

ORIGINAL

Prognostic significance of carcinoma extension from primary lesions and metastatic nodes in papillary thyroid carcinoma: appropriateness of three subdivisions of extension

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Abstract. Carcinoma extension to adjacent organs is an important prognostic factor in papillary thyroid carcinoma (PTC). However, the biological behavior of PTC with carcinoma extension varies according to the degree of extension. In this study, we investigated whether and how subdivision of PTC extension accurately reflects patients' prognosis, using a series of 5508 patients with PTC without distant metastasis at presentation, who underwent initial surgery between 1988 and 2004. We classified extension from primary lesions or metastatic nodes into 4 grades based on intraoperative findings (Grade 0-4, Grades 3 and 4 were subdivision of T4a). Prognostic significance for disease-free and cause-specific survivals (DFS and CSS) of extension from primary lesions did not differ from that of extension from metastatic nodes in the same grades except for DFS of Grade 3 patients. DFS of patients became worse with higher grades and CSS was also significantly linked to advanced grades except for Grade 1. On multivariate analysis, Grades 1, 2 and 3 and Grades 2 and 3 were independent prognostic factors for DFS and CSS, respectively, together with other conventional prognostic factors. Taken together, extension from metastatic nodes has a prognostic significance equivalent to that from primary lesions if classified in the same grades. Subdivision of PTC extension corresponding to T4a into two grades can accurately reflect the biological behavior of PTC.

Key words: Papillary thyroid carcinoma, Prognosis, Extrathyroid extension

PAPILLARY thyroid carcinoma (PTC) is the most common malignancy arising from follicular cells of the thyroid. Generally, it is an indolent disease, but cases demonstrating certain characteristics are likely to show recurrence and even become life-threatening. Carcinoma extension is an important prognostic factor of PTC patients, which is adopted in various classification systems such as AMES [1], MACIS [2] and CIH classification [3]. However, all these systems evaluate carcinoma extension based only on its existence but not on its degree, indicating that cases showing a wide range of biological behaviors are classified into the same category.

In the UICC TNM classification system [4], in contrast, there are three grades of extrathyroid extension; extension to sternothyroid muscle or perithyroid soft

tissues (T3), extension to subcutaneous soft tissues, larynx, trachea, esophagus and recurrent laryngeal nerve (T4a), and extension to prevertebral fascia, mediastinal vessels, and carotid artery (T4b), but curative surgery is generally difficult for T4b patients. We previously showed that extension corresponding to T4a but not to T3 based on intraoperative findings was an independent prognostic factor for disease-free survival (DFS) and cause-specific survival (CSS) of PTC patients [5, 6].

We also demonstrated that T4a patients having posterior extension showed a significantly worse DFS than those with anterior extension and, in the subset of patients with posterior extension, extension only to the recurrent laryngeal nerve predicts a more favorable DFS than extension to other organs [5]. These findings indicate that the biological behavior of PTC classified as T4a still varies according to the organs to which carcinoma extends and depth of extension. Furthermore, PTC can extend to other organs not only from primary lesions but also from metastatic nodes. Although prominent classification systems have only adopted

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extension from primary lesions [1-4], we previously showed that extension from metastatic nodes is also a strong prognostic factor for PTC patients [7-9]. In this study, therefore, we investigated whether and how subdivision of extrathyroid extension not only from primary lesions but also from metastatic nodes can accurately reflect biological behaviors and prognoses of PTC patients.

Patients and Methods

We enrolled 5508 patients with PTC without distant metastasis at presentation, who underwent initial surgery in Kuma Hospital, between January 1988 and December 2004. They consisted of 583 males and 4925 females, and patient age was 50.1 years on average (7-88 years). Patients with other coexisting thyroid malignancies such as follicular carcinoma, medullary carcinoma, anaplastic carcinoma and malignant lymphoma were excluded from the study. Patients who underwent locally non-curative surgery were also excluded from our series. All patients underwent ultrasonography before surgery to evaluate the location and size of primary lesions and lymph node metastases and diagnosed as or suspected of PTC on cytology. The extent of thyroidectomy was total thyroidectomy in 2761 patients, near total thyroidectomy (estimated remnant thyroid 1 gram or less) in 84 patients, and more limited thyroidectomy in the remaining 2663 patients. The extent of lymph node dissection was unilateral or bilateral modified radical neck dissection (MND) with central node dissection (CND) in 4147 patients, CND only in 1100 patients, and no or only partial dissection in the remaining 261 patients. Twelve patients also underwent dissection of the upper mediastinal compartment. All patients were diagnosed as having PTC on postoperative pathological examination.

