ORIGINAL ARTICLE

Central lymph node metastasis in cN0 papillary thyroid carcinoma

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Summary

Purpose: To evaluate the predictive factors of central lymph node (CLN) metastasis and the relationship between the number of metastatic CLN and risk factors for recurrence or metastasis in papillary thyroid carcinoma (PTC) patients.

Methods: Patients with PTC who had undergone subtotal or total thyroidectomy and ipsilateral CLN dissection were retrospectively reviewed. According to the number of metastatic CLN, patients were divided into 3 Groups: Group A: N=0; Group B: N=1-2; Group C: N ≥3.

Results: Occult ipsilateral CLN metastasis was present in 34.2% (78/228) of the patients. Univariate analysis revealed that ipsilateral CLN metastasis was significantly higher in younger patients (age <45 years), in those with maximal carcinoma diameter ≥1 cm and in those who presented with extrathyroid extension of carcinoma. Multivariate analysis showed tumor size and age were independent risk factors for ipsilateral CLN metastasis. Patient group distribution was as follows: Group A: N=150 (65.8%); Group B: N=50 (21.9%); Group C: N=28 (12.3%). Tumor size increased as the number of metastatic CLN increased, but age decreased when the number of metastatic CLN increased. Patients with CLN metastasis (Group B and C) had larger tumor size than those without metastasis. For patients with extrathyroid extension, patients in Group C had a significant odds ratio (0.215, p<0.05).

Conclusion: A maximal carcinoma diameter ≥1 cm and younger age are associated with a higher rate of ipsilateral CLN metastasis in unilateral PTC patients. Prophylactic ipsilateral CLN dissection may be effective in the management of these patients. The number of metastatic CLN is negatively associated with prognostic factors including age, tumor size and extrathyroid extension.

Key words: lymph node metastasis, neck dissection, papillary carcinoma, thyroid tumors

Introduction

PTC accounts for 80-85% of all thyroid malignancies, with a reported 10-year survival rate of >90% [1,2]. Cervical lymph node (LN) metastasis is frequently observed in PTC patients with an incidence ranging from 20 to 90% (mean: 60%) [3]. The most common sites of nodal metastases are the CLN in the neck (level VI) [4], followed by ipsilateral LNs. The boundaries of the central compartment include the hyoid bone superiorly and the carotid arteries laterally. The inferior border has been variably defined as the sternal notch or the innominate (brachiocephalic) artery [5]. Central lymph node dissection (CLND) is defined as the removal of level VI LNs (including pretracheal and paratracheal nodes), precricoid (Delphian) LNs and perithyroid LNs (including nodes along the recurrent laryngeal nerves) [5,6]. Historically, it has been accepted that LN metastasis may increase the likelihood of local recurrence without influencing survival [6]. However, emerging evidence from large studies shows an increase in mortality of patients with regional LN metastasis [2].

This study was designed to evaluate the predictive factors of CLN metastasis and the clinical implication of the number of metastatic CLN in patients with cN0 PTC. The relationship between the number of metastatic CLN and previously de-

fined prognostic factors for recurrence or metastasis (including age, gender, tumor size and extrathyroid extension) was evaluated.

Methods

Study population

Patients with PTC who were treated in Zhejiang Cancer Hospital from January 2007 to December 2009 were recruited into the present study which was approved by the Review Board of our hospital. Preoperative ultrasonography (US) and computerized tomography (CT) scan were performed to identify patients with cN0 PTC in unilateral lobes and no suspicious LNs. No patient had a history of thyroid or neck surgery for non-thyroid head and neck cancers. Patients with other types of thyroid malignancies or undergoing therapeutic neck dissection for clinically positive LNs in the central or lateral compartment of the neck were excluded. PTC and nodal metastasis were pathologically confirmed after thyroidectomy and dissection of the affected LNs. Patients were also excluded if they had PTC in the isthmus (N=12) or bilateral lobes (N=31). A total of 228 patients (34 males and 194 females, median age 44 years, range 15-78) were finally selected for analysis.

All patients were divided into 3 Groups according to the number of metastatic CLN: Group A (N=0), Group B (N=1-2) and Group C (N≥3).

