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*ORIGINAL RESEARCH ARTICLE*

# Retrospective analyses of false-positive 2-[$^{18}$F]FDG PET/CT lymph node findings in patients with papillary thyroid cancer

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**ABSTRACT**

**Introduction:** There are inconsistent results of studies on accuracy of 2-[$^{18}$F]fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (2-[$^{18}$F]FDG-PET/CT) for cervical lymph node (LN) staging. The aim of this study is to evaluate the accuracy of 2-[$^{18}$F]FDG-PET/CT in the cervical LN staging of patients with papillary thyroid cancer (PTC) and the factors associated with false-positive LNs in these patients.

**Methods:** A total of 234 patients with pathologically proven PTC, who underwent 2-[$^{18}$F]FDG-PET/CT for staging from January 2011 to December 2014, were analyzed. The gold standard for diagnosing LN is a combination of surgical pathology and clinical follow-up. Nodal uptake with a maximum standardized uptake value (SUVmax) > 2.0 was interpreted as PET/CT-positive.

**Results:** The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 2-[$^{18}$F]FDG-PET/CT in detecting cervical LN metastases were 42.7% (41/96), 77.7% (248/319), 36.6% (41/112), 81.9% (248/303), and 69.6% (289/415), respectively. The incidence of false-positive LN metastases was 63.4% (71 of 112 LNs). The factors significantly associated with false positives were age < 45 years old ($p = 0.032$) and SUVmax of the primary tumor < 4.0 ($p = 0.021$). In addition, false-positive LNs were correlated with a low LN SUVmax, location (central vs. lateral), and direction (ipsilateral vs. contralateral).

**Conclusion:** These findings suggest that cervical LN staging by 2-[$^{18}$F]FDG-PET/CT in PTC patients should be more carefully assessed in patients younger than 45 years old with a primary tumor SUVmax < 4.0 or contralateral LN.

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## INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, with an incidence that is markedly increasing worldwide. Most PTC patients have a good prognosis, with a 5-year overall survival rate > 90% [1, 2]. However, cervical lymph node (LN) metastasis occurs in approximately 30–80% of PTC patients, which is associated with an increased risk of regional recurrence, even in low-risk patients [3-6]. Therefore, accurately evaluating the presence or absence of cervical LN metastases is a critical factor that may determine the extent of surgical resection.

2-[$^{18}$F]fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (2-[$^{18}$F]FDG-PET/CT) is widely used for the staging of various malignancies and is useful for identifying occult LN or distant metastasis [7-10]. Although the value of 2-[$^{18}$F]FDG-PET/CT for preoperative regional LN staging of differentiated thyroid carcinoma has been reported [11-15], its role remains somewhat controversial. Moreover few studies have investigated false-positive cervical LN 2-[$^{18}$F]FDG-PET/CT findings in patients with thyroid cancer.

In this study, we analyzed the accuracy of 2-[$^{18}$F]FDG-PET/CT for cervical LN staging in PTC patients at our institute, and evaluated the factors associated with false-positive LNs in these patients.

## METHODS

### *Patients*

This retrospective study was approved by our institutional review board. We included patients with pathologically proven PTC who underwent 2-[$^{18}$F]FDG-PET/CT for staging from January 2011 to December 2014. The research protocol was approved by Ethics Committee of Inje University (approval no. 10018). All patients were treated by thyroidectomy with central neck node dissection with or without lateral neck dissection. The interval between 2-[$^{18}$F]FDG-PET/CT and surgery was within 2 months. A total of 234 patients with PTC were enrolled (22 males and 212 females; mean age, 49.7 years; range, 19–78 years).

