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Role of prophylactic ipsilateral central compartment lymph node dissection in papillary thyroid microcarcinoma

Mujgan Caliskan²⁾, Jae Hyun Park¹⁾, Jun Soo Jeong¹⁾, Cho-Rok Lee¹⁾, Seul Kee Park¹⁾, Sang-Wook Kang¹⁾, Jong Ju Jeong¹⁾, Woong Youn Chung¹⁾ and Cheong Soo Park¹⁾

¹⁾Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

²⁾Department of General Surgery, Umraniye Education and Research Hospital, Istanbul, Turkey

Abstract. Central compartment lymph node (CCLN) management in patients without clinical or radiologic evidence of CCLN metastasis is debatable. The aim of the present study was to evaluate outcomes of surgery for papillary thyroid microcarcinoma (PTMC) with prophylactic ipsilateral CCLN dissection (PI-CCND) in a large cohort of patients treated at one single institution in a 5-year follow-up. Between January 2000 and December 2005, 2192 patients with papillary thyroid carcinoma underwent thyroid surgery. Inclusion criteria were patients with PTMC, absence of clinical or radiologic evidence of CCLN metastasis, and a follow-up for a period ≥ 60 months. Data from 842 patients were retrieved in the current retrospective cohort study. PI-CCND was routinely performed in addition to thyroid surgery in all cases. Ipsilateral CCLN metastasis was found in 218 patients (25.9%). Postoperative complications included 76 cases of transient hypoparathyroidism (9%), 11 cases of permanent hypoparathyroidism (2.6%), four cases of vocal cord palsy (0.5%), and one case of bleeding (0.1%). Univariate analysis and multivariate logistic regression analysis revealed that CCLN metastasis was statistically significantly correlated with tumor size and extracapsular invasion. Recurrence has been observed to date in 19 patients (2.26%). No CCLN site recurrence occurred in patients who underwent PI-CCND. This study demonstrates the technical feasibility and safety of PI-CCND, which is a better way to determine lymph node status for a more accurate staging of disease and risk stratification. PI-CCND should be considered even if clinical or radiological exams are negative for CCLN metastasis.

Key words: Prophylactic central compartment node dissection, Papillary thyroid microcarcinoma, Recurrence, Surgical outcome

PAPILLARY THYROID MICROCARCINOMA (PTMC) is defined as thyroid cancer ≤ 10 mm in diameter [1]. Increasing incidence of thyroid carcinoma has been observed in recent decades. This may be mainly related to the growing use of imaging devices combined with continuing technological improvements, introduction of screening programs, wide use of ultrasonography (US) and US guided fine-needle aspiration biopsy (FNAB), higher socio-economic level, and better self-reported health. Thus, possibilities for detection of subclinical cancer in a greater proportion of the population have shown improvement [2, 3]. Therapeutic options for PTMC include close surve-

illance without surgery in selected patients, only unilateral lobectomy and isthmusectomy, or a more aggressive operative intervention in high-risk patients [4, 5]. However, optimal therapeutic strategy remains a matter of debate. Furthermore, central compartment lymph node (CCLN) management in patients without clinical or radiologic evidence of CCLN metastasis is another subject of debate [6, 7]. Numerous national and international guidelines have published specific recommendations for management of prophylactic central compartment node dissection (CCND). The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons (AAACE/AAES), the British Thyroid Association (BTA), and the National Comprehensive Cancer Network (NCCN) guidelines do not recommend prophylactic CCND, particularly in low-risk patients [8-10]. In contrast, the European Thyroid Association (ETA) has stated that prophylactic CCND might also provide useful patho-

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Correspondence to: Jong Ju Jeong, Department of Surgery, Yonsei University College of Medicine, C.P.O. Box 8044, 250 Seongsanno, Seodaemun-gu, 120-752, Seoul, Korea.
E-mail: jungjongj@yuhs.ac

logic N staging information that may guide subsequent treatment and follow-up [11]. The level of evidence for recommending prophylactic CCND by the American Thyroid Association (ATA) 2009 guidelines is considered insufficient; therefore, the issue still remains unresolved [12]. Numerous published studies have adopted a more aggressive treatment approach than that proposed in the guidelines of some scientific societies [13, 14].

The purpose of the present study was to evaluate outcomes of a large cohort on prophylactic ipsilateral CCND (PI-CCND) in patients with PTMC without clinical or radiologic evidence of CCLN metastasis treated at one single institution in a 5-year follow-up.

