

Clinico-Pathologic Features of Papillary Thyroid Cancer Patients with Central Lymph Node Metastasis: A Single Institution Study

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Objectives: This study aims to ascertain if there is an association between the clinico-pathologic features and characteristics of papillary thyroid cancer patients and the occurrence of central lymph node metastasis. The authors specifically looked at age, gender, tumor size, tumor multicentricity and extracapsular invasion.

Methods: Patients admitted at the Department of Surgery, University of Santo Tomas Hospital between January 2006 and December 2010 who underwent total thyroidectomy with Central Lymph Node Dissection (CLND) for papillary thyroid carcinoma were included in the study after fulfilling the exclusion/inclusion criteria. Descriptive statistics related to patient demographics and tumor characteristics were applied using Pearson chi-square, independent T-test and univariate and multivariate analysis using binary logistic regression.

Results: Out of 47 patients, 27 patients have positive pathologic Central Lymph Node (CLN) metastasis (57.4%). On univariate analysis, only gender had a significant effect on the occurrence of central lymph node metastasis. Age, capsular invasion, multicentricity and tumor size on the other hand, had no significant correlation with the presence of CLN metastasis. On multivariate analysis, none of the defined parameters are independent predictors of CLN metastasis.

Conclusion: Based on the patient population included in this study, gender is the only demographic characteristic that has a significant effect on the occurrence of CLN metastasis among patients with papillary thyroid carcinoma. Other demographic data and tumor features analyzed in this study had no significant association with the occurrence of positive cervical lymph nodes.

Key words: papillary thyroid cancer, central lymph node dissection, lymph node metastasis

Differentiated thyroid cancer (DTC) has a rapidly increasing incidence and is the most common endocrine malignancy accounting for almost 95 percent of all endocrine cancers, but with a generally favorable survival. Among the differentiated thyroid cancers, papillary

carcinomas (PTC) are known to metastasize through intrathyroidal lymphatic channels and involve regional lymph nodes. As much as 80 percent of patients with papillary thyroid cancer are later detected to have microscopic regional lymph node metastasis, however, only about 35 percent have cervical or mediastinal node metastases detected at the time of initial surgery. Lymph nodes typically involved in PTC are level VI (central compartment), levels II, III and IV along the internal jugular vein, and the level V posterior neck lymph nodes.¹

With regard to the extent of surgery, debate has shifted from whether to perform total thyroidectomy alone or to include prophylactic management of central (level VI) lymph nodes without evidence of involvement preoperatively.² The National Comprehensive Cancer Network (NCCN) recommends central neck dissection only in the presence of grossly positive metastases. This topic remains controversial, since some studies show survival benefit of such prophylactic procedure, however further studies are recommended. Although there is currently a trend toward more aggressive surgical therapy, including prophylactic CLND, complications such as hypoparathyroidism, and recurrent laryngeal nerve injury hinder surgeons in performing such procedure in all patients with DTC.³

Argument in favor of prophylactic CLND fall into several categories, it may decrease recurrence and mortality rates, improve accuracy of staging, achieve low or undetectable thyroglobulin levels, and facilitate RAI treatment and avoidance of reoperative surgery.²

The major argument against prophylactic CLND is a possibly increased risk of operative complications, and the concern that overtreatment or over-surgery would lead to a higher rate of debilitating complications, such as permanent hypoparathyroidism and nerve injury.²

In light of these arguments, it would be very important to determine the factors that could predict the risk for central node metastases. Hence, in this study, the authors aimed to determine which demographic and tumor characteristics are correlated with CLN metastases.

The study's objective was to identify demographic characteristics and tumor characteristics associated with central lymph node metastases.

Methods

Population and Sample

This study included all patients admitted at the UST Hospital between January 2006 to December 2010, who underwent total thyroidectomy with CLND for papillary thyroid carcinoma. The following clinico-pathologic parameters: age, sex, tumor size, extracapsular invasion and multicentricity were determined for each patient. All patients are diagnosed with papillary thyroid carcinoma preoperatively by FNAB. Not all patients had preoperative ultrasound. All thyroid surgeries were elective cases and performed by 4th and 5th year General Surgery residents. Specimens were properly labelled and sent immediately to pathology.

