

Risk factors of malignant fluorodeoxyglucose-avid lymph node on preablation positron emission tomography in patients with papillary thyroid cancer undergoing radioiodine ablation therapy

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Abstract

F-18 fluorodeoxyglucose (FDG)-avid metastatic lesions are associated with a poor response to radioiodine ablation therapy (RIT) in papillary thyroid cancer (PTC). This study evaluated the significance of preablative FDG positron emission tomography (PET) for the assessment of risk factors and frequency of malignant FDG-avid lymph nodes in patients with PTC undergoing RIT.

The study included 339 consecutive patients (mean age 46.3 ± 12.5 y; 260 females) with PTC referred for the first RIT and who underwent routine preablative FDG PET between April 2011 and February 2013. FDG-avid lymph nodes (FALNs) were identified using retrospective image reviews. The frequency of malignant FALN (mFALN), its contribution to persistent or recurrent PTC, and its risk factors were analyzed.

Among the patients, 112 had FALNs (33.0%): 11 mFALNs (3.2%) and 101 benign FALNs (bFALNs, 29.8%). mFALN contributed to 55% of persistent or recurrent PTC after RIT, which was observed in 20 of 339 patients (5.9%) during the post-RIT follow-up. Among preoperative risk factors, suspicious extrathyroidal extension and lateral neck lymph node metastasis on imaging studies were associated with mFALN. Among postoperative risk factors, T3/T4 and N1b stages, higher stimulated thyroglobulin, and higher numbers of metastatic lymph nodes and dissected lymph nodes, were associated with mFALN.

mFALNs were observed in a small number of patients with PTC undergoing RIT, but it contributed 55% of total recurrent or persistent disease. Increased frequency of mFALNs is associated with more advanced PTC. Preablative FDG PET has value in evaluation of patients with RIT-resistant lesions and may help determine further treatment strategies.

Abbreviations: bFALN = benign fluorodeoxyglucose-avid lymph node, CT = computed tomography, FALN = fluorodeoxyglucose-avid lymph node, FDG = fluorodeoxyglucose, mFALN = malignant fluorodeoxyglucose-avid lymph node, PET = positron emission tomography, PTC = papillary thyroid cancer, RIT = radioiodine ablation therapy, SUV = standardized uptake value, Tg = thyroglobulin, TgAb = anti-thyroglobulin antibody, TSH = thyroid-stimulating hormone, US = ultrasonography.

Keywords: disease persistence or recurrence, fluorodeoxyglucose-avid lymph node, papillary thyroid cancer, positron emission tomography, radioiodine ablation therapy

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1. Introduction

Sufficient delivery of radiation to tumor tissues is an important factor for successful radioiodine ablation therapy (RIT) in differentiated thyroid cancer. Higher effective doses delivered to the remnant thyroid tissue and metastatic lymph node are associated with better therapeutic outcomes.^[1,2]

To achieve higher effective doses, sufficient uptake of radioiodine by tumor cells is prerequisite, and this is promoted by a transmembrane glycoprotein known as sodium-iodide symporter (NIS). Histopathological studies indicate that the expression of the NIS gene is inversely related to that of the glucose transporter-1 (Glut-1) and hexokinase (HK) genes.^[3,4] Their expressions play key roles in the principle steps of F-18 fluorodeoxyglucose (FDG) accumulation by cancer cells.^[5,6] Therefore, positive FDG uptake on positron emission tomography (PET) implicates low iodine avidity and poorer response to RIT. Consistent clinical data show poorer prognosis for differentiated thyroid cancer with positive FDG PET findings.^[7–10]

The screening of FDG-avid metastatic lesions after surgery is important in determining the prognosis of differentiated thyroid cancers, considering that the most common sites of persistent or recurrent disease are the cervical lymph nodes.^[11] However, the

current guidelines do not include the evaluation of FDG-avid metastatic lesions for risk stratification and limit the use of FDG PET as an adjunctive imaging tool in patients with elevated serum thyroglobulin (Tg) levels but negative radioiodine whole body scan or neck ultrasonography (US) findings.^[11–13] There are no individualized indications of FDG PET for screening of FDG-avid metastatic lesions before surgery or RIT.

