

Central Lymph Node Metastasis Is an Important Prognostic Factor in Patients with Papillary Thyroid Microcarcinoma

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Papillary thyroid microcarcinoma (PTMC) has been increasing, without a consensus for the management of this condition. In the present study, we analyzed the clinicopathological features of patients with PTMC to examine the impact of initial therapy and establish appropriate treatment. A total of 2,018 patients with PTMC were enrolled at a single university hospital. Of them, 1,245 patients (61.8%) underwent total thyroidectomy, and 1,838 patients (91.3%) underwent central lymph node (LN) dissection. Five- and 10-yr recurrence rates were 3.2% and 4.6%, respectively. In univariate analysis, the prognostic factors for recurrence were N stage, the number of LN metastases, and extrathyroidal extension. However, multivariate analysis revealed LN metastases and N stage as the only significant prognostic factors after adjusting for confounding factors ($P < 0.001$). Additionally, multivariate analysis of a subgroup consisting of PTMC patients without N1b revealed the number of central LN metastases as the only significant factor. Therefore, intraoperative examination for central LN metastasis may discriminate high or low risk group.

Keywords: Papillary Thyroid Carcinoma, Lymph Node Metastasis, Recurrence

INTRODUCTION

Papillary thyroid cancer (PTC) is the most common endocrine malignancy (1) and accounts for about 80% of thyroid cancers (2). Additionally, papillary thyroid microcarcinoma (PTMC) accounts for 36%-60% of thyroid cancers (3, 4). While PTMC is indolent and grows slowly, PTMC with particular biological characteristics, such as clinically apparent node metastasis and extrathyroidal extension, are progressive.

According to several guidelines, total thyroidectomy or completion thyroidectomy is recommended for patients who have PTMC with radiologically or clinically detected cervical nodal metastasis, multifocal malignancy lesions, or extrathyroidal extension (5, 6). However, the management of PTMC varies from observation to total thyroidectomy (3, 7). A lobectomy is preferred over a total thyroidectomy and radioactive iodine (RAI) therapy in Japan, which is not the case in western countries. In addition, central compartment lymph node (LN) management is another subject of debate. The 2009 guideline from the American Thyroid Association (ATA) recommends therapeutic central compartment LN dissection. However, the European Thyroid Association (ETA) recommends prophylactic central compartment LN dissection as a useful strategy for subsequent treatment and follow-up (5, 8). This difference in management may be attributed to varying clinicopathological features among countries. For example, the frequency of the BRAF mutation is

45%-80% and the frequency of LN metastases is 14%-64% (9-12). Therefore, we retrospectively investigated clinicopathological features and prognostic factors for recurrence to determine proper initial surgical therapy in patients with PTMC.

MATERIALS AND METHODS

The records were reviewed for all patients with PTMC who were treated at Ajou University Hospital during 1994-2010. There were 2,018 patients who underwent primary surgical therapy at Ajou University Hospital with 5,865 person-years of follow-up. The median follow-up was 3.0 yr, and the longest follow-up was 16 yr. Death information for patients was confirmed from National Cancer Information Center. Death was due to PTC in seven cases.

Statistics

Comparisons of risk characteristics were performed using the chi-square tests or Fisher's exact test as necessary. Survival from the date of initial surgery to recurrence was analyzed using the Kaplan-Meier method. The log-rank test was used to determine group differences in cumulative recurrence-free curves. All tests were two-sided, with an alpha level of 0.05. All calculations were performed using SPSS 17.0 software (SPSS, Inc. Chicago, IL, USA).

Ethics statement

This study was approved by the institutional review board at Ajou University Hospital (IRB No. AJIRB-MED-MDB-10-337). Informed consent was waived by the board.

RESULTS

Total thyroidectomy was performed in 61.8% of 2,018 patients with PTMC, and central LN dissection in 1,838 (91.3%) patients. The remaining patients (9.7%) with occult PTMC did not undergo central LN dissection, because of preoperative benign diagnoses of Graves' disease, multinodular goiter, etc. Central LN metastases were present in 593 (29.4%) patients. RAI therapy was performed in 21.9%. Extrathyroidal extension and multiplicity were found in 48.8% and 30.1% respectively. Bilateral cancer of the thyroid was seen in 30.2% of total thyroidectomy. Recurrence from the remnant thyroid accounted for 39% of 41 total recurrences, and a recurrent tumor in a previously dissected central compartment was found in two patients. Lateral cervical LN metastases accounted for 60.9% of recurrences. There were 64 patients for whom the number of central LN metastases was not described in pathological reports. Metachronous distant metastases were found in 7.3% (Table 1).