Exclusion Criteria

Excluded in the study were patients who had prior radioactive ablation therapy, poorly or undifferentiated carcinomas, and patients with other primary malignancies or tumor recurrence.

Statistical Analysis

Descriptive statistics related to patient demographics and tumor characteristics were computed using Pearson

chi-square, Independent T-test and multivariate analysis using binary logistic regression. T-test statistical analysis was used to determine the association of between CLN metastasis and continuous variables (age, tumor size) and Pearson chi-square test on the other hand was utilized to determine significant difference between categorical parameters (multicentricity and extracapsular invasion). A P value of <0.05 indicated statistical significance. Multivariate analysis was done using binary logistic regression. All statistical analyses were performed using SPSS version 17.

Results

Between January 2006 and December 2010, there were 47 patients who underwent total thyroidectomy with prophylactic central lymph node dissection. This population included 27 (57.4%) who were positive for lymph node metastasis. The patient demographics and tumor characteristics are presented in Table 1. Patients with positive CLN metastasis were predominantly <45 years of age (51.85%) and majority of them were females (74%). With regards to tumor size, more than half of patients with positive LN status were in the range of 2-4cm (59.3%), almost one-third (29.6%) were <2cm. In terms of multicentricity, patients are almost equally distributed. For extracapsular invasion, 16 (59.2%) had no invasion compared to the remaining 10 patients who showed evidence of extracapsular spread.

Out of the 47 patients, 27 showed positive CLN metastasis (57.4%). On univariate analysis, there was a significant difference in CLN metastasis among female patients compared to male subjects with a P-value of 0.01. Age, capsular invasion, multicentricity and tumor size had no significant effect on the presence of CLN metastasis among patients who underwent total thyroidectomy with prophylactic CLN dissection. Table 2 shows the results of univariate analysis.

Multivariate analysis was performed thru logistic regression, however all computed P values were more than 0.10, hence, among the parameters analyzed, none were independent predictors of CLN metastasis. With the current data presented, none are independent predictors of CLN metastasis in papillary thyroid cancer patients.

Table 1. Patient demographic and pathologic features (N=32)

Demographic Data			
	All (N=47)	Positive CLN(+) n=27	Negative CLN(-) n=20
Age			
<45	26 (55.3%)	14 (51.85%)	12 (60%)
>45	21 (44.68%)	13 (48.14%)	8 (40%)
Gender			
Male	7 (14.9%)	6 (22.2%)	1 (5%)
Female	40 (87.23)	21 (77.7%)	19 (95%)
Tumor Characteristics			
	All (N=47)	Positive CLN(+) n=27	Negative CLN(-) n=20
Size			
<2cm	16 (34%)	8 (29.6%)	8 (40%)
2-4cm	27 (57.4%)	16 (59.3%)	11 (55%)
>4cm	4 (8.5%)	3 (11.1%)	1 (5%)
Multicentricity			
Yes	22 (46.8%)	14 (51.8%)	8 (40%)
No	25 (53.1%)	13 (48.14%)	12 (60%)
Extracapsular invasion			
Yes	11 (23.4%)	10 (37%)	1 (5%)
No	23 (48.9%)	16 (59.2%)	19 (95%)

Discussion

Thyroid cancer is relatively rare accounting for only 1% of all cancers. The most common type is the well-differentiated papillary thyroid carcinoma which represents 75 to 85 percent of thyroid cancer cases.⁴ Thyroid papillary carcinomas can be aggressive and metastasize through intrathyroidal lymphatic channels to form multifocal tumors and involve regional lymph nodes. In the literature, clinically detectable regional lymph node metastases are more common in children approximately 50 percent than adults.⁵ However, in this study, age was not an identifiable risk factor. Female gender, on the other hand, showed a significant result on univariate analysis in terms of CLN metastasis.

The incidence of nodal metastases in adults depends upon the extent of surgery. Among patients who undergo MRND up to 80 percent have lymph node metastases; one half has microscopic involvement only. Invasion of either the thyroid capsule or a lymph node capsule into surrounding soft tissue has been reported in 5- 35 percent of surgical specimens, where as vascular invasion is seen in only about 5 to 10 percent.⁶ There is considerable debate about what constitutes appropriate management of papillary thyroid cancer (PTC), including when and when not to perform central lymph node

Table 2. Demographic and tumor characteristics of patients who underwent total thyroidectomy with prophylactic CLN dissection on univariate analysis (Chi-square and T-test).

