Pattern, predictors, and recurrence of cervical lymph node metastases in papillary thyroid cancer

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Aim of the study: This study investigated the pattern, predictors, and recurrence of node metastasis in papillary thyroid cancer patients.

Material and methods: One hundred and 65 papillary thyroid cancer (PTC) patients who underwent total thyroidectomy and cervical lymph node (LN) dissection (LND), in which more than 12 lymph nodes were dissected, were examined. The nodes were classified from levels I to VI. Final pathologic diagnosis of positive lymph node metastases in the differential node levels was determined.

Results: Cervical metastases of PTC were most commonly encountered in level VI, followed by levels III and IV, and then levels II and V. Metastases in level I seldom occurred. Skip metastases occurred in nine patients. Univariate analysis suggested that multifocality and extracapsular invasion were associated with LN metastases. The metastatic ratio for micro PTC and local canceration derived from benign lesions and encapsulation was low. Multivariate analysis showed that LN metastases were closely related to invasion of the thyroid capsule and primary PTC. Standardized estimation showed that the encapsulating pattern had the greatest impact on developing cervical LN metastases. Lymph node recurrence was observed in 11 patients.

Conclusions: The metastatic pattern of PTC assists in delineating the extent of selective LND. Routine bilateral central node dissection at the time of thyroidectomy is recommended. Comprehensive selective LND is recommended in multifocal PTC and with capsular invasion.

Key words: papillary thyroid cancer (PTC), cervical lymph node metastases, lymph node dissection (LND).

Contemp Oncol (Pozn) 2013; 17 (6): 504–509
DOI: 10.5114/wo.2013.38910

Introduction

Differentiated thyroid cancer is one of the most common endocrine malignancies [1, 2]. Papillary thyroid cancer (PTC) accounts for approximately 80% of all thyroid cancers [1] and is associated with cervical lymph node metastases in 30% to 90% of patients [3–5]. Surgery is the primary treatment modality for PTC. Radioactive iodine and thyroid hormone suppression often complement the treatment plan. Although thyroid hormone suppression may decrease the incidence of recurrent disease and radioactive iodine may treat metastases, lymph node dissection (LND) is the regular treatment for clinically evident cervical lymph node metastases.

Therapeutic LND for patients with PTC includes the traditional and modified radical LNDs as well as the selective LND (compartment-based resection based on documented lymph node metastases) and a "berry picking" resection (in which only grossly abnormal lymph nodes are excised). However, the role of LND in the management of thyroid cancer is somewhat controversial. Moreover, ongoing controversy over the indications and extent of lymphadenectomy for patients with PTC was further complicated by the indolent history of most well-tolerated differentiated thyroid cancers [6–10]. A major concern involves the therapeutic benefits of a more or less extensive lymphadenectomy. However, recent reports indicate that cervical lymph node metastases increase overall mortality [11, 12].

The literature on the pattern, predictors, and recurrence of cervical lymph node metastasis from PTC is limited, and the distribution of nodes at risk remains ambiguous. A retrospective analysis of patients with initial presentation of PTC at our hospital (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China), who underwent total thyroidectomy and LND, was conducted. The dissected lymph node was reported with respect to the neck level to investigate the pattern of node metastasis, the different subsites of recurrence, and the influential factors for metastases.

Material and methods

Patients

From June 2003 to June 2007, 165 patients with PTC who underwent total thyroidectomy and selective LND, with more than 12 dissected nodes, were enrolled in this study. The cases were handled by several groups of doctors, and clinical data were registered by the sole nurse on duty. Most patients below fourteen years of age did not visit our center. Total thyroidectomy and central LND (CLND) were performed in all patients. Additional unilateral and bilateral selective LND were performed for 101 and 64 patients, respectively. The number of dissected LN varied from 12 to 56 (average = 33). (Patients with fewer

than 12 dissected lymph nodes were excluded to reduce the impact of possible "berry picking" and atypia lymphadenectomy on the statistical results). Clinical records and pathological reports concerning central, ipsilateral, and contralateral LND were reviewed to ascertain the prevalence and distribution of cervical metastases at the neck level. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Huazhong University of Science and Technology. Written informed consent was obtained from all participants.

