Original article

Risk factors for recurrence in patients with papillary thyroid carcinoma undergoing modified radical neck dissection

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Background: **This study evaluated the impact of lymph node-related factors on the risk of and site of recurrence in patients who had papillary thyroid carcinoma with lymph node metastasis in the lateral compartment (classified as pN1b).**

Methods: **Patients underwent total thyroidectomy with unilateral modified radical neck dissection for classical papillary thyroid carcinoma. Risk factors for recurrence were evaluated according to the pattern of recurrence.**

Results: **A total of 324 patients were included in the study. The median follow-up was 63 (range 14–181) months. Recurrence was detected in 47 patients (14·5 per cent). In the multivariable analysis, a maximum diameter of metastatic lymph nodes larger than 2·0 cm (hazard ratio (HR) 1·15, 95 per cent c.i. 1·06 to 1·25; $P = 0·033$) and a central compartment metastatic lymph node ratio of more than 0·42 (HR 3·35, 1·65 to 6·79; $P < 0·001$) were identified as independent risk factors for locoregional recurrence. Age 45 years or older (HR 5·69, 1·24 to 26·12; $P = 0·025$) and extranodal extension of metastasis (HR 12·71, 1·64 to 98·25; $P = 0·015$) were risk factors for distant metastasis. In subgroup analysis of locoregional recurrence, several lymph node-related factors affected the risk of recurrence according to the specific site of metastasis.**

Conclusion: **Lymph node-related factors are of importance for the risk of recurrence in patients with classical papillary thyroid carcinoma classified as pN1b.**

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Introduction

According to the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM staging system[1], lymph node (LN) metastasis classified as pN1b is an independent poor prognostic factor for disease-free and cancer-specific survival in patients with classical papillary thyroid carcinoma (PTC). However, clinical outcomes and prognosis may differ among patients with LN metastasis because pN1b is defined solely on the metastatic LN location, and categorized as stage I for patients younger than 45 years and stage IVa for those aged 45 years or older according to the AJCC/UICC. Various LN-related factors in patients with PTC classified as pN1b are not reflected in the staging system. The hypothesis for the present study was that LN-related factors other than metastatic LN location could influence recurrence-free survival (RFS), type of recurrence and site of locoregional recurrence in patients with LN metastasis classified as pN1b. The aim of the present investigation was therefore to identify risk factors for recurrence with special consideration to the impact of LN-related factors.

Methods

Patients who underwent total thyroidectomy with unilateral modified radical neck dissection for classical PTC and LN metastasis classified as pN1b at Asan Medical Centre, Seoul, Korea, were identified. The exclusion criteria were: distant metastasis at the initial diagnosis or within 12 months of the initial operation, follow-up of less than 12 months, and insufficient medical records. This study was approved by the institutional review board of Asan Medical Centre, and the requirement for informed consent from each patient was waived.

Data were gathered from the medical records. LN-related factors such as maximum diameter of

Table 1 Univariable Cox proportional hazards analysis of clinical and histopathological variables to identify risk factors for locoregional and distant metastatic recurrence in patients with papillary thyroid carcinoma classified as pN1b

	No. of patients* ($n = 324$)	Locoregional recurrence ($n = 40$)		Distant metastasis ($n = 13$)	
		Hazard ratio‡	*P*	Hazard ratio‡	*P*
Age (years)†	46·3(13·2)	1·01 (0·98, 1·03)	0·548	1·10 (1·06, 1·14)	< 0·001
Sex			0·001		0·826
F	248 (76·5)	1·00 (reference)		1·00 (reference)	
M	76 (23·5)	2·88 (1·53, 5·41)		1·16 (0·32, 4·23)	
Tumour size (cm)†	2·0(1·3)	1·34 (1·12, 1·60)	0·002	1·32 (0·98, 1·79)	0·073
Extrathyroid extension			0·365		0·856
No	53 (16·4)	1·00 (reference)		1·00 (reference)	
Yes	271 (83·6)	1·54 (0·60, 3·94)		1·15 (0·26, 5·30)	
T category			0·002		0·033
T1a	21 (6·5)	1·00 (reference)		1·00 (reference)	
T1b	21 (6·5)	0·33 (0·03, 3·14)		0·99 (0·06, 15·94)	
T2	9 (2·8)	0·76 (0·08, 7·33)		n.a.	
T3	241 (74·4)	0·75 (0·23, 2·48)		0·54 (0·07, 4·47)	
T4a	32 (9·9)	3·04 (0·85, 10·93)		3·76 (0·44, 32·25)	
Multifocal tumours			0·406		0·728
No	165 (50·9)	1·00 (reference)		1·00 (reference)	
Yes	159 (49·1)	1·30 (0·69, 2·43)		1·21 (0·41, 3·62)	
Bilateral tumours			0·378		0·794
No	215 (66·4)	1·00 (reference)		1·00 (reference)	
Yes	109 (33·6)	1·33 (0·71, 2·50)		0·86 (0·26, 2·78)	
Hashimoto thyroiditis			0·142		0·181
No	244 (75·3)	1·00 (reference)		1·00 (reference)	
Yes	80 (24·7)	0·52 (0·22, 1·24)		0·25 (0·03, 1·91)	
Lymphovascular invasion			0·818		0·491
No	280 (86·4)	1·00 (reference)		1·00 (reference)	
Yes	44 (13·6)	1·11 (0·47, 2·64)		0·49 (0·06, 3·76)	

