

# Relations Between Pathological Markers and Radioiodine Scan and $^{18}\text{F}$ -FDG PET/CT Findings in Papillary Thyroid Cancer Patients With Recurrent Cervical Nodal Metastases

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## Abstract

**Purpose** The aim of this study was to investigate relationships between the immunohistochemical results and radioiodine scan and  $^{18}\text{F}$ -FDG PET findings in papillary thyroid cancer (PTC) patients with recurrent cervical nodal metastases.

**Methods** A total of 46 PTC patients who had undergone a radioiodine scan and/or  $^{18}\text{F}$ -FDG PET/CT and a subsequent operation on recurrent cervical lymph nodes were enrolled. Twenty-seven patients underwent  $^{18}\text{F}$ -FDG PET/CT, 8 underwent radioiodine scans, and 11 underwent both scans. In all surgical specimens, the immunoexpressions of thyroglobulin (Tg), sodium-iodide symporter (NIS), glucose transporter 1 (Glut-1), and somatostatin receptor 1 and 2A (SSTR1

and SSTR2A) were assessed, and associations between these expressions and radioiodine scan and  $^{18}\text{F}$ -FDG PET findings were evaluated.

**Results** Of the 38 patients who underwent  $^{18}\text{F}$ -FDG PET/CT, all patients with weak Tg expression had positive  $^{18}\text{F}$ -FDG uptake, while only 45 % of the patients with moderate or strong Tg expression showed positive uptake ( $p=0.01$ ). The proportion of patients with positive  $^{18}\text{F}$ -FDG uptake increased as the degree of Glut-1 expression with luminal accentuation increased. Of the 19 patients who underwent a radioiodine scan, the proportion with positive radioiodine uptake was greater among patients with strong NIS and SSTR2A expression than among patients expressing these markers at weak levels ( $p=0.04$  for all). All three patients with weak Tg expression were negative for radioiodine uptake.

**Conclusion** The  $^{18}\text{F}$ -FDG uptakes of recurrent cervical nodes are related to strong Glut-1 expression with luminal accentuation and weak Tg expression, whereas radioiodine uptake is related to the strong expressions of NIS and SSTR2A.

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## Introduction

The prognosis of well-differentiated thyroid cancer (DTC) is favorable, with a 10-year survival rate exceeding 90 % [1]. However, up to 20 % of patients with DTC develop locoregional recurrence including cervical lymph node metastases, and 8 % of patients with recurrence will eventually succumb to the disease [2]. Although one of the main characteristics of DTC is its ability to trap radioiodine due to the

expression of sodium-iodide symporter (NIS), approximately 15–30 % of metastatic cancer lesions lose this ability and thus show no radioiodine uptake on post-therapeutic  $^{131}\text{I}$  scans [3–5]. This lack of an ability to accumulate radioiodine is problematic in patients with recurrent lymph nodes; hence, imaging modalities other than a radioiodine scan might be necessary in DTC patients with recurrent cervical nodes. Furthermore, conventional imaging modalities such as neck ultrasonography and computed tomography (CT) have also shown moderate sensitivity with a range of 63–82 % [6, 7].

$^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET) is recommended in patients with radioiodine-negative DTC [8, 9]. Glucose transporter 1 (Glut-1) is known to be the most important glucose transporter in thyroid cancer cells and is also known to be related to  $^{18}\text{F}$ -FDG uptake in various cancers [10–12]. Furthermore, some previous reports have been issued on the use of somatostatin receptor (SSTR)-targeted imaging in DTC patients with negative radioiodine uptake [9, 13]. However, no consensus exists concerning optimal imaging modalities for the follow-up of patients with recurrent cervical nodes. Although findings of radioiodine scans and  $^{18}\text{F}$ -FDG PET can provide important information for planning further treatment and predicting prognosis, there are few studies to evaluate the relationship between the histopathological findings and radioiodine scan and  $^{18}\text{F}$ -FDG PET findings. We considered that a deeper understanding of the relationships between the expressions of the pathological markers of DTC and the uptakes of various radiotracers would facilitate the imaging modality choice for the follow-up of DTC patients with recurrent neck nodes.

The objectives of this study were to evaluate the relationships between the expression levels of pathological markers [thyroglobulin (Tg), NIS, Glut-1, SSTR1 and SSTR2A] and radioiodine scan and  $^{18}\text{F}$ -FDG PET findings in DTC patients with recurrent cervical nodal metastases.

