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RESEARCH ARTICLE

CLINICOPATHOLOGICAL FACTORS ASSOCIATED WITH EXTRATHYROIDAL EXTENSION IN PAPILLARY THYROID CARCINOMA

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ABSTRACT: Extrathyroidal extension (ETE) is a key pathological feature of papillary thyroid carcinoma (PTC) associated with aggressive tumor behavior and adverse outcomes. However, clinicopathological factors associated with ETE remain incompletely characterized, particularly in Southeast Asian populations. This study aimed to identify factors associated with pathological ETE in patients with PTC. This prospective observational study included 346 consecutive patients with histopathologically confirmed PTC who underwent thyroidectomy at a tertiary referral center in Vietnam between April and August 2025. ETE was defined based on postoperative histopathological examination, including both minimal and gross ETE. Clinicopathological variables were evaluated using univariable analysis and multivariable logistic regression. ETE was identified in 66 patients (19.1%). In univariable analysis, age ≥ 55 years, symptomatic presentation, multifocality, tumor size, lymph node metastasis and thyroiditis were associated with ETE (all $p < 0.05$). In multivariable analysis, age ≥ 55 years (OR = 2.321; 95%CI 1.153-4.674; $p = 0.018$), tumor size (per 10 mm increase) (OR = 1.052; 95%CI 1.016-1.090; $p = 0.005$) and lymph node metastasis (OR = 2.932; 95%CI 1.565-5.492; $p < 0.001$) were independently associated with increased odds of ETE. In contrast, coexisting thyroiditis was associated with lower odds of ETE (OR = 0.440; 95%CI 0.231-0.839; $p = 0.013$). In conclusion, older age, larger tumor size and lymph node metastasis were independently associated with pathological ETE in PTC, whereas coexisting thyroiditis showed a potentially inverse association that should be confirmed in larger cohorts. These findings provide additional insight into clinicopathological factors associated with tumor invasiveness in PTC and may contribute to improved risk assessment.

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Impact statement: This prospective study identifies age, tumor size and lymph node metastasis as key factors associated with extrathyroidal extension in papillary thyroid carcinoma.

Key words: *Papillary thyroid carcinoma; extrathyroidal extension; lymph node metastasis; thyroiditis; tumor size.*

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INTRODUCTION

Thyroid cancer is the most common endocrine malignancy worldwide, with a rapidly increasing incidence over the past decades. In 2022, approximately 821,214 new cases were diagnosed globally, ranking seventh among all cancers and fifth among women, with an incidence rate of 9.1 per 100,000 population (1). Despite this increasing incidence, thyroid cancer is generally associated with an excellent prognosis, data from the Surveillance, Epidemiology and End Results (SEER) program indicate a 5-year survival rate of up to 98.4% (2). Papillary thyroid carcinoma (PTC), the most common histological subtype, accounts for approximately 85-90% of thyroid cancer cases and is typically characterized by indolent behavior and favorable treatment outcomes (3). Extrathyroidal extension (ETE), defined as tumor invasion beyond the thyroid capsule into adjacent soft tissues, is an important pathological feature associated with more aggressive disease behavior (4, 5). ETE can be broadly classified into minimal extrathy-

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roidal extension (mETE), which is identified only on histopathological examination and gross extrathyroidal extension (gETE), which is evident clinically, radiologically, or intraoperatively (6).

Historically, mETE was classified as T3 disease in earlier editions of the American Joint Committee on Cancer (AJCC) staging system (7). However, its independent prognostic significance has been increasingly questioned due to substantial interobserver variability and its strong dependence on histopathological interpretation (8, 9). In contrast, gETE has been consistently associated with advanced tumor stage, higher recurrence rates and increased disease-specific mortality (10). Consequently, the eighth edition of the AJCC staging system removed mETE from tumor staging and placed greater emphasis on gETE (11).

Despite these differences in prognostic impact, the presence of ETE at any extent may still reflect tumor invasiveness and local tumor aggressiveness (12, 13). From a clinical perspective, identifying factors associated with the occurrence of ETE, regardless of its extent, may provide insights into tumor behavior, particularly in settings where preoperative distinction between mETE and gETE remains challenging (14, 15). Assessment of potential differences between ETE subtypes may also improve the understanding of tumor invasiveness.

Although ETE is widely recognized as an important prognostic factor, its reported prevalence varies considerably across studies (5%-45%), largely reflecting differences in definitions, assessment methods and study populations (16). Reported clinicopathological factors associated with ETE also remain inconsistent and data from certain populations, particularly those in developing countries, remain limited (17, 18). In Vietnam, prospective data on clinicopathological factors associated with ETE in PTC remain scarce.

Therefore, this study aimed to identify clinicopathological factors associated with postoperative pathological ETE in patients with PTC. This study is reported in accordance with the STROBE reporting checklist.

MATERIALS AND METHODS

Study population

This prospective observational study was conducted at a tertiary referral oncology center in Vietnam. Patients were consecutively enrolled between April 2025 and August 2025. A total of 346 patients who underwent thyroidectomy and had a final histopathological diagnosis of PTC were included in the study.

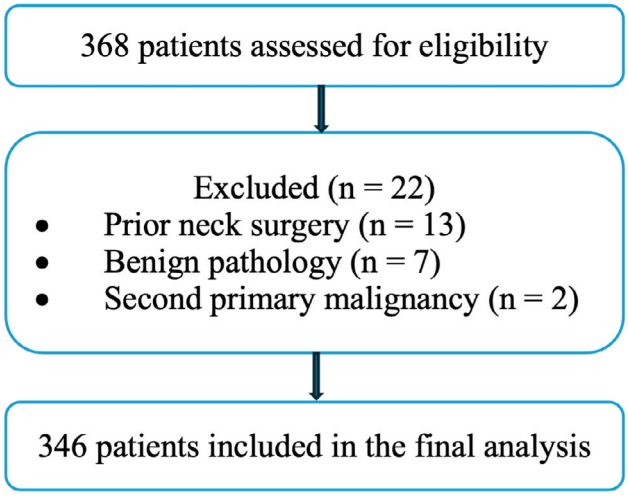

Figure 1. *Flowchart of patient selection and inclusion in the final analysis.*

The study was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments. Ethical approval was obtained from the Institutional Ethics Committee of Ho Chi Minh City Oncology Hospital (No. 542/BVUB-HDDD). Written informed consent was obtained from all participants prior to inclusion.

