Int J Clin Exp Pathol 2016;9(7):7402-7410
www.ijcep.com /ISSN:1936-2625/IJCEP0014077

Original Article

Expression and diagnostic availability of p63 and CD56 in papillary thyroid carcinoma

Ji Yun Jeong[1], Jin Hyang Jung[2], Ji Young Park[1]

Departments of [1]Pathology, [2]Surgery, Kyungpook National University Medical Center, Kyungpook National University School of Medicine, Daegu, Korea

Received August 6, 2015; Accepted September 25, 2015; Epub July 1, 2016; Published July 15, 2016

Abstract: The purpose of this study is to evaluate the expression and diagnostic availability of p63 and CD56, as well as Galectin-3 and HBME-1 in papillary thyroid carcinoma diagnosis. A total of 267 cases were studied, including 129 cases of PTC and 80 cases of follicular tumor (FT). Additionally, 40 cases of nodular hyperplasia (NH), and 18 cases of undifferentiated carcinoma (UC) were examined. Tissue microarrays were made using the representative lesions, and assessed expression of p63, CD56, Galectin-3 and HBME-1. P63 revealed positive in the following order: UC (22%), PTC (15%), FT (1%), NH (0%). P63 was not sensitive (sensitivity: 16%), but specific (specificity: 91%) and revealed very high positive predictive value (95%) for PTC. CD56 revealed a reverse-ordered tendency to that of p63, and was neither sensitive (sensitivity: 39%) nor specific (specificity: 59%) for PTC. Galectin-3 and HBME-1 were relatively sensitive (sensitivity: 88%, 80%) and specific (specificity: 83%, 58%) for PTC. It can be concluded that p63 is a useful marker for PTC in distinguishing from other thyroid lesions, and a cocktail with other markers including Galectin-3 and HBME-1 can further improve diagnostic accuracy. But CD56 is not thought to be considerably useful. Additionally, p63 and CD56 could be associated with the progression of thyroid carcinoma or a poor prognosis.

Keywords: Thyroid neoplasm, TP63 protein, CD56, human

Introduction

One of the most frequent difficulties in thyroid pathology is differentiating papillary thyroid carcinoma, including the follicular variant, from other thyroid tumors or lesions, in spite of great support from immunohistochemical and molecular techniques [1-20]. The current gold standard for the diagnosis of papillary thyroid carcinoma is still morphologic features, but these are highly subjective, and no single morphologic feature is pathognomic. In cases exhibiting the follicular variant of papillary thyroid carcinoma, the problem is more serious. Although the follicular variant of papillary thyroid carcinoma is generally recognized, there is a lack of morphologic definition. However, accurate diagnosis is critical for proper treatment and long term management. For this reason, Chan [5] suggests more detailed diagnostic criteria for the encapsulated follicular variant of papillary thyroid carcinoma, including 4 major criteria and 4 minor criteria. In addition, some investigators propose using the term "well-differentiated tumor of uncertain malignant potential" when a capsular of vascular invasion is absent, and "well-differentiated thyroid carcinoma, not otherwise specified" when there is definite capsular or vascular invasion, in cases of encapsulated tumors showing the focal, but not widespread, nuclear features of papillary thyroid carcinoma [21]. These suggestions have yet to entirely solve the problems that inter-observer or intra-observer disagreement.

Many studies have tried to find immunohistochemical and molecular markers helpful in the diagnosis of various thyroid lesions [4, 7, 8, 10, 13-15, 18]. Although some of these techniques are useful in confirming a diagnosis of papillary thyroid carcinoma, others are not reliable enough to distinguish papillary thyroid carcinoma from other lesions. We selected 4 candidate immunohistochemical markers expected to be of value in the diagnosis of papillary thyroid carcinomas which include the follicular variant.

p63, a member of the p53 gene family, is located on chromosome 3q27-29 and expresses at least six different isoforms. Three of the p63 isoforms encode proteins which transactivate on p53 activity and induct cells into apoptosis, whereas the other three isoforms encode proteins which have inhibitory effects on p53 activity. It is consistently expressed in basal, squamous, and myoepithelial cells [7, 16, 22, 23]. Only few studies about p63 expression in thyroid lesions have been reported so far [7, 16, 22-25].

CD56 is a neural cell adhesion molecule, so its expression may affect the migration of tumor cells. CD56 is expressed in NK cells, activated T cells, large granular lymphocytes, specific endocrine, and brain tissue normally [7, 8, 26, 27], and can also be expressed in follicular cells of the normal thyroid gland [7, 8, 28, 29]. Several studies have shown that loss of CD56 expression correlates with poor prognosis and metastatic potentials in some malignant tumors [30-35]. In cases of thyroid lesions, CD56 has been reported to be a very useful immunohistochemical marker in the diagnosis of papillary thyroid carcinoma in previous reported studies [7, 8], yet there have been few studies about CD56 expression in thyroid lesions.

