Original Research
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Relation of 18F-FDG PET/CT Positivity with Tumor Cytopathology, Galectin-3, PTEN, Ki-67 and NIS Expressions in Thyroid Nodules

Tiroid Nodüllerinde 18F-FDG PET/BT Tutulumu ile Tümör Sitopatolojisi, Galectin-3, PTEN, Ki-67 ve NIS Ekspresyonları Arasındaki İlişki

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Abstract

Objective: The expressions of certain molecular markers have been found to be related with 18F-FDG uptake in differentiated thyroid cancer. The goal of this study was to assess the relationship between NIS, galectin-3, PTEN, Ki-67 expressions and 18F-FDG positron emission tomography positivity in thyroid nodules.

Material and Methods: Fifteen patients with 27 nodules who had incidental focal 18F-FDG uptake in thyroid and underwent total thyroidectomy were included. Immunohistochemical staining with galectin-3, NIS, PTEN, and Ki-67 were performed.

Results: Among the 27 nodules, 19 nodules were diagnosed as papillary thyroid carcinoma. Malignant- positron emission tomography positive (n=13), malignant-positron emission tomography negative (n=6) and benign-positron emission tomography positive nodules (n=8) were classified as group A, B, and C, respectively. PTEN loss was frequent in the malignant nodules compared to the benign ones [19 (42.1%) vs. 1 (12.5%), p=0.01]. NIS positive staining was significantly frequent in older patients (p=0.019). Mean Ki-67 proliferation index, galectin-3, PTEN and NIS expressions were not different between the three groups. SUV_{max} values were not statistically different between the malignant and benign nodules with focal 18F-FDG uptake (7.7±5.4 vs. 7.0 ±4.4, p=0.8).

Conclusion: The FDG-positron emission tomography/computed tomography positivity was not associated with Galectin-3, NIS, Ki-67 and PTEN expressions. SUV_{max} values were not different in the malignant and benign nodules but the PTEN loss was frequent in malignant nodules. We suggest that the role of molecular markers in the development of differentiated thyroid cancer with 18F-FDG uptake should be investigated in further studies with a larger patient group.

Keywords: Differentiated thyroid cancer; PTEN; Ki-67; NIS; Galectin-3; 18F-FDG PET/CT

Özet

Amaç: Diferansiye tiroid kanserinde bazı moleküler belirteçlerin ekspresyonu ile 18F-FDG tutulumunun ilişkili olduğu gösterilmiştir. Bu çalışmada, tiroid nodüllerinde NIS, galectin-3, PTEN, Ki-67 ekspresyonları ile 18F-FDG pozitron emisyon tomografisi/bilgisayarlı tomografide tutulum varlığı arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Fokal 18F-FDG tutulumu olan ve total tiroidektomi uygulanan 15 hastanın 27 nodülü çalışmaya dahil edilmiştir. Galectin-3, NIS, PTEN ve Ki-67 immünohistokimyasal boyamaları değerlendirilmiştir.

Bulgular: Çalışmaya dâhil edilen 27 nodülün 19'unda papiller tiroid kanseri saptanmıştır. Malign-pozitron emisyon tomografisi pozitif (n=13), malign-pozitron emisyon tomografisi negatif (n=6) ve benign-pozitron emisyon tomografisi pozitif nodüller (n=8) sırasıyla Grup A, B ve C olarak gruplandırılmıştır. PTEN kaybı, malign nodüllerde benign nodüllerle karşılaştırıldığında daha sık saptanmıştır [19 (%42,1) vs. 1 (%12,5), p=0,01]. NIS pozitif boyanma sıklığı yaşlı hastalarda anlamlı olarak yüksek bulunmuştur (p=0,019). Ortalama Ki-67 proliferasyon indeksi, galectin-3, PTEN ve NIS ekspesyonları açısından üç grup arasında anlamlı fark görülmemiştir. Fokal 18F-FDG tutulumu olan malign ve benign nodüller arasında SUX_{max} değerleri açısından anlamlı fark görülmemiştir (7,7±5,4 vs. 7,0±4,4, p=0,8).

