Int J Clin Exp Pathol 2013;6(3):510-515
www.ijcep.com /ISSN:1936-2625/IJCEP1211043

Original Article

Correlation analysis on central lymph node metastasis in 276 patients with cN0 papillary thyroid carcinoma

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Received November 29, 2012; Accepted January 3, 2013; Epub February 15, 2013; Published March 1, 2013

Abstract: Objective: To explore the relationship between sex, age, capsule invasion, tumor size, tumor location, number and central lymph node metastasis. Methods: Correlation analysis was conducted on clinical data of 276 patients with cN0 papillary thyroid carcinoma who underwent central lymph node dissection. Results: There was significant difference between patients less than 45 years old and greater than or equal 45 years old ($P<0.05$), between patients with capsule invasion and without capsule invasion ($P<0.05$); there were significant differences in the central lymph node metastasis rate between group with $\Phi \leq 0.5$cm as well as $\Phi > 2$cm and the other three groups ($P<0.05$), and there was significant difference between upper pole group and middle/lower pole group ($P<0.05$) while no significant difference was found between middle pole and lower pole ($P>0.05$); there was also no significant difference in the central lymph node metastasis rate between groups with 1 tumor and greater as well as equal 2 ($P>0.05$). Conclusion: We considered the tumor located in middle and lower pole, $\Phi > 0.5$cm of tumor size, less than 45 years old and the present of capsule invasion were high risk factors of central lymph node metastasis, so we strongly recommend performing central lymph node dissection in synchronization.

Keywords: Hyroid tumors, papillary carcinoma, lymph node metastasis, neck dissection

Introduction

Thyroid carcinoma, the most common endocrine malignancy, approximately accounts for 1% of all human tumors and 1/3 of all head and neck tumors, papillary thyroid carcinoma(PTC)accounts for 80–85% of all thyroid malignancies with a reported 10-year survival of >90% [1]. Despite the excellent prognosis, cervical lymph node metastases are common, with an incidence between 40% and 90% [2] at final histological assessment. The most common sites of metastases are the central neck lymph nodes of the neck (level VI). Although, there has been no unified standard on treatment yet, an increasing number of scholars are prone to perform ipsilateral central neck lymph nodes dissection on cN0 patients with papillary thyroid carcinoma in China. The study retrospectively analyzed clinical data of cN0 PTC patients admitted into our department.

Material and methods

Clinical data

A total of 276 patients with tumor located in the lobes of thyroid gland and complete data from cN0 PTC patients who were admitted into the Department of Head and Neck Surgery, Zhejiang Cancer Hospital for first diagnosis and treatment between January 2008 and December 2010 were selected. Among those, 244 cases were unilateral lesions and 32 cases were bilateral; there were 42 males and 234 females with male/female ratio of 1:5.5, aged from 15 to 78 years old with a median age of 44.67; the medical histories ranged from 1 day to 20 years; 30 cases consulted for neck discomfort, 10 cases for hyperthyrea and 236 cases for neck mass or thyroid nodule found during medical examination.

Preoperative examination

Inclusion criteria were according to the clinical evaluation criteria of cervical lymph node pro-

posed by Kowalski et al. [3] The patients meeting the following conditions could be diagnosed as cN0 PTC: 1). no palpable enlarged lymph node in clinical examination or maximum diameter of enlarged lymph node was less than 2cm with soft texture; 2). no visible enlarged lymph node in imaging examination or the maximum diameter of enlarged lymph node was less than 1cm or the maximum diameter was 1~2cm with no central liquefaction necrosis, peripheral enhancement or disappeared fat gap adjacent to lymph node.

Surgical procedures

Unilateral thyroid lobectomy/isthmusectomy and ipsilateralcentral neck lymph nodes dissection for unilateral cN0 PTC patients while bilateral thyroid lobectomy/isthmusectomy and bilateral central neck lymph nodes dissection for bilateral cN0 PTC patients were performed. The central neck lymph nodes was Group VI lymph nodes in generally clinical grouping, including lymph nodes surrounding thyroid, pretracheal and paratracheal lymph nodes, lymph nodes prior to cricothyroid membrane, with the medial edge of carotid sheath as the lateral border, hyoid as upper border and sternal notch as lower border. The central neck lymph nodes are defined as those located within the region bordered laterally by the carotid sheath, medially by the trachea, superiorly by the hyoid bone, and inferiorly by the sternal notch. The central compartment can be subdivided into the pretracheal region (nodes located immediately anterior to the trachea) and the paratracheal region (nodes located adjacent to the trachea on either side).

