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ORIGINAL ARTICLE

Prophylactic central lymph node dissection in cN0 patients with papillary thyroid carcinoma: A retrospective study in China

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Summary *Objective:* The objective of the study was to assess the patterns of central cervical lymph node metastasis (CLNM) and evaluate the prophylactic central lymph node dissection (CLND) in papillary thyroid carcinoma (PTC) patients without clinical positive lymph nodes.
Methods: We retrospectively reviewed 1555 patients with PTC between 2003 and 2008. Lymph node metastatic risk factors and the pattern of lymph node metastasis in PTC were studied using multivariate analysis.
Results: Male patients, aged $\leq$ 45 years, the presence of extrathyroidal extension, and a primary tumor size $>$ 10 mm were identified as risk factors for CLNM with odds ratios of 2.089, 2.417, 1.534, and 3.079, respectively. Among 1555 patients, 97 cases (6.24%) had transient hypoparathyroidism, and only two patients (0.13%) had permanent hypoparathyroidism. Recurrent laryngeal nerve injury after thyroidectomy occurred in 14 patients (0.9%). In this group, nine cases were transient injury and the remaining five were permanent. During the period of follow-up, ranging from 5 years to 10 years, 18 patients (1.16%) were found with locoregional recurrence.
Conclusion: Taken together, in terms of the high incidence rate of CLNM in cN0 PTC patients, we believe that routine prophylactic CLND is optimal for clinically negative PTC patients, during their first treatment, especially for those with risk factors for CLNM.

Conflicts of interest: The authors declare no conflict of interest.

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1. Introduction

Papillary thyroid carcinoma (PTC) is the most common pathological type of thyroid malignancy, and exhibits a slow growth rate and good prognosis.[1] However, cervical lymphatic metastasis occurs in approximately 40—90% of PTC patients.[2] Cervical lymph node metastasis (CLNM) does not affect the overall prognosis of PTC but enhances the regional recurrence that is often life threatening. Therefore, local lymph node recurrence, after PTC operation, is a major issue that concerns clinicians.

Many studies have been performed to evaluate the risk factors of CLNM, however, those studies included both the patients with clinically negative (cN0) and clinically positive central lymph node. It is rare for studies to focus on the evaluation of risk factors as a predictor for CLNM only in cN0 patients. Therefore, identification of risk factors associated with CLNM may help surgeons to choose appropriate surgical strategies for cN0 PTC patients.

Since thyroid and neck lymphatic drainage patterns are relatively fixed, the pattern of metastatic lymph nodes is relatively predictable. Central lymph node is the most common site of cancer metastasis in the majority of PTC patients.[3,4] According to current American Thyroid Association recommendations, most surgeons would undertake central lymph node dissection (CLND) for T3 or T4 tumors in high-risk patients, but avoid CLND for T1 or T2 tumors in low-risk patients. However, the debate regarding prophylactic CLND for patients with cN0 central lymph node remains unresolved today. To this end, the objective of this study was to assess the patterns of central cervical lymph node metastasis and evaluate the value of prophylactic CLND for treatment of cN0 PTC patients.

2. Materials and methods

2.1. Patients

This study was approved by the Ethical Committee of The First Hospital of the Jilin University, Changchun, China. A total of 1555 cN0 patients with PTC were treated at the Department of Thyroid Surgery, The First Hospital of the Jilin University between July 2003 and July 2008. All patients recruited in the study met the following criteria: (1) their information was found in the hospital database; (2) they had a postoperative pathological diagnosis of PTC; and (3) no clinically positive central lymph node was detected preoperatively with either ultrasound or palpation. Patients were excluded from the study if they had a history of neck radiotherapy, distant metastasis, or previous thyroid surgery.

2.2. Surgical treatment

Clinical diagnosis was initially made with examination of ultrasound and fine needle aspiration. Because the results of pathologic examination of the frozen sections (FS) during surgery could guide the extent of the surgical operation in PTC patients, the FS was applied to all cN0 patients. To reduce the recurrence of the PTC, lobectomy plus ipsilateral CLND was performed as the initial surgical therapy for PTC patients with malignant lesions $<$ 1 cm that were limited to a single lobe. If malignant lesions in both lobes of the thyroid were confirmed in FS, or the diameter of the malignant lesion was larger than 1 cm, a total thyroidectomy plus bilateral CLND was performed.