Patients were eligible for inclusion if they had preoperative cytological findings from fine-needle aspiration (FNA) suggestive of or diagnostic for PTC and subsequently underwent thyroid surgery. Patients were excluded if they had a history of previous neck surgery, prior radioactive iodine (I-131) therapy or other treatments, the presence of another primary malignancy, incomplete clinical or operative data, or a postoperative histopathological diagnosis other than PTC.

During the study period, 368 patients with preoperative FNA results of PTC or suspicious for PTC underwent thyroidectomy. Of these, 22 patients were excluded, including 2 with a second primary malignancy, 13 with a history of prior neck surgery and 7 with benign postoperative histopathological findings. Ultimately, 346 patients were included in the final analysis.

The patient selection process is illustrated in **Figure 1**.

Data collection

Patients were prospectively enrolled and clinical and histopathological data were collected using a standardized case report form according to a predefined study protocol. Tumor characteristics, lymph node status and coexisting thyroid conditions were determined based on histopathological examination of the

surgical specimens. Surgical management, including lobectomy, near-total thyroidectomy, or total thyroidectomy with or without lymph node dissection, was performed according to institutional protocols and contemporary clinical guidelines. Central and/or lateral neck dissection was performed based on clinical indications.

The following variables were analyzed:

- Demographic characteristics: age, sex and body mass index (BMI).
- Clinical characteristics: reason for consultation and Graves' disease.
- Tumor characteristics: maximum tumor diameter, multifocality and histological variant.
- Lymph node status: lymph node metastasis and extranodal extension.
- Coexisting thyroid conditions: lymphocytic thyroiditis and multinodular goiter.
- Primary outcome: presence of ETE.

The reason for consultation was initially recorded in detailed categories, including health screening and specific symptoms (neck mass, throat discomfort, dysphagia, hoarseness, dyspnea, neck pain and palpitations). For analytical purposes, these were categorized into two groups: health screening (asymptomatic) and symptomatic presentation. Patients were classified as symptomatic if they presented with at least one of the above symptoms. This categorization was performed to improve statistical power and model stability given the relatively small number of events in individual symptom subgroups.

Lymph node metastasis was defined based on postoperative histopathological examination of resected lymph nodes. Only patients who underwent lymph node dissection were considered assessable for pathological nodal status, while those without lymph node dissection were classified as having no pathological evidence of nodal metastasis.

Coexisting thyroid conditions were defined based on postoperative histopathological examination of surgical specimens. Although these conditions may be suggested preoperatively based on cytological findings, including FNA, the final diagnosis in this study was established histopathologically. Thyroiditis in this study refers to lymphocytic thyroiditis and goiter was defined as multinodular goiter (nodular hyperplasia).

ETE was determined based on postoperative histopathological examination of surgical specimens. All slides were independently reviewed by two board-certified pathologists with approximately 10 years of experience in oncologic pathology and any discrepancies were resolved by consensus.

mETE was defined according to standard histopathological criteria as microscopic tumor extension beyond the thyroid capsule that was identified exclusively on histopathological examination and was not accompanied by gross operative, radiological, or macroscopic pathological evidence of invasion. Microscopic involvement of perithyroidal soft tissue, including adipose tissue, small foci of skeletal muscle fibers, or extension around or into vascular structures or nerves, was categorized as mETE only when it was detected microscopically. Cases with gross strap muscle invasion observed intraoperatively and confirmed histopathologically were not counted as mETE; these cases were classified as gETE (pT3b), consistent with the AJCC 8th edition staging framework and contemporary thyroid pathology recommendations (11,19-21). gETE was defined as macroscopic tumor invasion beyond the thyroid capsule, including invasion into strap muscles (pT3b) or extension beyond the strap muscles into adjacent structures such as subcutaneous soft tissue, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia, or major vessels (pT4) (11, 21). gETE was initially identified intraoperatively by the operating surgeon and correlated with histopathological findings. This classification was applied consistently for prevalence estimates and subgroup comparisons.

For statistical analysis, ETE was treated as a dichotomous variable (present *vs* absent), with both mETE and gETE categorized as ETE-positive. This approach was adopted to increase statistical power and model stability given the limited number of events in each subgroup.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD), whereas categorical variables were expressed as frequencies and percentages. Differences between groups were assessed using the chi-square test or Fisher's exact test, as appropriate.

Univariable logistic regression analysis was performed to evaluate clinicopathological factors associated with the presence of ETE and crude odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding P-values were reported. Variables with a P-value < 0.10 in the univariable analysis, together with clinically relevant variables, were entered into a multivariable logistic regression model to identify factors independently associated with ETE. Adjusted

odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. For the subgroup analysis of gETE, variables were selected based on clinical relevance and consistency with the primary model.

The number of events per variable (EPV) was assessed to evaluate the risk of overfitting in the multivariable model. A total of 66 events were included with 6 variables entered into the model, resulting in an EPV of 11, which exceeds the commonly recommended threshold and supports the robustness of the model. Multicollinearity among variables was assessed using the variance inflation factor (VIF) and no significant collinearity was observed (all VIF < 2). Extranodal extension was analyzed descriptively in the univariable analysis but was not included in the multivariable model because it occurs only in the presence of lymph node metastasis and is therefore not considered an independent predictor.

