Ulus Cerrahi Derg 2015; 31: 192-6
DOI: 10.5152/UCD.2015.2928

Serum Galectin-3: diagnostic value for papillary thyroid carcinoma

Serum Galectin-3'ün papiller tiroid kanserlerinde tanısal değeri

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ABSTRACT

Objective: Thyroid cancer constitutes approximately 1% of all cancers, approximately 90% of the endocrine malignancies, and is responsible for 0.4% of cancer-related deaths. Additional markers are required for the accurate diagnosis of thyroid malignancies. There is no marker that can accurately facilitate pre-operative benign-malignant differentiation of thyroid nodules. The present study aims to evaluate the diagnostic value of preoperative serum Galectin-3 levels in thyroid cancer and to avoid unnecessary aggressive interventions.

Material and Methods: Sixty-four patients who were operated between May 2009 and April 2011 were included in this study prospectively. Patients with toxic nodules and those with malignancies detected in preoperative fine needle aspiration biopsies (FNAB) were excluded. Patients with thyroid nodules of >3 cm in ultrasonography or having suspicious cytological findings in their preoperative FNABs regardless of the nodule size were included. Patients were divided into 2 groups, "control"and "cancer," according to the postoperative pathology results.

Results: The control group included 50 and cancer group included 14 patients. The mean age of the control group was 44.84±13.17 (19-79), while it was 44.14±15.94 (25-72) in the cancer group. A statistically significant difference was found between Galectin-3 levels in the cancer and control groups ($p<0.001$).

Conclusion: In the present study, serum Galectin-3 levels in patients with malignant nodules were statistically significant.

Keywords: Cancer, Galectin-3, serum biomarkers, thyroid

ÖZ

Amaç: Tiroid kanseri bütün kanserlerin yaklaşık %1'ini, endokrin malignitelerinin %90'ını oluşturur ve kansere bağlı ölümlerin %0,4'ünden sorumludur. Tiroid malignitelerinin doğru teşhisi için ek belirteçlere ihtiyaç vardır. Operasyon öncesinde tiroid nodüllerinin benign/malign ayrımını kesin olarak yapabilen bir belirteç henüz yoktur. Yapılan bu çalışmada amaç serum Galectin-3 değerinin tiroid kanserinde tanı değerini ölçmek ve gereksiz agresif girişimlerin önüne geçebilmektir.

Gereç ve Yöntemler: İleriye dönük verilerin derlenmesi ile oluşturulan bu çalışmaya Mayıs 2009-Nisan 2011 tarihleri arasında ameliyat edilen 64 hasta dahil edildi. Toksik nodülü olan hastalar ve preoperatif ince iğne aspirasyon biyopsisinde (İİAB) malignite saptanan hastalar çalışma dışı bırakıldı. Ultrasonografide üç santimetrenin üzerinde tiroid nodülleri olan veya nodül boyutuna bakılmaksızın İİAB'de şüpheli sitolojik bulguları olan hastalar çalışmaya dahil edildi. Hastalar postoperatif patoloji sonuçlarına göre kontrol grubu ve kanser grubu olmak üzere 2 gruba ayrıldı.

Bulgular: Kontrol grubunda 50, kanser grubunda 14 olgu mevcut idi. Kontrol grubunda hastaların yaş ortalaması 44,84±13,17 (19-79) ve kanser grubunda yaş ortalaması 44,14±15,94 (25-72) idi. Galectin-3 değerleri için gruplar arasında istatistiksel olarak anlamlı fark olduğu saptandı ($p<0,001$).

Sonuç: Bu çalışmada serum Galectin-3 değeri malign tiroid nodülü olanlarda istatistiksel olarak anlamlı derecede yüksek oranda saptandı.

Anahtar kelimeler: Kanser, Galectin-3, serum belirteçleri, tiroid

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Received / *Geliş Tarihi*: 26.09.2014
Accepted / *Kabul Tarihi*: 15.12.2014
Available Online Date / *Çevrimiçi Yayın Tarihi*: 09.04.2015

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INTRODUCTION

Thyroid cancer constitutes approximately 1% of all cancers, approximately 90% of the endocrine malignancies, and is responsible for 0.4% of cancer-related deaths (1). The importance of this type of cancer depends on the frequency in young adults rather than the prevalence in the population (2).

At present, thyroid ultrasonography (USG) and thyroid fine needle aspiration biopsy (FNAB) are the most commonly used methods in the preoperative diagnosis of thyroid cancers. Ultrasonography is a non-invasive and portable technique, providing information about the size and number of the nodules and is capable of solid-cystic differentiation without any radiation exposure to the patient. Further, USG is used as a guide during FNAB of nodules and lymphadenopathies in the neck.

