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Investigation of the prognosis of patients with papillary thyroid carcinoma by tumor size

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Abstract. In papillary thyroid carcinoma (PTC), extrathyroid extension (Ex) and clinical lymph node metastasis (N) significantly affect the prognosis. We investigated the prognosis of patients with PTC 1 cm or less (1,220 patients), 1.1-2 cm (2,101 patients), 2.1-3 cm (1,249 patients), 3.1-4 cm (645 patients), and larger than 4 cm (563 patients). We classified N factor into three categories: N0, no clinical node metastasis: N1, clinical node metastasis smaller than 3 cm and without extranodal tumor extension requiring at least partial excision of adjacent organs for node dissection: and N2, clinical node metastasis 3 cm or larger or showing extranodal tumor extension. N2 markedly affected lymph node and distant recurrence-free survivals and cause-specific survival, regardless of the tumor size. N1 also adversely affected lymph node and distant recurrence-free survival but not cause-specific survival. Ex did not affect patients' prognosis with PTC 1 cm or less. It became a prognostic factor with PTC larger than 1 cm, and worsened lymph node and distant recurrence-free survival not only for N0 but also for N1 PTC larger than 3 cm and larger than 2 cm, respectively. However, its influence is limited for N2 PTC patients. Furthermore, Ex worsened the CSS with PTC larger than 2 cm in combination with N2. We have to note that the prognostic significance for lymph node and distant recurrence-free and cause-specific survival of Ex and N varies according to the tumor size in order to accurately predict the clinical outcomes and establish therapeutic strategies for PTC patients.

Key words: Papillary thyroid carcinoma, Prognosis, Tumor size, Extrathyroid extension, Lymph node metastasis

PAPILLARY THYROID CARCINOMA (PTC) is the most common thyroid malignancy. It generally displays an indolent characteristic and is associated with a favorable prognosis, but cases with certain clinicopathological features can be progressive and show a poor prognosis. Age is an important background affecting patients' prognosis. It is adopted by various classification systems such as UICC TNM classification, AMES, MACIS and CIH classification [1-4]. We set the cutoff age at 55 years for evaluating the prognosis of PTC patients because it most clearly reflected disease-free survival (DFS) and cause-specific survival (CSS) of PTC patients [5].

The tumor size is the first factor to evaluate the biological characteristics of PTC, because it is easily measured by preoperative ultrasonography. Observation without immediate surgery is an alternative to therapy for PTC measuring 1 cm or less [6-8], and total thyroidectomy is not mandatory for PTC measuring 2 cm or less if no high-risk features are detected [9, 10]. In contrast, a tumor size larger than 2 cm shows a significantly more aggressive characteristic than PTC 2 cm or less even though it was classified as being otherwise low-risk [10].

There are two other important factors for evaluating the biological characteristics of PTC, which are lymph node metastasis and extrathyroid extension. In the UICC TNM classification system, extrathyroid extension is preoperatively and pathologically evaluated and classified into two categories, T3 and T4 [1]. However, we previously showed that T3 had little prognostic impact, and extrathyroid extension corresponding to T4 based on the intraoperative findings keenly reflected the clinical outcomes of patients [11, 12]. Another important factor is lymph node metastasis. We also demonstrated that clinical node metastasis in the lateral compartment (N1b in the TNM classification [1]) detected on preoperative imaging studies was a significant prognostic factor [13, 14]. Interestingly,

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the prognostic impacts of extrathyroid extension and lymph node metastasis vary according to the tumor size. In 2010, Fukushima *et al*. showed that N1b had a more significant prognostic value for DFS and CSS than extrathyroid extension with PTC measuring 3 cm or smaller, but their prognostic impacts switched in PTC larger than 3 cm [15].

However, more recently, we showed that the prognosis worsened in the order of patients with no clinical node metastasis, patients with metastasis smaller than 3 cm and without extranodal tumor extension requiring at least partial resection of adjacent organs, and patients with metastasis 3 cm or larger or with extranodal tumor extension [5, 16]. We also showed that the prognosis of N1b and N1a patients did not differ unless their metastases were 3 cm or larger or showed extranodal tumor extension [16]. Furthermore, of carcinoma recurrence, the clinical implication significantly differs between recurrence to the lymph node and to distant organs. Then, in this study, we investigated lymph node recurrence-free survival (LN-RFS), distant recurrence-free survival (DRFS), and CSS of PTC patients by dividing them into five groups based on the tumor size in order to elucidate how extrathyroid extension and lymph node metastasis influence the prognosis of PTC patients in each subset.