In univariate analysis for recurrence-free rate, extrathyroidal extension, N stage (Fig. 1A) and number of LN metastases (Fig. 1B) were found to be significant prognostic factors; however, neither the extent of thyroidectomy or RAI therapy were significant prognostic factors (Table 2). In additional univariate analysis of a subgroup consisting of PTMC patients with total thyroidectomy and central LN dissection, RAI therapy was not a significant prognostic factor ($P = 0.315$). In multivariate analysis, both N stage and number of LN metastases were prognostic factors (Table 3). There was no significant difference between the

Table 1. Clinicopathologic features of the 2,035 patients with papillary thyroid microcarcinoma

Variables	Clinicopathologic features
Age (yr)	45.3 ± 11.08
Gender (M/F)	1:5.8
Total thyroidectomy	1,245 (61.8%)
Central neck dissection	1,838 (91.3%)
Lateral neck dissection	95 (4.7%)
Radioiodine therapy	422 (21.9%)
Tumor size (cm)	0.63 ± 0.25
Extrathyroidal extension	984 (48.8%)
Multiplicity	608 (30.1%)
Subclassification	
Classical	1,872 (92.9%)
Follicular	131 (6.5%)
Diffuse sclerosing	3 (0.1%)
Oncocytic	8 (0.3%)
Clear cell	1
Solid	2
Macrofollicular	1
Number of LN metastases	
≤ 1	1,394 (75.6%)
≥ 2	383 (20.8%)
T stage	
T1	1,012 (50.2%)
T3	957 (47.5%)
T4	27 (1.3%)
N stage	
N0	1,155 (57.3%)
N1a	593 (29.4%)
N1b	95 (4.7%)
M stage	7 (0.3%)
BRAF mutation	393/519 (75.7%)
Hoarseness	38/2,013 (1.8%)
Permanent hypoparathyroidism (1 yr)	57/1,245 (4.5%)
Recurrence	
Remnant thyroid	16/41 (39.0%)
Central neck, previous dissected	2/41 (4.8%)
Lateral neck	25/41 (60.9%)
Distant metastasis	3/41 (7.3%)
Unknown site	2/41 (4.8%)

LN, lymph node ; BRAF, v-raf murine sarcoma viral oncogene homolog B1.