Fine needle aspiration biopsy is currently regarded as the most reliable method in the differentiation of benign and malignant thyroid nodules. In some cases, it is difficult to distinguish between benign and malignant lesions and distinguishing follicular carcinomas from follicular adenomas is particularly difficult. Although usually reported as well tolerated by patients, FNAB is actually an invasive procedure.

It is cost effective with a low complication rate; however, an accurate diagnosis requires an experienced pathologist.

Additional markers are required for the accurate diagnosis of thyroid malignancies. There is no marker that can accurately facilitate pre-operative benign–malignant differentiation of thyroid nodules. Many markers have been used, and partial success has been obtained in previous studies. There are many studies suggesting that Galectin-3 is one of those effective markers. However, search for an accurate, simple, inexpensive, and less invasive method is still ongoing (3-5).

The present study aims to evaluate the diagnostic value of preoperative serum Galectin-3 levels in thyroid cancer and to avoid unnecessary aggressive interventions.

MATERIAL AND METHODS

Sixty-four patients who were operated between May 2009 and April 2011 were included in this study prospectively. Written informed constent was obtained from all participants. Patients with toxic nodules and those with malignancies detected in preoperative FNABs were excluded. Further, patients with thyroid nodules of >3 cm in USG or having suspicious cytological findings in their preoperative FNABs regardless of the nodule size were included (Bethesda I-V). Age, sex, the duration of complaints, family history, concomitant diseases, physical examination findings, biochemical data, USG results, USG-guided FNAB results, operation and pathology results, preoperative serum TSH, free T4, free T3, Galectin-3 values of the patients were recorded. Patients were divided into 2 groups, "control" and "cancer," according to the postoperative pathology results.

Serum Galectin-3 levels were measured by ELISA. Layers were coated with 50 µL (1 µg/mL) of purified goat anti-galectin-3 antibodies and buffered with carbonate solution. Phosphate buffered saline (PBS) containing 10% fetal calf serum (FCS) was used to block non-specific bindings for 1 h. Standard or samples were added and incubated for 2 h. Purified rabbit anti-galectin-3 antibodies (1 µg/mL PBS contains 10% glycerol) were added and incubated for 1 h. After washing, goat and rabbit IgGs were flushed, and horseradish peroxidase (1:3000; Bio-Rad, Richmond, CA) was then added and incubated for 1 h. Tetramethylbenzidine (TMB) containing 0.001% H_2O_2 was used as the substrate, and the optical density was measured at 450 nm (Galectin-3: normal range, 0-40 ng/mL).

Statistical Analysis

Statistical analysis was conducted using one-sample Kolmogorow-Smirnov and Shapiro-Wilk tests; stem and leaf and histogram charts were drawn. Data were presented as mean, standard deviation, median, minimum, maximum, or inventory quality ratio values were calculated according to the specifications. Normally distributed variables were compared using t test in independent groups and Mann–Whitney U test in others. Significance level was assumed as $p<0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In this study, patients diagnosed with cancer according to the definitive pathology results belonged to the "cancer" group and those with no malignancy belonged to the "control" group. The control group included 50 and the cancer group included 14 patients. Overall, a majority of patients were women (7 men and 57 women). The mean age of the control group was 44.84±13.17 (19-79), while it was 44.14±15.94 (25-72) in the cancer group. There was no significant difference between the 2 groups in terms of age (p=0.822).

Table 1. Mean values and standard deviations of fT3, fT4, TSH, galectin-3 levels of the control and cancer groups

	Control	Cancer	p
fT3	3.11±0.59 pg/mL	3.11±0.59 pg/mL	0.871
fT4	1.09±0.21 ng/mL	1.01±0.17 ng/mL	0.109
TSH	1.08±0.91 mLU/L	1.30±0.75 mLU/L	0.142
Galectin-3	79.66±36.02 ng/mL	179.71±66.50 ng/mL	<0.001

fT3: free T3; fT4: free T4; TSH: thyroid-stimulating hormone

Mean values and standart deviations of fT3, fT4, TSH, Galectin-3 levels of the control and cancer groups were presented in Table 1.

There was no significant difference between the cancer and control groups in terms of fT3 and fT4 levels (p=0.871, p=0.109, respectively).

There was no significant difference between the TSH levels of each group (p=0.142). Among 32 patients with a family goiter history, definitive pathology results of 6 patients were malignant, and among 32 patients with no family goiter history, definitive pathology results of 8 patients were malignant. There was no statistically significant difference between the 2 groups in terms of the family goiter history.

Among 64 patients (7 men and 57 women) under evaluation, pathology results of 2 men and 12 women revealed malignancy. No statistically significant difference was observed between both groups in terms of sex.