### *2-[$^{18}$F]FDG-PET/CT procedure and interpretation*

After the patients fasted for at least 8 h, a 2-[$^{18}$F]FDG dose of 0.1 mCi/kg was injected intravenously. The serum level of glucose was measured in all patients and was below 160 mg/dL. A whole-body emission scan was performed 60 min after injecting the patient in the supine position with both arms raised above the head, covering an area from the skull base to the mid-thigh. The PET/CT scans were performed using the Discovery PET/CT 710 scanner (GE Medical System, Waukesha, WI, USA). Acquired data were corrected for attenuation using data from a low-dose CT scan without contrast enhancement performed before the whole-body emission scan. PET/CT images were reconstructed in the transaxial, coronal, and sagittal planes. The maximum standardized uptake value (SUVmax) of the primary tumor was calculated. The values were computed by normalizing the measured tumor radioactivity to the injected doses and body weights of the patients. If the primary tumor showed no obvious increased 2-[$^{18}$F]FDG uptake, the region of interest was drawn according to the findings from the CT portion of the PET/CT scan. In cases of multiplicity, the malignant nodule with the highest 2-[$^{18}$F]FDG uptake was selected. LN analysis was conducted on a level-by-level basis, using the cervical LN levels described in the American Joint Committee on Cancer staging manual [16]. The SUVmax of the LNs was also recorded for cases in which LNs were detected in the CT portion of the PET/CT. A nuclear medicine physician with more than 10 years of experience in PET/CT interpreted the images. In the 2-[$^{18}$F]FDG-PET/CT images, LNs with SUVmax > 2.0 were considered metastatic [17, 18]. The LN/tumor SUV ratio was defined as the SUVmax ratio of LN to primary tumor. For determination of the ipsilateral or contralateral side of the neck, the location of the primary tumor was used. When tumors were located on both sides of the thyroid lobes, metastatic LNs on either side of the neck were considered “ipsilateral.”

### *Gold standard for the final diagnosis*

LN analysis was performed on a level-by-level basis. The final diagnosis of LNs that were not removed during surgery was determined by follow-up assessment of serum thyroglobulin, ultrasound, or postoperative radioactive iodine scan (Table 1). Because the purpose of clinical follow-up is to confirm the status of LNs at the time of preoperative evaluation, the follow-up period was limited to 6 months after surgery.

### *Statistical analyses*

Descriptive statistics were calculated and are presented as the number (percentage) for categorical variables, and the mean ± standard deviation and median (range) for continuous variables. Differences between the false- and true-positive groups were compared using the independent samples *t*-test for continuous variables and the chi-square or Fisher’s exact test for categorical variables. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of PET/CT were measured for the detection of cervical LN metastases. Statistical analyses were performed using SPSS version 25.0 software (SPSS Inc, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

**Table 1.** Patient and tumor characteristics (n=234)

| Characteristics | Value |
|---|---|
| **Mean age (year)** | |
| Mean (SD) | 49.7 (11.0) |
| Range | 19-78 |
| **Sex (n)** | |
| Female | 212 |
| Male | 22 |
| **Operation type (n)** | |
| Total thyroidectomy | 210 |
| Hemithyroidectomy | 24 |
| **Primary tumor size (cm)** | |
| Mean (SD) | 1.1 (0.7) |
| Range | 0.1-5.5 |
| **Tumor-Node-Metastasis stage** | |
| **T stage (n)** | |
| T1 | 116 |
| T2 | 16 |
| T3 | 101 |
| T4 | 1 |
| **N stage (n)** | |
| N0 | 163 |
| N1a | 46 |
| N1b | 25 |
| **Tumor SUVmax** | |
| Mean (SD) | 5.6 (6.2) |
| Range | 1.2-40.9 |
| **Clinical follow-up methods to confirm (n)** | |
| Tg + US | 159 |
| Tg + US + RI | 75 |

SD: Standard deviation, SUVmax: The maximum standardized uptake value, Tg: Serum level of thyroglobulin, US: Neck ultrasonography, RI: Radioactive iodine whole body scan

## RESULTS

A total of 234 patients were enrolled. The patients' characteristics are described in Table 1. The average SUVmax of the primary tumor was 5.6 ± 6.2 (range, 1.2 to 40.9), and the average size of the primary tumor was 1.1 ± 0.7 cm (range, 0.1 to 5.5 cm).

