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Prognostic Factors for Recurrence of Papillary Thyroid Carcinoma in the Lymph Nodes, Lung, and Bone: Analysis of 5,768 Patients with Average 10-year Follow-up

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Abstract
Background Papillary thyroid carcinoma (PTC) frequently recurs to the lymph nodes, which may not be fatal immediately but is a stressor for physicians and patients. Recurrence to the distant organs, although less frequent, is often life-threatening, and the lung and bone are organs to which PTC is likely to recur. In the present study we investigated factors predicting recurrence of PTC to the lymph nodes, lung, and bone in a large number of patients undergoing long-term follow-up.
Methods A total of 5,768 PTC patients (608 males and 5,159 females) without distant metastasis at diagnosis who underwent initial surgery between 1987 and 2004 in Kuma Hospital were enrolled in this study. The postoperative follow-up ranged from 12 to 280 months, and was 129 months (10.8 years) on average.
Results To date, node, lung, and bone recurrences have been detected in 389 (7%), 118 (2%), and 33 patients (0.6%), respectively, and 57 patients (1%) have died of PTC. We examined the prognostic significance of the tumor size (T), extrathyroid extension (Ex), age 55 years or older (Age), male gender (Gender), clinical node metastasis (N), and extranodal tumor extension (LN-Ex) for each outcome on multivariate analysis. Age, Gender, $T > 2$ cm, N, and Ex were independent predictors of lymph node recurrence. Age, Ex, $T > 2$ cm, and N were independent prognostic factors for lung recurrence. Ex, $T > 4$ cm, and N independently predicted bone recurrence. Of these, $N \geq 3$ cm had the strongest prognostic value for lymph node, lung, and bone recurrences. In contrast, Age was the strongest predictor for carcinoma death. LN-Ex also had a prognostic value for carcinoma death, although it was not a predictor of carcinoma recurrence. Ex, $N \geq 3$ cm, and $T > 2$ cm also had a prognostic impact on carcinoma death.
Conclusions Large lymph node metastasis showed a strong prognostic impact on carcinoma recurrence not only to the lymph nodes but also to the lung and bone, and carcinoma death. Extrathyroid extension also independently predicted these recurrences and carcinoma death, although hazard ratios were lower than for large node metastasis. Age 55 years or older, in contrast, was the strongest predictor of carcinoma death. Extranodal tumor extension did not independently affect recurrence, but it had prognostic significance for carcinoma death. These findings suggest that recurring PTC lesions of older patients and/or extranodal tumor extensions are difficult to control and very progressive.

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Introduction

Papillary thyroid carcinoma (PTC) is the most common malignancy arising from follicular cells of the thyroid. Generally, it is an indolent disease, but cases having certain characteristics are likely to show recurrence and even become life-threatening. The organ to which PTC most likely recurs is the lymph node [1]. With a few exceptions, such recurrence is not immediately life-threatening, but is a

stressor for both physicians and patients. Therefore, extensive lymph node dissection is recommended for patients with PTC having characteristics that predict high incidence of lymph node recurrence [2]. Recurrence to distant organs such as the lung and bone is less frequent than recurrence to nodes, but it becomes life-threatening if the recurrent lesions are refractory to radioactive iodine (RAI) therapy.

In our previous studies, we demonstrated that older patient age, male gender, large tumor, large lymph node metastasis, and extranodal tumor extension are risk factors predicting poorer disease-free survival (DFS) and cause-specific survival (CSS) of PTC patients [1, 3–6]. However, there have been no studies investigating predictors for recurrence to the lymph node, lung, and bone separately, using the same series. In the present study, therefore, we investigated the prognostic factors of lymph node, lung, and bone recurrence in a series of 5,768 patients with over a 10-year follow-up on average.

