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Efficacy of Superselective Neck Dissection in Detecting Metastasis in Patients with cN0 Papillary Thyroid Carcinoma at High Risk of Lateral Neck Metastasis

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Background: This study aimed to evaluate superselective neck dissection (SSND) in patients with cN0 papillary thyroid carcinoma (PTC) at high risk of lateral cervical lymph node (LN) metastasis.

Material/Methods: This study enrolled 138 patients with PTC who underwent SSND. These patients were at high risk for LN metastasis and the rate of cervical LN metastasis was recorded.

Results: In all, 146 lateral neck dissections were performed in 138 patients. Intraoperative pathological data revealed LN metastasis from 55 cases, for which Level II and V dissection were performed. Ninety SSNDs were performed in the other 83 patients without metastasis identified in frozen sections. Occult lymph node metastasis (OLNM) rates were 56.8% and 43.5% in the central compartment and lateral neck, respectively. OLNM rates of Level II–VI were 17.8%, 31.5%, 36.3%, 1.4%, and 56.8%, respectively. Level VI metastasis ($p<0.001$), extra thyroidal extension ($p=0.003$), and tumor size ($p=0.011$) were significant factors for lateral neck LN metastasis.

Conclusions: SSND might be effective for early diagnosis of lateral neck metastases of PTC. Patients with OLNM should receive level II, III, and IV dissection, but level V dissection could be omitted.

MeSH Keywords: Lymph Nodes • Neck Dissection • Parathyroid Neoplasms

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Background

Thyroid cancer, the most common endocrine cancer [1], is the sixth most prevalent malignant tumor in Chinese women; its yearly incidence has increased on average by about 2% [2]. Approximately 80% of all thyroid cancers are papillary carcinomas [1], which are often less than 1 cm in size and found incidentally [3]. The treatment of thyroid cancer usually requires a multidisciplinary approach, including primary tumor resection, lymph node (LN) dissection, radioactive ablation of residual tissues, and thyroxine suppression therapy [3].

LN metastases are often diagnosed in thyroid cancer patients. Indeed, the rates of cervical LN and occult metastasis (metastasis undetectable by routine methods) to the lateral neck in thyroid cancer reportedly reach astounding high rates of 80% and 50%, respectively [4]. However, the value and treatment principles of LN metastasis, especially in the lateral neck, remain controversial. Studies suggest that potential lateral neck metastases in cN0 patients could be identified by superselective neck dissection (SSND) or modified radical neck dissection (MRND) [5–9], while others consider the policy of watch and wait more reasonable [10].

SSND is a complete resection of fibroadipose tissues (including LNs) with a high risk of metastasis along the defined boundaries of one or two contiguous neck levels [11]. It was first used to treat early stage laryngeal or hypopharyngeal cancer and is now employed for head and neck cancer followed by chemo-radiotherapy [12]. We hypothesized that early and accurate diagnosis and treatment of lateral cervical LN metastasis in patients with thyroid cancer not only could decrease the risk of metastasis, but also help in the postoperative review of patients. This was tested in patients with high risk factors for lateral cervical LN metastasis.

Since 2006 our study group has been exploring the use of SSND for the treatment of papillary thyroid carcinoma patients with high risk of lateral cervical LN metastasis with excellent effects of clinical application. All patients treated for papillary thyroid cancer by our study team are entered into a prospective database [13]. The aim of this study was to evaluate retrospectively the operative and long-term outcomes of the patients who underwent SSND of the lateral neck. The SSND procedure could not only provide the exact diagnosis, but also allow a timely treatment for patients, avoiding a second surgery, and achieving excellent therapeutic effects.

