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ORIGINAL ARTICLE

Clinical impact of microscopic extrathyroidal extension in patients with papillary thyroid microcarcinoma treated with hemithyroidectomy

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Abstract
Background Pathologically confirmed microscopic extrathyroidal extension (ETE) is often identified after hemithyroidectomy in patients with papillary thyroid microcarcinoma (PTMC). Without the presence of microscopic ETE, these patients would be optimal candidates for hemithyroidectomy.
Aim The present study aimed at evaluating the clinical impact of microscopic ETE on the recurrence of PTMC treated with hemithyroidectomy.
Subjects and methods We compared the clinicopathological characteristics and 5-year outcomes for 262 PTMC patients without ETE and 86 with microscopic ETE who were treated with hemithyroidectomy between January 2004 and December 2010.
Results The mean tumour size was larger (0.67 vs. 0.54 cm, $p < 0.001$) and the proportion of tumours measuring ≥0.5 cm was higher (84.9 vs. 66.8 %, $p = 0.001$) in patients with microscopic ETE as compared with patients without ETE. Occult multifocal disease was more frequent in patients with microscopic ETE than in those without ETE (14.0 vs. 6.5 %, $p = 0.030$). However, the recurrence rate was not different between the two groups during the mean 55.8-month follow-up period. In addition, univariate and multivariate analyses revealed no meaningful association between recurrence and microscopic ETE in patients with PTMC treated with hemithyroidectomy.
Conclusions Although microscopic ETE was associated with large tumour size and multifocal disease, its clinical impact on disease recurrence was not significant in PTMC patients treated with hemithyroidectomy. Therefore, microscopic ETE identified after hemithyroidectomy would not be an absolute indication for completion thyroidectomy in patients with PTMC.

Keywords Papillary carcinoma · Extrathyroidal extension · Hemithyroidectomy · Recurrence

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Introduction

Extrathyroidal extension (ETE) is a well-established risk factor for poor outcomes in patients with papillary thyroid carcinoma (PTC) [1, 2]. Macroscopic or gross ETE, which is defined as gross tumour invasion identified at the time of surgery and confirmed by pathologic examination, is associated with a worse prognosis for the disease, including as a higher incidence of metastasis and recurrence [1, 3]. Therefore, total thyroidectomy with central neck dissection and subsequent radioactive iodine remnant ablation (RAI) is indicated in patients with macroscopic or gross ETE. Microscopic ETE is defined as tumour invasion beyond the thyroid capsule identified only at

pathologic examination. There has been considerable debate on whether PTC with microscopic ETE actually behaves more aggressively as compared with PTC without ETE [4]. Therefore, one of the major issues in the extent of treatment for PTC revolves around the role of microscopic ETE.

Several recent studies found that the presence of microscopic ETE had a less adverse effect than the presence of macroscopic ETE, or had no significance as an independent prognostic parameter [3–5]. However, in most previous studies, the extent of disease at the time of diagnosis (from single micro-PTC to PTC with lateral neck metastasis) and the spectrum of treatments used (from isthmusectomy alone to total thyroidectomy with comprehensive neck dissection and subsequent RAI) were too diverse, thereby introducing critical selection bias [2–5]. There are few studies in which patients and treatments were uniform enough to allow evaluation of absolute impact of microscopic ETE on prognosis, particularly in PTC treated with less-than-total thyroidectomy.

In the clinical practice, we often encounter pathologically confirmed microscopic ETE after hemithyroidectomy in patients with papillary thyroid microcarcinoma (PTC, size $\leq$1 cm, PTMC). Without the presence of the microscopic ETE, these patients would be optimal candidates for hemithyroidectomy. According to the seventh edition of the Tumour-Node-Metastasis system classification of the American Joint Committee of Cancer, the tumour stage of such cases is T3, and the patient would be a candidate for total thyroidectomy according to the American Thyroid Association guidelines revised in 2009. However, the surgeon cannot make a strong recommendation for it when the favourable prognosis of PTMC and the lifelong discomfort from thyroid hormone replacement therapy are considered [6, 7]. In our institution, completion thyroidectomy is not performed routinely in this circumstance. Instead, we aid patients in selecting their own further management after providing sufficient information on the advantages and disadvantages of either completion thyroidectomy with or without RAI, or a close follow-up plan without further surgery.

In this study, we hypothesised that the microscopic ETE detected after hemithyroidectomy in patients with PTMC has no clinical impact. To test this hypothesis, we compared the clinicopathological characteristics and recurrence patterns in patients with or without microscopic ETE who underwent only hemithyroidectomy for the treatment of PTMC. In addition, we performed univariate and multivariate analyses to test association between microscopic ETE and disease recurrence.

