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Investigation of the Presence of Integrin Alpha-3 and Beta-1 Receptors on Tumor Tissue, Metastatic Lymph Node and Normal Tissue in Thyroid Cancer

Tiroid Kanseri Tümör Dokusu, Metastatik Lenf Nodu ve Normal Doku Üzerinde İntegrin Alfa-3 ve Beta-1 Reseptörlerinin Varlığının Araştırılması

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Abstract

Objectives: The important roles of integrins in tumor invasion, migration and proliferation are well known. In this study, we investigated the presence of integrin α3 and β1 receptors in tumor tissue, metastatic lymph node (LN) and normal thyroid tissue of patients diagnosed with thyroid cancer (TCa) and showed the prognostic and diagnostic value of these molecules as well as peptide-receptor.

Methods: Sixty-one patients with TCa were included in this study. The presence of integrin α3 and β1 expression was investigated by immunohistochemical methods from tumor tissue after total thyroidectomy. TNM system was used in tumor staging. The relationship between prognostic properties such as tumor size, LN metastasis, capsular invasion and the presence of integrin α3 and β1 expression was investigated.

Results: Classical type papillary TCa was the most common subtype in our study group with 31.1%. Integrin β1 was expressed in 4.9% (n=3) of normal tissue, 57.4% (n=35) of tumor tissue and 16.4% (n=10) of metastatic LN; integrin α3 was expressed in 50.8% (n=31) of normal tissue, 67.2% (n=41) of tumor tissue and 9.8% (n=6) metastatic LN. Integrin β1 expression was observed 21.3% (n=13), integrin α3 in 14.8% (n=9) and integrin α3 and β1 expression in 36.1% (n=22). Integrin β1 expression increased statistically significantly in the presence of LN metastasis and capsular invasion (p=0.022, 0.014, respectively). Furthermore, the expression of integrin α3 was found to be statistically significant in primary tumors of patients with LN metastasis (p=0.045).

Conclusion: Our study showed a significant increase in integrin α3 and β1 expression in LN metastasis or thyroid capsule invasion in tumor. Thus, it appears that the demonstration of the presence of integrin α3 and β1 expression in TCa is not only a prognostic biomarker but also has value as a potential theranostic target with peptide-bound radioactive agents.

Keywords: Thyroid cancer, papillary thyroid cancer, integrin alpha-3, integrin beta-1

Öz

Amaç: İntegrinlerin tümör invazyon, migrasyon ve proliferasyonu üzerindeki önemli rolleri iyi bilinmektedir. Çalışmamızda tiroid kanseri (TCa) tanılı hastaların tümör dokusunda, metastatik lenf nodunda (LN) ve normal tiroid dokusunda integrin α3 ve β1 reseptör varlığını araştırarak moleküllerin

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prognostik ve diagnostik değerini gösterme yanında ayrıca peptit-reseptör bağlı radyonüklidler ile TCa teranostik potansiyelini değerlendirmeyi amaçladık.

Yöntem: Çalışmaya TCa tanılı 61 hasta prospektif olarak dahil edilmiştir. Total tiroidektomi sonrasında tümör dokusu preparatlarından immünohistokimyasal yöntemler ile integrin α3 ve β1 ekspresyonu varlığı araştırıldı. Evrelemede TNM sistemi kullanılarak tiplendirme histopatolojik olarak yapıldı. Tümör boyutu, LN metastazı, kapsüler invazyon gibi prognostik özellikler integrin α3 ve β1 ekspresyon varlığı ile karşılaştırılarak incelendi.

Bulgular: Klasik tip papiller TCa %31,1 ile en sık bulunan alt tiptir. İntegrin β1'in normal dokuda %4,9 (n=3), tümörlü dokuda %57,4 (n=35) ve metastatik LN'de %16,4 (n=10) eksprese edildiği; integrin α3'ün; normal dokuda %50,8 (n=31), tümörlü dokuda %67,2 (n=41) ve metastatik LN'de %9,8 (n=6) eksprese edildiği gözlenmiştir. Hastaların %21,3'ünde (n=13) integrin β1, %14,8'inde (n=9) integrin α3 ve %36,1'inde (n=22) ise integrin α3 + β1 ekspresyonu birlikte gözlenmiştir. İntegrin β1 ekspresyonunun azalan tümör çapı, LN metastazı ve kapsüler invazyon varlığında istatistiksel olarak anlamlı şekilde arttığı saptanmıştır (sırasıyla p değerleri= 0,014, 0,022 ve 0,014). Ayrıca integrin α3 ekspresyonunun LN metastazlı olguların primer tümör odağında istatistiksel olarak anlamlı olacak şekilde yüksek oranda eksprese edildiği saptanmıştır (p=0,045).

