Risk factors for the lateral cervical lymph node metastasis of papillary thyroid carcinoma: A clinical study

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Abstract. Currently, there is a lack of evidence-based risk factors for the lateral cervical lymph node metastasis of papillary thyroid carcinoma (PTC). Thus, the risk factors and recurrence rate of lateral cervical lymph node metastasis were investigated in the present study for patients with PTC who underwent initial radical surgery. The data of 274 patients with PTC who underwent initial radical surgery over a 10-year period from January, 2009 to December, 2018 were retrospectively analyzed. By applying univariate analysis, lymphovascular invasion, venous invasion, extrathyroidal infiltration, paratracheal lymph node metastasis and tumor size were designated as significant risk factors for lateral cervical lymph node metastasis. As regards multivariate analysis, paratracheal lymph node metastasis and tumor size were identified as independent risk factors. The recurrence rate was higher in patients presenting with lateral cervical lymph node metastasis, and the disease-free survival rate was significantly lower in the patient group presenting with lateral cervical lymph node metastasis. On the whole, the present study demonstrated that paratracheal lymph node metastasis and tumor size were independent risk factors for lateral cervical lymph node metastasis.

Introduction

Thyroid carcinoma is the most common endocrine malignancy, accounting for approximately 3.8% of all newly diagnosed cancer cases (1). Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for ~85% of all thyroid cancer cases (2,3). It usually has a favorable outcome, with the 10-year survival rate exceeding 90% (4,5). However, previous studies have reported that the recurrence rate is 7-23% following initial surgical treatment (6,7).

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Lymph node metastasis is relatively frequent in PTC. However, it is unclear whether it is a risk factor for PTC recurrence. The American Thyroid Association (ATA) 2015, National Comprehensive Cancer Network (NCCN) 2019, and British Thyroid Association (BTA) 2014 are widely known international guidelines (8-10). However, comparisons between the guidelines reveals that small differences in risk factors for PTC recurrence among each guideline can be observed (Table I). This is largely attributed to the guidelines being mainly based on the Union for International Cancer Control/American Joint Commission on Cancer (UICC/AJCC) TNM classification (11). In previous reports, various factors, including age, sex, tumor size, extrathyroidal infiltration, lymphovascular invasion, paratracheal lymph node metastasis and lateral cervical lymph node metastasis have been shown to be associated with the recurrence of PTC (12-14). The main focus of the present study was lymph node metastasis, particularly lateral cervical lymph node metastasis. The difference in recurrence rate, depending on the presence or absence of lateral cervical lymph node metastasis at the time of the initial surgery and the risk factors for lateral cervical lymph node metastasis were investigated herein.

Patients and methods

Patients. The present study was conducted in accordance with the Declaration of Helsinki and approved by Ethics Committee of Nara Medical University (Approval no. 3048). Written informed consent was obtained from all patients involved. Between January, 2009 to December, 2018, 274 patients with PTC underwent lobectomy or total thyroidectomy at Nara Medical University (Kashihara, Japan) with or without paratracheal or lateral cervical lymph node dissection as an initial treatment. Patients were excluded if they were lost to follow-up for >3 years, had a history of distant metastasis at the time of the initial diagnosis, and had not undergone complete resection.

Methods. Fine-needle aspiration cytology was used for the diagnosis of PTC and for pre-operative evaluations. A breakdown analysis of the surgical procedures is presented in Fig. 1. Clear pre-operative evidence of paratracheal lymph node metastasis was observed in 12 cases. Lateral cervical lymph node dissection was performed along with lymph node metastasis dissection, which was evident on pre-operative echo and

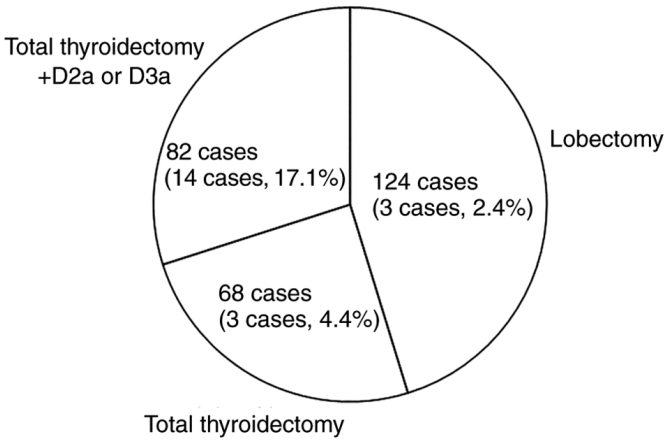

Figure 1. Breakdown analysis of the surgical procedures used for the patients in the present study.