Scintigraphy using a small amount of radioiodine (3-13 mCi) was performed at our outpatient clinic 1-2 month after total or near total thyroidectomy in 943 patients with tumors showing aggressive characteristics such as massive extrathyroid extension, or multiple clinically apparent lymph node metastases. None of these 943 patients who underwent scintigraphy showed abnormal uptakes.

We followed patients by ultrasonography once per year to monitor patients for signs of local recurrence. Either chest roentgenography or CT scan was also performed once per year. Postoperative follow-up ranged

from 12 to 268 months and median follow-up period was 116 months (average follow-up period was 126 months). We regarded a patient as having recurrence when recurrence was apparent on imaging studies such as CT scan, roentgenography and PET-CT. To date, 506 patients (9%) showed PTC recurrence to one or more organs. Recurrences to the lymph node, lung and bone were detected in 377 patients, 124 patients, and 31 patients, respectively. Local recurrence to sites other than regional lymph node and recurrence to distant organs other than the lung and bone were observed in 89 patients and 6 patients, respectively. Seventy-three patients showed recurrence to two or more organs. In total, 430 patients showed a local recurrence, 124 showed a distant recurrence and 48 showed both. To date, 54 patients (1%) have died of PTC. Fourteen patients died of local recurrence, and 35 died of distant recurrence. The details are unknown for the remaining 5, who died of thyroid carcinoma in other hospitals.

Statistical analysis was performed using StatView 5.0 (SAS). Kaplan-Meier curve with log rank test was adopted for univariate analysis. Cox-hazard regression model was used for multivariate analysis. A *p* value smaller than 0.05 was considered significant.

Results

Classification of PTC extension

We classified PTC extension from primary lesions or metastatic nodes to adjacent organs into 4 grades based on intraoperative findings. Grade 0 (4046 patients) indicates primary lesion and lymph node metastasis show no extension. Patients whose primary lesions or lymph node metastases showed extension only to the sternothyroid muscle or surrounding soft tissues were classified as Grade 1 (702 patients). Primary lesions or node metastases extending to the sternohyoid muscle, subcutaneous soft tissues, recurrent laryngeal nerve, cricothyroid muscle, inferior constrictor muscle, muscular layer of the esophagus, and tracheal cartilage (but not tracheal mucosa) were considered Grade 2 (571 patients). Grade 3 indicates patients whose primary lesions or node metastases extended to organs other than those in Grades 1 and 2 such as the esophageal mucosa, tracheal mucosa requiring airway resection, internal jugular vein, vagal nerve, phrenic nerve, and sternocleidomastoid muscle (189 patients). Our series did not include patients with PTC extending to the larynx and those with PTC that extended to prevertebral

fascia, mediastinal vessels and carotid artery and were classified as T4b. Patients showing extension of different grades between the primary lesions and metastatic nodes were classified based on the higher of the two grades.

Comparison of prognostic value between extension from primary lesions and extension from metastatic nodes

We compared prognosis between patients with extension from primary lesions and those with extension from metastatic nodes in each grade (Fig. 1a-f). In the subsets of patients with Grades 1 and 2, DFS and CSS of patients with extension from metastatic nodes did not significantly (N.S.) differ from those with extension from primary lesions in the corresponding grades (Fig. 1a-d). DFS of patients with Grade 3 extension from the primary lesion was significantly worse than that of those with Grade 3 extension from metastatic nodes ($p = 0.0189$) (Fig. 1e), but CSS did not differ between the two groups (Fig. 1f).

Relationship of extension grades to patient prognosis

We then investigated the relationship of extension grades to DFS and CSS of PTC patients. To date, 84 patients with Grade 3 (44%), 127 patients with Grade 2 (22%), 66 patients with Grade 1 (9%) and 229 patients with Grade 0 (6%) showed PTC recurrence during follow-up. Local recurrence was observed in 60 patients (32%) with Grade 3, 108 (19%) with Grade 2, 57 (8%) with Grade 1, and 207 (5%) with Grade 0. Distant recurrence was seen in 36 patients (19%) with Grade 3, 35 (6%) with Grade 2, 17 (2%) with Grade 1, and 36 (0.9%) with Grade 0. Radioactive iodine (RAI) therapy was performed for 12 patients (33%) with Grade 3, 17 (50%) with Grade 2, 11 (65%) with Grade 1, and 17 (47%) with Grade 0 who showed distant recurrence. Fig. 2a shows the Kaplan-Meier curves for DFS of patients with Grades 0-3. DFS of patients significantly worsened with higher grade ($p = 0.0003$ for Grade 1 vs Grade 0, $p < 0.0001$ for Grade 2 vs Grade 1, and for Grade 3 vs Grade 2).

