endogenous thyroid stimulating hormone (TSH) stimulation (ETS) on detecting recurrence in these circumstances.

Methods Eighty-four patients with negative diagnostic radioiodine scan and elevated serum Tg or positive TgAb under ETS were included. Correlation with clinicopathological features and recurrence, detectability of FDG PET/CT and cut-off value of serum Tg for recurrence in PTC patients with these circumstance were assessed. In addition, detectability of F-18 FDG PET/CT under ETS and suppression were compared.

Results In Cox regression analysis, only serum Tg level was significantly associated with recurrence ($P < 0.001$, HR = 1.13; 95 % CI, 1.061–1.208). The cut-off level of Tg was 21.5 ng/mL (AUC, 0.919; $P < 0.001$) for discriminating the recurrence

in the patients with positive PET/CT finding. The sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG PET/CT for detecting recurrence were 64 %, 94 %, 86 %, 81 %, and 83 %. In the analysis of F-18 FDG PET/CT under ETS, the sensitivity, specificity, PPV, NPV and accuracy was 64 %, 94 %, 88 %, 81 % and 83 %. Those under TSH suppression were 67 %, 92 %, 80 %, 85 % and 83 %.

Conclusions F-18 FDG PET/CT, although less sensitive, showed high specificity, PPV, NPV, and accuracy and therefore can be useful for the patients with negative diagnostic radioiodine scan and elevated serum Tg or positive TgAb. In addition, FDG PET/CT under ETS does not seem to have an additive role in detecting recurrence in these patients.

Keywords FDG · PET/CT · Papillary thyroid cancer · Thyroglobulin · Thyroid stimulating hormone

Introduction

Thyroid cancer is the most common endocrine malignancy. Recently, thyroid cancer was found to be the most rapidly increasing cancer in South Korea, with its incidence rates increasing by 24 % per year [1]. After total thyroidectomy for treatment of differentiated thyroid malignancy, radioiodine ablation is used to ablate the remnant thyroid tissue, except for tumors of less than 1 cm in size without risk factors [2]. Differentiated thyroid carcinoma is generally characterized by a good prognosis with a 5-year survival rate higher than 90 % after treatment, but it is necessary to have close clinical follow-ups because of a recurrence risk of 10–35 % [3, 4].

In general, serial monitoring of serum thyroglobulin (Tg) levels and anti-thyroglobulin antibody (TgAb) levels, and neck ultrasonography (US) have been used as postoperative follow-up methods for papillary thyroid cancer (PTC) [2].

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Recurrent disease commonly manifests itself as neck lymph node metastasis or local recurrence, but distant metastasis has been relatively rare, with rates of 4–27 % [3]. Following post-operative radioiodine ablation, elevated serum Tg levels suggest persistent or recurrent disease. Radioiodine scan is more than 99 % specific for detecting recurrence or metastasis in patients with differentiated PTC [5]. However, negative radioiodine scans have been reported in about 30–50 % of patients with recurrent or metastatic thyroid cancer [6]. Radioiodine scan could be negative, especially in patients with small-sized tumor or poorly differentiated carcinoma.

¹⁸F-Fluorodeoxyglucose (F-18 FDG) positron emission tomography (PET)/computed tomography (CT) has been used for the diagnosis and follow-up of various types of cancer, but its use is limited for differentiated thyroid cancer. In patients with negative radioiodine scan but elevated serum Tg levels, F-18 FDG PET/CT could be useful. According to the American Thyroid Association guidelines, F-18 FDG PET/CT scan is clinically useful for the detection of locoregional lymph node metastasis or distant metastasis in patients with thyroid stimulating hormone (TSH) stimulated serum Tg levels higher than 10 ng/mL after radioiodine therapy [2]. Several researches reported that patients with elevated Tg levels after TSH stimulation have high recurrence or metastasis potential. However, in previous studies, the cut-off values of Tg after TSH stimulation for F-18 FDG PET/CT varied between 2 to 30 ng/mL, and no consensus was reached [2, 5, 7, 8]. In addition, TgAb could interfere with the measurement of Tg. It would be difficult to interpret Tg levels in the presence of TgAb during follow-up [2]. Currently, whether to interpret increased TgAb alone as a surrogate marker is still controversial [4, 9, 10].

