Can ultrasonography be a surrogate marker for predicting clinical outcome of a patient with conventional papillary thyroid cancer?

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Can ultrasonography be a surrogate marker for predicting clinical outcome of a patient with conventional papillary thyroid cancer?

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ABSTRACT

Can ultrasonography be a surrogate marker for predicting clinical outcome of a patient with conventional papillary thyroid cancer?

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Background: Ultrasonography (US) features such as ill-defined margin and microcalcification were reported to be associated with recurrence. We investigated whether if US features as well as clinicopathologic factors can be a surrogate marker in predicting clinical outcome of a patient with conventional papillary thyroid carcinoma (PTC) in a relatively large sample data.

Methods: This retrospective study included 553 patients diagnosed with conventional PTC. Patient's clinical records, US and clinicopathologic features were reviewed. Patients were followed to observe recurrence (mean period of 67.6 months). Multivariable Cox proportional hazards regression model was used to identify the effect of the variable factors on tumor recurrence.

Results: Of 553 patients, 45 (8.1%) were confirmed to have tumor recurrence within the follow-up periods. Independent predictors of recurrence were male gender, tumor size, the presence of lateral LN metastasis, and not well-circumscribed margins, and taller than wide shape on US. Among the independent predictors, presence of lateral LN metastasis was the highest risk factor calculated for recurrence (HR=4.038) followed by taller than wide shape (HR=2.382) and not well-circumscribed margin (HR=2.314) on US.

Conclusions: Not well-circumscribed margin and taller than wide shape on US can be used as a surrogate marker for predicting clinical outcome of a patient with conventional PTC along with clinicopathologic factors such as the presence of lateral LN metastasis, male gender, and tumor size.

Key words : papillary thyroid carcinoma, ultrasonography, cystic thyroid cancer

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I. INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy worldwide, and most patients with PTC have shown excellent prognosis.[1] However, locoregional recurrence is common.[2,3] There have been several clinical factors such as patient age, male gender, tumor size, tumor grade or differentiation, presence of local invasion, and regional or distant metastases, and molecular factors, such as $BRAF^{V600E}$ mutation, which may be known to be associated with poor prognostic outcome of PTC.[4-11]

Some ultrasonography (US) features such as ill-defined margin and microcalcification can be associated with recurrence of PTMC.[12] On the other hand, cystic PTC is known to have favorable prognosis and has been classified as a subset of the encapsulated variant of PTC.[13] In this study, we investigated whether US features as well as clinicopathologic factors can be a surrogate marker in predicting clinical outcome of a patient with conventional papillary thyroid carcinoma in a relatively large sample data.

II. MATERIALS AND METHODS

The institutional review board of our institution approved of this

retrospective study, and required neither patient approval nor informed consent for review of images and patient records.

1. Patients

Between the periods of January 2003 to August 2004, a total of 923 consecutive patients underwent surgery for thyroid cancer at our institution. Among them, 888 patients were pathologically confirmed as conventional PTC. Patients were excluded from this study due to the following reasons: 1) no available preoperative US images (n=176), 2) coexisting cancer of other primary site which can affect prognosis and follow-up studies of the patient (n=39), 3) previous history of thyroid surgery due to thyroid cancer or recurred lesions (n=98), 4) pathology reports not available or insufficient (n=11), or 5) follow-up loss after surgery without any available clinical records (n=11). The largest lesion was selected in patients with multiple PTC to avoid data clustering. Finally, this study included 553 thyroid nodules in 553 patients. Seventy of them were men (mean age, 45.6 years; range, 22-74 years) and 483 were women (mean age, 45.9 years; range, 17 - 79 years). Mean age of the 553 patients were 45.9 years (range, 17-79 years). Detailed characteristics of the patients of this study are demonstrated in Table 1.