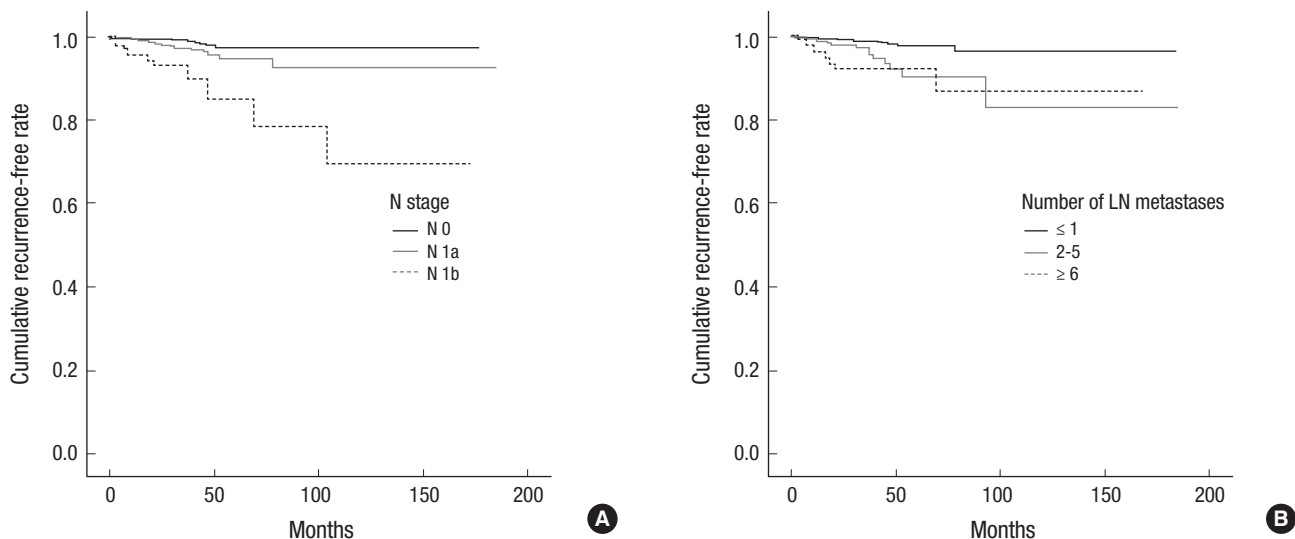


Fig. 1. Recurrence-free rate in patients with papillary thyroid microcarcinoma. (A) Related to N stage, (B) number of LN metastases.

Table 2. Univariate analysis for recurrence-free rate in PTMC patients

Variables	Patients No. (%)	Recurrences No. (%)	10 yr recurrence free rate (%)	Univariate analysis, <i>P</i>
Gender				0.361
Males	297 (14.7)	8 (2.6)	79.3	
Females	1,721 (85.2)	33 (1.9)	94.6	
Age at first treatment				0.915
< 45 yr	1,012 (50.1)	22 (2.1)	92.7	
≥ 45 yr	1,006 (49.8)	19 (1.8)	91.3	
Familial history with ≥ 3 1° familial members with thyroid cancer				0.891
Absent	1,837 (92.3)	39 (2.1)	91.6	
Present	153 (7.7)	3 (2.0)	97.5	
Extent of thyroidectomy				0.639
Total	1,245 (61.6)	26 (2.1)	91.2	
Less than total	773 (38.3)	14 (1.9)	93.5	
Primary tumor size				0.409
≤ 5 mm	857 (42.5)	13 (1.5)	91.5	
> 5 mm	1,161 (57.5)	28 (2.3)	92.3	
Multiplicity				0.691
Absent	1,399 (69.3)	29 (2.1)	92.9	
Present	608 (30.6)	13 (2.2)	87.8	
Extrathyroidal extension				0.022
Absent	1,012 (50.2)	13 (1.2)	95.0	
Present	984 (48.7)	26 (2.6)	89.7	
Subclassification				0.848
Classical	1,872 (92.7)	39 (2.0)	92.7	
Follicular	131 (6.4)	3 (2.2)	91.7	
Number of LN metastases				< 0.001
≤ 1	1,394 (75.6)	15 (1.0)	96.4	
≥ 2	383 (20.8)	20 (5.2)	83.9	
T stage				0.230
T1	1,012 (50.1)	15 (1.4)	94.5	
T3	957 (47.4)	23 (2.4)	89.9	
T4	27 (1.3)	1 (3.5)	96.3	
N stage				< 0.001
Nx	175 (8.6)	3 (1.7)	94.4	
N0	1,155 (57.2)	11 (0.9)	97.4	
N1a	593 (29.3)	17 (2.8)	92.7	
N1b	95 (4.7)	10 (10.5)	67.3	
Radioiodine therapy				0.193
Yes	422 (21.9)	10 (2.3)	95.8	
No	1,500 (78.0)	20 (1.3)	94.9	

Table 3. Multivariate analysis for recurrence-free rate in PTMC patients

Variables	<i>P</i> value	Exp (B)
Number of LN metastases	0.032	3.78
N stage	0.001	
N1a	0.735	0.8
N1b	0.115	3.16
Extrathyroidal extension	0.306	1.49

Table 4. Relationship between bilaterality and the number of metastatic LNs

Total number of metastatic LNs	Bilaterality		<i>P</i> value
	Absent	Present	
0-1	1,154 (82.2%)	251 (17.9%)	< 0.001
2-3	170 (81.6%)	39 (18.7%)	
4-5	50 (68.9%)	22 (30.6%)	
≥ 6	60 (60.6%)	39 (39.4%)	

patients without LN metastasis and with one LN metastasis (data not shown). The number of metastatic LN was correlated with

Table 5. Multivariate analysis for prognostic factors in PTMC patients without N1b

Variables	<i>P</i> value	Exp (B)
Number of LN metastases	< 0.001	
2-3	0.127	2.1
≥ 4	< 0.001	9.2
N stage	0.992	

bilaterality of cancer (Table 4) and recurrence (Table 5). Therefore, either lobectomy or subtotal thyroidectomy can be performed in patients with one LN metastasis or no LN metastasis.

