

The Clinical Importance of Minimal Extrathyroid Extension on Tumor Recurrence in Patients with Papillary Thyroid Carcinoma

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Background: We wanted to evaluate whether a minimal extrathyroid extension (METE) is associated with the clinicopathological parameters that are indicative of a poor prognosis, including lymph node metastasis, distant metastasis at the time of the initial diagnosis and tumor recurrence, in patients with papillary thyroid carcinoma (PTC), and especially in the patients with papillary thyroid microcarcinoma (PTMC).

Methods: We retrospectively evaluated the medical records of patients with PTC and who had undergone total thyroidectomy with/without subsequent ¹³¹I remnant ablation at the Korea Cancer Center Hospital from January 1998 through December 2005. A total of 557 patients with PTC were enrolled in the study. We excluded 13 patients with an unknown status of extension and 29 patients with massive ETE.

Results: Of the 515 patients, 401 were found to have a METE. We analyzed the 464 patients who were without distant metastasis at the time of the initial diagnosis and who had a follow-up duration of more than 6 months. METE was not significantly associated with tumor recurrence during the follow-up period (median follow-up period: 122 months, range: 6–142 months): 8% vs. 15% of the patients with and without METE had tumor recurrence, respectively ($P = 0.069$ by the log-rank test). We analyzed the effect of tumor size in the patients with METE. Size was not significantly associated with tumor recurrence ($P = 0.374$ by the log-rank test).

Conclusion: These findings suggest that METE might not be a prognostic factor to predict tumor recurrence in patients with PTC, including PTMC. (*Endocrinol Metab* 25:340-346, 2010)

Key Words: Extrathyroid extension, Papillary thyroid carcinoma, T3

INTRODUCTION

Extrathyroid extension (ETE) is defined as an extension of the primary tumor beyond the thyroid capsule and invasion into the surrounding structures (e.g., the strap muscles, trachea, larynx, vasculature, esophagus and recurrent laryngeal nerve) [1,2]. Massive ETE is defined as tumor extension beyond the thyroid capsule to invade the subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve, and tumor of any size with massive ETE is classified as T4a according to the 7th edition of the International Union Against Cancer TNM Classification (2010 TNM staging) [3]. Minimal ETE (METE) is defined as tumor extension to the

sternothyroid muscle or perithyroid soft tissues and any tumor with METE is classified as T3 according to the 2010 TNM staging.

Extrathyroid extension is well established as an important adverse prognostic factor for patients with papillary thyroid carcinoma (PTC) [1,2,4-7]. ETE is associated with high mortality [1,2,4-7] as well as with high tumor recurrence [1,2,6,7] in patients with PTC. Yet it is unclear that METE is associated with a poor prognosis, including increased mortality and recurrence in patients with PTC [8-12], and especially for patients with papillary thyroid microcarcinoma (PTMC) [10,13-19].

Despite of this uncertainty of the prognostic effect of METE, the presence of METE, regardless of tumor size, is classified as T3 and at least stage III (in patients older than 45 years) according to the 2010 TNM staging system, which mandates aggressive operations, including total thyroidectomy and lymph node dissection, in conjunction with adjuvant radioactive iodine therapy [20,21].

The aims of this study were to evaluate whether METE is associ-

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ated with clinicopathological parameters that are indicative of a poor prognosis such as lymph node metastasis, distant metastasis at the time of initial diagnosis and tumor recurrence in patients with PTC, and especially in patients with PTMC.

SUBJECTS AND METHODS

Subjects

We studied all the patients with PTC who underwent near-total or total thyroidectomy with lymph node dissection with/without subsequent ^{131}I remnant ablation treatment at Korea Cancer Center Hospital, Korea Institute of Radiological & Medical Sciences, Seoul, Korea from January 1998 through December 2005. Distant metastasis was confirmed by histological or cytopathological evidence of abnormal tissue and/or a positive signal on ^{131}I whole-body scan. Patients were selected for the study if their resected thyroid glands were available for further gross and histological examinations after being divided into 1-cm sections.

