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ORIGINAL ARTICLE – ENDOCRINE TUMORS

The Prognosis of Papillary Thyroid Cancer with Initial Distant Metastasis is Strongly Associated with Extensive Extrathyroidal Extension: A Retrospective Cohort Study

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ABSTRACT

Background. Extensive extrathyroidal extension (ETE) has a significant role in the prognosis of papillary thyroid cancer (PTC) without distant metastasis, but its role in PTC with initial distant metastasis has never been studied. This study aimed to evaluate the prognostic significance of extensive ETE regarding disease progression, survival, and remission in PTC patients with initial distant metastasis.

Methods. This retrospective cohort study included PTC patients with initial distant metastasis who underwent total thyroidectomy with a median follow-up period of 6.7 years. The prognostic significance of extensive ETE was assessed in terms of time to tumor progression (TTP), cancer-specific survival (CSS), and cumulative incidence of remission with all-cause death as the competing event.

Results. The study enrolled 64 patients. Of these patients, 21 (32.8%) had extensive ETE, which was associated with a shorter TTP (adjusted hazard ratio [HR], 4.10; $p = 0.015$) and a lower CSS rate ($p = 0.002$, log-rank), particularly for patients 55 years of age or older with stage 4b disease (10-year CSS rate: 33.3% in those with and 92.3% in those without extensive ETE; $p = 0.017$). Additionally, remission was observed only in patients without extensive ETE (10-year cumulative incidence of remission: 0.0% in those with and 29.3% in those without extensive ETE; $p = 0.013$).

Conclusions. Extensive ETE of the primary lesion results in poorer prognoses for PTC patients with initial distant metastasis. The high CSS rate for patients with stage 4b PTC but no extensive ETE indicates that the prognosis of this patient population should be distinguished from that of other stage 4 cases.

Papillary thyroid cancer (PTC), the predominant histologic subtype of thyroidal malignancies,[1,2] is considered indolent because most patients with PTC have favorable cancer-specific survival (CSS) outcomes.[3,4] Distant metastasis is among the major factors affecting the prognosis for patients with PTC, and PTC patients 55 years of age or older with initial distant metastasis (M1 classification) have the worst prognosis in the current tumor-node-metastasis (TNM) staging system.[4–7] However, many patients with M1 PTC have favorable prognoses, and the 5-year CSS rate for patients with stage 4 PTC is higher than 60%.[4] Therefore, further risk stratification of patients with M1 PTC is warranted to distinguish between low- and high-risk patients, which in turn would be helpful in providing optimal management and developing appropriate follow-up strategies.

Extensive extrathyroidal extension (ETE) beyond the strap muscle is another major prognostic factor for patients with PTC, and its prognostic importance for patients

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without initial distant metastasis has been further emphasized in the recently revised TNM staging system.[7] Nevertheless, no study has shown its prognostic significance for patients who have PTC with initial distant metastasis. This study aimed to evaluate the prognostic significance of extensive ETE in terms of disease progression, survival, and remission in PTC patients with initial distant metastasis.

MATERIALS AND METHODS

Patients

We performed a single-center, retrospective cohort study of patients who underwent total thyroidectomy for PTC with initial distant metastasis between October 1994 and August 2017 at Severance Hospital in Seoul, Republic of Korea. Patients with other types of thyroid cancer were excluded. This study was approved by the institutional review board of Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea (approval no. 4-2018-0400).

Diagnosis of Initial Distant Metastasis

Distant metastasis was diagnosed via various imaging methods including ^{131}I whole-body scanning (WBS) after thyroidectomy, chest computed tomography (CT), ^{18}F-fluorodeoxyglucose-positron emission tomography with or without CT, and single-photon emission CT with conventional CT. The diagnosis also was confirmed pathologically in certain cases. Initial distant metastasis was defined as that identified preoperatively or within the first 4 months after thyroidectomy according to the definition of M1 classification in the eighth edition of the TNM staging system.[7]

Treatment Protocols

All the patients underwent total thyroidectomy and central compartment node dissection. Modified radical neck dissection was performed after the existence of metastatic lateral neck lymph nodes was confirmed via preoperative fine-needle aspiration biopsy or intraoperative frozen biopsy.