## Materials and Methods

### Patients

This study was approved by our Institutional Review Board. The records of 185 patients with DTC who underwent surgical resection for recurrent cervical lymph nodal metastases between February 2006 and March 2009 were retrospectively reviewed. Of these patients, 46 were enrolled in this study after applying the following inclusion criteria: (1) a  $^{131}\text{I}$  scan and/or  $^{18}\text{F}$ -FDG PET/CT at most 6 months before surgery and (2) the availability of sufficient cancer tissue for immunohistochemical staining. The characteristics of the 46 study subjects are shown in Table 1. Of these 46 patients, 38 underwent

**Table 1** Patient characteristics ( $n=46$ )

Characteristics	Value (%)
Age (years)	49±12 (range: 24–73)
Sex	
Male	10 (22 %)
Female	36 (78 %)
Pathology	
Papillary	46 (100 %)
Radioiodine scan ( $n=19$ )	
Diagnostic $^{131}\text{I}$ scan	5 (26 %)
Post-therapeutic $^{131}\text{I}$ scan	14 (74 %)
Previous treatment	
TT only	8 (17 %)
TT+RAI	26 (57 %)
TT+neck LND+RAI	12 (26 %)
Pathological stage at initial operation	
T1-3N0	4 (9 %)
T1-T3N1	37 (80 %)
T4N0	1 (2 %)
T4N1	4 (9 %)

TT total thyroidectomy, RAI radioiodine treatment, LND lymph node dissection

$^{18}\text{F}$ -FDG PET/CT and 19 a radioiodine scan. Eleven patients underwent both  $^{18}\text{F}$ -FDG PET/CT and radioiodine scans.

### $^{18}\text{F}$ -FDG PET/CT and $^{131}\text{I}$ Scan Imaging

Mean time between an  $^{18}\text{F}$ -FDG PET/CT scan and surgery was 74±59 days. Scans were performed using a Gemini PET/CT scanner (Philips, Milpitas, CA). All patients were normoglycemic and fasted for at least 6 h before scans. Patients were injected with 5.18 MBq/kg of  $^{18}\text{F}$ -FDG 1 h prior to imaging. Initially, a CT scan was performed at 80 mA and 140 kVp for attenuation correction, then an emission scan was performed from the skull base to the proximal thigh in one bed position for 3 min. Emission scan images were reconstructed onto a 128 × 128 matrix using an iterative algorithm (ordered subset expectation maximization), and attenuation correction was performed.

Mean time between the radioiodine scan and surgery was 124±44 days. All patients discontinued replacement L-thyroxine ( $T_4$ ) therapy 4 weeks before radioiodine administration and received replacement L-triiodothyronine ( $T_3$ ) for up to 2 weeks before radioiodine administration. In addition, all patients followed a low-iodine diet from at least 2 weeks before radioiodine administration. At the time of radioiodine administration, serum thyroid-stimulating hormone (TSH) levels were higher than 30 IU/ml in all patients. Among 19 patients, 14 underwent a post-therapeutic  $^{131}\text{I}$  scan, and scanning was performed 3–5 days after an oral administration of a

therapeutic activity of  $^{131}\text{I}$  ranged between 1.1 and 7.4 GBq (30–200 mCi). The remaining five patients underwent a diagnostic  $^{131}\text{I}$  scan, and scanning was performed 2 days after administering of 185 MBq (5 mCi) of  $^{131}\text{I}$ . All radioiodine scans were performed using a large-field-of-view gamma camera (ON 410, Ohio Nuclear, Solon, OH) equipped with a medium-energy parallel-hole collimator, and a 20 % symmetric window was centered at 364 KeV. Anterior and posterior images of the neck, chest and abdomen were obtained during all radioiodine scans, and a minimum of 100,000 counts were collected for each image.

All  $^{18}\text{F}$ -FDG PET/CT and radioiodine scan images were retrospectively reviewed by experienced nuclear medicine physicians with consensus. The  $^{18}\text{F}$ -FDG uptakes and radioiodine uptake of the resected cervical lymph nodes on the scan images were visually assessed. The neck lymph nodes that showed higher  $^{18}\text{F}$ -FDG uptake than surrounding neck tissue uptake were classified as lymph nodes with positive  $^{18}\text{F}$ -FDG uptake, and the neck lymph nodes that showed similar uptake to surrounding neck tissue uptake were classified as lymph nodes with negative  $^{18}\text{F}$ -FDG uptake. Furthermore, focal increased  $^{131}\text{I}$  uptake in the neck area was classified as lymph nodes with positive  $^{131}\text{I}$  uptake. In patients with multiple lymph nodal metastases who underwent  $^{18}\text{F}$ -FDG PET/CT, the lymph node that showed the most intense  $^{18}\text{F}$ -FDG uptake was selected for the analysis, and the lymph node specimen that corresponded to the anatomical location on PET/CT was selected for immunohistochemical analysis. In patients with multiple lymph nodal metastases who underwent a  $^{131}\text{I}$  scan, the lymph node that had the largest metastatic foci at the area of  $^{131}\text{I}$  uptake was selected for the analysis.