Patients' clinicopathological parameters

We retrospectively reviewed the medical records of the subjects. A detailed pathological report was available, including information about the maximal tumor diameter, ETE, multifocality and lymph node metastasis. The demographics (age and gender), histopathological findings and clinical outcomes (distant metastasis and recurrence) were analyzed.

The central cervical lymph nodes were defined as lymph nodes of Level VI (i.e., the pretracheal, paratracheal and prelaryngeal/Delphian lymph nodes) and these nodes were classified as N1a according to the 2010 TNM staging system. Lateral cervical lymph nodes were defined as unilateral, bilateral, contralateral cervical or superior mediastinal lymph nodes, and these nodes were classified as N1b according to the 2010 TNM staging system.

We identified the patients with METE based on the pathological findings as well as intraoperative surgical findings, and the patients with tumor equal or less than 1.0 cm were classified as having PTMC based on the pathological findings.

Follow-up protocol & definition of recurrence

Physical examination and chest radiography were regularly performed on all the patients. A diagnostic ^{131}I whole-body scan (WBS) was routinely scheduled every 1–2 years after surgery and ^{131}I ablation treatment was done. Serum thyroglobulin measurements, anti-

thyroglobulin antibody assays and thyroid-stimulating hormone (TSH) measurements were done at the time of each WBS. When the clinical or biochemical data suggested recurrence, the normal and/or malignant thyroid tissue was localized by non-radioiodine imaging methods, including neck ultrasonography, ^{18}F -deoxyglucose positron emission tomography or chest computerized tomography.

Recurrence was defined as the reappearance of disease after complete ablation of the post-surgical thyroid remnants, and this was confirmed by cytological and/or histopathological examination or by the post-treatment ^{131}I WBS showing persistently definite ^{131}I uptake outside of the thyroid bed. Patients with distant metastasis at the time of the initial diagnosis were excluded from the analysis of recurrence.

Statistics

The categorical variables are presented as numbers and percentages, and they were compared using the chi-square test or Fisher's exact test. Continuous variables are presented as means \pm standard deviations and the range. Binary logistic regression analysis was used to assess the relationship between minimal extrathyroid extension and other possible prognostic factors. The Kaplan-Meier method, including the log-rank test, was used to compare recurrence. The endpoints for the analysis of disease-free survival included any relapse of PTC. Cox's proportional hazard model and the forward stepwise method were used to analyze the relative importance of the various prognostic factors for postoperative survival and recurrence. The possible prognostic factors analyzed included age, gender and the absence or presence of cervical lymph node metastasis. *P* values < 0.05 were considered significant. All the statistical analyses were performed using SPSS for Windows (version 14.0; SPSS, Chicago, IL, USA).

RESULTS

Clinicopathological characteristics

A total of 557 patients with PTC who underwent near-total or total thyroidectomy with lymph node dissection followed by subsequent ^{131}I remnant ablation treatment were identified at the Korea Cancer Center Hospital. We excluded 13 patients who had an unknown status of extension and 29 patients with massive ETE. Of the 515 patients, 114 patients had no METE (METE-) and the remaining 401 patients had METE (METE+). The prevalence of METE

was approximately 78% in our study. There was no significant difference in age (45 ± 12 vs. 47 ± 13 , $P = 0.057$) and gender between the METE- and METE+ groups.

There was a statistically significant difference in tumor size between the METE- and METE+ groups (1.5 ± 1.3 cm vs. 2.2 ± 1.5 cm, respectively, $P < 0.001$). There were multifocal tumors in 46% of the METE- group and in 48% of the METE+ group, and this showed no statistically significant difference. Lymph node metastasis was seen in 64% of the METE- group and in 77% of the METE+ group. Central cervical lymph node metastasis was shown in 40% of the METE- group and in 42% of the METE+ group. Lateral cervical lymph node metastasis was shown in 24% of the METE- group and in 35% of the METE+ group. There was a significant difference in the incidence of cervical lymph node metastasis between the METE- and METE+ groups ($P = 0.015$). There was no significant difference in the incidence of distant metastasis at the time of initial diagnosis (2% vs. 6%, respectively, $P = 0.059$) and ^{131}I remnant ablation therapy between the METE- and METE+ groups (Table 1).