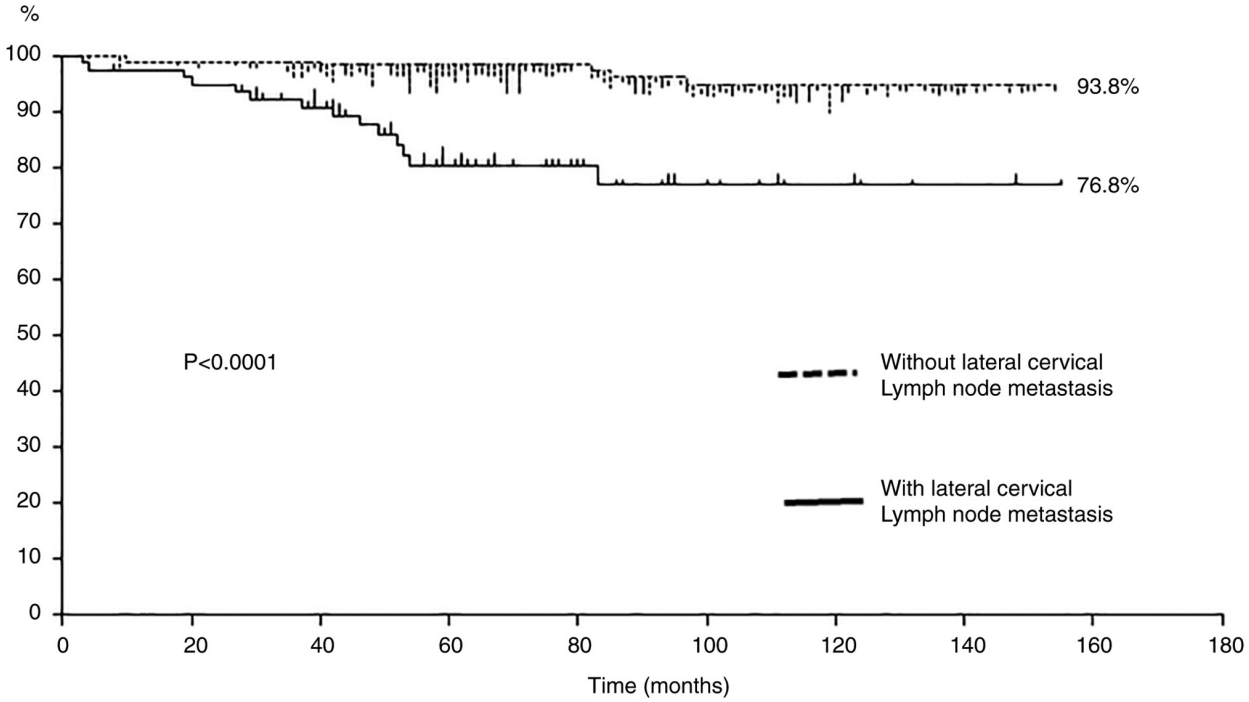

Figure 2. Differences in disease-free survival with and without lateral cervical lymph node metastasis. A significantly shorter disease-free survival was observed with lateral cervical lymph node metastasis (P<0.0001).

CT images. In order to monitor tumor recurrence, all patients underwent a thyroid function test, as well as thyroglobulin assessment and an ultrasonography of the neck, for the detection and localization of tumor recurrence. Additionally, computed tomography was also used at 1-year intervals.

Firstly, in order to demonstrate that lateral cervical lymph node metastasis is a risk factor for recurrence, the difference in disease-free survival (DFS) between patients with and without lateral cervical lymph node metastasis was examined, which was demonstrated to significantly shorten DFS, as presented in Fig. 2.