Patients and Methods

Patients

We enrolled 5,778 patients with PTC without distant metastasis at presentation who underwent initial surgery in Kuma Hospital, between 1987 and 2005. They consisted of 609 males and 5,169 females, and the age of patients was 50.0 ± 14.2 years on average. The extent of thyroidectomy was total or near total (estimated remnant thyroid 1 gram or less) thyroidectomy in 2,948 patients and more limited thyroidectomy such as subtotal thyroidectomy and lobectomy with isthmectomy in the remaining 2,830 patients. The extent of lymph node dissection was uni- or bilateral modified radical neck dissection (MND) with central node dissection (CND) in 4,367 patients, CND only in 1,137 patients, and no or only partial dissection in the remaining 274 patients. All patients were diagnosed as having PTC on postoperative pathological examination. Findings of the preoperative evaluation such as the location and size of primary lesions and lymph node metastases were predominantly obtained by ultrasonography. Patients who had other thyroid malignancies such as follicular carcinoma, medullary carcinoma, anaplastic carcinoma, and malignant lymphoma and those who could not be followed for 12 months or more after surgery were excluded from our series.

Evaluation and classification of extrathyroid extension and clinical node metastasis

Extrathyroid extension (Ex) of primary lesions was evaluated intraoperatively. We regarded cases corresponding to T4a in the UICC TNM classification as having extrathyroid extension [1]. Our series did not include T4b patients in the TNM classification. Clinical lymph node metastasis (N) was divided into three groups as described previously [5]: N0, no clinical node metastasis; N1, clinical node metastasis smaller than 3 cm and without extranodal tumor extension requiring at least partial excision of adjacent organs for node dissection; and N2, clinical node metastasis 3 cm or larger or showing extranodal tumor extension.

Categorization of patients

We subdivided PTC patients into five subsets based on the tumor size: 1 cm or less (1,220 patients), 1.1-2 cm (2,101 patients), 2.1-3 cm (1,249 patients), 3.1-4 cm (645 patients), and larger than 4 cm (563 patients). We then categorized patients in each subset into 6 categories based on Ex and N findings: C1, Ex(-)N0; C2, Ex(-)N1; C3, Ex(-)N2; C4, Ex(+)N0; C5, Ex(+)N1; and C6, Ex(+)N2.

Postoperative follow-up

Scintigraphy using a small amount of radioactive iodine (RAI) (3-13 mCi) was performed at our outpatient clinic 1-2 months after total or near total thyroidectomy in 1,031 patients with tumors showing aggressive characteristics such as massive extrathyroid extension, or multiple clinically apparent lymph node metastases. None of these patients showed abnormal uptakes. Patients who underwent postoperative ablation using larger dose of RAI were excluded from our series.

We followed patients by ultrasonography once per year to monitor them for signs of local recurrence. Either chest roentgenography or a CT scan was also performed once per year. The postoperative follow-up ranged from 12 to 280 months and was 129 months (10.8 years) on average. We regarded a patient as showing recurrence when it was apparent on imaging studies such as ultrasonography, CT scan, roentgenog-

raphy, and PET-CT.

Clinical outcomes of patients

To date, lymph node recurrence has been detected in 35 patients (3%) with PTC 1 cm or less, 89 patients (4%) with PTC 1.1-2 cm, 93 patients (7%) with PTC 2.1-3 cm, 75 patients (12%) with PTC 3.1-4 cm, and 100 patients (18%) with PTC larger than 4 cm, respectively. Distant recurrence such as that to the lung, bone and brain was seen in 5 patients (0.2%) with PTC 1 cm or less, 28 patients (1%) with PTC 1.1-2 cm, 33 patients (3%) with PTC 2.1-3 cm, 44 patients (7%) with PTC 3.1-4 cm, and 46 patients (8%) with PTC larger than 4 cm, respectively. Two patients (0.2%) with PTC 1 cm or less, 8 patients (0.4%) with PTC 1.1-2 cm, 15 patients (1%) with PTC 2.1-3 cm, 14 patients (2%) with PTC 3.1-4 cm, and 25 patients (4%) with PTC larger than 4 cm have died of carcinoma to date.

