

NOTE

## Tumor size is the strongest predictor of microscopic lymph node metastasis and lymph node recurrence of N0 papillary thyroid carcinoma

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**Abstract.** It is well-known that papillary thyroid carcinoma (PTC) frequently metastasizes to the regional (central and lateral) lymph nodes, even though it is diagnosed as node-negative on preoperative imaging studies. In this study, we investigated predictors of microscopic node metastasis and lymph node recurrence of PTC without node metastasis detected preoperatively (N0). Of the clinicopathological features that can be evaluated pre- and intraoperatively, tumor size ( $> 2$  cm) was the strongest predictor of microscopic central and lateral node metastasis on multivariate logistic analysis. Also, the tumor size most markedly affected lymph node recurrence, but not distant recurrence. Lymph node recurrence may not be immediately life-threatening, but it can be a stressor both for physicians and patients. Therefore, careful lymph node dissection is recommended for PTC with a large size, even though it is prophylactic.

**Key words:** Papillary thyroid carcinoma, Microscopic lymph node metastasis, Tumor size

**PAPILLARY THYROID CARCINOMA** (PTC), which is the most common malignancy arising from thyroid follicular cells, is generally indolent but very frequently metastasizes to the regional lymph nodes (central and lateral compartments). The recent prevalence of imaging studies, especially ultrasonography, has facilitated the preoperative evaluation of lymph node metastasis. One study showed a favorable result revealing the utility of preoperative ultrasonography [1]. However, in our study using a series of a larger number of patients, the diagnostic accuracy of ultrasonography for regional lymph nodes was not high, and its sensitivity for central and lateral node metastases was low, at 12 and 29%, respectively [2]. This indicates that lymph node metastasis is frequently overlooked and even PTC diagnosed as node-negative preoperatively (N0) is actually microscopic node-positive at a high incidence. Furthermore, the lymph node is the organ to which PTC most frequently recurs after surgery [2]. Therefore, the optimal extent of prophylactic

lymph node dissection remains debatable.

Currently, little is known about clinicopathological features significantly predicting microscopic regional node metastasis for N0 PTC. In this study, therefore, we investigated the predictors of microscopic lymph node metastasis to the central and lateral compartments and lymph node recurrence using a large series of N0 PTC patients.

### Patients and Methods

In this study, we enrolled 3,219 patients who underwent initial surgery for PTC without clinical node metastases at diagnosis between 1987 and 2005 in our hospital. All these patients underwent thyroidectomy (total thyroidectomy for 1,506 patients and limited thyroidectomy for the remaining 1,713 patients) and prophylactic central and uni- or bilateral lateral node dissection. They consisted of 288 males and 2,931 females, and the age was 49.5 years (11-87 years) on average. Patients who had other coexisting thyroid malignancies, distant metastasis at diagnosis, underwent locally non-curative surgery, had upper mediastinal node metastasis detected on preoperative imaging studies, and who were followed for less than 1 year after sur-

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gery were excluded from our series. All patients underwent ultrasonography to evaluate their primary lesions and lymph node metastasis, and none of the patients were diagnosed as positive for node metastasis preoperatively. Extrathyroid extension was evaluated based on intraoperative findings. We diagnosed patients as positive for extrathyroid extension only when extension corresponding to T4a in the UICC classification system was observed [3].

Five-hundred and fifty-nine patients underwent a whole-body scan using a small amount of radioiodine (3-13 mCi) 1-2 months after total or near total thyroidectomy, but no patients showed an abnormal uptake.

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. Postoperative follow-up ranged from 12 to 280 months (average follow-up period: 139 months). We regarded a patient as showing

recurrence when it was apparent on imaging studies such as a CT scan, roentgenography, and PET-CT. To date, 153 patients (5%) have shown lymph node recurrence, and 52 (2%) have shown recurrence to distant organs such as the lung, bone, and brain. Twenty-four patients (1%) have died of PTC, to date.

Statistical analysis was performed using StatFlex. Fishers' exact analysis was used for univariate analysis. For multivariate analysis, multivariate logistic analysis and the Cox-hazard regression model were employed. A *p*-value smaller than 0.05 was considered significant.