In this study, we assessed the frequency and high-risk features of FDG-avid metastatic lesions in patients with papillary thyroid cancer (PTC) undergoing RIT. Clarifying those issues may help define the appropriate indications of FDG PET in PTC.

2. Methods

2.1. Study subjects

We retrospectively enrolled 339 consecutive patients with PTC from Chonnam National University Hospital and Chonnam National University Hwasun Hospital referred for the first RIT between April 2011 and February 2013, during which preablative FDG PET was reimbursed by the National Health Insurance Service of Korea for thyroid cancer. They were referred for RIT if positive for metastatic lymph nodes, multifocal tumors, or the tumor stage $\geq T2$. Patients with unavailable post-RIT follow-up data, incomplete removal of the primary tumor, operation-RIT interval exceeding 12 months, recombinant human thyroid-stimulating hormone (TSH) injection for preparation of RIT, distant metastasis, and a history or suspicion of other malignancies were excluded from this study. The enrollment of patients and collection of data were approved by the Institutional Review Board of each hospital.

2.2. Workflows of surgery and RIT

Neck US and contrast-enhanced computed tomography (CT) were used for preoperative staging. Preoperative non-stimulated Tg, anti-Tg antibody (TgAb) and TSH were also checked before operation. The surgical procedures included total thyroidectomy with or without central and/or lateral neck dissection based on preoperative imaging/pathologic assessment or at the surgeons' discretion. As part of the preparation for RIT, patients switched their thyroid hormone medication from T4 to T3 for 2 weeks, and this was followed by 2 weeks of total hormone withdrawal and low-iodine diet until the end of admission for RIT (post-RIT day 2 or 3). One week prior to RIT, all the patients routinely underwent preablative I-123 whole body scan (185 MBq [5 mCi]) of I-123 and FDG PET. The levels of serum markers including stimulated Tg, TgAb and TSH were once again checked under TSH stimulation. Therapeutic I-131 dose was decided according to pathologic staging, stimulated Tg, and remnant burden on I-123 whole body scan. Relatively high doses (5550 MBq [150 mCi]) or 6660 MBq [180 mCi]) were prescribed for patients with positive lymph node metastasis during that period according to our intra-departmental instructions. Patients received RIT 110.0 \pm 40.7 days after surgery, regardless of the results of preablative FDG PET. The interval between contrast-enhanced CT scan and RIT was > 2 months in all the patients, excluding the concerns for decreased radioiodine uptake due to the administration of iodinated contrast. On post-RIT day 7, I-131 whole body scan was performed. The I-131 uptake and correlating FDG uptake of remnant functioning thyroid tissues was evaluated, using single photon emission computed tomography-CT as necessary.

2.3. Preablative FDG PET acquisition and image analysis

Patients fasted for 6 hours before FDG administration. Serum glucose was measured at the time of FDG injection to ensure that the level did not exceed 180 mg/dL. According to the patients' body weight, 3.7 or 5.55 MBq/kg of FDG was injected intravenously. The patients were informed to avoid physical activity and to rest in a quiet place for 50 minutes until image acquisition. Image acquisition was performed using dedicated PET-CT scanners (Discovery ST and Discovery ST 600, GE Healthcare) with a scan range from the brain to the thigh.

Images were retrospectively reviewed by 2 experienced nuclear medicine physicians blinded to the analyzed patients' clinicopathologic characteristics, and the follow-up results of FDG-avid lymph nodes (FALNs). Any lymph node with focal FDG uptake which is visually discriminable from surrounding background activity of soft tissue and/or blood vessels was considered FDG-avid. Equivocal lymph nodes were discussed by the 2 reviewers and their FDG avidity was confirmed by consensus. The sizes (short-axis diameter) and maximal standardized uptake values (SUVmax) were measured for FALNs by using Advantage Workstation 4.6 (GE Healthcare).