Tumor size was categorized into four groups (≤ 10 mm, > 10-20 mm, > 20-40 mm and > 40 mm) based on clinically relevant cutoffs derived from established thyroid cancer staging systems, including the 10 mm threshold defining papillary thyroid microcarcinoma. Tumor size categories were used for descriptive analyses, whereas continuous tumor size was entered into logistic regression models.

Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test and further evaluated using a calibration plot. Model discrimination was quantified using the area under the receiver operating characteristic curve (AUC). Internal validation was performed using bootstrap resampling. All statistical tests were two-sided and a P-value < 0.05 was considered statistically significant.

RESULTS

A total of 346 patients were included in the final analysis. The baseline clinicopathological characteristics of the study population are summarized in **Table 1**. The mean age was 42.6 ± 12.1 years, and most patients were aged < 55 years (82.9%). Females predominated, accounting for 86.1% of the cohort. The mean body mass index was 23.2 ± 3.3 kg/m^2, with the majority of patients having a normal BMI (64.7%).

Most tumors were incidentally detected during health screening (72.2%), whereas 27.8% of patients presented with symptoms. Graves' disease was identified in 2.6% of patients. Goiter and thyroiditis were observed in 14.7% and 14.2% of cases, respectively.

Regarding tumor characteristics, the mean tumor size was 11.3 ± 7.7 mm and 66.2% of tumors measured ≤ 10 mm. Multifocal tumors were present in 26.0% of patients. The classical variant was the predominant histological subtype (98.8%). Lymph node metastasis was identified in 28.3% of patients, extranodal extension in 3.8% and ETE in 19.1%.

Among these patients, 205 (59.2%) underwent total thyroidectomy, 3 (0.9%) underwent near-total thyroidectomy and 138 (39.9%) underwent lobectomy. Among patients who underwent total thyroidectomy, 81 (39.5%) had central neck dissection, 9 (4.4%) had lateral neck dissection and 39 (19.0%) had both central and lateral neck dissection. Among patients who underwent lobectomy, central neck dissection was performed in 9 patients (6.5%), while no lymph node dissection was performed in patients who underwent near-total thyroidectomy.

Larger tumor size was significantly associated with ETE (**Table 2**). Patients with ETE more frequently had tumors > 10 mm compared with those without ETE. In univariable analysis (**Table 3**), age ≥ 55 years, symptomatic presentation, multifocality, larger tumor size, lymph node metastasis, thyroiditis and extranodal extension were significantly associated with ETE (all p < 0.05).

In multivariable logistic regression analysis (**Table 4**), age ≥ 55 years (OR = 2.321, 95%CI 1.153-4.674; p = 0.018), tumor size (per 10 mm increase) (OR = 1.052, 95%CI 1.016-1.090; p = 0.005) and lymph node metas-

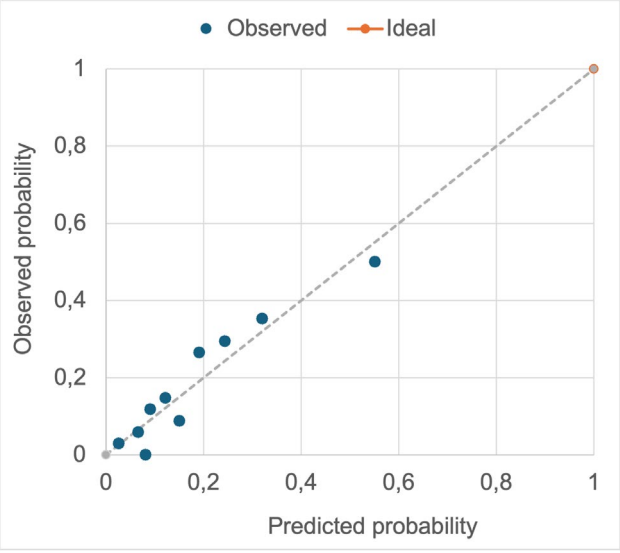

Figure 2. *Calibration plot of the multivariable logistic regression model evaluating the association between clinicopathological factors and extrathyroidal extension.*
The dashed diagonal line indicates perfect calibration.

Table 1. *Baseline clinicopathological and surgical characteristics of the study population.*

VARIABLES	VALUE (N = 346)
Age (years)	42.6 ± 12.1
<55 years	287 (82.9)
≥55 years	59 (17.1)
Sex	
Female	298 (86.1)
Male	48 (13.9)
Body mass index (kg/m²)	23.2 ± 3.3
<18.5	24 (6.9)
18.5–24.9	224 (64.7)
25.0–29.9	89 (25.7)
≥30	9 (2.6)
Reason for consultation	
Health screening	250 (72.2)
Neck mass	67 (19.4)
Throat discomfort	13 (3.7)
Dysphagia	3 (0.9)
Hoarseness	5 (1.4)
Dyspnea	2 (0.6)
Neck pain	4 (1.2)
Palpitations	2 (0.6)
Graves' disease	9 (2.6)
Maximum tumor diameter (mm)	11.3 ± 7.7
≤10	229 (66.2)
>10–20	82 (23.7)
>20–40	32 (9.2)
>40	3 (0.9)
Multifocality	
Yes	90 (26.0)
No	256 (74.0)
Histological variant	
Classic	342 (98.8)
Invasive follicular variant	4 (1.2)
Lymph node metastasis	98 (28.3)
Extranodal extension	13 (3.8)
Thyroiditis	49 (14.2)
Goiter	51 (14.7)
Extrathyroidal extension (ETE)	66 (19.1)
Gross ETE	46 (13.3)
Microscopic ETE	20 (5.8)
Surgical management	
Type of thyroidectomy	
Total thyroidectomy	205 (59.2)
Near-total thyroidectomy	3 (0.9)
Lobectomy	138 (39.9)
Lymph node dissection stratified by surgery type	
Total thyroidectomy (n = 205)	
None	76 (37.1)
Central	81 (39.5)
Lateral	9 (4.4)
Both central and lateral	39 (19.0)
Lobectomy (n = 138)	
None	129 (93.5)
Central	9 (6.5)
Near-total thyroidectomy (n = 3)	
None	3 (100.0)

Data are presented as mean ± standard deviation or number (%). ETE: extrathyroidal extension.

tasis (OR = 2.932, 95%CI 1.565-5.492; p < 0.001) were independently associated with higher odds of ETE. In contrast, thyroiditis was independently associated with lower odds of ETE (OR = 0.440, 95%CI 0.231-0.839; p = 0.013). Other variables were not significantly associated with ETE after adjustment.