Statistical analysis

The Kaplan-Meier curve with log rank test was adopted for univariate analysis. The Cox-hazard regression model was used for multivariate analysis. A p-value smaller than 0.05 was considered significant, and that 0.05 or greater but less than 0.1 was regarded as marginally significant.

Results

We investigated the prognostic factors of PTC measuring 1 cm or less, 1.1-2 cm, 2.1-3 cm, 3.1-4 cm, and larger than 4 cm and rates of LN-RFS, DRFS and CSS in each subset depending on the presence of extrathyroid extension (Ex) and clinical lymph node metastasis (N). We investigated the prognostic impacts of Ex, N, together with age and gender for lymph node recurrence, distant recurrence, and carcinoma death of PTC patients according to the tumor size on multivariate analysis and analyzed the prognosis of patients in each category for each subset of the tumor size with the Kaplan-Meier method. We set the cutoff age at 55 years, which most significantly reflected the patients' prognoses, as previously described [5].

Lymph node recurrence of PTC patients according to the tumor size

On univariate analysis, age ≥ 55 years (yrs) showed a significantly poorer LN-RFS in PTC 3.1-4 cm ($p < 0.0001$) and PTC larger than 4 cm ($p = 0.0001$), while it did not have a prognostic value in smaller PTC. On multivariate analysis, independent prognostic factors for LN-RFS were N2 and N1 ($p < 0.0001$) in PTC 1 cm or less, N2, N1 ($p < 0.0001$), and Ex ($p = 0.0074$) in PTC 1.1-2 cm, N2, N1 ($p < 0.0001$), and Ex ($p = 0.0115$) in PTC 2.1-3 cm, age ≥ 55 yrs ($p < 0.0001$), N2 ($p = 0.0005$), N1 ($p = 0.0029$), and Ex ($p = 0.0039$) in PTC 3.1-4 cm, and N2 ($p = 0.0003$), Ex ($p = 0.0012$), N1 ($p = 0.0012$), age ≥ 55 yrs ($p = 0.0201$), and male gender ($p = 0.0398$) in PTC larger than 4 cm.

Five-year and 10-year LN-RFS rates of PTC patients according to tumor size are summarized in Table 1. In PTC 1 cm or less, N1 or N2 significantly worsened the LN-RFS (C1 *vs*. C2, $p < 0.0001$, C2 *vs*. C3, $p = 0.0079$) and Ex did not have a prognostic value. In Ex(-) PTC 1.1-2 cm, LN-RFS rates became poorer in order of N status (C1 *vs*. C2, $p < 0.0001$, C2 *vs*. C3, $p = 0.0111$). Ex(+)N0 patients showed a poorer LN-RFS than Ex(-) N0 patients (C1 *vs*. C4, $p < 0.0001$), but Ex did not affect the LN-RFS of N1 or N2 patients. In Ex(-) PTC 2.1-3 cm, N1 reflected a poor LN-RFS (C1 *vs*. C2, $p < 0.0001$), although N2 did not. In contrast to smaller PTC, Ex affected LN-RFS also in N2 patients (C1 *vs*. C4, $p = 0.0328$; C3 *vs*. C6, $p = 0.0394$). Also in PTC 3.1-4 cm, N was related to a poor LN-RFS in Ex(-) patients (C1 *vs*. C2, $p = 0.0152$; C2 *vs*. C3, $p = 0.0712$). Additionally, Ex affected LN-RFS not only in N0 but also in N1 patients (C1 *vs*. C4, $p < 0.0001$; C2 *vs*. C5, $p = 0.0099$). Similar results were obtained in PTC larger than 4 cm (C1 *vs*. C2, $p = 0.0015$; C2 *vs*. C3, $p = 0.0344$; C1 *vs*. C4, $p < 0.0001$; C2 *vs*. C5, $p = 0.0316$).