Multivariate analysis was used to test the independence of asso-

Table 1. The clinicopathological characteristics according to the presence of minimal extrathyroid extension

Clinicopathological parameters	METE- (n = 114)	METE+ (n = 401)	P-value
Age (years)	45 ± 12	47 ± 13	0.057 [†]
Gender (M:F)	16:98	81:320	0.174 [§]
Size (cm)	1.5 ± 1.3	2.2 ± 1.5	<0.001
Lymph node metastasis			0.015
No metastasis	41 (36)	93 (23)	
Metastasis to central cervical lymph node*	45 (40)	168 (42)	
Metastasis to lateral cervical lymph node [†]	28 (24)	140 (35)	
Distant metastasis			0.059 [§]
Absent	112 (98)	376 (94)	
Present	2 (2)	25 (6)	
^{131}I Remnant ablation			0.057 [§]
No	11 (10)	20 (5)	
Yes	103 (90)	381 (95)	

Percentages are given in the parentheses.

*Central cervical lymph nodes are defined as lymph nodes of level VI (i.e., the pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes), and these are classified as N1a in 2010 TNM staging.

[†]Lateral cervical lymph nodes are defined as unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes, and these are classified as N1b according to the 2010 TNM staging system.

[‡]by Student's *t*-test

[§]by Fisher's exact test.

METE, minimal extrathyroid extension.

ciations between METE and various clinicopathological parameters showing statistical significance ($P < 0.1$) with univariate analysis (age, tumor size, lymph node metastasis, distant metastasis and ^{131}I remnant ablation therapy). The association between METE and age ($P = 0.048$), tumor size ($P < 0.001$) and ^{131}I remnant ablation therapy ($P = 0.026$) remained significant with multivariate analysis after controlling for clinicopathological parameters. However, the association between METE with cervical lymph node metastasis or distant metastasis disappeared with multivariate analysis (Table 2).

Recurrence and disease-free survival

We excluded the patients who had distant metastasis at the time of the initial diagnosis and the patients with a follow-up duration less than 6 months. Of the 464 patients, 64 (14%) experienced recurrence during the observation period. METE was shown to not be significantly associated with tumor recurrence during the follow-up period (median: 122 months, range: 6–142 months): 8% (9 patients) of the METE- group had tumor recurrence during the follow-up period compared with 15% (55 patients) of the METE+ group ($P = 0.069$ by the log-rank test; Fig. 1).

Tumor equal to or larger than 4 cm is classified as T3 and at least stage III (in patients older than 45 years) according to the 2010 TNM staging system, and tumor with METE is classified as the same. To exclude the effect of size, we re-analyzed tumor recurrence in the 429 patients with tumor smaller than 4 cm. METE was not shown to be significantly associated with tumor recurrence during the follow-up period (median follow up period: 123 months, range: 6–142 months): 8% (8 patients) of the METE- group had tumor recurrence during the follow-up period compared with 15% (48 patients) of the METE+ group ($P = 0.087$ by the log-rank test; Fig. 2). One hundred twenty one patients with PTMC showed the same results ($P = 0.303$ by the log-rank test; Fig. 3).

Table 2. Multivariate analysis of the associations between minimal extrathyroid extension and various clinicopathological parameters

Clinicopathological parameters	Minimal extrathyroid extension		
	Hazard ratio	95% CI	P-value
Age (years)	1.018	(1.000-1.036)	0.028
Tumor size (cm)	1.642	(1.319-2.045)	<0.001
Lymph node metastasis		N.I.	0.074
Distant metastasis		N.I.	0.114
^{131}I Remnant ablation	2.529	1.119-5.714	0.026

Statistical analysis performed by binary logistic regression analysis.

CI, confidence interval; N.I., not included.

