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Characteristics and significance of minimal and maximal extrathyroidal extension in papillary thyroid carcinoma

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SUMMARY

Objectives: Maximal extrathyroidal extension (ETE) is known to be an important prognostic factor in papillary thyroid carcinoma (PTC). However, the significance of minimal ETE is controversial. The aim of this study was to investigate the clinicopathologic characteristics and prognostic significance of minimal vs maximal ETE in PTC.

Materials and methods: A group of 967 patients who underwent thyroidectomy for PTC in a tertiary hospital between January 2000 and December 2011 were studied retrospectively. Patients were classified into three groups: absence of ETE, and minimal and maximal ETE. The minimal ETE group was further categorized into two subgroups according to invasion of strap muscles or no invasion (STI+ and STI−).

Results: Gender did not differ between the three groups of patients. The mean age of the patients with maximal ETE was significantly higher than in those belonging to the other groups. Tumor size, bilaterality, lymph node metastasis and stage increased significantly according to the degree of ETE. Recurrence and survival rates did not differ between the absence and minimal ETE groups, or between the STI− and STI+ subgroups of minimal ETE. However, the maximal ETE group had significantly higher recurrence and lower survival rates than the other groups ($P < 0.001$).

Conclusion: Maximal ETE is a significant factor for poor prognosis. However, minimal ETE is not associated with increased recurrence or decreased survival in patients with PTC.

Introduction

Extrathyroidal extension (ETE) is defined as extension of the primary tumor beyond the thyroid capsule into the perithyroidal soft tissues, strap muscles, and adjacent structures [1,2]. It has been considered an important prognostic factor in papillary thyroid carcinoma (PTC) although there are many others, such as age and sex of patients, primary tumor size, lymph node metastasis, and distant metastasis [1–6]. ETE is included in almost all prognostic classification systems, such as EORTC (European Organization for Research and Treatment of Cancer), MACIS (metastasis, age, completeness of resection, invasion, and size), AMES (age, metastasis, ETE, and size), AGES (age, grade, ETE, and size), and the AJCC (American Joint Committee on Cancer) TNM staging system [7–11].

In general, ETE has been reported as an adverse prognostic factor for survival and recurrence of PTC. Some authors found that it was associated with low survival and high recurrence rates [1,12], although others found that it did not adversely influence tumor behavior or survival in patients with PTC or follicular thyroid carcinoma [13].

ETE can be categorized as microscopic or macroscopic depending on the extent of invasion. It has been reported that the outcome of macroscopic gross ETE was worse than that of microscopic local invasion [14–17]. However, in the previous studies the definition of ETE was neither clear nor constant. The terms minimal ETE and maximal ETE have also been used inconsistently in many previous studies, so that it is somewhat difficult to interpret the results.

In particular, although maximal ETE is considered a factor for poor prognosis, the significance of minimal ETE has not been clearly established. Some studies have shown that microscopic ETE alone does not have a significant impact on oncologic outcomes [15,18,19], though in another study its significance was undetermined [16]. Other authors have reported that the 20-year overall survival rate with microscopic ETE did not differ from macroscopic ETE [2].

The aim of this study was to investigate the clinicopathologic characteristics and prognostic significance of ETE in patients with

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PTC, in relation to the degree of ETE, particularly minimal vs maximal ETE.

Materials and methods

Patients

The medical records of 967 patients who underwent thyroidectomy for PTC between January 2000 and December 2011 were studied retrospectively. The exclusion criteria were recurrent cases, other types of malignancy, concurrent PTC and other types of malignancy, and cases with follow-up of less than 24 months. Informed consent was obtained from each patient and the study was approved by the Institutional Review Board of Hanyang University Hospital.

Patients were categorized into three groups according to the extent of ETE on pathologic examinations: absence of ETE, minimal ETE, and maximal ETE. Absence of ETE was defined as the primary tumor confined within the thyroid capsule; minimal ETE was defined as extension of the primary tumor to the perithyroidal soft tissues or the strap muscles; maximal ETE was defined as extension of the primary tumor to the trachea, esophagus, recurrent laryngeal nerve, larynx, subcutaneous soft tissue, skin, internal jugular vein, or carotid artery. Minimal ETE was further divided into two subgroups in relation to strap muscle invasion (STI+, invasion of strap muscle; STI−, no invasion of strap muscle).

Comparison of clinicopathologic characteristics and prognosis

The groups of patients were analyzed with regard to age, gender, primary tumor size, multifocality, bilaterality, lymphovascular invasion, lymph node metastasis, TNM staging (AJCC 7th edition), extent of thyroidectomy and neck dissection, and postoperative radioactive iodine (RAI) ablation. Treatment outcomes such as overall survival, disease-specific survival and disease-free survival were compared. Recurrence was defined as the development of new structural abnormality on imaging studies such as neck ultrasonography, computed tomography (CT), whole-body iodine scan, or PET–CT.