### Immunohistochemistry

All specimens from the surgical resection of recurrent cervical lymph nodes were stained with hematoxylin and eosin and reviewed by an experienced pathologist to confirm the presence of recurrent thyroid cancer. Immunohistochemical staining in all 46 cases was performed automatically based on the conventional streptavidin-biotin-peroxidase method using the TechMate™ 500 Plus (DAKO, Glostrup, Denmark) according to the manufacturer's protocol. The primary antibodies used were as follows: Tg (1:200, TGB04+TGB05, Thermo Scientific, CA), anti-hNIS (1:200, Clone FP5A, Thermo Scientific, CA), Glut-1 (1:200, C-20, Santa Cruz Biotechnology, Heidelberg, Germany), SSTR1 (1:100, BioTrend, Cologne, Germany) and SSTR2A (1:150, BioTrend, Cologne, Germany). Cells were scored as 0, 1 or 2 (negative, weak, strong) for Glut-1 or 0, 1, 2 or 3 (negative, mild, moderate, strong) for Tg according to their staining intensities. For NIS, SSTR1 and SSTR2A, percentages of stained cells were determined, and a final histochemical score

(H-score) was calculated by summing the products of staining intensities [scored as 0 or 1 (negative and positive, respectively) for SSTR2A and as 0, 1 or 2 (negative, weak, strong) for NIS and SSTR1] and their distributions (0–100 %). Tg, NIS, SSTR1 and SSTR2A antibodies showed positivity in the cytoplasm, and Glut was positive in the cytoplasm and cytoplasmic membranes with luminal accentuation. Normal thyroid follicular cells (for Tg and NIS), red blood cells (for Glut) and normal pancreatic islet cells (for SSTR1 and SSTR2A) served as internal positive controls.

### Statistical Analyses

For the purpose of statistical analysis, the expressions of Tg, Glut-1, NIS, SSTR1 and SSTR2A were dichotomized; Tg immunoexpression was divided into two groups of staining intensities:  $\geq 2$  (score=2, 3) or  $\leq 1$  (score=0, 1). Glut-1 expression was categorized as positive (score=1, 2) or negative (score=0). In addition, to evaluate the significance of the luminal accentuation of Glut-1 expression, the expression of Glut-1 was also categorized as membranous with or without luminal accentuation. The expressions of NIS, SSTR1 and SSTR2A were dichotomized about the half maximal H-scores for each marker (100 for SSTR1 and 50 for SSTR2A). The cutoff value used for NIS was determined by considering the mean H-score because NIS expressions tended to be weak. The chi-square test and Fisher's exact test were performed to determine differences between the frequency of positive  $^{18}\text{F}$ -FDG or radioiodine uptakes in the two groups for each pathological marker. All statistical tests were performed using SPSS (version 15.0; SPSS Inc.). *P*-values  $< 0.05$  were considered statistically significant.

## Results

### $^{18}\text{F}$ -FDG PET/CT and Radioiodine Scan Results and Immunohistochemical Findings

All 46 patients had a diagnosis of recurrent papillary thyroid cancer (PTC). In the 38 patients who underwent  $^{18}\text{F}$ -FDG PET/CT, 21 (55 %) showed positive  $^{18}\text{F}$ -FDG uptake in recurrent cervical nodes, while the remaining 17 (45 %) were negative for  $^{18}\text{F}$ -FDG uptake. In the 19 patients who underwent a radioiodine scan, 6 (32 %) showed positive radioiodine uptake in recurrent lesions, and the remaining 13 (68 %) showed negative uptake. Of these six patients with positive radioiodine uptake, four underwent a post-therapeutic scan, and the other two underwent a diagnostic scan. Furthermore, of the 13 patients with negative uptake, 10 underwent a post-therapeutic scan, and 3 underwent a diagnostic scan.

The results of immunohistochemical staining for Tg, NIS, Glut-1, SSTR1 and SSTR2A are shown in Table 2. Among 46 study subjects, 39 (85 %) showed moderate or strong (staining intensity=2 or 3) Tg expression, and only 2 and 9 showed strong Glut-1 expression in the cytoplasm and cytoplasmic membrane, respectively. NIS expression tended to be weak among study subjects (mean H-score=54±42), and a cutoff H-score of 50 was used for NIS. SSTR2A expression was only mild (staining intensity=0 or 1), and overall expression of SSTR2A in enrolled patients was weaker than that of SSTR1.

#### Relationships Between <sup>18</sup>F-FDG PET/CT and Immunohistochemical Results

Relationships between <sup>18</sup>F-FDG PET/CT study and immunohistochemical results are summarized in Table 3. Recurrent cervical node <sup>18</sup>F-FDG uptake was found to be related to Tg expression and Glut-1 membranous expression with luminal accentuation. All patients with weak Tg expression (staining intensity=0 or 1) showed positive <sup>18</sup>F-FDG uptake (Fig. 1), whereas only 45 % of patients with strong Tg expression (staining intensity=2 or 3) showed positive <sup>18</sup>F-FDG uptake ( $p=0.01$ ). Cytoplasmic Glut-1 expression was not found to be associated with positive <sup>18</sup>F-FDG uptake. However, although a marginally significant relationship was found between Glut-1 expression with luminal accentuation and the

