

Original Article



Diagnostic Accuracy of PET/MR for Evaluating Central Lymph Node Status in Patients with Papillary Thyroid Carcinoma

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ABSTRACT

Purpose: Ultrasonography and computed tomography of the neck are commonly used for preoperative evaluation of neck lymph node (LN) status in papillary thyroid carcinoma (PTC). This study evaluated the accuracy of preoperative positron emission tomography/magnetic resonance (PET/MR) imaging of cervical LN status in PTC.

Methods: A retrospective chart review of 285 patients who received PET/MR and underwent open thyroidectomy due to primary PTC between August 2012 and October 2013 was performed. Visual ¹⁸F-fluorodeoxyglucose uptake and preoperative morphologic abnormalities of nodal shape, cortical thickness, and the fatty hilum of neck nodes were analyzed using PET/MR imaging.

Results: Total thyroidectomy and lobectomy were conducted in 78.2% (223/285) and 21.8% (62/285) of cases, respectively. The status of central neck LN were evaluated in all patients during surgery and additional evaluation of lateral neck LN were conducted in 11.9% (34/285) of patients through selective sampling or modified radical neck dissection. In total, 36.1% (103/285) of patients had pathologic neck LN metastasis (LNM). PET/MR imaging showed an accuracy of 68.8%, sensitivity of 32.7%, and specificity of 88.6% for the detection of central neck LNM; moreover, an accuracy of 95.1%, sensitivity 68.4%, and specificity of 97.0% for lateral neck LNM. PET/MR imaging showed higher accuracy for detecting neck LNM in the 164 patients who did not have suspected clinical thyroiditis than others.

Conclusion: PET/MR has a high specificity for detecting central LNM, especially for patients diagnosed with PTC without pathologic thyroiditis.

Keywords: Lymphatic metastasis; Thyroid neoplasms; Positron-emission tomography

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer. With early surgical intervention, it is known to have a good prognosis. However, PTC has also been shown to have a tendency to invade the adjacent structures of the neck via the lymphatic system, or to metastasize, albeit rarely, to the lung or bone (1). Regional lymph nodes (LNs) in the central neck compartment are the most common pathway of metastasis, accounting for 20% to 90% of patients with PTC (2,3).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

The National Comprehensive Cancer Network (NCCN, <http://www.nccn.org>) and the 2015 American Thyroid Association (ATA) strongly recommend therapeutic central compartment neck dissection (CCND) for patients with clinically involved central LNs (4). Metastatic LNs are hard to cure without surgical removal and any surgical intervention for recurrent LNs increases the risk of surgical complications due to postoperative adhesion. To overcome such challenges, many surgeons perform prophylactic CCND (5). However, unnecessary and excessive prophylactic CCND can also cause adverse events including permanent hypocalcemia or irreversible nerve injury. Thus, precise preoperative evaluation of the regional metastasis is critical.

Despite reported low sensitivity in cases of deeply located LN or small LN metastases (LNMs), the most commonly used preoperative modalities for detecting suspected LNs are ultrasonography (US) and computed tomography (CT) (6,7). Various alternative imaging modalities have been introduced to increase the sensitivity of the detection of metastatic LNs, such as magnetic resonance imaging (MRI) or ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET), despite problems associated with poor cost-effectiveness.

PET/MRI is a new hybrid imaging modality, which incorporates MRI for morphological imaging of soft tissues and PET for functional imaging (8). However, to the best of our knowledge, studies regarding the efficacy of PET/magnetic resonance (MR) in patients with PTC have rarely been reported due to highly limited application in the clinical setting.

The aim of this study is to evaluate the accuracy of FDG-PET/MRI as a preoperative evaluation tool for detecting metastatic LNs in patients with PTC.