Galectin-3 is a member of a family of β-galactosil-binding lectins, involved in regulating cell-to-cell and cell-to-matrix interactions, cell growth, neoplastic transformation, and apoptosis, and is expressed in normal breast epithelial cells, inflammatory cells, and various malignant cells [15, 36]. Many studies have found that Galectin-3 has value in distinguishing between benign and malignant thyroid lesions, and it has been suggested as a useful marker, especially in the diagnosis of papillary thyroid carcinoma [14, 15, 37, 38].

HBME-1, a monoclonal antibody generated against a suspension of malignant epithelial mesothelioma cells, reacts with the microvillous surface protein of mesothelial cells [15, 39]. It has also been suggested to demonstrate value in distinguishing malignant thyroid tumors from benign thyroid lesions [6, 14, 15, 37, 39-41].

In the current study, we evaluated the expression and diagnostic availability of p63 and CD56, as well as Galectin-3, and HBME-1 in distinguishing papillary thyroid carcinomas including the follicular variant from other thyroid lesions.

Materials and methods

Materials

A total of 267 cases exhibiting thyroid gland lesions and tumors were included in this study. The well differentiated thyroid tumors included 129 cases of papillary thyroid carcinoma, 80 cases of follicular tumor and 40 cases of nodular hyperplasia. 18 cases of undifferentiated carcinoma were also included for comparison. All patients underwent a lobectomy, a near-total thyroidectomy or a total thyroidectomy at Kyungpook National University Hospital between June 2003 and June 2008. The hematoxylin and eosin (H&E) stained slides from each case were reviewed by 2 pathologists (J.Y.J. and J.Y.P.), according to its WHO classification. The papillary thyroid carcinoma group included 69 cases of follicular variant papillary thyroid carcinoma, while 9 cases of follicular variant papillary thyroid carcinoma were encapsulated. In cases of encapsulated follicular variant papillary thyroid carcinoma, the authors followed the criteria proposed by Chan [5]. The follicular tumor group included 40 cases of follicular adenoma and 40 cases of follicular carcinoma.

Construction of the tissue microarray

The tissue microarray blocks were prepared with empty holes measuring 3 mm in diameter. The most representative areas were marked on each of the H&E stained slides, and tissue cores measuring 3 mm in a diameter were sampled from the formalin-fixed, paraffin-embedded tissue blocks. The sampled cores were arranged in the prepared tissue microarray blocks. All tissue microarray blocks contained the tissues of positive control for p63, CD56, Galectin-3, and HBME-1.

Immunohistochemistry and interpretation

Immunohistochemistry was performed on 4 μM thick sections from each tissue microarray block using an automated immunostainer (Ventana Medical Systems, Inc., AZ, USA, BenchMark®). Applied primary antibodies were p63 (Dako, Carpinteria, CA, USA, dilution

Table 1. Expression of the markers in various thyroid lesions

	p63 (%)	CD56 (%)	Galectin-3 (%)	HBME-1 (%)
NH (n=40)	0 (0)	31 (77.5)	3 (7.5)	5 (12.5)
FA (n=40)	1 (2.5)	27 (67.5)	12 (30)	13 (32.5)
FC (n=40)	0 (0)	14 (35)	6 (15)	21 (52.5)
PTC (n=129)	19 (14.7)	69 (53.5)	114 (88.4)	107 (82.9)
UC (n=18)	4 (22.2)	0 (0)	14 (77.8)	9 (50)

NH, nodular hyperplasia; FA, follicular adenoma; FC, follicular carcinoma; PTC, papillary thyroid carcinoma; UC, undifferentiated carcinoma.

1:200), CD56 (Novocastra, Newcastle, UK, dilution 1:100), Galectin-3 (Novacastra, Newcastle, UK, dilution 1:100), and HBME-1 (Dako, Carpinteria, CA, USA, dilution 1:100). An iView DAB Detection kit (Ventana Medical Systems, Inc., AZ, USA) was used as the secondary antibody. Counter-staining was performed using Hematoxylin (Ventana Medical Systems, Inc., AZ, USA), and treated with Bluing Reagent (Ventana Medical Systems, Inc., AZ, USA).

The immunohistocehmical stained slides were also evaluated by 2 pathologists (J.Y.J. and J.Y.P.) independently. For p63, cells showing nuclear staining were considered positive cells. For CD56, cells showing cytoplasmic membrane staining with or without cytoplasmic staining were considered positive cells. Galectin-3 was considered positive when nuclear and/or cytoplasmic staining was demonstrated. HBME-1 was considered positive when exhibiting cytoplasmic and cytoplasmic membrane staining with occasional luminal accentuation. The staining in over 5% of the tumor cells was regarded as positive for all immunohistochemical markers.