Histopathology

PTC was confirmed by intraoperative frozen section and histological examination which corresponded to postoperative pathological examination. According to the UICC staging for thyroid carcinoma, 150 cases were T1N0M0, 63 cases were T1N1aM0, 9 cases were T2N0M0, 18 cases were T3N0M0 and 21 cases were T3N1aM0; 233 cases were Stage I, 5 cases were Stage II and 48 cases were Stage III.

Grouping

A total of 308 lesions were included in the group, among which, 244 cases had unilateral lesions and 32 cases had bilateral lesions. As regards to lesion side, tumor locations could be clearly identified in 271 cases and were divided into upper pole, meddle pole and lower pole groups according to the position of tumors in the gland leaves. The patients were divided into the group with $\Phi \leq 0.5$cm, group with $0.5\text{cm} < \Phi \leq 1.0$cm, group with $1.0\text{cm} < \Phi \leq 2.0$cm and group with $\Phi > 2.0$cm based on the tumor size. According to tumor numbers, they were divided into group with 1 tumor and group with greater than or equal 2.The patients were divided into male and female groups based on sex. The patients were divided into group with less than 45 years old and group with greater than or equal 45 years old according to age. The groups with capsule invasion and without capsule invasion were divided based on the presence or absence of capsule invasion. And then we compared the rate of central lymph node metastasis among groups.

Statistics

All statistical analyses were performed using SPSS for Windows version 16.0. The differences among groups were tested using chi-square criterion. A level of $P<0.05$ was taken to denote statistical significance.

Results

There was no significant difference in the central lymph node metastasis rate between male and female groups; there was significant difference in between groups with less than 45 years old and greater than or equal 45 years old and the former was significantly higher than the latter; there was significant difference in between groups with or without capsule invasion and the former was significantly higher than the latter; there was no significant difference in the central lymph node metastasis rate between groups with 1 tumor and greater than or equal 2 (**Table 1**).

The of central lymph node metastasis rate in group with $\Phi \leq 0.5$cm was significantly lower than the other three groups; it was significantly higher in group with $\Phi > 2$cm than the other three groups while there was no significant difference between groups with $0.5\text{cm} < \Phi \leq 1$cm and $1\text{cm} < \Phi \leq 2$cm, however, the central lymph metastasis rate trended significantly to increase with the increase of tumor number (**Tables 1** and **2**).

Table 1. The cases number and positive rate under different groupings. Positive rate was defined as the coincidence rate between primary tumor imaging diagnosis and pathological diagnosis or the proportion of the cases of central lymph node metastasis of other groups accounting in this group

Term		Cases number	Positive rate (%)	*P*
Sex	Female	234	35	0.501
	Male	42	40	
Age(years old)	<45	139	40	0.041
	≥45	137	30	
Capsule invasion	Absent	267	33	0.004
	Present	41	56	
Tumor number	1	275	36	0.733
	≥2	33	33	
Tumor location	Upper pole	74	26	
	Middle pole	51	47	
	Lower pole	146	40	
Tumor size	Φ≤0.5cm	58	16	
	0.5cm<Φ≤1cm	126	30	
	1cm<Φ≤2cm	86	45	
	Φ>2cm	38	66	

Table 2. The statistical analysis among groups grouped by tumor size

Tumor size	0.5cm<Φ≤1cm	1cm<Φ≤2cm	Φ>2cm
Φ≤0.5cm	0.005	0.000	0.000
0.5cm<Φ≤1cm		0.190	0.000
1cm<Φ≤2cm			0.023

There were significant differences in the central lymph node metastasis rate between groups with tumor located in upper pole and in middle as well as lower pole and the former was significantly lower than the latter while there was no significant difference in the central lymph node metastasis rate between the groups with tumor located in middle pole and lower pole (**Tables 1** and **3**).