METHODS

1. Patients

This study was approved by the Institutional Review Board of Yeungnam University College of Medicine (2017-01-034). We evaluated the medical records of 949 patients who were diagnosed with thyroid carcinoma and underwent surgery in Yeungnam University Hospital from August 2012 to October 2013. The inclusion criteria were as follows: patients who were diagnosed with primary PTC, underwent open lobectomy or total thyroidectomy, and were evaluated with PET/MR and US as a routine preoperative evaluation, a maximum of 3 months prior to surgery. During the study period, the Korean National Health Insurance (NHI) covered the cost of PET/MR for all patients diagnosed with cancer. All patients received prophylactic or therapeutic CCND during thyroid surgery. Patients with suspicious or metastatic LNs of the lateral neck compartment received selective lateral neck node sampling or modified radical neck dissection (MRND) during surgery. Patients who were diagnosed with recurrent or contralateral thyroid carcinoma, patients who underwent endoscopic or robotic thyroidectomy or those who received PET evaluation in other hospitals were excluded. A total of 285 patients were included in this study.

2. US

All patients were preoperatively diagnosed with PTC by US-guided fine needle aspiration cytology (FNAC) and received US evaluation of suspicious LNs of the central and lateral neck areas prior to surgery. Suspicious LN was diagnosed if cervical LNs had one or

more of the followings: hypoechoic, rounded shape, absence of fatty hilum, or cystic or microcalcifications. FNAC was subsequently performed on such diagnoses.

3. PET/MR

Patients fasted for at least 6 hours and their blood glucose was pre-scanned, to ensure that the glucose level was <180 mg/dL. Patients received an intravenous injection of 3.7 Bq/kg of ¹⁸F-FDG, then rested quietly for 60–90 minutes before undergoing a PET/MR scan on a hybrid PET/MR scanner (Biograph mMR; Siemens Healthcare, Erlangen, Germany) with 3-Tesla MRI scanner with an inline PET system. Regional PET/MR was performed approximately 90–120 minutes after the injection, covering one bed position of the neck.

During the scan, patients were examined in the supine position using a dedicated multichannel head and neck coil, and a set of flexible body matrix coils. Regional neck PET/MRI was obtained during FDG-PET acquisition. The PET/MR examination consisted of 1) a 3-dimensional volumetric interpolated breath-hold examination Dixon sequence, used to correct for MR attenuation (Dixon-based 4 segment μ -map); 2) coronal turbo inversion recovery magnitude; 3) axial T2-weighted turbo spin echo imaging; and 4) pre- and post-contrast axial T1-weighted turbo spine echo sequences. A bolus injection of 0.1 mmol/L gadopentetate dimeglumine (MRbester; Taejoon Pharm, Seoul, Korea) per kilogram of body weight, followed by a 20 mL saline flush was administered intravenously at a rate of 2.0 mL/sec. PET events were accumulated for 10 minutes.

Two experienced nuclear medicine physicians interpreted hybrid PET/MR images, using a PET/MR workstation with Syngo.via software (Siemens Healthcare). They were blinded to the results of other tests. Diagnoses were made by consensus. The PET/MR images were analyzed visually, and primary PTC lesions as well as regional LNs were evaluated. Suspicious LNs were diagnosed if LNs had higher ¹⁸F-FDG uptake than the surrounding tissue and abnormal findings such as necrosis, cystic change, calcification, heterogeneous enhancement, or hyper-enhancement were present (9,10). Necrotic LNs with T2 MRI hyperintensity and irregular peripheral solid enhancement were considered to be a malignant feature, regardless of ¹⁸F-FDG avidity.

4. Surgery

All patients received ipsilateral lobectomy or total thyroidectomy depending on their tumor characteristics, including size, multiplicity, extracapsular invasion, or central LNM. During the study period, total thyroidectomy was recommended when the patient was suspected of having a thyroid tumor greater than 4 cm, extrathyroidal extension, bilateral nodularity or cervical LNM, based on the guidelines of 2012 NCCN. After intraoperative visual inspection of the central compartment LN, prophylactic or therapeutic CCND were performed in a routine manner, in all patients. In cases of suspicious LNs in the lateral neck compartment, including level II, III, or IV, selective lateral neck node sampling or MRND also took place during surgery. If a patient was diagnosed with cervical LNM by intraoperative frozen section, the lobectomy was converted to total thyroidectomy. To detect any recurrence and metastasis, US was performed at 6 months post-surgery, and annually thereafter.