Distant recurrence in PTC patients according to the tumor size

Age ≥ 55 yrs significantly affected the DRFS of PTC 1.1-2 cm ($p = 0.0262$), 2.1-3 cm ($p = 0.0023$), 3.1-4 cm ($p < 0.0001$), and larger than 4 cm ($p < 0.0001$). The independent prognostic factors on multivariate analysis for DRFS were N2 ($p = 0.0002$) in PTC 1 cm or smaller, N1 ($p = 0.0102$), Ex ($p = 0.0152$), N2 ($p = 0.0395$), and age ≥ 55 yrs ($p = 0.0436$) in PTC 1.1-2 cm, N2 ($p < 0.0001$), N1 ($p = 0.0001$), Ex ($p = 0.0021$), and age ≥ 55 yrs ($p = 0.0114$) in PTC 2.1-3 cm, N2 ($p < 0.0001$), N1 ($p = 0.0002$), age ≥ 55 yrs ($p = 0.0017$), and Ex(+) ($p = 0.0050$) in PTC 3.1-4 cm, and N2 ($p = 0.0070$), Ex ($p = 0.0038$), age ≥ 55 yrs ($p = 0.0070$), and N1 ($p = 0.0140$).

Five-year and 10-year DRFS of patients in each tumor size is summarized in Table 2. DRFS of PTC

Table 1 LN-RFS rates (%) of PTC patients according to tumor size (standard error)

Tumor 1 cm or smaller	5 yrs	10 yrs
C1 (n=1,034)	99(0)	99(0)
C2 (n=133)	92(3)	89(3)
C3 (n=27)	75(8)	70(10)
C4 (n=21)	100	100
C5 (n=5)	100	100
C6 (n=0)		

C1 *vs*. C2, $p < 0.0001$; C2 *vs*. C3, $p=0.0079$
C1 *vs*. C4, C2 *vs* C5, C4 *vs*. C5, Not significant

Tumor 1.1-2 cm	5 yrs	10 yrs
C1 (n=1,635)	99(0)	98(0)
C2 (n=264)	92(2)	87(3)
C3 (n=45)	76(7)	74(7)
C4 (n=90)	91(3)	89(4)
C5 (n=45)	87(5)	83(6)
C6 (n=22)	88(7)	78(10)

C1 *vs*. C2, $p < 0.0001$; C2 *vs*. C3, $p=0.0110$
C1 *vs*. C4, $p < 0.0001$ C2 *vs*. C5, C3 *vs* C6, Not significant
C4 *vs*. C5, C5 *vs*. C6, Not significant.

Tumor 2.1-3 cm	5 yrs	10 yrs
C1 (n=845)	98(0)	97(0)
C2 (n=160)	89(3)	85(3)
C3 (n=29)	90(6)	90(6)
C4 (n=117)	95(2)	90(3)
C5 (n=70)	88(4)	78(6)
C6 (n=28)	87(6)	58(11)

C1 *vs*. C2, $p < 0.0001$; C2 *vs*. C3, Not significant.
C1 *vs*. C4, $p=0.0328$ C2 *vs*. C5, Not significant
C3 *vs*. C6, $p=0.0397$
C4 *vs*. C5, $p=0.0243$ C5 *vs*. C6, Not significant

Tumor 3.1-4 cm	5 yrs	10 yrs
C1 (n=399)	96(1)	94(1)
C2 (n=84)	90(3)	86(4)
C3 (n=16)	81(1)	60(1)
C4 (n=81)	85(4)	79(5)
C5 (n=44)	75(7)	69(7)
C6 (n=21)	81(9)	67(12)

C1 *vs*. C2, $p=0.0152$; C2 *vs*. C3, $p=0.0712$
C1 *vs*. C4, $p<0.0001$ C2 *vs*. C5, $p=0.0099$
C3 *vs*. C6, Not significant
C4 *vs*. C5, $p=0.0999$ C5 *vs*. C6, Not significant.

Tumor larger than 4 cm	5 yrs	10 yrs
C1 (n=268)	96(1)	92(2)
C2 (n=88)	87(4)	76(6)
C3 (n=15)	60(1)	60(1)
C4 (n=100)	87(3)	71(5)
C5 (n=58)	73(6)	66(8)
C6 (n=34)	80(7)	48(11)

C1 *vs*. C2, $p=0.0015$; C2 *vs*. C3, $p=0.0347$
C1 *vs*. C4, $p<0.0001$ C2 *vs*. C5, $p=0.0316$
C3 *vs*. C6, Not significant
C4 *vs*. C5, C5 *vs*. C6, Not significant.