All but one patient underwent postoperative radioactive iodine (RAI) therapy to ablate the normal thyroid tissue, residual disease, and metastatic lesions. Moreover, they underwent repeated RAI treatments according to the clinical status and cumulative RAI activities. Lung metastasis was diagnosed in one patient via preoperative chest CT, but the patient did not receive ^{131}I therapy due to poor performance status. Two patients underwent surgery for removal of gross metastatic lesions (axillary lymph nodes and a single lumbar vertebra, respectively). Adjunctive external beam radiation therapy (EBRT) to the neck was not routinely performed, but one patient underwent EBRT to control neck lymph node recurrence that threatened airway patency.

All the patients were treated with levothyroxine to suppress thyrotropin. Regular follow-up evaluations were performed after surgery with clinical assessment, thyroid function tests, and measurement of serum thyroglobulin (Tg) and anti-Tg antibody (TgAb) levels, with appropriate imaging studies as needed.

Assessment of Baseline Characteristics

Age was recorded on the date of the thyroidectomy, and the cutoff age for risk stratification was set at 55 years as recommended by the eighth edition of the TNM staging system.[7] The degree of locoregional advancement (size of primary tumors, local invasions, and lymph node metastasis) was retrospectively reclassified according to the eighth edition of the TNM staging system. We considered T4 classification as extensive ETE.

The sites of metastasis were divided into four categories, namely, lung only, bone only, other single site, and multiple organs. Metastatic lesions without RAI uptake that nevertheless were evident in other imaging studies were defined as “RAI non-avid.” In one patient, all distant metastases (axillary lymph nodes) were surgically removed before RAI therapy, and no other metastatic lesions were found at WBS. Therefore, RAI avidity was unknown.

The timing of the metastasis diagnosis was classified into two categories: before RAI therapy (i.e., the metastasis was detected via perioperative radiologic images before initial RAI therapy) and at the first RAI therapy (i.e., the metastasis was detected via WBS during the initial RAI therapy). Suppressed Tg levels measured between 3 weeks after thyroidectomy and initial RAI therapy were considered baseline postoperative Tg levels.

Outcomes

Progressive disease was defined as a 20% increase or more (at least 5 mm) in the sum of the diameters of the measurable lesions compared with the smallest sum, identification of new lesions, and/or unequivocal progression of non-measurable lesions, regardless of the changes in serum Tg and TgAb levels.[8] Cancer-specific death was defined as death due to PTC or a PTC-related cause in the presence of PTC progression. Remission was defined as either a TSH-stimulated serum Tg lower than 1 ng/mL or a nonstimulated serum Tg lower than 0.2 ng/mL in the absence of structural evidence of residual disease and serum TgAb.[9]

Statistical Analyses

Descriptive statistics are presented as medians (interquartile ranges [IQRs]) and numbers (%) depending on the type of variables. Comparisons of characteristics according to the presence of extensive ETE were performed using the Mann–Whitney *U* test or Fisher's exact test as appropriate. The associations between clinicopathologic characteristics and time to tumor progression (TTP) from the thyroidectomy were evaluated using uni- and multivariable Cox proportional hazards models. The relative risks for TTP are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The Kaplan–Meier method was used to generate survival curves, whereas log-rank tests were performed to evaluate differences in CSS between groups.

To determine the prognostic significance of extensive ETE for the high-risk patients, the Kaplan–Meier method with log-rank tests was additionally performed for the subgroup of patients 55 years of age or older and for the subgroup of patients 55 years of age or older with other poor prognostic factors. The competing-risks method was used to generate cumulative incidence curves for remission, with all-cause death as the competing event, whereas log-rank tests were performed to evaluate differences in the probability of remission between groups.[10,11] Relative changes in suppressed Tg levels annually up to 5 years postoperatively with respect to the presence of extensive ETE were compared using the Mann–Whitney *U* test at each time point. Patients whose baseline postoperative Tg levels were missing or within the undetectable range and those who tested positive for anti-Tg antibodies were excluded from these analyses.

