

Prognostic Significance of Extrathyroid Extension of Papillary Thyroid Carcinoma: Massive but Not Minimal Extension Affects the Relapse-free Survival

Yasuhiro Ito, MD, Chisato Tomoda, MD, Takashi Uruno, MD, Yuuki Takamura, MD, Akihiro Miya, MD, Kaoru Kobayashi, MD, Fumio Matsuzuka, MD, Kanji Kuma, MD, Akira Miyauchi, MD

Department of Surgery, Kuma Hospital, 8-2-35, Shimoyamate-dori, Chuo-ku, Kobe City 650-0011, Japan

Abstract

Objectives: Extrathyroid extension has been recognized as a prognostic factor in papillary thyroid carcinoma. In the most recent version of the UICC TNM classification system, extrathyroid extension has been classified into two grades, minimal extension (extension to sternothyroid muscle or perithyroid soft tissues) and massive extension (extension to subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve). In this study, we investigated the prognostic significance of each of the two types of extension.

Patients and Methods: One thousand and sixty-seven patients with papillary thyroid carcinoma without distant metastasis at surgery, who underwent surgical treatment in Kuma hospital between 1990 and 1995 and had been followed postoperatively for 60 months or more, were enrolled in this study. The grading of extrathyroid extension was based on both pathological findings and intra-operative surgical findings.

Results: In univariate analysis, although patients with massive extension showed a significantly worse relapse-free survival (RFS) rate than those with no or minimal extension ($P < 0.0001$), there was no difference in the RFS rate between patients with no extension and those with minimal extension. Among patients with massive extension, the RFS rate tended to be worse in those with posterior extension than in those with anterior extension ($P = 0.0562$). Furthermore, the RFS rate of patients with massive posterior extension only to the recurrent nerve demonstrated a better RFS rate than those with extension to other posterior organs ($P = 0.0052$). Multivariate analysis demonstrated that massive extrathyroid extension is recognized as an independent prognostic factor for RFS ($P = 0.0003$).

Conclusions: These findings suggest that (1) upgrading of T category for tumors with massive extension is appropriate, whereas that for tumors with only minimal extension is not, and (2) careful surgical treatment and postoperative follow-up are required for tumors with massive extension to posterior organs other than the recurrent laryngeal nerve.

Table 1.

Comparison of International Union Against Cancer 5th and 6th editions classification system for thyroid papillary carcinoma

AJCC/UICC 5th edition	AJCC/UICC 6th edition
T: primary tumor	T: primary tumor
T1: tumor 1 cm or less in greatest dimension, limited to the thyroid	T1: tumor 2 cm or less in greatest dimension, limited to the thyroid
T2: tumor more than 1 cm but not more than 4 cm in greatest dimension, limited to the thyroid	T2: tumor more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
T3: tumor more than 4 cm in greatest dimension, limited to the thyroid	T3: Tumor more than 4 cm in greatest dimension, limited to the thyroid or any tumor with minimal extrathyroid extension (e.g. extension to sternothyroid muscle or perithyroid soft tissues)
T4: tumor of any size extending beyond the thyroid capsule	T4a: tumor extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissue, larynx, trachea, esophagus, recurrent laryngeal nerve T4b: tumor invades prevertebral fascia, mediastinal vessels, or encases carotid artery
N: regional lymph nodes	N: regional lymph nodes
N1: regional lymph node metastasis	N1: regional lymph node metastasis
N1a: metastasis in ipsilateral cervical lymph node (s)	N1a: metastasis in level VI (pretracheal and paratracheal, including prelaryngeal and Delphian lymph nodes)
N1b: metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node(s)	N1b: metastasis in other unilateral, bilateral, or contralateral cervical or upper/superior mediastinal lymph nodes
Stage grouping (papillary or follicular)	Stage grouping
Under 45 years of age	Under 45 years of age
Stage I Any T Any N M0	Stage I Any T Any N M0
Stage II Any T Any N M1	Stage II Any T Any N M1
45 years and over	Papillary or follicular 45 years or older and medullary
Stage I T1 N0 M0	Stage I T1 N0 M0
Stage II T2 N0 M0	Stage II T2 N0 M0
T3 N0 M0	Stage III T3 N0 M0
Stage III T4 N0 M0	T1, T2, T3 N1a M0
Any T N1 M0	Stage IVA T1, T2, T3 N1b M0
Stage IV Any T Any N M1	T4a N0, N1 M0
	Stage IVB T4b Any N M0
	Stage IVC Any T Any N M1