Sonuç: FDG-pozitron emisyon tomografisi/bilgisayarlı tomografi tutulumu ile galectin-3, NIS, Ki-67 and PTEN ekspresyonları arasında anlamlı ilişki bulunamamıştır. Malign ve benign nodüller arasında SUV_{max} değerleri açısından fark saptanmamıştır. Malign nodüllerde PTEN kaybı sıklığı daha yüksek saptanmıştır. Moleküler belirteçlerin 18F-FDG tutulumunu gösteren diferansiye tiroid kanseri gelişimindeki rolü, yeni araştırmalarda daha geniş hasta grupları ile değerlendirilmelidir.

Anahtar kelimeler: Diferansiye tiroid kanseri; PTEN; Ki-67; NIS; Galectin-3; 18F-FDG PET/BT

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Introduction

Thyroid incidentalomas are asymptomatic thyroid lesions that can be detected by imaging. 18F-fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET) is a functional technique, which is useful for diagnosis, staging, restaging, and follow-up of many cancer types. Thyroid incidentalomas are found in 1.2-2.3% of 18F-FDG-PET/CT scans and malignancy risk of these lesions varies between 25-50% (1, 2). The most frequent malignant thyroid tumor found incidentally by 18F-FDG-PET/CT is papillary thyroid carcinoma (3). Further, 18FDG-PET CT could be useful in preventing unnecessary surgery for benign nodules with indeterminate cytology results (4).

The reasons for 18F-FDG accumulation in benign or malignant lesions have not been clearly explained. However, the focal FDG uptake by benign, poorly differentiated, and also by well-differentiated nodules suggest that the molecular alterations, responsible for increased glucose metabolism in tumor tissue, may lead to a PET-CT positivity (3).

Previous studies have reported an association between expressions of molecular markers and uptake of 18F-FDG in FDG-PET scans in certain types of cancer including thyroid tumors. An inverse relationship between NIS expression and 18F-FDG uptake was reported in differentiated thyroid carcinomas (DTCs) (5). This finding was supported by the studies demonstrating that tumors without I^{131} uptake were positive at 18F-FDG-PET imaging (6, 7). The regulation of glucose transporter 1 (GLUT1) expression and glucose uptake in thyroid cancer cell lines by PTEN has also been suggested (8).

In our study, we aimed to investigate the relationship between Ki67 proliferation index, NIS, Galectin-3, PTEN expressions, tumor histopathology, and 18FDG-PET CT positivity in thyroid tumors.

Material and Methods

Patients

Fifteen patients without known thyroid disease showing the focal uptake in the thyroid gland during an 18F-FDG-PET scan and total thyroidectomy because of malignant (n=9) or indeterminate (n=6) cytological results according to Bethesda classification were included in this study. Screenings were performed for the detection of primary sites in unknown primary tumors, differential diagnosis of solitary lung nodules, staging, and restaging of malignant melanoma, breast and lung cancer. Undifferentiated thyroid carcinomas were not included.

Twenty-one nodules showing an 18F-FDG uptake (13 papillary thyroid carcinoma and 8 benign nodules) and six PET-negative nodules but found to be papillary thyroid carcinoma in surgical specimens were included. A focal uptake in thyroid lesion was defined as an area with increased FDG uptake in the PET/CT images. The demographical characteristics, 18F-FDG PET CT, and histopathology reports were assessed, retrospectively.

Malignant- PET positive (n=13), malignant-PET negative (n=6) and benign-PET positive nodules (n=8) were grouped as group A, B, and C, respectively.

The study was approved by the Ethical Committee of Ankara University (March 2014, 05.214.14).

Fluorine-18 fluorodeoxyglucose positron emission tomography/ computed tomography scan

18F-FDG PET/CT images were obtained using a GE Discovery ST PET/CT scanner (GE Medical Systems, Milwaukee, Wisconsin, USA). The patients fasted for at least six hours before the 18F-FDG injection and the blood glucose level was checked to verify normoglycemia. Whole-body 18F-FDG PET/CT imaging was performed one hour after an intravenous injection of 8-10 mCi (296-370 MBq) 18F-FDG, while the patients were in a supine position. The PET images were obtained for 4 minutes in each bed position and were reconstructed with non-contrast CT images obtained from the patients using a standardized protocol including 140 kV, 70 mA, a tube rotation time of 0.5 s/rotation, a pitch of 6, and a section thickness of 5 mm. Attenuation correction was performed by fusion images in three planes and reviewed by a Xeleris Workstation (GE Medical Systems).