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). ‡Values in parentheses are 95 per cent confidence intervals. n.a., Not applicable.

metastatic LNs, number of metastatic LNs, number of retrieved LNs, metastatic LN ratio (defined as number of metastatic LNs divided by number of retrieved LNs) and extranodal extension were recorded. The LN-associated variables were related to the total number of LNs, central compartment LNs (including levels VI and VII) and lateral LNs (level II, III, IV and Vb). Extranodal extension and the maximum diameter of metastatic LNs were assessed for all LNs. Recurrence was classified as locoregional recurrence or distant metastasis. Locoregional recurrence was subdivided into central LN recurrence, ipsilateral LN recurrence (recurrence in a previously dissected lateral compartment) and contralateral LN recurrence.

Surgical strategy and follow-up

Patients underwent total thyroidectomy with bilateral central compartment node dissection and unilateral modified radical neck dissection. Prophylactic lateral neck dissection for PTC is not performed at Asan Medical Centre, and therapeutic lateral neck dissection is carried out in patients with biopsy-proven metastatic lateral LNs. To confirm the diagnosis, fine-needle aspiration cytology (FNAC) was undertaken for lateral LNs suspected of metastasis, and thyroglobulin was measured in the washout of needles used for FNAC. All surgery was performed by two endocrine surgeons. Central compartment node dissection usually involved level VI. Dissection of level VII LNs was undertaken only in patients with suspected metastatic LNs. Modified radical neck dissection included levels IIa, III and IV. LN dissection of level IIb or Vb was done only for suspected metastatic LNs.

Patients received radioactive iodine remnant ablation with 150 mCi at 2–3 months after surgery. All patients were followed up every 6–12 months under thyroid-stimulating hormone suppression. Serum thyroglobulin and anti-thyroglobulin antibody measurement, and neck ultrasonography were carried out routinely during follow-up. Patients suspected of locoregional recurrence underwent ultrasonography-guided FNAC. Distant metastasis was diagnosed by using whole-body iodine scintigraphy, chest CT or [^{18}F]fluorodeoxyglucose PET combined with CT, and confirmed by serial imaging or biopsy. Recurrence was

Table 2 Univariable Cox proportional hazards analysis of histopathological lymph node-related variables to identify risk factors for locoregional and distant metastatic recurrence in patients with papillary thyroid carcinoma classified as pN1b

	No. of patients* ($n = 324$)	Locoregional recurrence ($n = 40$)		Distant metastasis ($n = 13$)	
		Hazard ratio‡	*P*	Hazard ratio‡	*P*
Extranodal invasion			0·018		0·013
No	164 (50·6)	1·00 (reference)		1·00 (reference)	
Yes	160 (49·4)	2·23 (1·15, 4·32)		13·32 (1·73, 102·42)	
Metastatic LN size (cm)†	1·3(1·6)	1·20 (1·09, 1·32)	< 0·001	1·09 (0·94, 1·27)	0·265
Total LNs†					
No. of metastatic LNs	9(6)	1·05 (1·01, 1·09)	0·002	0·95 (0·86, 1·05)	0·337
No. of retrieved LNs	42(16)	0·99 (0·97, 1·02)	0·550	0·95 (0·91, 0·99)	0·023
Metastatic LN ratio	0·23(0·14)	1·03 (1·01, 1·05)	0·001	1·01 (0·98, 1·05)	0·587
Central LNs†					
No. of metastatic LNs	4(4)	1·10 (1·05, 1·16)	< 0·001	0·99 (0·86, 1·13)	0·852
No. of retrieved LNs	11(6)	1·02 (0·97, 1·06)	0·511	0·93 (0·84, 1·03)	0·159
Metastatic LN ratio	0·41(0·29)	1·02 (1·01, 1·03)	< 0·001	1·01 (0·99, 1·03)	0·220
Lateral LNs†					
No. of metastatic LNs	5(4)	1·02 (0·94, 1·10)	0·709	0·86 (0·69, 1·06)	0·148
No. of retrieved LNs	31(12)	0·98 (0·96, 1·01)	0·266	0·94 (0·89, 0·99)	0·029
Metastatic LN ratio	0·17(0·12)	1·01 (0·99, 1·04)	0·448	0·99 (0·95, 1·04)	0·792