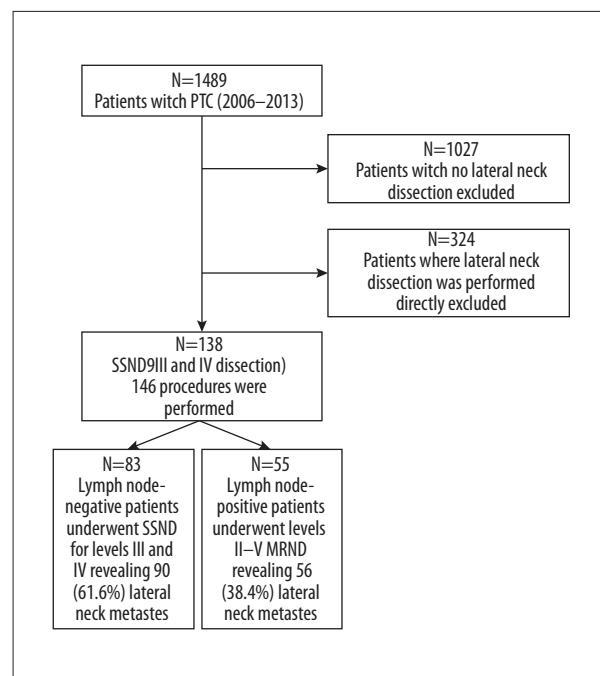


Figure 1. Flowchart showing the inclusion of patients in the study. PTC – papillary thyroid carcinoma; SSND – superselective neck dissection; MRND – modified radical neck dissection.

Material and Methods

Study design

This was a retrospective study of patients (≥ 16 years old) treated for a thyroid cancer and entered into the prospective database between July 2006 and December 2013. This study was approved by the ethical committee of the Cancer Hospital (Chinese Academy of Medical Sciences). Written informed consent was obtained prior to including the patients in the database.

Patients

During the study period, a total of 1,489 patients with papillary thyroid cancer underwent surgery at the Department of Head & Neck Surgery, Cancer Hospital, Chinese Academy of Medical Sciences, including the 138 cases that were treated with SSND and enrolled in this study (Figure 1). All these patients had been diagnosed with first-ever papillary thyroid cancer [3], and those with high risk of lateral neck metastasis were included in the study.

Inclusion criteria were: 1) tumor with extra thyroidal extension; or 2) tumor size > 2 cm; or 3) enlarged neck LNs in the central or lateral compartment determined by B-mode ultrasound and/or computed tomography (CT), but without definitive

metastases (cNO patients). Exclusion criteria were: 1) patients with follicular, medullar, or anaplastic thyroid carcinoma confirmed by pathological examination of the biopsy or surgical specimen; or 2) cN1b patients with LN metastases confirmed pre-operatively by physical examination, ultrasound, CT, and/or fine needle aspiration (FNA).

Data collection

Data regarding the tumor characteristics and cervical LN metastasis were collected. Occult LN metastasis (OLMN) was defined as LN metastasis in final pathological examinations that was undetectable by preoperative routinely methods employed (careful pathological, clinical, biochemical, and radiological evaluations) [14].

Surgical approach

Total thyroidectomy or lobectomy plus isthmus resection was performed according to the size and extension of the primary tumor. The central compartment (Level VI) [15] was routinely dissected. SSND use was based on potential factors related to metastasis, including hyperthyroidism, extra thyroidal invasion of the tumor, tumor size >2 cm, central compartment LN metastasis, and tumor localizing in the upper third of the thyroid lobe, as previously described [16].

SSND of Levels III and IV was performed. The patient's head was turned to the opposite side and the procedure was performed using the same incision as the thyroidectomy. The frontier of the lower sternocleidomastoid was dissected to the posterior border. The omohyoid muscle was dissected from the underlying tissue and kept *in situ*. The supra-omohyoid LNs at the intersection of the internal jugular vein and the omohyoid muscle (generally superficial to the internal jugular vein) were sent for frozen section. The carotid sheath was dissected to the level of the superior hyoid, lower to the supraclavicle, and deep to the prevertebral fascial. The LNs and adipose tissue were dissected in this region, preserving the cervical plexus, transverse cervical artery, jugular vein, and phrenic nerve. The thoracic duct was ligated to prevent chyle leakage [11]. One or two LNs in the superior part of the specimen (Level III, at the border region between Levels II and III) were sent to be processed into frozen sections.

