

Current trends of practical issues concerning micropapillary thyroid carcinoma

The Korean Society of Thyroid-Head and Neck Surgery

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Abstract

Although several thyroid associations have published various guidelines, controversies especially in cases of micropapillary thyroid cancer (MPTC) still exist. This survey was designed to collect information about diagnostic tests and treatments performed on patients with MPTC and help identify current trends in thyroid surgery.

We developed questionnaires about the management methods for MPTC, which were used to identify factors related to indications of fine needle aspiration (FNA), type of surgery, and central lymph node dissection (CLND). Active 60 members of the Korean Society of Thyroid-Head and Neck Surgery participated in the study in September 2016.

Ultrasound-guided FNA was usually initiated when the tumor was at least 5 mm (60%). All respondents preferred ultrasound-guided FNA and surgery for nodules with extrathyroidal extension (ETE). The preferred treatment option for intraglandular MPTC was lobectomy (92%) rather than active surveillance (8%). Posterolateral ETE increased the respondents' preference for total thyroidectomy (61.7%). Active surveillance was preferred for tumors <5 mm, which was decreased by the presence of ETE. The presence of ETE (73.3%) and its proximity to critical organs (46.7%) were the main determining factors for prophylactic CLND. For multiple metastatic lymph nodes at level III, selective neck dissection including levels IIb (23.3%) and V (78.3%) was preferred in addition to levels IIa, III, VI, and V.

Korean head and neck surgeons favored total thyroidectomy and CLND in cases wherein ETE, central lymph node metastasis, or critical organ involvement was suspected.

Abbreviations: ATA = American Thyroid Association, CLND = central lymph node dissection, ETE = extrathyroidal extension, FNA = fine needle aspiration, KTA = Korean Thyroid Association, MPTC = micropapillary thyroid cancer, SND = selective neck dissection, US = ultrasound.

Keywords: central lymph node dissection, Korea, micropapillary thyroid cancer, survey, thyroidectomy, trend

1. Introduction

Many medical societies have provided various guidelines for the treatment of well-differentiated thyroid cancer. Based on available

evidence and risk stratification, guidelines from the American Thyroid Association (ATA), British Thyroid Association, National Comprehensive Cancer Network, and Korean Thyroid Association (KTA) have been published to help physicians make practical decisions regarding the optimal treatment of patients diagnosed with thyroid cancer.^[1–3] However, not every guideline is applicable to all patients and physicians. In addition, these guidelines do not accurately take into consideration the clinical environment or the status of an individual patient, including the patient's tumor progression history or socioeconomic status. Thus, physicians prefer to use them as a reference rather than a strict guide during the treatment of individual patients.

One representative issue contained in these guidelines is the management of micropapillary thyroid carcinoma (MPTC), which ranges from diagnosis to the extent of surgery required. The 2015 ATA guidelines recommended a more conservative approach compared with previous guidelines.^[2,4] For example, active surveillance was another option for patients with MPTC and indications for lobectomy were expanded.

The incidence of thyroid cancer in South Korea has increased more than 10-fold compared with that documented in other countries (52.8/100,000 vs 4.0/100,000).^[5] Many Korean physicians who manage patients with thyroid cancer follow the general guidelines suggested by either ATA or KTA. Because of recent concerns regarding overdiagnosis and overtreatment in patients with MPTC, requirements for ultrasound (US) and surgery have been questioned by the public. Here, we investigate current trends in the management of patients with MPTC

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undertaken by Korean thyroid-head and neck surgeons for the purpose of optimization. The survey used here was designed to collect information about diagnostic tests and treatments performed on patients with MPTC and to help identify current trends in thyroid surgery.

2. Methods

We developed questionnaires based on the controversial diagnostic and management methods currently used in patients with MPTC. Results from these questionnaires were used to identify factors that affected decisions regarding fine needle aspiration (FNA), type of surgery (lobectomy vs total thyroidectomy), and central lymph node dissection (CLND). The questionnaires were emailed to active members of the Korean Society of Thyroid-Head and Neck Surgery in September 2016. A total of 60 members participated in both the first and second surveys. Ethical approval by the institutional review board was waived because this study was a physician-based survey without the need for patient information.