2.4. Clinical follow-up

The FALNs detected on preablative PET were classified into 2 categories, malignant (mFALN) and benign (bFALN). A mFALN was defined as a FALN that did not regress after RIT and was pathologically confirmed to be metastatic during the post-RIT follow-up. A bFALN was defined as a FDG-avid lymph node confirmed to be benign either pathologically or by demonstrating no progression with a stable Tg level for > 2 years after RIT.

All patients were regularly followed-up using neck US and serum markers including Tg, TgAb and TSH (median interval: 4.5 years after RIT). Radioiodine whole body scan was also performed at the first 6 to 12 months post-RIT in selected patients regarding their recurrence risk. Persistent or recurrent PTC was defined as the pathologic confirmation of PTC cells in the thyroid bed and/or cervical lymph nodes during the post-RIT follow-up, which included mFALN and non-mFALN-associated recurrences. Pathologic confirmation of persistent or recurrent PTC was triggered by elevated Tg levels and/or abnormal neck US findings.

2.5. Statistical analysis

The clinico-pathologic characteristics were compared between patients with and without mFALN to identify risk factor(s) of mFALN. The risk factors were classified into preoperative and postoperative categories according to their presence at a specific time point during PTC management. Student's *t*-test or Mann-Whitney *U* test was used for continuous variables; chi-square test or Fisher's exact test was used for binary variables, with regard to data distribution and numbers of cases. Multivariate logistic regression analysis was initially planned to define the factors independently related to the presence of mFALN. However, the number of mFALN-positive patients was too small and logistic regression analysis was considered inappropriate for our study population on the basis of a statistical expert's review. For continuous variables, optimal cutoffs were calculated using receiver-operating characteristics curve analysis to categorize patients with/without selected risk factors.

Values are represented as mean ± standard deviation for continuous variables with parametric distribution and as median (range) for those with nonparametric distribution according to Levene's test. A *P*-value < .05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp.).

3. Results

3.1. Patients characteristics and follow-up results

The mean age of the enrolled patients was 46.3 ± 12.5 years, and over three-fourths of patients were females (260, 76.7%). In respect to the preoperative image findings, the extrathyroidal extension and lateral neck lymph node metastasis were suspected in 64 (18.9%) and 100 (29.5%) patients, respectively. About two-thirds of the enrolled patients were found to have T1 (209, 61.7%) and N1a (222, 65.5%) on postoperative staging. Other clinico-pathological characteristics of the 339 enrolled patients are described in Table 1.

3.2. Results of image analysis and post-RIT follow-up

Retrospective reviews of the preablative FDG PET images revealed FALNs in 112 (33.0%) patients. During the post-RIT follow-up, 11 of them (3.2%) proved to be malignant and the remaining 101 (29.8%) were benign. Suspicious mFALNs were noticed in other 6 patients at the time of RIT, but they were pathologically confirmed to be benign during the post-RIT follow-up. Total persistent or recurrent PTC was observed in 20 cases, including 11 mFALNs (55%) and 9 non-mFALN-associated recurrences (45%) (Fig. 1).

mFALN was most frequently observed in neck level IV (n=4) followed by III (n=3; 2 patients had mFALN in both III and IV), VII (n=3), VI (n=2), and V (n=1), while most bFALNs were observed in neck level II (n=79). The sizes (7.0 [5.3–9.0] mm vs. 6.9 [0.4–11.4] mm for mFALN and bFALN, respectively; *P* = .37) and SUVmax (3.3 [2.2–16.6] vs. 2.7 [1.2–10.6]; *P* = .10) were similar between mFALN and bFALN. The median follow-up interval to confirm mFALN and bFALN was 0.9 (0.5–2.8) and 4.6 (2.2–5.7) years, respectively. Among the 11 mFALN-positive patients, 10 showed no radioiodine uptake in the correlating lymph nodes on I-131 whole body scan. Non-mFALN-associated recurrences were observed significantly later than were the mFALNs, with a median interval of 0.9 (0.5–2.8) years vs. 2.0 (0.8–5.5) years after RIT for mFALN and non-mFALN-associated recurrences, respectively (*P* = .03).