In the presence of metastatic LN on frozen sections, Levels II and V were then dissected using an extended skin incision (MRND group). Patients without metastatic LNs on frozen sections had no further LN surgery (SSND group). Since this study aimed to examine the outcomes of patients who underwent lateral neck dissection, the patients were grouped according to N0/1a (no metastasis or metastases in the central neck) and N1b (metastases in the lateral neck) for analysis of risk factors for lateral neck metastases.

All surgeries were performed by Dr. Zhengjiang Li, a senior head & neck surgeon with 20 years of clinical experience.

Non-surgical treatments

^{131}I was administered to patients with multiple metastases and extra thyroid extension according to the final pathological results. All patients were treated with thyroxine to suppress thyroid stimulating hormone (TSH) after their thyroid function was tested. Ultrasound and chest x-ray scans were performed to detect recurrent and metastatic lesions. FNA and CT scan were performed if necessary for suspicious findings.

Follow-up

All patients were followed every six months after surgery. Doses of levothyroxine were adjusted at each visit if necessary. Follow-up was ceased on June 30 2015. No patient was lost to follow-up.

Statistical analysis

Statistical analysis was performed with SPSS 18.0 (IBM, Armonk, NY, USA). Continuous data were reported as the median (range) or mean \pm standard deviation (SD), and analyzed using Student *t*-test or the Wilcoxon test, as appropriate. Categorical data are presented as frequencies and analyzed using the chi-square test. The primary measurement was the LN metastasis rate. Univariate logistic regression was used to estimate the relations between LN metastasis and clinical and pathological characteristics. Since this study aimed to examine the outcomes of patients who underwent lateral neck dissection, the patients were grouped into N0/1a (no metastasis in the central neck) and N1b (metastases in the lateral neck) for univariate logistic regression analyses. For patients with lateral LN metastases, a bilogistic regression of multivariate analysis (forward) was performed, which included the predictive factors significantly associated with LN involvement in univariate analyses. Two-sided *p* values <0.05 were considered statistically significant.

Results

Characteristics of the patients

A total of 138 patients were included in this study and followed for a median of 36 (range 18–106) months. There were 33 men and 105 women (Table 1). The median age was 41 (range 18–71) years; among them, 84 (60.9%) patients were <45 years old.

Characteristics of the tumors

Tumors of 74 (53.6%) patients were located on the left side and 64 (46.4%) on the right side. Tumors of 42 (30.4%) patients were

Table 1. Clinicopathological characteristics of the patients.

		No. of patients in the category	% of patients
Gender	Male	33	23.9
	Female	105	76.1
Age	<45	84	60.9
	≥45	54	39.1
Side	Left	74	53.6
	Right	64	46.4
Location	Upper	42	30.4
	Middle	69	50.0
	Lower	27	19.6
Multifocality	Single	102	73.9
	Multiple (≥2)	36	26.1
Surgery	Total thyroidectomy	54	39.1
	Lobectomy	84	60.9
Neck dissection*	Level III–IV	90	61.6
	Level II–V	56	38.4
pT classification	T ₁	55	39.9
	T ₂	22	15.9
	T ₃	57	41.3
	T ₄	4	2.9
pN classification	N ₀	45	32.6
	N _{1a}	26	18.8
	N _{1b}	67	48.6

* Eight patients were operated on both side.

located in the upper third of the thyroid gland, in the middle third in 69 patients (50.0%), and in the lower third in 27 patients (19.6%). One hundred and two patients (73.9%) had a single lesion and 36 patients (26.1%) had two foci or more. Median tumor diameter was 14.0 mm, ranging from 1.0 to 50.0 mm.