**Table 3** Relationships between <sup>18</sup>F-FDG PET/CT and immunohistochemical results ( $n=38$ )

Biologic marker (staining intensities)	PET (+)	PET (-)	<i>p</i> -value
Thyroglobulin			
2, 3 ( $n=31$ )	14 (45 %)	17 (55 %)	
0, 1 ( $n=7$ )	7 (100 %)	0 (0 %)	0.01
Glut-1 (Memb)			
2 with luminal accentuation ( $n=8$ )	6 (75 %)	2 (25 %)	
1 with luminal accentuation ( $n=14$ )	9 (64 %)	5 (36 %)	
No luminal accentuation ( $n=16$ )	6 (38 %)	10 (62 %)	0.06
Glut-1 (Memb)			
Positive (1, 2) ( $n=28$ )	17 (61 %)	11 (39 %)	
Negative (0) ( $n=10$ )	4 (40 %)	6 (60 %)	0.3
Glut-1 (Cyt)			
1 ( $n=36$ )	20 (56 %)	16 (44 %)	
2 ( $n=2$ )	1 (50 %)	1 (50 %)	1.0
NIS			
H-score>50 ( $n=17$ )	11 (65 %)	6 (35 %)	
H-score≤50 ( $n=21$ )	10 (48 %)	11 (52 %)	0.3
SSTR1			
H-score>100 ( $n=20$ )	12 (60 %)	8 (40 %)	
H-score≤100 ( $n=18$ )	9 (50 %)	9 (50 %)	0.8
SSTR2A			
H-score>50 ( $n=26$ )	16 (62 %)	10 (38 %)	
H-score≤50 ( $n=12$ )	5 (42 %)	7 (58 %)	0.4

*Memb* cytoplasmic membrane, *Cyt* cytoplasm, *Glut-1* glucose transporter 1, *NIS* sodium-iodide symporter, *SSTR* somatostatin receptor

**Table 2** Immunohistochemical results ( $n=46$ )

Biologic marker (staining intensities)	Value (%)
Thyroglobulin	
0	0 (0 %)
1	7 (15 %)
2	29 (63 %)
3	10 (22 %)
Glut-1 (Cyt)	
0	0 (0 %)
1	44 (96 %)
2	2 (4 %)
Glut-1 (Memb)	
0	13 (28 %)
1	7 (15 %)
1 with luminal accentuation*	17 (37 %)
2	0 (0 %)
2 with luminal accentuation*	9 (20 %)
NIS (H-score)	55±41 (range: 0–160)
SSTR1 (H-score)	114±47 (range: 50–200)
SSTR2A (H-score)	70±23 (range: 25–100)

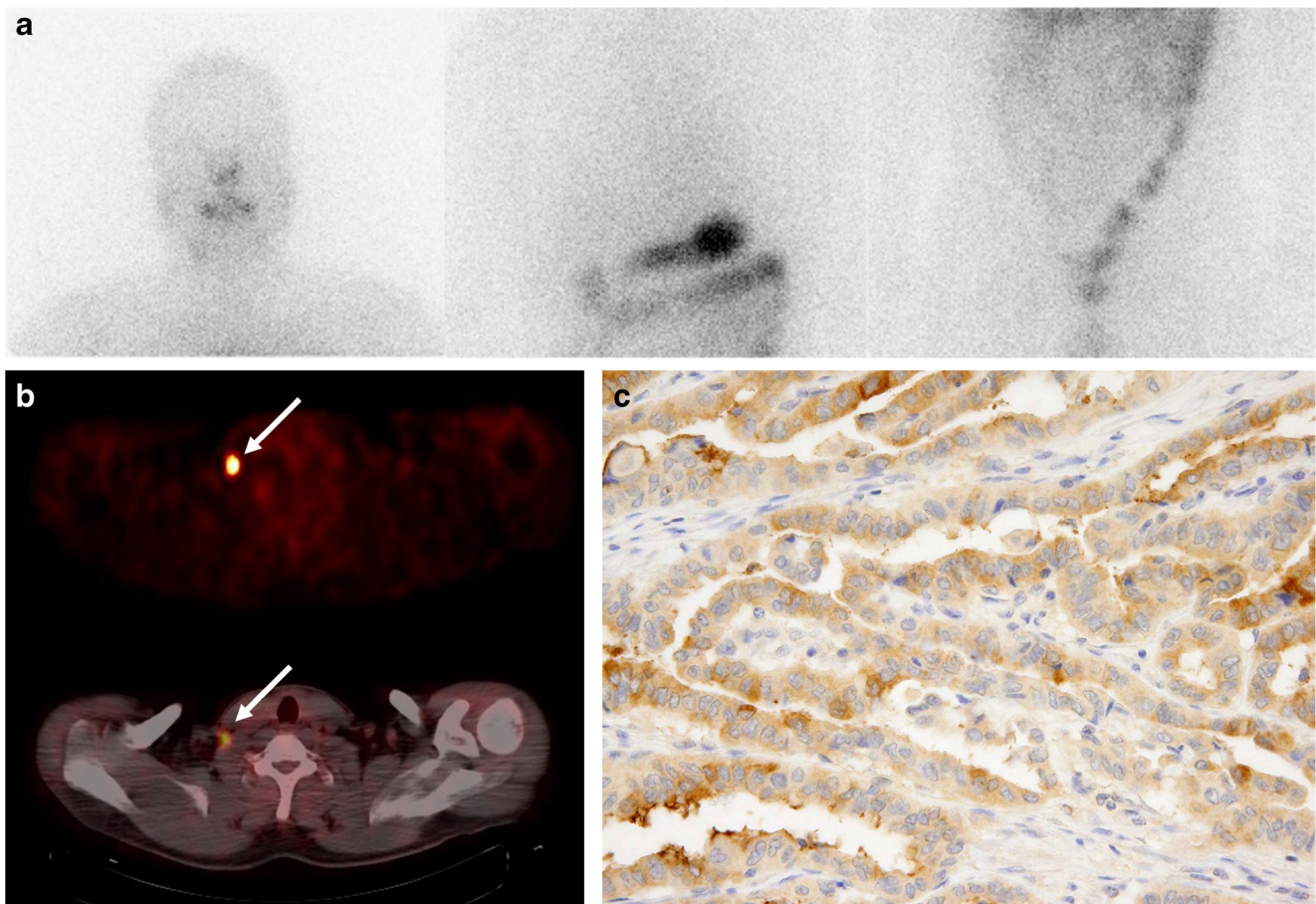
*Cyt* cytoplasm, *Memb* cytoplasmic membrane, \*positive in the cytoplasmic membrane with luminal accentuation, *Glut-1*: glucose transporter 1, *NIS*: sodium-iodide symporter, *SSTR*: somatostatin receptor

