

Predictors of central lymph node metastasis in papillary thyroid cancer



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INTRODUCTION: Papillary thyroid carcinoma (PTC) is the most common malignancy of the thyroid gland and although PTC has excellent prognosis, central lymph node (CLN) metastases are not uncommon. Studies have shown that CLN metastases are associated with an increased recurrence rate. The necessity for prophylactic CLN dissection (pCCND) in clinical lymph node negative (cN0) patients remains controversial. The aim of this study was to determine predictors of CLN metastases in cN0 PTC patients who underwent prophylactic CLN dissection.

MATERIALS AND METHODS: The medical charts of 97 patients with cN0 PTC who had undergone total thyroidectomy (TT) and pCCND were evaluated retrospectively. The relationship between CLN metastases and risk factors were analyzed.

RESULTS: CLN metastases were found in 32 (32.9%) patients. Univariate analysis showed that CLN metastases were significantly associated with male sex and tumor size. In multivariate analysis, tumor size greater than 0.7 cm and male sex were independent predictors for CLN metastases.

DISCUSSION: Although oncological benefits of the pCCND in cN0 PTC patients remain controversial, tumor size greater than 0.7 cm and male gender may be possible indicators of central lymph node metastasis.

KEY WORDS: Central lymph node metastasis, Central lymph node dissection, Papillary Thyroid Cancer, Total thyroidectomy

Introduction

Papillary thyroid carcinoma (PTC) is the most common malignancy of the thyroid gland. Patients with PTC have an excellent prognosis, with 10-year survival rates exceeding 90%¹. Total thyroidectomy (TT) is generally accepted as the procedure of choice for all PTC exceeding 10 mm in diameter².

Despite the excellent prognosis, cervical lymph node metastases are common, occurring in 20 to 50% of patients. Micrometastases are even more common and may be found in 90% of patients. The most common sites of metastases are the central neck lymph nodes (CLN) (level VI)²⁻⁶.

Currently, it is widely accepted that CLN dissection is necessary for clinical lymph node positive patients, while the need for pCCND in clinical lymph node negative (cN0) patients remains controversial⁶. In spite of the controversy concerning treatment, an increasing number of authors propose to perform pCCND, is supported by evidence of reduced local recurrence rates². On the other hand, potential increased risk of hypoparathyroidism is associated with pCCND^{7,8}.

The aim of this retrospective study was to evaluate the candidate predictive factors of CLN metastasis, in order to make a more appropriate selection of patients for pCCND.

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ABBREVIATIONS

PTC: Papillary thyroid carcinoma
 CLN: Central lymph node
 TT: Total thyroidectomy
 US: Ultrasound
 pCCND: Prophylactic CLN dissection
 FNAC: Fine-needle aspiration cytology

Material and Methods

This was a retrospective cohort study. We reviewed the medical records of 97 patients with PTC who had undergone TT and pCCND between April 2010 and September 2013. All patients were identified from the hospital records, aided by a computer search. For each patient, a preoperative diagnosis of PTC had been obtained by ultrasound (US)-guided fine-needle aspiration cytology (FNAC) or intraoperatively. The preoperative work-up consisted of free thyroid hormone (FT3, FT4), thyrotropin (TSH), Tg and anti-Tg antibody (TgAb) measurements, and high resolution US of the neck by a skilled sonographer. A pre- and postoperative fibrolaryngoscopy was performed in all patients. Patient demographics and postoperative complications were recorded, including neck hematomas, transient or permanent hypoparathyroidism, and transient or permanent vocal cord palsy by postoperative surveillance. Our work is fully compliant with the STROBE criteria ⁹.

Independent variable

The following variables were used to analyze risk factors of CLN metastases: sex, age at initial treatment, tumor size, and tumor location in thyroid lobe, US features of the nodule, preoperative Tg, TgAb and TSH value extrathyroid extension, capsular invasion, multifocality, presence of hashimoto thyroiditis. Tumor size, hashimoto thyroiditis, capsular invasion and multifocality were all confirmed by pathological findings. Extrathyroid extension was defined as a tumor extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve based on intraoperative findings, and multifocality was defined as more than 1 tumor lesion in the thyroid. Tumor size in multifocal cases was measured according to maximum diameter of the primary tumor. T stage was decided according to the 2010 AJCC staging system.

Dependent variable

Presence of metastatic CLN was the primary end point.