All tests were two-sided, and *p* values lower than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline Characteristics

The study enrolled 64 patients. Table 1 shows the clinicopathologic characteristics of the patients. The median age at thyroidectomy was 43.9 years (IQR, 28.0–60.1 years), and a predominance of women was observed (65.6%). Extensive ETE (T4 classification) was observed in 21 patients (32.8%), and 9 patients (14.1%) had N0, 3 patients (4.7%) had N1a, and 52 patients (81.3%) had N1b disease. A total of 21 patients (32.8%) were classified in the stage 4b group because they were older than 55 years.

Complete resection with negative margins for the primary tumor was achieved in all patients. The main pathologic subtype was classical PTC (73.4%), and most metastases occurred in the lung alone (81.3%). Distant metastasis was discovered before RAI therapy in 64.1% of the patients, and 15.6% of the lesions were RAI non-avid. Anti-Tg antibody positivity was observed in six patients (9.4%), and the median baseline postoperative Tg levels in patients who did not test positive for anti-Tg antibodies was 15.0 ng/mL (IQR, 4.0–86.5 ng/mL).

Several clinicopathologic characteristics differed according to the presence of extensive ETE (Table 1). Extensive ETE was associated with male sex ($p = 0.050$), higher N classifications ($p = 0.016$), and more aggressive pathologic subtypes including solid and diffuse sclerosing variants ($p = 0.024$).

Overall Outcomes

During the postoperative follow-up period (median, 6.7 years; IQR, 2.6–10.5 years), 11 cases of remission, 21 cases of progression, 1 case of non-cancer-related death, and 10 cases of cancer-specific death were recorded (Table S1; 10-year CSS rate, 82.4%). Of the 21 patients who experienced disease progression, 2 had recurrences in the neck lymph nodes before the progression of distant lesions, and the remaining 19 had progression of distant lesions (new distant lesions or increase in size) without local recurrence. The progression of distant lesions was the cause of the 10 cancer-specific deaths.

Prognostic Significance of Extensive ETE for Cancer Progression

The associations between clinicopathologic characteristics and TTP were evaluated using Cox regression analyses (Table 2). In unadjusted models, extensive ETE (T4) and gross extrathyroidal extension that involved only the strap muscle (T3b) were associated with shorter TTP. In addition, male sex, solid or diffuse sclerosing variant PTC, and RAI non-avidity or no RAI therapy were associated with shorter TTP. However, multivariable Cox regression analysis showed that only extensive ETE (HR, 4.10; 95 CI, 1.31–12.84; $p = 0.015$) and male sex (HR, 3.90; 95% CI, 1.33–11.42; $p = 0.013$) were independently associated with shorter TTP.

TABLE 1 Baseline characteristics of the patient cohort

Characteristics	Total (n = 64) n (%)	Extensive ETE (+) (n = 21) n (%)	Extensive ETE (−) (n = 43) n (%)	p value[a]
Median age at thyroidectomy: years (IQR)	43.9 (28.0–60.1)	32.0 (24.6–62.3)	44.4 (30.8–57.9)	0.553
Sex				**0.050**
Male	22 (34.4)	11 (52.4)	11 (25.6)	
Female	42 (65.6)	10 (47.6)	32 (74.4)	
Median follow-up period: years (IQR)	6.7 (2.6–10.5)	5.4 (2.8–10.1)	9.3 (2.8–10.9)	0.407
T classification				NA
T1	18 (28.1)	0 (0.0)	18 (41.9)	
T2	8 (12.5)	0 (0.0)	8 (18.6)	
T3a	6 (9.4)	0 (0.0)	6 (14.0)	
T3b	11 (17.2)	0 (0.0)	11 (25.6)	
T4a	21 (32.8)	21 (100.0)	0 (0.0)	
N classification				**0.016**
N0	9 (14.1)	0 (0.0)	9 (20.9)	
N1a	3 (4.7)	0 (0.0)	3 (7.0)	
N1b	52 (81.3)	21 (100.0)	31 (72.1)	
Stage group				> 0.999
II	43 (67.2)	14 (66.7)	29 (67.4)	
IVb	21 (32.8)	7 (33.3)	14 (32.6)	
Pathologic subtypes				**0.024**
Classical PTC	47 (73.4)	15 (71.4)	32 (74.4)	
Follicular variant	7 (10.9)	0 (0.0)	7 (16.3)	
Solid variant	2 (3.1)	2 (9.5)	0 (0.0)	
Diffuse sclerosing variant	8 (12.5)	4 (19.0)	4 (9.3)	
Site of metastasis				0.254
Lung only	52 (81.3)	20 (95.2)	32 (74.4)	
Bone only	5 (7.8)	0 (0.0)	5 (11.6)	
Other single site	1 (1.6)	0 (0.0)	1 (2.3)	
Multiple organs	6 (9.4)	1 (4.8)	5 (11.6)	
Radioactive iodine avidity				0.488
Avid	52 (81.3)	16 (76.2)	36 (83.7)	
Non-avid	10 (15.6)	4 (19.0)	6 (14.0)	
Unknown	1 (1.6)	0 (0.0)	1 (2.3)	
Not performed	1 (1.6)	1 (4.8)	0 (0.0)	
Discovery of metastasis before radioactive iodine therapy	41 (64.1)	17 (81.0)	24 (55.8)	0.058
Anti-Tg antibody positivity	6 (9.4)	2 (9.5)	4 (9.3)	> 0.999
Baseline postoperative Tg levels: ng/mL (IQR)[b]	15.0 (4.0–86.5)	13.5 (8.9–118.4)	16.2 (3.3–75.4)	0.226