proportion of patients with positive <sup>18</sup>F-FDG uptake ( $p=0.06$ ), the proportion of patients positive for <sup>18</sup>F-FDG uptake among patients with Glut-1 membranous expression (staining intensity=2) with luminal accentuation (75 %; Fig. 2) was two-fold higher than the proportion of patients with Glut-1 expression without luminal accentuation (38 %). In contrast, irrespective of luminal accentuation, the intensity of Glut-1 membranous expression was not found to be related to <sup>18</sup>F-FDG uptake ( $p=0.3$ ). Furthermore, no relationship was found between the expressions of NIS, SSTR1 or SSTR2 and the number of patients with positive <sup>18</sup>F-FDG uptake ( $p>0.05$ ). In patients with strong SSTR1 or SSTR2A expression, 40 and 38 %, respectively, were negative for <sup>18</sup>F-FDG uptake.

#### Relationship Between Radioiodine Scans and Immunohistochemistry

Relationships between radioiodine scan results and immunohistochemical results are shown in Table 4. The proportion of patients with positive radioiodine uptake in recurrent cervical nodes was found to be significantly related to NIS and SSTR2A expression ( $p=0.04$  for all; Fig. 3) and to be





**Fig. 1** Anterior post-therapeutic  $^{131}\text{I}$  scan image (**a**) and  $^{18}\text{F}$ -FDG PET and fused PET/CT images (**b**) of a 42-year-old male patient with papillary thyroid cancer.  $^{18}\text{F}$ -FDG PET and PET/CT images (**b**) showing focal intense  $^{18}\text{F}$ -FDG uptake in the right lower neck lymph node (*arrow*),

whereas the  $^{131}\text{I}$  scan image (**a**) shows no abnormal  $^{131}\text{I}$  uptake. Immunostaining for thyroglobulin (Tg) in the surgical specimen of the right lower neck node (**c**) showed weak Tg expression

marginally related to SSTR1 expression ( $p=0.06$ ). Over 90 % of patients with weak NIS and SSTR1 expression and 100 % of patients with weak SSTR2 expression showed negative radioiodine uptake, but only 50–60 % of patients strongly expressing these markers showed positive radioiodine uptake. All three patients with weak Tg expression (staining intensity=0 or 1) were negative for radioiodine uptake. In addition, no relationship was found between the cytoplasmic or membrane expressions of Glut-1 and the proportion of patients showing radioiodine uptake ( $p>0.05$ ).