5. Methods

Patient age, gender, preoperative evaluation method, operation records, and pathology reports were reviewed retrospectively. Tumor size, multiplicity, LNM, extracapsular invasion, lymphovascular invasion, and the number of retrieved LNs were recorded from pathology

reports. The following clinical and pathologic criteria were used to classify patients as having thyroiditis: presence of thyroid antibodies, abnormal thyroid function, and/or medical history such as Hashimoto thyroiditis or Graves' disease. Patients with lymphocytic or Hashimoto thyroiditis on pathology reports were classified as having pathologic thyroiditis.

6. Statistical method

All statistical analyses were performed using IBM SPSS version 19.0 (IBM Co., Armonk, NY, USA). Chi-square test and independent-samples t-test were used to analyze correlations between clinicopathologic factors and other variables. Univariate and multivariate analysis using logistic regression were performed. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to evaluate the accuracy of the PET/MRI technique. A statistical significance was accepted for P values of <0.05.

RESULTS

A total of 285 patients who received PET/MR prior to total thyroidectomy or lobectomy were included in this study. Patient demographic information and tumor characteristics are shown in **Table 1**. The mean age of patients was 48.47 ± 11.41 years, and patients under the age of 45 years accounted for 35.1% of the study population. A total of 223 patients (78.2%) underwent total thyroidectomy, and 62 patients (21.8%) underwent lobectomy. Intraoperative evaluation for LNM in the central compartment of the neck and CCND were conducted in all patients. Thirty-four patients (11.9%) with suspicious lateral neck node underwent additional MRND or selective lateral neck dissection (LND), including level III or IV, during surgery. The mean follow-up period was 21.26 ± 5.46 months.

PET/MRI showed a high detection rate for main PTC tumors (98.2%, 280/285) with a 1.8% (5/285) false negative rate. For the detection of central neck nodes metastasis, 54 patients (18.9%) had suspicious LNs on PET/MRI. According to a univariate analysis, larger tumor size, clinical thyroiditis, pathologic thyroiditis, and central neck node metastasis were

Table 1. Patient demographics and tumor characteristics

Characteristics	No. of patients (n=285)
Tumor size (cm)	0.9±0.6
Age (yr)	48.5±11.4
<45:≥45	100 (35.1):185 (64.9)
Female:male	243 (85.3):42 (14.7)
Lobectomy:total thyroidectomy	62 (21.8):223 (78.2)
CCND only:CCND+LND*	251 (88.1):34 (11.9)
N0:N1a:N1b	182 (63.9):84 (29.5):19 (6.7)
Presence of clinical thyroiditis	121 (42.5)
Presence of pathologic thyroiditis	76 (26.7)
Interval between PET/MR and operation (day)	21.3±16.7
Presence of suspicious main tumor on PET/MR	280 (98.2)
Presence of suspicious central LN on PET/MR	54 (18.9)
Presence of suspicious lateral LN on PET/MR	21 (7.4)
Presence of suspicious central LN on US	40 (14.0)
Presence of suspicious lateral LN on US	26 (9.1)
Presence of central LNM on pathology	101 (305.4)
Presence of lateral LNM on pathology	19 (6.7)

Values are presented as mean±standard deviation or number (%).

CCND = central compartment neck dissection; LND = lateral neck dissection; PET/MR = positron emission tomography/magnetic resonance; LN = lymph node; US = ultrasonography; LNM = lymph node metastasis.

*LND include selective level II, III, or IV LN dissection, or modified radical neck dissection.

significantly correlated with suspicious findings on PET/MR (**Table 2**). Multivariate analysis showed pathologic thyroiditis (odds ratio [OR], 2.96; 95% confidence interval [CI], 1.42–6.21; P=0.004), tumor size (OR, 2.29; 95% CI, 1.32–4.09; P=0.004), pathologic central LNM (OR, 2.25; 95% CI, 1.08–4.69; P=0.029), and the number of retrieved LNs (OR, 1.08; 95% CI, 1.01–1.16; P=0.023) were independently related with suspicious LNs for metastasis on PET/MR (**Table 3**).