Total thyroidectomy was performed in 54 patients (39.1%) and lobectomy in 84 patients (60.9%). Central neck dissection was routinely performed. Of the 146 lateral neck dissections performed in these 138 patients, eight patients required bilateral dissection. According to the 2012 tumor node metastasis (TNM) staging system, T1 lesions were found in 55 patients, T2 in 22 patients, T3 in 57 patients, and T4 in four patients. After surgery, 45 (32.6%), 26 (18.8%), and 67 (48.6%) patients had N0 classification, N1a classification, and N1b classification, respectively. Primary tumor size was 13.82 ± 8.71 , 13.58 ± 6.54 , and 16.54 ± 8.86 in patients with N0 classification, N1a classification, and N1b classification, respectively ($p=0.151$).

Sensitivity of intraoperative frozen section in tumor classification

Of the 138 cases, 45, 26, and 67 patients were found to have pN0 classification, pN1a classification, and pN1b classification, respectively, by postoperative pathology. All pN0 classification and pN1a classification cases were identified by frozen section analysis as well. However, a total of 12 patients had negative intraoperative frozen section results (without regional LN metastasis), but positive postoperative pathological results (with regional LN metastasis, i.e. pN1b classification). These findings indicated a false negative rate of 14.5% (12/83) (Table 2). Sensitivity and specificity of this method were 82.1% (55/67) and 85.5% (71/83), respectively; positive and negative predictive values were 100% (55/55) and 85.5% (71/83), respectively (Table 2).

Table 2. Properties of intraoperative frozen section in tumor classification.

Intraoperative frozen section results	Postoperative pathological results			
	pN0	pN1a	pN1b	Total
Negative	45	26	12	83
Positive	0	0	55	55
Total	45	26	67	138

Table 3. Lymph node metastases of each level according to the postoperative pathological examination.

	No. of patients	No. of lymph node dissections (per neck)	No. of necks with LNM (per neck)	% of lymph node metastases (%)
Level II	55	56	26	17.8
Level III	138	146	46	31.5
Level IV	138	146	53	36.3
Level V	55	56	2	1.4
Level VI	138	146	83	56.8

LNM – lymph node metastasis.

Neck dissection

Ninety (61.6%) SSND (Level III–IV) were performed in 83 patients and 56 (38.4%) MRND (Level II–V) in 55 cases. A mean of 29.4 (range 5–75) LNs and 3.4 (range 1–19) positive LNs were found per neck dissection. The rates of OLMN were 56.8% and 43.5% in the central compartment and lateral neck, respectively. The rates of metastases in Level II–VI were 17.8%, 31.5%, 36.3%, 1.4%, and 56.8%, respectively (Table 3).

Univariate analysis

In univariate analysis, lateral neck metastases were more frequent in patients with large tumors, extensive invasion, advanced T classification, and level VI LN metastasis. No relationship was seen with gender, age, tumor side, location, or multifocality (Table 4).

Multivariate analysis

All factors that were associated with lateral neck LN metastases were included in the multivariate regression analysis. In the multivariate analysis, central compartment metastasis (odds ratio (OR)=11.472, 95% confidence interval (CI) 4.533–29.037; $p<0.001$), extensive invasion (OR=2.555, 95% CI 1.365–4.783; $p=0.003$), and large tumors (OR=1.96, 95% CI 1.170–3.285; $p=0.011$) were independently and positively associated with lateral neck metastases (Table 5), indicating that these parameters are significant risk factors for lateral neck metastases.

Complications, recurrence, and prognosis

Chyle leakage was the most frequent complication (5.5%, 8/146) after lateral neck dissection. The amount of leakage in the first day ranged from 30 mL to 500 mL. All eight patients were cured with fasting and parenteral nutrition. Seven of the eight cases of chyle leakage happened in the first year of the study period. Then we improved the surgical techniques by ensuring that all lymphatic ducts in the area of the venous angle were systematically ligated and only one case of chyle leakage was observed thereafter.

Only one patient with recurrence was observed, resulting in a regional control rate of 99.3% after a median follow-up of 36 (range 18–106) months. She was in the SSND group and had Level II LN metastases 42 months after surgery. Levels II and V neck dissection were then performed. All patients were alive at their last follow-up, and the survival rate was 100%.