3. Statistical analysis

Statistical analyses were performed using SPSS software version 20.0 (Chicago, IL). The χ^2 analysis was performed to analyze the relationship between the proportion of respondents who favored each diagnostic test and the treatment method. All reported *P* values are 2-sided.

4. Results

4.1. Demographics of the respondents

Most respondents worked in a referral or university hospital (n = 58), whereas only 2 respondents worked in a private clinic. Majority (82%) of the respondents had been performing thyroidectomy for more than 5 years, typically performing more than 10 thyroidectomies per year. Furthermore, 38% performed 100 thyroidectomies per year, whereas 64% reported performing >500 thyroidectomies during their careers (Table 1).

Table 1

Demographic data of the survey participants.

	No. (%)
Age, y	
<40	16 (26.7)
40–49	28 (46.7)
50–59	12 (20.0)
≥60	4 (6.7)
Number of cases of thyroidectomy per year	
10–99	37 (61.7)
100–299	18 (30.0)
≥300	5 (8.3)
Experience of thyroidectomy, y	
1–4	11 (18.3)
5–9	19 (31.7)
≥10	30 (50.0)
Experience of thyroidectomy (number of cases)	
<500	20 (33.3)
500–999	18 (30.0)
1000–1999	11 (18.3)
≥2000	11 (18.3)

4.2. Indications for US-guided FNA

We asked the survey respondents what the cutoff value was for US-guided FNA when a highly suspicious or benign thyroid nodule was found after US. Thyroid nodules that were hypoechoic (taller-than-wide) or had microcalcifications, irregular margins, or extrathyroidal extensions (ETEs) were defined as highly suspicious, whereas those with cystic lesions or a spongiform appearance were defined as benign.^[2,3] Most respondents reported initiating US-guided FNA for nodules at least 5 mm in size (60%) in the presence of malignant features (Fig. 1A). The preference for active surveillance over US-guided FNA for nodules <5 mm increased from 22% to 63% for nodules measuring ≥5 mm (*P* = .047). Respondents noted bimodal patterns for benign lesions, indicating that cutoff values for US-guided FNA were either ≥10 mm (43.3%) or ≥20 mm (45.0%) (Fig. 1B). All respondents preferred US-guided FNA for ETEs-positive nodules,

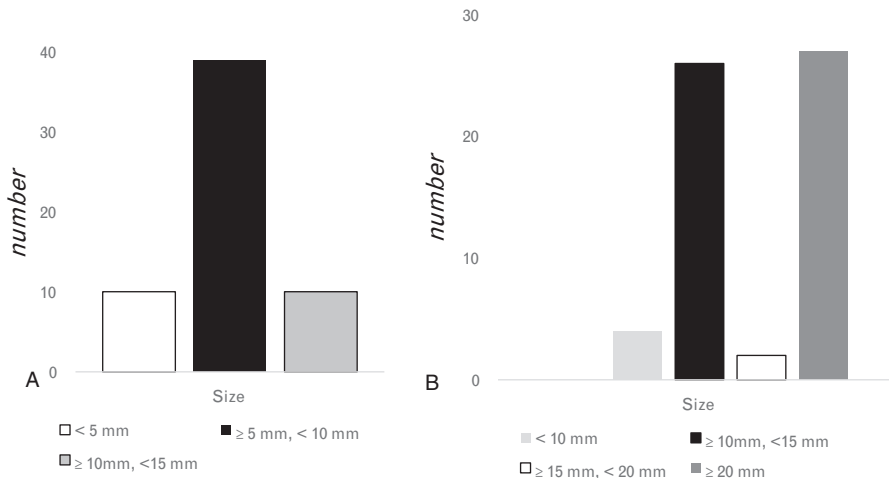


Figure 1. Size criteria for ultrasound-guided fine needle aspiration of a thyroid nodule. A=Nodule with malignant features, B=Nodule with benign features.

whereas 13 respondents (21.7%) preferred US-guided FNA for ETE-negative nodules, irrespective of patient age ($P < .05$).

