Outcome of papillary thyroid microcarcinoma: Study of 1,990 cases

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Abstract. The present study examines the requirement of prophylactic neck node dissection in papillary thyroid microcarcinoma (PTMC) patients by analyzing high-risk factors of neck lymph node metastasis in PTMC. The clinical pathological data was a review of 1,990 patients diagnosed between January 2013 and January 2014. The data included information on patient gender, age, tumor size, multifocal, tumor pathological staging, bilateral thyroid cancer, the subtypes, $BRAF^{V600E}$ mutation, human telomerase reverse transcriptase ($hTERT$), extrathyroidal invasion and neck lymph node metastasis. The univariate analysis (χ^2 test) showed that a number of factors were significantly associated with neck lymph node metastasis in PTMC (P<0.05): Male gender, aged <45 years, extrathyroidal invasion, bilateral thyroid cancer, various subtypes (package type, follicular variant, diffuse sclerosing variant, eosinophils, tall cell and column variant), $BRAF^{V600E}$ mutation-positive, $hTERT$ mutation-positive, pt3/4 and multifocality. The multivariate analysis (regression binary logistic) showed that the male gender, <45 years, tumor size >5 mm, extrathyroidal invasion, bilateral thyroid tumors, multifocality, $BRAF^{V600E}$ mutation-positive, $hTERT$ mutation-positive and pt3/4 are associated with the neck lymph node metastasis in PTMC (P<0.05). These paired analysis results show that the subtypes of PTMC with tumor size >5 mm is more common than the specific types of PTMC in which the tumor is ≤5 mm in neck lymph node metastasis. The neck lymph node metastasis incidence of the >45 years age group patients without high-risk factors in PTMC is 8.13 and 6.80%, respectively. In conclusion, PTMC patients with high-risk factors only are recommended to undergo a prophylactic lymph node dissection.

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Introduction

With increasing numbers of patients, thyroid carcinoma has recently become the most common malignancy, ranking as the second to sixth malignancy in female cancers. Papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid carcinoma (PTC) with the greatest dimensions ≤1.0 cm, according to the World Health Organization classification system for thyroid tumors (1), and is often discovered incidentally during screening. However, PTMC has recently become the most common pathological subtype in PTC with the ultrasonography-guided fine-needle aspiration biopsy (FNAB) that facilitates the detection of PTMC in particular, and therefore, the incidence continues to rise. Since the prognosis of PTMC is good and is one of the few cancers that can be cured by surgery, which is often followed by radioiodine treatment, surgical treatment for PTMC requires certain standard guidelines to reduce recurrence and metastasis (2-8). The present study reviewed the clinical and pathological data of 1,990 patients that underwent PTMC surgery and analyzed the high-risk factors of neck lymph node metastasis in PTMC to determine the clinical necessity for neck lymph node dissection.

Materials and methods

Study population. The clinical data was reviewed on 1,990 PTMC patients between January 2013 and January 2014 in the Department of Head and Neck Oncology of Tianjin Medical University (Tianjin, China). The data included patients that underwent a side thyroidectomy and a central neck dissection or ipsilateral neck dissection on the same side, when lateral lymph node metastasis was confirmed by fine-needle aspiration cytology (FNAC). This was in accordance with the Chinese management guidelines for patients with thyroid nodules and differentiated thyroid cancer (8). The pathology of all the patients was identified as PTMC, as indicated by FNAC-guided by high-resolution ultrasonography and the aspiration pathology was confirmed by the surgical pathology. Two infant PTMC patients were excluded as thyroid cancer in children has different biological characteristics compared to adults. In addition, four patients of lymphoma with PTMC were excluded. The age range of patients with PTMC was

13-74 years (median, 45 years) and the male to female ratio was 1:3.85. Among them, 1,339 were pN0, whilst 645 were pN1. The average number of lymph node metastases for lymph node positive patients was 3-16 (median, 4.8). The clinical and pathological data are listed in Table I.