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). ‡Values in parentheses are 95 per cent confidence intervals. LN, lymph node.

defined as biopsy-proven malignant tissue or structural lesions on imaging studies, regardless of the serum thyroglobulin levels. Biochemical recurrence with a raised thyroglobulin level, but without clinical evidence of structural disease, was not classified as true recurrence.

Statistical analysis

Continuous variables are presented as mean(s.d.). Risk factors for recurrence were evaluated using univariable and multivariable Cox proportional hazard models, and the results presented as hazard ratio (HR) with 95 per cent confidence interval. Multivariable analysis included all variables. To improve the clinical value, some continuous variables confirmed as independent risk factors by multivariable analysis were converted into categorical variables on the basis of cut-off values calculated by the Rmax stat package, based on the log rank test. RFS curves were constructed by the Kaplan–Meier method, and log rank tests were used to evaluate differences in RFS between groups. *P* values were two-sided, and $P < 0{\cdot}050$ was considered statistically significant. R version 2.11.1 and the R libraries car and Cairo were used for the statistical analysis (R Foundation for Statistical Computing, Vienna, Austria).

Results

From 1996 to 2010, 528 patients underwent total thyroidectomy with unilateral modified radical neck dissection for classical PTC. After the exclusion criteria had been applied, 324 patients were finally included in this study.

Table 3 Multivariable Cox proportional hazards analysis of risk factors for local recurrence according to anatomical compartment

	Hazard ratio	*P*
Risk factor related to central LN compartment recurrence		
Central metastatic LN ratio (> 0·53 *versus* ≤ 0·53)*	6·39 (1·63, 25·12)	0·008
Risk factor related to ipsilateral LN compartment recurrence		
Extranodal extension (yes *versus* no)	9·68 (1·23, 76·49)	0·033
Risk factors related to contralateral LN compartment recurrence		
Sex (M *versus* F)	4·26 (1·54, 11·85)	0·005
Multifocal tumours (yes *versus* no)	3·47 (1·23, 9·93)	0·021
Metastatic LN size (> 2·0 *versus* ≤ 2·0 cm)*	1·12 (1·01, 1·24)	0·027
Central metastatic LN ratio (> 0·83 *versus* ≤ 0·83)*	3·89 (1·38, 10·96)	0·011

Values in parentheses are 95 per cent confidence intervals. *Cut-off values calculated by Maxstat of R based on log rank test statistics. LN, lymph node.

The clinicopathological characteristics of these patients are summarized in *Tables 1* and *2*. The mean tumour size was 2·0 cm. Most patients had combined central and lateral LN metastasis, whereas 43 patients (13·3 per cent) had only lateral LN metastasis (skip metastasis). The median follow-up was 63 (range 14–181) months. Recurrence developed in 47 patients (14·5 per cent): locoregional recurrence in 34 patients, distant metastasis in seven, and combined locoregional and distant metastasis in six