Twenty-seven patients with Grade 3 (14%), 18 patients with Grade 2 (3%), 3 patients with Grade 1 (0.4%) and 6 patients with Grade 0 (0.1%) have died of PTC to date. Fig. 2b compared the CSS rates among patients with the four grades. The CSS rate of patients with Grade 1 did not differ from that of those with Grade 0. However, CSS of patients with Grades 2

and 3 were significantly worse than that of those with Grade 1 and 2, respectively ($p = 0.0008$ for Grade 2 vs Grade 1, $p < 0.0001$ for Grade 3 vs Grade 2).

Multivariate analysis for extension grades and other prognostic factors

In our series, conventional prognostic factors such as advanced age (55 years or older) ($p < 0.0001$), male gender ($p < 0.0001$), lymph node metastasis measuring 3 cm or larger ($p < 0.0001$) and tumor size larger than 4 cm ($p < 0.0001$) also significantly affected DFS of patients on univariate analysis. We then performed multivariate analysis for these factors together with extension grades. As shown in Table 1, age 55 years or older ($p = 0.0233$), lymph node metastasis 3 cm or larger ($p < 0.0001$) and tumor size larger than 4 cm ($p < 0.0001$) were recognized as independent prognostic factors for DFS. Extension grades 1, 2, and 3 also independently predicted worse DFS of patients (Grade 1, $p = 0.0033$, Grade 2, $p < 0.0001$, and Grade 3, $p < 0.0001$). Hazard ratio of Grade 1 for Grade 0 was 1.51. Hazard ratios of Grade 2 were 3.36 for Grade 0 and 2.23 (3.36/1.51) for Grade 1, respectively, and those of Grade 3 were 6.09 for Grade 0, 4.03 (6.09/1.51) for Grade 1 and 1.81 (6.09/3.36) for Grade 2, respectively.

Age 55 years older ($p < 0.0001$), male gender ($p = 0.00242$), node metastasis 3 cm or larger ($p < 0.0001$) and tumor larger than 4 cm ($p < 0.0001$) were also recognized as prognostic factors for CSS on univariate analysis. On multivariate analysis, age 55 years or older ($p < 0.0001$), node metastasis 3 cm or larger ($p = 0.0081$) and tumor larger than 4 cm ($p = 0.0038$) were independent prognostic factors for CSS (Table 2). Extension grades 2 and 3 also independently affected the CSS of patients ($p < 0.0001$). However, Grade 1 was not recognized as an independent prognostic factor ($p = 0.2816$, hazard ratio 2.15 for Grade 0). Hazard ratios of Grade 2 were 13.62 for Grade 0 and 6.35 (13.62/2.15) for Grade 1, respectively, and those of Grade 3 were 41.92 for Grade 0, 19.50 for Grade 1 (41.92/2.15), and 3.08 (41.92/13.62) for Grade 2, respectively.

Discussion

In this study, we analyzed whether and how PTC extension from primary lesions and metastatic nodes reflects the prognosis of PTC patients depending on the organ to which carcinoma extends and depth of extension by dividing the extension into four grades.

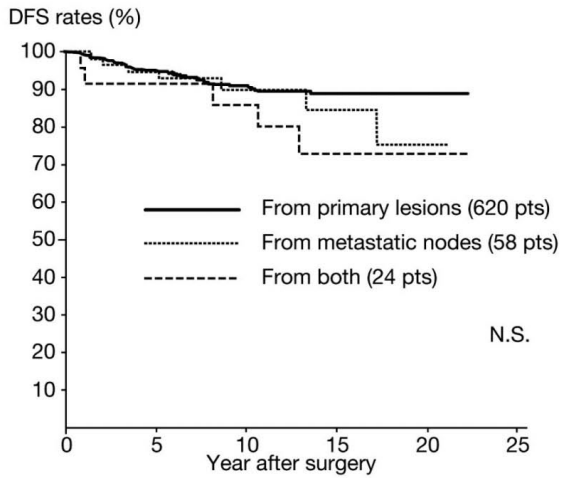


Fig. 1a DFS of patients with Grade 1 extension from primary lesions, metastatic nodes and both.