The purpose of this study was to assess the usefulness of F-18 FDG PET/CT in patients with PTC who had negative radioiodine scan and elevated serum Tg levels or positive TgAb following total thyroidectomy and high-dose radioiodine ablation, and to evaluate the effect of endogenous TSH stimulation on detectability for recurrent lesion of F-18 FDG PET/CT.

Materials and Methods

Patients

We enrolled a total of 84 patients with PTC in whom F-18 FDG PET/CT was performed at a local tertiary hospital between November 2006 and April 2014. The patients' medical records were retrospectively reviewed. This study was approved by the institutional review board of this hospital.

The inclusion criteria for this study were as follows: (1) patients with pathologically proven PTC, (2) who had undergone near total or total thyroidectomy and high-dose radioiodine ablation, and (3) had negative follow-up radioiodine scan.

Seventy-five patients who had Tg levels >2 ng/mL and normal TgAb levels under TSH stimulation (TSH >30 IU/mL) were included in the Tg-positive group. Nine patients who had increased TgAb levels and negative Tg were categorized as the TgAb-positive group. Patients who had increased both Tg and TgAb levels were not included in this analysis. Patients with Hashimoto thyroiditis or lymphocytic thyroiditis were also excluded from this study. Tg and TgAb measurement, radioiodine scan, and neck US were performed 6 months and/or 12 months after high-dose radioiodine ablation.

Tg and TgAb measurements, and radioiodine scans were performed 4 weeks after thyroid hormone withdrawal. The radioiodine scans were performed 24 h after administration of 148 MBq of I-123 or 48 h after administration of 111 MBq of I-131 using a dual-head gamma camera. I-123 was used in 75 patients and I-131 was used in nine patients. Tg and TSH levels were measured using electrochemiluminescence assays (Modular E; Roche, Basel, Switzerland). TgAb was measured using a chemiluminescent microparticle immunoassay (Architect anti-Tg reagent kit; Abbott Laboratories, Abbott Park, IL, USA) after September 2011 and the electrochemiluminescence assays (Modular E; Roche) before that time. Reference TgAb values were less than 4.11 IU/mL and 115 IU/ml, respectively.

F-18 FDG PET/CT Scans and Image Analysis

All patients fasted for more than 6 h, and their blood glucose level was measured just before the FDG injection. The patients were injected intravenously with 370 MBq of F-18 FDG. Intravenous contrast agents were not administered. Torso PET/CT images from the skull base to the upper third of the leg were obtained 60 min after injection. Images were acquired using a dedicated PET/CT scanner (Discovery STE; GE Healthcare, Milwaukee, WI, USA). The CT images were acquired using a multidetector CT equipment with the standard protocol that consists of 140 kV, 80 mA, a tube rotation time of 0.8 s per rotation, a pitch of 3, and a section thickness 3.6 mm. Emission PET images were then obtained and fused with CT images.

In the Tg-positive group, F-18 FDG PET/CT was performed under TSH stimulation (TSH >30 IU/mL) in 57 of the 75 patients, and under TSH suppression in the remaining 18 patients. In TgAb-positive group, F-18 FDG PET/CT was obtained under the TSH-stimulated condition in seven of the nine patients, and under TSH suppression in the remaining two patients.

All PET/CT images were visually analyzed by two experienced nuclear medicine physicians. The PET/CT diagnostic criterion suggesting recurrent lesions was hypermetabolic foci compared with physiologic activity in the adjacent background, with CT findings suggestive of malignancy such as cystic or necrotic change and calcification [11]. All PET/CT images were also assessed semi-quantitatively. The SUVmax

of a region of interest (ROI) was measured for quantification of suspicious cancer lesions in the AW VolumeShare 5 Workstation (GE Healthcare).

