Efficiency of intraoperative frozen section analysis of central neck lymph node dissection in patients with papillary thyroid carcinoma

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Background and Objective: Because of the high survival rate and low recurrence rate of thyroid carcinoma, the therapeutic process is changing from aggressive treatment to submissive treatment. Currently, choosing central node dissection (CND) as a treatment option is considered controversial since. This approach has been shown to have poor outcomes. Therefore, we conducted this study to confirm whether the intraoperative frozen section analysis (IFSA) of CND during surgery affects treatment outcomes of patients with this type of cancer.

Materials and Methods: First, we collected the medical records of 265 patients who underwent surgery for papillary thyroid cancer at the Presbyterian Medical Center from 2014 to 2016. The patients were divided into 2 groups: IFSA and non-IFSA. The outcomes of treatment options were then assessed. We analyzed the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of IFSA of CND.

Results: Of the 265 patients in the study, 74 patients (89%) in the IFSA group and 95 patients (52.2%) in the non-IFSA group were treated appropriately ($P$-value = 0.000). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of IFSA of CND were 93.5%, 100%, 100%, 96.3%, and 97.5%, respectively.

Conclusions: The IFSA of CND is a useful method to confirm central node metastasis during surgery. Determining the range of surgery required for each patient using this method is useful for ensuring minimal complications and for providing a successful, effective oncologic surgery.

Keywords: Thyroid cancer, Well-differentiated thyroid cancer, Central neck node dissection, Intraoperative frozen section analysis, Papillary thyroid cancer, Thyroid cancer optimal treatment

The paradigm for the treatment of differentiated thyroid carcinoma is gradually changing. In the past, when thyroid carcinoma was identified in patients, total thyroidectomy and postoperative radio-iodine (RI) ablation therapy was performed. After the primary treatment, whole body scans were performed as part of continuous follow-ups. However, treatment options gradually changed to a method that determines the range and scope of surgery according to the size of thyroid carcinoma or extent of disease. In recent years, some authors have reported that active follow-up evaluations are performed in place of surgery to delay surgery in older patients with subclinical low-risk papillary thyroid microcarcinoma[1].

According to a study published in the British Journal of Surgery in 2016, thyroid cancer at a pathologic stage of T3 or less did not affect survival rate; the authors suggest that this has been a reoccurring finding in many studies[2]. No differences in were noted in the overall survival or disease-specific survival (DSS) for lesions <4 cm. In addition, the total overall survival and DSS were not affected when total thyroideectomy and lobectomy were performed[3]. Furthermore, reports of possible complications following thyroid operations were more common in total thyroideectomy than in unilateral thyroid lobectomy, as well as in central node dissection (CND) cases.

In other words, more aggressive surgical treatment results in complications such as hypocalcemia and nerve damage, as well as increasing the economic burden. Together these factors can decrease the quality of life in patients due to continuous administration of hormone.

Although, high survival rates, low recurrence rates, and distant metastasis rates of differentiated thyroid carcinoma have been reported, questions regarding the adequacy of aggressive treatment have also been raised.

In addition, there is no significant difference between survival rate and recurrence rate between unilateral thyroid lobectomy and total thyroideectomy. Furthermore, several researchers have begun to reduce the range of treatment to help determine the scope of surgical management for thyroid cancer.
Reducing the range of treatment without accurate guidelines for performing safe thyroid surgery may increase the risk of localized recurrence or distant metastasis. This raises the question of whether the recent treatment methods for thyroid carcinoma are appropriate. Especially the central lymph node metastasis, the most common metastasis of thyroid carcinoma, is known have no effect on survival rate. However, it is reported as a risk factor for recurrence.

Conversely, several other reports suggest that node metastasis affects survival. For those who had a modified neck dissection, the lymph node recurrence-free survival rate was found to be significantly higher than for those who had a nonmodified neck dissection. When total thyroidectomies performed alone were compared with those performed with CND, there was a statistically significant difference between DSS and compartment VI recurrence-free survival. Therefore, adequate response is needed.