Central lymph node dissection and pathologic examination

Lobe, subtotal or total thyroidectomy was performed. All PTC patients underwent ipsilateral prophylactic CLND. The ipsilateral central compartment was defined as the prelaryngeal/pretracheal and paratracheal region ipsilateral to PTC. After the recurrent la-ryngeal nerve was identified and dissected, the thyroid lobe was removed. The fibrofatty tissue and LNs were dissected from the nerve and retracted medially, and then dissected from the trachea. The specimen was collected en bloc as complete as possible. Particular attention was payed to the identification of the parathyroid glands. Tumor size, extrathyroid extension, and lymphovascular invasion were carefully examined with postoperative pathology. The total number of LNs and the number of positive LNs in each central region were determined.

Statistics

The SPSS version 16.0 was used for statistical analysis. Univariate analysis with chi-square test was performed to investigate the relationships between CLN metastasis and patients' demographics. The correlation between tumor size and number of metastatic CLN was estimated with linear regression analysis and Games-Howell tests. Logistic regression analysis was used to evaluate the relationship between number of metastatic CLN and extrathyroid extension.

Results

Demographics

The patient mean age was 44.71±12.762 years for males and 43.99±10.220 years for females. The mean follow-up period was 51.6±9.00 months. All patients underwent thyroidectomy and unilateral CLN dissection without lateral node dissection (LND). Extrathyroid extension was observed in 36 (15.8%) cases. In addition, 50 out of 120 patients (41.7%) younger than 45 years had CLN

Table 1. Correlation between risk factors and CLN metastasis

Clinical factors	Incidence of CLN metastasis [a]	Univariate analysis	Multivariate analysis	
	N (%)	p-value [b]	p-value [c]	Odds ratio (95% CI)
Age (years)		0.012	0.008	2.235 (1.229-4.066)
<45	50/120 (41.7)			
≥45	28/108 (25.9)			
Gender		0.353	0.365	1.451 (0.649-3.246)
Male	14/34 (41.2)			
Female	64/194 (33.0)			
Tumor size (cm)		0.000	0.000	0.327 (0.176-0.605)
<1	33/141 (23.4)			
≥1	45/87 (51.7)			
Extrathyroid extension		0.003	0.086	2.024 (0.905-4.526)
Yes	20/36 (55.6)			
No	58/192 (30.2)			

CLN:central lymph node, CI: confidence interval.
[a] Incidence of CLN metastasis in each group regardless of the number of metastatic lesions; [b] Chi-square test was confirmed by Fisher's exact test; [c] Logistic regression analysis
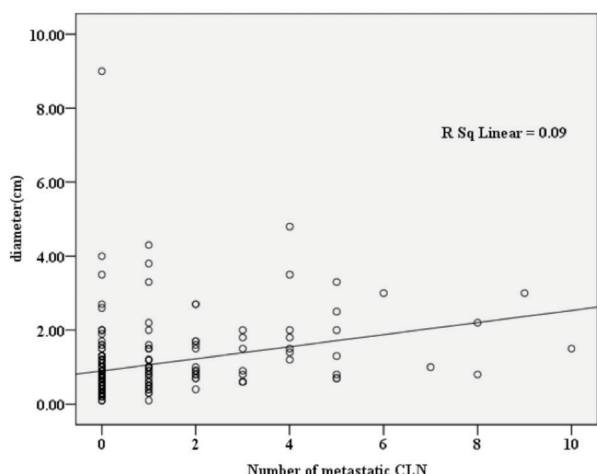
Figure 1. Correlation between the diameter of the primary tumor and the number of metastatic central lymph nodes (CLN) (linear regression analysis, tumor size = 0.899+ 0.163×number of CLN).
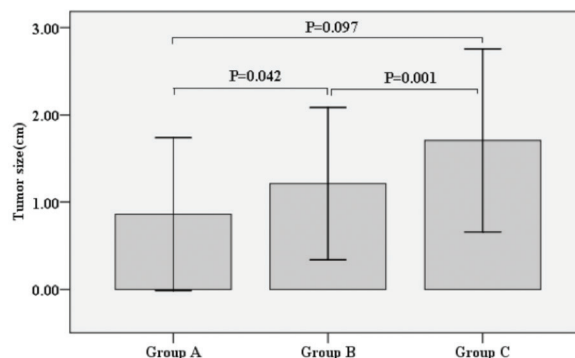

Figure 2. Average tumor size in each group (Games-Howell method). Average tumor size in Group B and Group C differed significantly from that in Group A (p=0.042, and 0.001, respectively). There was no significant difference between Group B and Group C (p=0.097).

metastasis. This rate was significantly higher than that in patients older than 45 years (25.9%; p<0.05). The incidence of CLN metastasis did not differ between males and females (Table 1). Correlation analysis showed age was related to the number of metastatic CLN (Pearson's correlation = -0.227, p=0.000), but gender had no influence on the number of metastatic CLN.