Recurrence Assessment

When lesions suggestive of recurrence were found on PET/CT images, the lesions were compared with histological results, other imaging modalities such as post-therapy radioiodine scan, US, CT, magnetic resonance imaging (MRI), and sequential Tg and TgAb levels. Cases were considered as recurrence when histopathological findings were positive or other imaging findings were suggestive of recurrence or sequential Tg or TgAb levels were consistently increasing and empirical radioiodine therapy was applied. Cases were considered as non-recurrence when they had negative histopathological findings or negative conventional imaging findings and normalized Tg levels without any further treatment.

Statistical Analysis

Statistical analyses were performed using SPSS (version 21.0; Chicago, IL, USA). A P value <0.05 was considered to indicate statistical significance. Cox regression analysis was used to evaluate the correlation between clinicopathological features and recurrence. Hazard ratio and their 95 % confidence intervals (95 % CIs) were estimated for categorical variables (multiple tumor, perithyroidal extension, central lymph node metastasis) and continuous variables (tumor size, serum Tg under TSH stimulation). The receiver operating characteristic (ROC) curve analysis was used to determine cut-off Tg levels that had a higher sensitivity and specificity in detection of recurrence. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET/CT were calculated to evaluate the detection rate of recurrence according to Tg and TgAb levels. In patients with positive findings of F-18 FDG PET/CT, the ROC curve analysis was used to obtain the Tg cut-off values that had a higher sensitivity and specificity in detection of recurrence. The t -test was used to determine the differences in SUV_{max} of the recurrent lesions. Sensitivity, specificity, PPV, NPV and accuracy of F-18 FDG PET/CT for detecting the recurrent lesions were compared between TSH stimulated and TSH suppressed condition.

Results

Clinical Characteristics

Histopathological and laboratory findings of the Tg-positive group are summarized in Table 1. All patients had high-dose radioiodine ablation. The mean cumulative radioiodine

therapy dose was 5.8 GBq (range, 3.7–13.3 GBq). The mean time interval between radioiodine ablation and Tg measurement was 270 days (range, 191–780 days). All PET/CT scans were performed after thyroidectomy and radioiodine ablation. The mean time interval from thyroidectomy to PET/CT scanning was 16 months (range, 9–77 months). And mean interval from radioiodine ablation to PET/CT scanning was 11 months (range, 6–59 months).

In the Tg-positive group, 28 patients (37 %) showed recurrence. It was confirmed pathologically in 16 of the patients. Two patients presented with newly developed pulmonary nodules strongly suggestive of metastasis on contrast-enhanced CT but did not have pathologic confirmation of tumor recurrence. Five showed small-sized metastatic lymph nodes on neck US and the remaining five patients had empirical radioiodine ablation due to persistently increasing Tg levels. There was no recurrence in the other 47 patients (63 %). There was no statistically significant correlation between recurrence and clinicopathological findings such as tumor size, multiplicity of tumor, perithyroidal extension, and central lymph node metastasis (Table 2). Only serum Tg level shows statistically significant correlation with recurrence ($P < 0.001$, HR = 1.13; 95 % CI, 1.061–1.208).

F-18 FDG PET/CT Findings in the Tg-Positive Group

F-18 FDG PET/CT scans revealed positive results in 21 (28 %) out of the 75 patients who showed increased Tg (Tg > 2 ng/mL) under TSH stimulation (Table 3). In 21 patients with positive F-18 FDG PET/CT scans, 18 patients (86 %) had true positive (TP) F-18 FDG PET/CT findings, and 3 patients had false positive (FP) findings. One of the three patients with FP finding was diagnosed with suture granuloma, and the remaining two patients showed Tg normalization without further treatment and no recurrence on other conventional imaging modalities for follow-up.

In 54 patients with negative F-18 FDG PET/CT scans, 44 patients (81 %) had true negative (TN) F-18 FDG PET/CT findings and 10 patients had false negative (FN) findings. Five out of the ten patients with FN findings showed metastatic lymph nodes on neck US during follow-up, and the remaining five patients had additional radioiodine therapy due to persistently elevated Tg levels.

The sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG PET/CT for detecting recurrence were 64 %, 94 %, 86 %, 81 %, and 83 %, respectively in 75 patients with Tg values higher than 2 ng/mL. The patients were grouped into two groups according to Tg levels, 2–10 ng/mL and more than 10 ng/mL, as the cut-off Tg level of 10.2 ng/mL determined by ROC analysis (AUC 0.919 with 93 % sensitivity and 79 % specificity, $P < 0.001$). In 36 patients with Tg levels higher than the 10 ng/mL Tg cut-off value, the sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG PET/CT

Table 1 Clinical characteristics of papillary thyroid cancer patients with elevated serum thyroglobulin

Characteristic	Value
Age, years	47.4 (12.7)
Sex	
Men	21
Women	54
Histopathological finding	
Papillary cancer, <i>n</i> (%)	74 (99 %)
Papillary cancer, follicular variant, <i>n</i> (%)	1 (1 %)
Tumor size, cm	1.5 (0.3-7.0)
Multiple tumors, <i>n</i> (%)	43 (57 %)
Perithyroidal extension, <i>n</i> (%)	49 (65 %)
Central lymph node metastasis, <i>n</i> (%)	67 (89 %)
Laboratory findings	
TSH, range, μ IU/mL	≥ 30.5
Thyroglobulin, ng/mL	40.3 (2.1-496.2 ng/mL)
Interval between ablation and Tg measurement, days	270

Data are mean (SD) or median (25-75th percentile) unless otherwise indicated

for detection of recurrent lesions were 65 %, 80 %, 89 %, 47 %, and 69 %, respectively. In 39 patients with Tg levels between 2-10 ng/mL, the sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG PET/CT were 50 %, 97 %, 50 %, 97 %, and 97 %, respectively (Table 3).

In 21 patients with positive F-18 FDG PET/CT, cut-off Tg level for prediction recurrence was 21.5 ng/mL using the ROC curve analysis. The AUC for a Tg cut-off level of 21.5 ng/mL was 0.926 ($P < 0.001$) with 83 % sensitivity and 100 % specificity for predicting the recurrence.

The mean SUVmax was 5.0 ± 3.1 in 18 patients with TP findings and the mean was 2.4 ± 0.7 in three patients with FP lesions. The difference between SUVmax values for TP and

Table 2 Univariate Cox regression analysis of histopathological features and serum Tg values associated with recurrence in Tg-positive group

Variables	Hazard ratio	95 % CI	<i>P</i> value
Tumor size	1.37	0.513–0.741	0.116
Multiple tumors			
Positive vs Negative	1.36	0.525–3.518	0.524
Perithyroidal extension			
Positive vs Negative	0.93	0.348–2.476	0.883
Central lymph node metastasis			
Positive vs Negative	2.27	0.438–11.813	0.301
Serum Tg under TSH stimulation	1.13	1.061–1.208	<0.001

Table 3 Results of F-18 FDG PET/CT according to Tg levels under TSH stimulation

	Tg, 2-10 ng/mL (<i>n</i> =39)	Tg>10 ng/mL (<i>n</i> =36)
TP	1	17
TN	36	8
FP	1	2
FN	1	9
Sensitivity	50 %	65 %
Specificity	97 %	80 %
PPV	50 %	89 %
NPV	97 %	47 %

TP true positive, TN true negative, FP false positive, FN false negative, PPV positive predictive value, NPV negative predictive value

FP lesions were statistically significant ($P=0.007$). The cut-off value of SUVmax for detecting recurrence was found to be 2.5 using ROC analysis (AUC, 0.750; sensitivity, 77.8 %; specificity, 66.7 %).

F-18 FDG PET/CT Findings in TgAb-Positive Group

F-18 FDG PET/CT scans showed positive findings in four (44 %) out of nine patients with positive TgAb. In four patients, two patients had TP findings and the remaining two patients had FP findings. One of the two patients with TP findings displayed a pathologically proven metastatic lymph node in the neck and the other showed a pathologically proven metastatic lymph node in the mediastinum. The two patients with FP findings showed a suture granuloma and a benign neck lymph node, respectively. In nine patients with positive TgAb, the sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG PET/CT for detection of recurrent lesion were 100 %, 71 %, 50 %, 100 %, and 78 %, respectively.