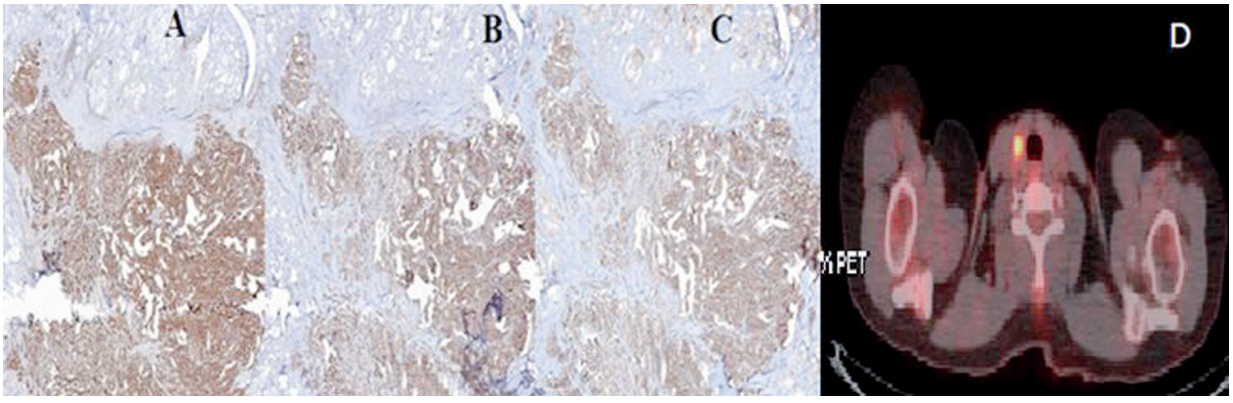


Figure 1: (A) PTEN, **(B)** Galectin-3 and **(C)** NIS strong positivity in a malignant thyroid nodule. **(D)** PET-CT transaxial fusion image of same patient shows focal 18F-FDG uptake in the right lobe of the thyroid gland (SUVmax=9.9).

Immunohistochemistry

The immunohistochemical analysis for NIS, PTEN, Ki67, and Galectin-3 was performed in 27 nodules (Figure 1). Galectin-3 (QC4, NeoMarkers, 1:40 dilution), NIS (Monoclonal Antibody to SLC5A5, ACRIS, 1:600 dilution), PTEN (PTEN/MMAC1 Ab-4, Thermo Scientific, 1:40 dilution), and Ki-67 (SP6, Cell Marque,1:200 dilution) antibodies were used for immunohistochemistry.

The appropriate paraffin-embedded tissues to determine the histological characteristics of the tumor were chosen and sliced into 4-µm sections by a microtome. These sections were stained through the streptavidin-biotin-peroxidase method with a Ventana automated immunostainer (BenchMark XT Staining Module, Ventana Medical Systems). Positive control tissues of the antibodies were taken into account during all procedures. The results of immunostaining were evaluated by two independent pathologists. Cytoplasmic staining was evaluated for Galectin-3 and PTEN. Both cytoplasmic and basolateral membrane staining were evaluated for NIS. Immunostaining intensity was classified as - 0: no staining, 1: mild, 2: moderate and 3: strong positivity for these antibodies. Immunostaining extensity was classified as - 0: no, 1: <50% and 2:>50% staining. Nuclear staining with Ki-67 was defined as positive and percentage of staining was given.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM Corp, NY, and USA). The categorical variables were compared using the chi-square and Fisher's exact test. The group variables with a normal distribution were compared using Student's *t*-test or analysis of variance, and the nonparametric variables were compared using the Mann-Whitney *U* test or Kruskal-Wallis test). A value of $p < 0.05$ was considered statistically significant.