Some studies have reported using computed tomography (CT) scans or ultrasonography before surgery to confirm lymph node metastasis to help determine the appropriate treatment range before subsequent treatment. However, there is no definitive guideline on the treatment range and treatment methods for the central lymph node, and the current existing treatment guidelines are very fragmented.

Therefore, the goal of this research was to find out whether confirming central node metastasis in patients with thyroid carcinoma by the frozen section analysis during surgery can be a helpful approach to treatment.

Materials and methods

We investigated the records of patients who had undergone primary surgical treatment for papillary thyroid carcinoma at the department of head and neck surgery at the Presbyterian Medical Center from 2014 to 2016. The study was approved by the appropriate Ethical Review Board committee of our institution. Research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. This study was performed by the Institutional Review Board of the Presbyterian Medical Center.

Patient population

The database was queried to identify patients with a diagnosis of thyroid carcinoma using the International Classification of Diseases for Oncology, Ninth Revision (C73).

There were 333 patients who underwent definitive primary surgical therapy at the medical center after being diagnosed with thyroid carcinoma. Our exclusion criteria included the following: (1) patients who required a bilateral thyroidectomy as determined by a preoperative evaluation; patients with thyroid papillary carcinoma of both thyroid lobes; patients with a strong suspicion of node metastasis based on a preoperative evaluation; patients with extrathyroidal extension (ETE) identified during a preoperative evaluation, (2) those with another type of thyroid cancer, (3) patients who had received a previous thyroid operation, and (4) those who did not have a CND. We excluded these patients as the most effective scope of treatment could not be confirmed. For our preoperative evaluations, we used ultrasonography and CT scan. Clinical lymph node metastasis was defined as a pathologic change within the lymph node noted in both tests.

A total of 68 patients were eventually excluded. Of these patients, 45 had already received a diagnosis of thyroid carcinoma in both thyroid lobes, 3 patients were diagnosed with thyroid medullary carcinoma, 1 patient had combined parathyroid and thyroid carcinoma, 1 patient had undergone a thyroid operation due to a nodular goiter, and 15 patients did not have a CND.

The final study group consisted of 265 patients with papillary thyroid cancer (PTC) who underwent thyroid surgery with neck node dissection.

All relevant clinical information was reviewed including: histologic materials, type of operation, age at diagnosis, size of the nodule at diagnosis, ETE of thyroid carcinoma, and information on lymph node metastases.

Surgical protocol and histopathologic analyses

Three thyroid surgeon specialists performed the surgeries, all of whom were skilled surgeons with a history of experience doing thyroid surgery for > 5 years. Initial thyroid surgery was divided into 2 groups: (a) bilateral total thyroidectomy and (b) unilateral thyroid lobectomy, which was synonymous with ipsilateral total lobectomy with isthmectomy. A unilateral thyroid lobectomy included patients who underwent a unilateral thyroid lobectomy and a benign thyroid mass wedge resection of the contralateral thyroid lobe.

Nodal dissection was divided into 4 categories: (a) ipsilateral CND (level VI), (b) bilateral CND (level VI), (c) ipsilateral jugular neck dissection (JND) with CND (level II, III, IV, VI), and (d) ipsilateral modified radical neck dissection (mRND) (level I, II, III, IV, V, VI).

The operation method differed according to the time period. Patients who were diagnosed with thyroid carcinoma in early 2014 received a total thyroidectomy with ipsilateral CND after thyroid carcinoma was confirmed through intraoperative frozen section analysis (IFSA) of the thyroid lobe. However, gradually over time, the treatment paradigm shifted from total thyroidectomy to unilateral thyroid lobectomy if the cancer size was found to be small, if gross ETE was not seen, or if neck lymph node metastasis was not observed on the preoperative evaluation, such as neck ultrasonography or CT. In the CT scan, the cervical node was defined as a reactive lymph node enlargement, only if it was enlarged without changing the hilum shape, and metastatic lymph nodes were deemed present when at least one of the following CT criteria was fulfilled: strong enhancement, calcification, cystic or necrotic change, lymph node hilum change, or larger than normal size, and evidence of other pathologic problems.