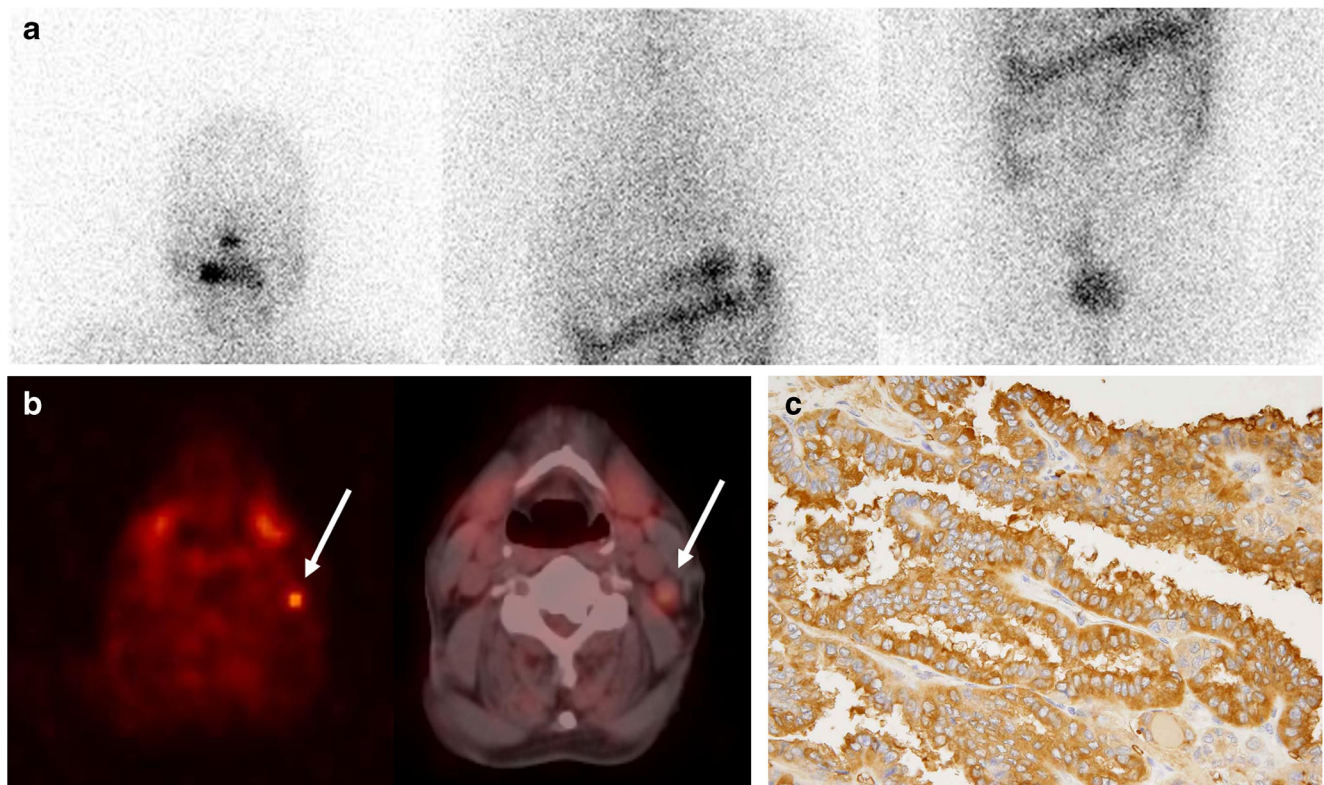
## Discussion

This study shows that all patients with weak Tg expression had positive  $^{18}\text{F}$ -FDG uptake or negative radioiodine uptake, and positive radioiodine uptake was found to be related to the expressions of NIS and SSTR2A, which suggests that the uptakes of  $^{18}\text{F}$ -FDG and radioiodine are associated with the differentiation of thyroid cancer cells. Furthermore,  $^{18}\text{F}$ -FDG uptake was found to be related to the luminal accentuation of

Glut-1 expression rather than the membrane expression of Glut-1.

In the present study, all cervical nodal metastases with weak Tg expression showed positive  $^{18}\text{F}$ -FDG uptake or negative radioiodine uptake. It has been previously reported that the production and expression of Tg suggests a differentiated thyroid cancer phenotype and that anaplastic thyroid cancer shows significantly lower Tg expression than DTC [14, 15]. Papillary thyroid carcinomas can be classified as relatively well differentiated or as relatively less differentiated, and the relatively well-differentiated cancers show higher levels of NIS and Tg expression and a lower level of Glut-1 expression [16]. Accordingly, decreased Tg expression could imply an anaplastic change in papillary cancer. Thus,  $^{18}\text{F}$ -FDG PET rather than a radioiodine scan should be adopted to follow-up patients with weak Tg expression.