TX, T0, NX, N0, and M: distant metastasis were abbreviated in this table because they are the same in the 5th and 6th editions of the TNM classification.

istic and grows slowly, but there are some clinicopathological parameters predicting a poor prognosis. Extrathyroid extension has been recognized as a prominent prognostic factor of thyroid carcinoma, and it has been adopted by the TNM classification established by the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC). The presence of extrathyroid extension has been involved in the T category, and in the 5th edition of the UICC classification published in 1997,¹ all tumors of any size extending beyond the thyroid capsule were classified as T4 (Table 1). However, in Japan, surgeons were doubtful that tumors with only minimal extrathyroid extension also have an aggressive character and questioned whether it

is appropriate for such cases to be upgraded to the highest T category. Thus, a category to evaluate the degree of extrathyroid extension, ex, has been separately established. Tumors with only minimal extension, such as extension to the sternothyroid muscle or perithyroid soft tissues, were graded as ex1, and those with massive extension, such as extension to subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve, as ex2. Then, although tumors with ex2 were upgraded to T4, ex1 tumors were graded in the same T category as ex0 tumors. In the 6th edition of the UICC classification (Table 1), the T category has been partially revised.² In this version, ex2 tumors of any size are upgraded to T4a or T4b, while ex1 tumors are downgraded

Table 2.
Range of thyroidectomy and lymph node dissection in 1167 patients with papillary carcinoma

Thyroidectomy	Number of patients	Lymph node dissection	Number of patients
Total or near total thyroidectomy	662	Bilateral MND	117
Subtotal thyroidectomy	70	Unilateral MND	891
Lobectomy	427	Central node dissection	132
Isthmectomy	5	Not done	27
Partial lobectomy	3		

MND: modified radical neck dissection.

to T3 from T4. However, it remains debatable whether ex1 tumors measuring 4 cm or less (classified as T2 or T1 if the lesion is ex0) should be classified into a higher T grade.

Regarding this point, we previously demonstrated that the relapse-free survival (RFS) of patients aged over 45 years with ex1 tumors does not significantly differ from that of those with ex0 tumors, if the tumor measures 4 cm or less, whereas patients with ex2 tumors showed a worse RFS rate than those with ex1 or ex0 tumors on univariate analysis.³ However, there have not been any studies of the prognostic significance of ex1 or ex2 tumors in a large series including patients of all ages by multivariate as well as univariate analyses. In this study, therefore, we used the Kaplan-Meier method and Cox-Hazard regression models to investigate whether and how ex2 and ex1 affected the prognosis of 1167 patients, who underwent curative surgery for papillary thyroid carcinoma.

PATIENTS AND METHODS

Patients

One thousand one hundred sixty-seven patients with primary papillary carcinoma, who underwent curative surgery at our hospital between January 1992 and December 1995 and had been followed postoperatively for 60 months or more, were enrolled in this study. Subjects consisted of 72 males and 1095 females with an average patient age of 47.4 + 13.5 years (range: 8–82 years). The range of thyroidectomy and extent of lymph node dissection in these patients are summarized in Table 2.

Evaluation of Extrathyroid Extension

We categorized tumors in three grades of extrathyroid extension, no extension (ex0), minimal extension

(extension to the sternothyroid muscle, perithyroid soft tissues: ex1) and massive extension (extension to subcutaneous soft tissues, larynx, trachea, esophagus, and recurrent laryngeal nerve: ex2), based on the degree of extrathyroid extension. The grading of extrathyroid extension was based on pathological findings as well as intraoperative surgical findings. Of 1167 patients, 134 were graded as ex2, 356 were as ex1, and the remaining 677 were as ex0.

Follow-up of Patients

After surgery, patients were continuously followed as outpatients by ultrasonography, computed tomography, and scintigraphy to identify carcinoma recurrence in lymph nodes, remnant thyroid, and/or distant organs. We diagnosed recurrence in lymph node and/or remnant thyroid by performing ultrasonography-guided fine-needle aspiration biopsy of suspicious lesions. Postoperative follow-up periods averaged 110.7 ± 33.9 months (range: 60–175 months). Recurrence has been identified in 118 patients (10.1%). The organs showing recurrence were the central lymph node in 12 patients, lateral node in 68 patients, mediastinal node in 3 patients, other nodes in 5 patients, lung in 13 patients, skin in 4 patients, residual thyroid in 13 patients, thyroid bed after thyroidectomy in 4 patients, muscle in 3 patients, bone in 1 patient, and brain in 1 patient. Eleven patients showed recurrence in 2 or more organs.