Tumor size

Two methods were used to evaluate the relationship between number of metastatic CLN and tumor size. Linear regression analysis showed the diameter of the primary tumor increased as the number of metastatic CLN increased (r=0.299, p=0.000, Figure 1). Despite the positive correlation between number of metastatic CLN and tumor size, 17 patients (7.5%) with micropapillary thyroid carcinomas (<1 cm) presented with multiple metastatic CLNs (N≥2). The mean tumor size in Groups A, B and C was 0.86 ±0.88, 1.21 ±0.87, and 1.71 ±1.05 cm, respectively. Patients in Group B and C had significantly larger tumor size than those in Group (Games-Howell, p=0.042, and

0.001, respectively), but no significant difference was detected between Group B and Group C.

Extrathyroid extension

The incidence of CLN metastasis was higher in patients with extrathyroid extension vs those without (Table 1). The incidence of extrathyroid extension was 10.7% (16/150), 20.0% (10/50), and 35.7% (10/28) in Groups A, B and C, respectively. The odds ratio was 0.478 between Group A and Group B, without statistical significance (p=0.094). The incidence of extrathyroid extension was dramatically different between Group C and Group A (odds ratio=0.215, p=0.001; Table 2). There was a difference in the rate of extrathyroid extension in each group and patients in Group C were more likely to develop extrathyroid extension.

Postoperative complications

At the end of the study, 48 out of 228 patients (21.1%) developed transient postoperative hypocalcemia. Of these patients, only 6 (2.6%) had obvious symptoms requiring calcium supplementation, and recovered within 6 months after surgery. In no patient vocal cord paralysis was observed.

Table 2. Relationship between number of metastatic CLN and extrathyroid extension

No.of metastatic CLN	B	SE	Wald	p-value	Exp(β)*	95% CI	
						Lower	Upper
Group A			10.878	0.004			
Group B	-0.739	0.442	2.801	0.094	0.478	0.201	1.135
Group C	-1.537	0.475	10.482	0.001	0.215	0.085	0.545
Constant	2.125	0.265	64.559	0.000			

CLN: central lymph node, SE: standard error, CI: confidence interval
* Odds ratio

Follow-up and recurrence

The mean follow-up duration was 51.6 months (range: 36-71). As most patients underwent total or subtotal thyroidectomy, postoperative I^{131} ablation was not performed. None experienced a recurrence in the central compartment of the neck, and only one patient (0.4%) experienced recurrent PTC in the lateral cervical compartment and subsequently underwent lateral neck dissection. One patient (0.4%) developed lung metastasis 2 years after surgery and underwent contralateral lobe thyroidectomy and postoperative I^{131} therapy. At the end of the study all patients remained alive and free of disease without regional or distant metastasis.

Discussion

PTC has a high incidence of occult nodal metastasis. Because the LNs in the central compartment are generally the first and most commonly involved in metastasis, there may be a significantly higher risk for recurrence in this compartment. Some reports have shown that LN metastases are associated with high rates of locoregional recurrence and poor survival even after adjusting for TNM stage [2,7]. In addition, it is relatively difficult to reoperate patients developing regional recurrence in the central compartment [8]. Reoperation after cervical recurrence may increase the risk for recurrent laryngeal nerve injury, hypoparathyroidism, and cosmetic problems. The TNM staging system developed by the American Joint Committee on Cancer (AJCC,2002, 6th Edn) reflected the importance of LN metastasis [9]. However, the number of metastatic CLN in the TNM staging system is not considered [9]. Lee et al. [10] reported that the number of metastatic CLN correlated with negative prognostic factors, including tumor size, extrathyroid extension and lateral neck LN metastasis. Although therapeutic CLND is a well-accepted procedure in patients with macroscopic nodal metastasis in the central neck at the time of initial surgery, the benefit of prophylactic CLND in patients without evident LN metastasis remains controversial [11]. Herein, a retrospective study was conducted in 228 patients who had undergone surgical treatment for PTC in our department, and the predictive factors and importance of the number of metastatic CLN were evaluated.