DISCUSSION

A large part of thyroid tumors are well-differentiated tumors developing from follicular cells, and they have a good prognosis (6, 7). Although FNAB is a helpful tool in diagnosing thyroid neoplasms, distinguishing between benign and malignant lesions is sometimes quite difficult. FNAB is insufficent particularly in distinguishing follicular carcinomas from the more prevalent follicular adenomas (3). For the exact diagnosis, it may be necessary to wait for the postoperative final pathology report. Therefore, additional markers are required for an accurate diagnosis of thyroid malignancies. Many studies have suggested that Galectin-3 is one of the effective markers. However, search for an accurate, simple, inexpensive, and less invasive method is still ongoing.

The benefit of using Galectin-3 as a diagnostic marker for thyroid cancer has recently attracted considerable attention, and it has been the most investigated molecule for diagnosing thyroid cancers. Galectin-3, a protein which bonds to β-galactoside residues of glycoproteins on the cell surface, is also defined in cytoplasmic and nuclear compartments (8, 9).

Galectin-3 expression has been reported to be a valuable marker for distinguishing between benign and malignant thyroid nodules. Galectin-3 is generally suggested as a biomarker for thyroid malignancies, and it has been found valuable, particularly in papillary carcinoma because of its high sensitivity and specificity (10, 11).

Galectin-3 has been detected in human thyroid carcinomas, however, not in benign tumors or in normal thyroid tissues (12, 13). To date, 14 varieties have been defined for galectin (14, 15).

Galectin-3 has been involved in the development of malignancies in organs, such as the gastrointestinal tract, central nervous system, head and neck, breast, pancreas, uterus, bladder, tongue, and thyroid (16-18).

Galectin-3 allows clinicians to identify the subgroup of the patients with a suspicious lesion but a low risk of malignancy, for whom a careful follow-up would be more appropriate rather than surgery (19). To avoid unnecessary aggressive surgery, Galectin-3 is recommended for the histological diagnosis of follicular lesions and for preoperative evaluation of the lesions with indeterminate thyroid cytology (20-24).

Among the biochemical parameters, mean values of Galectin-3 levels were significantly higher in the cancer group compared with the control group, while mean values of fT3, fT4, and TSH levels were observed to be close to each other. No statistically significant differences were observed between the two groups for fT3 and fT4 values.

Many previous researches have reported that the immunohistochemical expression of Galectin-3 increases in thyroid tissues of the patients with thyroid cancer. Therefore, we may consider that serum levels of Galectin-3 can present significant preoperative information. However, studies showing serum levels are insufficient and also inconsistent. In the present study, we investigated whether the serum levels of Galectin-3 are a determinant in distinguishing benign and malignant thyroid lesions.

In 1995, for the first time, Xu et al. (13) analyzed the association of Galectin-3 and thyroid cancers. Xu examined the immunohistochemical expression in differentiated thyroid cancers and suggested that this expression could be associated with malignant transformation of the thyroid epithelium and that Galectin-3 can be used as a marker for distinguishing between benign thyroid adenomas and differentiated thyroid carcinomas.

In 2005, Ouyang et al. (25), examined Galectin-3 expressions in preoperative FNABs and postoperative pathology specimens and reported that it is widely observed in well-differentiated thyroid neoplasms, while no expression was detected in benign thyroid nodules and thyroid adenomas.

Htwe et al. (26) indicated that although definite regulation mechanisms are not yet known, Galectin-3 still could be a useful tumor marker for tumor progression in thyroid cancers.

Saggiorato et al. (22) have reported that cytoplasmic Galectin-3 expression is a reliable preoperative molecular marker in minimally invasive thyroid carcinoma, definitely increasing the accuracy of conventional cytological examination and enabling a better selection of the surgical patients.

Cvejic et al. (27) have emphasized that the immunohistochemical expression of Galectin-3 is not the indicator of local metastasis and extrathyroidal invasion in papillary thyroid cancer and is an excellent marker for classic papillary thyroid carcinomas; however, it should be used carefully to avoid false negative results because of the existence of non-conventional variants of papillary thyroid carcinoma.

Papotti et al. (28) have investigated Galectin-3 and HBME-1 immunoexpression in well-differentiated thyroid carcinomas with follicular structure and have found that tumors containing both markers were associated with papillary thyroid carcinoma. Saleh et al. (29) have examined the immunoexpression of Galectin-3, CK19, HBME-1, and RET oncoprotein in thyroid FNAB specimens and emphasized that Galectin-3 was the most sensitive and specific marker in distinguishing benign thyroid nodules from the malignant ones.

Saleh et al. (29) have performed 1-DE immunoblotting for detecting Galectin-3 levels and stated that papillary carcinoma can be easily discriminated from follicular adenoma, follicular carcinoma, and non-neoplastic diseases using this method.

Niedziela et al. (30) have detected Galectin-3 expression in Hashimoto thyroiditis. However, except Hashimoto thyroiditis, the diagnostic value of Galectin-3 in thyroid malignancies is still very high.