4.3. Extent of surgery required

When asked about the specific management of patients with intraglandular MPTC, which include lesions measuring 7 mm without ETEs or lymph node metastasis after US in patients aged <45 years, most respondents (92%) preferred lobectomy, whereas only 8.2% preferred active surveillance (Fig. 2). Although no one chose total thyroidectomy in this case, increased rates of total thyroidectomy were seen in patients being treated for hypothyroidism (15%) or hyperthyroidism (62.7%). A *BRAF*-positive mutation identified in the tissue obtained by US-guided FNA was not a determining factor for total thyroidectomy. Moreover, 25% of the respondents preferred active surveillance for patients aged >45 years. Most respondents also preferred lobectomy (68.3%) in such patients, whereas only a few (7%) chose total thyroidectomy.

We next asked what impact ETE, which was detected using US, had on the extent of surgery required (Fig. 3). For MPTC lesions ≥ 5 mm, none of the respondents chose active surveillance as the primary therapy. Although no one chose total thyroidectomy as an initial surgical approach for this nodule without ETE, preference rates for total thyroidectomy increased to 50% when anterior ETE was found ($P < .05$). Posterolateral ETE increased the respondents' preference for total thyroidectomy (61.7%), For ETEs found in MPTC lesions <5 mm, only 2 respondents preferred active surveillance, whereas 70% and 26.7% chose lobectomy and total thyroidectomy, respectively.

When asked about CLND, respondents regarded the presence of ETE (73.3%) and its location (invading or abutting the

trachea, esophagus, or recurrent laryngeal nerve) (46.7%), which were detected either using preoperative US or at the operative field, as the main determining factors for performing prophylactic CLND (Table 2). Pathology-based indications for completion thyroidectomy following hemithyroidectomy were asked. Margin involvement (68.3%), macroscopic ETE (58.3%), and extranodal extension (56.7%) were the main determining factors (Table 3). Aggressive variants and multiple metastatic lymph nodes can also affect the selection of completion thyroidectomy.

Respondents were then asked about their preferred areas for lymph node dissection after metastatic lymph nodes were ascertained by US-guided FNA preoperatively. In cases involving a single metastatic lymph node at level III, levels IIb (28.3%) and V (58.3%) were included upon selective neck dissection (SND) (Table 4). SND at levels IIa, III, and IV or levels IIa, III, IV, and Vb was also favored (28.3% and 30%, respectively). However, in cases involving multiple metastatic lymph nodes at level III, inclusion rates of levels IIb (45%) and V (78.3%) were increased compared with those for single lateral lymph node metastasis. SND at levels IIa, III, VI, and Vb or levels II, III, IV, and V was also favored (26.7% and 23.3%, respectively).

4.4. Other analyses

Most respondents (88.3%) reported examining vocal cord motility both pre- and postoperatively. Approximately 50% of the respondents also reported performing voice tests, such as perceptual analyses and psychoacoustic tests. A transcervical approach, including transaxillary and retroauricular approaches, was more often favored (83.3%) than either an endoscopic or robotic approach. Except for 1, most surgeons preferred an energy device.