Materials and methods

Patients

We retrospectively reviewed the electronic database of the Department of Otorhinolaryngology-Head and Neck Surgery, Kyungpook National University Hospital, Daegu, Korea; the database was established upon inception of the Head and Neck Cancer Centre of our institution in 1997. Analysis of patient data revealed that 986 patients underwent thyroid surgery in a 7-year period between January 2004 and December 2010. We selected patients (1) who had pathologically confirmed conventional PTC of $\leq$1 cm in size (PTMC); (2) whose tumours were staged as N0 based on preoperative evaluations that included neck ultrasonography (US), computed tomography (CT), and/or positron emission tomography/CT (PET/CT) scans; (3) who underwent hemithyroidectomy alone for the initial treatment of PTMC; [4] who had regular follow-up more than 24 months after surgery; and (5) who had medical records and pathology slides that were available for review. Patients were excluded from this evaluation if they had a pathological diagnosis other than conventional PTMC (such as benign thyroid disease, any PTC variants, follicular thyroid carcinoma, medullary thyroid carcinoma, or anaplastic thyroid carcinoma) or underwent more than hemithyroidectomy (such as total/near-total thyroidectomy or total thyroidectomy with additional concomitant neck dissection). Patients who had PTC with macroscopic ETE were also excluded from this study regardless of tumour size, as total thyroidectomy with central neck dissection was performed for such cases. We did not perform routine central neck dissection in PTMC cases that were candidates for the hemithyroidectomy, unless there was evidence of central metastasis on preoperative imaging studies including US, CT, and/or PET/CT scans. CT and PET/CT scans are not routinely recommended preoperative imaging modalities for PTC. In South Korea, however, CT scans are usually performed in conjunction with US as important preoperative evaluations that increase the sensitivity of metastatic lymph nodes detection and identification of vascular anomalies such as retro-oesophageal subclavian arteries, which could indicate the presence of non-recurrent laryngeal nerves [8, 9]. Additional PET/CT scans are often performed to identify distant metastasis because our country's national insurance system provides 95 % of the costs of CT and PET/CT scans for cancer patients.

From the initial cohort of 986 patients, 348 met the inclusion criteria and were enrolled in the present study. The cohort of 348 patients comprised 40 men (14.7 %) and 308 women (85.3 %) with a mean age of 46.8 $\pm$ 11.2 years at the time of surgery. The mean tumour size was 0.57 $\pm$ 0.21 cm, and the mean follow-up period was

55.8 ± 18.5 months. Among these patients, 86 had microscopic ETE and 262 patients did not.

Review of histopathological parameters

The histopathological parameters of each patient's tumour were determined by one co-author specialised in thyroid pathology (J.Y. Jeong). Serial 2-mm sections were prepared from the pathologic specimens. All slides were reviewed for primary tumour size; presence of occult multifocal disease (defined as additional PTC tumour, which was detected during the pathologic examination of the hemithyroidectomy specimen); microscopic ETE; and coexisting Hashimoto's thyroiditis (HT).

Follow-up strategy

During the follow-up period, all patients received regular physical examinations every 3–6 months and plain chest radiographs, once a year. Routine neck US and PET/CT scan were scheduled at 6- and 12-month intervals, respectively. When suspicious recurrent lesions were identified by imaging studies, we performed fine needle aspiration cytology and surgery to remove and confirm the disease. A thyroid function test was also performed every 6 months to detect hypothyroidism. Routine thyroxine administration was not used to suppress thyrotropin levels in patients with PTMC who underwent hemithyroidectomy, regardless of microscopic ETE. However, if hypothyroidism developed during the follow-up period, adequate doses of thyroxine were administered to maintain thyrotropin levels within the normal range.

Statistical analyses

SPSS for Windows (version 12.0; SPSS, Chicago, IL, USA) was used to analyse the data. Continuous data are presented as mean ± standard deviation. To test for differences between groups of continuous variables of age, tumour size, and follow-up period, an independent Student's t test was used. To assess the association of the microscopic and prognostic variables [age ≥45 years, sex, primary tumour size ≥0.5 cm (diameter), occult multifocality, and concurrent HT] with outcomes, Chi-square test or Fisher's exact test was used. Multivariate analysis was performed using binary logistic regression to assess the impact of the variables on the risk for recurrence. Results are presented as the odds ratio (OR) with a 95 % confidence interval (CI) and p value. The Kaplan–Meier method with a log-rank test was used to determine differences in disease-free survival probabilities between the groups during the follow-up period. Statistical significance was defined as $p < 0.05$ and all p values were two-sided throughout.