Firstly, the predictors of initial CLN involvement were evaluated. Our results showed tumor size and extrathyroid extension, which were major determinants of T-stage classification in the 2002 AJCC staging system, were independent predictors of CLN involvement. Of note, there was a correlation between age and central node involvement,which was consistent with findings in previous studies [12]. In addition, our results revealed that the age decreased when the number of metastatic CLN increased. Nevertheless, this epidemiological factor was not associated with risk for recurrence [12].

Secondly, the correlation between number of metastatic CLN and risk factors was evaluated. Some studies have shown that metastasis to CLN increases when tumor size increases [13,14]. Some investigators have reported that PTC with maximal diameter > 1 cm is associated with high rate of ipsilateral CLN metastasis, and is a potential independent predictor of contralateral CLN metastasis [15]. In the present study, the number of metastatic CLN was positively correlated with tumor size. Patients with CLN metastasis (Group B and C) had a larger tumor size compared to those without such metastasis. In addition, extrathyroid extension was associated with a high rate of metastasis, in agreement with previous findings showing that extrathyroid extension or capsular invasion of PTC was related to increased rates of CLN metastases [10,16]. Extrathyroid extension itself is presumed to have a negative impact on survival and local control rate [13,17,18].

Hypocalcemia is a common complication of thyroidectomy. The incidence of temporary hypocalcemia was reported to be 6.9 - 25% [19,20]. Other investigators, however, reported that transient reduction in serum calcium level occurred in nearly all patients following thyroid surgery [21]. Recent studies on LN dissection in differentiated thyroid cancer patients reported permanent hypoparathyroidism in 3 - 4% of the patients [22,23]. However, Lee et al. [24] reported that transient hypoparathyroidism was more frequently found in patients undergoing routine bilateral CLND than in those receiving routine unilateral CLND. In our study, permanent hypoparathyroidism was not noted, but transient hypocalcemia was found in 21.1% (48/228) of the patients.

During the follow-up period, there was no local or ipsilateral central neck nodal recurrences. No cancer was found in the contralateral lobe and contralateral central neck. "Limited'' CLND, which spares contralateral paratracheal LNs, has been suggested for patients with US-node-negative PTC who are at risk of disease recurrence

[25]. However, although the unaffected side of the thyroid is spared, it should be further investigated, and occult PTC in the contralateral lobe and neck should be accurately diagnosed for proper surgical management [26]. In this study, only one patient developed recurrence in the lateral neck, after which he was subjected to lateral neck dissection. Prophylactic LND was not performed in patients without preoperative suspicious metastatic LNs in the lateral neck, and because no increased morbidity has been reported when LND is delayed and performed as a secondary procedure after confirmation of metastatic LNs [9,27].

Due to the short follow-up period, the relationship between the number of metastatic CLN and survival or local control rate could not be evaluated. We postulated that a prospective long-term follow-up in this population is necessary for further evaluation of locoregional control and disease-free survival.

Conclusion

The incidence of occult CLN metastasis is high in patients with cN0 PTC (78/228; 34.2%).Younger age (<45 years), tumor size ≥1cm and extrathyroid extension are associated with higher incidence of CLN involvement. For cN0 PTC patients with previous risk factors, prophylactic ipsilateral CLND should be routinely performed. Prophylactic lateral neck dissection is not recommended in the initial surgery for patients with cN0 PTC. The number of metastatic CLN is related with poor prognostic factors, including age, tumor size and extrathyroid extension. Thereby, the number of metastatic CLN has clinical importance in the prognosis of cN0 PTC.

References

1. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994; 97: 418-428.

2. Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer 2006; 106: 524-531.

3. Rotstein L. The role of lymphadenectomy in the management of papillary carcinoma of the thyroid. J Surg Oncol 2009; 99: 186-188.