Patient and disease factors were selected to examine the risk factors for lateral cervical lymph node metastasis. Patient factors included sex and age. Disease factors included the presence or absence of lymphovascular invasion, venous invasion, extrathyroidal infiltration, intraglandular metastasis, paratracheal lymph node metastasis, and tumor size based on the post-operative pathological diagnosis. Univariate analysis was performed for each factor, and multivariate analysis was performed for items demonstrating significant differences. Kaplan-Meier analysis of DFS was used to compare the difference in recurrence rates between patients with and without lateral cervical lymph node metastasis.

Statistical analysis. Statistical analyses were performed using StatMate V statistical software (ATMS Co., Ltd.). The Chi-squared test was used for univariate analysis, and logistic regression analysis was employed for multivariate analysis. DFS was analyzed using the Kaplan-Meier method, and the groups were compared using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Risk classification for each guideline (high risk).

Risk factor	NCCN 2019	ATA 2015	BTA 2014
Tumor size	>4 cm	>4 cm	>4 cm
Extrathyroidal infiltration	cT4	cT4	pT3 and pT4
Lymph node metastasis	cN1	cN1	cN1
Distant metastasis	cM1	cM1	cM1
Intraglandular metastasis	Opposite side	-	Multiple
History of cervical irradiation	+	-	-
Family history of thyroid cancer	-	-	+
Undifferentiated component	+	-	-

ATA, American Thyroid Association; BTA, British Thyroid Association; NCCN, National Comprehensive Cancer Network (8-10).

Table II. TNM classification.

Characteristic	<55 years old N classification		≥55 years old N classification	
Age	0	1	0	1
T classification				
1	20	14	32	29
2	4	11	8	5
3	7	32	25	65
4	0	3	7	12
Stage				
I	91		40	
II	0		124	
III			19	

Table III. Duration and treatment until recurrence.

Duration to recurrence	Value
Median	41 months
Range	3-97 months
Treatment (combination treatment in some patients)	
Untreated	10
Operation	7
Unsealed radionuclide therapy	3
Lenvatinib	3

Results

The present study included 59 males (21.5%) and 215 females (78.5%), aged 19-86 years (median age, 66 years). The TNM classification of the patients is presented in Table II. Among the 274 patients, PTC recurred in 20 (7.3%) patients in total. The duration to recurrence and treatment are presented in Table III. Of the 274 participants, 78 (28.5%) presented with lateral cervical lymph node metastasis (Table IV). Since neck dissection was performed only in cases with obvious metastases on pre-operative imaging, there were no cases with no metastases post-operatively.

Age was classified as ≥55 and <55 years, as age is crucial for thyroid cancer staging. No significant differences in age were detected. Similarly, no significant differences were found with respect to sex (Table IV).

Several items revealed significant differences (Table IV). Multivariate analysis of the significantly different items revealed that paratracheal lymph node metastasis and tumor size were independent risk factors for lateral cervical lymph node metastasis (Table V).

As illustrated in Fig. 2, the DFS of patients with lateral cervical lymph node metastasis was significantly lower than that of those without lateral cervical lymph node metastasis. The 10-year DFS rates following initial treatment were 76.8 and 93.8%, respectively (P<0.0001).

Discussion

The prognosis of the majority of patients with PTC is favorable, with 10-year disease-specific survival rates exceeding 90%, and patients who undergo curative surgery have a better prognosis. Additionally, a good prognosis has been frequently reported for patients with PTC (15-17). Recurrence has been reported to occur in ~7-23% of patients with PTC. In addition to TNM, other risk categories that have been proposed for PTC include age, grade, extent and size (AGES), age, metastasis, extent and size (AMES) and metastasis, age, complete resection, invasion and size (MACIS), with the corresponding factors including age, sex, extrathyroidal infiltration, tumor size, lymph node metastasis, distant metastasis, and differentiation by pathological diagnosis (8-11). Although there are some differences of race or in the medical care system, key risk factors are common, indicating that there is universality in factors derived from previous reports. The most critical issue associated with PTC is to reduce the recurrence rate, and thus there is an urgent need to investigate strategies with which to achieve this aim. In the present study, lateral cervical lymph node metastasis was the main focus, which is considered a risk factor for PTC recurrence.