Table 1. Detailed demographics of the 553 patients included

Age (years)	
Mean ± standard deviation	45.9 ± 12.4
Gender	
Female: male	483:70
Surgery (%)	
Total or near total	361 (65.3)
Subtotal	71 (12.8)
Hemithyroidectomy	121 (21.9)

Pathologic size (mm)	
Mean ± standard deviation	12 ± 9.3
Range	1 - 65
Extrathyroidal extension (%)	
No	321 (58)
Perithyroidal	218 (39.4)
Strap muscle	9 (1.6)
Massive	5 (0.9)
Central lymph node metastasis (%)	241 (43.6)
Lateral lymph node metastasis (%)	64 (11.6)
Underlying Hashimoto thyroiditis (%)	89 (16.1)
Multiplicity (%)	
Ipsilateral	31 (5.6)
Bilateral	114 (20.6)
Radioactive iodine ablation (%)	291 (52.6)
30mCi	19 (3.4)
60mCi	271 (49.0)
120mCi	1 (0.2)
Recurrence (%)	45 (8.1)

Patient's clinical and pathologic reports were reviewed by two radiologists. All patients included underwent total/near total thyroidectomy with bilateral central neck lymph node dissection (CCND) or subtotal thyroidectomy/hemithyroidectomy with unilateral CCND. Eighty-five patients also underwent lateral neck lymph node dissection for metastatic lymph nodes. Two hundred and ninty-four patients underwent subsequent radioactive iodine ablation after thyroidectomy for adjuvant therapy.

Pathology reports were reviewed based on findings of pathological nodule size, extrathyroid extension, multiplicity, lymph node metastases, and underlying thyroid disease. Extrathyroidal extension was categorized into

perithyroidal soft tissue extension, skeletal muscle invasion or massive extension into the trachea, larynx, esophagus, or recurrent laryngeal nerve. Metastatic lymph nodes were categorized according to its location; central and lateral neck lymph nodes. Multiplicity of thyroid included multifocality (one lobe) or bilaterality (both lobes) of PTCs.

2. Ultrasonographic analysis

All patients had undergone preoperative US examinations. One radiologist (J.Y.K.) with 10 years of experience in thyroid imaging retrospectively reviewed the preoperative US images. HDI 3000 or 5000 scanners (Phillips, Bothell, WA) using a bandwidth of 7 with a 12-MHz transducer was used in US examinations. Twenty-five patients had US examinations done in outside hospitals. These patients were included in this study because the US images obtained were available and determined as good quality.

US characteristics of the nodules were analyzed according to composition, echogenicity of the solid portion, margin, presence of calcification, shape, and the echogenicity of the underlying thyroid parenchyma. Composition of the cancer was divided into three categories such as solid (< 5% cystic), predominantly solid (≥ 5% cystic and < 50% cystic), or predominantly cystic (≥ 50% cystic) according to the percentage of cystic component within the cancer. Echogenicity was categorized into hyperechogenicity, isoechogenicity, hypoechogenicity, which was decided upon after comparison with the surrounding thyroid parenchyma, or marked hypoechogenicity, showing relative hypoechogenicity compared to the echogenicity of adjacent strap muscle. Margin was divided into well-circumscribed or not well-circumscribed (microlobulated and irregular). Shape was divided into wider than tall or taller than wide. Calcification was divided into microcalcifcation, macrocalcification, and no calcifications. Microcalcifications were defined as calcifications that

were equal to or less than 1 mm in diameter which was visualized as tiny, punctate, hyperechoic foci, either with or without acoustic shadows. If tiny bright reflectors with a clear-cut comet-tail artifact were present on conventional US, these were considered colloid material. Macrocalcifications were defined as hyperechoic foci larger than 1 mm, including rim or eggshell calcifications.[14] When the nodules had both types of calcifications (macrocalcifications including rim calcifications intermingled with microcalcifications), the nodule was considered to have microcalcifications.

3. Postoperative follow up

Follow-up clinical examinations were performed every 6 months during the first 3 years after surgery, and annually thereafter. Blood analysis of serum thyroid stimulating hormone (TSH), free thyroxine, thyroglobulin (Tg), anti-Tg antibody were included in the routine follow up examinations every 12 months. TSH-suppressed serum-Tg measurements were routinely used in the follow-up of patients with thyroid cancer,[15] but in some patients, stimulated Tg-values were used based on the physician's decision. Neck US examinations were also performed routinely. ^{18}F-Fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET-CT), ^{131}I-iodine whole body scan (WBS), or neck CT examinations were performed, selectively. Follow-up interval of patients was clinically defined and calculated as the time from initial thyroid operation to the most recent clinical evaluation.