However, in patients with a small carcinoma size of <1 cm (microcarcinoma), central node metastasis was frequently confirmed in the final pathologic report, therefore we started an additional IFSA was performed on a specimen obtained during the CND.

During surgery, the surgeon performed a CND and that specimen was then sent to the pathologic department immediately. The specimen was taken by a pathologist, who then manually identified each node. In addition, 1 frozen set was made from 1 lymph node to perform the test. At this time, the slides were made with a thickness of 5 μm per slice, and the results were reported to the surgeon during surgery.

Through these processes, the surgeon could assess cervical lymph node metastases through IFSA during the operation.
The Student Statistical analysis in the presence of lymph node metastasis, cancer size and surgery as either adequate or inadequate. We defined treatment effectiveness according to the Surgical Treatment Guidelines for Patients with Differentiated Thyroid Cancer: The Korean Association of Thyroid and Endocrine Surgeons (KATES) Guidelines Taskforce.

Treatment was considered adequate if a total thyroidectomy was performed in the presence of lymph node metastasis, gross ETE, or a cancer size of >4 cm (T3a). Inadequate treatment was further divided into excessive treatment and insufficient treatment. If the surgeon performed a total thyroidectomy in cases of no lymph node metastasis, cancer size <1 cm, and no gross thyroidal extension, it was considered excessive treatment. Insufficient treatment was defined as those patients who received a unilateral thyroid lobectomy in the presence of lymph node metastasis, cancer size >4 cm, or gross thyroid extension (Table 1).

Statistical analysis
The Student t test was used to determine differences between the IFSA group and the non-IFSA group according to clinicopathologic characteristics. We analyzed the differences between the results of IFSA of the central lymph node during icopathologic characteristics. We analyzed the differences between the 2 groups. And the type of operation was significantly different between the 2 groups. Bilateral total thyroidectomy was more common in the group without IFSA (P-value = 0.0004). Histology revealed follicular variant types of

Table 1
Definition of treatment based on the Korean Association of Thyroid and Endocrine Surgeons (KATES) Guidelines Taskforce.

| Characteristics                                      | Total Patients (265) | IFSA [83 (32%)] | Non-IFSA [182 (68%)] | P     |
|------------------------------------------------------|---------------------|-----------------|-----------------------|-------|
| Male/female [n (%)]                                  |                     |                 |                       |       |
| Male                                                 | 43 (16.3)           | 10 (12.1)       | 34 (18.7)             | 0.1540|
| Female                                               | 222 (83.7)          | 74 (33.2)       | 148 (78.3)            |       |
| Median age at diagnosis (y)                          |                     |                 |                       |       |
| Male                                                 | 50.15 (16-79)       | 46.41 ± 12.71   | 52.03 ± 11.49         | 0.0004|
| Female                                               | 50.21               | 47.05           | 51.97                 |       |
| Histology [n (%)]                                    |                     |                 |                       |       |
| Classic type                                         | 252 (95)            | 82              | 170                   |       |
| Follicular variant                                   | 13 (5)              | 1               | 12                    | 0.1148|
| pT stage at initial diagnosis (size) [n (%)]         |                     |                 |                       |       |
| T1a                                                  | 196 (73)            | 67              | 147                   |       |
| T1b                                                  | 58 (22)             | 13              | 26                    |       |
| T2                                                   | 12 (4)              | 4               | 8                     |       |
| T3a (<1)                                             | 1                   | 0               | 1                     |       |
| More than T3a                                        | 0                   | —               | —                     | 0.0787|
| ETE [n (%)]                                          |                     |                 |                       |       |
| No                                                   | 155 (62)            | 55              | 100                   |       |
| Yes                                                  | 110 (43)            | 29              | 82                    |       |
| Gross ETE                                            | 21 (7.9)            | 3               | 18                    |       |
| Node metastasis [n (%)]                              |                     |                 |                       |       |
| No                                                   | 177 (67)            | 55 (66)         | 122 (67)              |       |
| Yes                                                  | 88 (33)             | 28 (34)         | 60 (33)               |       |
| Node dissection [n (%)]                              |                     |                 |                       |       |
| Ipsilateral CND                                      | 245 (92)            | 76              | 168                   |       |
| Bilateral CND                                        | 0                   | —               | —                     | 0.9262|
| JND + CND                                            | 13 (5)              | 6               | 7                     |       |
| mRND                                                 | 9 (3)               | 2               | 7                     |       |
| Operation [n (%)]                                    |                     |                 |                       |       |
| Lobectomy                                            | —                   | 53              | 72                    | 0.0004|
| Bilateral thyroidectomy                              | —                   | 30              | 110                   |       |