ETE extrathyroidal extension, *IQR* interquartile range, *NA* not assessed, *PTC* papillary thyroid carcinoma

[a]Significant p values are in boldface type

[b]Patients who were positive for anti-Tg antibodies (n = 6) or had missing postoperative baseline Tg levels (n = 5) were excluded from the analyses

TABLE 2 Uni- and multivariable Cox proportional hazard models for time to tumor progression

Variables	Univariable analyses		Multivariable analyses	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value[a]
Age at thyroidectomy (years)	1.01 (0.98–1.03)	0.532	1.01 (0.98–1.04)	0.574
Male sex	**6.18 (2.43–15.74)**	**< 0.001**	**3.90 (1.33–11.42)**	**0.013**
Gross extrathyroidal extension				
Absent	1.00 (reference)		1.00 (reference)	
Only strap muscle (T3b)	**4.83 (1.38–16.88)**	**0.014**	2.12 (0.53–8.45)	0.289
Extensive (T4)	**4.96 (1.68–14.59)**	**0.004**	**4.10 (1.31–12.84)**	**0.015**
Lateral lymph node metastasis	2.55 (0.59–11.02)	0.210		
Pathologic subtypes				
Classical/follicular variant	1.00 (reference)		1.00 (reference)	
Solid/diffuse sclerosing variant	**2.62 (1.00–6.87)**	**0.050**	1.33 (0.44–4.07)	0.613
Site of metastasis				
Single organ	1.00 (reference)			
Multiple organs	1.04 (0.64–1.70)	0.866		
Radioactive iodine avidity				
Avid or unknown	1.00 (reference)		1.00 (reference)	
Non-avid or not performed	**3.84 (1.53–9.66)**	**0.004**	2.47 (0.72–8.47)	0.149
Discovery of metastasis before radioactive iodine therapy	2.31 (0.84–6.38)	0.105		

HR hazard ratio, *CI* confidential interval

[a]Significant hazard ratios and confidence intervals are in boldface

Prognostic Significance of Extensive ETE for Cancer-Specific Survival

Extensive ETE was associated with a lower CSS rate (Table 3 and Fig. 1a; $p = 0.002$). It also was a significant prognostic factor for patients 55 years of age or older (Fig. 1b; 10-year CSS rate: 92.3% for patients without extensive ETE and 33.3% for patients with extensive ETE; $p = 0.017$), indicating that patients assigned to the stage 4b group in the TNM staging system could be further divided into two groups with markedly different CSS rates according to the presence of extensive ETE.

The log-rank tests showed that RAI non-avidity or no RAI therapy ($p = 0.021$) and the discovery of metastasis before RAI therapy ($p = 0.018$) also were associated with a lower CSS rate (Table 3). Therefore, they were used as "other poor prognostic factors" to define the high-risk subgroup in the subsequent subgroup analysis. Patients 55 years of age or older with one or more other poor prognostic factors had a different CSS rate according to the presence of extensive ETE (Fig. 1c; $p = 0.025$), and the 10-year CSS rate for patients 55 years of age or older with one or more other poor prognostic factors but without extensive ETE was as high as 88.9%.