Cancer recurrence was evaluated by reviewing all available examinations for each patient. Recurrence was conclusively confirmed by 1) cytopathology, 2) abnormal uptake on radioactive iodine WBS which suggests regional or distant metastasis, 3) highly suspicious findings of metastasis on ^{18}F-FDG PET-CT or other cross-sectional imaging, 4) newly developed cancer at the contralateral lobe confirmed by cytopathology during follow-up in patients who underwent thyroid lobectomy as a first surgical approach. Patients

with undetectable serum Tg, no regional recurrence on neck US or benign cytology results, and no regional or distant metastasis on WBS or other imaging studies were considered free of disease.

4. Statistical analysis

Chi-square test or Fisher's exact test was used in comparison of categorical variables. Continuous variables were compared between the groups using independent 2-sample *t*-test. Multivariable analysis was used to identify the independent prognostic factors for recurrence using the Cox proportional hazards regression model with all factors found to be statistically significant by univariate analysis, with adjustment of the various established US features as well as clinicopathological factors. *P* values less than 0.05 was considered as statistically significant. Statistical analyses were performed with SAS statistical software (SAS system for Windows, version 9.1.3; SAS Institute, Cary, NC).

III. RESULTS

Of 553 patients, 45 (8.1%) were confirmed to have tumor recurrence within the follow-up periods (Table 2). Patients were followed up for over a mean period of 67.6 months (range 5-92 months). Recurrence in 40 patients was diagnosed on the basis of cytopathologic results (n=40) or imaging features (n=5) showing uptake in the neck area on WBS (n=4) and highly suspicious features of metastasis on cross-sectional imaging (n=1). Thirty-nine patients had regional metastasis, 2 had distant metastasis, and 4 had both regional and distant metastasis.

The mean size of PTCs in patients with recurrence (19.8 ± 15.1 mm) was significantly larger than that those without (11.3 ± 8.3 mm) ($P < 0.001$). Tumor recurrence was more significantly seen in male patients. The extent of surgery, extrathyroidal extension and neck lymph node metastasis (both central and lateral) also showed significant association to recurrence. There were no

significant associations in patient age, presence of underlying thyroiditis, tumor multiplicity, or additional adjustment for radioiodine treatment after surgery to recurrence (Table 3). Among US features, the presence of calcifications was significantly associated to recurrence on univariate analysis. Multivariable Cox proportional hazards regression model with adjustment of the clinicopathological and US factors showing significance on univariate analysis was performed to identify independent factors of recurrence. Independent predictors of recurrence were male gender, tumor size, the presence of lateral LN metastasis, and not well-circumscribed margins, taller than wide shape among the US features. Of these predictors, the presence of lateral LN metastasis had the highest risk factor for recurrence (HR=4.038), followed by taller than wide shape (HR=2.382), and not well-circumscribed margin (HR=2.314) on US (Table 4).

Table 2. Demographic and clinicopathologic characteristics of 45 patients with recurrence

Mean age (years) (range)	46 (25-79)
Gender	
Female: male	32 : 13
Surgery (%)	
Total or near total	37 (82.2)
Subtotal	2 (4.4)
Hemithyroidectomy	6 (13.3)
Mean pathologic size (mm) (range)	12 (3-65)
Extrathyroidal extension (%)	
No	14 (31.1)
Perithyroidal	27 (60.0)
Strap muscle	1 (2.2)
Massive	3 (6.7)
Central lymph node metastasis (%)	29 (64.4)

Lateral lymph node metastasis (%)	19 (42.2)
Radioactive iodine ablation (%)	
Yes	26 (57.8)
No	19 (42.2)
Recurrence site (%)	
Contralateral thyroid	5 (11.1)
Operation bed	6 (13.3)
Neck LN metastasis	24 (53.3)
Distant metastasis	2 (4.4)
Multiple site metastasis	8 (17.8)

Table 3. Univariate analysis of clinicopathological and ultrasound parameters in 553 cases of papillary thyroid carcinoma using recurrence as the end point

	With Recurrence (n=45)	Without Recurrence (n=508)	*P*-value
Clinicopathologic features			
Age			0.661
Mean ± standard deviation	46.7±15.0	45.8±12.1	
Gender			0.002
Female	32 (5.8)	451 (81.6)	
Male	13 (2.4)	57 (10.3)	
Surgery			0.041
Total_or_near_total	37 (6.7)	324 (58.6)	
Subtotal	2 (0.4)	69 (12.4)	
Hemithyroidectomy	6 (1.1)	115 (20.8)	
Pathologic size (mm)			<0.001
Mean ± standard deviation	19.8±15.1	11.3±8.3	
Extrathyroidal extension			<0.001
No	14 (2.5)	307 (55.5)	
Perithyroidal extension	27 (4.9)	191 (34.5)	