### *Characterization of cervical LNs*

The levels of 415 cervical LNs were evaluated (201 central and 214 lateral); 58 central neck LNs and 38 lateral neck LNs were determined to be metastatic. To detect cervical LN metastasis, the sensitivity, specificity, PPV, NPV, and accuracy of 2-[$^{18}$F]FDG-PET/CT were 42.7% (41/96), 77.7% (248/319), 36.6% (41/112), 81.9% (248/303), and 69.6% (289/415), respectively (Table 2). In assessments of lateral cervical LN levels, the sensitivity, specificity, PPV, NPV, and accuracy of 2-[$^{18}$F]FDG-PET/CT were 81% (34/42), 60.2% (106/176), 32.7% (34/104), 93.0% (106/114), and 64.2% (140/218). False-positive and false-negative LNs depending on LN location were assessed according to the American Joint Committee on Cancer staging manual (Table 3).

### *Factors associated with false-positive LNs*

The demographic differences between false- and true-positive patients are presented in Table 4. In all, 54 patients who had cervical LN SUVmax > 2.0 were diagnosed as positive cases by 2-[$^{18}$F]FDG-PET/CT; 31 were confirmed to be false-positive cases. Age ($p = 0.032$) and tumor SUVmax ($p = 0.021$) were correlated with false-positive outcomes. Patients were younger than 45 years in 10 of the 31 cases, and tumor SUVmax was <4.0 in 65% of the cases (Figures 1, 2 and 3).

**Table 2.** Value of the PET/CT in assessing 415 cervical LNs

| | LN positive | LN negative | Total |
|---|---|---|---|
| PET/CT + (SUVmax >2.0) | 41 (TP) | 71 (FP) | 112 |
| PET/CT– (SUVmax ≤ 2.0) | 55 (FN) | 248 (TN) | 303 |
| Total | 96 | 319 | 415 |

PET/CT: Positron emission tomography /computed tomography, SUVmax: The maximum standardized uptake value, LN: Lymph node, TP: True positive, FP: False positive, FN: False negative, TN: True negative

**Table 3.** Value of PET/CT assessment according to lymph node location

| LN location | Total No. of LNs | No. of LNs with SUVmax > 2.0 | No. of false-positive LNs (%) | No. of LNs with SUVmax ≤ 2.0 | No. of false-negative LNs (%) |
|---|---|---|---|---|---|
| Level I | 29 | 10 | 10 (100) | 19 | 0 (0) |
| Level II | 102 | 54 | 44 (81.5) | 48 | 2 (4.2) |
| Level III | 46 | 19 | 10 (52.6) | 27 | 2 (7.4) |
| Level IV | 27 | 12 | 2 (16.7) | 15 | 3 (20.0) |
| Level V | 10 | 6 | 4 (66.7) | 4 | 0 (0) |
| Level VI | 201 | 11 | 1 (8.3) | 189 | 47 (24.9) |
| Total | 415 | 112 | 71 (63.4) | 303 | 55 (18.2) |

SUVmax: The maximum standardized uptake value, LN: Lymph node

**Table 4.** Patient factors related to false-positive assessments based on PET/CT

| Variable | False-positive (n = 31) | True-positive (n = 23) | P-value |
|---|---|---|---|
| **Sex** | | | |
| male | 3 | 4 | 0.443 |
| female | 28 | 19 | |
| **Age, year** | | | |
| <45 | 10 | 3 | 0.032 |
| ≥45 | 21 | 20 | |
| **Tumor SUVmax** | | | |
| <4.0 | 20 | 11 | 0.021 |
| ≥4.0 | 11 | 12 | |

SUVmax: The maximum standardized uptake value

*Analysis of risk factors associated with false-positive LNs*
A total of 112 LNs with a SUVmax > 2.0 were diagnosed as positive cases by 2-[$^{18}$F]FDG-PET/CT; 71 LNs were confirmed to be false-positive cases. False-positive LNs had a lower LN SUVmax ($p$ = 0.000) and greater lateral neck LN metastasis ($p$ = 0.000) and contralateral neck LN metastasis ($p$ = 0.002) (Table 5).