Oestreicher-Kedem et al. (31) have stated that Galectin-3 expression in Hurthle cell proliferation or in minimally invasive follicular carcinomas may lead to problems in diagnosis.

To date, almost all studies investigating the association between Galectin-3 levels and thyroid carcinomas used thyroid tissue, immunohistochemical examination, and mRNA measurements, while there are very few studies conducted on the association between serum levels of Galectin-3 and thyroid carcinomas.

The first of these studies was conducted by Saussez et al. (32); they found higher serum levels of Galectin-3 in patients with thyroid disease compared with healthy individuals. With serum Galectin-3 measurements, micro- and macropapillary carcinomas were distinguished from non-malignant thyroid diseases with a specificity of 74%, sensitivity of 73%, positive predictive value of 57%, and negative predictive value of 85%. With high Galectin-3 concentrations, 87% of macropapillary thyroid carcinomas and 67% of micropapillary thyroid carcinomas were detected.

In a study conducted by Inohara et al. (33) in patients with thyroid nodules, FNABs of 118 patients and serum Galectin-3 levels of 46 patients were examined and compared with histological findings in post-thyroidectomy specimens. Galectin-3 concentration in FNAB specimens of patients with papillary carcinoma were markedly higher than the other thyroid entities, while no specific difference was found in serum Galectin-3 levels between healthy individuals and patients with thy-

roid nodules. Therefore, the study indicated serum Galectin-3 levels as inappropriate for being a marker for papillary thyroid carcinomas.

Isic et al. (34) compared preoperative serum Cyfra 21.1 [cytokeratin (CK19) soluble fragment] and Galectin-3 levels of patients with thyroid tumors with tissue expressions. High serum Galectin-3 levels were found in thyroid carcinomas but also in adenomas. No significant correlation was found between serum and tissue levels. As a result, CK19 and Galectin-3 were evaluated as being good tissue markers; however, serum levels of these markers were not a reliable indicator for the diagnosis of thyroid malignancies and follow-up of thyroid cancers.

Gang et al. (35) have measured Galectin-3 levels in serum and surgical specimens of a group of patients comprising of 159 patients with thyroid malignancy and 16 patients without thyroid malignancy. They found markedly higher values in patients with malignancy. They stated that Galectin-3 measurements in serum and surgical specimens would result in higher diagnostic rates in thyroid cancers.

Maki et al. (36) have revealed markedly higher serum Galectin-3 levels in patients with papillary cancer compared with that in the control group.

In several studies, the immunoexpression of Galectin-3 was stated as a highly sensitive and specific marker for the thyroid carcinomas with follicular origin, particularly for papillary thyroid carcinomas (17-22, 30).

Data obtained during this study are consistent with those of previous studies by Saussez (32), Gang (35) and Makki et al. (36), and serum Galectin-3 levels markedly increased in papillary thyroid malignancies.

It has been reported that FNABs showed a sensitivity of 65%-98% and specificity of 72%-100% in thyroid malignancies (37-39).

In the present study, only patients with suspicious FNAB results were included, while those who underwent surgery immediately after getting definite malignant diagnosis in FNAB were excluded. The number of false positive and true positive cases was zero. Therefore, sensitivity and specificity rates were not reported.

CONCLUSION

In the present study, serum Galectin-3 values in patients with malignant nodules were statistically significant. As studies supporting this finding are limited so far, we can say that serum Galectin-3 levels can only be regarded as a helpful tool for distinguishing between benign and malignant nodules before the operation. Being non-invasive, simple, and inexpensive are other advantages in addition to being reliable.

Further research, testing the diagnostic value of the serum Galectin-3 levels in thyroid cancers, is required for the widespread clinical use of the data presented in this study.

Ethics Committee Approval: Approval of the ethics committee was not required at the date of this study was conducted.

Informed Consent: Written informed consent was obtained from patients who participated this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.Y., T.K., S.T.; Design - E.Y., T.K., S.T.; Supervision - T.K., S.T.; Funding - E.Y., C.T.; Materials - E.Y., C.T.; Data Collection and/or Processing - E.Y., C.T.; Analysis and/or Interpretation - E.Y., T.K.; Literature Review - E.Y., T.K.; Writer - E.Y., C.T.; Critical Review - T.K., S.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışmanın yürütüldüğü tarihte etik komite onayı zorunluluğu bulunmadığından alınmamıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - E.Y., T.K., S.T.; Tasarım - E.Y., T.K., S.T.; Denetleme - T.K., S.T.; Kaynaklar - E.Y., C.T.; Malzemeler - E.Y., C.T.; Veri toplanması ve/veya işlemesi - E.Y., C.T.; Analiz ve/veya yorum - E.Y., T.K.; Literatür taraması - E.Y., T.K.; Yazıyı yazan - E.Y., C.T.; Eleştirel İnceleme - T.K., S.T.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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