Statistical Analyses

The Kaplan-Meier method and the log rank test were used to estimate survival rates and to test the quality of survival curves, respectively. Furthermore, multivariate analysis was performed by Cox-Hazard regression model. These analyses were performed using StatView-J 5.0. A *P* value less than 0.05 was regarded as significant, and a value between 0.05 and 0.1 was regarded as marginally significant.

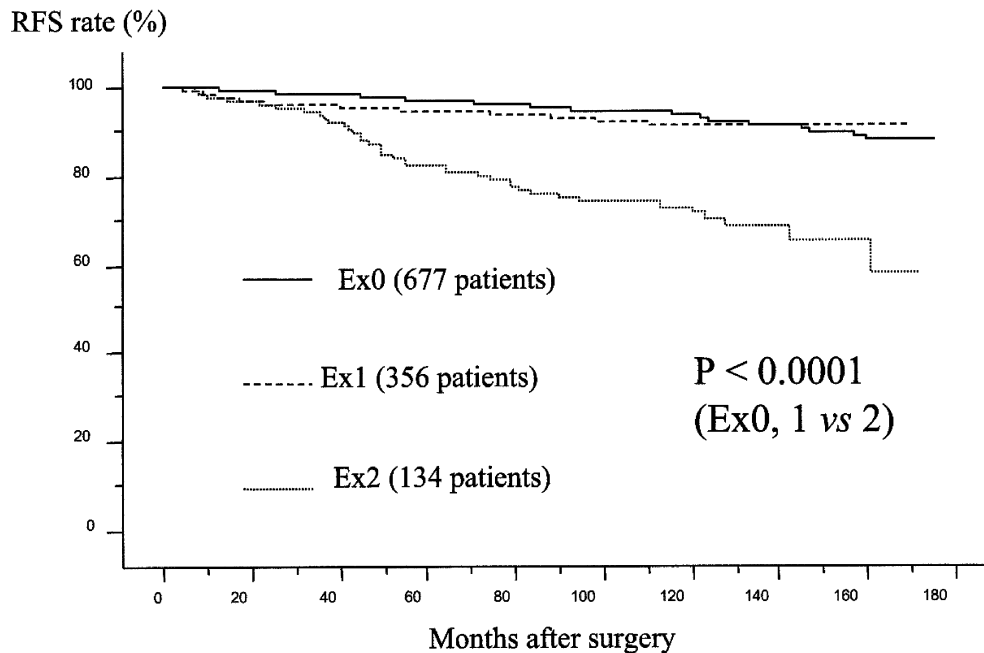


Figure 1. Comparison of relapse-free survival (RFS) among papillary carcinoma patients with no, minimal, and massive extrathyroid extension.

RESULTS

Prognostic Impact of Extrathyroid Extension

First, we investigated whether and how the two grades of extrathyroid extension affected the relapse-free survival (RFS) of patients. To date, 40 of 134 ex2 patients (29.9%), 28 of 356 ex1 patients (7.8%), and 50 of 677 ex0 patients (7.4%) have shown recurrence. The 10-year recurrence rate was 29.9% for ex2, 8.6% for ex1, and 6.5% for ex0 patients. Figure 1 indicates the Kaplan-Meier curve of patients with ex2, ex1 and ex0. Ex2 patients showed a worse RFS rate than ex1 or ex0 patients ($P < 0.0001$), but there was no significant difference in the RFS rate between ex1 and ex0 patients. The same results were obtained on analysis of the subset of patients aged over 45 years (data not shown).

For the next phase of the study, we studied the difference of prognostic impact of the organs to which carcinoma extended for ex2 patients. Of the 134 ex2 tumors, 15 extended only to the anterior direction, and the remaining 119 to the posterior direction or to both anterior and posterior directions. To date, 39 patients with tumors demonstrating posterior extension (32.8%) showed recurrence, whereas recurrence could be observed in only one patient with tumor demonstrating anterior extension only (7.1%). As shown in Figure 2, tumors with posterior extension tended to show a worse RFS rate than those with only anterior extension ($P = 0.0566$).

