Negative Prognostic Implication of Fibrotic change in Papillary Thyroid Cancer

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ABSTRACT

Purpose
Lymph node metastasis in papillary thyroid cancer (PTC) occurs 40-60%. Extrathyroidal extension and large tumor size are most reliable predicting factors for central lymph node metastasis whose prognostic value is controversial. In this study, we evaluated the relationship between a specific finding of primary tumor in the thyroid, fibrosis, and negative prognostic factors.

Materials and Methods
We reviewed the patients who underwent total thyroidectomy and central lymph node (CLN) dissection with or without lateral lymph node dissection (LND) for PTC, from January to December, 2011. We defined (+) finding when the degree of fibrosis comprises 10% or more of the primary tumor. Correlation between degree of fibrosis and negative prognostic factors, including age, gender, tumor size, extrathyroidal extension (ETE), number of CLN metastasis, and lateral cervical lymph node metastasis (LCLNM), was analyzed.

Results
Of the 481 patients, fibrosis (+) group includes 387 patients (80.5%). On the chi-square test, age, gender, tumor size, and LCLNM were not correlated with fibrosis. ETE (+) group comprised of higher rate of fibrosis (+) group (90.4%) compared to ETE (-) group (64.9%, $p < 0.001$). CLN metastasis (+) comprised of higher rate of fibrosis (+) group (84.6%) compared to CLN metastasis (-) group (76.5%, $p = 0.017$). On the multivariate analysis, ETE was a significant risk factor of fibrosis (odds ratio = 2.545, $p < 0.001$, confidence interval from 1.775 to 3.649).

Conclusions
To Fibrosis in PTC can be a risk factor of extrathyroidal extension, a negative prognostic factor. This suggests that the behavior of fibrotic tumor is, possibly, more aggressive than non-fibrotic tumor.

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INTRODUCTION

Although there is no definite standard for determining therapeutic modality, more aggressive treatment is recommended in high risk patients in papillary thyroid cancer (PTC).Prognostic factors of PTC contains age, tumor size, multifocality, histologic variant, extrathyroidal extension, and lymph node metastasis. Among them**, lymph node metastasis and extrathyroidal extension (ETE)** are representative clinicopathological prognostic factors of PTC.

Spread of primary tumor and prognosis are related to various types of **histopathologic findings** in other types of cancer. One of them is **fibrosis**, which is related to poor prognosis in hepatocellular carcinoma, gastric cancer, and ovarian cancer. However, clinical implication of fibrotic change in PTC is still unknown. In this study, we found the **distribution of fibrotic change** in PTC and analyzed **relationship between fibrotic change and the poor prognostic factors**, including tumor size, extrathyroidal extension, as well as, lymph node metastasis.

METHODS AND MATERIALS

- Study design: cross-sectional study after IRB approvement
- Enrolled patients: 481
- Operation: total thyroidectomy + central lymph node (CLN) dissection ± lateral lymph node dissection
- Prognostic factors: age, gender, tumor size, ETE, (number of) CLN metastasis, and lateral cervical lymph node metastasis (LCLNM)
- Pathology review: D.H. Shin (faculty member of the institute)

Fibrotic change (+): proportion of fibrotic stroma **> 10%**

- Statistical analysis: linear regression test, Student's *t*-tes, chi-square test, multiple logistic regression test

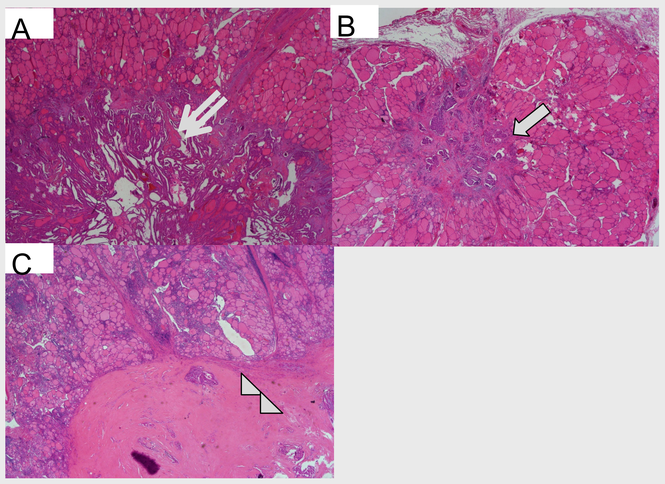
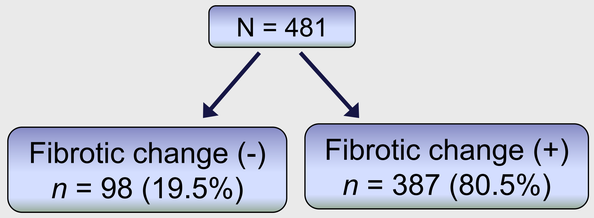


Fig. 1.
Representative histologic findings of fibrotic change in primary papillary thyroid cancer. (A) Tumor cells with a little fibrotic stroma (<10%) are surrounded by normal glandular structure. (B) Tumor cell nest (thick arrow)consists of fibrotic stroma (10-50%). (C) Dense fibrotic stroma (arrow head) infiltrates glands and distorted structure (>50%).