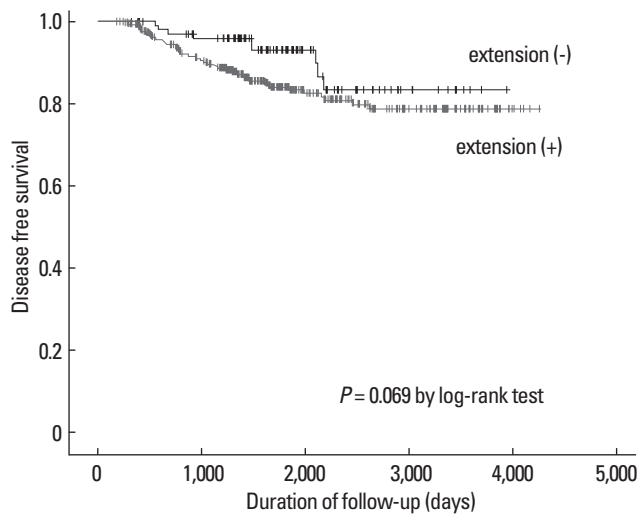


Fig. 1. Disease-free survival according to extrathyroid extension in 464 patients who were without distant metastasis at the time of the initial diagnosis. The Kaplan-Meier method for recurrence with the log rank test was used for statistical comparisons.

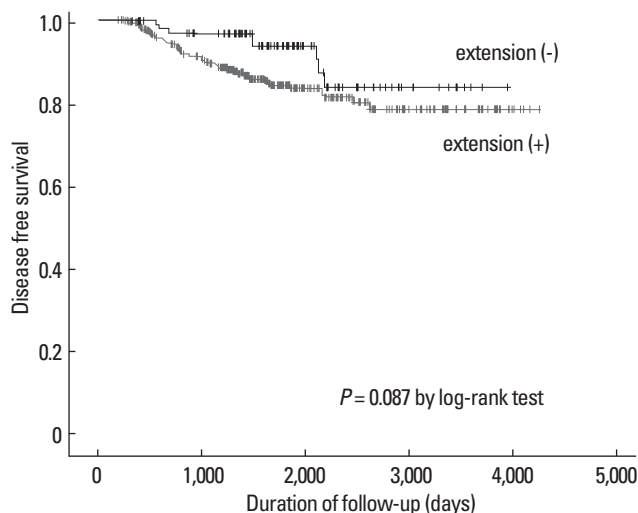


Fig. 2. Disease-free survival according to extrathyroid extension in the 429 patients with tumor smaller than 4 cm and without distant metastasis at the time of the initial diagnosis. The Kaplan-Meier method for recurrence with the log rank test was used for statistical comparisons.

The effect of tumor size in the patients with METE

If METE is not a prognostic factor, then the effect of size will be prominent in patients with tumor with METE. So, we analyzed the patients with tumor with METE. According to the reason described above, we included 401 patients with METE. Seventy four patients had tumors equal to or smaller than 1 cm (the small group), 286 patients had tumors 1-4 cm (the intermediate group) and the remaining 41 patients had tumors larger than 4 cm (the large group). There was no statistically significant difference of age, gender and

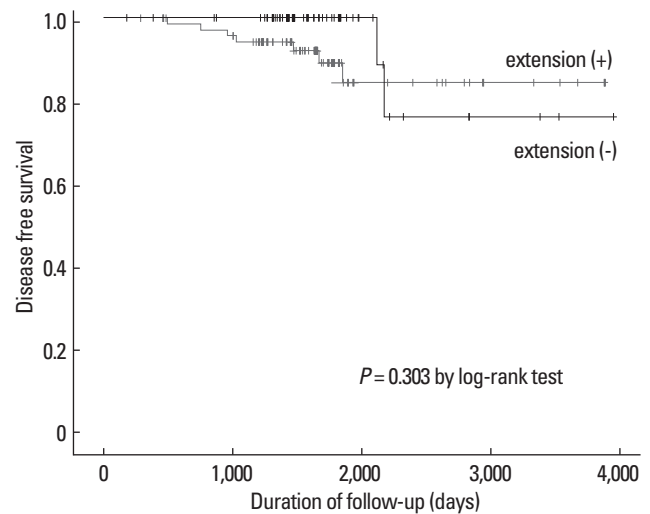


Fig. 3. Disease-free survival according to extrathyroid extension in the 121 patients with papillary thyroid microcarcinoma and without distant metastasis at the time of the initial diagnosis. The Kaplan-Meier method for recurrence with the log rank test was used for statistical comparisons.