Among the 11 patients with mFALN, 4 were upstaged to N1b by the presence of mFALN while the remaining were initially considered as N1b. Two of the upstaged patients were considered as having no lymph node metastasis even after surgery (Table 2).

3.3. Preoperative risk factors of mFALN

Patients with mFALN were older with more males, but the findings were not statistically significant. Suspected extrathyroidal extension and lateral neck lymph node metastasis were more frequently observed in patients with mFALN. The latter supposedly led to significantly more lateral neck dissection in patients with mFALN (8/11 [72.7%] vs 76/328 [23.2%] for patients with and without mFALN, respectively; *P* < .01). Elevated preoperative Tg levels more than our institutes'

Table 1

Characteristics of the enrolled patients (n=339).

Age, years	46.3 ± 12.5
Sex	
Female	260 (76.7%)
Male	79 (23.3%)
Preoperative imaging findings	
Tumor diameter, mm	13.7 ± 8.1
Extrathyroidal extension	64 (18.9%)
Suspected lateral neck lymph node metastasis	100 (29.5%)
Central neck dissection performed	335 (98.8%)
Lateral neck dissection performed	84 (24.8%)
Postoperative pathologic findings	
Tumor diameter, mm	11.6 ± 7.2
Tumor multiplicity	47 (13.9%)
T stages	
T1	209 (61.7%)
T2	23 (6.8%)
T3	74 (21.8%)
T4	33 (9.7%)
N stages	
NO/Nx	38 (11.2%)
N1a	222 (65.5%)
N1b	79 (23.3%)
No. of dissected lymph nodes	7.0 (0–77)
No. of metastatic lymph nodes	2.0 (0–22)
MLNR*	0.39 ± 0.29
AJCC stages (8th edition)	
I	250 (73.7%)
II	76 (22.4%)
III	13 (3.8%)
Risk stratification†	
Low	13 (3.8%)
Intermediate	269 (79.4%)
High	57 (16.8%)
Serum markers	
Preoperative Tg, ng/mL	19.3 (0.1–1000.0)
Preoperative TgAb, U/mL	15 (10–4000)
Preoperative TSH, μU/mL	1.7 (0.0–17.7)
Stimulated Tg, ng/mL	0.5 (0.0–299.1)
Stimulated TgAb, U/mL	21 (1–3749)
Stimulated TSH, μU/mL	94.0 (19.8–178.0)
RIT dose, mCi	
100	1 (0.3%)
150	37 (10.9%)
180	301 (88.8%)

Data are mean ± SD or median (range) for continuous variables, and n (%) for dichotomous variables. AJCC = American Joint Committee on Cancer, MLNR = metastatic lymph node ratio (no. of metastatic lymph nodes/no. of dissected lymph nodes), RIT = radioiodine ablation therapy, Tg = thyroglobulin, TgAb = antithyroglobulin antibody, TSH = thyroid-stimulating hormone.

* MLNR was calculated only in patients with the number of dissected lymph nodes ≥ 3 (n = 293) [10].

† Risk stratification was based on 2015 American Thyroid Association guidelines [11].

reference value (>78 ng/mL) was more frequently observed in patients with mFALN, showing borderline statistical significance (*P* = .05) (Table 3).