Discussion

Papillary thyroid carcinoma (PTC), a low-grade malignancy, has relatively good prognosis and good response to surgery; however, it still may recur if the first treatment was improper. The treatment for differentiated thyroid cancer has been a subject of considerable debate over the past two decades. Currently, there has been no unified standard on the treatment of the primary tumor and cervical lymph nodes yet.

In terms of the treatment on unilateral PTC primary tumor, there are four main views: 1). ipsilateral thyroid lobectomy/ isthmusectomy; 2). ipsilateral thyroid lobectomy/ isthmusectomy plus contralateral partial thyroidectomy; 3). total thyroidectomy; 4). near-total thyroidectomy. Variety of views has their own theoretical basis. Most scholars advocate performing thyroid lobectomy/isthmusectomy on primary tumor and consider the 10-year survival rate of the surgery is similar to total thyroidectomy while long-term quality of life of patients is superior to that of near-total thyroidectomy, which is also agreed by us. Wu et al. analyzed greater than 4000 clinical data of patients with differentiated thyroid cancer who admitted into Cancer Hospital of Fudan University in the past 40 years and found that bilateral thyroid carcinoma only accounted for 4% with 91.95 of 10-year survival rate, so they maintained performing thyroid lobectomy/isthmusectomy on patients with unilateral differentiated thyroid carcinoma. In our group, the bilateral cases accounted for 11.6% in all cases which was significantly higher than that of Wu [4]. In foreign countries, total thyroidectomy, is now the accepted standard of care for the treatment for patients with PTC greater than 1 cm [5]. It trends to perform total thyroidectomy if thyroid cancer is greater than 1cm in foreign countries while we prefer ipsilateral thyroid lobectomy/ isthmusectomy in unilateral thyroid carcinoma in domestic. The paper focused on the relationship between clinical indicators andcentral lymph node metastasis as well as treatment on primary tumor.

As regards to the process of the cervical lymph node, there is no controversy in performing neck dissection on cN PTC patients while controversy exists in whether it should perform selective neck dissection on cN0 PTC patients. The role of routine central neck lymph nodes dissection (CLND) for PTC remains controversial without preoperative evidence of lymph node disease (cN0). It has generally been accepted in the past that lymph node status impacts on local recurrence rates rather than survival. This belief has recently been questioned, with the findings of a large population

Table 3. The statistical analysis among groups grouped by tumor location

Tumor location	Upper pole	Lower pole
Upper pole	0.015	0.042
Middle pole		0.196

based study showing significantly higher mortality rates for differentiated thyroid cancer involving lymph nodes [1].

All available studies on LN metastasis of PTC are in agreement that the central neck compartment is involved most frequently. Central neck lymph node metastases are often small, and very difficult to identify even with high resolution ultrasound. Choi [6] have shown that the sensitivity for detecting metastases to the central neck lymph nodess using sonography is only 40%. Vergez et al. [7], have shown that 66% of central neck lymph nodes metastases are <5 mm.

The addition of routine CLND in cN0 PTC is associated with lower postoperative Tg levels and reduces the need for reoperation in the central compartment. This finding suggests that routine CLND provides a more thorough surgical clearance of disease when combined with TT. The majority of reoperations were due to recurrence in the regional lymph nodes [8]. Lin [9] have reported a correlation between node invasion and an increased rate of local recurrence. Lundgren [1] in a nested caseecontrol study of 5123 patients with differentiated thyroid carcinoma, reported a higher mortality in the pN1 group. Noguchi S suggest neck node dissection significantly improves overall survival [10]. Currently, an increasing number of studies support routine central lymph node dissection in synchronization, even some scholars consider central lymph node as important as primary tumor [11]. The significances lie in: 1) timely lymph node dissection can improve cure rate of cN(+) PTC patients, at the same time, it can avoid overtreatment on pN0 PTC patients and reduce complications; 2) complete radical treatment of primary tumor and central lymph node dissection at one time and most of them are functional surgeries which have short operation time and little effect on function as well as appearance with small trauma; 3) during the first surgery, it has clear anatomical structure which makes for the thoroughness of cleaning; 4) if lateral cervical lymph node metastasis was found, it won't need to perform central lymph node dissection, which can reduce the damage to recurrent laryngeal nerve and parathyroid caused by postoperative adhesions and unclear as well as changed anatomical structure.(the potential benefits of a prophylactic CLND are: 1) the removal of subclinical metastatic disease with subsequent improvement in recurrence rates; 2) avoidance of reoperation in the central compartment, which may be associated with increased risks. Some authors, regard that the prognosis is not influenced by node surgery [12]. prophylactic CLND is not helpful in decreasing short-term locoregional recurrence in patients with clinically node-negative PTC,the risk of permanent hypocalcemia may increase after CLND. Hay suggest that prophylactic CLND should not be recommended in the majority of cN0 PTC patients, even though a greater incidence of subclinical LNM is expected [13].