Methods

According to the 1991 American Academy of Otolaryngology-Head and Neck Surgery Foundation, cervical lymph nodes are divided into the following levels: level 1, submental and submandibular nodes; level 2, upper internal jugular vein nodes; level 3, middle internal jugular vein nodes; level 4, lower internal jugular vein nodes; level 5, nodes draining posterior triangle of neck; and level 6, pretracheal, paratracheal, precricoid (Delphian), perithyroidal nodes, superior mediastinal below the sternal notch, bound by the hyoid bone superiorly, the innominate vein inferiorly, and bilaterally by the common carotid arteries. "Central neck node" is synonymous to level 6, and lateral compartment nodes indicated levels 2 to 5. "Skip metastasis" is defined as lateral lymph node metastasis without central lymph node metastasis. The node levels on the dissected specimen were marked individually by the surgeon and identified by a pathologist.

The follow-up period covered from June 2003 to March 2012 (average = 88 months). ^{131}I ablation treatment was indicated for patients with multifocality, extrathyroidal invasion, and nodal metastases. All patients received TSH-suppressive doses of L-thyroxine, periodic determination of serum thyroglobulin and anti-thyroglobulin levels, neck high-resolution ultrasound, and whole body scan evaluation on the subsequent follow-ups.

Lymph node recurrence was documented once pathology confirmed that lymphatic metastases developed in the cervical lymph nodes. The "berry picking" procedure was applied on nine patients for lymphatic metastasis that recurred in a previous anatomical dissection. Selective LND was performed on two patients for a regional recurrence on the contralateral side that had not been previously operated on.

Statistical analysis

The SAS 9.1 software package was used for statistical analysis. Pearson χ^2 test and stepwise logistic regression were used for univariate and multivariate analyses. The maximum likelihood method was used to estimate the model parameter. *P*-values less than 0.05 were considered statistically significant.

Results

Univariate analysis

Data including patient demographics, tumor and lymph node pathology, types of surgery at the time of thyroidectomy, and time of recurrence were reviewed. All patients (36 males and 129 females, with male/female ratio of 1 : 3.6) were aged from 14 to 76 years at the time of initial treatment, in which 119 patients (72.1%) were below 50 years old, with an average age of 39.7 years. The mean diameter of lesion was 3.3 cm (range = 0.5 cm to 8.6 cm), including 28 papillary thyroid microcarcinoma (PTMC, diameter ≤ 1 cm). A total of 122 and 43 malignant lesions were located only in one side and both sides, respectively. Overall, 61 out of 165 (37%) patients were documented to have multifocal PTC. A total of 100 (77.5%) female and 28 (77.8%) male patients had positive lymph nodes. The LN metastasis rate for patients under 50 years old was 80.7% (96/119), compared with 69.6% (32/46) in patients above 50 years old. All the pathological types were PTC, in which the follicular variant accounted for 21 cases. Nodal involvement in the follicular variant and classical papillary type of pathology were 90.5% (19 out of 21) and 75.7% (109 out of 144), respectively. However, no significant difference was observed in the χ^2 test ($p = 0.129$). Univariate analysis revealed that gender, age, and the follicular variant of pathology were not associated with LN metastases. The results of bivariate analysis for the risk factors in relation to LN metastases are listed in Table 1.

The positive node rate for multiple lesions (including multi-lesion and double-sided PTC) was 96.7% (59/61), compared with that of single PTC at 66.3% (69/104) ($p < 0.001$). Extracapsular invasion was found in 29.1% (48 out of 165) of patients, and LN metastases were observed in 47 (97.9%) patients. Univariate analysis revealed that multifocality and extracapsular invasion were significantly higher in LN metastases compared with cases with a single lesion and without extracapsular invasion.

Pathology showed that PTMC, canceration from benign diseases (11 from nodular goiter and 4 from Hashimoto's thyroiditis), and encapsulation PTC (refers to PTC characterized by the presence of a capsule around the lesion) were found in 28, 15, and 24 patients, respectively. Nodal metastasis rates were lower in these patients (13 of 28, 46.4%; 3 of 15, 20%; 3 of 24, 12.5%, respectively).