1 cm significantly depended on the presence of N (C1 *vs*. C2, $p = 0.0771$; C2 *vs*. C3, $p = 0.0010$) and Ex did not affect the DRFS. In Ex(-) PTC 1.1-2 cm, N factor significantly reflected DRFS, because DRFS of C2 patients was poorer than that of C1 patients ($p < 0.0001$) and although not significant, 10-year DRFS rate of C3 patients (89%) was lower than that of C2 patients (97%). Ex had a prognostic value for N0 patients (C1 *vs*. C4, $p < 0.0001$) but not for N1 or N2 patients. Similar results were obtained for DRFS of Ex(-) PTC 2.1-3 cm (C1 *vs*. C2, $p = 0.0068$). In contrast to smaller PTC, Ex had a prognostic significance not only for N0 but also for N1 PTC 2.1-3 cm (C1 *vs*. C4, $p = 0.0248$; C2 *vs*. C5, $p = 0.0061$). Although not significant, 10-year DRFS of C6 patients (72%) was lower than that of C3 patients (90%). These findings were also observed in PTC 3.1-4 cm and PTC larger than 4 cm, because of the significant difference in DRFS between C1 and C4 patients ($p = 0.0001$ and $p = 0.0005$), and C2 and C5 patients ($p = 0.0042$ and $p = 0.0013$). In PTC 3.1-4 cm, 10-year DRFS of C6 patients (56%) was lower than that of C3 patients (62%), although these DRFS did not significantly differ.

Carcinoma death of PTC patients according to the tumor size

Age ≥ 55 yrs significantly worsened or tended to worsen the CSS of all subsets of PTC (PTC 1 cm or less, $p = 0.0779$; 1.1-2 cm, $p = 0.0170$; 2.1-3 cm, 3.1-4 cm, and larger than 4 cm, $p < 0.0001$). We could not identify independent predictors of carcinoma death in PTC 1 cm or less because only 2 patients, who were classified into C3, died of PTC. Independent prognostic factors for CSS in other subsets were N2 ($p = 0.0037$) and age ≥ 55 yrs ($p = 0.0443$) in PTC 1.1-2 cm, N2 ($p = 0.0002$), age ≥ 55 yrs ($p = 0.0014$) in PTC 2.1-3 cm, N2 ($p = 0.0032$), age ≥ 55 yrs ($p = 0.0054$), and Ex ($p = 0.0355$) in PTC 3.1-4 cm, and age ≥ 55 yrs, Ex ($p = 0.0004$), and male gender ($p = 0.0149$) in PTC larger than 4 cm. In contrast to LN-RFS and DRFS, N1 did not have a significant prognostic value for CSS in any subsets.

Table 3 summarizes the CSS of PTC according to tumor size. CSS of PTC 1 cm or less was significantly affected only by N2 (C2 *vs*. C3, $p < 0.0001$). In PTC 1.1-2 cm, N2, but not N1, also worsened the CSS of Ex(-) patients (C2 *vs*. C3, $p = 0.0003$). Ex was also related to poor CSS of N0 patients (C1 *vs*. C4, $p = 0.0003$), but not N1 or N2 patients. Although not

Table 2 DRFS rates (%) of PTC patients according to tumor size (standard error)

Tumor 1 cm or smaller		
	5 yrs	10 yrs
C1 (n=1,034)	100	100(0)
C2 (n=133)	99(1)	99(1)
C3 (n=27)	88(7)	88(7)
C4 (n=21)	100	100
C5 (n=5)	100	100
C6 (n=0)		

C1 *vs*. C2, $p = 0.0771$; C2 *vs*. C3, $p = 0.0010$
C1 *vs*. C4, C2 *vs*. C5, C4 *vs*. C5, Not significant

Tumor 1.1-2 cm		
	5 yrs	10 yrs
C1 (n=1,635)	100(0)	99(0)
C2 (n=264)	98(1)	97(0)
C3 (n=45)	100	89(5)
C4 (n=90)	95(2)	93(4)
C5 (n=45)	98(2)	98(2)
C6 (n=22)	100	93(6)

C1 *vs*. C2, $p < 0.0001$; C2 *vs*. C3, Not significant
C1 *vs*. C4, $p < 0.0001$ C2 *vs*. C5, C3 *vs*. C6, Not significant
C4 *vs*. C5, C5 *vs*. C6, Not significant