Lesion Detectability of F-18 FDG PET/CT According to TSH Stimulation

The result of F-18 FDG PET/CT according to TSH stimulation is summarized on Table 4. In the cases of F-18 FDG PET/CT under endogenous TSH stimulation ($n=57$), 16 patients showed hypermetabolic foci on their PET/CT imaging. Among these patients, 14 patients were determined as recurrence. In the 41 patients without any abnormal hypermetabolic lesion, 8 patients showed recurrence.

In the cases of F-18 FDG PET/CT under TSH suppression ($n=18$), five patients showed positive finding and 13 patients showed negative finding on their PET/CT imaging. In those patients, recurrence was confirmed in four and two patients, respectively.

Table 4 Results of PET/CT finding in patients according to endogenous TSH stimulation status

	Recurrence or metastasis		Total
	Positive	Negative	
PET/CT under TSH stimulation			
Positive	14	2	16
Negative	8	33	41
PET/CT under TSH suppression			
Positive	4	1	5
Negative	2	11	13
Total	28	47	75

The sensitivity, specificity, PPV, NPV and accuracy of FDG PET/CT under TSH stimulation was 64 %, 94 %, 88 %, 81 % and 83 %, respectively. Those under TSH suppression was 67 %, 92 %, 80 %, 85 % and 83 %, respectively.

Discussion

Elevated Tg levels coupled with a negative radioiodine scan present problems for diagnosis and treatment of recurrent PTC [12]. Previous studies reported that elevated Tg levels and negative radioiodine scans had been found in 10–15 % of the patients with PTC [13]. In the literature, F-18 FDG PET/CT was shown to be a potentially useful imaging modality to localize recurrent or metastatic lesions in patients with elevated Tg and negative radioiodine scan [5, 8, 14, 15]. The purpose of present study was to evaluate the usefulness of F-18 FDG PET/CT in patients with PTC who had elevated Tg level or positive TgAb and negative radioiodine scans after total thyroidectomy and high dose radioiodine ablation.

Several studies have reported that the sensitivity of F-18 FDG PET correlates to Tg levels, the tumor burden generally correlates to the Tg level whether it is measured after levothyroxine withdrawal or during treatment [5, 14, 16, 17]. In our study, the sensitivities of F-18 FDG PET/CT with Tg levels between 2–10 ng/mL and more than 10 ng/mL were 50 % and 65 %, respectively. Although the sensitivity of F-18 FDG PET/CT for detecting recurrence in the patients with more than 10 ng/mL of Tg level seems to be higher than that of 2–10 ng/mL, they were not quite different.

In our study, relatively low sensitivity of F-18 FDG PET/CT was due to FN results (13 %). Five out of ten patients with FN findings displayed a small sized metastatic lymph node on neck US. The partial volume effect of PET and high spatial resolution of US for detection of neck lymph nodes could explain the FN results of F-18 FDG PET/CT. Disease recurrence could not be localized using any of the conventional imaging modalities in the remaining five patients with persistently increasing Tg levels. After additional ablation therapy,

sequential Tg levels had normalized in the five patients. The tumor volume might be too small to be detected by F-18 FDG PET/CT and other conventional imaging procedures, and that might explain the FN results.

Twenty-one out of 75 patients with increased Tg showed positive F-18 FDG PET/CT findings. TP and FP findings for detecting disease recurrence were shown in 18 and 3 patients, respectively. Two out of three patients with FP findings showed reactive neck lymph nodes and the other was displayed a suture granuloma in the thyroid bed. In accordance with the previous studies [8, 14], median SUVmax of TP and FP lesions was not significantly different (5.0 ± 3.1 vs 2.4 ± 0.7 , $P=0.007$) [8, 14]. However, SUVs between TP and FP lesions showed overlaps. It would therefore be difficult to assess the lesions using only SUVs [18]. In terms of Tg level in this clinical setting, our result showed the cut-off value of 21.5 ng/mL for discriminating TP and FP patients (AUC 0.926, $P<0.001$, with 83 % sensitivity and 100 % specificity), further study for larger population can be worth consideration.