2.3. Perioperative management and follow-up

The levels of *parathyroid hormone* (PTH), calcium, phosphorus, and ionized calcium of all patients were examined preoperatively and also measured routinely at 2 days after surgery. Postoperative hypoparathyroidism is defined as any hypocalcemic symptom with a decreased PTH level ($<$ 15 pg/mL) and decreased serum calcium level ($<$ 8.0 mg/dL) or ionized calcium ($<$ 1.00 mmol/L) level, with an elevated phosphorus level ($<$ 5.0 mg/dL). Permanent hypoparathyroidism is defined as a case of decreased PTH level that requires compensation with medication $>$ 12 months after surgery. Transient hypoparathyroidism is defined as the absence of hypocalcemic symptoms and decreased PTH level if the medication was stopped within the 12-month period. Calcium and vitamin D were administered, according to the laboratory findings and hypocalcemic symptoms.

Before surgery and on Day 1 after surgery, laryngoscopy (either indirect or direct video laryngoscopy) was mandatory. An additional examination was scheduled at 1 month, 2 months, 4 months, 6 months, and 12 months after surgery in patients with recurrent laryngeal nerve paresis, or until the vocal cord function was recovered. Vocal cord paresis for $>$ 12 months after surgery was regarded as permanent palsy.

Thyroid stimulating hormone-suppressive hormonal therapy was applied to all postoperative patients and radioactive iodine therapy was used in cases with gross extrathyroidal extension of the tumor regardless of tumor size, primary tumor size $>$ 4 cm, or 1—4 cm thyroid cancers confined to the thyroid who have documented lymph node metastases, or other higher risk features. Postoperative physical examinations were performed every 3—6 months. During the period of follow-up, all patients underwent ultrasound examinations of the neck as well as a thyroid function test. Patients with total thyroidectomy plus bilateral CLND were monitored with a thyroglobulin examination and Iodine-131 scan. We took both the central and lateral compartment into account as the local regional recurrence. A follow-up between 5 years and 10 years postsurgery was achieved for all patients.

2.4. Statistical analysis

Statistical analyses were performed using χ^2 tests. Odds ratios and 95% confidence intervals for relationships between each variable and lymph node metastasis (yes or no) were calculated using binary logistic regression. SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing and bilateral inspection; $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 1555 cN0 PTC patients aged from 14–85 years (mean 43.25 ± 10.38 years) were enrolled. The male-to-female ratio was 1:5.2 (267 males 267 and 1388 females). The largest tumor was 8.0 cm, and the smallest tumor was < 0.1 cm. The mean number of tumors was 1.62 and ranged from one tumor to eight tumors. Bilateral tumors were found in 504 cases and unilateral tumors in 1051 cases. The rate of CLNM was 45.85% (713 out of 1555 cases). The mean number of central lymph nodes harvested was 5.46 (ranging from 1 to 46). We found nodular goiters in 788 cases, thyroid adenoma in 104 cases, and Hashimoto's thyroiditis in 607 cases.

3.2. Risk factors of CLNM

In an independent variable χ^2 test, variables including young age (i.e., < 45 years of age), male gender, extrathyroidal extension (ETE), multifocal tumors, bilateral tumors, and a tumor size > 1 cm were significantly associated with CLNM (Table 1). But, Hashimoto's thyroiditis was not associated with CLNM in the above test. However, when these variables were included in multivariate logistic regression models, multifocal and bilateral tumors were not statistically significant predictors of CLNM (Table 2).