Extension to the recurrent laryngeal nerve is a phenomenon that is most frequently observed in ex2 tumors extending in the posterior direction, and 77 of the 119 ex2 tumors (64.7%) extended to the nerve. Among these, 50 tumors extended only to the recurrent laryngeal nerve. Figures 3 and 4 demonstrate the prognostic significance of ex2 extension to the recurrent laryngeal nerve only. Although 50 patients with ex2 tumors extending only to the recurrent laryngeal nerve showed a worse RFS rate than those having ex1 or ex0 tumors ($P = 0.0372$) (Fig. 3), their RFS rates were significantly better than those of 69 patients having ex2 tumors that extended to other organs such as the trachea and esophagus ($P = 0.0018$) (Fig. 4).

Prognostic Significance of Other Conventional Clinicopathological Parameters

We investigated other parameters that have been recognized as having prognostic value and found that male sex ($P = 0.0001$), advanced age (older than 60 years; $P = 0.0001$), large tumor size (larger than 4.0 cm; $P < 0.0001$), lymph node metastasis detectable by preoperative ultrasonography ($P < 0.0001$), and pathologically confirmed lymph node metastasis ($P < 0.0001$) significantly affect the RFS of patients on univariate analysis.

Multivariate Analysis of Prognostic Factors

To confirm whether massive extrathyroid extension is an independent prognostic factor of RFS, we performed

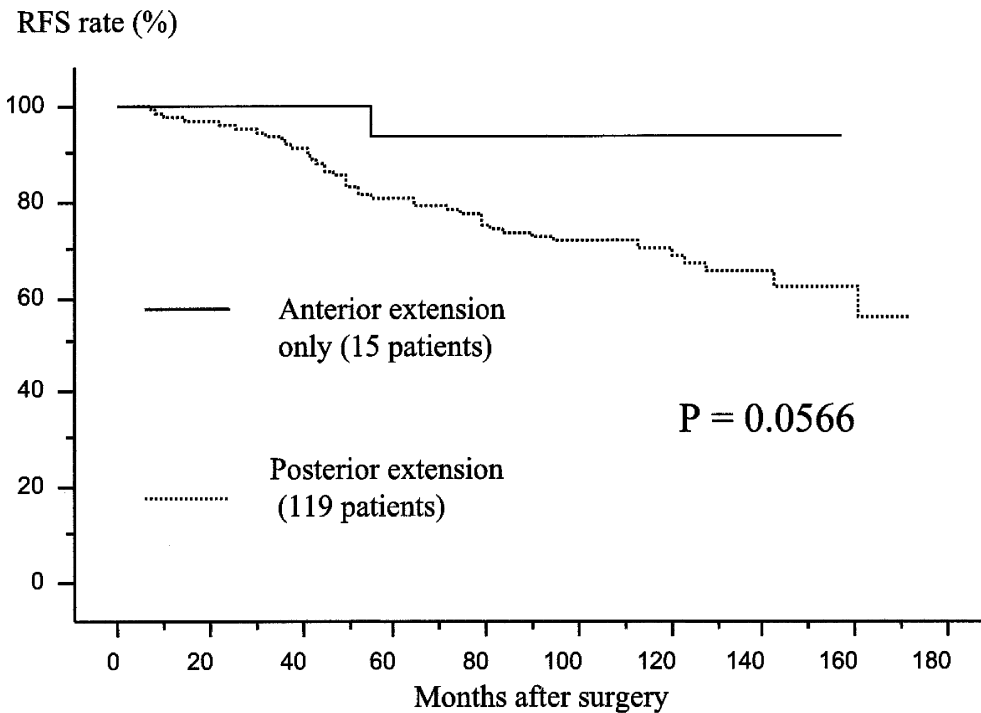


Figure 2. Comparison of RFS between papillary carcinoma patients with massive posterior extension and with massive anterior extension only.