Prognostic Significance of Extensive ETE for Remission

Remissions were observed only in patients without extensive ETE, and the cumulative incidences of remission differed significantly according to the presence of extensive ETE (Table S2; Fig. 2a; the 10-year cumulative incidence of remission was 29.3% for patients without extensive ETE and 0.0% for patients with extensive ETE; $p = 0.013$). Extensive ETE similarly discriminated the probability of remission for patients 55 years of age or older and for patients younger than 55 years, although the statistical significance was lost for patients age 55 years or older (Fig. 2b, c).

Effect of Extensive ETE on Changes in Suppressed Tg Levels

Percentage changes in suppressed Tg levels were evaluated annually up to 5 years postoperatively with respect to the presence of extensive ETE (Fig. 3). Patients whose baseline postoperative Tg levels were missing ($n = 5$) or within an undetectable range ($n = 6$) and those who tested positive for anti-Tg antibodies ($n = 6$) were excluded from these analyses. The suppressed Tg levels in patients with extensive ETE were higher than those at baseline every year from 1 to 5 years postoperatively (i.e., median

TABLE 3 Cancer-specific survival rate according to the clinicopathologic factors

Variables	5-Year (%)	10-Year (%)	*p* value (log-rank test)[a]
Age at thyroidectomy (years)			0.094
< 55	94.6	90.1	
≥ 55	89.5	70.5	
Sex			0.094
Female	94.8	87.2	
Male	89.8	73.5	
Extensive extrathyroidal extension			**0.002**
Absent (T1–T3)	97.6	93.5	
Present (T4)	84.3	60.4	
Lateral lymph node metastasis			0.092
Absent	100.0	100.0	
Present	91.3	78.5	
Pathologic subtypes			0.970
Classical/follicular variant	93.6	81.8	
Solid/diffuse sclerosing variant	90.0	90.0	
Site of metastasis			0.363
Single organ	92.3	80.7	
Multiple organs	100.0	100.0	
Radioactive iodine avidity			**0.021**
Avid or unknown	93.5	89.9	
Non-avid or not performed	90.0	58.3	
Discovery of metastasis			**0.018**
On the first RAI	100.0	100.0	
Before RAI therapy	88.5	71.5	

RAI radioactive iodine therapy

[a]Significant *p* values are in boldface type

percentage change in suppressed Tg levels vs baseline was more than 0% every year). During the same period, suppressed Tg levels in patients without extensive ETE decreased annually. As a result, percentage changes in suppressed Tg levels differed significantly between the two groups ($p < 0.05$ at each time point of 1, 2, 3, 4, and 5 years postoperatively using the Mann–Whitney U test).

DISCUSSION

We found that extensive ETE is an important poor prognostic factor for cancer progression, CSS, and probability of remission for patients who underwent thyroidectomy for PTC with initial distant metastasis. Its prognostic significance for CSS also was maintained in the high-risk subgroups, and patients 55 years of age or older who were classified in the stage 4b group in the current TNM staging system had a favorable CSS if they did not have extensive ETE of primary lesions. Additionally, patients with extensive ETE showed unfavorable changes in Tg levels over time relative to those without extensive ETE despite similar baseline postoperative Tg levels between the two patient groups.

Patients with PTC but no metastasis have a poorer prognosis than those who have PTC without such metastasis.[4–6,12] However, patients with distant metastasis from PTC have much better survival rates than those with distant metastasis arising from other malignancies.[4,13] Therefore, identifying the appropriate prognostic factors that can distinguish high-risk subpopulations of PTC patients with distant metastasis may help to establish appropriate treatment plans, and much effort has been made in this regard.[5,6,14–38] However, except for old age, the impacts of various potential predictors on patient prognoses have not been consistent among studies.