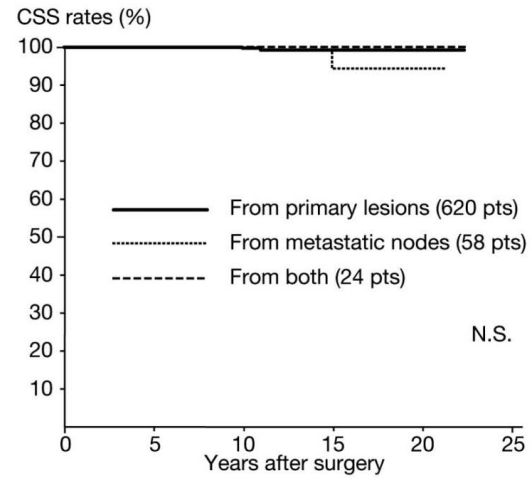


Fig. 1b CSS of patients with Grade 1 extension from primary lesions, metastatic nodes and both.

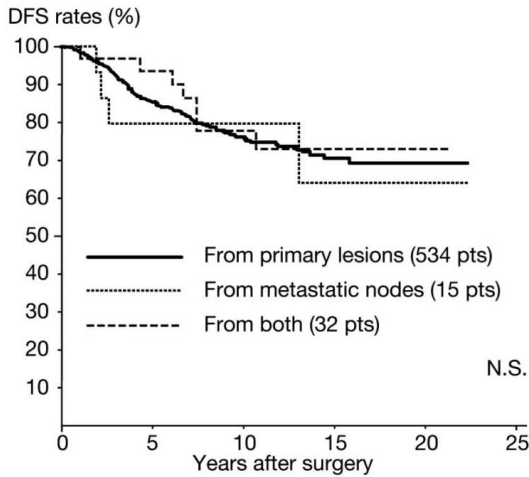


Fig. 1c DFS of patients with Grade 2 extension from primary lesions, metastatic nodes and both.

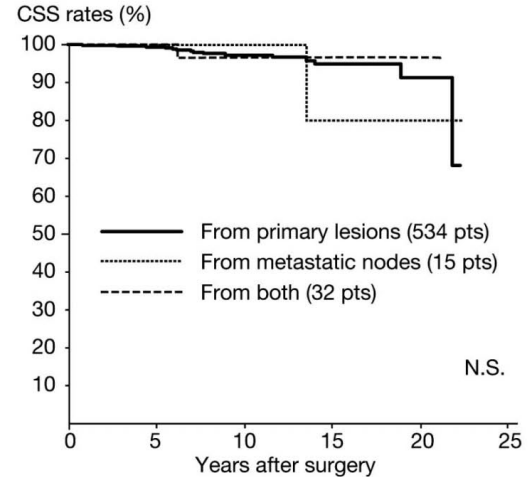


Fig. 1d CSS of patients with Grade 2 extension from primary lesions, metastatic nodes and both.

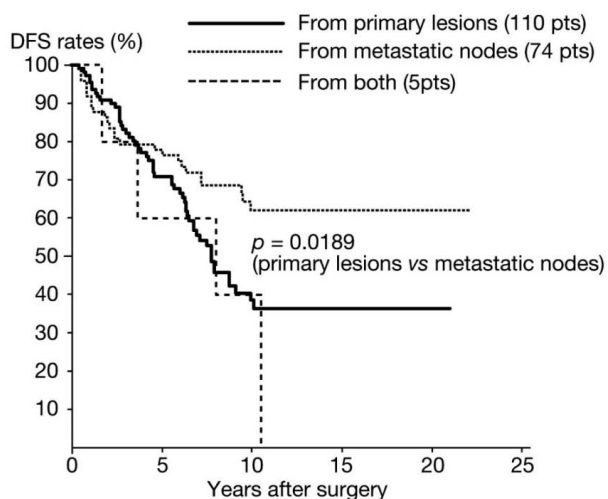


Fig. 1e DFS of patients with Grade 3 extension from primary lesions, metastatic nodes and both.