Tumor 2.1-3 cm		
	5 yrs	10 yrs
C1 (n=845)	100	99(0)
C2 (n=160)	99(1)	95(2)
C3 (n=29)	96(4)	90(7)
C4 (n=117)	98(1)	96(2)
C5 (n=70)	97(2)	80(6)
C6 (n=28)	89(6)	72(10)

C1 *vs*. C2, $p = 0.0068$; C2 *vs*. C3, Not significant
C1 *vs*. C4, $p = 0.0248$ C2 *vs*. C5, $p = 0.0061$
C3 *vs*. C6, Not significant
C4 *vs*. C5, $p = 0.0048$ C5 *vs*. C6, Not significant

Tumor 3.1-4 cm		
	5 yrs	10 yrs
C1 (n=399)	100(0)	98(1)
C2 (n=84)	96(2)	93(3)
C3 (n=16)	87(4)	62(15)
C4 (n=81)	98(2)	90(5)
C5 (n=44)	91(5)	73(7)
C6 (n=21)	86(8)	56(12)

C1 *vs*. C2, $p = 0.0079$; C2 *vs*. C3, $p = 0.0050$
C1 *vs*. C4, $p = 0.0001$ C2 *vs*. C5, $p = 0.0042$
C3 *vs*. C6, Not significant
C4 *vs*. C5, $p = 0.0129$; C5 *vs*. C6, Not significant

Tumor larger than 4 cm		
	5 yrs	10 yrs
C1 (n=268)	99(1)	96(1)
C2 (n=88)	96(2)	95(3)
C3 (n=15)	86(9)	75(12)
C4 (n=100)	94(2)	86(4)
C5 (n=58)	85(5)	77(6)
C6 (n=34)	84(7)	73(10)

C1 *vs*. C2, Not significant; C2 *vs*. C3, $p = 0.0259$
C1 *vs*. C4, $p = 0.0005$; C2 *vs*. C5, $p = 0.0013$
C3 *vs*. C6, Not significant
C4 *vs*. C5, $p = 0.0011$; C5 *vs*. C6, Not significant

Table 3 CSS rates (%) of PTC patients according to tumor size (standard error)

Tumor 1 cm or smaller		
	5 yrs	10 yrs
C1 (n=1,034)	100	100
C2 (n=133)	100	100
C3 (n=27)	100	90(7)
C4 (n=21)	100	100
C5 (n=5)	100	100
C6 (n=0)		

C1 *vs*. C2, Not significant; C2 *vs*. C3, $p < 0.0001$
C1 *vs*. C4, C2 *vs*. C5, C4 *vs*. C5, Not significant

Tumor 1.1-2 cm		
	5 yrs	10 yrs
C1 (n=1,635)	100	100
C2 (n=264)	100	100
C3 (n=45)	100	90(7)
C4 (n=90)	99(1)	97(2)
C5 (n=45)	100	96(4)
C6 (n=22)	100	100

C1 *vs*. C2, Not significant; C2 *vs*. C3, $p = 0.0003$
C1 *vs*. C4, $p < 0.0001$ C2 *vs* C5, C3 *vs*. C6, Not significant
C4 *vs*. C5, C5 *vs*. C6, Not significant

Tumor 2.1-3 cm		
	5 yrs	10 yrs
C1 (n=845)	100	100(0)
C2 (n=160)	99(1)	98(2)
C3 (n=29)	96(4)	97(4)
C4 (n=117)	99(1)	98(2)
C5 (n=70)	100	95(5)
C6 (n=28)	97(4)	85(8)

C1 *vs*. C2, C2 *vs*. C3, Not significant
C1 *vs*. C4, C2 *vs*. C5, C3 *vs*. C6, Not significant
C4 *vs*. C5, Not significant; C5 *vs*. C6, $p = 0.0502$

Tumor 3.1-4 cm		
	5 yrs	10 yrs
C1 (n=399)	100	100
C2 (n=84)	100	96(4)
C3 (n=16)	100	100
C4 (n=81)	98(2)	95(3)
C5 (n=44)	96(3)	94(4)
C6 (n=21)	95(5)	82(10)

C1 *vs*. C2, $p = 0.0013$; C2 *vs*. C3, Not significant
C1 *vs*. C4, $p < 0.0001$; C2 *vs*. C5, Not significant
C3 *vs*. C6, $p = 0.0855$
C4 *vs*. C5, Not significant; C5 *vs*. C6, $p = 0.0699$