We noted that the patient populations investigated in previous studies were heterogeneous. Patients who had differentiated thyroid cancers with different histologic types,[15–37] as well as those with initial distant metastasis and metachronous metastasis (distant metastasis detected during follow-up assessment),[5,6,14–31] were previously

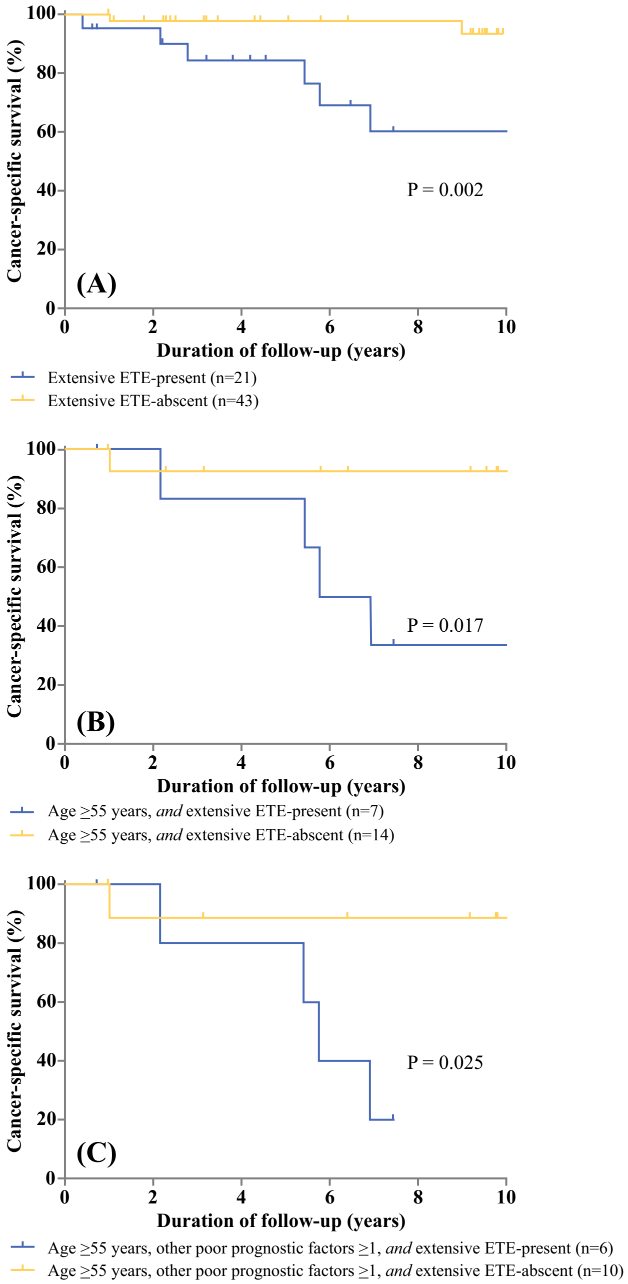


FIG. 1 Cancer-specific survival (CSS) curves of patients who had papillary thyroid cancer with initial distant metastasis according to the presence of extensive extrathyroidal extension. Shown are CSS curves in **a** the overall cohort, **b** patients 55 years of age or older, and **c** patients 55 years of age or older with one or more additional poor prognostic factors. *ETE* extrathyroidal extension