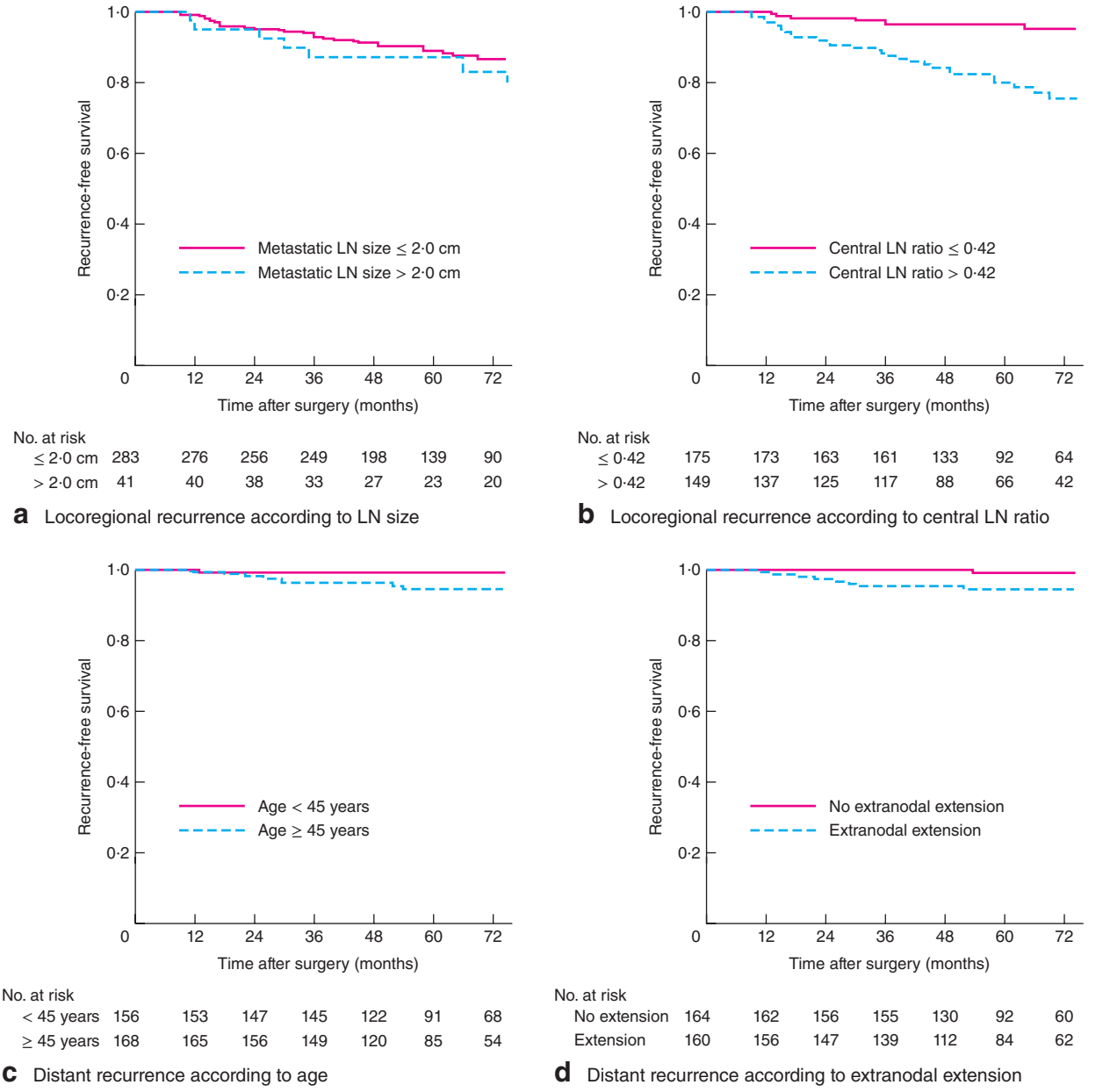

Fig. 1 Influence of various risk factors on recurrence-free survival. Locoregional recurrence according to **a** size of metastatic lymph nodes (LNs) (larger than 2·0 cm *versus* 2·0 cm or smaller) and **b** central LN ratio (higher than 0·42 *versus* 0·42 or lower). Distant metastasis according to **c** age (45 years and older *versus* less than 45 years) and **d** presence of extranodal extension of LN metastasis. **a** $P = 0{\cdot}214$, **b** $P < 0{\cdot}001$, **c** $P = 0{\cdot}007$, **d** $P = 0{\cdot}001$ (log rank test)

patients. Thus, a total of 40 patients had locoregional recurrence and 13 had distant metastasis. The site of locoregional recurrence included the central compartment in 11 patients, ipsilateral LN recurrence in ten patients, and contralateral LN recurrence in 19. Distant metastases were found in the lung (10 patients), lung and bone (2), and multiple organs (1). Nine patients (2·8 per cent) died from PTC.

Overall recurrence

In univariable analysis, age, male sex, primary tumour size, tumours classified as T4a, extranodal extension of

metastasis, maximum diameter of metastatic LNs, total number of metastatic LNs, total metastatic LN ratio, number of metastatic LNs in the central compartment and central metastatic LN ratio were all risk factors for overall recurrence. In the multivariable analysis, a maximum diameter of metastatic LNs larger than 2·0 cm (HR 1·17, 95 per cent c.i. 1·07 to 1·28; $P = 0·024$) and a metastatic LN ratio of more than 0·27 (HR 5·27, 2·03 to 13·71; $P = 0·001$) were independent risk factors for overall recurrence.

Locoregional recurrence

In univariable analysis, male sex, primary tumour size, tumours classified as T4a, extranodal extension of metastasis, maximum diameter of metastatic LNs, total number of metastatic LNs, total metastatic LN ratio, number of central metastatic LNs and central metastatic LN ratio were risk factors for locoregional recurrence (*Tables 1* and *2*). In multivariable analysis, maximum diameter of metastatic LNs larger than 2·0 cm (HR 1·15, 95 per cent c.i. 1·06 to 1·25; $P = 0·033$), and central metastatic LN ratio of more than 0·42 (HR 3·35, 1·65 to 6·79; $P < 0·001$) were independent risk factors for locoregional recurrence.