Statistical analysis

The χ^2 test and Fisher's exact test were used for comparing the expressions of the applied immunohistochemical markers in papillary thyroid carcinomas and the other thyroid lesions. The statistical analysis was performed using SAS 9.1, and results with the *p*-value of <0.05 were considered statistically significant. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the markers in diagnoses of papillary thyroid carcinoma were compared.

Results

The expression of p63, CD56, Galectin-3, and HBME-1 in 267 cases of thyroid lesions is summarized in **Table 1**. p63 revealed positive in this order: undifferentiated carcinoma (22.2%), papillary thyroid carcinoma (14.7%), follicular adenoma (2.5%), follicular carcinoma (0%), and nodular hyperplasia (0%) (**Figures 1** and **2**). The single case of follicular adenoma that was positive for p63 showed focal weak positivity (**Figure 1E**). The expression of CD56 showed a nearly reverse-ordered tendency (**Figures 1** and **2**). CD56 revealed itself absent from expression only in cases of undifferentiated carcinoma, and showed decreased expression rates in malignant thyroid tumors including papillary thyroid carcinoma (53.5%) and follicular carcinoma (35%) compared with benign thyroid tumors or follicular adenoma (67.5%) (**Figure 1**). The non-tumorous lesions or nodular hyperplasia expressed itself even more frequently (77.5%) than follicular adenoma. Galectin-3 and HBME-1 revealed the highest expression in papillary thyroid carcinoma; 88.4% and 82.9%, respectively. Galectin-3 and HBME-1 showed higher expression in thyroid tumors than nodular hyperplasia, but no specific tendency between various lesions.

The expressions of applied immunohistochemical markers in papillary thyroid carcinoma were compared to other thyroid lesions (**Tables 1** and **2**). When comparing papillary thyroid carcinoma with follicular adenoma, the expression of both p63 (P<0.0001) and Galectin-3 (P=0.0024) were significantly higher in papillary thyroid carcinoma than in follicular adenoma. When comparing papillary thyroid carcinoma with follicular carcinoma, the expression of p63 (P<0.0001) and HBME-1 (P=0.0161) were significantly higher in papillary thyroid carcinoma than follicular carcinoma. When comparing papillary thyroid carcinoma with nodular hyperplasia, the expression of p63 (P<0.0001) alone was significantly higher in papillary thyroid carcinoma than nodular hyperplasia. Lastly, comparing papillary thyroid carcinoma with differentiated thyroid lesions (excepting papillary thyroid carcinoma), the expression of p63 (P<0.0001) and HBME-1 (P=0.0149) were significantly higher in papillary thyroid carcinoma than the other lesions, including follicular tumor and nodular hyperplasia. p63 was significantly higher in papillary thyroid carcinoma than in any of the other compared groups. CD56 did