Results

Twenty-seven nodules of fifteen patients [11 females (73.3%) and 4 males (26.7%)] were evaluated. The mean age of patients was 59.2 ±10.1 years. Six (40%) patients were younger than 60 years. Focal uptake in 18FDG-PET CT was present in 21 (78%) nodules. Among all nodules, 19 (70%) were malignant according to immunohistochemistry.

The malignancy risk was not associated with 18F-FDG PET positivity in thyroid nodules (p=0.136). SUVmax values were not statistically different between malignant and benign nodules with focal 18FDG uptake (7.7±5.4 vs. 7.0±4.4, p=0.75). Thirteen nodules (48%) were negative for Galectin-3 and the remaining fourteen (52%) had staining extensity higher than 50%. Galectin-3 staining extensity or intensity was not associated with malignancy or 18F-FDG uptake (Table 1). Galectin-3 staining intensity was not different between Group A, B and C nodules (Table 2).

NIS staining extensity was negative in 10 (37%), <50% in 7 (26%) and >50% in 10 (37%) patients. Eleven out of 12 nodules in patients older than 60 years showed positive staining with NIS. NIS positive staining was significantly more frequent in older patients [11 (91.6%)] than the others [6 (40%)] (p=0.019). Nine out of nineteen (47.4%) malignant nodules had NIS staining with high extensity, whereas only one benign nodule took intense staining. NIS staining intensity was not different between Group A, B and C nodules (Table 2). The nodule characteristics according to the NIS staining extensity are summarized in Table 1.

PTEN was negative in eight of 19 malignant nodules (42.1%) whereas only one (12.5%) benign nodule was negative (p=0.01). The staining extensity was not different between Group A, B and C nodules (Table 2). The associations between PTEN staining extensity and nodule characteristics are summarized in Table 1.

Ki-67 proliferation index was not associated with age, gender, and malignancy. One out of six nodules (16.7%) without 18F-FDG uptake had Ki-67 proliferation index higher than 3% and 8 out of 21 nodules (38.1%) with pathological 18F-FDG uptake had Ki-67 proliferation index higher than 3% (p=0.3). Mean Ki67 proliferation index was not different between three groups (2.46±1.19, 2.0±1.09 and 1.75±1.16, in group A, B, and C, respectively) (p=0.38) (Table 2). There was no association between Ki-67 proliferation index and SUVmax values (p=0.08).

Discussion

Thyroid lesions with focal 18F-FDG uptake may be either benign or malignant tumors (9, 10). Fine needle aspiration biopsy is recommended for the nodules equal to or greater than 10 mm observed by PET-CT (9). The factors that have an influence on FDG uptake of thyroid nodules have not yet been determined. In this study, we investigated the relationship between 18F-FDG uptake and molecular markers including Galectin-3, PTEN, NIS, and Ki-67 proliferation index.

Galectin-3 is a β-galactoside-binding protein that plays critical roles in cell growth, proliferation, cell to cell and matrix adhesion, transformation, tumorigenesis, and angiogenesis (11, 12). Galectin-3 expression was demonstrated in both benign and

Table 1. Association between Galectin-3, NIS, PTEN staining extensity and patient-nodule characteristics.

	Galectin- 3				NIS				PTEN			
	Negative	<%50 staining	≥%50 staining	P	Negative	<%50 staining	≥%50 staining	P	Negative	<%50 staining	≥%50 staining	P
18F-FDG PET												
Uptake - (n=6)	3 (50)	0 (0)	3 (50)	NS	3 (50)	0 (0)	3 (50)	NS	3 (50)	0 (0)	3 (50)	0.058
Uptake + (n=21)	10 (47.6)	0 (0)	11(52.4)		7 (33,3)	7 (33,3)	7 (33,3)		6 (28,6)	9 (42,8)	6 (28,6)	
Pathology												
Benign (n=8)	6 (75)	0 (0)	2 (25)	NS	2 (25)	5 (62,5)	1 (12,5)	0.01	1 (12,5)	6 (75)	1 (12,5)	0.012
Malignant(n=19)	7 (36.8)	0 (0)	12(63.2)		8 (42,1)	2 (10,5)	9 (47,4)		8 (42,1)	3 (15,8)	8 (42,1)	

Table 2. Galectin-3, NIS, PTEN immunostaining extensity and Ki-67 proliferation index, according to malignancy and 18F-FDG uptake.