## Results

We investigated the relationship between microscopic central and lateral node metastasis and various clinicopathological features of N0 PTC patients (Tables 1 and 2). Tumor size was evaluated based on ultrasonographic findings. For a patient having multiple carci-

**Table 1** Relationship between microscopic central node metastasis and various clinicopathological features of N0 PTC patients (%)

Node metastasis		(+)	(-)	Total	<i>p</i> -values
Age	≥ 55yrs	689 (57)	527 (43)	1,216	< 0.0001
	< 55yrs	1,366 (68)	637 (32)	2,003	
Gender	Male	212 (74)	76 (26)	288	0.0002
	Female	1,843 (63)	1,088 (37)	2,931	
Multiplicity	(+)	532 (67)	268 (33)	800	0.0746
	(-)	1,523 (63)	896 (37)	2,419	
Tumor size	> 2 cm	1,156 (73)	437 (27)	1,593	< 0.0001
	≤ 2 cm	899 (55)	727 (45)	1,626	
Extrathyroid extension	(+)	264 (70)	115 (30)	379	0.0123
	(-)	1,791 (63)	1,049 (37)	2,840	

**Table 2** Relationship between microscopic lateral node metastasis and various clinicopathological features of N0 PTC patients (%)

Node metastasis		(+)	(-)	Total	<i>p</i> -values
Age	≥ 55yrs	664 (55)	552 (45)	1,216	0.0153
	< 55yrs	1,182 (59)	821 (41)	2,003	
Gender	Male	194 (67)	94 (33)	288	0.0003
	Female	1,652 (56)	1,279 (44)	2,931	
Multiplicity	(+)	474 (59)	326 (41)	800	0.2162
	(-)	1,372 (57)	1,047 (43)	2,419	
Tumor size	> 2 cm	1,094 (69)	499 (31)	1,593	< 0.0001
	≤ 2 cm	752 (46)	1,094 (54)	1,626	
Extrathyroid extension	(+)	287 (76)	92 (24)	379	< 0.0001
	(-)	1,559 (55)	1,281 (45)	2,840	

noma lesions, size of the largest tumor was adopted for this study. A tumor size larger than 2 cm showed a significant direct correlation with microscopic node metastasis together with other clinicopathological features, such as a young age, male gender, and extrathyroid extension.

Tables 3 and 4 show the results of multivariate logistic

**Table 3** Multivariate logistic analysis for factors predicting microscopic central node metastasis in N0 PTC patients

Variables	<i>p</i> -values	Odds ratio (95%CI)
Age < 55 yrs	< 0.0001	1.7428 (1.4934-2.0330)
Male gender	0.0050	1.4928 (1.1287-1.9746)
Multiplicity	0.0012	1.3345 (1.1209-1.5880)
Size > 2 cm	< 0.0001	2.0716 (1.7772-2.4140)
Extrathyroid extension	0.0718	1.1201 (0.9900-1.2670)

CI, Confidence interval

**Table 4** Multivariate logistic analysis for factors predicting microscopic lateral node metastasis in N0 PTC patients

Variables	<i>p</i> -values	Odds ratio (95%CI)
Age < 55 yrs	0.0002	1.3351 (1.1459-1.5550)
Male gender	0.0130	1.4003 (1.0741-1.8264)
Multiplicity	0.0146	1.2352 (1.0427-1.4630)
Size > 2 cm	< 0.0001	2.3199 (2.0000-2.6910)
Extrathyroid extension	< 0.0001	1.4784 (1.2991-1.6820)

CI, Confidence interval

**Table 5** Multivariate analysis for factors predicting lymph node recurrence in N0 PTC patients

Variables	<i>p</i> -values	Odds ratio (95%CI)
Age ≥ 55 yrs	0.0010	1.7476 (1.2530-2.4374)
Male gender	0.0048	1.8199 (1.2089-2.7925)
Multiplicity	0.2784	0.8027 (0.5396-1.1943)
Size > 2 cm	< 0.0001	2.7880 (1.8756-4.1444)
Extrathyroid extension	< 0.0001	1.7683 (1.4809-2.1115)

CI, Confidence interval

**Table 6** Multivariate analysis for factors predicting distant recurrence in N0 PTC patients

Variables	<i>p</i> -values	Odds ratio (95%CI)
Age ≥ 55 yrs	0.0013	2.6868 (1.4717-4.9051)
Male gender	0.3547	1.7378 (0.5392-5.6006)
Multiplicity	0.1635	0.5983 (0.2905-1.2323)
Size > 2 cm	0.0169	2.2901 (1.1604-4.5195)
Extrathyroid extension	< 0.0001	2.2402 (1.6633-3.0171)

CI, Confidence interval

analysis for factors predicting microscopic central and lateral node metastases, respectively. Based on *p*-values and odds ratios, a tumor size larger than 2 cm was most markedly related to central and lateral node metastases.