CND indicates central node dissection (level VI); IFSA, intraoperative freeze section analysis; JND, jugular neck dissection (level II, III, IV, VI); mRND, modified radical neck dissection (level I, II, III, IV, VI).
PTC in 13 patients, 1 from the IFSA group and 12 from the non-IFSA group. Cancer size was 7.98 ± 4.88 mm for the IFSA group which was not significantly different from the non-IFSA group, which had an average cancer size of 7.93 ± 5.57 mm \((P\text{-value }= 0.9531)\). One patient had a permanent histologic report which revealed the cancer size to be > 4 cm. However, this patient was included in the study because the preoperative CT scan and ultrasound (US) evaluations showed that the cancer size was < 4 cm.

Among the patients included in this study, 13 patients underwent JND and 9 patients underwent mRND. In these patients, the preoperative clinical lymph node metastasis was not prominent, but the enlarged jugular lymph node was identified during the operation, and additional JND was performed during the operation. Node metastasis was confirmed in 6 of the 13 patients who underwent JND. In addition, mRND was performed if there was evidence of the following: (1) a prominent strap muscle cancer invasion during surgery, (2) a prominent recurrent laryngeal nerve invasion, and (3) a large lymph node confirmed during surgery. Node metastasis was confirmed in 7 of the 9 patients who underwent mRND.

ETE, node metastasis, and node dissection were not statistically different between the 2 groups.

In 265 patients, the mean number of lymph nodes removed by node dissection was 6.2. In patients with node metastasis, an average of 9.4 nodes were removed and an average of 3.7 nodes were found to have metastasis. The mean node size of the largest metastatic nodes was 5.7 mm.

The appropriateness of treatment between the IFSA group and the non-IFSA group was examined. In the IFSA group, 74 (89%) patients were treated effectively according to the guidelines, and 9 (11%) patients had received ineffective treatment. It was also determined that 5 (6%) patients received ineffective treatment and 4 (5%) patients had received excessive treatment. Within the non-IFSA, 95 (52.2%) patients had received effective treatment according to the guidelines, while 87 (47.8%) patients received ineffective treatment. In addition, 21 (11.5%) patients received ineffective treatment and 66 (36.3%) patients received excessive treatment. Overall, there was a statistically significant correlation between the IFSA approach and treatment effectiveness \((P\text{-value }= 0.0000)\) (Fig. 1 and Table 3).

We also investigated the relationship between IFSA and the final permanent biopsy report of specimen in central lymph node dissection. As a result, we confirmed that statistical significance was obtained, and the diagnostic agreement rate between the IFSA and the permanent report was very high \((\kappa \text{ index } = 0.9478)\). And its Likelihood ratio was 84.39 \((P\text{-value }= 0.000)\) (Table 4).