Multivariate analysis

Stepwise logistic regression (enter = 0.1, stay = 0.1) was used for multivariate analysis (Table 2). Only extracapsular invasion, encapsulation type (whether the lesion is surrounded by a capsule), and tumor original type (primary or canceration from a benign disease) were selected for the final model. Extracapsular invasion (OR, 27.462; $p = 0.027$), without encapsulation (unencapsulated PTC) (OR, 0.007; $p < 0.001$), and primary PTC (OR, 0.004; $p < 0.001$) presented significant risk factors for LN metastases. Encapsulation type was found to have the greatest impact on LN metastases.

Central and lateral compartment lymph node metastasis

Selective LND resulted in 95.2% of level I, 65.5% of level II, and 35.8% of level V lymph nodes left *in situ* after the initial LND, whereas levels III, IV, and VI were dissected

Table 1. Bivariate analysis for the risk factors of lymph node metastases

Influence factor		Positive LN(+) (*N* = 128)	Negative LN(–) (*N* = 37)	χ^2 value	*P*-value
Gender	male (*n* = 36) female (*n* = 129)	28 100	8 29	0.0011	0.9738
Age	> 50 y (*n* = 46) ≤ 50 y (*n* = 119)	32 96	14 23	2.353	0.125
Extracapsular invasion	yes (*n* = 48) no (*n* = 117)	47 81	1 36	16.1	< 0.001
Number of lesions	single (*n* = 104) multifocal (*n* = 61)	69 59	35 2	20.39	< 0.001
Size of lesion	> 1 cm (*n* = 137) ≤ 1 cm (*n* = 28)	115 13	22 15	18.806	< 0.001
Classical type or follicular variant	follicular variant (*n* = 21) papillary (*n* = 144)	19 109	2 35	2.302	0.129
Encapsulation	yes (*n* = 24) no (*n* = 141)	3 125	21 16	68.37	< 0.001
Primary or canceration	canceration (*n* = 15) primary (*n* = 150)	3 125	12 25	31.44	< 0.001

LN – lymph node
Canceration means the development of thyroid papillary carcinoma in a site previously involved by a benign thyroid disease.

Table 2. Multivariate regression analysis for the risk factors of lymph node metastases

Variable	Estimate	Wald χ^2	Standardized estimate	OR	*P*-value
Extracapsular invasion	3.313	4.879	0.832	27.462	0.027
Encapsulation	–4.926	37.645	–0.960	0.007	< 0.001
Primary or canceration	–5.472	22.858	–0.870	0.004	< 0.001

in all patients. Out of 165 patients, 128 (77.6%) patients were LN-metastasis positive, with metastatic rates higher in the central compartment (level VI) than in the lateral compartment (levels II to V) [119 of 165 (72.1%) vs. 86 of 165 (52.1%); $p < 0.001$). Skip metastasis was determined in nine patients. The rates of nodal metastases in the central compartment in patients with unilateral and bilateral PTC were 63.9% (78/122) and 95.3% (41/43) ($p < 0.001$), respectively, and those in the lateral compartment were 41.8% (51/122) and 81.4% (35/43) ($p < 0.001$) (χ^2 test) in patients with unilateral and bilateral PTC, respectively (Table 3).

Lymph node recurrence characteristics

The mean duration of follow-up was 64 months (ranging from 56 to 110 months). All patients with multifocal extrathyroidal invasion, and lymph node metastases at our department were recommended to undergo post-thyroidectomy radioiodine (RAI) ablation. The results of this treatment were excluded from the analysis. A total of 11 recurrences (6.7%) occurred in the central compartment (5 out of 11) and/or in the lateral cervical region (9 out of 11). Four patients had recurrences within nine months (2.5 to 8.9 months postoperatively, mean = 4.8 months) at levels II and V, whereas seven patients had recurrences at an average of 48 months (range = = 24 to 80 months) in the central and/or lateral compartments. The recurrence rates for levels I to VI were 9.1% (1 of 11), 36.4% (4 of 11), 18.2% (2 of 11), 27.3% (3 of 11), 36.4% (4 of 11) and 45.5% (5 of 11), respectively. Subsequent recurrences were found in the lateral compartment, including two on the contralateral side that had not been previously operated on. Eight patients had documented distant metastases, most commonly to the lungs (7 out of 8). One PTMC patient died of lung metastases 15 months after the operation.