STATISTICAL ANALYSIS

Shapiro-Wilk test was used for assessing normality. If continuous data nonnormally distributed presented as median value (interquartile range) otherwise presented as mean±SD. Differences between nonnormally distributed data was analyzed by means Mann Whitney U test. Differences between normally distributed data were analyzed by means of Student t test. Categorical variables were analyzed with χ^2 or Fischers exact test.

Multivariate analysis was performed using binary logistic regression for variables with a p value of ≤ 0.2 on univariate analysis. The presence of the metastases was the dependent variable, whereas clinical and pathologic variables were considered as numerical or categorical covariates.

Results

A total of 97 patients with PTC were included in this study, among whom 76 (78.4%) were female and 21(21.6%) were male. Patient age at time of initial treatment ranged from 18 to 76 years (45.3 ± 12.5). The median size of the primary tumor was 1.45 cm (IQR:0.6-1.2). Multifocal lesions were found in 33 (34.02%) patients. Capsular invasion was found in 46 (47.4%) patients. The number of patients in T1/T2/T3/T4 stages were 37 (38.1%), 39 (40.2%), 16 (16.4%), and 7 (5.3%), respectively. Hashimoto thyroiditis was detected in 41 (42.2%) patients. CLN metastases were found in 32 (32.9%) patients.

The median numbers of total and positive lymph nodes collected during CLN dissection were 7(2-12) and 0 (0-1) respectively. Patient's demographic data is summarized in Table I.

Univariate analysis showed that CLN metastases were significantly associated with male sex and tumor size. ROC curve analysis was used to identify cutoff value for tumor size. Optimal cutoff value was 0.7 cm after ROC curve analyses.

In multivariate analysis, tumor size >0.7 cm, and male sex were independent predictors for CLN metastases (Table II, III).

SURGICAL MORBIDITY

Permanent hypocalcemia was found in 8 (8.2 %) patients and permanent nerve injury was observed in 3(3.09%) patients.

Discussion

The question of whether a pCCND should be performed in all cN0 PTC patients, is still a matter of discussion ¹⁰.

TABLE I - Clinicopathological characteristics of patients

Characteristics	Values
Number of patients	97
Gender (Male/Female) (%)	21/76 (21.6/78.4)
Age (years), mean ±SD (range)	45.3±12.5 (18-76)
Tumor size (cm), median (IQR)	1.45 (0.6 - 1.2)
Solitary lesion, n (%)	64 (66)
Multifocal lesions, n (%)	33 (34)
Extrathyroidal extension, n (%)	2(2.06)
T1/T2/T3/T4, n (%)	37/39/16/7(38.1, 40.2, 16.4, 5.3)
TSH (mIU/L), mean ±SD (range)	1.99±1.66 (0.02–14.25)
Tg level median(IQR)	91.02 (34.90-252.88)
Anti Tg median(IQR)	20.93 (12.8-187.30)
Hashimoto's thyroiditis, n (%)	41 (42.2)
Central lymph node metastasis, n (%)	32 (32.9)
Number of dissected lymph nodes, median (IQR)	7 (2–12)
Number of metastatic lymph nodes, median (IQR)	0 (0–1)

IQR: interquartile range, TSH: Thyrotropin, Tg: Thyroglobulin

TABLE II - Clinicopathological variables and CLN metastases.

Variables	CLN metastases number (%)	p value
Gender		<0.001
Male	15 of 21 (71.4)	
Female	8 of 76 (10.5)	
Tumor size (cm)		<0.001
≤0.7	2 of 34 (5.8)	
>0.7	30 of 63 (47.6)	

CLN: Central lymph node

Postoperative complications such as hypocalcemia¹¹ and recurrent laryngeal nerve injury may increase with pCCND^{7,12}.

The presence of CLN metastases has been reported to be associated with a higher risk of recurrence, and there are studies showing that their surgical removal improves survival rates^{13,14}.

The main reason preventing us from initiating prophylactic CLND is the potential postoperative complications. Also; the need for reoperation in the central compartment for the treatment of the recurrence would lead to severe complications. Therefore, it is reasonable to perform selective pCCND if the presence of CLN metastases can be predicted preoperatively¹⁵.

In our study, CLN metastases were detected in 33% of cN0 PTC patients; this finding was a little different from previous studies, which differ between 42.9% to 51%¹⁵⁻¹⁸.