Strap muscle invasion	1 (0.2)	8 (1.4)	
Massive extension	3 (0.5)	2 (0.2)	
Central lymph node metastasis			0.004
Yes	29 (5.2)	212 (38.3)	
No	16 (2.9)	296 (53.5)	
Lateral lymph node metastasis			<0.001
Yes	19 (3.4)	45 (8.1)	
No	26 (4.7)	463 (83.7)	
Underlying thyroiditis			0.832
Yes	6 (1.1)	83 (15.0)	
No	39 (7.1)	425 (76.9)	
Multiplicity			0.331
Negative	31 (5.6)	377 (68.2)	
Ipsilateral	1 (0.2)	30 (5.4)	
Bilaterality	13 (2.4)	101 (18.3)	
Radioactive iodine ablation			0.537
Yes	26 (4.7)	268 (48.5)	
No	19 (3.4)	240 (43.4)	
Ultrasound features			
Composition			0.243
Solid (< 5% cystic)	39 (7.1)	469 (84.8)	
Mainly solid (≥ 5% cystic and < 50% cystic)	5 (0.9)	33 (6.0)	
Mainly cystic (≥ 50% cystic)	1 (0.2)	6 (1.1)	
Echogenicity			0.537
Isoechogenicity	5 (0.9)	36 (6.5)	
Hypoechogenicity	38 (6.9)	433 (78.3)	
Marked hypoechogenicity	2 (0.4)	39 (7.1)	
Margin			0.735
Well-circumscribed	12 (2.2)	155 (28.0)	
Not well-circumscribed	33 (6.0)	353 (63.8)	

Calcifications			0.006
Microcalcification	35 (6.3)	279 (50.5)	
Macrocalcifications	3 (0.5)	40 (7.2)	
No	7 (1.3)	189 (34.2)	
Shape			0.087
Taller than wide	29 (5.2)	257 (46.5)	
Wider than tall	16 (2.9)	251 (45.4)	

Table 4. Hazard Ratio of Recurrence from a Multivariable Cox Proportional Hazards Regression Model

	HR (95% CI)	P-value
Gender (Male vs. Female)	2.004 (1.009-3.979)	0.047
Pathologic size (1 mm increase)	1.055 (1.029-1.081)	<0.001
Lateral lymph node metastasis (Yes vs. No)	4.038 (2.039-7.997)	<0.001
Margin (Not well-circumscribed vs. Well-circumscribed)	2.314 (1.128-4.747)	0.022
Shape (Taller than wide vs. Wider than tall)	2.382 (1.198-4.737)	0.013

IV. DISCUSSION

Papillary thyroid cancer is the most common endocrine tumor arising from follicular cells of the thyroid, and its incidence has increased during the recent years.[16,17] Although most PTCs have excellent prognosis, factors known to be related to poor prognosis as well as tumor recurrence are ages over 45 years, male gender, tumor size, presence of extrathyroidal invasion or distant metastases at the time of diagnosis.[18-22] As in the previously mentioned studies, male gender, tumor size, and the presence of lateral LN metastasis were significant risk factors of recurrence in our study. Although minimal extrathyroidal extension did not have an impact on recurrence,[15] massive

extrathyroidal extension was a meaningful risk factor of recurrence.[8] In this study, massive extrathyroidal extension as well as minimal extrathyroidal extension was not a risk factor of recurrence because the small number of patients with massive extrathyroidal extension might affect the result of this study.

Based on vast amount of studies, many staging systems for thyroid cancer have been made, such as the European Organization for Research and Treatment of Cancer (EORTC),[23] AJCC/UICC TNM Staging System,[24] Mayo Clinic (Age, Grade, Extent, Size or AGES),[25] Lahey Clinic (Age, Metastases, Extent, Size or AMES),[26] National Thyroid Cancer Treatment Cooperative Study (NTCTCS),[27] and Mayo Clinic (Metastases, Age, Completeness of resection, Invasion, Size or MACIS)[21] to provide proper prognostic information to clinicians and their patients, using various clinicopathologic characteristics. However, none of the previously reported and popularly used staging systems has included imaging features as prognostic factors for thyroid cancer.