Patients and methods

This study enrolled 5,768 patients with PTC without distant metastasis at presentation who underwent initial surgery in Kuma Hospital, between 1987 and 2004. They consisted of 608 males and 5,159 males, and the age of patients was 48.9 years on average. The extent of thyroidectomy was total thyroidectomy in 2,855 patients, near-total thyroidectomy (estimated remnant thyroid 1 g or less) in 88 patients, and more limited thyroidectomy in the remaining 2,825 patients. The extent of lymph node dissection was unilateral or bilateral modified radical neck dissection (MND) with central node dissection (CND) in 4,366 patients, CND only in 1,128 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 preoperative evaluation, such as the location and size of primary lesions and lymph node metastases, were predominantly obtained by ultrasonography. Extrathyroid extension of primary lesions and extranodal tumor extension were evaluated intraoperatively. We do not adopt microscopic findings of extrathyroid extension. We regarded cases corresponding to T4a in the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification as having extrathyroid extension [7], and those with lymph node metastasis requiring at least partial excision of adjacent organs for node dissection as having extranodal tumor extension [4, 8].

Scintigraphy using a small amount of radioiodine (3–13 mCi) was performed at our outpatient clinic 1–2 months after total or near-total thyroidectomy in 990 patients with tumors showing aggressive characteristics, such as massive extrathyroid extension or multiple clinically apparent lymph node metastases. Radioactive iodine ablation using 30–100 mCi was performed in 84 patients following hospitalization. None of these patients showed abnormal uptakes. In our series, none of the patients underwent external radiotherapy after the initial surgery.

We followed patients by ultrasonography once a year to monitor for signs of local recurrence. Either chest roentgenography or a CT scan was also performed annually. 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 recurrence was apparent on imaging studies such as a CT scan, roentgenography, or positron emission tomography (PET)-CT. To date, 528 patients (9%) have shown PTC recurrence to one or more organs. Recurrences to the lymph nodes, lung, and bone were detected in 389, 118, and 33 patients, respectively. Local recurrence to sites other than regional lymph nodes and recurrence to distant organs other than the lung and bone were observed in 93 and 8 patients, respectively. These recurrences were not analyzed in this study. Seventy-seven patients showed recurrence to two or more organs. To date, 57 patients (1%) have died of PTC. Seventeen 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.

A Cox-hazard regression model was used for multivariate analysis. A p value smaller than 0.05 was considered significant, and a value of 0.05 or greater but less than 0.1 was regarded as marginally significant.

Results

We investigated the prognostic significance of six clinicopathological characteristics: age ($\geq$55 versus $<$55 years) (Age), male gender (Gender), extrathyroid extension (Ex), tumor size (T) ($>$4 cm [T2] and 2.1–4 cm [T1]), clinical lymph node metastasis (N) ($\geq$3 cm [N2] and $<$3 cm [N1]), and extranodal tumor extension (LN-Ex), for recurrence to the lymph nodes, lung, and bone, and carcinoma death. We set the cut-off age at 55 years, because this reflected patients' prognoses more closely than the age of 45 years used in the UICC TNM classification [4]. Table 1 summarizes the background and clinicopathological features of the 5,768 patients.

To date, 389 patients (7%) have shown recurrence of PTC to the regional lymph nodes. As shown in Table 2, all factors except LN-Ex were independent predictors of lymph node recurrence. Especially, N2 strongly reflected the recurrence. N2 patients were 6.18 and 3.32 times (6.18/1.86) more likely to show lymph node recurrence than N-negative and N1 patients, respectively. Regarding the T

Table 1 Backgrounds of 5,768 patients in our series

Age, years	
≥55	2,257 (39%)
<55	3,511 (61%)
Gender	
Male	608 (11%)
Female	5,159 (89%)
Tumor size, cm	
>4	564 (10%)
2.1–4	1,892 (33%)
≤2	3,312 (57%)
Extrathyroid extension	
Present	737 (13%)
Absent	5,031 (87%)
Clinical node metastasis	
≥3 cm	180 (3%)
<3 cm	993 (17%)
None	4,595 (80%)