Discussion

Thyroid cancer is the most common endocrine cancer and has a high rate of LN metastases, but the usefulness of lateral neck dissection remains controversial. Therefore, the aim of this study was to evaluate the value of SSND in the early diagnosis and treatment of patients with cN0 thyroid cancer at high risk of metastasis in the lateral neck. Results showed that the rates of OLMN according to pathological examination

Table 4. Univariate analysis of factors associated with lateral neck metastasis.

		No. of patients with N0/1a	No. of patients with N1b	P value
Gender	Male	15	18	0.141
	Female	63	42	
Age	<45	47	37	0.866
	≥45	31	23	
Side	Left	46	28	0.151
	Right	32	32	
Location	Upper	22	20	0.688
	Middle	39	30	
	Lower	17	10	
Size	<1 cm	36	10	0.002
	1–2 cm	26	34	
	2–3 cm	14	11	
	>3 cm	2	5	
Extrathyroidal extension	Intrathyroid	17	4	0.002
	Capsule localized	38	20	
	Min. extension	22	33	
	Max. extension	1	3	
Multifocality	Unifocal	54	48	0.153
	Multifocal	24	12	
T	T1–2	53	24	0.001
	T3–4	25	36	
Level VI metastasis	Yes	26	51	<0.001
	No	52	9	

N0 – no metastases; N1a – metastases in the central compartment; N1b – metastases in the lateral neck.

Table 5. Multivariate logistic analysis of factors for the presence of lateral neck metastases.

Risk factors	P value	OR	95%CI
Level VI metastasis	<0.001	11.472	4.533–29.037
Extrathyroidal extension	0.003	2.555	1.365–4.783
Size	0.011	1.96	1.170–3.285

OR – odds ratio; 95% CI – 95% confidence interval.

after surgery were 56.8% and 43.5% in the central compartment and lateral neck, respectively. The OLNM rates of Levels II to VI were 17.8%, 31.5%, 36.3%, 1.4%, and 56.8%, respectively. In multivariate analysis, lateral neck metastases were

significantly associated with central compartment metastasis, extensive invasion, and tumor size.

Prophylactic lateral neck dissection for papillary thyroid carcinoma is controversial mainly because the prognostic value of cervical metastasis has not been determined. Nevertheless, cervical LN metastasis is not only an important factor for lateral recurrence, but also for prognosis and the occurrence of distant metastases [17–20]. According to the TNM staging system, the presence of lateral neck metastasis is classified as N1b and patients with N1b cancer and aged >45 years old are classified IV. Compared to the watch and wait approach [10,21,22], some clinicians are more proactive and perform lateral neck dissection [4,6,16,23]. Lateral neck dissection is already recommended by Japanese guidelines [24]. Ito et al. [25] performed prophylactic MRND in order to identify the risk factors for lateral neck metastases. Male gender, age >55 years old, tumor size >3 cm, and massive extra thyroid extension were risk factors for lateral neck metastasis. In addition, all recurrences in N1a patients were in the lateral compartment [6].

Historically, SSND was first used for early laryngeal or hypopharyngeal cancer, especially for localized residual disease after radio- or chemo-radiotherapy [11,12]. Recently, it was also applied to thyroid cancer for early diagnosis and treatment [7,26,27] because the results of radiological examinations and FNA guided by B-mode ultrasound were not satisfactory [28,29]. The sensitivity of ultrasound and CT for the detection of lateral neck metastases is poor (27%) [4]. Kang concluded that patients with image-based, isolated lateral Level IV involvement and no macroscopic extra nodal extension are potential candidates for limited Levels III-IV dissection [9]. SSND is associated with minimal morbidity and does not compromise oncological outcomes [7]. Since 2006, patients at high risk of lateral neck metastases are candidates for Level III–IV dissection [13]. In addition, the procedure is completed after thyroidectomy using the same incision, decreasing scarring.