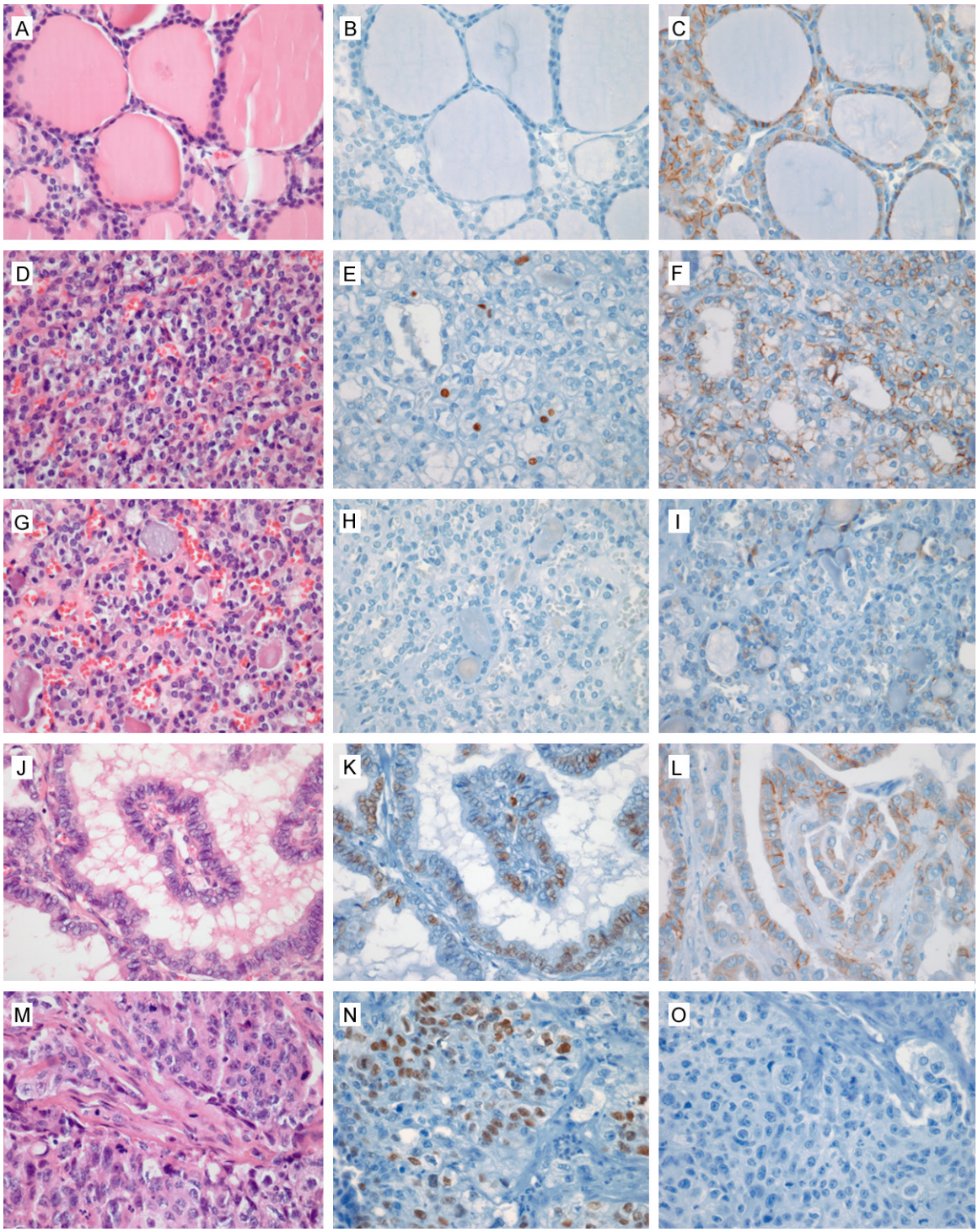

Figure 1. Expression of p63 and CD56 in various thyroid diseases. Nodular hyperplasia (A) is completely negative for p63 (B), but positive for CD56 (C) in high percentage. Follicular adenoma (D) arranged in trabecular and solid pattern shows only weak positivity rarely for p63 (E), but positive for CD56 diffusely (F). Follicular carcinoma (G) is completely negative for p63 (H), but positive for CD56 focally in some cases (I). Papillary thyroid carcinoma (J) is positive for p63 (K), and positive for CD56 (L) also in some cases. Undifferentiated carcinoma (M) composed of marked atypical cells with numerous mitoses is positive for p63 (N), but completely negative for CD56 (O).

not significantly differ between either of the two groups.

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy

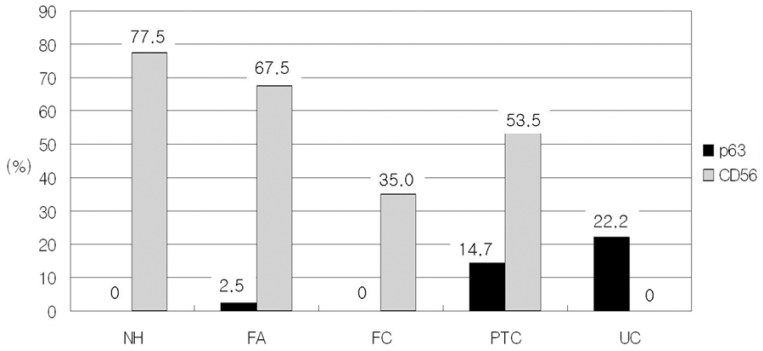

Figure 2. Differential expression tendencies of p63 and CD56. The more that tumors or lesions show poor prognosis or a progression of the disease, the more the expression rate of p63 and the less the expression rate of CD56 are revealed generally. (NH, nodular hyperplasia; FA, follicular adenoma; FC, follicular carcinoma; PTC, papillary thyroid carcinoma; UC, undifferentiated carcinoma).

Table 2. The *p*-values of differential expression of immunohistochemical markers between papillary thyroid carcinoma and the other lesions

Markers	*p*-value of PTC vs FA	*p*-value of PTC vs FC	*p*-value of PTC vs NH	*p*-value of PTC vs FT+NH
P63	<0.0001	<0.0001	<0.0001	<0.0001
CD56	0.7136	0.8188	0.2241	0.8464
Galectin-3	0.0024	0.3356	0.1768	0.0589
HBME-1	0.0612	0.0161	0.3912	0.0149

PTC, papillary thyroid carcinoma; FA, follicular adenoma; FC, follicular carcinoma; NH, nodular hyperplasia; FT, follicular tumor (FA+FC).