Characteristics		Positive CLN	Negative CLN	P-value
Age	<45	14	12	0.193
	>45	13	8	
Gender	Female	20	19	0.010
	Male	7	1	
Multicentricity	Yes	14	8	0.283
	No	13	12	
Extracapsular invasion	Yes	10	1	0.104
	No	16	19	
Tumor size	<2cm	8	8	0.695
	2-4cm	16	11	
	>4cm	3	1	

dissection. Disagreement continues, in part, because of the lack of prospective randomized trials that may aid in decision making in these cases. Complications of hypoparathyroidism and recurrent laryngeal nerve injury are the primary reasons why not all surgeons advocate such prophylactic surgery in all patients. The American Thyroid Association recommends that a routine LN (level VI) dissection should be considered for all patients with papillary cancer, but the benefits are controversial, and there is no conclusive evidence that routine CND reduces recurrence and mortality. The ATA classifies this recommendation at level B. The rationale for prophylactic CLND is based on 2 assumptions: 1) that patients with PTC have high rates of metastasis, and 2) regional recurrence in the central compartment in the neck.

Regional lymph node metastases are present at the time of diagnosis in 20 to 90 percent of patients with papillary carcinoma and a lesser proportion of patients with other histotypes. In many cases, these lymph nodes do not appear abnormal to inspection.³ Bilateral central (compartment VI) node dissection may improve survival (compared to historic controls) and reduce the risk for nodal recurrence. This central compartment dissection can be achieved with low morbidity in experienced hands.⁷

Even after thyroidectomy there is still 15-30 percent of chance for recurrence and 33-50 percent of these patients who develop recurrence from papillary thyroid cancer die.⁸ Almost 90 percent of these recurrences are in the cervical lymph nodes-surgical excision of the recurrence provides the best opportunity for cure.⁸

Currently, bilateral central neck lymph node removal is recommended due to the high incidence of recurrence because of microscopic metastases that are not identified during operation. Studies show that doing routine central neck lymph node dissection increases the risk for hypoparathyroidism. In a study by Shen WT, et al.⁹ where complications of reoperative and initial dissection of central lymph node were compared, it was stated that the procedures bring about complications such as temporary hypocalcemia, permanent hypoparathyroidism, temporary recurrent laryngeal nerve paresis and also permanent recurrent laryngeal nerve paresis. These complications are present

but of low percentage having a highest incidence of 12% and lowest of 0%.

Currently, the area of most controversial management is the utilization of prophylactic central lymph node dissection. Prophylactic central lymph node dissection is the removal of lymph nodes that appear normal by palpation and imaging studies done preoperatively and intraoperatively. Therapeutic dissection on the other hand is the removal of lymph nodes that likely contains metastatic disease by palpation and also by imaging studies.

It was proposed that a strategy to avoid prophylactic dissection is to evaluate the central compartment for metastases and rather than prophylactic dissection, do a therapeutic dissection instead; however, the central compartment lymph nodes cannot be fully assessed by either preoperative ultrasound or also intraoperative examination. This assessment strategy cannot fully replace prophylactic lymph node dissection due to low reliability in the capability to identify nodal metastasis. Currently, there is still no prospective, randomized data that exist to explain the effect of central lymph node dissection on recurrence or disease specific mortality in papillary thyroid cancer.

In this study, future guidelines and recommendations for routine prophylactic lymph node dissection in all diagnosed papillary thyroid cancer patients can be established in our institution. Identifying patients that are high risk for metastasis and knowing the incidence as well, would aid surgeons in deciding patients who would benefit from CLND.

Conclusion

In conclusion, on univariate analysis, patient's gender was the only demographic characteristic that would have a significant effect on the occurrence of CLN metastasis. Patient's age as well as tumor multicentricity, extracapsular invasion and tumor size had no significant effect on lymph node metastasis and cannot be classified as independent clinico-pathologic features of the disease. On multivariate analysis, none of the measured parameters were independent predictors of CLN metastasis in papillary thyroid cancer patients.

Currently, no conclusive evidence exists to indicate that a prophylactic CLND for patients with PTC with negative lymph nodes have a beneficial effect on recurrence or overall survival, however it would be of great value in identifying patients predisposed to the development of CLN metastasis.

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