Table 5 shows multivariate analysis for factors predicting lymph node recurrence in N0 PTC patients. An advanced age, male gender, large tumor size and extrathyroid extension independently affected lymph node recurrence and, of these, tumor size had the greatest prognostic value. Tumor size was also an independent predictor of distant recurrence, but extrathyroid extension and an advanced age showed a similar to or even stronger prognostic value than tumor size (Table 6). Prognostic factors for carcinoma death could not be analyzed on multivariate analysis because of the small number of patients who died of PTC.

## Discussion

In this study, we showed that, of the clinicopathological features that can be pre- or intraoperatively evaluated, a tumor size larger than 2 cm was the strongest predictor of microscopic central and lateral node metastasis and lymph node recurrence on multivariate analysis of N0 PTC patients. Lymph node recurrence is not immediately life-threatening, but might be a stressor both for physicians and patients. Therefore, it is preferable for physicians to do their best to minimize lymph node recurrence.

There are pros and cons of prophylactic lymph node dissection of PTC [4-11]. Leading guidelines published from Western countries do not actively recommend prophylactic lymph node dissection [12-14]. Central nodes can be comparably easily dissected *via* the same wound as that for thyroidectomy, but its indication is still limited [12-14]. In guidelines published by the Japanese Association of Endocrine Surgeons (JAES) and Japanese Society of Thyroid Surgeons (JSTS), however, prophylactic central node dissection is routinely recommended [15, 16]. This is because re-operation for recurrence to this compartment may induce significant complications such as recurrent laryngeal nerve injury and persistent hypoparathyroidism. We have no high-grade evidence of whether routine prophylactic central node dissection can improve patients' prognosis, but, here, we showed that a large tumor is more likely to be microscopically central node-positive and show lymph node recurrence. Therefore, we can conclude that careful prophylactic central node

dissection should be recommended for N0 PTC with a large size.

None of the leading guidelines, including Japanese guidelines, recommended prophylactic lateral node metastasis [12-15]. However, we previously showed that the incidence of microscopic lateral node metastasis increased with the tumor size, and lymph node recurrence-free survival became poorer with a large tumor size on univariate analysis in a series of N0 or N1a patients [17]. This study, using a series of N0 patients and employing multivariate analysis, also showed that a large tumor size is the strongest predictor of microscopic lateral node metastasis. To date, no comparative studies of the prognosis between patients who underwent and did not undergo prophylactic lateral node dissection have been published, but prophylactic lateral node dissection may possibly reduce the lymph node recurrence rate. Therefore, prophylactic lateral node dissection might be considered for large PTC, although no other high-risk features are detected. The guidelines of JSTS/JAES describe that prophylactic lateral node dissection is recommended for PTC larger than 5 cm and as a consensus of committee, it can be considered for a tumor larger than 4 cm [15], which might be reasonable.

In our series, young patients were more frequently positive for regional lymph nodes in univariate analysis (Tables 1 and 2), which is consistent with a previous study [18]. Furthermore, a young age is a predictor

of being microscopic central and lateral node-positive on multivariate logistic analyses (Tables 3 and 4). However, as shown in Table 5, old patients were more likely to show lymph node recurrence. This may be because PTC in old patients has a more aggressive and progressive characteristic than that in younger patients. An advanced age was also an independent predictor of distant recurrence, and its prognostic value was even greater than tumor size (Table 6). Furthermore, in our previous study, an advanced age was the strongest predictor of carcinoma death of the entire series of PTC patients [19]. These can explain, at least in part, our findings in this study.

Unlike lymph node recurrence, the tumor size was not the strongest predictor of distant recurrence, indicating that biological characteristics inducing lymph node and distant recurrence significantly differ. It is, therefore, suggested that prognostic factors of lymph node and distant recurrence should be analyzed separately, rather than in a single group.

In summary, we showed that, of clinicopathological features that can be pre- and intraoperatively evaluated, the tumor size was the strongest predictor of microscopic central and lateral node metastasis and lymph node recurrence in the series of N0 PTC patients. Careful prophylactic dissection of PTC with a large size should be performed to minimize lymph node recurrence.

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