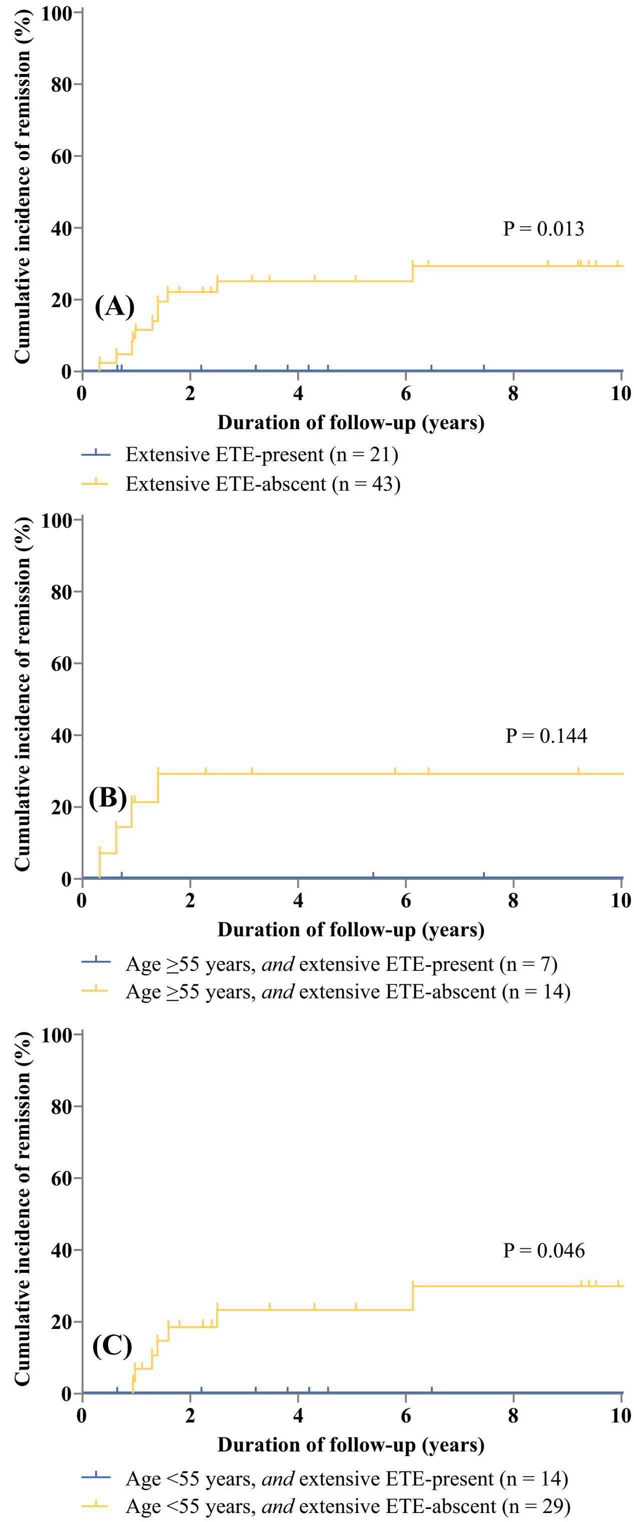
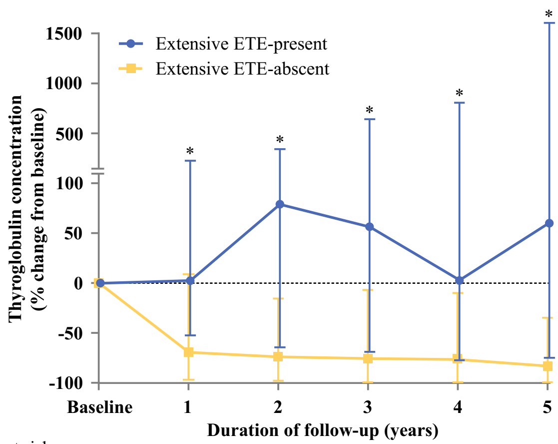


FIG. 2 Cumulative incidence curves of remission for patients who had papillary thyroid cancer with initial distant metastasis according to the presence of extensive extrathyroidal extension. Shown are cumulative incidence curves for **a** the overall cohort, **b** patients 55 years of age or older, and **c** patients younger than 55 years. *ETE* extrathyroidal extension

assessed together in most studies. However, PTCs and follicular thyroid cancers (FTCs) have distinct clinicopathologic features and prognostic factors.[38,39]

Additionally, several studies have reported that patients with distant metastasis arising from FTCs have a worse prognosis than those with distant metastasis from PTCs.[28–34,38] Similarly, the clinicopathologic features,



Number at risk

	Baseline	1	2	3	4	5
Extensive ETE-present	17	17	15	10	10	7
Extensive ETE-abscent	30	30	25	21	14	13