Glut-1 expression is known to be related to a poor prognosis in thyroid cancer and to be significantly elevated in papillary thyroid cancers without radioiodine uptake [17, 18]. Moreover, previous studies have shown that Glut-1 expression in DTC is more often cytoplasmic than membranous



**Fig. 2** Anterior diagnostic  $^{131}\text{I}$  scan image (a) and  $^{18}\text{F}$ -FDG PET and fused PET/CT images (b) in a 70-year-old male patient with papillary thyroid cancer.  $^{18}\text{F}$ -FDG PET and PET/CT images (b) showing focal intense  $^{18}\text{F}$ -FDG uptake in a left neck lymph node (arrow), whereas the

$^{131}\text{I}$  scan image (a) shows no abnormal  $^{131}\text{I}$  uptake. Immunostaining for glucose-transporter 1 (Glut-1) in the surgical specimen of the left neck node (c) showed strong Glut-1 expression in cytoplasmic membranes with luminal accentuation

**Table 4** Relationships between radioiodine scan (RI) and immunohistochemical results ( $n=19$ )

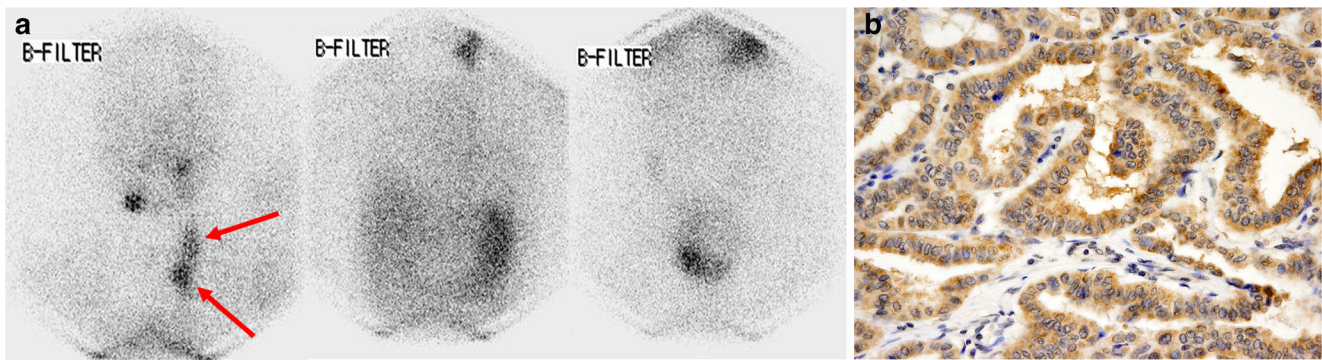
Biologic marker (staining intensities)	RI (+)	RI (-)	<i>p</i> -value
Thyroglobulin			
2, 3 ( $n=16$ )	6 (37 %)	10 (63 %)	0.5
0, 1 ( $n=3$ )	0 (0 %)	3 (100 %)	
Glut-1 (Memb)			
Positive (1, 2) ( $n=12$ )	4 (33 %)	8 (67 %)	1.0
Negative (0) ( $n=7$ )	2 (30 %)	5 (70 %)	
Glut-1 (Cyt)			
1 ( $n=19$ )	6 (32 %)	13 (68 %)	0
2 ( $n=0$ )	0	0	
NIS			
H-score >50 ( $n=8$ )	5 (63 %)	3 (37 %)	0.04
H-score ≤50 ( $n=11$ )	1 (9 %)	10 (91 %)	
SSTR1			
H-score >100 ( $n=9$ )	5 (56 %)	4 (44 %)	0.06
H-score ≤100 ( $n=10$ )	1 (10 %)	9 (90 %)	
SSTR2A			
H-score >50 ( $n=12$ )	6 (50 %)	6 (50 %)	0.04
H-score ≤50 ( $n=7$ )	0 (0 %)	7 (100 %)	

*Memb* cytoplasmic membrane, *Cyt* cytoplasm, *Glut-1* glucose transporter 1, *NIS* sodium-iodide symporter, *SSTR* somatostatin receptor

[17, 19]. In the present study, it was also found that all 46 patients exhibited positive cytoplasmic Glut-1 expression and that 70 % exhibited positive membranous Glut-1 expression. Membranous Glut-1 expression is most prominent around necrotic cancer areas, and hypoxia has been shown to result in the translocation of Glut-1 to the plasma membrane [19, 20]. It is reasonable to assume that membranous Glut-1 expression is more important and significant than its cytoplasmic expression when evaluating tumor aggressiveness [21]. In a previous study by Haber et al. [22], two Glut-1 staining patterns were described on the membranes of thyroid cancer cells: circumferential and asymmetric membranous staining (referred to as luminal accentuation in the present study). According to our results, membranous Glut-1 expression is not related to  $^{18}\text{F}$ -FDG uptake, but membranous Glut-1 expression with luminal accentuation was found to show a marginally significant relationship, which suggests that this pattern of Glut-1 positivity might play a significant role in  $^{18}\text{F}$ -FDG uptake in DTC.