Methods

Patients

Between January 2000 and December 2005, 2192 patients with papillary thyroid carcinoma underwent thyroid surgery. The study was approved by the Institutional Review Board of Yonsei University Health System. Patient clinical characteristics and stratification for pathological features were included in a specific database. Information was completed using data from the institutional register and additional specific data directly from medical records. Parameters included gender, age, symptoms, tumor size, multifocality, bilaterality, extracapsular invasion, surgical extension, CCLN metastasis, postoperative complications, and recurrence.

Inclusion criteria were patients with PTMC, no clinical or radiologic evidence of CCLN metastasis, and a follow-up period ≥ 60 months. Exclusion criteria included radiologic or pathologic evidence of CCLN or lateral neck node metastasis, past history of previous surgery for benign or malignant thyroid / parathyroid diseases, past history of other previous malignancy, and a follow-up period < 60 months. Finally, data of 842 patients were retrieved for the current study.

All patients with suspicious thyroid US imaging underwent FNAB. In the presence of suspicious findings in FNAB, diagnosis of the tumor was confirmed by intraoperative histologic examination. PI-CCND was routinely performed in addition to thyroid surgery in all cases. Laryngeal examination by videolaryngoscopy was performed before surgery in patients suspected of recurrent laryngeal nerve invasion, and 24 hours, 3 months, and 6 months after the procedure in patients

with postoperative voice change. Normalization of vocal cord mobility within a period of 6 months was defined as transient palsy. All of our hypocalcemic patients were given routine oral calcium replacement therapy and vitamin D supplements in the postoperative period. Transient hypocalcemia was defined as recovery from symptoms and normalization of total calcium and low parathyroid hormone (PTH) serum level within 6 months. Presence of extracapsular invasion was determined by the final pathologic result. Indication for radioiodine ablation in this cohort of patients was based on ATA guidelines [12]. A ^{131}I whole body scan was taken on day 2 following radioiodine therapy. All patients received thyroid-stimulating hormone suppression treatment with levothyroxine according to ATA guidelines [12]. Patient follow-up was based on physical examination, neck US, and serum thyroglobuline measurement at intervals of 3 or 6 months. In case of recurrence in remnant thyroid or lymph node, diagnosis was confirmed by FNAB. The mean follow-up period was 65 ± 21.52 months. Eleven patients were lost to follow-up.

Operative methods

At our institution, thyroid resection consisted of total thyroidectomy and less than total thyroidectomy. The definition of "less than total thyroidectomy" is specified by unilateral thyroid lobectomy, ipsilateral total and contralateral partial thyroidectomy, and ipsilateral total and contralateral subtotal thyroidectomy. The choice of surgical extension was based on ATA guidelines [12]. During thyroid resection, only CCLNs located in the ipsilateral site of the primary tumor were dissected. The CCLN or level VI included the pretracheal, paratracheal, prelaryngeal, perithyroidal nodes, and lymph nodes located along the recurrent laryngeal nerve. The central compartment was delimited superiorly by the hyoid bone, inferiorly by the substernal notch, laterally by the median portion of the carotid sheath, and dorsally by the prevertebral fascia. Recurrent laryngeal nerves and parathyroid glands were identified and preserved in all cases. The procedures were performed by the same surgical team.

Statistical analysis

Pearson chi-square test, Fisher's exact test, and Yates (continuity correction) for univariate analysis were used for calculation of statistical significance. Logistic regression was used for multivariate analysis. Statistical

analyses were performed using SPSS software (version 13.0; SPSS, Chicago, IL, USA). Statistical significance was based on a *p* value < 0.05. All data are presented as mean ± standard deviation (SD).

Results

We reviewed 842 cases for the current study. The cohort included 769 females (91.3%) and 73 males (8.7%). The mean age of patients at the time of diagnosis was 46.27 ± 10.41 years. Diagnosis of PTMC in 751 patients (89.2%) was found incidentally during the screening program, whereas the remaining patients visited a physician due to symptoms including anterior neck mass (n=79), hoarseness (n=5), voice color change (n=5), and lateral neck mass (n=2).

A total of 428 patients (50.8%) underwent total thyroidectomy and 414 patients (49.2%) underwent less than total thyroidectomy. All patients then received PI-CCND. Three hundred twenty six patients were documented as having PTMC ≤ 5 mm (38.7%), whereas 516 patients had a tumor size > 5 mm but ≤ 10 mm (61.3%). The rate of multifocality and bilaterality was 24.8% and 15.4%, respectively. Ipsilateral CCLN metastasis was found in 218 patients (25.9%). Extracapsular invasion was observed in 407 patients (48.4%) and 23 had adjacent structure invasion, such as strap muscles, recurrent laryngeal nerve, and trachea.