Statistical analysis. Fisher's exact test or χ^2 test was used to analyze the differences between the categorical data, whereas binary logistic regression was used to investigate the multifactor data, in which P<0.05 was considered to indicate a statistically significant difference. SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA) was used for the data analysis.

Results

Univariate analysis outcome of the high-risk factors of neck lymph metastasis in PTMC. Univariate analysis showed that males, <45 years, extrathyroidal invasion, bilateral thyroid cancer, subtypes (package type, follicular variant, diffuse sclerosing variant, eosinophils, tall cell and column variant), $BRAF^{V600E}$ mutation-positive, human telomerase reverse transcriptase (*hTERT*) mutation-positive, pt3/4 and multifocality were all significantly associated with the neck lymph node metastasis in PTMC (P<0.05). However, the difference between tumor sizes of ≤5 and >5 mm (211/630 vs. 179/546, respectively) did not reach statistical significance (P=0.782) (Table I), which means that tumor size is not associated with neck lymph node metastasis in PTMC.

Multivariate analysis outcome of the neck lymph metastasis risk factors in PTMC. Multivariate analysis (binary logistic regression) showed that males, <45 years, tumor size >5 mm, extrathyroidal extension, bilateral thyroid tumors, multifocality, $BRAF^{V600E}$ mutation-positive, *hTERT* mutation-positive and pt3/4 were all significantly associated with the neck lymph node metastasis in PTMC (P<0.05). By contrast, the difference between the subtypes and non-subtypes in PTMC did not reach statistical significance (P=0.118) (Table II), which means that this factor is also not associated with the neck lymph node metastasis in PTMC.

Paired analysis outcome of tumor size and the subtypes in PTMC. The paired analysis showed that the tumor size is associated with the neck lymph node metastasis (P<0.05). Subtypes of PTMC with tumor size >5 mm have a greater tendency of neck lymph node metastasis (Table III).

Outcome of neck lymph metastasis incidence without the high-risk factors. Hierarchical age group data shows that in patients without univariate analysis risk factors (such as males, extrathyroidal invasion, bilateral thyroid tumors, subtypes of tumor, multifocal, $BRAF^{V600E}$ mutation-positive and pt3/4) and those aged ≥45 years in lymph node metastasis incidence is 8.13%, which is statistically significant compared to those aged <45 years (P<0.05). The neck lymph metastasis incidence without multivariate analysis risk factors (such as males, bilateral thyroid cancer, tumor size >5 mm, multifocal, extrathyroidal invasion, $BRAF^{V600E}$ mutation-positive and pt3/4) in those aged ≥45 years is 6.80%, which was

statistically significant compared to those aged <45 years (P<0.05) (Table IV).

Discussion

The incidence of thyroid carcinoma is 6.2% per year and has increased in recent years (9). With the use of FNAB, which facilitates the detection of PTMC, the incidence is continuing to increase. Despite favorable biological features and good overall prognosis of thyroid carcinoma, there remain large differences in the surgical treatments for PTMC globally, which is particularly true in association with performing preventive prophylactic neck lymph dissection and is the focus of much controversy at present. With the progress of

Table I. Univariate analysis of PTMC neck lymph metastasis.

Risk factor	Lymph node cases, n	Total metastasis, n (%)	P-value
Age, years			
20-30	128	74 (57.81)	<0.001
30-44	761	272 (35.74)	
≥45	1,095	299 (27.31)	
Gender			
Male	409	202 (49.39)	<0.001
Female	1,575	443 (28.13)	
Tumor size, mm			
≤5	630	211 (33.49)	0.782
>5	1,354	179 (32.78)	
Extrathyroidal invasion			
No	631	106 (16.80)	0.510
Yes	1,353	539 (39.84)	
Single or double side tumor			
Single side	1,513	416 (27.50)	<0.001
Double side	471	229 (48.62)	
Subtypes			
No	1,895	607 (32.03)	0.020
Yes	89	39 (43.82)	
Tumor pathological staging			
pt1a	621	115 (18.52)	<0.001
pt3/4	1,363	529 (38.81)	
$BRAF^{V600E}$ mutation			
+	1,244	687 (55.23)	0.023
-	740	369 (49.86)	
hTERT			
+	794	529 (66.63)	<0.001
-	1,190	577 (48.49)	
Number of primary lesion			
Single	1,182	284 (24.03)	<0.001
Multifocality	802	361 (45.01)	

PTMC, papillary thyroid microcarcinoma; *hTERT*, human telomerase reverse transcriptase.