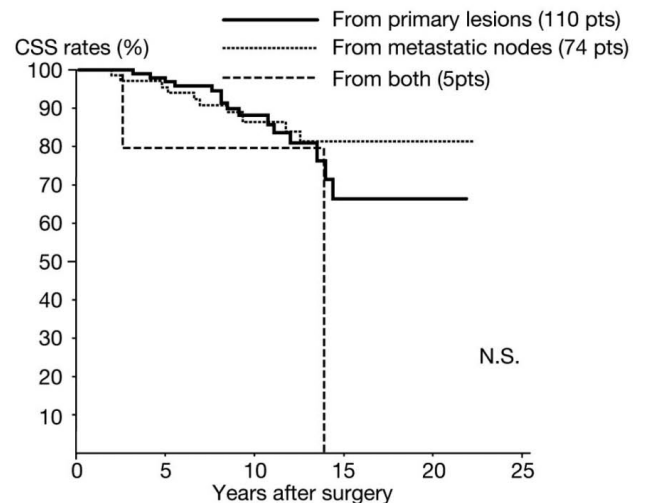


Fig. 1f CSS of patients with Grade 3 extension from primary lesions, metastatic nodes and both.

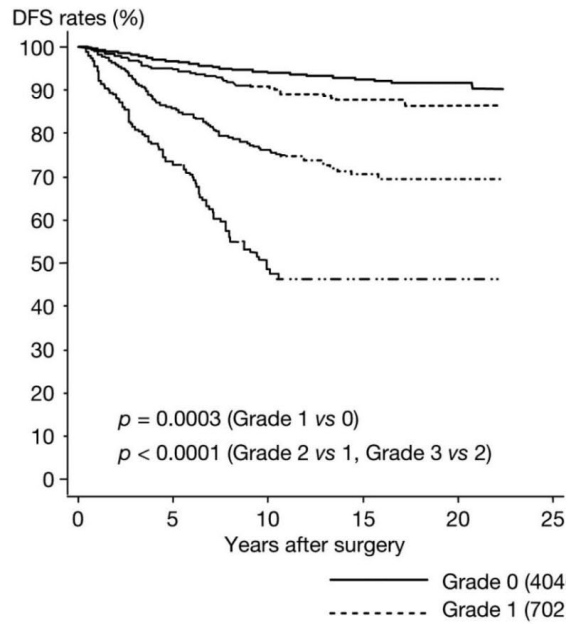


Fig. 2a DFS of patients with Grades 0, 1, 2, and 3.

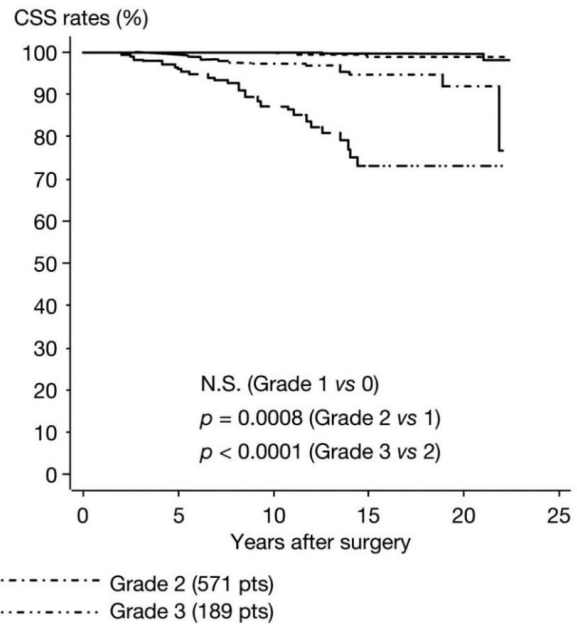


Fig. 2b CSS of patients with Grades 0, 1, 2, and 3.