RESULTS



Clinical variables		*n* (%)
Age	≤45 years	194 (40.2)
	>45 years	287 (59.8)
Gender	Male	73 (15.2)
	Female	408 (84.8)
Tumor size	≤ 1 cm	352 (73.3)
	> 1 cm	129 (26.7)
Extrathyroidal extension	-	187 (39.0)
	+	293 (61.0)
CLNM	-	247 (51.5)
	+	233 (48.5)
LCLNM	-	435 (90.6)
	+	45 (9.4)

Table 1.
Demographic findings of enrolled patients.

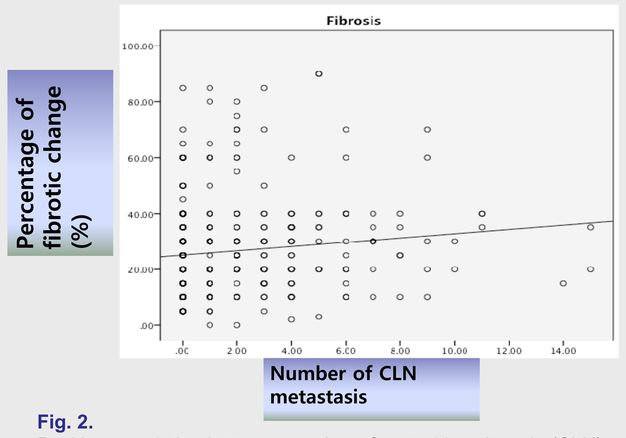


Fig. 2.
Positive correlation between number of central lymph node (CLN) metastasis and proportion of fibrotic change in papillary thyroid cancer on linear regression test (Y = 0.761 * X + 25.118, *P* = 0.008).

Clinical variables		Patients with Fibrotic change (%)	P-value
Age	≤45 years	153 (79.3)	0.065
	>45 years	246 (85.7)	
Gender	Male	58 (79.5)	0.363
	Female	341 (83.8)	
Tumor size	≤ 1 cm	21 (27.7)	0.012
	> 1 cm	18 (57.1)	
ETE	-	126 (67.4)	< 0.001
	+	274 (93.2)	
CLNM	-	195 (78.9)	0.012
	+	204 (87.6)	
LCLNM	-	360 (82.8)	0.505
	+	39 (86.7)	

Table 2. Univariate analysis to determine the significant relationship between fibrotic change and clinical variables s (Chi-square test)

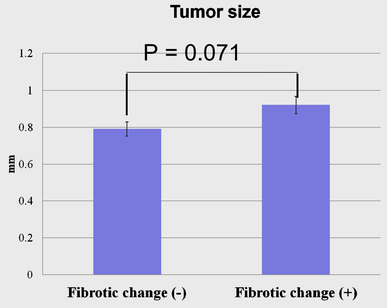


Fig. 3.
Mean size of the tumor with fibrotic change is likely to be larger than that without fibrotic change (Student's *t*-test)

Clinical variables	*P*-value	Odds Ratio	CI (95%)	
			Lower	Upper
Age	0.917	0.361	0.130	0.838
Tumor size	0.208	3.861	1.521	10.492
CLN metastasis	0.306	1.491	1.303	4.793
ETE	0.000	2.545	1.775	3.649

Table 3. Multivariate analysis to determine relationship between fibrotic change and clinical variables (Binary logistic regression analysis)

DISCUSSION

Histologic findings are related to the prognosis in other types of cancer. In PTC, there have been rare report revealing correlation between prognosis and histologic pattern. **Fibrosis** is one of histological change found in malignant tumor and it results from tissue damage or trauma and shows **excessive deposition of connective tissue** such as collagen and blood vessel. Fibroblasts in healthy adult lung are quisecent, synthesizing little collagen, yet during fibrosis they activate becoming key producers of ECM compoenents, such as collagen and fibronectin. **During fibrosis**, procollagen I is modified (crosslinking) in the extracellular space to create an insoluble fibrotic matrix of collagen fibers. **Collagen I** plays a key role in metastatic microenvironment and affect poor prognosis in breast cancer. **Secreted material or induced signals** during fibrotic change are related to metastatic progression. Tissue fibrosis comprises increased matrix deposition and remodeling which **change microenvironment** and enhance pathogenic signaling pathway related to metastasis. Lysyl oxidase (LOX)-mediated crosslinking of collagen I a the primary tumor site has already been implicated in **cell invasion and malignant progression**. In PTC, similar process may induce fibrotic change and extrathyroidal extension in primary lesion.

CONCLUSIONS

In conclusion, fibrosis in PTC can be a **risk factor of extrathyroidal extension**, a negative prognostic factor. This suggests that the **behavior of fibrotic tumor** is, possibly, **more aggressive** than non-fibrotic tumor.

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