Tumor larger than 4 cm		
	5 yrs	10 yrs
C1 (n=268)	100	99(1)
C2 (n=88)	100	100
C3 (n=15)	100	100
C4 (n=100)	98(1)	90(4)
C5 (n=58)	94(4)	88(5)
C6 (n=34)	87(6)	87(6)

C1 *vs*. C2, $p = 0.0905$; C2 *vs*. C3, Not significant
C1 *vs*. C4, $p < 0.0001$; C2 *vs*. C5, $p = 0.0039$
C3 *vs*. C6, Not significant
C4 *vs*. C5, C5 *vs*. C6, Not significant

significant, 10-year CSS rate of C6 patients with PTC 2.1-3 cm was low, at 85%, while others ranged from 95 to 100%. In PTC 3.1-4 cm, Ex affected CSS not only of N0 but also of N2 patients (C1 *vs*. C4, $p < 0.0001$, C3 *vs*. C6, $p = 0.0855$). In Ex(-) patients, N1 had a prognostic value (C1 *vs*. C2, $p = 0.0013$). In the subset of PTC larger than 4 cm, Ex had a significant value for CSS, because CSS of C4 and C5 patients were poorer than C1 ($p < 0.0001$) and C2 patients ($p = 0.0039$) and 10-year CSS rate of C6 patients (87%) was poorer than that of C3 patients (100%), although not significant.

Discussion

It is well-known that the regional lymph node is the organ to which PTC most likely recurs. Although lymph node recurrence is not always immediately life-threatening, it is a stressor both for physicians and patients, and physicians should do their best to avoid it. In this study, N1 and N2 very strongly affected lymph node recurrence in all subsets of patients, because LN-RFS of Ex(-) patients became poorer in the order of C1, C2, and C3 patients in most subsets, which was not discrepant with the results of previous studies [5, 16]. C4 patients showed a poorer LN-RFS than C1 patients in all subsets except for that of PTC 1 cm or less, but LN-RFS of C5 patients was significantly poorer than in C2 patients only in the subsets of PTC 3.1-4 cm and PTC larger than 4 cm. These findings indicate that the prognostic impact of extrathyroid extension became stronger according to the tumor size, and can affect LN-RFS in N1 PTC larger than 3 cm, which was not inconsistent with our previous findings [15]. In the subset of PTC 2.1-3 cm, C6 patients showed a significantly poorer LN-RFS than C3 patients, and, although not significant, the 10-year LN-RFS rate of C6 patients with PTC larger than 4 cm was lower than that of C3 patients. Therefore, it is possible that extrathyroid extension also affects LN-RFS of N2 patients with large PTC, but its impact on N2 patients is weaker than that on N1 patients.

Also, for distant recurrence, N1 and N2 had a very strong prognostic impact. Especially, N2 was the strongest prognostic factor for distant recurrence with PTC 4 cm or less, as shown in multivariate analysis. The prognostic impact of extrathyroid extension was limited in PTC 2 cm or less, because none of the patients with Ex(+) PTC 1 cm or less showed distant recurrence and DRFS between C5 and C2 patients with PTC 1.1-2 cm did not differ. However, in the subsets of PTC larger than 2 cm, C5 patients showed a significantly poorer DRFS than C2 patients. Therefore, it is concluded that the prognostic value of extrathyroid extension was more significant in PTC larger than 2 cm than in PTC 2 cm or smaller. Although not significant, the 10-year DRFS of C6 patients tended to be poorer than in C3 patients with PTC 2.1-3 and 3.1-4 cm, indicating that extrathyroid extension also reflects N2 patients' DRFS to some extent.

N2 was the strongest prognostic factor for carcinoma death with PTC 4 cm or smaller, but N1 did not show a significant prognostic impact in any subsets. Extrathyroid extension was a significant prognostic factor for carcinoma death of the subsets of PTC larger than 3 cm, and its prognostic impact was even stronger than N2 in PTC larger than 4 cm in multivariate analysis. In our univariate analysis, the 10-year CSS rate of C3 patients with PTC 1 cm or less was rather poor at 90%, but the other 10-year CSS rates of C1-C5 patients with PTC 4 cm or less were generally good, ranging from 94-100%. In contrast, the 10-year CSS rates of C6 patients with PTC 2.1-3 cm, 3.1-4 cm, and larger than 4 cm, were poor at 85, 82, and 87%, respectively. It is therefore suggested that extrathyroid extension and N2 synergistically worsen the CSS of patients with PTC larger than 2 cm.