Table 2 Multivariate analysis of recurrence to the regional lymph nodes of 5,768 patients

	p Value	Hazard ratio	95% CI
Age	0.0001	1.50	1.22–1.84
Gender	0.0102	1.40	1.08–1.82
Ex	<0.0001	1.39	1.23–1.57
T1	<0.0001	1.86	1.46–2.36
T2	<0.0001	2.88	2.18–3.84
N1	<0.0001	1.86	2.75–4.33
N2	<0.0001	6.18	4.38–8.54
LN-Ex	0.8998	1.01	0.84–1.23

95% CI 95% confidence interval

factor, hazard ratios of T2 were lower than those of N2, which were 2.88 for T-negative patients and 1.55 (2.88/1.86) for T1 patients, respectively. Ex was also a strong predictor of lymph node recurrence based on the *p* value.

Recurrence to the lung was detected in 118 patients (2%). N, T, Ex, and Age independently affected lung recurrence (Table 3). Based on the hazard ratio, N2 most strongly predicted lung recurrence. T2 and T1 also had a prognostic impact, but the hazard ratio of T2 for T1 was only 1.11 (3.35/3.01). Ex and Age were also prognostic factors for lung recurrence based on *p* values.

Bone recurrence was detected in 33 patients (0.6%). Ex, T, and N had independent prognostic impacts. Also, for bone recurrence, N2 was the strongest predictor. Based on the *p* value, Ex also strongly affected bone recurrence (Table 4). T only moderately affected bone recurrence.

Table 3 Multivariate analysis of recurrence to the lung in 5,768 patients

	p Value	Hazard ratio	95% CI
Age	<0.0001	2.16	1.47–3.16
Gender	0.6431	1.25	0.52–1.50
Ex	<0.0001	1.77	1.43–2.18
T1	<0.0001	3.01	1.85–4.91
T2	<0.0001	3.35	1.90–5.94
N1	<0.0001	3.97	2.59–6.06
N2	<0.0001	8.01	4.53–14.13
LN-Ex	0.8463	1.18	0.71–1.32

Table 4 Multivariate analysis of recurrence to the bone in 5,768 patients

	p Values	Hazard ratio	95% CI
Age	0.1093	1.78	0.88–3.62
Gender	0.1215	1.87	0.85–4.13
Ex	0.0199	1.60	1.01–2.39
T1	0.0811	2.21	0.91–5.38
T2	0.0361	2.95	1.07–8.14
N1	0.0209	2.81	1.17–6.77
N2	<0.0001	11.19	4.21–28.72
LN-Ex	0.4340	1.22	0.74–2.03

To date, 57 patients (1%) have died of PTC. In contrast to recurrence, Age is the strongest predictor of carcinoma death based on the *p* value and hazard ratio (Table 5). LN-Ex also independently predicted carcinoma death, although it did not have independent prognostic significance for carcinoma recurrence. N2, T2, and T1 had prognostic significance, although the hazard ratio of T2 for T1 (1.98: 5.46/2.76) was lower than that of N2 for N1 (3.55; 5.58/1.57).

Discussion

The extent of lymph node dissection varies according to institutions and countries. In Western guidelines, prophylactic

Table 5 Multivariate analysis of carcinoma death in 5,768 patients

	p Value	Hazard ratio	95% CI
Age	<0.0001	12.11	5.67–26.84
Gender	0.0647	1.84	0.96–3.52
Ex	<0.0001	2.16	1.57–2.98
T1	0.0195	2.76	1.28–5.96
T2	0.0095	5.46	2.41–12.38
N1	0.2083	1.57	0.78–3.14
N2	<0.0001	5.58	2.56–12.18
LN-Ex	0.0002	1.96	1.38–2.78