In the detection of lateral LNM in the 34 patients who underwent LND (including MRND), 18 had suspicious LNs on PET/MRI. Patients with lateral neck node metastasis on pathology report showed a tendency for suspicious findings on PET/MR, but without statistical significance (P=0.091). Other clinicopathologic factors were not found to be related to suspicious findings for LNM on PET/MR.

Clinicopathologic factors correlated with central neck node metastasis are shown in **Table 3**. Age <45 years, larger main tumor size, and the number of retrieved LNs were independent factors according to multivariate analysis (**Table 4**).

Finally, PET/MR showed 68.8% accuracy (sensitivity 32.7%, specificity 88.6%, PPV 61.1%, and NPV 70.6%) for detecting central LNM, and 95.1% accuracy (sensitivity 68.4%, specificity 97.0%, PPV 61.9%, and NPV 97.7%) for detecting lateral LNM in all patients (**Table 4**). PET/

Table 2. Relationships between clinicopathologic factors and suspicious LN metastatic findings on PET/MR in central LNs on univariate and multivariate analysis

Factors	Univariate		Multivariate	
	OR	P value	OR	P value
Male	0.83 (0.32–1.89)	0.683	-	-
Age ≥45 (yr)	0.56 (0.31–1.02)	0.057	-	-
Tumor size	2.97 (1.84–4.95)	<0.001	2.45 (1.43–4.32)	0.001
Clinical thyroiditis	2.55 (1.40–4.75)	0.003	-	-
Pathological thyroiditis	3.36 (1.81–6.26)	<0.001	4.12 (2.11–8.21)	<0.001
Extracapsular invasion	1.38 (0.76–2.50)	0.291	-	-
LVI	2.10 (0.71–5.60)	0.154	-	-
Multiplicity	1.22 (0.67–2.22)	0.509	-	-
Pathological central LNM	3.77 (2.05–7.06)	<0.001	2.77 (1.37–5.63)	0.005
Pathological lateral LNM	2.10 (0.71–5.60)	0.154	-	-

Values are presented as OR (95% CI).

LN = lymph node; PET/MR = positron emission tomography/magnetic resonance; OR = odds ratio; CI = confidence interval; LVI = lymphovascular invasion; LNM = lymph node metastasis.

Table 3. Clinicopathologic factors affecting the central LNM

Factors	Univariate		Multivariate	
	OR	P value	OR	P value
Male	1.62 (0.83–3.15)	0.153	2.02 (0.89–4.52)	0.088
Age ≥45 (yr)	0.38 (0.23–0.63)	<0.001	0.48 (0.27–0.87)	0.015
Tumor size	5.38 (3.14–9.76)	<0.001	3.12 (1.68–6.10)	<0.001
Clinical thyroiditis	1.07 (0.66–1.75)	0.779	-	-
Pathological thyroiditis	1.01 (0.58–1.73)	0.985	-	-
Extrathyroidal invasion	2.55 (1.55–4.21)	<0.001	1.58 (0.86–2.89)	0.135
LVI	7.85 (2.75–28.17)	<0.001	2.97 (0.89–11.83)	0.091
Multiplicity	1.60 (0.98–2.61)	0.061	-	-
Central LNM on PET/MR	3.77 (2.05–7.06)	<0.001	2.02 (0.98–4.20)	0.057
Central LNM on US	2.90 (1.47–5.81)	0.002	-	-
No. of retrieved LNs	1.12 (1.07–1.18)	<0.001	1.09 (1.03–1.16)	0.002

Values are presented as OR (95% CI).

PET/MR = positron emission tomography/magnetic resonance; OR = odds ratio; CI = confidence interval; LVI = lymphovascular invasion; LNM = lymph node metastasis; US = ultrasonography; LN = lymph node.