Table IV. Comparison of the characteristics of patients with or without lateral cervical lymph node metastasis.

Characteristic	Total no. Of patients	Patients with lateral cervical lymph node metastasis (n=78)	Patients without lateral cervical lymph node metastasis (n=196)	Univariate analysis P-value
Sex				0.0901
Male	59	22	37	
Female	215	56	159	
Age (years)				0.5881
<55	183	54	129	
≥55	91	24	67	
Lymphovascular invasion				<0.0001
Yes	64	31	33	
No	210	47	163	
Venous invasion				<0.0001
Yes	78	36	42	
No	196	43	153	
Extrathyroidal infiltration				<0.0001
Yes	148	57	91	
No	126	21	105	
Intraglandular metastasis				0.1412
Yes	58	21	37	
No	216	57	159	
Paratracheal lymph node metastasis				<0.0001
Yes	170	74	96	
No	104	4	100	
Tumor size (mm)				<0.0001
>40	91	17	74	
≤40	183	62	121	

Table V. Multivariate analysis of risk factors for lateral cervical lymph node metastasis of papillary thyroid carcinoma.

Variable	Odds ratio of recurrence	P-value
Lymphovascular invasion	0.7326	0.3920
Venous invasion	0.0728	0.7873
Extrathyroidal infiltration	1.6483	0.1992
Paratracheal lymph node metastasis	24.2279	<0.0001
Tumor size	3.9379	0.0472

In the univariate analysis, lymphovascular invasion, venous invasion, extrathyroidal infiltration, paratracheal lymph node metastasis and tumor size were designated as risk factors for cervical lymph node metastasis. In the multivariate analysis, paratracheal lymph node metastasis and tumor size at initial treatment were found to be independent risk factors for lateral cervical lymph node metastasis. Extrathyroidal infiltration also tended to be a risk factor, although not significantly. Lymphovascular invasion surely causes a high rate of lymph node metastasis. Actually, 31 out of 64 patients with lymphovascular invasion, or about half, had lateral cervical lymph node metastasis (Table IV). In ATA 2015, NCCN 2019 and BTA 2014, extrathyroidal infiltration and lymph node metastasis (N1) were listed as high-risk factors (8-10). Lateral cervical lymph node metastasis was present in 57 out of 148 patients with extrathyroidal infiltration and in 74 out of 170 patients with paratracheal lymph node metastasis.

As regards the extent of lymph node dissection in the absence of obvious metastases, paratracheal lymph node dissection is recommended from the viewpoint of complications during reoperation; however, it has been reported that prophylactic lateral cervical lymph node dissection may be unnecessary, excluding cases where the primary tumor is large in diameter or distant metastases are detected (18-20). According to the results of the present study, prophylactic lateral cervical lymph node dissection may be considered in patients with obvious pre-operative paratracheal lymph node metastasis.

There was a notable difference in the DFS between patients with and without lateral cervical lymph node metastasis, indicating that patients with lateral cervical lymph node metastasis are more likely to have recurrence. This result is consistent with the aforementioned guideline risk factors. Although it is difficult to eliminate recurrence, the most critical task is to clarify the risk factors for recurrence and to improve the

recurrence rate by accumulating such studies. It is suggested that it is necessary to keep accumulating additional cases and conduct more detailed studies.

In conclusion, in the present study, 274 cases of PTC were reviewed and the presence of lateral cervical lymph node metastasis was determined. Paratracheal lymph node metastasis and tumor size were found to be independent risk factors for lateral cervical lymph node metastasis. Japanese guidelines generally recommend prophylactic paratracheal lymph node dissection (18,20). The procedure is relatively simple, and based on the present data, it is that prophylactic dissection may be beneficial. Increase in recurrence rate was observed to be significantly associated with lateral cervical lymph node metastasis.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

TM wrote the manuscript. TM, SA and HU collected the patient data. TM, SA, HU and TKimura analyzed the data and prepared the tables. TM and TKitahara conceived the study and revised the final manuscript. TM and SA confirm the authenticity of all the raw data. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and approved by Ethics Committee of Nara Medical University (Approval no. 3048). Written informed consent was obtained from all patients involved.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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