node dissection is not actively recommended, whereas the Japanese guidelines recommend routine central node dissection [9–14]. In the past, almost routine prophylactic modified radical neck dissection (MND) was performed in many Japanese institutions, including ours, which is the reason that our series includes many patients who underwent MND. Whatever the extent of lymph node dissection, it is important to perform it carefully to avoid recurrence to the compartments dissected at the initial surgery. This is because reoperation for previously dissected compartments is difficult and can induce various complications such as permanent hypoparathyroidism, chyle leakage, and injury to adjacent organs. In the present study we demonstrated that the presence of clinical node metastasis, a large tumor, and extrathyroid extension are strongly predictive of lymph node recurrence. Of these factors, node metastasis 3 cm or larger most significantly reflected lymph node recurrence. We can hypothesize that PTC with large metastasis has a marked capability of inducing metastatic lesions, which may be a reason for the high incidence of recurrence to the nodes. Furthermore, we previously showed that N0 or N1a PTC patients with extrathyroid extension or a large tumor were likely to show recurrence to the nodes in the lateral compartment even though these patients underwent prophylactic MND [2]. In the present study we obtained findings similar to those described above, suggesting that not only primary lesions but also metastatic lesions are progressive for PTC demonstrating these characteristics. It is therefore suggested that careful and extensive lymph node dissection is necessary for patients with large node metastasis, extrathyroid extension, or a large tumor, and close postoperative follow-up by ultrasonography is also recommended.

In our series, extrathyroid extension independently predicted recurrence to the lung and bone. It is speculated that, in PTC patients with extrathyroid extension, carcinoma cells can easily spread to distant organs through the bloodstream. Interestingly, the presence of a metastatic node 3 cm or larger most strongly reflected the likelihood of recurrence to the lung and bone. Sugitani et al. demonstrated that elderly patients having metastatic nodes 3 cm or larger are at high risk and likely to die of PTC [14]. We also showed the adverse prognosis of patients with a large node metastasis [4]. These findings indicate that PTC with large metastatic node fundamentally has an aggressive and progressive character and is likely to show recurrence not only to lymph nodes but also to distant organs.

In contrast, an age of 55 years or older was the strongest predictor of carcinoma death. Also, extranodal tumor extension strongly predicted a worse cause-specific survival of patients, although it was not an independent predictor of carcinoma recurrence, which was not inconsistent with our previous findings [4, 6, 8]. These findings indicate that prognostic factors of carcinoma death were not completely consistent with those of carcinoma recurrence, although extrathyroid extension, a large tumor, and large node metastasis also significantly predicted carcinoma death. It is therefore suggested that recurring lesions of patients with an advanced age and/or PTC showing extranodal tumor extension are difficult to control and life-threatening. Therefore such patients should be very carefully treated, including surgery and postoperative follow-up.

In the present study, we showed that the tumor size had a prognostic impact on PTC recurrence and carcinoma death. In the past, we set the cut-off tumor size only at 4 cm to discriminate between high- and low-risk patients [1, 2]. We recently showed that, in the subset of otherwise low-risk patients without significant extrathyroid extension or clinical node and distant metastases, the prognosis of patients with PTC measuring 2 cm or less had an excellent prognosis [15]. However, carcinoma recurrence rates and carcinoma death rates of otherwise low-risk patients with tumors larger than 2 cm were higher than those of patients with tumors 2 cm or less [16]. We also demonstrated that tumor size larger than 2 cm was an independent prognostic factor for the prognoses of otherwise low-risk PTC patients on multivariate analysis [16]. Therefore, in this study, we set two cut-offs at 2 and 4 cm, similar to the UICC classification [4]. We demonstrated that, although tumor size was recognized as having a prognostic value, the hazard ratios of T2 for T1 were generally low, suggesting that a cut-off of 4 cm is less important than that of 2 cm for predicting the prognosis of PTC patients.

In summary, large lymph node metastasis showed the strongest prognostic impact on recurrence, not only to the lymph node but also to the lung and bone, and carcinoma death. Extrathyroid extension also independently predicted these recurrences and carcinoma death, although the hazard ratios were lower than for large node metastasis. An age of 55 years or older, in contrast, was the strongest predictor of carcinoma death. Extranodal tumor extension did not independently affect recurrence, but it had a prognostic significance for carcinoma death. Therefore, patients having these two characteristics should be carefully treated when their carcinomas recur.

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