Table II. Multivariable analysis of PTMC neck lymph metastasis.

Risk factor	Partial regression coefficient B	SE	Wald	DOF	P-value	Exp(B)
Extrathyroidal invasion	-1.242	0.283	17.211	1	<0.001	0.276
Subtypes	-0.368	0.226	2.540	1	0.109	0.684
Bilateral thyroid	-0.325	0.135	5.014	1	0.025	0.712
Tumor size	-0.362	0.146	6.133	1	0.013	0.697
Gender	-1.014	0.122	68.754	1	<0.001	2.757
Age	0.570	0.104	30.162	1	<0.001	1.764
$BRAF^{V600E}$ mutation-positive	-0.395	0.189	9.276	1	0.037	0.771
$hTERT$ mutation-positive	-0.847	0.136	35.864	1	<0.001	1.897
T pathological staging	-0.382	0.172	8.463	1	0.027	0.747
Multifocality	-0.832	0.153	29.457	1	0.001	0.435

PTMC, papillary thyroid microcarcinoma; SE, standard error; DOF, degrees of freedom; $hTERT$, human telomerase reverse transcriptase.

Table III. Analysis of PTMC subtypes and differences in tumor size with lymph metastasis in PTMC.

	Subtypes		Non-subtypes			
Item, mm	Yes	No	Yes	No	P-value	OR
≤5	2	11	118	498	0.031	0.202
>5	36	40	489	790	<0.001	0.383

PTMC, papillary thyroid microcarcinoma; OR, odds ratio.

Table IV. Neck lymph metastasis incidence without high-risk factors in the hierarchical age groups.

Neck lymph node metastasis incidence	Age group (years), n (%)			P-value
	14-30	31-44	≥45	
Without univariate analysis risk factor	8/20 (40.00)	19/138 (13.77)	17/209 (8.13)	<0.05
Without multivariate analysis risk factor	2/11 (18.18)	16/105 (15.24)	10/147 (6.80)	<0.05

the surgical techniques and the application of advanced equipment, preventive prophylactic lymph node dissection decreases the damage to the parathyroid glands and the laryngeal recurrent nerve. However, excessive treatment increases the probability of temporary parathyroid laryngeal damage and laryngeal nerves injury (10). Simultaneously, whether excessive treatment can generate maximum benefits to patients remains unknown.

The present study found that the neck lymph metastasis is associated with the male gender, those aged <45 years, extrathyroidal invasion, bilateral thyroid cancer, multifocality, $BRAF^{V600E}$ mutation-positive, $hTERT$ mutation-positive and pt3/4. For tumor size and the subtypes, univariate analysis showed that a tumor size >5 mm is associated with PTMC lymph node metastasis, but not the subtypes. However, the multivariate analysis conclusion showed that the tumor size and subtypes are associated with PTMC lymph node metastasis. PTMC is defined by the tumor diameter length, which differs from the early cancer and also low-risk cancers. Although the PTMC carcinoma subtypes have the characteristics of lymph node metastasis, tumor size remains as another of the biologically invasion signs (11). Evaluating the PTMC subtype carcinoma by clinical TNM and risk stratification is extremely valuable. The study of the paired statistics showed that the subtypes and tumor size correlated with lymph node metastasis in PTMC, particularly the subtypes with primary

tumor sizes >5 mm have a greater tendency of neck lymph nodes metastasis and invasion.