The mean number of retrieved central lymph nodes per patient was 5.15 ± 3.54, whereas the mean number of metastatic lymph nodes was 2.26 ± 1.8. Table 1 shows the patient's characteristics and stratification for pathological features.

Despite the small size of tumors, nine patients underwent a shaving procedure due to recurrent laryngeal nerve invasion (n=5) and trachea invasion (n=4). Postoperative complications included 76 cases of transient hypoparathyroidism (9%), 11 cases of permanent hypoparathyroidism (2.6%), four cases of permanent vocal cord palsy (0.5%), and one case of bleeding (0.1%) (Table 2). Transient hypocalcemia was observed in 68 patients undergoing total thyroidectomy and in eight patients having less than total thyroidectomy. Transient hypoparathyroidism resolved within 3–6 months, whereas hypocalcemia was permanent in 11 patients undergoing total thyroidectomy. Most of patients (410 out of 428, 95.8%) who received a total thyroidectomy were managed by adjuvant radioiodine ablation at 4–6 weeks postoperatively.

Table 1 Clinicopathologic characteristics

| Characteristics | Values |
|-------------------------------|----------------|
| Total number | 842 |
| Age at diagnosis (years) | 46.27 ± 10.41* |
| <45 | 405 |
| ≥45 | 437 |
| Gender | |
| Female | 769 (91.3%) |
| Male | 73 (8.7%) |
| Symptoms | |
| Asymptomatic | 751 (89.2%) |
| Symptomatic | 91 (20.8%) |
| Tumor size (mm) | |
| ≤ 5 | 326 (38.7%) |
| >5 but ≤10 | 516 (61.3 %) |
| Multifocal neoplasms | 209 (24.8%) |
| Bilateral neoplasms | 130 (15.4%) |
| Extracapsular invasion | 407 (48.4%) |
| Adjacent structures extension | 23 (2.7%) |
| Operation type | |
| Total thyroidectomy | 428 (50.8%) |
| Less than thyroidectomy | 414 (49.2%) |
| CCLN metastasis | 218 (25.9%) |

*Mean value ± standard deviation.
CCLN, central compartment lymph node

Table 2 Postoperative complications

| Complications | Number (%) |
|----------------------------------|-----------------|
| Transient hypoparathyroidism | 76 / 842 (9.0) |
| Total thyroidectomy | 68 / 428 (15.9) |
| Less than total thyroidectomy | 8 / 414 (1.9) |
| Permanent hypoparathyroidism | |
| Total thyroidectomy | 11 / 428 (2.6) |
| Less than total thyroidectomy | 0 |
| Recurrent laryngeal nerve injury | 4 / 842 (0.5%) |
| Bleeding | 1 / 842 (0.1%) |
| Seroma | 0 |
| Chyle leak | 0 |
| Tracheal leak | 0 |

Univariate analysis revealed a statistically significant correlation of CCLN metastasis with tumor size and extracapsular invasion (Table 3). Multivariate logistic regression analysis showed that tumor size (odds ratio, 1.819; *p*=0.001) and extracapsular invasion (odds ratio, 1.683; *p*=0.002) were independently predictive of CCLN metastasis (Table 4).

Recurrence has been observed to date in 19 patients (2.26%). The site of local relapse was the remnant thyroid gland (n=8), ipsilateral lateral neck node area (n=6), contralateral CCLN (n=1), thyroid bed (n=1), contralateral lateral neck node area (n=1), thyroid bed and ipsilateral lateral neck node area (n=1), and thyroid

Table 3 Clinicopathologic characteristics of patients and central compartment lymph node metastasis.

| Parameters | CCLN metastasis | |
|-------------------------------|------------------|-----------------|
| | Number (%) | <i>p</i> value* |
| Age (years) | | |
| <45 | 111 / 405 (27.4) | 0.333 |
| ≥45 | 107 / 437 (24.5) | |
| Gender | | |
| Male | 25 / 73 (34.2) | 0.117 |
| Female | 193 / 769 (25.1) | |
| Tumor size (mm) | | |
| ≤ 5 | 59 / 326 (18.1) | 0.010 |
| > 5 but ≤ 10 | 159 / 516 (30.8) | |
| Operation type | | |
| Total thyroidectomy | 118 / 428 (27.6) | 0.258 |
| Less than total thyroidectomy | 100 / 414 (24.2) | |
| Multifocal neoplasm | | |
| Solitary | 154 / 633 (24.3) | 0.072 |
| Multifocal | 64 / 209 (44.3) | |
| Bilateral neoplasm | | |
| Absent | 177 / 712 (24.9) | 0.110 |
| Present | 41 / 130 (31.5) | |
| Extracapsular invasion | | |
| Absent | 89 / 435 (20.5) | 0.0005 |
| Present | 129 / 407 (31.7) | |