Ill-defined margin and microcalcification of PTMC on US have been proven to have association to with recurrence.[12] Similarly, psammoma bodies were a useful predictor of patient outcome in PTCs, which usually manifest as microcalcifications on US.[28] Other studies showed that some US features (calcifications, hypo or marked hypoechogenicity) were predictive factors related to lymph node metastasis.[29-31] On the other hand, round shape, well-defined margin, and isoechoic echogenicity on US were negative predictive factors for extrathyroid extension and central lymph node metastasis.[30] Also, patients with predominantly cystic cancers are known to have favorable prognoses, roughly categorized them into cystic and marked cystic changes when evaluated on pathology specimen.[32] Therefore, we evaluated whether there was an association between US features as well as clinicopathologic factors and clinical outcome of a patient with PTC. Similar to other reports, not well-circumscribed margins and taller than wide shape on US

were independent factors associated with recurrence in this study. The presence of calcification on US was not an independent predictive factor, although it showed significance to recurrence on univariate analysis. Although we often come across PTCs with cystic change on US, there have been few studies on the outcome of PTC according to tumor composition on US. Although our study did not exclusively include cancers with cystic change on US, cystic component of the mass was not a risk factor for recurrence in this study. Besides the known clinicopathologic prognostic factors,[18-22] visually discernible ^{18F}FDG uptake or BRAF^{V600E} mutation of papillary thyroid microcarcinoma (PTMC) have been introduced as potential risk factors.[4,33] While these studies demand radiation exposure and additional costs, US is a simple, cost-effective method which can be performed without worrying about these adverse effects. The results of this study may suggest novel prognostic factors using US which are related to recurrence of PTC, combined with clinicopathologic factors.

There were some limitations to our study. First, the small number of recurrences makes meaningful statistical comparisons difficult. Second, selection bias may exist during patient exclusion according to various reasons. Third, most recurrences in this study were not biochemical recurrences but structural ones. Because we rarely obtain stimulated Tg values during postoperative follow-up of patients in our institution, we could not demonstrate or include biochemical recurrences in this study. Fourth, all US images were retrospectively analyzed by one radiologist, and not during the real-time examinations. Therefore, to verify the results of this study, further studies are needed.

V. CONCLUSION

In conclusion, not well-circumscribed margin and taller than wide shape on US can be used as a surrogate marker for predicting clinical outcome

of a patient with conventional PTC along with clinicopathologic factors such as male gender, tumor size, and the presence of lateral LN metastasis.

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ABSTRACT(IN KOREAN)

갑상선 유두암 환자의 임상적인 예후를 예측하는데 초음파가 대리표식이 될 수 있는가?

<지도교수 곽진영>

연세대학교 대학원 의학과

김 자 영

목적: 갑상선 유두암으로 수술 받은 많은 환자들을 대상으로 하여 암의 초음파 소견을 비롯하여 임상적 그리고 병리학적인 소견이 환자의 임상적인 예후를 예측하는 대리 표식이 될 수 있는지에 대해 알아본다.

대상 및 방법: 2003년 1월부터 2004년 12월까지 수술을 통해 갑상선 유두암으로 진단된 환자 553명을 대상으로 하였다. 이 환자들의 초음파 소견과 임상적 특징, 병리학적 소견 등을 후향적 연구방법으로 조사하였다. 환자들의 재발 여부를 확인하기 위해 평균 67.6개월의 추적 검사기간을 거쳤다. Cox 의 비례위험 회귀분석 모델을 통해 재발의 독립적인 위험인자에 대해 알아보았다.

결과: 총 553명의 환자 중 45명의 환자에서 추적검사 기간 중에

재발이 확인되었다. 재발의 독립적인 예측인자로는 남성, 암의 크기, 외측 경부림프절 전이가 있는 경우, 초음파상 불분명한 경계 와 앞뒤가 긴 모양 등이었다. 그 중에서 외측 경부 림프절 전이가 있는 경우 재발의 위험비율이 가장 높았고 (HR=4.038), 다음으로 앞뒤가 긴 모양 (HR=2.382), 초음파상 불분명한 경계 (HR=2.314)의 순서로 위험 비율이 높았다.

결론: 갑상선 유두암에서 초음파상 불분명한 경계와 앞뒤가 긴 모양을 가지고 있는 경우 환자의 임상적인 예후를 예측하는데 대리표식이 될 수 있다.

핵심되는 말 : 갑상선 유두암, 초음파, 낭성 갑상선암.