Table 1 Clinicopathological features of the 348 patients according to the presence of microscopic extrathyroidal extension (ETE)

	Without ETE ($n = 262$)	With microscopic ETE ($n = 86$)	p value
Age (years)	46.3 ± 11.6	48.4 ± 10.5	0.138
≥45	146 (55.7 %)	57 (66.3 %)	0.085
Sex (male:female)	30:232	10:76	0.964
Primary tumour size (cm)	0.54 ± 0.21	0.67 ± 0.20	<0.001*
≥0.5	175 (66.8 %)	73 (84.9 %)	0.001*
Occult multifocal disease	17 (6.5 %)	12 (14.0 %)	0.030*
Concurrent Hashimoto's thyroiditis	74 (28.2 %)	13 (15.1 %)	0.015*

* Statistically significant

Results

Clinicopathological features according to the presence of microscopic ETE

The clinicopathological features of the 262 patients without ETE and the 86 patients with microscopic ETE are listed in Table 1. The patients with microscopic ETE were slightly older (48.4 vs. 46.3 years, $p = 0.138$) with higher proportion of patients aged ≥45 year as compared to those without ETE (66.3 vs. 55.7 %, $p = 0.085$). However, these differences were not statistically significant. The ratio of men to women was also not significantly different between the two groups ($p = 0.964$).

The mean tumour size was larger (0.67 vs. 0.54 cm, $p < 0.001$) and the proportion of tumours ≥0.5 cm in size was higher (84.9 vs. 66.8 %, $p = 0.001$) in patients with microscopic ETE as compared to those without ETE. Occult multifocal disease was more frequently found in patients with microscopic ETE as compared to those without ETE (14.0 vs. 6.5 %, $p = 0.030$), and concurrent HT was observed less frequently in patients with microscopic ETE (15.1 vs. 28.2 %, $p = 0.015$). All the above-mentioned differences were statistically significant.

Recurrence according to the presence of microscopic ETE

During the mean 55.8-month follow-up period (55.4 months for patients without ETE and 57.0 months for patients with microscopic ETE, $p = 0.503$), 17 of 348

Table 2 Clinicopathological features of the 348 patients according to the presence of recurrence

	Recurrence ($n = 331$)	No recurrence ($n = 17$)	p value
Age (years)	46.8 ± 11.5	47.5 ± 7.1	0.782
≥45	193 (58.3 %)	10 (58.8 %)	0.966
Sex (male:female)	40:291	0:17	0.237
Primary tumour size (cm)	0.57 ± 0.21	0.56 ± 0.16	0.781
≥0.5	235 (71.0 %)	13 (76.5 %)	0.787
Occult multifocal disease	26 (7.9 %)	3 (17.6 %)	0.160
Concurrent Hashimoto's thyroiditis	82 (24.8 %)	5 (29.4 %)	0.774

Table 3 Recurrence according to the presence of microscopic extrathyroidal extension (ETE)

	Without ETE ($n = 262$)	With microscopic ETE ($n = 86$)	p value
Mean follow-up (months)	55.4 ± 18.7	57.0 ± 18.0	0.503
Recurrence	11 (4.2 %)	6 (7.0 %)	0.385
Involving contralateral thyroid gland	9 (81.8 %)[a]	4 (66.7 %)[a]	0.584
Involving ipsilateral central neck	1 (9.1 %)[a]	3 (50.0 %)[a]	0.099
Involving ipsilateral lateral neck	2 (18.2 %)[a]	2 (33.3 %)[a]	0.584
Death	1 (0.4 %)	1 (1.2 %)	0.434
Disease specific	0 (0.0 %)	0 (0.0 %)	–

[a] Denominators were patient number with recurrence in each group (11 in the no-ETE group and 6 in the microscopic ETE group)

patients experienced recurrence, representing an overall recurrence rate of 4.9 %. The clinicopathological features of the 331 patients without recurrences and the 17 patients with recurrences are listed in Table 2. There were no significant differences according to the recurrence status.