Various factors and the staging system have been used to predict the prognosis Age, sex, tumor size, extrathyroidal extension, and lateral neck lymph node metastasis are generally accepted variables that were related to survival and local control rates [14]. Besides this, family history, multifocality, and incomplete excision were regarded as prognostic parameters. In our data, the age, tumor size, capsule invasion and tumor location were related to central lymph node metastasis while there was no statistical correlation between sex, multiple lesions and central lymph node metastasis.

Some studies have shown that the metastasis to the CLN increased when tumor size increased. Koo BS and Lim suggest that Tumor size greater than 1and 0.5 cm presented a high risk of ipsilateral CLN metastasis respectively [15, 16]. The data showed that there were significant differences in the central lymph node metastasis rate between both group with $\Phi \leq 0.5$cm as well as group with $\Phi > 2$cm and the other three groups ($P<0.05$) while there was no significant difference in the rate of central lymph node metastasis between groups with $0.5\text{cm}<\Phi \leq 1\text{cm}$ and $1\text{cm}<\Phi \leq 2\text{cm}$ ($P>0.05$), which were also confirmed in our previous study [17].

Many authors found that patients with extrathyroidal extension seemed to have higher mortal-

ity and recurrence rates than patients without that. The extrathyroidal extension itself was presumed to have a negative effect on survival and local control rates [18]. The evident extrathyroidal extension increased the rate of CLN metastasis and had an effect on the survival rate [19]. In previous data [17], there was no significant difference in the rate of central lymph node metastasis between groups with or without capsule invasion, however, there were significant differences in the rate of central lymph node metastasis between the two groups after increasing samples, $P<0.05$.

It has not been reported on grouping based on tumor location. In our study, there were significant differences in the central lymph node metastasis rate between the upper/middle pole group and the middle/lower pole group, $P<0.05$; there was no significant difference between middle pole and lower pole groups, $P>0.05$; The central lymph node metastasis rate in lower/middle pole group was significantly higher than that of upper pole group, which was also confirmed in our previous study [17]. There was no significant difference in the central lymph node metastasis rate between male and female groups; there was significant difference in the central lymph node metastasis rate between group with less than 45 years old and greater than or equal 45 years old; there was no significant difference in the central lymph node metastasis rate between groups with 1 tumor and greater than or equal 2.

Koo et al [15] believed that correlation factors affecting central lymph nodes metastasis were age, condition of thyroid capsule invasion, more than 1 cm of tumor size and lymphatic invasion. Yan et al. [20] considered correlation factors were less than 45 years old, greater than 3cm of tumor size and invaded fibrous capsule of thyroid gland while the effect of multiple lesions, tumor location and sex on the rate of central lymph node metastasis had no significant difference. In this study, the rate of central lymph node metastasis in group with tumor located in middle/the lower pole group was significantly higher than that of upper pole group; group with $\Phi \leq 0.5$cm was significantly lower than the other three groups while group with $\Phi > 2$cm was significantly higher than the other three groups. Overall, it was significant that the rate of central lymph node metastasis was increased with the increase of tumor numbers; the group with less than 45 years old was significantly higher than group with greater than or equal 45 years old in the rate of central lymph node metastasis; the group with capsule invasion was significantly higher in the rate of central lymph node metastasis than group without capsule invasion. Accordingly, we considered the tumor located in middle and lower pole, $\Phi > 0.5$cm of tumor size, less than 45 years old and the present of capsule invasion were high risk factors of central lymph node metastasis, so we strongly recommend performing central lymph node dissection in synchronization.

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