Table 3. Diagnostic value of the markers in diagnosis of papillary thyroid carcinoma

Markers	Sensitivity	Specificity	PPV	NPV	Accuracy
P63 (+)	14.7%	99.2%	95%	52%	55.4%
CD56 (-)	46.5%	60%	55.6%	51.1%	53%
Galectin-3 (+)	88.4%	82.5%	84.4%	86.8%	85.5%
HBME-1 (+)	82.9%	67.5%	73.3%	78.6%	75.5%

PPV, positive predictive value; NPV, negative predictive value.

of the markers used in the diagnosis of papillary thyroid carcinoma among differentiated thyroid lesions including nodular hyperplasia, follicular tumor, and papillary thyroid carcinoma are shown in **Table 3**. p63 was not sensitive, but specific and revealed very high positive predictive value for papillary thyroid carcinoma. CD56 was neither sensitive nor specific for papillary thyroid carcinoma. Galectin-3 and HBME-1 were relatively sensitive and specific for papillary thyroid carcinoma, yet not fully diagnostic.

Discussion

Few studies of p63 expression in thyroid lesions have been reported to date [7, 16, 22-25]. Unger et al. [25] and Demellawy et al. [7] describe that p63 is positive in a high percentage of papillary thyroid carcinomas, 81.8% and 70%, respectively. Accordingly they suggested that p63 can aid in the differentiation of papillary thyroid carcinoma from other thyroid tumors or lesions. Preto et al. [16] found 33.3% of papillary thyroid carcinomas and 50% of anaplastic carcinomas were positive for p63. Kim et al. [22] described that p63 was detected in 12.5% of papillary thyroid carcinomas, 11.1% of poorly differentiated carcinomas, and 71.4% of anaplastic carcinomas, while normal thyroid follicles, hyperplastic thyroid follicles, follicular carcinomas, and medullary carcinomas were all negative for p63. Therefore, Kim et al. [22] concluded that p63 is usually expressed late in the course of thyroid tumor progression. In the current study, p63 was expressed from most frequent to least in undifferentiated carcinoma (22.2%), papillary thyroid carcinoma (14.7%), follicular tumor (1.3%), and nodular hyperplasia (0%). These results suggest that p63 is associated with poor prognosis factors in thyroid tumors or thyroid tumor progression. The only exception was the single case of follicular adenoma that was positive for p63. As the case showed only focal (about 10%) weak positivity, it might be associated with progression to a worse state. The expression rate of p63 in papillary thyroid carcinoma was somewhat lower than other preceding studies, that is, p63 was not sensitive for papillary thyroid carcinoma. Nevertheless, p63 is thought to be helpful in the diagnosis of papillary thyroid carcinoma by its high specificity (99.2%) and positive predictive value (95%). We further attempted to evaluate the expression of p63 in distinguishing papillary thyroid carcinoma from other thyroid

tumors or lesions, statistically. Undifferentiated carcinoma was excluded from this comparison, because undifferentiated carcinoma can be easily distinguished from papillary thyroid carcinoma by means of a routine histology using hematoxylin and eosin (H&E) staining. It was found that the expression of p63 was significantly more frequent in papillary carcinoma when compared with follicular adenoma, follicular carcinoma, and nodular hyperplasia ($P<0.0001$). Thus, p63 may be useful in distinguishing papillary thyroid carcinoma from other thyroid tumors or lesions.

Recently, Scarpino et al. [42] conducted a study regarding the expression of CD56 in papillary thyroid carcinoma using immunohistochemistry and polymerase chain reaction (PCR), and they described that a low or absent expression of CD56 was noted in papillary thyroid carcinoma. Other investigators, Demellawy et al. [7, 8], reported that CD56 was consistently expressed in normal, lesional, and neoplastic follicular cells, except for papillary thyroid carcinomas including follicular variant. Demmellawy et al. [7, 8] suggested that CD56 can prove valuable in distinguishing papillary thyroid carcinoma from other thyroid tumors or lesions, and that CD56 is extremely useful in the diagnosis of papillary thyroid carcinoma, with a sensitivity of 100% and a specificity of 100%. In our study, CD56 revealed absent expression only in the cases of undifferentiated carcinoma, and showed decreased expression rate in malignant thyroid tumors including papillary thyroid carcinoma (53.5%) and follicular carcinoma (35%) compared with benign thyroid tumors or follicular adenoma (67.5%). Non-tumorous lesions or nodular hyperplasia showed an even higher expression (77.5%) than follicular adenoma. These results have something in common with the study of Scarpino et al. [42] in that the expression of CD56 is low or absent in carcinoma including papillary thyroid carcinoma compared with other benign thyroid tumors or lesions, but differ from studies conducted by Demellawy et al. [7, 8]. In cases of the follicular variant of papillary thyroid carcinoma, CD56 was positive 75.4% of the time, which is much higher than in conventional papillary thyroid carcinoma (28.3%) and follicular carcinoma (35%), and even above that of follicular adenoma (67.5%). However, CD56 is not thought to be highly useful in the diagnosis of papillary thyroid carcinoma with a sensitivity and specificity of 100%, based on the results that CD56 was expressed at a considerable rate not only in follicular variant of papillary thyroid carcinoma but in typical conventional papillary thyroid carcinoma. Actually, CD56 revealed a sensitivity of 46.5% and a specificity of 60% for papillary thyroid carcinoma in the current study, begging the conclusion that CD56 is neither sensitive nor specific for papillary thyroid carcinoma. When comparing the expression of CD56 in papillary thyroid carcinoma with other thyroid tumors or lesions, the expression of CD56 in papillary thyroid carcinoma does not significantly differ from the expression of CD56 in follicular adenoma, follicular carcinoma, and nodular hyperplasia. When considering these results together, CD56 is not considerably useful in the diagnosis of papillary thyroid carcinoma. But a meaningful result was found that the expression of CD56 showed a nearly reverse-ordered tendency to that of p63 among various thyroid tumors or lesions. That is, the more that tumors or lesions show poor prognosis or a progression of the disease, the less the expression rate of CD56 was revealed. These results suggest that CD56 might also be associated with poor prognosis factors in thyroid tumors or thyroid tumor progression, similar to p63.