Table 1 Univariate and multivariate analyses of DFS of PTC patients

	Univariate	Multivariate	Hazard ratio (95% CI)
Age > 55 yrs	< 0.0001	0.0233	1.23 (1.01-1.47)
Male gender	< 0.0001	0.0523	1.34 (0.99-1.62)
Metastatic node \geq 3cm	< 0.0001	< 0.0001	2.49 (1.87-3.31)
Tumor size > 4cm	< 0.0001	< 0.0001	2.35 (1.90-2.89)
Extension grades			
Grade 1 vs 0	< 0.0025	0.0033	1.51 (1.15-1.99)
Grade 2 vs 0	< 0.0001	< 0.0001	3.36 (2.68-4.23)
Grade 3 vs 0	< 0.0001	< 0.0001	6.09 (4.59-8.08)

Table 2 Univariate and multivariate analyses of CSS of PTC patients

	Univariate	Multivariate	Hazard ratio (95% CI)
Age > 55 yrs	< 0.0001	< 0.0001	9.28 (4.07-21.17)
Male gender	0.0024	0.2646	1.49 (0.74-3.01)
Metastatic node \geq 3cm	< 0.0001	0.0081	2.61 (1.28-5.29)
Tumor size > 4cm	< 0.0001	0.0038	2.32 (1.31-4.10)
Extension grades			
Grade 1 vs 0	0.1257	0.2816	2.15 (0.54-34.90)
Grade 2 vs 0	< 0.0001	< 0.0001	13.62 (5.32-34.90)
Grade 3 vs 0	< 0.0001	< 0.0001	41.92 (16.46-106.78)

As the first step of this study, we investigated whether the prognostic significance of extension from metastatic nodes differs from that of extension from primary lesions classified in the same grade. We demonstrated that DFS and CSS of patients with Grades 1 and 2 extensions from primary lesions did not differ from

those with extensions from metastatic nodes of the corresponding grades. Although Grade 3 patients based on primary lesions showed a worse DFS than those based on metastatic nodes, CSS of these two groups did not differ. These findings suggested that extension from metastatic nodes has a prognostic significance

equivalent to extension from primary lesions in PTC patients, if they are classified as the same grades. In this study, therefore, we adopted extension from primary lesions and node metastases as a single group for further analysis.

We subdivided significant extension from primary lesions or metastatic nodes corresponding to T4a [4] into two grades (Grades 2 and 3) based on the organs to which PTC extended and depth of extension. Grade 2 patients showed a significantly worse DFS and CSS than Grade 1 or 0 patients, and DFS and CSS of Grade 3 patients were significantly more adverse than those of Grade 2 patients on univariate analysis. On multivariate analysis, Grades 1, 2 and 3 and Grades 2 and 3 were independent prognostic factors for DFS and CSS, respectively. Especially, Grade 3 patients were 1.81 times more likely to show recurrence and 3.08 times more likely to die of carcinoma than Grade 2 patients. It is therefore suggested that the subdivision of extension corresponding to T4a into two grades is appropriate and accurately reflects patient prognosis.

These findings imply that PTC extending to principal organs such as the jugular vein and vagal nerve or extending deeply to adjacent organs such as the esophageal mucosa and tracheal mucosa has a significantly worse prognosis than PTC with superficial or less significant extension. It is speculated that PTC can be disseminated to other organs from the extending lesions, indicating that PTC showing wider and deeper extension is more likely to show recurrence, resulting in a worse prognosis. This speculation is supported by the finding that rate of distant recurrence increased with advanced Grades. Furthermore, PTC with wider and

deeper extension should have an aggressive character overall, including local proliferating activity and metastatic activity to the lymph node and distant organs, which could induce a higher incidence of carcinoma recurrence and carcinoma death. Our findings that incidence of patients with Grade 3 who showed distant recurrence was higher but that of patients who underwent RAI therapy was lower than those in other grades may support, at least in part, this hypothesis.

In this series, Grade 1 patients had significantly worse DFS than Grade 0 patients and Grade 1 independently affected DFS on multivariate analysis, which was somewhat discrepant with our previous findings [5, 9, 10]. This is possibly because the patient series analyzed in this study is larger and average follow-up period is longer than those in the previous studies. However, the difference of DFS between Grade 1 and Grade 0 was smaller than the differences among other grades (Fig. 2a). Furthermore, CSS of Grade 1 patients did not differ from that of Grade 0 patients (Fig. 2b). It is therefore suggested that the prognostic value of Grade 1 is much less significant than that of Grades 2 and 3.

In this study, we demonstrated that extension from metastatic nodes has a prognostic significance equivalent to that from primary lesions if classified as the same extension grades. We also showed that PTC extension has a different clinical significance according to the organs to which primary lesions and node metastases extend and the depth of their extension. Especially, subdivision of extension corresponding to T4a into two grades can more accurately evaluate the biological characteristics and risk classification of PTC.

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