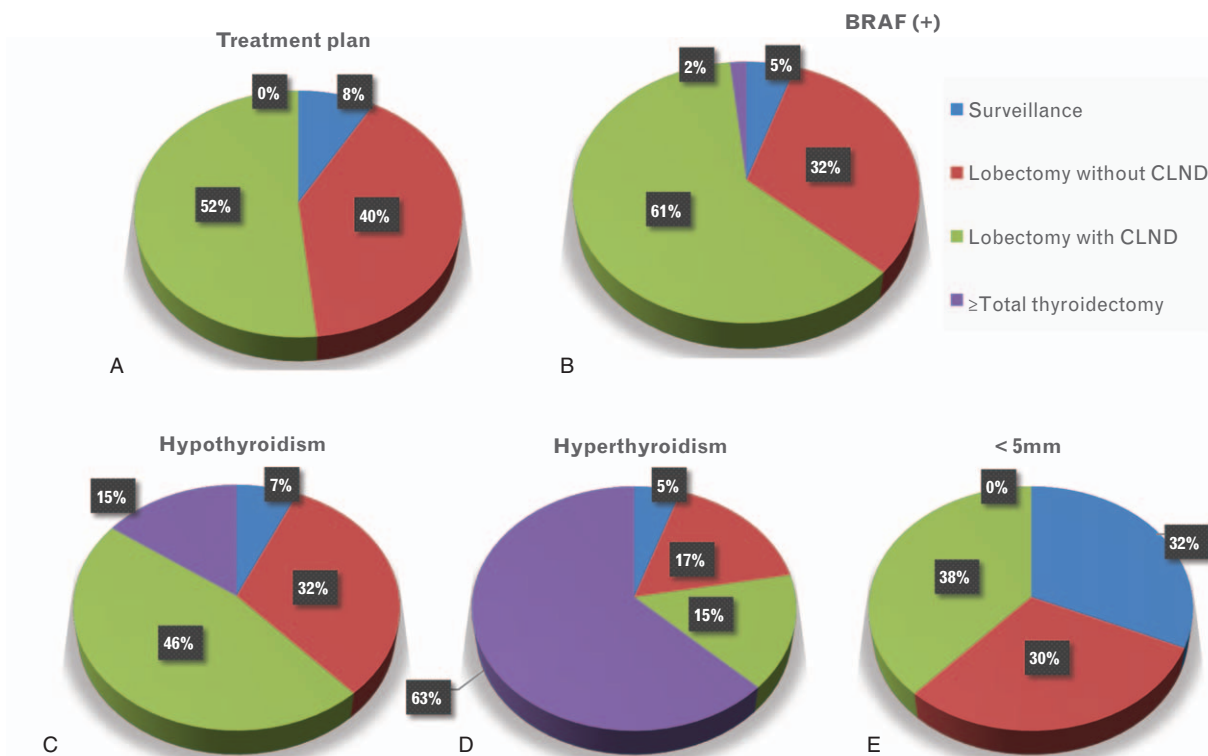


Figure 2. Treatment modality for micropapillary thyroid cancer of ≥ 5 mm in size. A, Treatments without a combined condition. B=BRAF (+), C=Hypothyroidism, D=Hyperthyroidism, E=Patients aged >45 years.

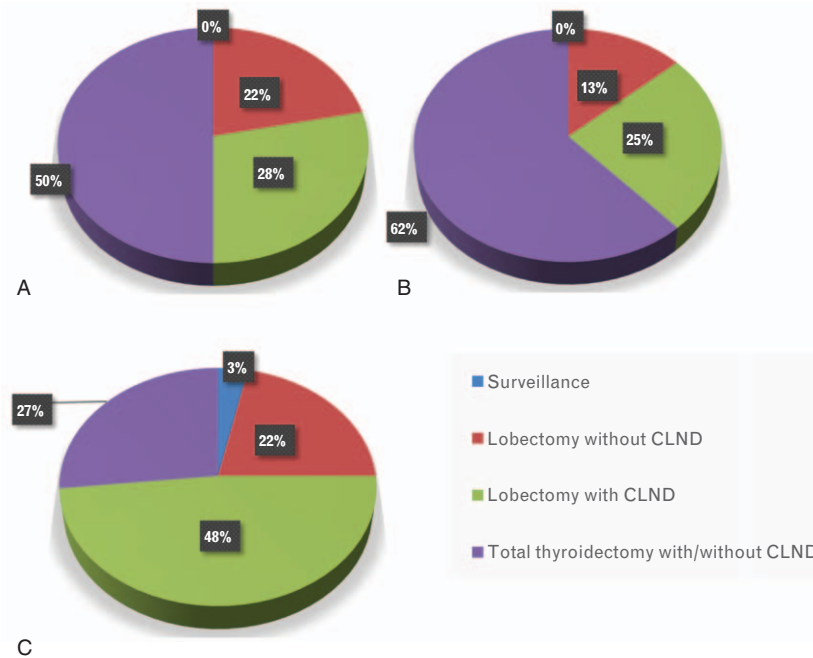


Figure 3. Treatment modality for micropapillary thyroid cancer with extrathyroidal extension. A=Anterior extension, B=Posterior extension, C=Tumors <5 mm.

5. Discussion

The management of MPTC is controversial, likely because of its excellent prognosis and slow growth rate. The present survey aimed to investigate current practices performed by active members of the Korean Society of Thyroid-Head and Neck Surgery after the 2015 ATA guidelines for differentiated thyroid cancer were published. We asked them regarding the establishment of diagnostic and therapeutic modalities according to preoperative US findings suggesting ETE and pathologically proven metastatic lymph nodes at the lateral compartment. Active surveillance emerged as a growing preference among these guidelines. Considering the cutoff size indications for the use of US-guided FNA, total thyroidectomy, and CLND, Korean members favored more active approaches for the management of MPTC contrary to what these guidelines suggest.