We previously showed that the prognostic significance of extrathyroid extension increased with the tumor size [15]. Also, in this study, extrathyroid extension affected the prognosis of patients with N-positive PTC of a large size, 3 cm or larger for lymph node recurrence and 2 cm for distant recurrence. This may be because of the increased range of carcinoma extension in large tumors. In our recent study, we subdivided extrathyroid extension into two categories according to the organs to which carcinoma extends, and showed that carcinoma extending more deeply and widely led to the worse prognosis [17], which may also support our speculation in part.

In our previous studies, the age and gender were also recognized as prognostic factors of PTC [18]. More recently, we showed that gender had a moderate prognostic value for lymph node recurrence and carcinoma death [19]. In this study, male gender was an independent prognostic factor of lymph node recurrence with PTC larger than 4 cm and carcinoma death when larger than 2 cm. Regarding patient age, we set the cutoff age at 55 years, because this most strongly reflected the

prognosis [5]. Old age was an independent prognostic factor for lymph node recurrence, lung recurrence, and carcinoma death, as previously described [18, 19]. Especially, age was the strongest prognostic factor for carcinoma death [19]. In our series, old age independently affected lymph node recurrence with PTC larger than 3 cm, distant recurrence, and carcinoma death for PTC larger than 1 cm. These findings suggest that age and gender significantly affected the prognosis, especially for large tumors.

We previously showed that total thyroidectomy is not mandatory for Ex(-)N0 (C1) patients 2 cm or smaller [9], but we also demonstrated that prognosis of C1 patients with PTC larger than 2 cm was significantly poorer than that 2 cm or less [10]. In this series, C1 patients showed an excellent prognosis regardless of tumor size and 10-year DRFS rate and CSS rate of C1 patients even larger than 4 cm were excellent, at 96% and 99%, respectively. Therefore, extensive thyroidectomy and lymph node dissection might not be mandatory for these patients even with large PTC because of low incidence of distant recurrence and carcinoma death. In contrast, even though diagnosed as Ex(-), LN-RFS, DRFS and CSS rates of N2 patients were low and 10-year DRFS rates of C3 PTC ranged from 62 to 90% in all 5 subsets. Therefore, extensive surgery such as total thyroidectomy with therapeutic node dissection with careful follow-up by thyroid stimulating hormone (TSH) suppression and thyroglobulin monitoring is mandatory for these patients regardless of tumor size. Although patients who underwent RAI ablation were excluded from this study, it could be considered as an adjuvant therapy for these patients. Extrathyroid extension did not strongly affect patients' prognosis in small PTC in our series. However, 10-year DRFS of C4 patients became low, at 90%, in PTC 3.1-4 cm and 86% in PTC larger than 4 cm. Therefore, careful and extensive surgery and postoperative follow-up are mandatory for also Ex(+) PTC with large size even though they are classified as N0. It remains controversial whether total thyroidectomy with therapeutic node dissection is mandatory for Ex(-)N1 patients. In our series, 10-year LN-RFS rates and DRFS rates of C2 patients ranged from 76-89% and 93-99%, respectively. LN-RFS of C2 patients was significantly poorer than C1 patients in all subsets and DRFS of C2 patients were significantly poorer than or tended to be poor comparing C1 patients in the subsets of 4 cm or less. Therefore, it may be better to perform total thyroidectomy for N1 patients, which is not discrepant with the recommendation of Japanese guidelines [20].

In summary, we investigated the prognosis of PTC patients by size. Node metastasis 3 cm or larger and/or extranodal tumor extension very strongly affected prognosis of patients, regardless of the tumor size. Extrathyroid extension became a prognostic factor with PTC larger than 1 cm, and worsened lymph node recurrence-free survival and distant recurrence-free survival even for clinical node-positive PTC larger than 3 cm and larger than 2 cm, respectively. Furthermore, extrathyroid extension worsened the CSS in combination with large node metastasis or extranodal tumor extension for PTC larger than 2 cm. We have to note that prognostic significance for lymph node and distant recurrence-free, and cause-specific survival of Ex and N varies according to the tumor size in order to accurately predict the clinical outcomes of PTC patients and decide their therapeutic strategies.

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