3.3. Complications, follow-up, and recurrence

Among 1555 cN0 patients, 97 cases (6.24%) had transient hypoparathyroidism and only two patients (0.13%) had permanent hypoparathyroidism. Recurrent laryngeal nerve injury after thyroidectomy occurred in 14 patients (0.9%); nine of those cases were transient and the remaining five were permanent. The permanently recurrent laryngeal nerve paralyses were caused by serious tumor invasion. For the patients' follow-ups, postsurgical thyroid function test and ultrasound examination were performed every 3–6 months. When tumor recurrence was suspected, fine needle aspiration was performed for pathologic confirmation. All patients adhered to follow-up for at least 5 years, and many had a longer period of follow-up. During the period of follow-up, ranging from 5 years to 10 years, 18 patients (1.16%) were found with locoregional recurrence, but none had distant metastasis or died (Table 3).

Table 1 Independent variable χ^2 test for CLNM.

Independent variable		CLNM		χ^2 value	p
		Positive	Negative		
Gender	male	163	104	29.983	0.000
	female	550	738		
Age	< 45 y	471	373	73.658	0.000
	≥ 45 y	242	469		
Multifocal	Positive	389	361	21.109	0.000
	Negative	324	481		
Extrathyroidal extension	Positive	535	477	57.417	0.000
	Negative	178	365		
Size	≤ 1 cm	379	680	135.429	0.000
	> 1 cm	334	162		
Bilateral carcinoma	Positive	272	232	19.784	0.000
	Negative	441	610		
Combined with nodular goiter	Positive	318	470	19.442	0.000
	Negative	395	372		
Combined with adenoma	Positive	35	69	6.681	0.010
	Negative	678	773		
Combined with lymphocytic thyroiditis	Positive	262	345	2.90	0.089
	Negative	451	497		

CLNM = cervical lymph node metastasis.

Table 2 Multivariate logistic regression for CLNM.

	p	Odds ratio
Male Gender	< 0.001	2.089
Age less than 45 y	< 0.001	2.417
Multifocal	0.083	1.318
Extrathyroidal extension	0.001	1.534
Maximum tumor diameter > 10 mm	0.000	3.079
Bilateral carcinoma	0.184	1.251
Combined with nodular goiter	0.228	0.872
Combined with adenoma	−0.23	0.789

CLNM = cervical lymph node metastasis.

4. Discussion

4.1. Risk factors for CLNM

During multivariate logistic regression analysis, we found that male gender, young age (≤ 45 years of age), the presence of ETE, and a primary tumor size > 10 mm were risk factors of CLNM (odds ratio of 2.089, 2.417, 1.534, and 3.079, respectively). In a retrospective study, Jung et al[5] indicated that risk factors for CLNM including age < 45 years, tumor size of ≥ 1 cm, and ETE predicted lymph node metastasis. Randolph et al[6] reported that tumor size, number of metastatic lymph nodes, and presence of extranodal extension of the tumor were correlated with CLNM. Moreover, Lim et al[7] reported that besides tumor diameter, the number of central lymph nodes also belong as risk factors for CLNM, predicting the prognosis of PTC patients. In our study, the positive rate of CLNM was up to 45.85% among patients with clinically negative lymph node metastasis. We suggest that surgeons should not make a decision for CLND only according to the T-stage of the tumor. Meanwhile, many risk factors for CLNM, such as male gender, young age (≤ 45 years of age), the presence of ETE, and a primary tumor size > 10 mm should be also considered. Therefore, as for making a decision for CLND, a pathological examination of FS during operation is necessary.

There is an increased incidence of PTC in patients with Hashimoto's thyroiditis, implying the presence of more than an incidental association between these two diseases.

Table 3 The characteristics of recurrent cases.