We also analyzed the effect of endogenous TSH stimulation on detectability for recurrent lesion of F-18 FDG PET/CT. In our study, there was no significant difference in lesion detectability between the TSH stimulation and suppression conditions. There has been debate on the effect of endogenous TSH stimulation on FDG uptake for different thyroid cancer lesions. Moog et al. [19] reported that they found more lesions or higher tumor-to-background ratio could be achieved under TSH stimulation compared with TSH suppression, while Wang et al. [20] reported that elevated TSH level did not increase the ability to detect lesions. Although comparison in our study was performed between different populations, our result is identical to Wang et al.'s study. The different conclusion between these studies might have resulted from different study populations. Wang et al. analyzed only well-differentiated thyroid cancer patients with negative radioiodine scan and elevated serum Tg levels, while Moog et al. enrolled a relatively small number of patients with not only negative radioiodine scan but also positive scan. It is well known that the degree of FDG uptake is related to dedifferentiation of thyroid cancer lesion [20, 21], and thyroid cancer cells lose the ability to concentrate radioiodine and to express the TSH receptor during the dedifferentiation process. We also enrolled only patients with elevated serum Tg and negative radioiodine scan, so we carefully suggest that endogenous TSH stimulation does not increase detectability of F-18 FDG PET/CT for recurrent lesion in the thyroid cancer patients with elevated serum Tg and negative radioiodine scan. Although a few researchers suggested usefulness of F-18 FDG PET/CT under recombinant human TSH (rhTSH) stimulation for detecting recurrent thyroid cancer lesions [22–24], we did not apply rhTSH

during the study period. Hence we should limit our result to the cases under endogenous TSH stimulation.

Similarly to other studies [5, 18], F-18 FDG PET/CT provided additional information when conventional imaging modalities had failed to localize the disease in four patients with increased Tg, but could not result in a direct change of treatment plan in our study (two cases of pulmonary metastasis and two cases of cervical lymph node metastasis).

In our study, F-18 FDG PET/CT was performed in nine patients with increased TgAb levels and negative radioiodine scan to detect recurrence. TgAb positivity leads to clinical problems after total thyroidectomy and ablation because TgAb interferes with Tg measurement. Even though TgAb levels do not directly correlate with tumor load, the trend of TgAb levels is used as a surrogate marker of residual benign or malignant thyroid tissue. Therefore, increasing or persistent positive TgAb levels suggest the presence of thyroid tissue [25–27]. The recurrence rate has been reported as 20–30 % in patients with increased TgAb levels. In our study, the specificity and sensitivity of F-18 FDG PET/CT were 100 % and 71 % for detection of recurrence in patients with increased TgAb and negative radioiodine scan. F-18 FDG PET/CT could be useful for detection of recurrence or metastasis in PTC patients with TgAb.

This study had some limitations. Firstly, because our study was performed retrospectively, comparing the detectability of F-18 FDG PET/CT for the recurrent lesions between the patient group under endogenous TSH stimulation and TSH suppression was performed for different patient group. Secondly, a trend of increasing TgAb levels has been regarded as an important surrogate marker for PTC. Unfortunately, a change of TgAb test kits in our institute had made it impossible to analyze trends in TgAb levels. Thirdly, conventional imaging studies such as neck US, CT, and MRI were not performed for all patients. Therefore, in the Tg-positive group or the TgAb-positive group, the performance of F-18 FDG PET/CT in detecting recurrence or metastasis compared with conventional imaging modalities could not be fully evaluated.

Conclusion

F-18 FDG PET/CT, although less sensitive, showed high specificity, PPV, NPV and accuracy and can be useful for those patients with negative diagnostic radioiodine scan and elevated serum Tg level or positive anti-Tg Ab. In addition, F-18 FDG PET/CT under ETS does not seem to have an additive role in detecting recurrent malignant lesion in these patients.

Conflict of Interest Su Jung Choi, Kyung Pyo Jung, Sun Seong Lee, Yun Soo Park, Seok Mo Lee, and Sang Kyun Bae declare that they have no conflict of interest.

Ethical Statement This study was approved by the Busan Paik Hospital Ethics Committee.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

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