3.4. Postoperative risk factors of mFALN

Advanced T (T3/T4) and N (N1b) stages were more frequently observed in patients with mFALN. The numbers of both dissected lymph nodes and metastatic lymph nodes were also significantly higher in those with mFALN. However, the metastatic lymph node ratio was similar between those with and without mFALN. Among the serum markers, stimulated Tg level was significantly

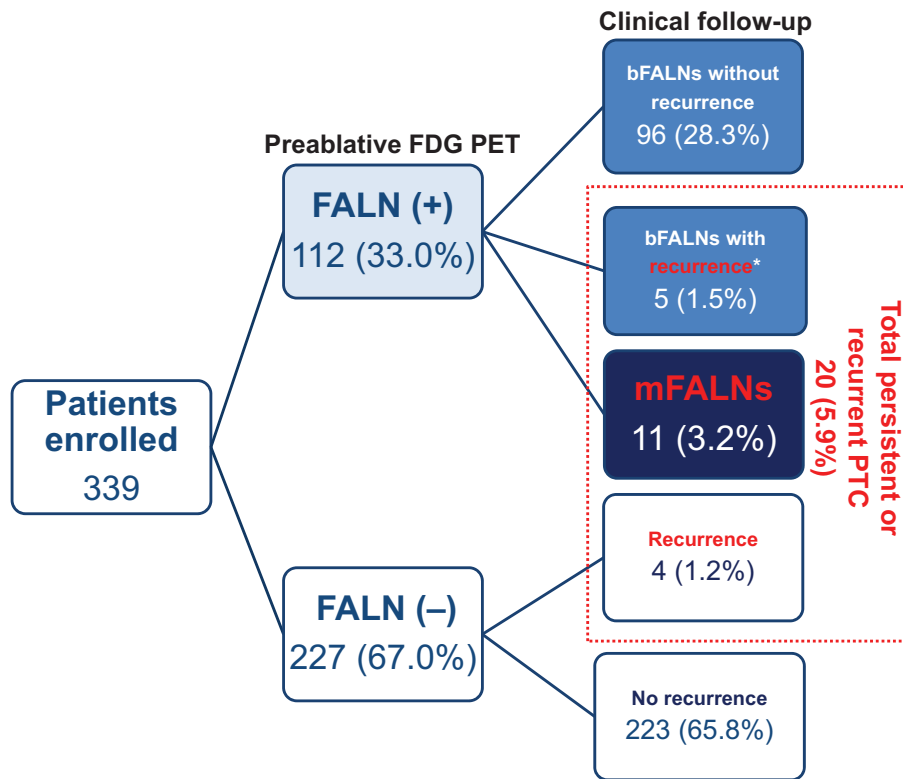


Figure 1. Classification of patients on the basis preablative FDG PET and follow-up results. mFALN was present in 3.2% of patients with PTC undergoing RIT, contributing to 55% of total persistent or recurrent PTC. bFALN=benign FDG-avid lymph node, FALN=fluorodeoxyglucose-avid lymph node, FDG=fluorodeoxyglucose, mFALN=malignant FDG-avid lymph node, PET=positron emission tomography, PET=positron emission tomography, PTC=papillary thyroid cancer, RIT=radioiodine ablation therapy, *Indicates recurrences in other areas without bFALNs.

higher in patients with mFALN, while other serum marker levels were similar between the 2 groups (Table 3).

3.5. Frequency of mFALN according to combined risk factors

The observed frequency of mFALN and odds ratios according to the respective risk factors are shown in Table 4. In the preoperative setting, the frequency of mFALN increased in a stepwise manner according to the presence/absence of suspected lateral neck lymph node metastasis and extrathyroidal extension (3/202 [1.5%], 1/33 [2.9%], 3/67 [4.3%] and 4/26 [13.3%], respectively; *P for trend*=.01) and was well above 10% when both the risk factors were present. In the postoperative setting, the frequency of mFALN also increased in a stepwise manner according to the presence/absence of high stimulated Tg and number of metastatic lymph nodes (stimulated Tg ≥ 2.3; number

of metastatic lymph nodes ≥ 5) (1/206 [0.5%], 1/57 [1.7%], 2/43 [4.4%] and 7/22 [24.1%], respectively; *P for trend* < .01) and was well above 20% when both numbers were high. However, significant inter-group difference was found only between number of metastatic lymph nodes ≥ 5 vs. < 5 when stimulated Tg was ≥ 2.3 ng/mL (*P*=.01) (Fig. 2).