The Hosmer–Lemeshow goodness-of-fit test indicated an adequate model fit (p = 0.543). The model demonstrated good discriminatory ability, with an area under the receiver operating characteristic curve (AUC) of 0.777 (95%CI 0.717-0.838).

Calibration of the model was assessed using a calibration plot, which showed good agreement between predicted and observed probabilities of ETE across deciles of risk (**Figure 2**). Most data points were closely aligned with the 45-degree reference line, indicating satisfactory calibration. Minor variability was observed in the lower-risk range, while a slight tendency toward overestimation was noted at higher predicted probabilities.

Internal validation using bootstrap resampling (1,000 iterations) demonstrated stable model performance, supporting the robustness and reliability of the model.

In a supplementary analysis, clinicopathological characteristics were further compared across ETE subgroups (no ETE, mETE and gETE) (**Supplementary Table 1**). Several key variables differed across subgroups, with a tendency toward more aggressive features in the gETE group compared with mETE

Table 2. *Comparison of clinicopathological characteristics according to extrathyroidal extension status.*

VARIABLES	ETE (N = 66)	NO ETE (N = 280)	P-VALUE
Age			0.037
<55 years	49 (74.2)	238 (85.0)	
≥55 years	17 (25.8)	42 (15.0)	
Sex			0.128
Male	13 (19.7)	35 (12.5)	
Female	53 (80.3)	245 (87.5)	
Body mass index (kg/m²)			0.336
<18.5	6 (9.1)	18 (6.4)	
18.5–24.9	44 (66.7)	180 (64.3)	
25.0–29.9	13 (19.7)	76 (27.1)	
≥30	3 (4.5)	6 (2.1)	
Reason for consultation			0.008
Health screening	39 (59.1)	211 (75.4)	
Symptomatic	27 (40.9)	69 (24.6)	
Graves' disease			1.000
Yes	1 (1.5)	8 (2.9)	
No	65 (98.5)	272 (97.1)	
Tumor size (mm)			<0.001
≤10	25 (37.9)	204 (72.9)	
>10–20	31 (47.0)	51 (18.2)	
>20–40	8 (12.1)	24 (8.6)	
>40	2 (3.0)	1 (0.4)	
Multifocality			<0.001
Yes	28 (42.4)	62 (22.1)	
No	38 (57.6)	218 (77.9)	
Histological variant			0.166
Classic	64 (97.0)	278 (99.3)	
Invasive follicular	2 (3.0)	2 (0.7)	
Lymph node metastasis			<0.001
Yes	34 (51.5)	64 (22.9)	
No	32 (48.5)	216 (77.1)	
Extranodal extension			<0.001
Yes	8 (12.1)	5 (1.8)	
No	58 (87.9)	275 (98.2)	
Thyroiditis			0.013
Yes	3 (4.5)	46 (16.4)	
No	63 (95.5)	234 (83.6)	
Goiter			0.916
Yes	10 (15.2)	41 (14.6)	
No	56 (84.8)	239 (85.4)	

Values are presented as number (%). P-values were calculated using the chi-square test or Fisher's exact test, as appropriate. ETE: extrathyroidal extension.

and no ETE. Larger tumor size and a higher frequency of lymph node **metastasis** were observed in patients with gETE.

In a separate multivariable analysis focusing on gETE (**Table 5**), older age (≥ 55 years), larger tumor size and lymph node metastasis remained inde-

Table 3. *Univariable logistic regression analysis of factors associated with extrathyroidal extension.*

VARIABLES	CRUDE OR	95%CI	P-VALUE
Age			
<55 years	1 (reference)		
≥55 years	1.966	1.035–3.735	0.039
Sex			
Female	1 (reference)		
Male	0.582	0.289–1.176	0.131
Body mass index (kg/m²)			
18.5–24.9	1 (reference)		
<18.5	2.045	0.492–8.501	0.325
25.0–29.9	1.500	0.284–7.934	0.633
≥30	2.923	0.649–13.174	0.163
Reason for consultation			
Health screening	1 (reference)		
Symptomatic	2.117	1.208–3.710	0.009
Graves' disease			
No	1 (reference)		
Yes	0.523	0.064–4.256	0.545
Tumor size (mm)			
≤10	1 (reference)		
>10–20	6.000	0.478–75.344	0.165
>20–40	3.290	0.286–37.811	0.339
>40	16.320	1.428–186.515	0.025
Multifocality			
No	1 (reference)		
Yes	2.591	1.474–4.553	<0.001
Histological variant			
Classic	1 (reference)		
Invasive follicular	4.344	0.601–31.420	0.146
Lymph node metastasis			
No	1 (reference)		
Yes	3.586	2.053–6.262	<0.001
Extranodal extension			
No	1 (reference)		
Yes	7.586	2.396–24.023	<0.001
Thyroiditis			
No	1 (reference)		
Yes	0.242	0.073–0.805	0.021
Goiter			
No	1 (reference)		
Yes	0.961	0.454–2.034	0.916

CI: confidence interval; OR: odds ratio. Reference categories are indicated for each variable. Tumor size was analyzed as a categorical variable. Variables with p < 0.10 in univariable analysis were considered for multivariable analysis.