Patient ID	Age/ Sex	Max Tumor size (cm)	ETE	Multifocality/ No. of foci	Tumor bilaterality	Stage by TNM	CLNR	CLNM	Postablation sTg (μg/L)	Time to recurrence (mo)	$BRAF^{V600E}$ mutation	Site of locoregional recurrence
1	54/F	2.3	+	−	+	III	5/6	+	12.1	32	+	Ipsilateral lateral
2	42/F	4.2	+	+/2	+	I	3/4	+	11.3	26	+	Contralateral central
3	29/F	0.6	−	−	−	I	5/5	+	[a]	56	+	Ipsilateral lateral
4	37/M	0.9	−	−	+	I	3/6	+	6.1	11	+	Bilateral central
5	77/F	1.3	−	+/2	+	III	8/9	+	9.3	17	+	Contralateral lateral
6	59/F	1.6	−	+/3	+	IV	7/12	+	22.8	47	+	Ipsilateral lateral
7	42/F	1.7	−	−	−	I	4/4	+	4.9	32	+	Ipsilateral lateral
8	44/F	1.1	−	−	+	I	4/8	+	3.2	38	+	Bilateral central
9	57/F	1.0	−	−	+	III	2/5	+	5.1	24	+	Ipsilateral lateral
10	63/F	0.1	−	−	−	III	6/17	+	[a]	58	+	Contralateral lobe and central
11	18/F	0.6	−	−	−	I	3/5	+	[a]	22	+	Contralateral lobe and central
12	38/M	0.9	+	−	+	I	4/6	+	7.6	48	+	Ipsilateral lateral
13	67/F	2.1	+	+/4	+	III	8/9	+	46.8	44	+	Ipsilateral central and lateral
14	68/F	1.3	+	−	−	III	7/11	+	5.7	25	+	Contralateral central
15	59/M	0.7	−	+/2	+	III	5/8	+	12.9	48	+	Ipsilateral central and lateral
16	71/F	0.9	−	+/7	+	III	7/9	+	33.9	10	+	Ipsilateral central
17	48/F	1.4	+	+/4	+	IV	9/11	+	21.5	26	+	Ipsilateral lateral
18	66/F	0.6	−	+/5	+	III	2/4	+	8.8	61	+	Ipsilateral lateral

CLNM = central lymph node metastasis; CLNR = central lymph node ratio; ETE = extrathyroid extension.
[a] Case did not receive Iodine-131 ablation.

Accordingly, Hashimoto's thyroiditis may be considered as a precursor of PTC.[8,9] However, the positive rate of Hashimoto's thyroiditis is up to 39.04% among the 1555 PTC patients in our study. We found that the presence of Hashimoto's thyroiditis was not associated with CLNM ($p = 0.089 > 0.05$; Table 1).

4.2. Prophylactic CLND

At present, there is an argument regarding the necessity of routine prophylactic CLND. Some surgeons advocate that prophylactic CLND could not only provide a grading basis for the prognosis of patients, postoperative treatment, and follow-up of Iodine-131, but also reduce the thyroglobulin levels after operation. It has been reported that a high proportion (40—80%) of cN0 patients were changed to clinically positive after CLND, similar to our findings (45.85%).[10] But, some scholars still believed, even without CLND, the prognosis of PTC remains good. In addition, those scholars also believed that CLND is more prone to causing permanent hypoparathyroidism. However, in terms of the high incidence rate of CLNM in PTC patients, we believe that routine prophylactic CLND is very important in treating PTC patients. An evaluation of PTC patients, mainly based on the pathological examination of FS during operation, also including many risk factors for CLNM, might be essential to CLND. Furthermore, in our study, among 1555 cN0 patients, 97 cases (6.24%) had transient hypoparathyroidism and only two patients (0.13%) had permanent hypoparathyroidism. Those results suggest that, with advanced surgery devices, the complication rate, such as permanent hypoparathyroidism after operation was much lower than that previously observed. Moreover, performance of CLND also can reduce the recurrence rate near the recurrent laryngeal nerve and the morbidity rate of the follow-up surgery. In our study, among 1555 cN0 patients receiving prophylactic CLND, only 18 patients (1.16%) had locoregional recurrence, but none had distant metastasis or were deceased. Therefore, we support the opinion that routine prophylactic CLND should be performed in cN0 PTC patients, because the second operation after recurrence not only causes higher complication rates, but also increases unnecessary economic and psychological burden to patients.