It has been suggested that Galectin-3 and HBME-1 have value in distinguishing malignant thyroid tumors from benign thyroid lesions, and Galectin-3 has been tagged as a useful marker, especially in the diagnosis of papillary thyroid carcinoma [6, 14, 15, 36-38, 40, 41]. In the current study, Gelectin-3 and HBME-1 showed positive in higher percentages in papillary thyroid carcinoma than other thyroid tumors or lesions, 88.4% and 82.9%, respectively. The expression rate of Galectin-3 and HBME-1 was even higher in papillary thyroid carcinoma than in undifferentiated carcinoma. Benign thyroid lesions including follicular adenoma and nodular hyperplasia showed positivity in much lower percentages when compared with malignant thyroid tumors - not only in papillary thyroid carcinoma, but also follicular carcinoma and undifferentiated carcinoma. These results are in accord with preceding studies conducted by other investigators. The attempt was made to evaluate the availability of Galectin-3 and HBME-1 in distinguishing papillary thyroid carcinoma from other thyroid tumors or lesions sta-

tistically, as well. The expression of Galectin-3 was significantly higher in papillary thyroid carcinoma than in follicular adenoma alone. The expression of HBME-1 was significantly higher in papillary thyroid carcinoma than in follicular carcinoma when compared with other thyroid tumors or lesions separately, and was significantly higher in papillary thyroid carcinoma when compared with the sum of other thyroid tumors or lesions, excepting undifferentiated carcinoma. Thus both Galectin-3 and HBME-1 provide value in distinguishing papillary thyroid carcinoma from other thyroid tumors or lesions. In the daily practice of diagnosis, HBME-1 is thought to be more useful in the differential diagnosis of papillary thyroid carcinoma than Galectin-3, because the distinction between papillary thyroid carcinoma and all other thyroid tumors or lesions is critical for proper treatment and long term management. Galectin-3 and HBME-1 further prove relatively sensitive and specific for papillary thyroid carcinoma, yet remain not fully diagnostic. The high sensitivity and specificity of Galectin-3 and HBME-1 could improve the value of p63 in the diagnosis of papillary thyroid carcinoma when using an immunohistochemical panel consisted of Galectin-3, HBME-1, and p63.

In conclusion, p63 is a useful immunohistochemical marker in distinguishing papillary thyroid carcinoma from other thyroid tumors or lesions, and in a cocktail with other markers, including Galectin-3 and HBME-1, can improve diagnostic accuracy. As p63 is specific for papillary thyroid carcinoma and undifferentiated carcinoma, it might be associated with poor prognosis factors or the progression of thyroid tumors. The sudden absence of CD56 expression could further be associated with poor prognosis or disease progression. However, CD56 cannot be considered useful in the diagnosis of papillary thyroid carcinoma.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ji Young Park, Department of Pathology, Kyungpook National University Hospital, 50 Samduk 2 Ga, Jung Gu, Daegu 700-721, Korea. Tel: +82-53-200-2166; Fax: +82-53-200-2027; E-mail: jyparkmd@knu.ac.kr

References

[1] Al-Brahim N and Asa SL. Papillary thyroid carcinoma: an overview. Arch Pathol Lab Med 2006; 130: 1057-1062.

[2] Asa SL. The role of immunohistochemical markers in the diagnosis of follicular-patterned lesions of the thyroid. Endocr Pathol 2005; 16: 295-309.

[3] Baloch ZW and LiVolsi VA. The quest for a magic tumor marker: continuing saga in the diagnosis of the follicular lesions of thyroid. Am J Clin Pathol 2002; 118: 165-166.

[4] Beesley MF and McLaren KM. Cytokeratin 19 and galectin-3 immunohistochemistry in the differential diagnosis of solitary thyroid nodules. Histopathology 2002; 41: 236-243.

[5] Chan J. Strict criteria should be applied in the diagnosis of encapsulated follicular variant of papillary thyroid carcinoma. Am J Clin Pathol 2002; 117: 16-18.