Our study revealed that the overall sensitivity, specificity, PPV, NPV, and diagnostic accuracy of the CT scan according to the per patient analyses, were 25.6%, 91.6%, 61.1%, 70.5%, and 69.2%, respectively \((\kappa \text{ index } = 0.2002)\). We did a reanalysis of reactive lymph nodes that showed that the overall sensitivity specificity, PPV, NPV, and diagnostic accuracy, were 53.5%, 68.3%, 46.5%, 74.0%, and 63.2%, respectively \((\kappa \text{ index } = 0.2098)\) (Table 5).

**Discussion**

PTC is the most common type of well-differentiated thyroid carcinoma. Discussions involving the scope of treatment for thyroid carcinoma have been ongoing and have been controversial, especially for cervical lymph node dissection. In the past, if a patient was diagnosed with thyroid carcinoma, a total thyroidectomy and cervical lymphadenectomy were performed, and an additional RI ablation therapy was applied for local control of residual cancer, and regular follow-ups using whole body scans were the standard treatment. Severe treatment complications such as hypocalcemia, nerve palsy, and long-term use of thyroid hormone were reported with the implementation of these aggressive treatments. However, the high survival rates, the low recurrence rates, and low distant metastasis rates of differentiated thyroid carcinoma have recently been reported. Therefore, there has been an increase in the number of claims of patients to change aggressive treatment modalities, as the treatment complications have been known to severely impair the patient’s quality of life [7]. Accordingly, unilateral thyroidectomy is being performed rather than total thyroidectomy. Some researchers suggest that CNDs should not be implemented,

| Table 3 | Relationship of IFSA of central node dissection and treatment adequacy. |
|---------|---------------------------------------------------------------|
| Treatment | Inadequate | Insufficient | Excess | Total | \(\chi^2 (P)\) |
| IFSA [n (%)] |
| Yes | 74 (89) | 5 (6) | 4 (5) | 83 (100) | 26.64 (0.000) |
| No | 95 (52.2) | 21 (11.5) | 66 (36.3) | 182 (100) | |

IFSA indicates intraoperative frozen section analysis.
because it is not easy to preserve nerves and the parathyroid glands[2,8]. In addition, recent studies have shown aggressive follow-up may also be delayed without surgical treatment. This may be a problem as it can lead to inadequate treatment. Studies have shown that regional lymph node metastasis of thyroid carcinoma has no effect on survival and is a risk factor for recurrence[6,9,10]. The risk for nodal recurrence increases 10-fold when metastatic nodes are found during the initial examination and it is reported to be 20%–60% depending on the degree of risk[7,11]. However, some studies have reported that regional metastasis reduces survival, especially in elderly patients. Therefore, reducing the therapeutic range of thyroid cancer without effectively implementing adequate treatment for regional metastasis will negatively affect long-term outcomes. For patients with PTC with lymph node metastasis, it is necessary to determine the extent and method of treatment. However, there is no definitive guideline on the treatment range and treatment methods for addressing pathologies associated with central lymph nodes, and the recommendations according to various treatment guidelines are controversial. In addition, there is still a lot of controversy regarding the most effective range of surgery for treatment of the thyroid. The National Comprehensive Cancer Network (NCCN) guidelines recommend total thyroidectomy when there is evidence of distant metastasis, ETE positivity, a tumor size >4 cm, previous radiation exposure, or bilateral nodularity. The NCCN guidelines also recommends that a total thyroidectomy should be performed only if there are >3 lymph node metastases and if the metastatic distance is >2 mm in the presence of a cervical lymph node component[12]. In addition, according to the Korean Endocrinological Society guidelines, total thyroidectomy is still indicated for T1b patients >1 cm. These guidelines also recommend unilateral thyroid lobectomy to reduce postoperative complications if the patient presents with a carcinoma <1 cm in diameter and the cancer is localized within the thyroid gland without neck lymph node metastasis[13].