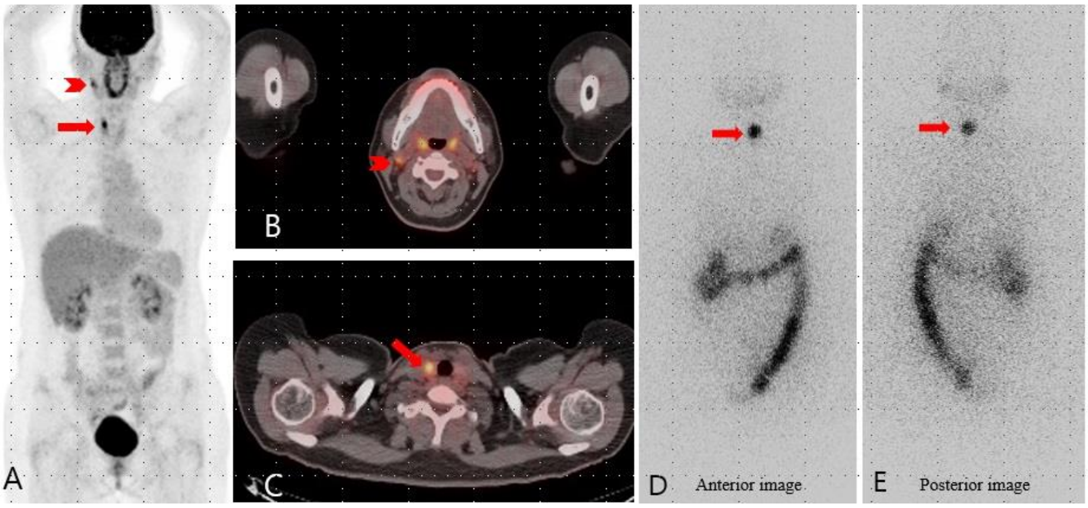


**Fig 1.** A 37-year-old woman with a 1.5 cm papillary thyroid carcinoma in her right thyroid gland. On maximal-intensity-projection image (A) and transaxial image (B, C) of 2-[$^{18}$F]FDG-PET/CT images, areas of increased focal uptake are noted in right thyroid lobe (arrow, SUVmax = 5.4) and the ipsilateral level II lymph node (aroowhead, SUVmax = 4.1), which suggested malignancy. The final surgical pathology demonstrated reactive cells in the right level II lymph node group. Also postoperative radioactive iodine scan (D, E) showed focal uptake of the remnant thyroid tissues in the mid anterior neck and no abnormal iodine accumulation in lateral neck