4.3. Locoregional recurrence

The locoregional recurrence rate is 1.16% in our study, which was lower than that reported in other papers, especially for cN0 PTC patients.[11—13] Prophylactic CLND could decrease locoregional recurrence, because of the removal of a large proportion of the occult positive central lymph nodes. In our study, the characteristics of recurrent cases as shown in Table 3 suggested that ipsilateral lateral lymph node was the most vulnerable region of recurrence. Many studies suggested that many factors, such as gender (male), tumor size, bilaterality, extrathyroid extension, lymph node metastasis, vascular invasion, and postablation sTg were associated with locoregional recurrence.[11—15] However, in our study, we did not perform statistical analyses to study the risk factors for recurrence in terms of the fewer recurrent cases (only 18 cases). According to the characteristics of recurrent cases as shown in Table 3, we found that three factors including positive CLNM, postablation sTg $\geq$ 1 μg/L and $BRAF^{V600E}$ mutation were the possible risk factors for recurrence, because those three factors are all positive in recurrent cases. We need a large randomized controlled trial and longer period follow-up to ascertain risk factors of recurrence for cN0 patients with prophylactic CLND.

5. Conclusion

Taken together, in terms of the high incidence rate of CLNM in cN0 PTC patients, we believe that routine prophylactic CLND is optimal for cN0 PTC patients during their first treatment, especially for those with risk factors for CLNM.

References

1. Kepenekci I, Demirkan A, Cakmak A, Tug T, Ekinci C. Axillary lymph node metastasis as a late manifestation of papillary thyroid carcinoma. *Thyroid*. 2009;19:417—419.
2. Lee BJ, Wang SG, Lee JC, Son SM, Kim IJ, Kim YK. Level IIb lymph node metastasis in neck dissection for papillary thyroid carcinoma. *Arch Otolaryngol Head Neck Surg*. 2007;133:1028—1030.
3. Xiao GZ, Gao L. Central lymph node metastasis: is it a reliable indicator of lateral node involvement in papillary thyroid carcinoma? *World J Surg*. 2010;34:237—241.
4. Moo TA, Umunna B, Kato M, et al. Ipsilateral versus bilateral central neck lymph node dissection in papillary thyroid carcinoma. *Ann Surg*. 2009;250:403—408.
5. Jung CK, Kang YG, Bae JS, Lim DJ, Choi YJ, Lee KY. Unique patterns of tumor growth related with the risk of lymph node metastasis in papillary thyroid carcinoma. *Mod Pathol*. 2010;23:1201—1208.
6. Randolph GW, Duh QY, Heller KS, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid*. 2012;22:1144—1152.
7. Lim YS, Lee JC, Lee YS, et al. Lateral cervical lymph node metastases from papillary thyroid carcinoma: predictive factors of nodal metastasis. *Surgery*. 2011;150:116—121.
8. Sclafani AP, Valdes M, Cho H. Hashimoto's thyroiditis and carcinoma of the thyroid: optimal management. *Laryngoscope*. 1993;103:845—849.
9. Okayasu I, Fujiwara M, Hara Y, Tanaka Y, Rose NR. Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. *Cancer*. 1995;76:2312—2318.
10. Hartl DM, Travagli JP. Central compartment neck dissection for thyroid cancer: a surgical technique. *World J Surg*. 2011;35:1553—1559.
11. Lang BH, Chan DT, Wong KP, Wong KK, Wan KY. Predictive factors and pattern of locoregional recurrence after prophylactic central neck dissection in papillary thyroid carcinoma. *Ann Surg Oncol*. 2014;21:4181—4187.
12. Ahn D, Sohn JH, Park JY. Surgical complications and recurrence after central neck dissection in cN0 papillary thyroid carcinoma. *Auris Nasus Larynx*. 2013;1778:1—6.
13. Suh YJ, Kwon H, Kim SJ, et al. Factors affecting the locoregional recurrence of conventional papillary thyroid carcinoma after surgery: a retrospective analysis of 3381 patients. *Ann Surg Oncol*. 2015. http://dx.doi.org/10.1245/s10434-015-4448-9.

14. Prescott JD, Sadow PM, Hodin RA, et al. *BRAF*^{V600E} status adds incremental value to current risk classification systems in predicting papillary thyroid carcinoma recurrence. *Surgery*. 2012;152:984—990.

15. Guo K, Wang Z. Risk factors influencing the recurrence of papillary thyroid carcinoma: a systematic review and meta-analysis. *Int J Clin Exp Pathol*. 2014;7:5393—5403.