SSTRs are often expressed in human endocrine tumors, such as parafollicular C cell-derived medullary thyroid carcinomas, but the expression of SSTR in DTC has rarely been reported and remains controversial. Pisarek et al. [23] reported that SSTR1 and SSTR2A were expressed in 89 and 44 % of





**Fig. 3** Anterior diagnostic <sup>131</sup>I scan image (**a**) in a 27-year-old female patient with papillary thyroid cancer. <sup>131</sup>I scan image (**a**) showing multifocal <sup>131</sup>I uptake in the left neck area (*arrow*). The patient

underwent left neck lymph node dissection. Immunostaining for sodium-iodide symporter (NIS) in the surgical specimen showed increased NIS expression with an H-score 100 (**b**)

DTC cases, respectively; however, Druckenthaner et al. [24] reported that SSSTR2 was predominantly expressed in DTC. In the present study, the immunoexpression of SSSTR1 was more intense than that of SSSTR2. Furthermore, in patients with strong SSSTR1 expression, only 50 and 60 % showed positive radioiodine uptake and <sup>18</sup>F-FDG uptake, respectively, suggesting that a selective SSSTR1-targeted imaging agent might be useful in patients with negative radioiodine uptake or <sup>18</sup>F-FDG uptake. Currently most of the radiotracers available for SSSTR imaging, such as <sup>111</sup>In-DTPA-octreotide, <sup>99m</sup>Tc-depreotide and <sup>68</sup>Ga-DOTATOC, target SSSTR2 [9, 13, 25]; we also assessed the expression of SSSTR2A, along with SSSTR1, to determine whether a radiotracer for SSSTR2 imaging could be used for the detection of recurrent PTC. The results of our study showed that the expression of SSSTR2A was weaker than that of SSSTR1 in enrolled patients, implying that the use of radiotracers for SSSTR2 might not be suitable for PTC patients with recurrent neck lymph node metastasis. Furthermore, over 50 % of patients with a negative radioiodine scan (7 of 13 patients) had weak SSSTR2A expression, suggesting that SSSTR2A expression is correlated with the degree of differentiation in DTC. Radiotracers for SSSTR2A would be of limited use for the imaging of less-differentiated DTC with negative radioiodine uptake.

Although NIS expression and Glut-1 expression with luminal accentuation were found to be related to <sup>131</sup>I and <sup>18</sup>F-FDG uptake, respectively, some patients showed negative radioiodine uptake with strong NIS expression, and other showed positive <sup>18</sup>F-FDG uptake with negative or weak membranous Glut-1 expression without luminal accentuation. These findings could be the result of various factors that influence radioiodine uptake or <sup>18</sup>F-FDG uptake. A previous study showed attenuated thyroperoxidase and pendrin expressions in cancers with no <sup>131</sup>I uptake and suggested that low expressions of the genes involved in the radioiodine organification process might result in a short radioiodine retention time and negative findings for these cancers on radioiodine scans [18]. Glut-3 and hexokinase I could also

be associated with <sup>18</sup>F-FDG uptake in DTC. Glut-3 expression appears to predominate in more differentiated thyroid tumor cells, whereas Glut-1 overexpression appears to predominate in more de-differentiated thyroid cancers [10]. Additionally, it has also been reported that <sup>18</sup>F-FDG uptake is associated with the overexpression of hexokinase I and that reciprocal staining patterns of NIS and hexokinase I are observed in thyroid cancer cells [19, 26].

The present study has several limitations. First, different types (diagnostic and post-therapeutic) of radioiodine scans were performed on the enrolled patients. Of the 19 patients who underwent a radioiodine scan, 26 % underwent diagnostic <sup>131</sup>I scans, and previous studies have shown that diagnostic <sup>131</sup>I scans have lower sensitivity for the detection of metastatic lesions than post-therapeutic <sup>131</sup>I scans in patients with DTC [27, 28]. Second, only 11 patients underwent both <sup>18</sup>F-FDG PET and radioiodine scans; thus, relationships between the immunohistochemical results and <sup>18</sup>F-FDG PET and radioiodine scans were evaluated separately. Third, because the present study was performed retrospectively, a selection bias is inevitable. Furthermore, the exact location of the metastatic lymph node was not always clearly identified in the surgical reports; therefore, there might be some mismatches between imaging and histopathological findings. Lastly, because of insufficient cancer tissue for immunohistochemical staining in most of metastatic lymph nodes and poor resolution of <sup>131</sup>I scans, a lesion-based analysis could not be performed.

In conclusion, the present study demonstrates that positive radioiodine uptake by recurrent neck nodes is related to the strong expressions of NIS and SSSTR2A and that <sup>18</sup>F-FDG uptake is associated with the luminal accentuation of membranous Glut-1 expression. Furthermore, all recurrent cervical nodal lesions with weak Tg expression showed positive <sup>18</sup>F-FDG uptake or negative radioiodine uptake. The evaluations of the expressions of pathological markers in thyroid cancer cells can facilitate choices regarding optimal imaging

and therapeutic modalities during the follow-up of thyroid cancer patients with recurrent cervical nodes.

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**Conflict of Interest** Jeong Won Lee, Hye Sook Min, Sang Mi Lee, Hyun Woo Kwon and June-Key Chung declare that they have no conflict of interest.

**Informed Consent** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The study design and exemption of informed consent were approved by the Institutional Review Board of Seoul National University Hospital.

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