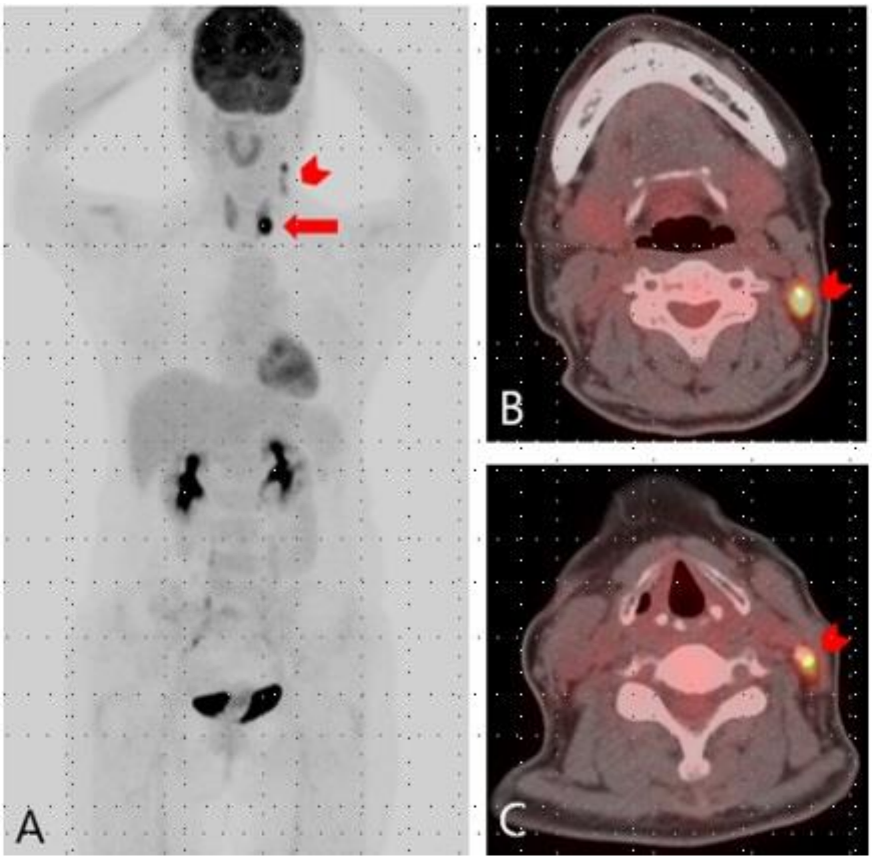


**Fig 2.** A 55-year-old woman with a 0.9 cm papillary thyroid carcinoma in her left thyroid gland. Maximal-intensity-projection image (A) and transaxial image (B, C) showed a few focal areas of 2-[$^{18}$F]FDG uptake in left thyroid lobe (arrow in A, SUVmax = 15.9), left cervical level II(arrowhead in B, SUVmax = 7.3) and III(arrowhead in C, SUVmax = 3.8). All lymph nodes that showed abnormal findings on 2-[$^{18}$F]FDG-PET/CT were proven to be metastatic at surgery