For highly suspicious nodules measuring at least 5 mm, respondents preferred US-guided FNA. This criterion was recommended by previous versions of the ATA and KTA guidelines,^[4,6] which were likely affected by the high prevalence of thyroid cancer in Korea and the development of high-resolution US.^[7,8] Some surgeons reportedly favor active surveillance for MPTC without ETEs, but they do not recommend neglecting MPTC-proven lesions.^[9,10] Thus, deciding to embark on either careful observation or lobectomy for MPTC lesions requires consideration of whether suspicious lesions require regular observation, generally after careful assessment through US screening. Considering that US-guided FNA is safer and more cost-effective than US alone,^[11] most surgeons prefer US-guided FNA over US alone.

In the Korean population, the detection rate of a *BRAF* mutation is approximately 70%, which is higher than that

Table 2
Indications for central lymph node dissection in micropapillary thyroid cancer.

Indications	No. (%)
Extrathyroidal extension on US	44 (73.3)
Location (trachea, esophagus, or recurrent laryngeal nerve)	28 (46.7)
Size, ≥5 mm	17 (28.3)
<i>BRAF</i> mutation	17 (28.3)
Isthmus	13 (21.7)
Age, ≥45 y	12 (20.0)
Ultrasound findings (echogenicity, calcification, or irregular margin)	11 (18.3)
Familial history	11 (18.3)
Contralateral benign lesions	8 (13.3)
Gender	7 (11.7)
Preservation of the ipsilateral parathyroid gland	5 (8.3)
Graves disease (hyperthyroidism)	4 (6.7)
Hashimoto thyroiditis (hypothyroidism)	1 (1.7)

Table 3
Indications for completion thyroidectomy in micropapillary thyroid cancer.

Indications	No. (%)
Margin involvement	41 (68.3)
Macroscopic extrathyroidal extension	35 (58.3)
Extranodal extension in metastatic lymph nodes	34 (56.7)
Variant type (follicular, solid, diffuse sclerosing, tall cell, columnar cell)	27 (45.0)
Number of metastatic lymph nodes ≥ 5	26 (43.3)
Number metastatic lymph nodes/whole dissected lymph nodes ≥ 0.5	18 (30)
Number of metastatic lymph nodes ≥ 3	17 (28.3)
Presence of metastatic lymph node	15 (25.0)
Multiple primary tumors	14 (23.3)
Number metastatic lymph nodes/whole dissected lymph nodes ≥ 0.4	13 (21.7)
Age ≥ 45	6 (10.0)
Microscopic extrathyroidal extension	5 (8.3)
Gender	2 (3.3)

Table 4
Extent of neck dissection for lateral cervical lymph node metastasis.

Levels of neck dissection	Number of metastatic lymph nodes	
	Single	Multiple
Berry picking	0	0
Levels III and IV	1	2
Levels IIa, III, and IV	17	6
Levels IIa, IIb, III, and IV	7	5
Levels IIa, III, IV, and Vb	18	16
Levels IIa, III, IV, Va, and Vb	7	10
Levels IIa, IIb, III, IV, and Vb	4	7
Levels IIa, IIb, III, IV, Va, and Vb	6	14

reported in Western countries (45%).^[12,13] Because of the high detection rate and slow growth of MPTC, the prognostic value of a *BRAF* mutation is unclear. Thus, many surgeons do not believe that a positive *BRAF* mutation is a factor that determines the extent of surgery required, which ranges from lobectomy to total thyroidectomy.^[12] However, other medical conditions that require treatment, such as hyperthyroidism and hypothyroidism, may increase the extent of surgery required. Recent guidelines on the management of MPTC with concomitant hyperthyroidism or hypothyroidism are unavailable. Hypothyroidism due to Hashimoto thyroiditis induces the autoimmune destruction of thyroid cancer cells and improves thyroid cancer prognosis.^[14,15] Based on these reports, we do not recommend expanding the surgical area for resection in such cases. Patients who underwent lobectomy were expected to have hypothyroidism and could not avoid thyroid hormone replacement therapy thereafter. Thus, the rate of preference for total thyroidectomy was increased. As the prognostic value of coexistent Graves disease is ambiguous, the extent of surgery required in such cases cannot be determined.^[16] Total or near-total thyroidectomy may negate the need for antithyroid hormone therapy, which would justify its use over confined thyroidectomy. Patient's quality of life following lobectomy versus that following total thyroidectomy for MPTC with concomitant hypothyroidism or hyperthyroidism should be evaluated in future studies.