[6] Cheung CC, Ezzat S, Freeman JL, Rosen IB and Asa SL. Immunohistochemical diagnosis of papillary thyroid carcinoma. Mod Pathol 2001; 14: 338-342.

[7] El Demellawy D, Nasr A and Alowami S. Application of CD56, P63 and CK19 immunohistochemistry in the diagnosis of papillary carcinoma of the thyroid. Diagn Pathol 2008; 3: 5.

[8] El Demellawy D, Nasr AL, Babay S and Alowami S. Diagnostic utility of CD56 immunohistochemistry in papillary carcinoma of the thyroid. Pathol Res Pract 2009; 205: 303-309.

[9] Elsheikh TM, Asa SL, Chan JK, DeLellis RA, Heffess CS, LiVolsi VA and Wenig BM. Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. Am J Clin Pathol 2008; 130: 736-744.

[10] Huang Y, Prasad M, Lemon WJ, Hampel H, Wright FA, Kornacker K, LiVolsi V, Frankel W, Kloos RT, Eng C, Pellegata NS and de la Chapelle A. Gene expression in papillary thyroid carcinoma reveals highly consistent profiles. Proc Natl Acad Sci U S A 2001; 98: 15044-15049.

[11] Kawachi K, Matsushita Y, Yonezawa S, Nakano S, Shirao K, Natsugoe S, Sueyoshi K, Aikou T and Sato E. Galectin-3 expression in various thyroid neoplasms and its possible role in metastasis formation. Hum Pathol 2000; 31: 428-433.

[12] Lloyd RV, Erickson LA, Casey MB, Lam KY, Lohse CM, Asa SL, Chan JK, DeLellis RA, Harach HR, Kakudo K, LiVolsi VA, Rosai J, Sebo TJ, Sobrinho-Simoes M, Wenig BM and Lae ME. Observer variation in the diagnosis of follicular