4. Discussion

The present study found that mFALN was present in 3.2% of patients with PTC undergoing RIT. It contributed to 55% of total persistent or recurrent PTC after RIT. The preoperative risk factors included suspected extrathyroidal extension and lateral neck lymph node metastasis on preoperative imaging; the postoperative risk factors included advanced tumor and nodal stages (T3/T4, N1b), higher number of dissected and metastatic lymph nodes, and higher stimulated Tg levels.

It is clinically important that mFALN contributed to more than 50% of persistent or recurrent PTC, regarding that the recurrence rate of PTC was 4.4% and 8.9% at 5 and 10 years in a recent multicenter study.^[14] The present study demonstrates that appropriate screening should be performed in selected patients. Two potential options are available for screening mFALN: preoperative and preablative FDG PET. Currently the most recommended imaging modality for the preoperative staging of PTC is neck US and/or CT.^[11] They are readily available modalities but their sensitivity for detecting metastatic cervical lymph nodes is generally <80%, and varies according to primary tumor size and compartments evaluated.^[15,16] Although the

Table 2
Changes in N stages by preablation FDG PET in patients with mFALN (n=11).

N stages	Preoperative	Postoperative	Postoperative + mFALN
N0	4	2*	0
N1a	0	2*	0
N1b	7	7	11

* NO on preoperative staging.

FDG PET=fluorodeoxyglucose positron emission tomography, mFALN=malignant fluorodeoxyglucose-avid lymph node.

Table 3
Comparison of clinico-pathologic characteristics between patients with and without mFALN.

	mFALN (+) (n = 11)	mFALN (-) (n = 328)	P
Age, years	43.7 ± 13.3	46.4 ± 12.5	.49
Sex			
Female	6 (54.5%)	254 (77.4%)	.14
Male	5 (45.5%)	74 (22.6%)	
Preoperative imaging findings			
Tumor diameter, mm	16.4 ± 7.0	13.6 ± 8.2	.26
Extrathyroidal extension	5 (45.5%)	59 (18.0%)	.04*
Suspected lateral neck lymph node metastasis	7 (63.6%)	93 (28.4%)	.02*
Postoperative pathologic findings			
Tumor diameter, mm	14.1 ± 7.2	11.6 ± 7.2	.25
Tumor multiplicity	3 (27.3%)	44 (13.4%)	.19
T stages			
T1	3 (27.3%)	206 (62.8%)	<.01*
T2	0 (0.0%)	23 (7.0%)	
T3	4 (36.4%)	70 (21.3%)	
T4	4 (36.4%)	29 (8.8%)	
Advanced T stage (≥T3)	8 (72.7%)	99 (30.2%)	<.01*
N stages			
N0/Nx	2 (18.2%)	36 (11.0%)	<.01*
N1a	2 (18.2%)	220 (67.1%)	
N1b	7 (63.6%)	72 (22.0%)	
Advanced N stage (N1b)	7 (63.6%)	72 (22.0%)	<.01*
No. of dissected lymph nodes	16 (1–34)	7 (0–77)	<.04*
No. of metastatic lymph nodes	7 (0–19)	2 (0–22)	.02*
MLNR†	0.48 ± 0.28	0.35 ± 0.25	.10
AJCC stages (8th edition)			
I	6 (54.5%)	244 (74.4%)	
II	5 (45.5%)	71 (21.6%)	
III	0 (0.0%)	13 (3.8%)	.158
Risk stratification‡			
Low	0 (0.0%)	13 (3.8%)	
Intermediate	6 (54.5%)	263 (80.2%)	
High	5 (45.5%)	52 (15.9%)	.03*
Preoperative Tg, ng/mL	21.6 (0.1–197.4)	19.1 (0.1–1000.0)	.65
Elevated preoperative Tg (>78 ng/mL)	4 (36.4%)	43 (13.1%)	.05
Preoperative TgAb, U/mL	12 (10–1040)	15 (10–4000)	.48
Preoperative TSH, μU/mL	1.7 (0.7–3.1)	1.7 (0.0–17.7)	.92
Stimulated Tg, ng/mL	8.0 (0.0–299.1)	0.4 (0.0–152.6)	<.01*
Stimulated TgAb, U/mL	21 (2–1861)	21 (1–3749)	.97
Stimulated TSH, μU/mL	98.2 (81.6–107.7)	93.6 (19.8–178.0)	.13
RIT dose, MBq			
3,700	0 (0.0%)	1 (0.3%)	.96
5,550	1 (9.1%)	36 (11.0%)	
6,660	10 (90.9%)	291 (85.8%)	