*Pearson chi-square test, Yates (Continuity Correction) test
CCLN, central compartment lymph node

Table 4 Multivariate analysis for risk factors of central lymph node metastasis

| | <i>p</i> value* | 95% CI for EXP(β) | | |
|-----------------------------------|-----------------|-------------------|-------|-------|
| | | Exp(β) | Lower | Upper |
| Tumor size (≤ 5 vs. > 5 but ≤ 10) | 0.001 | 1.819 | 1.282 | 2.581 |
| Extracapsular invasion | 0.002 | 1.683 | 1.226 | 2.329 |

*Logistic regression analysis Exp(β): odds ratio for subclinical central lymph node metastasis CI, confidence interval of Exp(β)

bed and contralateral lateral neck node area (n=1). No recurrence has occurred in the ipsilateral CCLN. The mean time of appearance of recurrence was 47.18 ± 22.33 months. Univariate analysis was performed for assessment of statistically significant predictive factors for recurrence. Recurrence was not related to gender (*p*=1.000), age (*p*=1.000), type of surgery (*p*=0.251), tumor size (*p*=0.637), multifocality (*p*=1.000), bilaterality (*p*=1.000), extracapsular invasion (*p*=0.395), or CCLN metastasis (*p*=0.291) (Table 5). Patients with recurrence in the remnant thyroid tissue underwent completion total thyroidectomy and radioiodine ablation treatment, whereas patients having recurrence in lateral neck node area underwent ipsilateral modi-

Table 5 Clinicopathologic characteristics and recurrence

| Characteristics | Recurrence | |
|-------------------------------|----------------|-----------------|
| | Number (%) | <i>p</i> value* |
| Age (years) | | |
| <45 | 9 / 405 (2.0) | 1.000 |
| ≥45 | 10 / 437 (2.1) | |
| Gender | | |
| Male | 1 / 73 (1.4) | 1.000 |
| Female | 18 / 769 (2.3) | |
| Tumor size (mm) | | |
| ≤ 5 | 6 / 326 (1.8) | 0.637 |
| > 5 but ≤ 10 | 13 / 516 (2.5) | |
| Operation type | | |
| Total thyroidectomy | 7 / 428 (1.6) | 0.251 |
| Less than total thyroidectomy | 12 / 414 (2.9) | |
| Multifocality | | |
| Solitary | 15 / 633 (2.4) | 1.000 |
| Multifocal | 4 / 209 (1.9) | |
| Bilaterality | | |
| Absent | 16 / 712 (2.2) | 1.000 |
| Present | 3 / 130 (2.3) | |
| CCLN metastasis | | |
| Absent | 12 / 624 (1.9) | 0.291 |
| Present | 7 / 218 (2.3) | |
| Extracapsular invasion | | |
| Absent | 12 / 435 (2.8) | 0.395 |
| Present | 7 / 407 (1.7) | |

*Pearson chi-square test, Fischer Exact test and Yates (Continuity Correction) test CCLN, central compartment lymph node

fied radical neck dissection and radioiodine ablation treatment.

To date, 11 patients have been lost to follow-up. In the remaining 831 patients, distant metastasis has not been found, and all of them, except for one who died of another malignancy, are still alive.

Discussion

Therapeutic CCND in PTMC patients is always necessary, whereas prophylactic CCND remains a subject of considerable debate. Numerous studies have documented the beneficial effects on one hand and supported arguments against prophylactic CCND on the other hand. A high proportion of autopsy findings and pathological specimens have shown metastasis in CCLN [14-17]. Although US has been regarded as a sensitive imaging modality for thyroid screening and diagnosis, US has a low sensitivity in evaluation of metastasis in CCLN [19]. Similarly, in our study, imaging studies were not useful in detection of metastasis in CCLN; presently, 25.9% of patients without evi-

dence of metastasis had lymphatic invasion.

There is no scoring system that determines those patients who can benefit from prophylactic CCND. After analysis of risk factors for CCLN metastasis, one study concluded that high risk patients for CCLN metastasis should be taken into consideration for a prophylactic CCND approach [13]. Cases with CCLN metastasis were found to be consistently associated with gender, multifocality, extrathyroidal extension, tumor size, extracapsular invasion, and bilaterality [13, 20]. In our data, the size of the tumor and extracapsular invasion were independently predictive of CCLN metastasis. The rate of extracapsular invasion in our study was 48.4%. Similarly, in another study, extrathyroidal extension was reported to be 53.0% [13]. The relevance of the high rate may be explained by the fact that microscopic extension outside the thyroid capsule was included in the diagnosis of extrathyroidal extension.