variant of papillary thyroid carcinoma. Am J Surg Pathol 2004; 28: 1336-1340.
[13] Nakamura N, Erickson LA, Jin L, Kajita S, Zhang H, Qian X, Rumilla K and Lloyd RV. Immunohistochemical separation of follicular variant of papillary thyroid carcinoma from follicular adenoma. Endocr Pathol 2006; 17: 213-223.
[14] Park YJ, Kwak SH, Kim DC, Kim H, Choe G, Park do J, Jang HC, Park SH, Cho BY and Park SY. Diagnostic value of galectin-3, HBME-1, cytokeratin 19, high molecular weight cytokeratin, cyclin D1 and p27(kip1) in the differential diagnosis of thyroid nodules. J Korean Med Sci 2007; 22: 621-628.
[15] Prasad ML, Pellegata NS, Huang Y, Nagaraja HN, de la Chapelle A and Kloos RT. Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 immunohistochemistry is useful for the differential diagnosis of thyroid tumors. Mod Pathol 2005; 18: 48-57.
[16] Preto A, Reis-Filho JS, Ricardo S and Soares P. P63 expression in papillary and anaplastic carcinomas of the thyroid gland: lack of an oncogenetic role in tumorigenesis and progression. Pathol Res Pract 2002; 198: 449-454.
[17] Renshaw AA and Gould EW. Why there is the tendency to "overdiagnose" the follicular variant of papillary thyroid carcinoma. Am J Clin Pathol 2002; 117: 19-21.
[18] Xu XC, el-Naggar AK and Lotan R. Differential expression of galectin-1 and galectin-3 in thyroid tumors. Potential diagnostic implications. Am J Pathol 1995; 147: 815-822.
[19] Zhu Z, Gandhi M, Nikiforova MN, Fischer AH and Nikiforov YE. Molecular profile and clinicopathologic features of the follicular variant of papillary thyroid carcinoma. An unusually high prevalence of ras mutations. Am J Clin Pathol 2003; 120: 71-77.
[20] Zidan J, Karen D, Stein M, Rosenblatt E, Basher W and Kuten A. Pure versus follicular variant of papillary thyroid carcinoma: clinical features, prognostic factors, treatment, and survival. Cancer 2003; 97: 1181-1185.
[21] Williams ED. Guest Editorial: Two Proposals Regarding the Terminology of Thyroid Tumors. Int J Surg Pathol 2000; 8: 181-183.
[22] Kim YW, Do IG and Park YK. Expression of the GLUT1 glucose transporter, p63 and p53 in thyroid carcinomas. Pathol Res Pract 2006; 202: 759-765.
[23] Levrero M, De Laurenzi V, Costanzo A, Gong J, Wang JY and Melino G. The p53/p63/p73 family of transcription factors: overlapping and distinct functions. J Cell Sci 2000; 113: 1661-1670.
[24] Burstein DE, Nagi C, Wang BY and Unger P. Immunohistochemical detection of p53 homolog p63 in solid cell nests, papillary thyroid carcinoma, and hashimoto's thyroiditis: A stem cell hypothesis of papillary carcinoma oncogenesis. Hum Pathol 2004; 35: 465-473.
[25] Unger P, Ewart M, Wang BY, Gan L, Kohtz DS and Burstein DE. Expression of p63 in papillary thyroid carcinoma and in Hashimoto's thyroiditis: a pathobiologic link? Hum Pathol 2003; 34: 764-769.
[26] Hoos A, Stojadinovic A, Singh B, Dudas ME, Leung DH, Shaha AR, Shah JP, Brennan MF, Cordon-Cardo C and Ghossein R. Clinical significance of molecular expression profiles of Hurthle cell tumors of the thyroid gland analyzed via tissue microarrays. Am J Pathol 2002; 160: 175-183.
[27] Lanier LL, Testi R, Bindl J and Phillips JH. Identity of Leu-19 (CD56) leukocyte differentiation antigen and neural cell adhesion molecule. J Exp Med 1989; 169: 2233-2238.
[28] Zeromski J, Dworacki G, Jenek J, Niemir Z, Jezewska E, Jenek R and Biczysko M. Protein and mRNA expression of CD56/N-CAM on follicular epithelial cells of the human thyroid. Int J Immunopathol Pharmacol 1999; 12: 23-30.
[29] Zeromski J, Lawniczak M, Galbas K, Jenek R and Golusinski P. Expression of CD56/N-CAM antigen and some other adhesion molecules in various human endocrine glands. Folia Histochem Cytobiol 1998; 36: 119-125.
[30] Cavallaro U, Niedermeyer J, Fuxa M and Christofori G. N-CAM modulates tumour-cell adhesion to matrix by inducing FGF-receptor signalling. Nat Cell Biol 2001; 3: 650-657.
[31] Fogar P, Basso D, Pasquali C, De Paoli M, Sperti C, Roveroni G, Pedrazzoli S and Plebani M. Neural cell adhesion molecule (N-CAM) in gastrointestinal neoplasias. Anticancer Res 1997; 17: 1227-1230.
[32] Gratsa A, Rooprai HK, Rogers JP, Martin KK and Pilkington GJ. Correlation of expression of NCAM and GD3 ganglioside to motile behaviour in neoplastic glia. Anticancer Res 1997; 17: 4111-4117.
[33] Owens GC, Orr EA, DeMasters BK, Muschel RJ, Berens ME and Kruse CA. Overexpression of a transmembrane isoform of neural cell adhesion molecule alters the invasiveness of rat CNS-1 glioma. Cancer Res 1998; 58: 2020-2028.
[34] Prag S, Lepekhin EA, Kolkova K, Hartmann-Petersen R, Kawa A, Walmod PS, Belman V, Gallagher HC, Berezin V, Bock E and Pedersen N. NCAM regulates cell motility. J Cell Sci 2002; 115: 283-292.
[35] Rutishauser U, Acheson A, Hall AK, Mann DM and Sunshine J. The neural cell adhesion molecule (NCAM) as a regulator of cell-cell interactions. Science 1988; 240: 53-57.

[36] Krzeslak A and Lipinska A. Galectin-3 as a multifunctional protein. Cell Mol Biol Lett 2004; 9: 305-328.
[37] de Matos PS, Ferreira AP, de Oliveira Facuri F, Assumpcao LV, Metze K and Ward LS. Usefulness of HBME-1, cytokeratin 19 and galectin-3 immunostaining in the diagnosis of thyroid malignancy. Histopathology 2005; 47: 391-401.
[38] Herrmann ME, LiVolsi VA, Pasha TL, Roberts SA, Wojcik EM and Baloch ZW. Immunohistochemical expression of galectin-3 in benign and malignant thyroid lesions. Arch Pathol Lab Med 2002; 126: 710-713.
[39] Sheibani K, Esteban JM, Bailey A, Battifora H and Weiss LM. Immunopathologic and molecular studies as an aid to the diagnosis of malignant mesothelioma. Hum Pathol 1992; 23: 107-116.
[40] Mase T, Funahashi H, Koshikawa T, Imai T, Nara Y, Tanaka Y and Nakao A. HBME-1 immunostaining in thyroid tumors especially in follicular neoplasm. Endocr J 2003; 50: 173-177.
[41] Miettinen M and Karkkainen P. Differential reactivity of HBME-1 and CD15 antibodies in benign and malignant thyroid tumours. Preferential reactivity with malignant tumours. Virchows Arch 1996; 429: 213-219.
[42] Scarpino S, Di Napoli A, Melotti F, Talerico C, Cancrini A and Ruco L. Papillary carcinoma of the thyroid: low expression of NCAM (CD56) is associated with downregulation of VEGF-D production by tumour cells. J Pathol 2007; 212: 411-419.