pendently associated with higher odds of gETE. Specifically, each 10 mm increase in tumor size was independently associated with higher odds of gETE (OR = 1.090, 95%CI 1.048-1.134; p < 0.001), while lymph node metastasis was associated with more than a threefold increase in risk (OR = 3.486, 95%CI 1.662-

Table 4. *Multivariable logistic regression analysis of factors associated with extrathyroidal extension.*

VARIABLES	ADJUSTED OR (95%CI)	P-VALUE
Age (≥55 *vs* <55 years)	2.321 (1.153–4.674)	0.018
Reason for consultation (symptomatic *vs* health screening)	1.613 (0.863–2.983)	0.135
Multifocality (Yes *vs* No)	1.649 (0.882–3.081)	0.117
Tumor size (per 10-mm increase)	1.052 (1.016–1.090)	0.005
Lymph node metastasis (Yes *vs* No)	2.932 (1.565–5.492)	<0.001
Thyroiditis (Yes *vs* No)	0.440 (0.231–0.839)	0.013

CI: confidence interval. Tumor size was modeled as a continuous variable per 10-mm increase. Variables were selected for multivariable analysis based on clinical relevance and a univariable screening threshold of p < 0.10.

Table 5. *Multivariable logistic regression analysis of factors associated with gross extrathyroidal extension.*

VARIABLES	ADJUSTED OR (95%CI)	P-VALUE
Age (≥55 *vs* <55 years)	2.936 (1.306–6.600)	0.009
Multifocality (Yes *vs* No)	1.393 (0.665–2.920)	0.379
Tumor size (per 10-mm increase)	1.090 (1.048–1.134)	<0.001
Lymph node metastasis (Yes *vs* No)	3.486 (1.662–7.316)	<0.001
Thyroiditis (Yes *vs* No)	0.337 (0.091–1.248)	0.104

CI: confidence interval. Tumor size was modeled as a continuous variable per 10-mm increase. Variables included in the multivariable model were selected based on clinical relevance and consistency with the primary model.

7.316; p < 0.001). Age ≥ 55 years was also significantly associated with gETE (OR = 2.936, 95%CI 1.306-6.600; p = 0.009). In contrast, multifocality and thyroiditis were not significantly associated with gETE after adjustment.

DISCUSSION

ETE is a well-recognized adverse prognostic factor in PTC and is associated with an increased risk of locoregional recurrence and poorer oncologic outcomes. In this prospective observational study, older age (≥ 55 years), larger tumor size and lymph node metastasis were independently associated with ETE, whereas thyroiditis was associated with lower odds of ETE.

Although gETE is clearly associated with disease recurrence and disease-specific mortality, the clinical significance of mETE remains controversial (9, 22-24). Consistent with AJCC 8th edition concepts, mETE was not used for T upstaging in this study; it was analyzed only as a histopathological marker of local microscopic invasion (11). Macroscopic strap muscle invasion and invasion into deeper adjacent structures were classified as gETE. This distinction is important because mETE and gETE differ in prognostic relevance and in the reliability of pathological assessment.

Older age (≥ 55 years) was independently associated with ETE in our cohort, suggesting a more aggressive clinicopathological phenotype in older patients. This observation is consistent with previous studies reporting a higher likelihood of ETE or aggressive clinicopathological features in older individuals with PTC (18, 25). This association may reflect longer subclinical tumor growth, progressive local extension and the accumulation of biological alterations over time. Molecular events associated with aggressive PTC, including coexisting BRAF V600E and TERT promoter mutations, may also contribute to invasive behavior in some patients (44). Age-associated metabolic alterations, including increased reliance on aerobic glycolysis (the Warburg effect) and age-related changes in immune function have also been proposed as possible contributors to invasive cancer phenotypes (26-28). Because metabolic profiling and molecular testing were not performed, these explanations should be considered speculative. The present finding should therefore be interpreted as a clinicopathological association rather than evidence of a direct biological mechanism.

Tumor size also emerged as an independent factor associated with ETE, reinforcing its role as an important indicator of tumor aggressiveness. Larger tumors are more likely to penetrate the thyroid capsule and