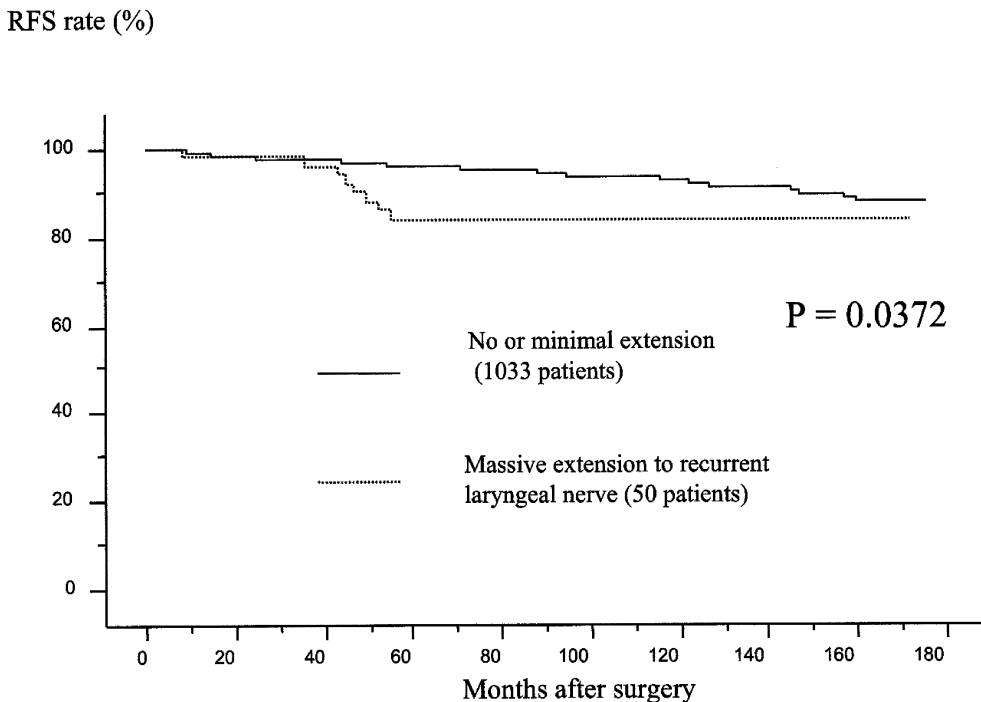


Figure 3. Comparison of RFS between papillary carcinoma patients with massive extension to the recurrent laryngeal nerve only and those with no or minimal extrathyroid extension.

multivariate analysis of extrathyroid extension together with other prognostic factors. As shown in Table 3, the P value of massive extrathyroid extension was 0.0003, indicating that it can be recognized as an independent prognostic factor for RFS, together with other parameters. We performed the same analysis for the subset of

patients aged 45 years or over and obtained similar results (Table 4). Furthermore, for the subset of those younger than 45 years, although gender and pathologically confirmed lymph node metastasis did not affect the prognosis of patients, extrathyroid extension, tumor size, and preoperatively detectable node metastasis were still

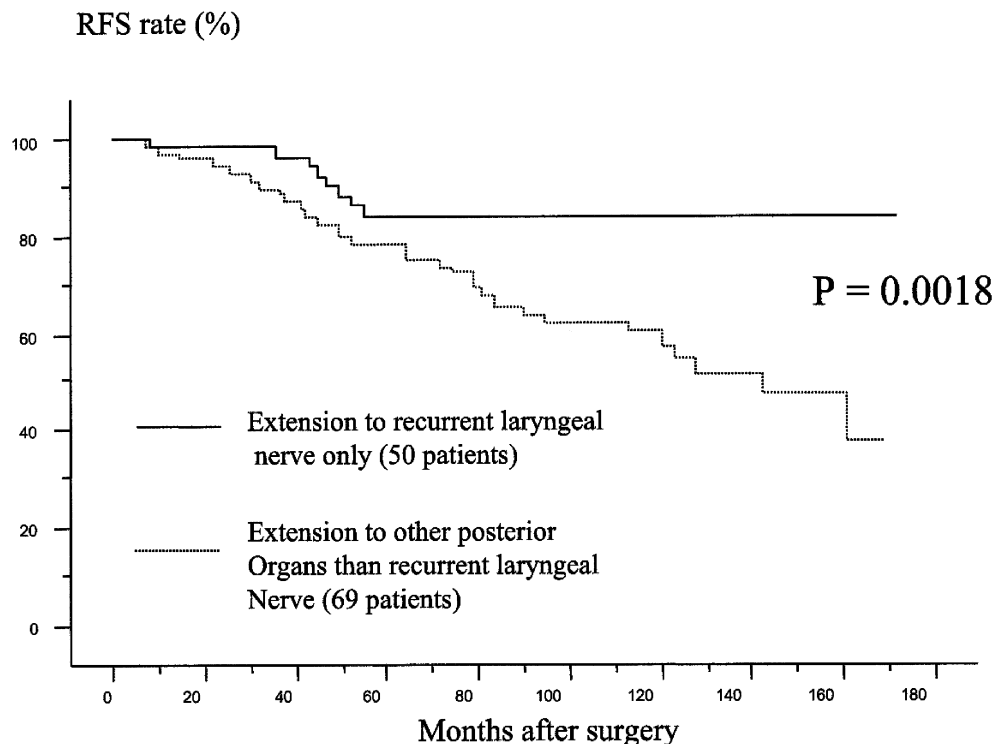


Figure 4. Comparison of RFS between papillary carcinoma patients with massive extension to recurrent laryngeal nerve only and those with massive posterior extension to other organs.