Among patients experiencing recurrence, 11 (4.2 %) did not have ETE and 6 (7.0 %) had microscopic ETE ($p = 0.385$). Comparing the detailed recurrence patterns between the two groups (Table 3), we found that among all recurrent tumours, the proportion of recurrence involving contralateral thyroid gland was higher in patients without ETE than in those with microscopic ETE (81.8 vs. 66.7 %, $p = 0.584$). The proportion of recurrent tumours involving the central and lateral neck was higher in patients with microscopic ETE than in patients without ETE (50.0 vs. 9.1 %, $p = 0.099$ and 33.3 vs. 18.2 %, $p = 0.584$, respectively). However, these differences were not

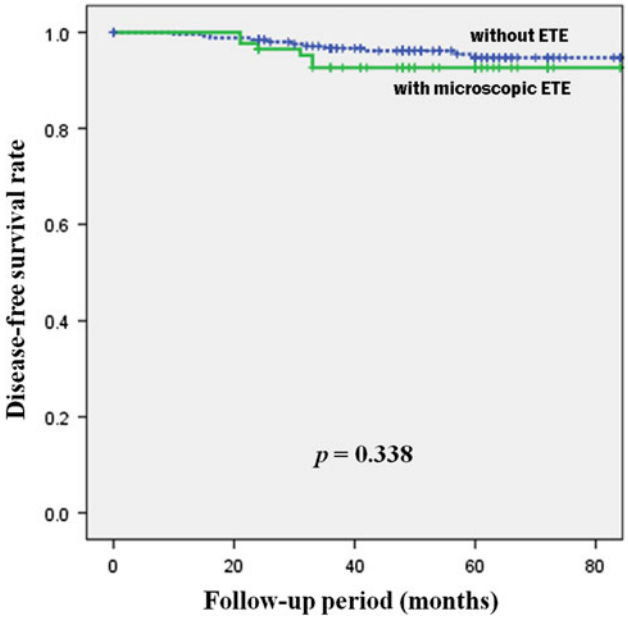

Fig. 1 Kaplan–Meier curves for disease-free survival according to the presence of microscopic extrathyroidal extension

statistically significant. The 5-year disease-free survival, analysed using the Kaplan–Meier method, was found to be comparable in patients without ETE and those with microscopic ETE (94.7 vs. 92.7 %; $p = 0.338$) (Fig. 1).

Mortality occurred in 2 (0.6 %) patients during the follow-up period: 1 (0.4 %) patient without ETE and 1 (1.2 %) patient with microscopic ETE died of causes not related to thyroid cancer.

Univariate and multivariate analyses for association of microscopic ETE with recurrence

The results of the univariate and multivariate analyses for the association of clinicopathological variables with disease recurrence are stated in Table 4. None of the variables tested, i.e. age ≥45 years, male gender, tumour size ≥0.5 cm, occult multifocal disease, or concurrent HT, were correlated with recurrence after hemithyroidectomy in patients with PTMC. Although patients with PTMC with microscopic ETE were 1.7 times more likely to develop recurrence than those without ETE (OR = 1.67; 95 % CI, 0.57 –4.91), this finding had no statistical significance.

Discussion

The reported incidence of ETE in PTMC varies, ranging from 4.5 to 31.9 % [5, 10, 11]. In the study that included only the minimal or microscopic ETE of PTMC, the

Table 4 Univariate and multivariate analyses for association of several clinicopathological features and disease recurrence

	Univariate	Multivariate	Odds ratio	Confidence interval 95 %
Age ≥45 years	0.966	0.888	0.930	0.337–2.563
Male gender	0.237	0.998	<0.001	–
Tumour size ≥0.5 cm	0.787	0.888	1.088	0.334–3.543
Occult multifocal disease	0.160	0.177	2.516	0.659–9.608
Concurrence HT	0.774	0.724	1.221	0.403–3.697
Microscopic ETE	0.385	0.349	1.672	0.570–4.910

HT Hashimoto's thyroiditis, *ETE* extrathyroidal extension

incidence was approximately 30 %, which was comparable to the 24.8 % (86/262) in our study [5, 12]. This suggests that microscopic ETE is not uncommon, even in PTMC. However, the clinical implications of microscopic ETE in PTMC are controversial. There are few studies on whether microscopic ETE found after hemithyroidectomy is associated with a poor prognosis and should be an indication for total thyroidectomy, even in PTMC cases.

In this study, microscopic ETE was associated with a larger primary tumour size and a higher incidence of occult multifocal disease. However, the results that microscopic ETE is associated with several poor prognostic parameters should be separated from the hypothesis that microscopic ETE plays independent role on prognosis of PTC, particularly in PTMC. The overall recurrence rate was not different between the two groups in our study (4.2 % in the group without ETE vs. 7.0 % in the group with microscopic ETE). The univariate and multivariate analyses revealed no meaningful association between recurrence and microscopic ETE in patients with PTMC treated with hemithyroidectomy. In addition, interestingly, the proportion of local recurrence involving the contralateral thyroid gland was higher in patients without ETE than in patients with microscopic ETE, although the significance of this finding was not verified. These results raise the question of whether further management, such as completion thyroidectomy with or without subsequent RAI ablation, should be recommended for PTMC patients who had microscopic ETE at the pathological examination after hemithyroidectomy.