	Group A (n:13)	Group B (n:6)	Group C (n:8)	p
Galectin-3 negative (n:13)	4 (30.8%)	3 (50%)	6 (75%)	0,143
Galectin-3 positive (n:14)	9 (69.2%)	3 (50%)	2 (25%)	
NIS negative (n:10)	5 (38.5%)	3 (50%)	2 (25%)	0,620
NIS positive (n:17)	8 (61.5%)	3 (50%)	6 (75%)	
PTEN negative (n:9)	5 (38.5%)	3 (50%)	1 (12.5%)	0,259
PTEN positive (18)	8 (61.5%)	3 (50%)	7 (87.5%)	
Ki-67 proliferation index (mean±SD)	2.46±1.19	2.0±1.09	1.75±1.16	0,38

malignant thyroid nodules but not in the normal thyroid gland (13). Inohara et al. showed an intense and strong Galectin-3 expression in malignant thyroid tumors (14). The determination of Galectin-3 and HBME-1 panel in needle biopsy has been suggested as a second-line diagnostic method for nodules with indeterminate cytology (15, 16). FDG-PET/CT has also been suggested as a cost-effective method for differential diagnosis of indeterminate nodules (4). We investigated any possible association between these two diagnostic methods. Galectin-3 staining intensity or extensity was not different between the three nodule groups.

Well-differentiated thyroid tumors with I^{131} uptake are usually negative for 18F-FDG uptake (6, 7). An inverse relationship between 18F-FDG uptake and NIS expression in tumor tissue and metastatic lymph nodes was reported previously (5). In a subsequent study, Lee et al. evaluated 46 DTCs and reported that there was no association between NIS expression in tumor tissue and 18F-FDG positivity (17). The decreased expression of the NIS gene was observed to be frequent in DTCs (18, 19). In our study, a highly intense NIS staining was frequent in malignant nodules compared to the benign ones but 18F-FDG uptake was not associated with NIS expression. The NIS expression intensity or extensity was not different between the three nodule groups.

Glucose transporter 1 (GLUT1) is the most important glucose transporter in differentiated thyroid cancers (20). The expression of GLUT proteins was shown to be controlled by PI3k/AKT pathway (21). A genetic manipulation of PTEN expression was suggested to be related to the increased GLUT1 expression, leading to 18F-FDG uptake in PTEN negative tumors (8). It was concluded that malignant thyroid tumors with loss of PTEN expression may be diagnosed with PET-CT. However, in our study PTEN expression was not statistically different between the three nodule groups.

High Ki67 proliferation index was found to predict the recurrence of DTC and shortened disease-free survival in certain studies (22). Previous studies revealed a positive correlation between Ki-67 proliferation index, focal 18F-FDG uptake, and SUVmax values in certain types of cancer, and the proliferative activity was linked to the metabolic activity of tumor (23-25). To the best of our knowledge, the relationship between Ki67 labeling index and 18F-FDG uptake in thyroid nodules has not been studied yet. We observed that one out of the six nodules (16.7%) without 18F-FDG uptake had Ki-67 proliferation index higher than 3% and eight out of nineteen nodules (38.1%) with pathological 18F-FDG uptake had Ki-67 proliferation index higher than 3%. This finding was not statistically significant. However, the possible association may be masked because of relatively low Ki-67 levels and a limited number of nodules included in the study.

The important limitation of this study was relatively small sample size.

Conclusions

18F-FDG uptake is not associated with Ki67, Galectin-3, PTEN or NIS expression in tumor tissues. The importance of PET positivity in thyroid nodules may be explained by the identification of molecular markers related to FDG uptake.

