



## Clinical implications of microscopic extrathyroidal extension in patients with papillary thyroid carcinoma



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### ABSTRACT

**Background:** Extrathyroidal extension (ETE) is a poor prognostic factor in papillary thyroid carcinoma (PTC). However, the impact of the degree of ETE, especially microscopic ETE, has not been well established. The purpose of present study was to compare differences in clinicopathological characteristics and clinical outcomes according to the presence or extent of ETE.

**Methods:** Data from 381 patients who underwent total thyroidectomy with/without lymph node (LN) dissection for PTC between 2004 and 2010 were analyzed. Clinicopathological features such as age, gender, LN metastasis, capsular invasion, lymphovascular invasion, and recurrence were compared among three groups divided according to degree of ETE: no ETE (n = 144), microscopic ETE (n = 191), and macroscopic ETE (n = 46).

**Results:** Tumor size, LN metastasis, lymphovascular invasion, extent of surgery, and administration of postoperative radioactive iodine (RAI) were significantly correlated with degree of ETE. Especially, among the patients with a primary tumor size  $\leq 4$  cm, the patients with microscopic ETE showed more LN metastasis and lymphovascular invasion than those without ETE, whereas less LN metastasis and lymphovascular invasion than those with macroscopic ETE. In addition, the microscopic ETE group had a significantly lower 5-year recurrence free survival (RFS) than the no-ETE group (92.1% vs. 99.3%,  $p < 0.001$ ) and a significantly higher 5-year RFS than the macroscopic ETE group (92.1% vs. 65.2%,  $p < 0.001$ ).

**Conclusions:** The degree of ETE is correlated with clinicopathologic features and tumor recurrence. Patients with microscopic ETE have a poorer clinical outcome than those without ETE, but they showed a better outcome than patients with macroscopic ETE.

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### Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for ~90% of all thyroid carcinomas [1]. It is a differentiated carcinoma with a relatively good prognosis and a low mortality rate. However, PTC frequently spreads to the cervical lymph nodes (LN), which is associated with a higher locoregional recurrence. Various clinicopathological factors, including age, gender, tumor size, extrathyroidal extension (ETE), and distant metastasis, are associated with the prognosis of PTC [2–4].

ETE refers to the invasion of the primary tumor into adjacent tissues beyond the thyroid gland [5–8]. It is an important prognostic factor that is associated with adverse outcomes [9–12]. The American Joint Committee on Cancer (AJCC) includes ETE as part of the staging system [13]. It defines T3 as a tumor  $>4$  cm in diameter that is limited to the thyroid or any tumor with minimal ETE. In this staging system, minimal ETE means extension to the sternothyroid muscle or perithyroidal soft tissues, whereas extensive ETE involves the subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve. Microscopic ETE can be detected histologically using microscopic evaluation, but there is no evidence of ETE in gross findings during surgery [14]. Even when the primary tumor is sized  $\leq 4$  cm, if microscopic ETE is found in the postoperative biopsy, the tumor stage is increased to T3. This means that further treatments, such as radioactive iodine ablation, need to be considered, which differs from cases involving patients who have no ETE or macroscopic

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ETE (as determined by the surgeon during thyroidectomy). However, the clinical significance of microscopic ETE and its prognostic significance, such as whether it is associated with recurrence, remain controversial [14–20].

The present study aimed to compare the clinicopathological features among groups of patients divided according to presence or absence and the extent (microscopic or macroscopic extension) of ETE and to investigate the effect of microscopic ETE on tumor recurrence.

## Patients and methods

The medical records of patients who underwent a total thyroidectomy and/or cervical LN dissection for PTC at the Department of Otolaryngology-Head and Neck Surgery of Chungnam National University Hospital from January 2004 to December 2010 were reviewed retrospectively. The study population included patients who had postoperative follow up for at least 5 years. A total of 381 patients with PTC were enrolled in the study. According to preoperative imaging and cytologic results, central LN dissection or lateral LN dissection were performed as necessary. Patients who received only a lobectomy, those with another confirmed pathologic disease or with positive resection margins, and those whose medical records were unclear were excluded. Based on findings during surgery and histopathologic examinations, the patients were divided into three groups: no ETE, microscopic ETE (tumor invasion beyond the thyroid capsule identified at the time of pathologic examination), and macroscopic ETE (gross tumor invasion identified at the time of surgery confirmed by histopathologic review) [14]. Then, relationships between the presence or absence and extent of ETE and demographic variables (e.g., age, gender, tumor size, multifocality), oncological characteristics (e.g., ETE and LN metastasis), surgical method, the presence or absence of adjuvant treatment, and recurrence were analyzed.