Data are mean ± SD or median (range) for continuous variables, and n (%) for dichotomous variables.
 AJCC = American Joint Committee on Cancer, mFALN = malignant fluorodeoxyglucose-avid lymph node, MLNR = metastatic lymph node ratio (no. of metastatic lymph nodes/no. of dissected lymph nodes), RIT = radioiodine ablation therapy, Tg = thyroglobulin, TgAb = anti-thyroglobulin antibody, TSH = thyroid-stimulating hormone.
 * P < .05.
 † MLNR was calculated only in patients with the number of dissected lymph nodes ≥ 3 (n = 293) [10].
 ‡ Risk stratification was based on 2015 American Thyroid Association guidelines [11].

Table 4
Odds ratios of preoperative and postoperative risk factors of mFALN.

Risk factors*	Prevalence of mFALN		Odds ratios (95% CI)	P
	Risk factor (+)	Risk factor (-)		
Preoperative risk factors				
Suspected lateral neck lymph node metastasis	7.0%	1.7%	4.42 (1.27–15.46)	.01
Extrathyroidal extension on imaging studies	7.8%	2.2%	3.80 (1.12–12.87)	.02
Postoperative risk factors				
Stimulated Tg ≥ 2.3	12.2%	0.8%	18.21 (3.84–86.31)	<.01
No. of metastatic lymph nodes ≥ 5	9.2%	1.2%	8.41 (2.18–32.45)	<.01
N1b	8.9%	1.5%	6.22 (1.77–21.85)	<.01
T3/T4	7.5%	1.3%	6.17 (1.60–23.74)	<.01
No. of dissected lymph nodes ≥ 11	6.7%	1.4%	5.14 (1.34–19.77)	<.01
High-risk patient†	8.8%	2.1%	4.42 (1.30–15.03)	.02

CI = confidence interval, mFALN = malignant fluorodeoxyglucose-avid lymph node.
 * Risk factors are given in the order of odds ratios among the preoperative and postoperative risk factors.
 † Risk stratification was based on 2015 American Thyroid Association guidelines [11].