PTMC usually spreads to the lymph nodes in consecutive order from central nodes, lateral nodes to the mediastinal nodes, and occurs more commonly in the ipsilateral central node of the primary tumor. Although nodal metastasis to the lateral compartment without central neck node involvement remains rare, spreading can occur when the tumor is located in the upper lobe [21]. Metastasis to the mediastinal compartment is a more rare condition. By careful removal of ipsilateral CCLN, lymphatic flow to central, lateral, and intrathoracic lymph nodes may be effectively interrupted. Presently, no recurrence in ipsilateral CCLN or distant metastasis was evident. In considering clinical behavior, a 5-year follow-up period may be short in patients with PI-CCND in PTMC. Therefore, data from longer follow-up studies are needed.

One of the arguments against prophylactic CCND is that more severe complications may be observed due to a wider dissection [22]. The most common complications are hypoparathyroidism and recurrent laryngeal nerve injury. In the literature, no difference is apparent in terms of permanent hypoparathyroidism (6.8% vs. 6.1%) and recurrent laryngeal nerve paralysis (0.8% vs. 0.7%) in patients managed by total thyroidectomy with CCND, as compared with those undergoing only total thyroidectomy [23]. Other authors have reported the rate of permanent hypoparathyroidism after thyroidectomy with CCND as 11.3% and 12% [18, 24], rates that are much higher than our result. In another study, patients who underwent thyroid surgery with bilateral CCND showed an increased rate of transient hypopa-

rathyroidism [25]. Comparing our reasonable morbidity data with those selected from the literature, we propose the use of PI-CCND, which is a less aggressive surgical approach than bilateral CCND.

When PI-CCND has been previously performed, reoperation at the time when lateral or contralateral central neck metastasis is found may be a safe and feasible option, because ipsilateral central node fields have not been dissected. Even if some authors reported that reoperation in the same field was performed without additional morbidity, numerous studies have concluded that reoperation due to recurrence in Level VI is associated with an increase in postoperative complications, such as recurrent laryngeal nerve injury and hypoparathyroidism [26, 27]. Furthermore, secondary operation is associated with a requirement for general anesthesia, patient stress, and higher cost of care. Therefore, prophylactic CCND during thyroid surgery appears to be a reasonable management option [25, 28].

In some eastern countries, radioactive iodine treatment is strictly limited by the government; therefore, prophylactic CCND has been selected for treatment of PTMC [18]. In contrast, some western countries have adopted a more conservative surgery in PTMC patients, due to the fact that, if necessary, ablation of lymph node metastasis can be achieved by application of postoperative radioactive iodine treatment [29].

Because CCLN metastasis rarely becomes clinically significant, the rate of recurrence remains low, no survival benefit has been added, and patients with PTMC have a good prognosis, some authors have considered prophylactic CCND as an overtreatment [30, 31]. But, another study concluded that in order to evaluate lymph node status and to provide a more accurate staging, CCND should be considered even in PTMC patients without lymphatic invasion [32]. Thus, better treatment and follow-up will be possible.

Presently, at a mean follow-up time of 65 ± 21.52 months, recurrence rate was 2.26% and the most commonly found site of recurrence was the remnant thyroid and ipsilateral lateral neck node and no distant metastasis was found. Similarly, in one study, the rate of disease recurrence in remnant thyroid and lymph nodes was 2.2%, and none of the patients showed distant metastasis or died of PTMC [17]. A higher rate of recurrence was reported in patients with CCLN metastasis and those who underwent hemithyroidectomy, and multifocality and CCLN metastasis have been associated with recurrence [16, 33, 34]. Even if not statisti-

cally significant, age, gender, tumor size, multifocality, extracapsular invasion, and CCLN metastasis should be taken into consideration because they are important factors for the evaluation of patients. Thus, more aggressive treatment and careful close follow-up is required in these patients.

In conclusion, this study demonstrates the technical feasibility and safety of PI-CCND, which is a better way to determine lymph node status for a more accurate staging of disease and risk stratification. PI-CCND

should be considered in performance even if clinical or radiological exams are negative for CCLN metastasis. In order to understand the efficacy of PI-CCND in terms of risk reduction for recurrence and survival, more longer and controlled randomized prospective studies are needed.

Disclosure Summary

The authors have nothing to declare.

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