Of the 381 patients, 91 received a total thyroidectomy alone, 242 underwent a total thyroidectomy and central LN dissection, and 48 had a total thyroidectomy and central and lateral LN dissections at the same time. All patients had postoperative thyroid-stimulating hormone (TSH) suppressive therapy, and application and dose of postoperative radioactive iodine (RAI) treatment were determined by the presence of ETE, cervical LN metastasis, patient age, and performance status. Patients received a routine clinical examination every 3 months in the initial year and were then examined at yearly intervals. Recurrence during follow up was monitored by measuring serum-free T4, thyroid-stimulating hormone (TSH), thyroglobulin (Tg), and anti-Tg antibodies; neck ultrasonography; and computed tomography (CT). For patients suspected for disease recurrence, we conducted fine needle aspiration biopsy and CT scan. The following criteria were used to define recurrence: either pathologic evidence of disease on excision or cytology, or recurrent disease confirmed by elevated Tg and WBS. Recurrence was diagnosed after finding new evidence of disease in patients who initially met the criteria for remission (no clinical or imaging evidence of tumors, serum Tg level <2 ng/ml during TSH suppression, and stimulation in the absence of interfering antibodies).

SPSS version 19.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis. Relationships among clinicopathologic factors, including age, gender, tumor size, LN metastasis, multifocality, and recurrence, and the extent of ETE (no ETE, microscopic ETE, or macroscopic ETE) were determined using Chi square or Fisher's exact tests. The Kaplan–Meier method was used for recurrence-free survival analysis. Statistical significance was defined as  $p < 0.05$ .

## Results

### Patients and tumor characteristics

Of the 381 patients, 61 were male and 320 were female; there were 5.2 times more females than males. The median age at diagnosis was 48 years (range, 18–81 years), and 57.7% of patients were aged  $\geq 45$  years. The median follow-up period was 87 months (range, 60–142 months), and the median tumor size was 1.26 cm (range, 0.3–5 cm). In terms of tumor size, 215 patients (56.7%) had microcarcinomas sized  $\leq 1$  cm, and 12 patients (1.9%) had tumors sized  $> 4$  cm. Of the 237 patients (62.2%) with ETE, 191 (80.6%) exhibited microscopic ETE, and 46 patients (19.4%) were recognized intraoperatively as having macroscopic ETE. Metastasis in the cervical LN was found in 162 patients (42.5%) during surgery, and lymphovascular invasion in permanent pathology was identified in 264 patients (68.8%). In total, 350 (91.9%) underwent postoperative radioactive iodine therapy. Recurrence was identified in 32 patients (8.4%) during follow up; among the recurrences twenty-five were identified at the lateral neck LN, three were at thyroid bed and central neck LN, one at central neck LN, one at both lateral and central neck LN, one at the lung, and one at the bone. The mean duration until recurrence was 26.8 months (Table 1).

### Clinicopathological features according to extent of ETE

Table 2 shows the clinicopathological characteristics of the patient groups according to the extent of ETE. The gender and the multifocality of the primary tumor did not significantly differ between cases with and without ETE. Compared with patients without ETE, those with microscopic ETE had a significantly larger tumors, positive LN metastasis, and lymphovascular invasion. Patient with macroscopic ETE also had a significantly larger tumors, LN metastasis, and lymphovascular invasion compared with the no-ETE group. When the clinicopathological characteristics of patients with microscopic and macroscopic ETE were compared, patients with macroscopic ETE had significantly larger tumors, positive LN metastasis, and lymphovascular invasion than those with microscopic ETE. With respect to the extent of surgery or postoperative RAI treatment, more aggressive treatment was applied to patients with ETE. A significantly wider extent of neck dissection and higher dose RAI treatment were also performed in the macroscopic ETE group compared with the microscopic ETE group. Consistent with this, recurrence was found in one patient (0.7%) in the no-ETE group, 15 patients (7.9%) in the microscopic ETE group, and 16 patients (34.8%) in the macroscopic ETE group; recurrence was significantly more common in the following order: macroscopic ETE group, microscopic ETE group, and without-ETE group (Table 2). The mean duration until recurrence was 19 months in the no-ETE group, 26.2 months in the microscopic ETE group, and 27.8 months in the macroscopic ETE group; there were no significant differences among the groups.

### Effects of microscopic ETE in patients with cT1/T2 stage primary tumors sized $\leq 4$ cm

Patients with a primary tumor size  $\leq 4$  cm, preoperatively diagnosed as a T1/T2 clinical stage were postoperatively divided into two groups based on permanent biopsy results: patients without histological ETE (pT1/T2) and patients with microscopic ETE (pT3). The clinicopathological characteristics were compared between the two groups. Of the 328 patients with tumors sized  $\leq 4$  cm who were not clinically suspected to have ETE, 141 (43.0%) were diagnosed with pT1/T2 due to the absence of microscopic ETE and 187 (57.0%) were diagnosed with pT3 due to the

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