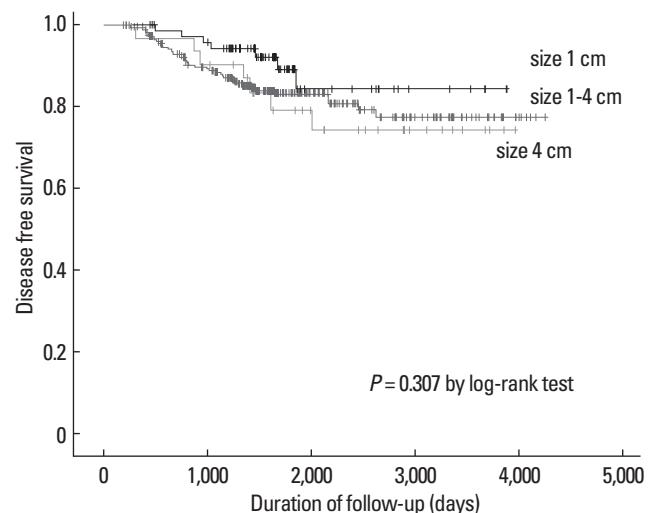


Fig. 4. Disease-free survival according to tumor size in the 358 patients with tumor with minimal extrathyroid extension and without distant metastasis at the time of the initial diagnosis. The Kaplan-Meier method for recurrence with the log rank test was used for statistical comparisons.

the incidence of distant metastasis at the time of the initial diagnosis among the groups (data not shown). However, multifocality ($P = 0.013$) and lymph node metastasis ($P < 0.001$) were significantly different among the 3 groups. To analyze tumor recurrence, we excluded the patients with distant metastasis at the time of the initial diagnosis and also the patients with a follow-up duration less than 6 months. Of the 358 patients, 55 (15%) had experienced recurrence during the observation period. According to an increase of size, we observed the trend of increasing tumor recurrence. How-

ever, there was no significant association between tumor size and tumor recurrence during the follow-up period (median follow-up period: 121 months, range: 6–141 months): 9% (7 patients) of the small group, 16% (41 patients) of the intermediate group and 23% (7 patients) of the large group ($P = 0.307$ by the log-rank test; Fig. 4).

DISCUSSION

In this study, we evaluated the clinical importance of METE on tumor recurrence in PTC patients. We found that METE was not associated with the clinicopathological parameters that were indicative of a poor prognosis such as lymph node metastasis, distant metastasis at the time of the initial diagnosis and tumor recurrence in patients with PTC and PTMC.

The presence of ETE is directly related to the appropriate surgical intervention, a high incidence of local recurrence and high mortality in patients with PTC [1,2,4-7]. Most authors who reported ETE was a prognostic factor for patients with PTC did not consider differences in the degree of extension [1,2,4-7]. Some authors have reported that gross METE was associated with a poor prognosis, such as high recurrence, in patients with PTC, but microscopic METE was not [8,10-12]. However, Arora *et al.* [8] reported that microscopic METE, similar to gross METE, was significantly associated with lymph node metastasis, positive surgical margins and angiolymphatic invasion, although microscopic METE was not significantly associated with tumor recurrence. Hu *et al.* [9] reported that microscopic METE was associated with a high incidence of tumor recurrence. Although there have been reports that METE was associated recurrence in patients with PTMC [16,19], most studies have reported that METE does not affect relapse-free survival [13-15,17,18]. Ito *et al.* [10] reported 8 of a total 129 patients (6%) with PTMC had gross METE, which did not affect the relapse-free survival. But regardless of size, the presence of METE is classified as T3, the same as for tumor with a size larger than 4 cm according to the 2010 TNM staging. Patients with higher stages of disease are subjected to more aggressive operation in conjunction with adjuvant radioactive iodine therapy [20,21]. At our institute, patients with any form of ETE were given total thyroidectomy and high doses of radioactive iodine therapy, and even for the cases with PTMC. This study suggests it is not reasonable that tumor with METE is classified into the same stage, regardless of size.