invade surrounding tissues, reflecting progressive tumor growth. This observation is consistent with prior studies demonstrating a strong association between increasing tumor diameter and the risk of ETE (17, 29, 30). Notably, papillary thyroid microcarcinoma (≤ 10 mm) accounted for a substantial proportion of cases in our cohort (66.2%), reflecting the increasing detection of early-stage disease through health screening and routine imaging (31-33). Although microcarcinomas are generally considered indolent, ETE can still occur in a subset of these tumors, albeit at a lower frequency than in larger tumors (34). This pattern supports a continuum of tumor behavior, in which the risk of extrathyroidal invasion increases progressively with tumor size rather than being defined by a strict size threshold.
Lymph node metastasis was another factor independently associated with ETE, reflecting a more aggressive tumor biology characterized by enhanced invasive and metastatic potential. Previous studies have consistently reported a close association between lymph node metastasis and ETE (5, 17, 29, 35-39). From a clinical perspective, the presence of lymph node metastasis may therefore raise suspicion for concurrent ETE and should prompt careful preoperative and intraoperative evaluation. However, the detection of lymph node metastasis may be influenced by the extent of surgical dissection and the strategy of lymph node evaluation, potentially leading to underestimation in patients who do not undergo systematic lymph node dissection.
Coexisting lymphocytic thyroiditis was associated with lower odds of ETE in our study. This finding is consistent with several previous reports suggesting a potential association between autoimmune thyroiditis and less aggressive tumor behavior in PTC (40-43). Nevertheless, only 49 patients (14.2%) had thyroiditis and the confidence interval for the adjusted estimate was relatively wide, indicating uncertainty in the magnitude and stability of the association. This result should therefore be regarded as hypothesis-generating rather than evidence of a protective effect. Potential biological explanations, such as enhanced immune surveillance, have been proposed, but these mechanisms were not directly evaluated in the present study (45). Conflicting evidence has also been reported, and further studies are warranted to clarify the relationship between autoimmune thyroiditis and tumor invasiveness (18).
Although ETE was analyzed as a composite outcome in the primary analysis to reflect tumor invasion across its full spectrum, supplementary analyses focusing on gETE were performed because mETE and gETE may represent distinct biological and prognostic entities. Clinicopathological characteristics differed across ETE subgroups, with gETE showing more aggressive features, including larger tumor size and a higher prevalence of lymph node metastasis. In a separate multivariable model, these factors remained independently associated with gETE, whereas the association between thyroiditis and gETE was attenuated and no longer statistically significant. These findings are consistent with the concept that gETE represents a more advanced and clinically relevant form of tumor invasion (10, 11).
The prospective observational design, standardized histopathological review and multivariable analysis strengthen the reliability of this study. The model also showed acceptable stability, discrimination and calibration, supporting the internal consistency of the findings.
Several limitations should be acknowledged. The single-center setting and relatively short enrollment period may limit generalizability. Variations in surgical technique and intraoperative assessment were not fully controlled and may have introduced residual confounding. Assessment of lymph node metastasis was limited to patients who underwent lymph node dissection, which was generally performed in those with clinical or intraoperative suspicion of nodal involvement. Therefore, the detection of lymph node metastasis may have been influenced by the surgical strategy and extent of lymph node dissection, potentially leading to underestimation of subclinical or occult nodal disease in patients who did not undergo surgical evaluation. ETE was primarily analyzed as a composite outcome combining both minimal and gross ETE, which may have obscured differences in biological behavior and clinical significance. Although a supplementary analysis focusing on gETE was performed, the relatively limited number of mETE cases precluded a more detailed comparative analysis between mETE and gETE. Interobserver variability in the assessment of ETE cannot be entirely excluded, particularly for minimal extension, despite the use of standardized histopathological criteria. Imaging features, metabolic data and molecular markers, such as BRAF and TERT promoter mutations, were not included because the primary focus was on clinicopathological factors and molecular testing was not routinely performed during the study period. Some variables were determined based on postoperative histopathological findings; therefore, caution is needed when applying these

results to preoperative risk assessment. Long-term oncologic outcomes were not assessed. In patients with multifocal disease, only the dominant tumor was included in the analysis, which may have underestimated the contribution of smaller tumor foci to ETE. However, this approach reflects routine clinical practice and current staging principles.

Beyond discrimination, the model demonstrated adequate calibration, with only minor deviations at higher predicted probabilities. These findings support the internal consistency of the multivariable model.

CONCLUSIONS

In this study, older age (≥ 55 years), larger tumor size and lymph node metastasis were independently associated with pathological ETE in patients with PTC. Coexisting thyroiditis showed a potentially inverse association with ETE; however, given the relatively small number of thyroiditis cases and the uncertainty around the effect estimate, this finding should be interpreted cautiously and requires confirmation in larger cohorts. These results provide further insight into clinicopathological factors related to tumor invasiveness. Supplementary analyses suggested that gETE may represent a more aggressive disease phenotype, characterized by stronger associations with tumor size and lymph node metastasis, as well as a significant association with older age. Further multicenter studies with larger populations, standardized ETE classification, imaging variables and molecular data are warranted to validate these findings and to determine their potential value in preoperative risk stratification.

COMPLIANCE WITH ETHICAL STANDARDS

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None.

Conflicts of interest

The authors declare no competing of interests.

Availability of data and materials

The data underlying this article cannot be shared publicly due to patient privacy and ethical restrictions. The data can be made available from the corresponding author upon reasonable request.

Authors' contributions

KN: conceptualization. KV: project administration. ND: data curation, formal analysis, writing – original draft. All authors: writing – review & editing.

Ethical approval

Human studies and subjects

This study was performed in accordance with the principles of the Declaration of Helsinki and its subsequent amendments. Ethical approval was obtained from the Institutional Ethics Committee of Ho Chi Minh City Oncology Hospital (No. 542/BVUB-HDDD). Written informed consent was obtained from all participants.

Publications ethics

Plagiarism

We hereby declare that this manuscript is an original work and has not been published or submitted for publication elsewhere. All appropriate references have been cited wherever required. This manuscript does not contain plagiarism.

Data falsification and fabrication

The authors declare that no data fabrication, falsification, or manipulation has been carried out in the preparation of this work.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263. doi: 10.3322/caac.21834.
2. National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Program Populations (1969-2020). Cancer Stat Facts: Thyroid Cancer. Available from: https://seer.cancer.gov. Accessed on January 15, 2026.
3. Harahap AS, Jung CK. Cytologic hallmarks and differential diagnosis of papillary thyroid carcinoma subtypes. J Pathol Transl Med. 2024;58(6):265-282. doi: 10.4132/jptm.2024.10.11.
4. International Collaboration on Cancer Reporting. Carcinoma of the Thyroid Histopathology Reporting Guide. Version 2.0. Sydney: ICCR; 2020.