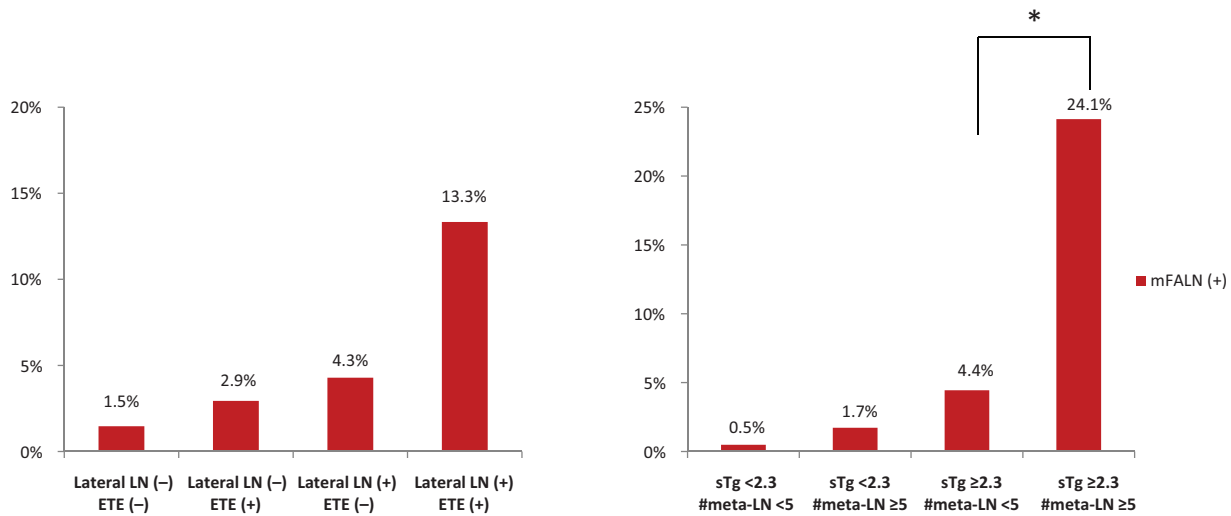


Figure 2. Frequency of mFALN according to the combined presence/absence of preoperative and postoperative risk factors. Lateral LN, findings of lateral neck lymph node metastasis on preoperative imaging studies; ETE, findings of extrathyroidal extension on preoperative imaging studies; sTg, stimulated thyroglobulin; #meta-LN, the number of metastatic lymph nodes on pathologic examination. * $P < .05$.

overall diagnostic accuracy of FDG PET was not superior to those of US or CT, FDG PET was apparently more sensitive in detecting lateral neck lymph node metastasis in a previous head-to-head comparison.^[17] A recent retrospective multicenter study also found that contrast-enhanced FDG PET had significantly higher sensitivity than did contrast-enhanced CT, especially in lateral neck lymph node staging.^[18] More than half of mFALNs were detected in lateral neck compartments (I-V); therefore, patients with suspected lateral neck lymph node metastasis on preoperative imaging may need to undergo FDG PET before thyroidectomy. Preoperative FDG PET may reveal more metastatic lymph nodes in lateral neck compartments and ensure more complete surgery in such patients. Preablative FDG PET can also play complimentary roles in patients with advanced PTC. Similar to the present study, several reports have suggested that patients with positive preablative FDG PET findings have higher stimulated Tg and more advanced pathologic stages.^[19–21] Since radioiodine whole body scan yields false-negative results in most cases of FDG-positive lesions,^[20,21] preablative FDG PET should be considered in patients with advanced PTC. It may also help detect occult, RIT-resistant lesions and determine further treatment strategies in 10% of patients undergoing RIT.^[21]

This study has several limitations. The small number of mFALNs limited the application of multivariate analysis and could not clarify the independent risk factors of mFALN. Only the patients referred for high-dose RIT were included; therefore, patients with a relatively low-risk might have been precluded. Although we assessed preoperative risk factors, such selection bias limits the application of the present results to preoperative FDG PET. However, the suggestion for preoperative FDG PET in selected patients is still meaningful because patients with advanced PTC on preoperative imaging are likely to be referred for high-dose RIT. Stimulated TSH level may have affected the FDG uptake of occult tumor lesions^[22,23] and the sensitivity of preablative FDG PET. TSH level was heterogeneous in our study, but it did not differ between patients with and without mFALN. Moreover, the follow-up duration after RIT in our study (median

4.5 years) may be insufficient to detect all the recurrent PTCs after RIT, considering a substantial number of recurrences even 10–20 years after diagnosis.^[24]

5. Conclusion

mFALNs were observed in a small number of patients with PTC undergoing RIT, but it contributed 55% of total recurrent or persistent disease. Increased frequency of mFALNs is associated with more advanced PTC. Preablative FDG PET has value in evaluation of patients with RIT-resistant lesions and may help determine further treatment strategies.

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