FIG. 3 Percentage changes in suppressed Tg levels with respect to the presence of extensive extrathyroidal extension. Results are presented as medians with interquartile ranges. Patients whose baseline postoperative Tg levels were missing (n = 5) or within an undetectable range (n = 6) and those who tested positive for anti-Tg antibodies (n = 6) were excluded from the analyses. *Significant difference between groups ($p < 0.05$, Mann–Whitney U test)

prognostic factors, and survival rates of patients with initial metastasis differ from those of patients with metachronous metastasis.[23–29,35] Therefore, the validity of potential prognostic factors in PTC patients with initial distant metastasis should be investigated separately from those of patients with other types of thyroid cancer and from those of patients with metachronous metastasis. Nevertheless, to the best of our knowledge, only one study has separately evaluated the prognostic factors of PTCs with initial distant metastasis to date.[38]

In our study, extensive ETE showed a pronounced adverse influence on the disease progress in several aspects. The extent of gross extensive ETE is an important prognostic factor for patients with differentiated thyroid cancers.[7,12] However, in most previous studies that investigated prognostic factors for patients who had differentiated thyroid cancer with distant metastasis, neither ETE including microscopic extension nor extensive ETE was associated with worse outcomes in progression, survival, and remission.[5,14,21–23,29,31,33–35,37,38] Furthermore, in one study, differentiated thyroid cancer patients with extensive ETE (T4 classification according to the seventh edition of the TNM staging system) showed better overall survival than those without extensive ETE (T3 classification).[32] These unexpected results in the previous studies may be explained by the negative association between the presence of ETE and the relative frequency of FTC.[39] In two studies[5,14] that included only patients with PTC who had distant metastasis, ETE was found to be associated with short CSS in only one study.[14] Both of these studies, however, evaluated initial and metachronous metastasis together and did not distinguish between microscopic and gross ETE.

Recently, Kim et al.[38] performed a study including a subgroup analyses of PTC patients with initial distant metastasis and reported that gross ETE was not associated with short CSS in these patients. However, the extent of gross ETE was not further distinguished in the study. In contrast to these previous studies, we appropriately selected only PTC patients with initial metastasis and subdivided the ETE according to its severity. Consequently, we demonstrated the prognostic importance of extensive ETE in PTC patients with initial distant metastasis.

Interestingly, the effect of extensive ETE on a patient's outcome in our cohort seemed to be mainly due to the unfavorable response of distant metastatic lesions to therapy. Complete resection with negative margins for primary tumors was achieved in all patients, and no patients had gross residual lesions in the neck after the surgery, regardless of extensive ETE. Moreover, the progression of distant metastatic lesions was the cause of all cancer-specific deaths. Additionally, under appropriate treatments, serum Tg levels decreased over time in patients without extensive ETE but not in those with extensive ETE. Further studies are needed to determine which characteristics of distant metastatic lesions lead to poor therapeutic response when extensive ETE is observed in primary lesions.

This study had several limitations. Because it was a single-center investigation in South Korea, further research is needed to confirm the reproducibility of our findings in other patient cohorts, including those of other races. The number of patients also was limited, but it was comparable with that in previous studies.[5,6,14–37] Because there were no patients in the T4bM1 classification during the study period, all extensive ETE in this study corresponded to the T4a classification. However, the patients with T4bM1 PTC were not expected to have a better prognosis than those with T4aM1 PTC. Therefore, this limitation would not undermine the validity of our conclusion that extensive ETE predicts a poor prognosis for PTC patients with initial distant metastasis. Changes in treatment patterns during a long study duration could have affected the outcomes, although we did not observe any significant prognostic differences based on the year of surgery (data not shown).

To the best of our knowledge, this is the first study to evaluate the prognostic importance of extensive ETE in PTC patients with initial distant metastasis. As a prognostic marker, extensive ETE has important clinical utility that potentially outweighs other prognostic factors. The extent of gross ETE could be easily confirmed during the surgery or even estimated earlier via preoperative imaging workup. Moreover, because the degree of gross extension is directly related to T classification, its prognostic significance could be well defined under the TNM staging system. Additionally, the high CSS rate for the patients 55 years of age or older without extensive ETE (i.e., T1–3 M1 PTC) suggests that these patients might be downstaged from the current stage 4b group for a more reliable risk stratification, although further studies are needed to validate this suggestion.

In conclusion, extensive ETE, the classic prognostic factor in PTC without distant metastasis, is a helpful basis for physicians in the development of treatment and follow-plans for postoperative PTC patients with initial metastasis.

DISCLOSURE There are no conflicts of interest.

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