The aggregated pathology results of reoperation, variability contrast of final lymph node metastases between the ipsilateral and contralateral regions in the unilateral

Table 3. Frequency distribution of selective lymph node dissection and the number of positive lymph nodes in different subsites

Level of LN dissection		I	II	III	IV	V	VI
Unilateral lobe disease (*N* = 122)	ipsilateral (*N* = 122) contralateral (*N* = 21)	1 (5) –	14 (29) 2 (9)	51 (122) 5 (21)	44 (122) 6 (21)	12 (64) 1 (5)	78 (122) 58 (122)
Bilateral lobe disease (*N* = 43)		1 (3)	7 (28)	35 (43)	31 (43)	16 (42)	41 (43)

Positive N. (LND N.) / the number of positive lymph nodes (the number of lymph node dissection)

Table 4. Variability contrast of ipsilateral and contralateral lymph node metastases in unilateral lobe

Level of LN dissection		I	II	III	IV	V	VI
Unilateral lobe disease (*N* =122)	ipsilateral	2	18	51	44	14	78
	contralateral	0	2	7	8	1	58
p-value		0.159	0.006	< 0.001	< 0.001	0.001	0.168

lobe disease, and different subsites in the unilateral and bilateral lobe are shown in Tables 4 and 5.

Lateral compartment lymph node metastasis pattern

Pathological examination showed that the ipsilateral lateral compartment was more frequently affected than the contralateral lateral neck by lymphatic nodal metastases when lesions were confined to the unilateral lobe. However, no significant difference was found between the ipsilateral and contralateral central nodes. For patients with unilateral lesions, levels III and IV were commonly involved (36.1% to 41.8%), followed by levels II and V (11.5% to 14.8%), and level I was rarely involved. No difference was found between levels III and IV. However, a significant difference in lymph node metastases was found between levels II and III or IV, and levels V and III or IV ($p < 0.05$), with levels III and IV more frequently affected than levels II and V. When lymph node metastasis metastasized to the contralateral lateral compartment in patients with unilateral lesions, the distinction decreased among subsites as indicated by the absence of a difference between levels II and III or IV and a difference between levels V and III or IV. In addition, level V was the least frequently affected. The rates of lymph node metastasis of bilateral lesions from levels II to VI were 16.3% (7/43), 81.4% (35/43), 72.1% (31/43), 37.2% (16/43) and 95.3% (41/43), respectively. Similar results were found among subsites in patients with bilateral lesions, in which the distinction decreased among subsites, and no difference was observed between levels IV and V.

Table 5. Variability contrast of lymph node metastases in different subsites

Variability contrast	*P* value		Bilateral lobe disease (*n* = 43)
	Unilateral lobe disease (*n* = 122)		
	Ipsilateral	Contralateral	
II vs. III	< 0.001	0.1016	0.042
II vs. IV	0.003	0.0629	< 0.001
III vs. V	< 0.001	0.0368	0.0269
IV vs. V	< 0.001	0.0219	0.0624

Discussion

Regional lymph node metastases in PTC are traditionally perceived to increase local recurrence rates but do not affect overall survival [1, 4]. However, recent reports have indicated that cervical lymph node metastases increase overall mortality [11, 12]. Thus, the operative control of nodal disease for PTC has gained renewed interest. The extent of surgical treatment of cervical lymph nodes in PTC remains controversial [6, 10].

The rate of nodal metastasis was higher in patients with extracapsular invasion than in those with no invasion ($p < 0.001$), and in patients with multifocality than in those with a single lesion ($p < 0.001$). Univariate analysis revealed extracapsular invasion, multifocality, large tumor (> 1 cm), primary tumor, and PTC without an obvious boundary as significant risk factors for nodal metastases. Nodal involvement is commonly associated with extracapsular invasion and multifocality [13–15]. Most of these pathological features can be identified during the operation. Hence, for PTC with multifocality, large cancerous tumor, and extracapsular invasion, extended LND was recommended. Encapsulation type had the greatest impact on LN metastases in multivariate analysis. For this reason, low-risk patients with encapsulated PTC (the tumor consisting of thyroid carcinoma surrounded by a fibrous capsule) can undergo a more conservative management.