According to the revised American Thyroid Association Guideline [22], the presence of METE belongs to the intermediate-risk

category. For cases of PTC with METE, and especially smaller than 4 cm, radioiodine remnant ablation is recommended in selected cases because it did not affect the risk of death and the effect on the risk of recurrence has been controversial [22]. Our current study showed results that corresponded with the revised ATA guideline, although our study did not show the disease-specific survival but the disease-free survival. The presence of METE should not belong to a higher TNM stage, rather, such a case should be downgraded and especially in respect to tumor recurrence.

Although METE is not high risk prognostic factor, according to 2010 TNM staging, only the presence of ETE calls for classifying these patients as a high stage and so they should undergo more aggressive treatment. Shaha [21] suggested that every patient with well-differentiated thyroid cancer does not require total thyroidectomy and radioactive iodine treatment, and about 80% of the patients do well with lobectomy alone, while 15% will require aggressive treatment, including radioactive iodine treatment, and 5% will die with locally aggressive thyroid cancer or with distant metastasis.

The tumor size was significantly larger in the presence of METE than that in the absence of METE (2.2 cm vs. 1.5 cm, respectively). Considering the length (approximately 4-5 cm), width (1.5-2 cm), and thickness (2-3 cm) of the thyroid gland, this mean size of tumors is not small. It is natural that as the size of tumor was increased, the incidence of METE was increased ($P < 0.001$, data not shown). If the tumors have same anatomical site, then the size of tumor may be an important factor affecting the possibility of having METE. Further study on the relation between the anatomical site or size of thyroid tumor and ETE is needed.

Because METE was not associated with tumor recurrence, we assumed the effect of size would be prominent in patient with the same status of METE. However, size was not associated with tumor recurrence. We can suggest several causes of this phenomenon. First, the size of tumor is the best predictor for cancer-specific survival [23,24], but not for tumor recurrence [25-27]. In this study, in all the patients with or without METE or in the patients with METE, size was not associated with tumor recurrence. Second, there was the possibility that tumor with more aggressiveness, such as distant metastasis at the time of diagnosis, was excluded from the analysis for tumor recurrence. In this study, the tumors with a larger size had more distant metastasis at the time of diagnosis, although there was not a significant association. Another study reported that the size of tumor was associated distant metastasis at the time of diagnosis from the results that tumors larger than 0.5 cm had the in-

creased incidence of ETE and cervical lymph node metastasis, and tumors larger than 2 cm had the increased incidence of distant metastasis in the patients with PTC [28].

This study has some limitations. First, we analyzed only the patients with near total or total thyroidectomy and who underwent lymph node dissections. During the duration of this study, the number of the patients who underwent surgery at our hospital was approximately 1,500. More than half of the total patients of underwent surgery were excluded because the patients underwent less than total thyroidectomy or they did not undergo lymph node dissection. Second, we did not divide METE into microscopic and macroscopic. "Microscopic" or "macroscopic" was determined depending on where we detected the METE. For example, if we detected METE on the operation field during surgery, then this was classified as macroscopic. If we detected METE during histological examinations, then this was classified as microscopic. However, we had difficulty to determine whether METE was macroscopic or microscopic.

In summary, METE was not a poor prognostic factor for patients with PTC, including PTMC. Therefore, we suggest that the patients with METE could be downgraded to the low risk group in patients with PTC.

CONCLUSIONS

In conclusion, METE is not associated with clinical recurrence in patients with PTC. METE might not be a prognostic factor to predict tumor recurrence in patients with PTC, including PTMC.

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