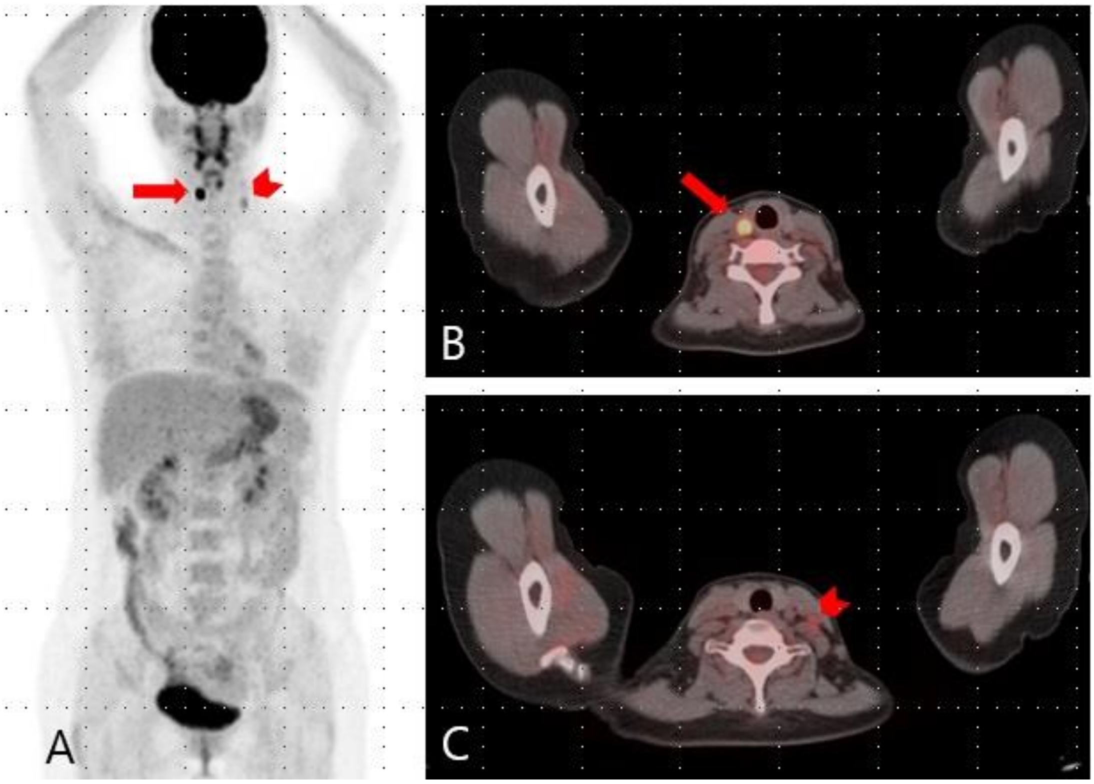


**Fig 3.** A 43-year-old woman with a 0.9 cm papillary thyroid carcinoma in her right thyroid gland. The maximal-intensity-projection image (A) and transaxial images (B and C) of 2-[$^{18}$F]FDG-PET/CT showed areas of increased focal uptake in right thyroid lobe (arrow, SUVmax = 11.4) and contralateral cervical level IV lymph node (arrowhead, SUVmax = 2.3), suggesting metastatic lesion. Neck lymph node lesion was histopathologically diagnosed as reactive hyperplasia

**Table 5.** Factors associated with false-positive lymph nodes in PET/CT assessment

| Variable | False-positive (n = 71) | True-positive (n = 41) | P-value |
|---|---|---|---|
| **LN SUVmax** | | | 0.000 |
| Mean (SD) | 2.6 (0.9) | 10.9. (10.6) | |
| Range | 2.1-9.3 | 2.1-42.6 | |
| LN/tumor SUV ratio | 0.96 | 1.15 | 0.589 |
| Central LN: Lateral LN | 1:70 | 10:31 | 0.002 |
| Ipsilateral LN: contralateral LN | 43:28 | 41:0 | 0.000 |

LN: Lymph node; SUVmax: The maximum standardized uptake value, SD: Standard deviation

## DISCUSSION

LN metastasis is considered a risk factor for regional recurrence or distant metastasis in patients with thyroid cancer [3, 4]. The success of surgery for thyroid cancer depends on accurate preoperative imaging, which enables the complete clearance of metastatic LNs [18, 19]. In a meta-analysis [20], the pooled sensitivity and specificity for the detection of all cervical LN metastases were 30.0% and 94.0%, respectively, suggesting that 2-[$^{18}$F]FDG-PET/CT has more specificity but less sensitivity for LN staging. Thus, we conducted this study to improve the accuracy of 2-[$^{18}$F]FDG-PET/CT and evaluate the factors associated with false-positive LNs. In our study, false negatives and false positives accounted for 18.2% (55/303) and 63.4% (71/112) of patients, respectively. Some studies reported the diagnostic role of 2-[$^{18}$F]FDG-PET/CT in the assessment of preoperative cervical LN status [11-15, 17, 20, 21]. Jeong et al. suggested that 2-[$^{18}$F]FDG-PET/CT does not provide any additional benefit when compared to US and contrast enhanced computed tomography (CECT) for the initial evaluation of cervical node levels in patients with PTC [17]. Similarly, Choi et al. compared diagnostic accuracies of PET/CT and sonography for detecting cervical node metastasis in patients with PTC. They reported that false-negative, false-positive rate and accuracy of sonography and 2-[$^{18}$F]FDG-PET/CT were 29.5%, 67.2%, and 60.6% and 28.3%, 45.8%, and 70.3%, respectively. Also, when assessing lateral cervical LN levels, false-negative and false-positive rate of 2-[$^{18}$F]FDG-PET/CT were 21.9%, and 45.0%. They concluded that 2-[$^{18}$F]FDG-PET/CT could not provide additional information compared to neck US [21]. Also, Morita S et al. compared the diagnostic accuracy of 2-[$^{18}$F]FDG-PET/CT, CECT, and

US in the diagnosis of preoperative cervical LN metastasis in PTC patients. They reported that false-negative, false-positive rate and accuracy for 2-[$^{18}$F]FDG-PET/CT were 25.2%, 32.7%, and 73.1%, respectively for all cervical nodes; 38.6%, 6.3%, and 64.9%, respectively for central cervical nodes; 16.1%, 45.5%, and 79.1%, respectively for lateral cervical nodes [11]. We found a lower false-negative and higher false-positive rate compared to previous studies. This discrepancy may be related to different selection criteria. We defined positive LN involvement as maximum 2-[$^{18}$F]FDG uptake above 2.0 on PET/CT. Different studies have used using different criteria to define LN positivity on PET/CT.