The number of surgeons favoring active surveillance for proven MPTC has substantially increased after the new guideline was published. Active surveillance was introduced in the 2015 ATA and 2016 KTA guidelines because of the slow growth of MPTC.^[2,3] In this survey, the prerequisite for active MPTC surveillance was an intraparenchymal lesion without lymph node metastasis. The presence of a suspicious ETE increased the preference for surgical resection of the thyroid, either lobectomy or total thyroidectomy, with none of the respondents preferring active surveillance alone in such cases. These results imply that the presence of a macroscopic ETE has prognostic significance.^[17,18] According to the present survey, even a tumor <5 mm with ETE was an indication for surgery rather than active surveillance (3.3%). Had we emphasized cases with macroscopic ETEs in the questionnaire, the rate of total thyroidectomy would have increased. The presence of indicators for a T4a stage lesion, including invasion of the trachea, esophagus, or recurrent laryngeal nerve, increased the preference for total thyroidectomy. Surgical resection following adjuvant radioactive iodine ablation therapy is also anticipated in such cases, necessitating total thyroidectomy.

Convincing evidence of a preference for CLND in MPTC cases where no definite metastatic lymph nodes are present is not well established. The 2009 and 2015 ATA guidelines recommend CLND for patients with definitive N1a or N1b MPTC or cT3 or cT4 with ETE. Approximately 50% of the respondents favored routine CLND, regardless of the presence of ETE. However, the presence of ETE and its location might influence the preference for CLND in this survey. ETEs increase the rate of central lymph node metastasis,^[18,19] the prognostic value of which remains unclear. The risk for hypoparathyroidism following CLND is not higher than expected because it can be prevented by unilateral CLND, careful preservation of the vascular supply to the parathyroid gland, and autotransplantation.^[20,21] Definitive evidence for the prognostic benefit of elective CLND is currently lacking. However, low postoperative serum thyroglobulin levels after total thyroidectomy and reduced rate of repeated surgery are some of the benefits of CLND,^[22] although this survey showed mixed preferences for this approach among surgeons.

Improvements in diagnostic methods for detecting lateral lymph node metastasis are likely to determine the extent of therapeutic neck dissection required for a single metastatic lesion.^[23,24] The presence of multiple metastatic lymph nodes necessitates the expansion of the neck dissection area, unlike the presence of only a single metastatic lymph node. A level-IIb lesion can be contained when multiple metastatic lymph nodes, which are indicators of level-IIb metastasis, are detected. Approaches for a level-IIb lesion and comorbidity rates after comprehensive neck dissection were the primary considerations for the determination of the extent of neck dissection required. Because voice quality postoperatively cannot be overlooked, most head and neck surgeons favor laryngoscopic examination both pre- and postoperatively.

This study has some limitations. No individual preferences on diagnostic tests or the extent of surgery required were recorded. Thus, this study cannot suggest critical factors that could change a surgeon's preference for a particular MPTC treatment. This limitation can be overcome by establishing a hierarchy of indications for CLND. Because we surveyed surgeons' preferences in specific findings, we were unable to analyze the relationship between preoperative US or operative findings and histological results. The number of respondents was insufficient to determine the statistical power of the survey. Nevertheless, the survey results did suggest preferences for specific surgical treatments, which were dependent on clinical variables, such as the presence and location of ETE, central lymph node metastasis, and other environmental factors.

In conclusion, current guidelines regarding the diagnosis and treatment of patients with MPTC are more conservative than previous ones. In Korea, head and neck surgeons favored total thyroidectomy and CLND in cases wherein ETE, central lymph node metastasis, or critical organ involvement was suspected. These findings suggest that while the conservative approach for MPTC treatment is expanding, more aggressive treatments other than those recommended in the ATA or KTA guidelines still remain.

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