5. Bortz MD, Kuchta K, Winchester DJ, Prinz RA, Moo-Young TA. Extrathyroidal extension predicts negative clinical outcomes in papillary thyroid cancer. Surgery. 2021;169(1):2-6. doi: 10.1016/j.surg.2020.04.003.
6. Wan F, He W, Zhang W, Zhang Y, Zhang H, Guang Y. Preoperative prediction of extrathyroidal extension: radiomics signature based on multimodal ultrasound in papillary thyroid carcinoma. BMC Med Imaging. 2023;23(1):96. doi: 10.1186/s12880-023-01049-8.
7. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al. AJCC Cancer Staging Manual. 6th ed. New York: American Joint Committee on Cancer; 2002.
8. Parvathareddy SK, Siraj AK, Qadri Z, DeVera F, Siddiqui K, Al-Sobhi SS, et al. Microscopic extrathyroidal extension results in increased rate of tumor recurrence and is an independent predictor of patient outcome in Middle Eastern papillary thyroid carcinoma. Front Oncol. 2021;11:724432. doi: 10.3389/fonc.2021.724432.
9. Diker-Cohen T, Hirsch D, Shimon I, Bachar G, Akirov A, Duskin-Bitan H, et al. Impact of minimal extrathyroidal extension in differentiated thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab. 2018;103(6):2100-2106. doi: 10.1210/jc.2018-00081.
10. Moritani S. Impact of gross extrathyroidal extension into major neck structures on prognosis of papillary thyroid carcinoma according to AJCC 8th edition. Endocr J. 2020;67(9):941-948. doi: 10.1507/endocrj.EJ19-0523.
11. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis staging system for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? Thyroid. 2017;27(6):751-756. doi: 10.1089/thy.2017.0102.
12. Liu L, Oh C, Heo JH, Park HS, Lee K, Chang JW, et al. Clinical significance of extrathyroidal extension according to primary tumor size in papillary thyroid carcinoma. Eur J Surg Oncol. 2018;44(11):1754-1759. doi: 10.1016/j.ejso.2018.05.009.
13. Yuan SS, Zhang XR, Yu XQ, Hu JJ, Chen QQ, Lu F, et al. Prediction model for extrathyroidal extension in papillary thyroid carcinoma based on ultrasound radiomics. Sci Rep. 2025;15(1):19908. doi: 10.1038/s41598-025-19908-5.
14. Javid M, Mirdamadi A, Javid M, Keivanlou MH, Amini-Salehi E, Norouzi N, et al. The evolving role of MRI in the detection of extrathyroidal extension of papillary thyroid carcinoma: a systematic review and meta-analysis. BMC Cancer. 2024;24(1):1531. doi: 10.1186/s12885-024-13288-1.
15. Chung SR, Baek JH, Choi YJ, Sung TY, Song DE, Kim TY. Sonographic assessment of the extent of extrathyroidal extension in thyroid cancer. Korean J Radiol. 2020;21(10):1187-1195. doi: 10.3348/kjr.2019.0983.
16. Kwak JY, Kim EK, Youk JH, Kim MJ, Son EJ, Choi SH, et al. Extrathyroidal extension of well-differentiated papillary thyroid microcarcinoma on ultrasonography. Thyroid. 2008;18(6):609-614. doi: 10.1089/thy.2007.0345.
17. Wang H, Zhao S, Yao J, Yu X, Xu D. Factors influencing extrathyroidal extension of papillary thyroid cancer and evaluation of ultrasonography for its diagnosis: a retrospective analysis. Sci Rep. 2023;13(1):18344. doi: 10.1038/s41598-023-45642-x.
18. Kuo CY, Yang PS, Chien MN, Cheng SP. Preoperative factors associated with extrathyroidal extension in papillary thyroid cancer. Eur Thyroid J. 2020;9(5):256-262. doi: 10.1159/000506474.
19. Ghossein R. Update to the College of American Pathologists reporting on thyroid carcinomas. Head Neck Pathol. 2009;3(1):86-93. doi: 10.1007/s12105-009-0109-2.
20. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, et al. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022;33(1):27-63. doi: 10.1007/s12022-022-09707-3.
21. Haddad RI, Bischoff L, Agosto Salgado S, Applewhite M, Berner V, Blomain E, et al. NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. Version 1.2025. Plymouth Meeting: National Comprehensive Cancer Network; 2025. Available from: https://www.nccn.org. Accessed on January 15, 2026.
22. Marongiu A, Nuvoli S, De Vito A, Vargiu S, Spanu A, Madeddu G. Minimal extrathyroid extension (mETE) as the only risk factor in patients with papillary thyroid carcinoma: its clinical impact on recurrence and outcome during long-term follow-up. Biomedicines. 2024;12(2):350. doi: 10.3390/biomedicines12020350.
23. Amit M, Boonsripitayanon M, Goepfert RP, Tam S, Busaidy NL, Cabanillas ME, et al. Extrathyroidal extension: does strap muscle invasion alone influence recurrence and survival in patients with differentiated thyroid cancer? Ann Surg Oncol.