DISCUSSION

Controversy exists regarding the extent of thyroidectomy and central LN dissection in patients with PTMC. Retrospective studies have reported that recurrence within the thyroid bed decreases in patients who have undergone total thyroidectomy

compared with those treated with subtotal thyroidectomy (13, 14). However, other thyroid cancer specialists have reported that unilateral lobectomy is sufficient as an initial therapy for low-risk patients with papillary and follicular thyroid cancer because of low mortality and high complication rates reported with a more extensive thyroidectomy (15-17).

The frequency of bilateral thyroid carcinoma in low-risk patients who undergo total thyroidectomy is 16.7%-38% (17-20). Among the 1,244 patients in our study, 30.3% had contralateral carcinoma. This incidence rate was similar to previously reported rates for thyroid carcinoma in the contralateral lobe. The recurrence in the remnant contralateral lobe was 1.6% of 772 patients who underwent either lobectomy or subtotal thyroidectomy in our study. The incidence of recurrent thyroid cancer occurring in the residual contralateral lobe of the thyroid gland is 4.7%-46% in such patients (19). In our study, the recurrence rate of the remnant thyroid was lower than previously reported rates. This low recurrence rate may be attributed to our lobectomy criteria. At our institution, lobectomy is performed in patients without clinical LN metastasis, tumor multiplicity, macroscopic extrathyroidal extension and familial history. Another cause of low recurrence in our study may be that the high incidence of bilateral thyroid cancer may not always be clinically significant (20). However, total thyroidectomy can be considered in PTMC patients with more than three central LN metastases, because the recurrence rates between total thyroidectomy and less than total thyroidectomy were not statistically different in our study due to one of several selection (or therapeutic) biases (Table 4, 5) The general consensus is that a central LN dissection is indicated when LN are discovered preoperatively on ultrasound (US) or clinical examination (21, 22). However, prophylactic central LN dissection was performed in patients without clinically apparent central LN metastasis in our institution because of some advantages. Firstly, although US has been regarded as a sensitive imaging modality for LN metastasis screening and diagnosis, it has a low sensitivity in evaluation of LN metastasis in central compartment (23) and the accuracy of preoperative US for central LN metastasis is lower than that of lateral cervical LN metastasis (24). Secondly, central LN dissection was reported to reduce RAI dosage (18) and rate of postoperative detectable thyroglobulin (Tg), which is related with recurrence (25). Thirdly, reoperative central LN dissections represent significant risk of recurrent laryngeal nerve injury and permanent hypoparathyroidism due to the presence of scar tissue and distorted anatomy (26). Fourthly, number of LN metastases was correlated with both recurrence and bilaterality of cancer. Despite these merits of central LN dissection, it is related with the risk of hypoparathyroidism. The frequency of permanent hypoparathyroidism ranges from 2.7%-25% after total thyroidectomy and central compartment LN dissection (18, 27, 28). The frequency of permanent hypoparathyroidism

was 4.5% at our institution, which was similar to previous reported rates. If central LN dissections were performed by skilled surgeons, the frequency of permanent hypoparathyroidism may decrease. Therefore, prophylactic central LN dissection can be recommended in PTMC patients. Otherwise, intraoperative examination of ipsilateral central LN metastasis may be useful for prognosis of patients with PTMC and in tailoring postoperative management (29).

This study has several limitations. Firstly, the mean follow-up period was relatively short, because of most of the subjects (88%) had been enrolled after 2006. Secondly, we could not investigate the relationship between LN micrometastasis and recurrence-free rate because usually one or two tissue block from each lymph node had been sliced and stained with hematoxyline-eosin. Thirdly, we could not define the effectiveness of radioactive iodine therapy in intermediate-risk group for recurrence. Therefore, these problems should be investigated in a future prospective randomized controlled study.

In conclusion, lobectomy may be sufficient for initial surgery in selected patients with PTMC, and intraoperative examination for central LN metastasis may be performed to predict the recurrence and to tailor postoperative management.

DISCLOSURE

We declared no competing interests.

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