In this study, patient age < 45 was identified as a risk factor for false-positive LNs. 2-[$^{18}$F]FDG uptake in the LNs is not specific for a malignant neoplasm. Physiological and inflammatory LNs can cause 2-[$^{18}$F]FDG uptake. The increasing tendency of false-positive LNs in younger patients is thought to be caused by a robust immune response in infectious or inflammatory conditions in the head and neck.

We found that primary tumor with SUVmax < 4.0 was correlated with false-positive LNs. This finding is in line with Jung et al. [14], who reported that 2-[$^{18}$F]FDG avidity and the SUVmax of primary tumors on preoperative [$^{18}$F]FDG PET/CT can be used to predict LN metastasis in patients with PTC. In addition, the mean SUVmax of true- and false-positive LNs was 10.9 (range, 2.1–42.6) and 2.6 (range, 2.1–9.3), respectively, and the SUVmax of the true-positive LN was significantly higher than that of the false-positive LN (p = 0.000). In a previous study, the SUVmax values for physiological, inflammatory, and malignant LNs were 1.09 ± 0.33, 2.36 ± 0.60, and 6.31 ± 2.74, respectively, in 2-[$^{18}$F]FDG-PET/CT scans of patients with head and neck cancer [22].

We found a significantly higher SUVmax in true-positive LNs, which is not surprising, given its aggressiveness. Only one false-positive LN with the highest SUVmax of 9.3 was proven to be a tuberculous lymphadenitis. The SUVmax of the other LNs ranged from 2.1 to 4.2. Our study indicated that in false-positive LNs, lateral LN metastasis numbers were higher than central LN metastasis numbers (P = 0.002), and contralateral LN metastasis numbers were higher than ipsilateral LN metastasis numbers (0.000). All contralateral LNs with SUV max > 2.0 were false positives, and only one central LN was a false-positive. The lymphatic drainage of the thyroid gland is extensive and flows in a multidirectional pattern. The right and left lateral drainage patterns originate from lymphatic trunks from the lateral border of each lobe, and the lymphatic channels travel laterally, anteriorly, or posteriorly to the carotid sheath to reach the LNs of the internal jugular vein [23, 24]. Theoretically, lymphatic systems that bypass the central LN compartment enable contralateral LN metastasis. However, in this study, the contralateral LNs were all false positive.

To the best of our knowledge, this is the first study to focus on cervical LN direction in 2-[$^{18}$F]FDG-PET/CT findings of thyroid cancer. Unlike other head and neck cancers, the stage does not change according to the LN direction in thyroid cancer. Nevertheless, an accurate assessment of cervical LN status is essential for establishment of a treatment plan.

All cervical level I LNs were false positives, and more than 80% of level II LNs were false positives. Levels I and II show a high false-positive ratio, so it is necessary to be very careful when predicting cervical level I and II LN metastasis by SUVmax only. Interestingly, level IV LNs had a significantly low false-positive rate compared to other LN levels. Moreover, level IV LN showed a significantly high false-negative rate compared to other LN levels. Considering these findings, it is possible that level IV LN can metastasize, although 2-[$^{18}$F]FDG-PET/CT cannot detect LN metastasis.

This study had several limitations. First, it was a single-institution retrospective study, which may restrict its validity. Second, the number of LN metastases in some cervical levels was relatively small. Third, we did not evaluate the presence or absence of inflammation in the head and neck, which can also be assessed preoperatively.

## CONCLUSION

The false-positive rate of 2-[$^{18}$F]FDG-PET/CT for cervical LN metastasis in PTC patients was 63.4%. Therefore, cervical LN staging of 2-[$^{18}$F]FDG-PET/CT should be assessed carefully for an awareness of the possibility of false positives, particularly for patients younger than 45 years old with a primary tumor SUVmax < 4.0 or contralateral LN.

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