Clinical assessment based on intraoperative inspection and palpation had poor sensitivity and specificity in identifying metastatic CLN, regardless of the level of experience of the surgeon¹⁹.

Recently, several studies have described clinicopathological factors associated with CLN metastases in patients with PTC, but results from those studies were not consistent¹⁸. In addition, there has been no uniform evaluation criterion for CLN metastases. In our study, tumor size greater than 0.7cm and male sex were independent predictors for CLN metastases.

Recent evidences have focused on the BRAF^{V600E} mutation as a novel prognostic marker that may be useful in stratifying the risk of CLN metastases. Some studies have established a strong association of BRAF^{V600E} mutation with aggressive clinicopathologic characteristics of primary PTC, including extrathyroidal extension, histological subtypes with a poorer prognosis and advanced disease stages, as well as disease persistence/recurrence. Yang et al. reported BRAF^{V600E} mutation in fine-needle aspiration biopsy specimens was found in 42.6% of patients with PTC, significantly associated with CLN metastases and an independent predictor of CLN metastases²⁰.

A meta-analysis of thirty studies shows that 992 male patients, 512 (51.6%) were BRAF mutation positive, and

Table III - Multivariate analysis for risk factors of central lymph node metastasis.

Variables	β (SE)	P value	Exp (β)	95% CI of exp (β)
Gender (male vs. female)	1.119 (0.262)	0.001	3.316	1.872 - 5.641
Size (>0.7cm vs. ≤0.7cm)	2.014 (0.791)	0.001	2.555	1.590 - 35.339

2046 (48.2%) of 4246 female patients were BRAF mutation positive. There was a significant association between BRAF mutation and male gender ²¹.

Several studies have also shown that tumor size was significantly associated with CLN metastases, but the cut-off points were different. Liang et al. and Ito et al. ^{18,22} reported tumor size greater than 2 cm to be the strongest predictor of CLN metastases in PTC, Bozec et al. ²³ Choi et al. ²⁴ and Koo et al. ²⁵ reported tumor size greater than 1 cm to be associated with CLN metastases in PTC.

A study by Delogu D et al. ¹ evaluated patients who had undergone total thyroidectomy and prophylactic central lymph node dissection for papillary thyroid cancer that were smaller than 4cm, without cervical lymphadenopathy. They reported that prophylactic central lymph node dissection could be avoided in patients with T1 or T2 papillary thyroid cancer unless the disease was multifocal.

Patients under 45 years of age exhibit a statistically significant association with CLN metastases in previous studies ²⁵. However, in our study there was no association between age and CLN metastases. Also preoperative TSH level was not risk factor in our study, which was also consistent with previous studies ²⁵.

There is no consensus about tumor localization and CLN metastases. In contrast to Liang et al. ¹⁸, Wang et al. ²⁶ found an association between tumor localization and CLN metastases. Multifocality was not an independent predictor of CLN metastases in our study, which is consistent with previous reports ¹⁸. Although other studies have shown extrathyroidal extension to be a risk factor for CLN metastases ^{16,26} this was not a finding in our study.

Male gender, tumor size, extracapsular spread, lateral lymph node metastasis and BRAF^{V600E} mutation were found to be independent predictors of CLN metastases for micro PTC in other studies ²⁰.

A significantly higher incidence of transient hypocalcemia following TT and pCCND versus TT alone has been confirmed ⁷. However, the addition of pCCND did not result in a significant increase in the incidence of permanent complications. The reported permanent hypocalcemia rates vary between 0% to 11.4% and permanent nerve injury vary between 0% to 3.6% ^{27,28}.

Our results should be interpreted within the context of the study limitations. First, our study was an observational cohort study, and prognosis was not investigated. Second, our study population was from a single center. Thus, multicenter research and long-term follow-up are needed to better understand the risk factors and the significance of pCCND.

A wider use of immunocytochemical and genetic markers could prove useful in better defining the high-risk population. For example, patients with RET/PTC and BRAF oncogene expression have a higher rate of CLN metastases, and this could constitute a useful factor to consider in the

future. The development of techniques for the intraoperative identification of metastatic lymph nodes could also help the surgeon in this difficult choice ^{2,21}.

In conclusion, tumor size greater than 0.7cm and male gender may be possible indicators of central lymph node metastasis and these patients are good candidates for pCCND.

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