Table 4. Prevalence of LNM according to the PET/MR and US finding

Findings	Central LNM			Lateral LNM		
	Yes (n=101)	No (n=184)	P value	Yes (n=19)	No (n=266)	P value
Suspicious LNM on PET/MR			<0.001			<0.001
Yes	33 (32.7)	21 (11.4)		13 (68.4)	8 (3.0)	
No	68 (67.3)	163 (88.6)		6 (31.6)	258 (97.0)	
Suspicious LNM on US			0.003			<0.001
Yes	23 (22.8)	17 (9.2)		10 (52.6)	16 (6.0)	
No	78 (77.2)	167 (90.8)		9 (47.4)	250 (94.0)	

Values are presented as number (%).

PET/MR = positron emission tomography/magnetic resonance; US = ultrasonography; LNM = lymph node metastasis.

MR showed a higher accuracy for detecting neck LNM in the 164 patients who were not suspected of clinical thyroiditis. During the follow-up period, 2 patients had regional LN recurrence and there were no reported patient deaths.

DISCUSSION

Reginal LNM in PTC do not always result in disease-related mortality. Nowadays, NCCN and ATA only recommend CCND in patients with highly advanced PTC or clinically involved LNs. Lin et al. (11) reported that preoperative evaluation of cervical LN is necessary to determine whether to perform prophylactic CCND, allowing for greater accuracy in determining the disease progression stage and avoiding leaving residual metastatic LNs, which may increase the likelihood of recurrence. As surgical complications of thyroidectomy caused by over-diagnosis have become a social problem (12), the importance of accurate preoperative evaluation is now more emphasized than ever. ATA recommends preoperative CT, MRI, and PET studies in addition to US, for patients with suspected advanced stage disease progression, invasive primary tumor, or clinically apparent multiple bulky and wide LN involvement (4).

US is known to be a preoperative diagnostic method of choice and is considered the best modality to discover loco-regional recurrences in patients with PTC. The reported sensitivity and specificity of US in assessing suspicious LNs varies between 5%–87% and 43%–100%, respectively (13) and have been shown to be different according to sonographic features. In the case of LNs with absence of hilum, the sensitivity increased to 100% and specificity decreased to 29% (4). Limitations of US include the variability of accuracy depending on the sonographer's subjective point of view and difficulty in detecting suspicious LNs deeply located in the neck. When US was combined with CT to overcome these problems, sensitivity still remained low. Lee et al. (14) studied 252 patients with PTC to detect cervical and lateral LNM, using a combined method of US and CT. In the central compartment, the sensitivity, specificity, and diagnostic accuracy were 46%, 88%, and 74%, respectively. On the other hand, in the lateral neck, they were 88%, 61%, and 74%, respectively. In our study, US showed a sensitivity of 22.8% and a specificity of 90.8% for detecting metastatic central LNs. Because all patients received CCND, it is possible that occult metastatic central LNs may have remained undetected on preoperative US and were included in the study, thus resulting in a relatively low sensitivity.

Currently, FDG-PET is used to detect recurrence and metastasis in thyroid cancer, especially in patients with poorly differentiated thyroid cancer or with elevated thyroglobulin and normal US findings (15,16). PET/MR is a new diagnostic method that combines morphological and functional imaging, and has been widely adopted in clinical fields such as oncology,

cardiology, and neurology (17,18). To date, studies regarding the efficacy of PET/MR in thyroid carcinoma have rarely been reported. Initially, Binse et al. (19) reported that the detection rate of iodine-positive metastasis in PET/MR was superior to that in PET/CT. On the other hand, Derce et al. (20) reported that PET/MR does not show any advantage over PET/CT in detecting primary diseases of the neck. We could not compare the accuracy of PET/MR with PET/CT, because the patients in this study did not receive PET/CT or neck CT. However, PET/MR does have some benefits. Patients can avoid X-ray exposure and MRI does not require iodinated contrast administration which delays radioiodine therapy for at least 4 weeks.

In this study, the PET/MRI main tumor detection rate was relatively high at 98.2% and the false negative rate was only 1.8%. FDG uptake and morphologic abnormalities in PET/MR may increase the detection rate. However, because this study was a retrospective study and not a blind study, there is a possibility for biases when reading PET/MR images.