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Authorship Contributions

Idea/Concept: Sevim Güllü, Güzin Çakmak, Berna İmge Aydoğan, Cevriye Cansız Ersöz, Elgin Özkan, Serpil Dizbay Sak;Design: Sevim Güllü, Güzin Çakmak, Berna İmge Aydoğan; Control/Supervision: Sevim Güllü, Güzin Çakmak, Berna İmge Aydoğan, Serpil Dizbay Sak, Elgin Özkan; Data Collection And/Or Processing: Güzin Çakmak, Berna İmge Aydoğan, Elgin Özkan, Cevriye Cansız Ersöz; Analysis and/or Interpretation: Güzin Çakmak, Cevriye Cansız Ersöz, Elgin Özkan, Sevim Güllü, Berna İmge Aydoğan; Literature Review: Güzin Çakmak, Berna İmge Aydoğan, Sevim Güllü; Writing the Article: Sevim Güllü, Berna İmge Aydoğan, Güzin Çakmak; Critical Review: Sevim Güllü, Güzin Çakmak, Berna İmge Aydoğan; References and Fundings: Berna İmge Aydoğan, Sevim Güllü, Serpil Dizbay Sak, Cevriye Cansız Ersöz; Materials: Serpil Dizbay Sak, Elgin Özkan, Güzin Çakmak, Cevriye Cansız Ersöz, Berna İmge Aydoğan, Sevim Güllü.

References

1. Chu QD, Connor MS, Lilien DL, Johnson LW, Turnage RH, Li BD. Positron emission tomography (PET) positive thyroid incidentaloma: the risk of malignancy observed in a tertiary referral center. Am Surg. 2006;72:272-275.
2. Cohen MS, Arslan N, Dehdashti F, Doherty GM, Lairmore TC, Brunt LM, Moley JF. Risk of malignancy in thyroid incidentalomas identified by fluorodeoxyglucose-positron emission tomography. Surgery. 2001;130:941-946.
3. Bertagna F, Treglia G, Piccardo A, Giubbini R. Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid incidentalomas. J Clin Endocrinol Metab. 2012;97:3866-3875.
4. Vriens D, Adang EM, Netea-Maier RT, Smit JW, de Wilt JH, Oyen WJ, de Geus-Oei LF. Cost-effectiveness of FDG-PET/CT for cytologically indeterminate thyroid nodules: a decision analytic approach. J Clin Endocrinol Metab. 2014;99:3263-3274.
5. Moon SH, Oh YL, Choi JY, Baek CH, Son YI, Jeong HS, Choe YS, Lee KH, Kim BT. Comparison of 18F-fluorodeoxyglucose uptake with the expressions of glucose transporter type 1 and Na+/I- symporter in patients with untreated papillary thyroid carcinoma. Endocr Res. 2013;38:77-84.
6. Feine U, Lietzenmayer R, Hanke JP, Held J, Wöhrle H, Müller-Schauenburg W. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J Nucl Med. 1996;37:1468-1472.
7. Chung JK, So Y, Lee JS, Choi CW, Lim SM, Lee DS, Hong SW, Youn YK, Lee MC, Cho BY. Value of FDG PET in papillary thyroid carcinoma with negative 131I whole-body scan. J Nucl Med. 1999;40:986-992.
8. Morani F, Phadngam S, Follo C, Titone R, Aimaretti G, Galetto A, Alabiso O, Isidoro C. PTEN regulates plasma membrane expression of glucose transporter 1 and glucose uptake in thyroid cancer cells. J Mol Endocrinol. 2014;53:247-258.
9. Jamsek J, Zagar I, Gaberscek S, Grmek M. Thyroid lesions incidentally detected by (18)F-FDG PET-CT-a two centre retrospective study. Radiol Oncol. 2015;49:121-127.
10. Demir Ö, Köse N, Özkan E, Ünlütürk U, Aras G, Erdoğan MF. Clinical significance of thyroid incidentalomas identified by 18F-FDG PET/CT: correlation of ultrasonograpy findings with cytology results. Nucl Med Commun. 2016;37:715-720.
11. Inohara H, Akahani S, Raz A. Galectin-3 stimulates cell proliferation. Exp Cell Res. 1998;245:294-302.
12. Wang L, Guo XL. Molecular regulation of galectin-3 expression and therapeutic implication in cancer progression. Biomed Pharmacother. 2016;78:165-171.
13. Cvejic D, Savin S, Paunovic I, Tatic S, Havelka M, Sinadinovic J. Immunohistochemical localization of galectin-3 in malignant and benign human thyroid tissue. Anticancer Res. 1998;18:2637-2641.
14. Inohara H, Honjo Y, Yoshii T, Akahani S, Yoshida J, Hattori K, Okamoto S, Sawada T, Raz A, Kubo T. Expression of galectin-3 in fine-needle aspirates as a diagnostic marker differentiating benign from malignant thyroid neoplasms. Cancer. 1999;85:2475-2484.
15. Trimboli P, Guidobaldi L, Amendola S, Nasrollah N, Romanelli F, Attanasio D, Ramacciato G, Saggiorato E, Valabrega S, Crescenzi A. Galectin-3 and HBME-1 improve the accuracy of core biopsy in indeterminate thyroid nodules. Endocrine. 2016;52:39-45.
16. Zhang L, Krausz T, DeMay RM. A pilot study of galectin-3, HBME-1, and p27 triple immunostaining pattern for diagnosis of indeterminate thyroid nodules in cytology with correlation to histology. Appl Immunohistochem Mol Morphol. 2015;23:481-490.
17. Lee JW, Min HS, Lee SM, Kwon HW, Chung JK. Relations between pathological markers and radioiodine scan and (18)F-FDG PET/CT findings in papillary thyroid cancer patients with recurrent cervical nodal metastases. Nucl Med Mol Imaging. 2015;49:127-134.
18. Morari EC, Marcello MA, Guilhen AC, Cunha LL, Latuff P, Soares FA, Vassallo J, Ward LS. Use of sodium iodide symporter expression in differentiated thyroid carcinomas. Clin Endocrinol (Oxf). 2011;75:247-254.
19. Ringel MD, Anderson J, Souza SL, Burch HB, Tambascia M, Shriver CD, Tuttle RM. Expression of the sodium iodide symporter and thyroglobulin genes are reduced in papillary thyroid cancer. Mod Pathol. 2001;14:289-296.
20. Ciampi R, Vivaldi A, Romei C, Del Guerra A, Salvadori P, Cosci B, Pinchera A, Elisei R. Expression analysis of facilitative glucose transporters (GLUTs) in human thyroid carcinoma cell lines and primary tumors. Mol Cell Endocrinol. 2008;291:57-62.