Statistical analysis

The IBM Statistical Package for Social Science (SPSS) Statistics version 21.0 for Windows (IBM Incorporated, Armonk, NY, USA) was used for the analysis. Differences between the groups were assessed using independent *t*-tests, Fisher's exact tests, and Pearson's χ^2 tests. Rates of overall survival, disease-specific survival, and disease-free survival were calculated using the Kaplan–Meier method. The Kaplan–Meier curves for each group were compared using the log-rank test, and binary logistic regression analysis was used for multivariate analysis. $P < 0.05$ was considered significant.

Results

Among 967 patients with PTC, 491 (50.8%) had no ETE, 403 (41.7%) had minimal ETE, and 73 (7.5%) had maximal ETE. The STI+ and STI− subgroups of the 403 patients with minimal ETE comprised 121(30.0%) and 282 (70.0%) patients, respectively. All patients of the STI+ subgroup showed invasion only to the sternothyroid muscle. In the maximal ETE group, the most commonly involved structures were the recurrent laryngeal nerve (49 cases), trachea (36 cases), esophagus (15 cases), and larynx (13 cases), and followed by the sternocleidomastoid muscle (8 cases), internal jugular vein (7 cases), pharynx (6 cases), vagus nerve (2 cases), and common carotid artery (2 cases) in multiple counting of involved sites.

Patient demographics and clinicopathologic characteristics

Patient demographics and clinicopathologic characteristics are shown in Table 1. There were no significant differences in demographic features between the absence of ETE and minimal ETE groups, but the maximal ETE group was older and its follow-up period longer than in the other groups. The STI+ subgroup had a higher female ratio than the STI− subgroup (89.3% vs 80.9%, respectively, $P = 0.038$).

The minimal and maximal ETE groups had larger tumor sizes and higher rates of bilaterality than the absence of ETE group, and the maximal ETE group also had a larger tumor size and higher bilaterality than the minimal ETE group ($P < 0.001$ and $P = 0.031$, respectively). Multifocality tended to increase in relation to the degree of ETE although this did not reach statistical significance. The STI+ subgroup had a larger tumor size and higher multifocality than the STI− subgroup ($P < 0.001$ and $P = 0.013$, respectively).

Lymphovascular invasion and cervical lymph node metastasis were more common in the minimal ETE and maximal ETE groups than in the group without ETE. The maximal ETE group had a higher frequency of lymph node metastasis than the minimal ETE group. The rates of lymphovascular invasion and cervical lymph node metastasis did not differ between the STI− and STI+ subgroups.

The minimal ETE group had significantly more advanced disease than the absence of ETE group, as did the maximal ETE group. There was no significant difference in TNM stage between the STI− and STI+ subgroup.

Surgical treatment and radioactive iodine ablation

Patients in the maximal ETE group more frequently underwent total thyroidectomy and neck dissection including central and lateral neck dissection, as well as postoperative RAI ablation than those in the other two groups (Table 2). Total thyroidectomy was more frequent in the STI+ subgroup than in the STI− subgroup ($P < 0.001$), but the frequencies of neck dissection and postoperative RAI ablation did not differ between them.

Factors related to extrathyroidal extension

ETE was associated with tumor size, lymphovascular invasion, and lateral node metastasis in the multivariate analysis. In the stratification analysis according to the extent of ETE, minimal ETE was associated with tumor size, lymphovascular invasion, and lateral node metastasis (Table 3), whereas maximal ETE was associated with age, tumor size, and lateral node metastasis in the multivariate analysis (Table 4).

Recurrence and survival outcomes

Overall, there were 46 (4.8%) cases of recurrence: 16 (3.3%) in the absence of ETE group; 10 (2.5%, $P = 0.491$) in the minimal ETE group; 20 (27.4%) in the maximal ETE group, which was significantly higher than in the other two groups ($P < 0.001$ for both). There was no significant difference in recurrence between the STI− (7 cases, 2.5%) and STI+ (3 cases, 2.5%) subgroup ($P = 0.999$). The mean times to recurrence in the absence of ETE, minimal ETE, and maximal ETE groups were 58.4 ± 35.8 months (range, 14–137), 34.5 ± 17.5 months (range, 16–69), and 41.3 ± 24.5 months (range, 7–115), respectively.

10-year disease-free survival rates were 94.8%, 96.5% and 59.1% in the absence of ETE, minimal ETE, and maximal ETE groups, respectively (Fig. 1). Survival of the maximal ETE group was