2018;25(11):3380-3388. doi: 10.1245/s10434-018-6563-x.
24. Tran B, Roshan D, Abraham E, Wang L, Garibotto N, Wykes J, et al. An analysis of the American Joint Committee on Cancer 8th edition T staging system for papillary thyroid carcinoma. J Clin Endocrinol Metab. 2018;103(6):2199-2206. doi: 10.1210/jc.2017-02551.
25. Kaliszewski K, Diakowska D, Nowak Ł, Wojtczak B, Rudnicki J. The age threshold of the 8th edition AJCC classification is useful for indicating patients with aggressive papillary thyroid cancer in clinical practice. BMC Cancer. 2020;20(1):1166. doi: 10.1186/s12885-020-07636-0.
26. Hsu YC, Liu CL, Yang PS, Tsai CH, Lee JJ, Cheng SP. Interaction of age at diagnosis with transcriptional profiling in papillary thyroid cancer. World J Surg. 2016;40(12):2922-2929. doi: 10.1007/s00268-016-3625-8.
27. Hay N. Reprogramming glucose metabolism in cancer: can it be exploited for cancer therapy? Nat Rev Cancer. 2016;16(10):635-649. doi: 10.1038/nrc.2016.77.
28. Wu Y, Wei J, Chen X, Qin Y, Mao R, Song J, et al. Comprehensive transcriptome profiling in elderly cancer patients reveals aging-altered immune cells and immune checkpoints. Int J Cancer. 2019;144(7):1657-1663. doi: 10.1002/ijc.31875.
29. Lee HS, Park C, Kim SW, Park T, Chun BK, Hong JC, et al. Correlation of minimal extrathyroidal extension with pathologic features of lymph node metastasis in patients with papillary thyroid carcinoma. J Surg Oncol. 2015;112(6):592-596. doi: 10.1002/jso.24051.
30. Walczyk A, Gąsior-Perczak D, Pałyga I, Kopczyński J, Kuchareczko A, Niedziela E, et al. Risk characteristics of papillary thyroid cancer 1-4 cm associated with increased tumour size. Clin Exp Med. 2025;25(1):155. doi: 10.1007/s10238-025-01596-0.
31. Park S, Oh CM, Cho H, Lee JY, Jung KW, Jun JK, et al. Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study. BMJ. 2016;355:i5745. doi: 10.1136/bmj.i5745.
32. Xu S, Han Y. The overdiagnosis of thyroid micropapillary carcinoma: the rising incidence, inert biological behavior and countermeasures. J Oncol. 2021;2021:5544232. doi: 10.1155/2021/5544232.
33. Hau NX, Quang LV. Cervical lymph node metastasis presentation of patients with thyroid carcinoma. Vietnam Med J. 2022;515(1). doi: 10.51298/vmj.v515i1.2705. (In Vietnamese).
34. Lombardi CP, Bellantone R, De Crea C, Paladino NC, Fadda G, Salvatori M, et al. Papillary thyroid microcarcinoma: extrathyroidal extension, lymph node metastases and risk factors for recurrence in a high prevalence of goiter area. World J Surg. 2010;34(6):1214-1221. doi: 10.1007/s00268-009-0375-x.
35. Kim JW, Roh JL, Gong G, Cho KJ, Choi SH, Nam SY, et al. Extent of extrathyroidal extension as a significant predictor of nodal metastasis and extranodal extension in patients with papillary thyroid carcinoma. Ann Surg Oncol. 2017;24(2):460-468. doi: 10.1245/s10434-016-5594-4.
36. Seok J, Ryu CH, Park SY, Lee CY, Lee YK, Hwangbo Y, et al. Factors affecting central node metastasis and metastatic lymph node ratio in papillary thyroid cancer. Otolaryngol Head Neck Surg. 2021;165(4):519-527. doi: 10.1177/0194599821991465.
37. Feng JW, Qin AC, Ye J, Pan H, Jiang Y, Qu Z. Predictive factors for lateral lymph node metastasis and skip metastasis in papillary thyroid carcinoma. Endocr Pathol. 2020;31(1):67-76. doi: 10.1007/s12022-019-09599-w.
38. Mao J, Zhang Q, Zhang H, Zheng K, Wang R, Wang G. Risk factors for lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2020;11:265. doi: 10.3389/fendo.2020.00265.
39. Wang Y, Nie F, Wang G, Liu T, Dong T, Sun Y. Value of combining clinical factors, conventional ultrasound and contrast-enhanced ultrasound features in preoperative prediction of central lymph node metastases of different sized papillary thyroid carcinomas. Cancer Manag Res. 2021;13:3403-3415. doi: 10.2147/CMAR.S299157.
40. Osborne D, Choudhary R, Vyas A, Kampa P, Abbas LF, Chigurupati HD, et al. Hashimoto's thyroiditis effects on papillary thyroid carcinoma outcomes: a systematic review. Cureus. 2022;14(8):e28054. doi: 10.7759/cureus.28054.
41. Tang Q, Pan W, Peng L. Association between Hashimoto thyroiditis and clinical outcomes of papillary thyroid carcinoma: a meta-analysis. PLoS One. 2022;17:e0269995. doi: 10.1371/journal.pone.0269995.
42. Wu K, Shi L, Wang J, Xie L. Association between papillary thyroid carcinoma and lymphocytic thyroiditis: a retrospective study. Oncol Lett. 2023;25(4):148. doi: 10.3892/ol.2023.13734.
43. Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and his-

tologically proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol. 2013;168(3):343-349. doi: 10.1530/EJE-12-0903.

44. Xing M, Liu R, Liu X, Murugan AK, Zhu G, Zeiger MA, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. J Clin Oncol. 2014;32(25):2718-2726. doi: 10.1200/JCO.2014.55.5094.
45. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms and consequences. Immunity. 2019;51(1):27-41. doi: 10.1016/j.immuni.2019.06.025.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. *Comparison of clinicopathological characteristics according to extrathyroidal extension subgroups.*

VARIABLES	NO ETE	METE	GETE	P-VALUE
Age				0.080
<55 years	238 (82.9)	16 (5.6)	33 (11.5)	
≥55 years	42 (71.2)	4 (6.8)	13 (22.0)	
Sex				0.314
Male	35 (72.9)	4 (8.3)	9 (18.8)	
Female	245 (82.2)	16 (5.4)	37 (12.4)	
Reason for consultation				0.02
Health screening	211 (84.4)	8 (3.2)	31 (12.4)	
Symptomatic	69 (71.9)	12 (2.5)	15 (15.6)	
Tumor size (mm)				<0.001
≤10	204 (89.1)	13 (5.7)	12 (5.2)	
>10–20	51 (62.2)	7 (8.5)	24 (29.3)	
>20–40	24 (75.0)	0 (0.0)	8 (25.0)	
>40	1 (33.3)	0 (0.0)	2 (66.7)	
Lymph node metastasis				<0.001
Yes	64 (65.3)	7 (7.1)	27 (27.6)	
No	216 (87.1)	13 (5.2)	19 (7.7)	
Extranodal extension				<0.001
Yes	5 (38.5)	0 (0.0)	8 (61.5)	
No	275 (82.6)	20 (6.0)	38 (11.4)	
Thyroiditis				0.035
Yes	46 (93.9)	0 (0.0)	3 (6.1)	
No	234 (78.8)	20 (6.7)	43 (14.5)	

ETE: extrathyroidal extension; mETE: minimal extrathyroidal extension; gETE: gross extrathyroidal extension. Values are presented as n (row %). P-values were calculated using the chi-square test or Fisher's exact test, as appropriate.