Table 3.

Univariate and multivariate analyses of RFS for clinicopathological parameters

Variables	Univariate	Multivariate
Extrathyroidal extension (ex2 vs 0, 1)	< 0.0001	0.0003
Age (≥60 vs <60)	0.0001	0.0030
Gender	0.0011	0.0295
Tumor size (>4.0 cm vs ≤4.0)	<0.0001	<0.0001
Preoperatively detectable lymph node metastasis	<0.0001	<0.0001
Pathologically confirmed lymph node metastasis	<0.0001	0.0010

Table 4.

Univariate and multivariate analyses of RFS for clinicopathological parameters for the subset of patients aged 45 years or over

Variables	Univariate	Multivariate
Extrathyroidal extension (ex2 vs 0, 1)	< 0.0001	0.0023
Age (≥60 vs <60)	<0.0001	0.0009
Gender	0.0074	0.0576
Tumor size (>4.0 cm vs ≤4.0)	<0.0001	0.0021
Preoperatively detectable lymph node metastasis	<0.0001	0.0003
Pathologically confirmed lymph node metastasis	<0.0001	0.0021

recognized as prognostic factors for RFS by univariate analysis. Furthermore, these three parameters also independently affected RFS by multivariate analysis (Table 5).

DISCUSSION

To date, studies regarding the prognostic significance of extrathyroid extension have been performed by other groups by classifying tumors into two categories based on the presence or absence of extension.⁴⁻¹⁰ In the present study, we investigated this issue by dividing

extrathyroid extension into two degrees, massive and minimal, and examined the prognostic impact of each degree of extension. One notable finding is that minimal extrathyroid extension did not have any prognostic significance, either in the subset of patients aged over 45 years³ or in patients of all age ranges. It is therefore suggested that tumors measuring 4 cm or less with minimal extrathyroid extension should be classified into the same T grade as those without extension, instead of upgrading to T3. The reason for the similarity of prognosis between ex1 and ex0 tumors remains unclear, but we hypothesize that the biological aggressiveness of these tumors is similar.

Table 5.

Univariate and multivariate analyses of RFS for clinicopathological parameters for the subset of patients younger than 45 years

Variables	Univariate	Multivariate
Extrathyroidal extension (ex2 vs 0, 1)	0.0003	0.0457
Tumor size (>4.0 cm vs ≤4.0)	0.0004	0.0030
Preoperatively detectable lymph node metastasis	<0.0001	0.0002

In contrast, our study demonstrated entirely different results for tumors with massive extension. On univariate analysis, the RFS of tumors with massive extension is significantly worse than that of tumors with minimal or no extension. Also in multivariate analysis, massive extension is recognized as an independent prognostic factor, together with several parameters such as age, gender, tumor size, and lymph node metastasis, all of which been recognized as prognostic factors.^{4,8,9,11} These findings indicate that the biological characteristic of tumors with massive extension is significantly more aggressive than that of tumors with minimal or no extension. As we obtained the same results not only in the subset of patients aged under 45 years of age but also in the subset of those aged 45 years or over, upgrading of T category, as well as upstaging of patients with tumors demonstrating massive extension, seems appropriate.

However, for tumors showing massive extension, the biological characteristics are not uniform but depend on the organs to which the tumor extends. We demonstrated that tumors with massive extension in the posterior direction showed a worse RFS rate than those with extension in the anterior direction. Furthermore, the RFS rate of tumors with posterior massive extension to the recurrent laryngeal nerve alone was significantly better than that of tumors with extension to other organs, such as the trachea and esophagus. Such a difference in RFS depending on the organs to which tumors extend might be due to differences in the difficulty of achieving curative surgery. Although "grossly curative surgery" can be performed, microscopically, residual tumor can often remain undissected, and the metastatic potential to lymph nodes and distant organs could therefore be high, especially in cases showing massive extension to posterior organs other than recurrent laryngeal nerve. It is therefore suggested that

surgeons perform careful surgical resection and post-operative follow-up for patients with such tumors.

In summary, we demonstrated that massive but not minimal extrathyroid extension is an independent prognostic factor for RFS in patients with papillary carcinoma. Further studies regarding overall patient survival based on longer term follow-up should be performed to more accurately determine the significance of massive extrathyroid extension.

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