To the best of our knowledge, there have not been any publications regarding the accuracy of PET/MR in detecting preoperative LNM to date. PET/MR is not widely used for preoperative evaluation in patients with PTC due to its relatively high expense. Hempel et al. (21) studied 46 patients who were suspected of locally-recurring thyroid cancer or metastatic LNs, and reported the diagnostic performance of FDG-PET/CT, MRI, and FDG-PET/CT combined with MRI as follows: sensitivity of 94%; specificity of 33%; PPV of 89%; NPV of 50%; and diagnostic accuracy of 85%. Although some reported studies attempted to predict LNM using FDG-PET/CT in other cancers (22), this is the first study reporting the accuracy of PET/MR in PTC patients. In our study, PET/MR showed a sensitivity of 32.7% and a specificity of 88.6% in detecting central LNM, and a sensitivity of 68.4% and a specificity of 97.0% in detecting lateral LNM. The sensitivities of MRI and PET for detecting cervical LNM were reported to be relatively low (30%–40%) (23), but there are relatively few studies. Inflammatory LNs also show FDG uptake on PET imaging, which could be regarded as metastasis and MRI is affected by respiratory artifact (4). In this study, PET/MR was also conducted for patients who were not clinically suspected of having cervical LNM. These problems may have reduced the sensitivity. Regarding the sensitivity of US; all patients received CCND, and LND was performed in some patients with suspicious clinical US or PET/MR findings, which resulted in a low sensitivity of PET/MR in detection of central LNM and a relatively high sensitivity in the detection of lateral LNM. This is because undetected occult metastatic LNs were removed during CCND.

When occult metastatic LNs (undetected in preoperative evaluation) were observed, the prognosis became difficult to predict. To avoid regional recurrence, predictive factors for regional LNM, such as primary tumor size, extracapsular invasion, or maximum Standardized Uptake Value (SUVmax) on PET were vigorously investigated (22), and prophylactic neck dissections were required in some studies (5). In this study, the factors affecting central LNM were age, main tumor size, and the number of retrieved central LNs, according to multivariate analysis. Suspicious LNs on US or PET/MR were correlated with central LNM, according to the univariate analysis; however, there was no statistical significance in multivariate analysis. A suspicious finding of cervical LNs on PET/MR has the propensity to affect the number of retrieved central LNs.

There were some limitations in our study. First, morphologic abnormalities or FDG uptake were used as the criteria to identify suspicious LNs on PET/MR. Benign lymphadenopathy accompanied by thyroiditis is sometimes confused with metastatic LNs. Lim et al. (24) reported that a specific cut-off level of SUVmax in cervical LN is more useful than visual

inspection, even though Lim's study was conducted on squamous cell carcinoma. In our study, a specific cut-off level of SUVmax was not applied, and thyroiditis affected PET/MR findings of central LNs. The influence of thyroiditis on LNM is controversial. However, thyroiditis did not affect the pathologic central LNM on either univariate and multivariate analyses.

Second, the follow-up period of 21.26 ± 5.46 months may be too short. In this study, accuracy was calculated according to pathologic LN metastases, which were identified on neck dissection. It is important that appropriate prophylactic neck dissection by PET/MR evaluation results in a decrease in recurrence or metastasis. Two regional recurrences occurred during the follow-up period. To identify the overall survival or disease free survival rates in patients with PTC, at least 5–10 years of follow-up is necessary. Since PET/MR is a relatively new diagnostic method in this field, further follow-up study is warranted.

Lastly, there is an issue of poor cost-effectiveness. From December 2014, the Korean NHI does not cover the cost of PET/MR in patients who are diagnosed with early stage PTC. Patients are required to pay for the relatively expensive PET/MR themselves. The 2015 ATA guidelines do not recommend routine ^{18}F -FDG-PET for preoperative staging because of insufficient evidence. This study may help influence the decision of thyroid cancer patients and physicians to consider PET/MRI.

In conclusion, in spite of the aforementioned limitations, this study is the first of its kind to determine the accuracy of PET/MR for evaluating preoperative cervical LNs in patients with PTC. PET/MRI has high specificity for detecting central LNM, especially in patients diagnosed with PTC without pathologic thyroiditis.

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