The $BRAF$ mutation was only present in the PTC and anaplastic/undifferentiated thyroid carcinomas, but not in the follicular or medullary thyroid carcinomas. In addition, it was associated with invasion, advanced pathological stage, lymph node metastasis and distant metastasis of PTC. As the $BRAF$ mutation appears to play an important role in PTC tumorigenesis, it has been postulated that this mutation may have a prognostic value. The present study found that the $BRAF^{V600E}$ mutation-positive rate was 62.70% and was associated with the neck lymph metastasis in PTMC. Besides, $hTERT$ is the most common mutation in the promoter of the gene in thyroid cancers, which is prevalent in aggressive types of thyroid cancer, such as anaplastic thyroid cancer and poorly differentiated thyroid cancer, as well as $BRAF^{V600E}$ mutation-positive PTC. The study found that the $hTERT$ mutation-positive rate was 40.02%, and it is also associated with the neck lymph metastasis in PTMC. Therefore, $BRAF$ and $hTERT$ mutations may be useful molecular markers for assisting in the risk stratification for patients with PTMC. The results of the study are consistent with those in the studies by Xing et al (12,13).

The male gender has been consistently recognized as an independent risk factor of lymph node metastasis in thyroid carcinoma (14). Females are comparatively prone to thyroid

carcinoma due to their estrogen levels (ratio of males to females was 1:3.85 in the present study). However, the male incidence of thyroid carcinoma is associated with their living environment, in which certain protection mechanisms possibly exist. Once the protection mechanism is damaged, males will be exposed to malignant thyroid progression and lymph node metastasis. Therefore, once a male is diagnosed with PTMC, surgical intervention would possibly improve their prognosis.

Adolescents are more likely to develop neck lymph node metastasis (15). The present study shows that the incidence of neck lymph node metastasis for those who are <30 years old (except children) without univariate and multivariate risk factors was 18.18 and 40%, respectively, whereas in those who are >45 years without the risk factors, the incidence was only 6.8 and 8.13%, respectively; the incidences are statistically significant. Although it is commonly recognized that those aged >45 years are at risk of tumor recurrence and lymph node metastasis, those >45 years without risk factors and those without clinically palpable lymph nodes or ultrasound results that are suggestive of metastasis are not recommended to undergo prophylactic lymph dissection.

Extrathyroidal invasion (16), multifocality (17) and bilateral thyroid tumors of PTMC (18) are the important risk factors in lymph node metastasis that represent biological characteristics of progress. Although the study by McCarthy *et al* (19) reported that multifocality is highly homologous within the gland and is not associated with tumor invasion, Shindo *et al* (17) and Chow *et al* (20) found that neck lymph node metastasis and tumor multifocality remain significantly correlated, which is the major reason for lymph node metastasis. The present study is consistent with their findings.

The incidence of papillary thyroid carcinoma has been reported in the range of 0.5-5.2% and neck lymph node metastasis is 3.1-18.2% in autopsy specimens (21). By contrast, the prevalence of clinical thyroid papillary carcinoma was 1.9-11.7 per 100,000 people of all ages (22), suggesting that the subclinical thyroid carcinoma is almost one thousand times lower than the apparent clinical type. A previous study (23) even suggested that patients without high-risk factors of thyroid carcinoma should not immediately undergo surgery. Neck lymph node metastasis does not affect the PTMC prognosis (24), even with re-operation following recurrence. A previous study (25) reported that the recurrence during prophylactic neck lymph nodes dissection is higher compared to those not undergoing surgery. In addition, prophylactic neck lymph nodes dissection can increase the temporary postoperative parathyroid functional damage and the risk of injury to laryngeal nerves, which can affect the patient quality of life. The present study shows that the neck lymph node metastasis incidence without a high-risk factor in PTMC is only 6.80-8.13%, so it is suggested that prophylactic neck lymph nodes dissection should not to be performed for PTMC patients without high-risk factors.

In conclusion, neck lymph node metastasis significantly correlated with males, aged <45 years, extrathyroidal invasion, multifocal, bilateral, *BRAF*[V600E] mutation-positive, *hTERT* mutation-positive and pt3/4, and tumor size >5 mm with the subtypes in PTMC. PTMC patients without high-risk factors should be individually treated according to these strategically high-risk factors. PTMC patients without high-risk factors are not recommended to undergo prophylactic lymph node dissection to maximize functionality.

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