21. Samih N, Hovsepian S, Aouani A, Lombardo D, Fayet G. Glut-1 translocation in FRTL-5 thyroid cells: role of phosphatidylinositol 3-kinase and N-glycosylation. Endocrinology. 2000;141:4146-4155.
22. Müssig K, Wehrmann T, Dittmann H, Wehrmann M, Ueberberg B, Schulz S, Bares R, Petersenn S. Expression of the proliferation marker Ki-67 associates with tumour staging and clinical outcome in differentiated thyroid carcinomas. Clin Endocrinol (Oxf). 2012;77:139-145.
23. Tural D, Kivrak Salim D, Mutlu H, Erkilic M, Gunduz S, Karakurt M, Musri F, Tuna S, Boz A, Aydin F, Karayalcin B, Bozcuk H, Senol Coskun H. Is there any relation between PET-CT SUVmax value and prognostic factors in locally advanced breast cancer? J BUON. 2015;20:1282-1286.
24. Güreşci S, Özmen Ö, Uzman M, Şimşek G, Tatci E, Gökçek A, Yeniova AÖ. Correlation of Ki-67 proliferation index and 18-fluorodeoxyglucose uptake in colorectal incidental lesions detected by positron emission tomography-computed tomography. Turk J Med Sci. 2016;46:1182-1187.
25. Yamamoto Y, Nishiyama Y, Ishikawa S, Nakano J, Chang SS, Bandoh S, Kanaji N, Haba R, Kushida Y, Ohkawa M. Correlation of 18F-FLT and 18F-FDG uptake on PET with Ki-67 immunohistochemistry in non-small cell lung cancer. Eur J Nucl Med Mol Imaging. 2007;34:1610-1616.