4. Machens A, Hinze R, Thomusch O, Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg 2002; 26: 22-28.

5. American Thyroid Association Surgery Working Group; American Association of Endocrine Surgeons, American Academy of Otolaryngology-Head and Neck Surgery. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 2009; 19: 1153-1158.

6. White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. World J Surgery 2007; 31: 895-904.

7. Giles Senyurek Y, Tunca F, Boztepe H, Alagöl F, Terzioglu T, Tezelman S. The long term outcome of papillary thyroid carcinoma patients without primary central lymph node dissection: expected improvement of routine dissection. Surgery 2009; 146: 1188-1195.

8. Kim MK, Mandel SH, Baloch Z et al. Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. Arch Otolaryngol Head Neck Surg 2004; 130: 1214-1216.

9. Ito Y, Miyauchi A, Jikuzono T et al. Risk factors contributing to a poor prognosis of papillary thyroid carcinoma: validity of UICC/AJCC TNM classification and stage grouping. World J Surg 2007; 31: 838-848.

10. Lee YS, Lim YS, Lee JC, Wang SG, Kim IJ, Lee BJ. Clinical Implication of the Number of Central Lymph Node Metastasis in Papillary Thyroid Carcinoma: Preliminary Report. World J Surg 2010; 34: 2558-2563.

11. Shaha AR. Prophylactic central compartment dissection in thyroid cancer: a new avenue of debate. Surgery 2009; 146: 1224-1227.

12. Bozec A, Dassonville O, Chamorey E et al. Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid carcinoma:a retrospective analysis of 368 cases. Eur Arch Otorhinolaryngol 2011; 268: 1205-1212.

13. 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.

14. Sadowski BM, Snyder SK, Lairmore TC. Routine bilateral central lymph node clearance for papillary thyroid cancer. Surgery 2009; 146: 696-703 (discussion 703–695).

15. Koo BS, Choi EC, Yoon YH, Kim DH, Kim EH, Lim YC. Predictive factors for ipsilateral or contralateral central lymph node metastasis in unilateral papillary thyroid carcinoma. Ann Surg 2009; 249: 840-844.

16. So YK, Son YI, Hong SD et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. Surgery 2010; 148: 526-531.

17. Arora N, Turbendian HK, Scognamiglio T et al. Extrathyroidal extension is not all equal: Implications

of macroscopic versus microscopic extent in papillary thyroid carcinoma. Surgery 2008; 144: 942-947 (discussion 947-948).

18. Ortiz S, Rodriguez JM, Soria T et al. Extrathyroid spread in papillary carcinoma of the thyroid: clinicopathological and prognostic study. Otolaryngol Head Neck Surg 2001; 124: 261-265.

19. Farrar WB, Cooperman M, James AG. Surgical management of papillary and follicular carcinoma of the thyroid. Ann Surg 1980; 192: 701-704.

20. Jacobs JK, Aland JW Jr, Ballinger JF. Total thyroidectomy. A review of 213 patients. Ann Surg 1983; 197: 542-549.

21. Szubin L, Kacker A, Kakani R et al. The management of post-thyroidectomy hypocalcemia. Ear Nose Throat J 1996; 75: 612–614, 616.

22. Goropoulos A, Karamoshos K, Christodoulou A et al. Value of the cervical compartments in the surgical treatment of papillary thyroid carcinoma. World J Surg 2004; 28: 1275-1281.

23. Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S, Delbridge L. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 2006; 140: 1000-1005.

24. Lee YS, Kim SW, Kim SW et al. Extent of routine central lymph node dissection with small papillary thyroid carcinoma. World J Surg 2007; 31: 1954-1959.

25. Son YI, Jeong HS, Baek CH et al. Extent of prophylactic lymph node dissection in the central neck area of the patients with papillary thyroid carcinoma: comparison of limited versus comprehensive lymph node dissection in a 2-year safety study. Ann Surg Oncol 2008;15:2020–2026.

26. Koo BS, Lim HS, Lim YC et al. Occult contralateral carcinoma in patients with unilateral papillary thyroid microcarcinoma. Ann Surg Oncol 2010;17:1101–1105.

27. Pacini F, Castagna MG, Brilli L, Pentheroudakis G; ESMO Guidelines Working Group.Differentiated thyroid cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol2009;20 (Suppl 4):143-146.