Furthermore, the overall recurrence rate of PTC after less-than-total thyroidectomy (lobectomy or hemithyroidectomy) was reported to be 4.4–14.3 % during a 4- to 10-year follow-up period, which is comparable to the rate noted in the present study [4.9 % (17/348) during about 5 years of follow-up] [13–16]. Even in patients with microscopic ETE, the 5-year disease-free survival was 92.7 % in our population. Considering this recurrence rate, total thyroidectomy might be unnecessary in more than 90 % of PTMC patients, regardless of the presence of microscopic ETE.

Recently, in addition to the debates concerning ETE, some studies recommended total thyroidectomy rather than hemithyroidectomy even in PTMC patients with tumours ≥0.5 cm in size or intrathyroidal multifocal disease [13, 16, 17]. However, a primary tumour size ≥0.5 cm and occult multifocality were not associated with recurrence after hemithyroidectomy in the present study. Concurrent HT was less frequently observed in patients with microscopic ETE. This result is in accordance with recent reports that evaluated the relationships between HT and PTC, and suggested that HT was related to a better prognosis of PTC, with the assumption that ETE is associated with worse prognosis [18, 19]. However, the clinical impact of concurrent HT and microscopic ETE on recurrence was not verified in either the univariate or multivariate analyses in the present study. Therefore, although microscopic ETE was associated with parameters such as tumour size, multifocality, and HT, the results suggest that hemithyroidectomy is sufficient extent of surgery to control nearly all PTMCs, even if they are subclassified according to the minor criteria for risk stratification.

In the present study, routine thyroxine administration was not used to suppress thyrotropin levels. Although the guidelines issued by the thyroid associations of Europe and the United States recommend thyrotropin suppression therapy after initial surgical treatment for PTC, there is a lack of clear evidence derived from randomised control studies on the benefits of thyrotropin suppression therapy, particularly in low-risk patients [7, 20, 21]. The only randomised prospective study was published in 2010 by Sugitani et al. [22.]. The authors randomised 400 patients who were undergoing surgery for PTC into either a group treated with thyroxine to achieve thyrotropin suppression or a group treated to maintain thyrotropin levels within the normal range, which was the same policy used in our study population. The authors found that after a mean follow-up period of 7 years, there were no significant differences between the two groups with regard to the disease-free duration, relapse, time of relapse, distant metastases, overall mortality, or specific mortality. In addition to the lack of evidence for its effects, thyrotropin suppression therapy is not without risk. The long-term administration of supraphysiologic doses of thyroxine could induce serious side effects, including thyrotoxicosis, osteoporosis, angina, and arrhythmia [23]. Moreover, a recent review noted that thyroid hormone supplementation could increase the incidence of kidney, pancreas, ovarian, and breast cancers [24–26]. Therefore, we believe that the absolute benefits of

thyrotropin suppression therapy are questionable, considering that a recent randomised study failed to reveal any effects of thyrotropin suppression therapy in addition to the possible risk of other cancer developments.

The present study has some limitations. First, in patients with PTMC and microscopic ETE, we did not compare factors between those who underwent hemithyroidectomy alone with those who underwent completion thyroidectomy to evaluate benefits of total thyroidectomy. Second, the approximately 56 months of follow-up is not sufficient to evaluate survival. This is because we do not recommend regular follow-ups beyond 5 years to patients with PTMC who undergo hemithyroidectomy, unless they experience recurrences during the follow-up period. Despite these limitations, the strength of this study is that we used a homogeneous population with respect to both tumour characteristics and treatment. In addition, we believe that 56 months of follow-up is sufficient to evaluate recurrence, although it is not sufficient to evaluate survival. However, it would be judicious to propose a longer and more meticulous follow-up strategy for patients with PTMC and microscopic ETE, given the results that microscopic ETE was associated with a larger tumour size, occult multifocal disease, and a relatively higher incidence of nodal recurrence.

In conclusion, although microscopic ETE was associated with larger tumour size and occult multifocal disease, its clinical impact on disease recurrence was not significant in PTMC patients treated with hemithyroidectomy. Therefore, microscopic ETE, when identified during the pathological examination after hemithyroidectomy in patients with PTMC, would not be an absolute indication for total thyroidectomy, and a close follow-up plan without further surgery could be an alternative option with regard to the patient's preference.

Conflict of interest The authors D. Ahn, J.H. Sohn, J.H. Jeon, and J.Y. Jeong declare that they have no conflicts of interest.

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