Consistent with previous reports [4, 6, 15, 16], our data suggest that the risk of metastases to the central lymph nodes is higher than that in the lateral compartment ($p < 0.001$). Cross-metastasis via the lymphatic drainage system might occur to the contralateral and paratracheal, mainly distributed in the paratracheal and superior mediastinal below the sternal notch, especially when the tumor is located in the lower pole of the thyroid. Thus, routine bilateral CLND at the time of the initial operation should be performed. In spite of the controversy surrounding the recommendation of and the role of routine CLND in differentiated thyroid cancer [8, 10], the current guidelines from the American Thyroid Association suggest that prophylactic CLND might be performed for papillary thyroid cancer, especially for advanced tumors (T3 and T4) [17]. Skip metastases, involving lateral lymph nodes without central lymph nodes, occurred in a minority of PTC patients, and no clinical pathology features of the primary thyroid tumor were associated with the development of skip metastases, as shown by Chung *et al.* [13].

Pathological examination of node dissections showed that levels III and IV were most frequently affected by LN metastases, followed by levels II and V. Level I and metastasis to the contralateral lateral neck were rarely involved, consistent with the findings from previous studies [14–16, 18]. Based on our study, cervical lateral neck metastases in PTC usually spread contiguously, with varying frequency of LN metastases. Primary tumor located in the upper part of the thyroid lobe has a predilection for metastasis to levels II and III. Level V nodal involvement was hardly observed in the absence of levels III and IV metastasis, and metastatic

disease occurs in level II only without level III nodal involvement. Furthermore, ipsilateral involvement of level V was associated with contralateral lymph node metastases. One patient with big palpable lymph nodes in the contralateral neck region was confirmed to have lymph tuberculosis by pathology. Contralateral skip metastases (no positive ipsilateral neck LN) were not observed in our study.

Eleven (6.7%) recurrence cases were included in our series. Similar to other studies [7, 19], LN recurrence was frequently observed in patients with multiple node involvement. Four cases of early recurrence/persistent disease were mainly presented at levels II and V. Such recurrence might have been caused by the incomplete removal of metastatic LN at the initial LND, especially at levels II-B and V-A. These cases might be related to a shortage in experience and operative skills among surgeons because these cases occurred in the inchoate stage. The mean duration of the other seven recurrences was 48 months. Nodal recurrences commonly occurred in the central nodes (5 cases), then ipsilateral jugular nodes (3 cases), and contralateral jugular nodes (2 cases). Among the five central compartment recurrences, three were in the external branch of the superior laryngeal nerve, and two in the deep retrosternal area, above the arch of the aorta. The 5 subsequent recurrences in the lateral compartment, including two on the contralateral side that had not been previously operated on, were mainly observed in the lower cervical portion of the jugular vein and the carotid artery. Considering the recurrence pattern, the superior mediastinal central nodes, nodes along the external branch of the superior laryngeal nerve, and nodes in the lower cervical portion of the jugular vein should be covered in therapeutic node dissection to avoid further recurrence.

In addition, accurate preoperative and intraoperative assessment for levels II and V are very important for surgeons. No enlarged nodes were palpated in the sites of recurrence prior to or during surgery. However, a few small lymph nodes were seen during preoperative imaging (CT or MRI). Preoperative radio-imaging was conducted to identify cervical lymph node metastases and allowed optimal and effective treatment at the initial surgery. Therefore, imaging scans (especially CT and MRI) are advocated for aggressive diseases.

This study reviewed the clinical data on the extent of lymph node dissection variation among different surgeons because of the diverse understanding of thyroid cancer and operative habit. Meanwhile, error in medical records and operation samples also affected the dissection of lymph nodes. These considerations might result in a reduction of the differences in lymph node metastasis rates. The patients in our series with more than 12 selective LND nodes were severe cases and may artificially increase the LN metastasis rates.

Some recurrences were not detected or were confirmed to have resulted from numerous factors, such as PTC indolent growth, short follow-up time, limitation of current inspections, and some reoperation-reluctant patients. The application of RAI therapy might ablate the remaining positive lymph nodes. These factors could reduce the real LN metastasis rates. Within the context of the different groups of surgeons, the diversities of modus operandi and surgical skill might lead to the insufficiency of LND, which might result in high recurrence rates in certain domains.

In this study, genetic testing was not performed or reported specifically regarding some predictors of lymph node metastases, such as multifocality, extrathyroidal invasion, and encapsulation type. The predictors found may be markers of an underlying genetic mutation that needs further research.

The authors declare no conflict of interests.

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Submitted: 20.02.2013
Accepted: 8.05.2013