Distant metastasis

Univariable analysis revealed that age, tumours classified as T4a, extranodal extension of metastasis, total number of retrieved LNs and number of lateral retrieved LNs were significant risk factors for distant metastasis (*Tables 1* and *2*). In multivariable analysis, age 45 years or older (HR 5·69, 95 per cent c.i. 1·24 to 26·12; $P = 0·025$) and the presence of extranodal extension of metastasis (HR 12·71, 1·64 to 98·25; $P = 0·015$) were independent risk factors for distant metastasis.

Subgroup analysis of risk factors according to site of locoregional recurrence

A central compartment metastatic LN ratio of more than 0·53 (HR 6·39) was the only independent risk factor for central LN recurrence, whereas the presence of extrathyroid extension of metastasis (HR 9·68) was the sole independent risk factor for ipsilateral LN recurrence (*Table 3*). For recurrence in the contralateral compartment, male sex, presence of multifocality, maximum diameter of metastatic LNs larger than 2·0 cm and a metastatic LN ratio of more than 0·83 were identified as independent risk factors (*Table 3*).

Recurrence-free survival according to risk factors

The 10-year RFS rates for overall recurrence, locoregional recurrence and distant metastasis were 77·6, 81·9 and 90·7 per cent respectively. For the subgroup of patients with locoregional recurrence, the 10-year RFS rates were 96 per cent for central LN recurrence, 93 per cent for ipsilateral LN recurrence and 93 per cent for contralateral LN recurrence. The RFS rates for patients with identified risk factors for locoregional and distant metastasis are shown in *Fig. 1*, and for the different LN compartments in *Fig. S1* (supporting information).

Discussion

This study has shown that several LN-related factors may influence the type of recurrence, locoregional site of recurrence and RFS in patients with classical PTC staged as pN1b. Patients with PTC and a central metastatic LN ratio of more than 0·42, or maximum diameter of metastatic LNs larger than 2·0 cm, are likely to develop locoregional recurrence. On the other hand, extranodal extension of metastasis and age 45 years or older are risk factors for distant metastasis. Subgroup analysis of patients with locoregional recurrence identified a central metastatic LN ratio of more than 0·53 as a predictor of central LN compartment recurrence, and extranodal extension metastasis as a predictor of ipsilateral LN recurrence. Men and patients with multiple primary tumours, a maximum diameter of metastatic LNs larger than 2·0 cm or central metastatic LN ratio of more than 0·83 are especially likely to develop contralateral LN recurrence.

In addition to the well established prognostic factors for PTC and the location of metastatic LNs, other LN-related factors have been studied previously. The metastatic LN ratio[1–5], maximum size of metastatic LNs[6–9], total number of metastatic LNs[10–13] and extranodal extension of metastasis[14,15] have been reported to have prognostic value. However, in the present study, all LN-related factors were analysed with regard to the different anatomical LN compartments. The impact of these risk factors on recurrence and RFS in relation to locoregional and distant recurrence, and central and contralateral LN compartments, was evaluated.

Unlike previous studies[6–10,14,15], variables related to the tumour itself, such as tumour size or T category, although adjusted for in the multivariable analysis, were not risk factors for recurrence in the present analysis. This might be because many patients had a relatively small PTC; the mean tumour size was 2·0 cm. This is probably one of the reasons for the relatively low overall recurrence rate here.

The present investigation suffered from limitations inherent to retrospective studies. However, the study included only patients whose initial operation for classical PTC at a single institution was total thyroidectomy with routine bilateral central compartment node dissection and unilateral modified radical neck dissection of metastasis confirmed before surgery. To minimize selection bias and clearly evaluate the impact of LN-related factors on recurrence and RFS, patients who had distant metastasis at initial diagnosis or within 12 months after the initial operation, and those who were followed up for less than 12 months, were excluded. Patients diagnosed with variants of PTC were also excluded. Thus, the study cohort comprised a relatively large and homogeneous group of patients, and the length of follow-up was comparatively long.

This study has shown that LN-related factors are of importance for the risk of locoregional and distant recurrence as well as the anatomical site of metastatic LN recurrence in patients with PTC classified as pN1b. These findings could be of importance for a follow-up programme in this subgroup of patients.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Influence of various risk factors on recurrence-free survival rates for different lymph node compartments (Word document)