Various researchers are conducting studies on preoperative evaluation to help determine the scope of surgery needed[6,11,14,15]. Preoperative CT scan is performed to estimate the preoperative ETE or whether node metastasis[6,11,14]. Preoperative neck US has been reported to help identify suspicious neck lymphadenopathy. The US scans characteristics of metastatic lymph nodes included increased size, rounded shape, hyper-echogenicity, absence of a visible hilum or loss of echogenic fatty hilum, irregular reflection pattern, unsharp borders, cystic change, calcification, and nonhilar vasculature[11,13]. Preoperative evaluations of the neck lymph node metastasis using ultrasonography shows that the results of the central and lateral lymph nodes are reported inconsistently. However, sensitivity is reported up to 27.3%–55%, specificity is reported up to 69%–90.3%, and accuracy up to 71%–95%. The sensitivity of CT scan to the neck lymph node metastasis was reported to range from 34.8% to 77%, with specificity ranging from 70% to 93% and accuracy ranging from 74% to 81%. Recently, there have also been reports about using CT and US scans together to increase the diagnostic accuracy.

In this study, our results did not show a high sensitivity, specificity, NPV, PPV, or accuracy compared with previous reports. In categorizing all enlarged lymph nodes as metastasis, the sensitivity and NPV were increased, but specificity, PPV, and accuracy were decreased. This suggests that the accuracy of central node metastasis using CT scans was much less than the 93.5%, 100%, 100%, 96.3%, and 97.5% values found using the IFSA. This study has some limitations. First, this study is retrospective in design, including surgeries from a time-period. Second, in this study, we could not evaluate the long-term outcomes. Knowing the long-term outcome of a patient is necessary to evaluate the treatment and surgical management that the patient received. Therefore, the long-term outcome of the patients included in this study should be evaluated based on whether recurrence occurred or if the patient experienced distant metastasis. Third, the study was based on the Korean Association of Thyroid and Endocrine Surgeons (KATES) guidelines. As these are not international guidelines, this was considered as a limitation of this study. Fourth, there is a limitation that metastasis can be missed according the pathologists make single frozen section in one lymph node. Therefore, it is not yet established but it is necessary to additionally study at what interval to cut the paraffin block and how to make several slices from one lymph node to confirm the final pathology. Fifth, there was a difference in age and type of operation between the patients who underwent IFSA and those who did not. In this study, the average age of the IFSA group was 46.41 ± 12.71 years and for the non-IFSA group it was 52.03 ± 11.49 years. Therefore, there was a statistically significant difference in age between the 2 groups. However, this may not be a problem as both groups were older than 45 years, which is a staging standard in the American Joint Committee on Cancer (AJCC) seventh edition, and all groups were younger than 55 years, which is a staging standard AJCC eighth edition. The statistical difference between the surgical methods appears to be due to total thyroidectomy was most common surgical method at the initial period without IFSA.

### Table 4

| Relationship between IFSA and permanent pathologic result. |
|-------------------------------------------------------------|
| Permanent Biopsy Report                                    |
| IFSA report        | Positive | Negative | χ² (P) |
| Positive          | 29       | 0        | 70.71 (0.0000) |
| Negative          | 2        | 52       |         |

κ index = 0.0478.
IFSA indicates intraoperative frozen section analysis.

### Table 5

| Diagnostic accuracy of head and neck CT scan and IFSA. |
|--------------------------------------------------------|
| Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
| CT 1            | 25.6          | 91.6    | 61.1    | 70.5         | 69.2         |
| CT 2            | 53.5          | 68.3    | 46.5    | 74.0         | 63.2         |
| IFSA            | 93.5          | 100     | 100     | 96.3         | 97.5         |

CT indicates computed tomography; IFSA, intraoperative frozen section analysis; NPV, negative predictive value; PPV, positive predictive value.

### Conclusions

In conclusion, despite these limitations of our study, IFSA of CND during surgery for PTC is an effective test with high diagnostic concordance rate that can be very helpful in determining the scope of surgical treatment and management.
Ethical approval

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the PMCIRB, Presbyterian Medical Center, Korea. PMCIRB composition and voting members meets KGCP & ICH-GCP requirement and all applicable laws and regulations.

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The authors declare that they have no financial conflict of interest with regard to the content of this report.

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