Level II–V dissection is a standard procedure for thyroid cancer with confirmed cervical metastasis [21,22,30]. After the operation, the patients usually have skin numbness, shoulder movement disorders, and other complications including phrenic nerve injury, brachial plexus injury, cervical sympathetic trunk, and thoracic duct injury [21]. Therefore, Level II–V dissection is associated with significant morbidities.

The most frequently involved thyroid cancer metastasis levels are II, III, and IV [8,23,27,31,32], so compared to conventional dissection, SSND of Level III and IV might have the following advantages. First, using the same incision as thyroidectomy does not increase skin scarring for aesthetic consideration. Second, as a diagnostic method for determining N classification this avoids a second operation, therefore, SSND is likely to reduce medical costs. Third, preserving vital structures, such as the cervical plexus, transverse cervical artery, and phrenic nerve, avoids the common complications of conventional dissection.

Level VI is the most common metastatic site for thyroid cancer [33–35]. The prognostic value of the central compartment was also indeterminate because adequately powered randomized controlled trials are almost impossible [36,37]. Contrary to some opinion [38], multiple studies suggested that routine central compartment dissection not only avoids patients' unnecessary worry during follow-up, but is also better at preserving the function of lower parathyroid glands [24,33,34,39]. In this study, the rate of occult lateral neck metastases was 43.5% (60/138), similar to previous studies [4,5,16,23,26,31,40,41]. These patients received timely diagnosis and treatment, avoiding reoperation. This rate may have been higher if all patients had MRND including Levels II–V [25]. One study also found that Level II could be omitted if no positive LNs were found in Level III [8]. In our study, at least two suspicious LNs were sent for pathological examination. If metastases were confirmed, Levels II and I were dissected. Level V was not necessarily dissected if positive LNs were found during SSND. Lim et al. [32] also concluded that Level V could be omitted if no positive LN was found in Level IV. In this study, the dissection extent was consistent with the National Comprehensive Cancer Network (NCCN) guidelines [30].

In this study, the rates of occult metastases in Levels III and IV were 31.5% and 36.3%, respectively, significantly higher than that of Levels II and V (17.8%, 1.4%, respectively). The distribution was similar to previous studies [7,8,23]. As shown above, a total false negative rate of 14.5% was obtained in frozen sections, indicating that negative results with frozen sections should be interpreted with caution.

In this current study, univariate analyses showed that large primary tumors, extra thyroidal extension, advanced T classification, and central LN metastases were associated with lateral metastases. In the multivariate analysis, central compartment metastases, extra thyroidal extension, and large tumors were independent factors associated with lateral cervical metastases, in agreement with previous studies [4,6,9,17,31,39,41–43]. Level VI is the first drainage level of the thyroid gland, especially for tumors located in the lower part of the gland [44]. We routinely carry out neck dissections for the management of thyroid cancer. Compared to patients without metastasis, the risk of lateral neck metastasis in individuals with central compartment LN metastasis is increased by a mean of 11.5 times.

Extra thyroidal extension was also a risk factor for cervical LN metastasis. Ito et al. indicated that obvious external invasion, rather than minor invasion, overtly affects prognosis [43]. Although we did not clearly distinguish external and minor invasion, extra thyroidal extension is considered an overt influencing factor for lateral LN metastasis. In addition, tumor size was also found to be a crucial factor for tumor metastasis, corroborating multiple reports [6,16,17,20]. In our study, these

factors were fully taken into account during patient enrollment. In our study, no patient died during follow-up. Disease recurrence was observed in one patient at 42 months after SSND.

This study was not without limitations. It was a retrospective study performed on a small sample size from a single center. In addition, follow-up was relatively short for these patients with thyroid cancer; indeed, cervical LN metastasis and recurrence of thyroid cancer may occur even ten years after surgery, and long-term follow-up is required to fully explore the treatment effects. Therefore, additional well-designed multicenter trials are warranted to confirm these findings.

Conclusions

In conclusion, SSND of Levels III and IV could be an effective method for the early diagnosis of lateral neck metastases. Indeed, SSND allowed the detection of lateral cervical LN

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