Sonuç: Çalışmamızda tümör dokusu yanında LN metastazı ve tiroid kapsül invazyonu varlığında integrin α3 ve β1 ekspresyonundaki anlamlı artış gösterilmiştir. Böylece TCa'da integrin α3 ve β1 ekspresyon varlığının gösterilmesinin prognostik biomarker olması yanında, peptit bağlı radyoaktif ajanlar ile görüntülemede kullanılabilecek potansiyel diagnostik ve terapötik hedef olarak değeri ortaya konulmuştur.

Anahtar kelimeler: Tiroid kanseri, papiller tiroid kanseri, integrin alfa-3, integrin beta-1

Introduction

Thyroid cancers (TCa) with high incidence among endocrine system neoplasms, are the most common malignant tumors of the head and neck region. Papillary TCa (PTCa) is the most common and least aggressive type of TCa (1). Five-year survival rates more than 95% have been shown in TCa, which generally shows a good prognosis (2). However, 2-5% of these tumors lose their differentiated phenotype and the chance of radionuclide treatment with ^{131}I is eliminated since there is be no radioiodine uptake (3).

Integrins are heterodimeric transmembrane receptors that regulate cell-to-cell and cell extracellular matrix (ECM) interactions. The human genome encodes 24 integrin receptors with restricted combinations of 18α and 8β subunits. The functions of integrins are generally focused on ECM interactions and adhesion regulation; alpha 3 integrin has been associated with cellular motility, while beta 1 integrin has been associated with adhesion in stromal cells (4). The α3β1 integrin heterodimer that acts as a laminin receptor has been reported to be closely related to the migration of tumor cells. Studies have shown that integrins increase the aggressive property of the tumor due to their important role in tumor invasion, migration, proliferation, drug resistance and angiogenesis in many types of cancer, including TCa (5,6).

Although the incidence of TCa has increased due of easy and early diagnosis, mortality rates have decreased, especially in developed countries (7). However, the detection and treatment of indolent, asymptomatic TCa with population-based screening programs is a controversial issue because it does not cause a significant change in long-term mortality rates, increased complications and healthcare costs (8). This study provides the presence and ratio of integrin α3 and β1 in tumor tissue, metastatic lymph node (LN), and normal tissue in patients with TCa. Thus, it was investigated the potentials of integrin α3 and β1 as indicators in the differential diagnosis of aggressive subtypes of TCa.

Materials and Methods

Patients

Resection materials of 61 TCa patients [mean ± standard deviation (SD) age: 49.0±13.3, range: 25-80 years, 48 female, 13 male] were included in this retrospective study. Approval from the Institutional Review Board, University of Health and Sciences Turkey, Istanbul Training and Research Hospital Ethics Committee of our hospital was obtained (2670/2021). Additionally, the medical findings of all patients can be used for research through oral and written consent is obtained. TNM system was used in tumor staging.

Immunohistochemical Staining

In our study, resection materials of 61 patients diagnosed with TCa were retrospectively re-evaluated at our pathology clinic between 2015 and 2018. Immunohistochemical study auto-staining (Ventana Bench Mark ULTRA, Ventana Medical Systems, Inc., Tucson, AZ) was performed out in accordance with the manufacturer's protocols. The Ventana ultraviolet dab Detection kit for detection (Ventana Medical Systems, Inc.) was used. 2 sections of 2 µm thick were taken from the paraffin blocks of tissue samples. Sections EZ Prep solution (Ventana Medical Systems, Inc.) was deparaffinized with heat-induced antigen recovery (heat-induced antigen retrieval) cell conditioning 1 solution at 98 °C for 20 min for integrin β1 (4B7R) antibody (Ventana Medical Systems, Inc.) for Integrin α3 (a-3) antibody with

cell conditioning 2 solution at 98 °C for 56 min (Ventana Medical Systems, Inc.) performed. Endogenous peroxidase activity in 3% H_2O_2 for 4 min is an ultraviolet inhibitor (Ventana Medical Systems, Inc.) using blocked. Then a section β1 integrin (4B7R) (1:50 dilution, Santa Cruz biotechnology, Dallas, TX, USA, catalog no: sc-9970) and the other Integrin α3 (A-3): (1:100 dilution, Santa Cruz biotechnology, Dallas, TX, USA, catalog no: sc-374242) with, respectively, 1 h, 40 min and 20 min for periods of 1 h at 37 °C were incubated. It was then incubated at 37 °C with diaminobenzidine tetrahydrochloride and H_2O_2 for 8 min. After incubation, preparations were prepared by first painting with hematoxylin for 16 min and bluing reagent for 4 min.

Scoring;

Score 0: No staining,

Score 1: 1-25% staining in cells,

Score 2: 26-50% staining in cells,

Score 3: More than 50% staining was revealed in the cells.

According to this scoring system, patients with a score of 0 were defined as having negative receptor expression, and patients with a score of 1, 2, and 3 were defined as having positive receptor expression.

Laboratory Analysis

Three months after ablation of radioactive iodine 131 (RAI), serum thyroglobulin (Tg) levels were checked. Reactions for Tg detection were measured and reported using electro-chemiluminescence method in Roche brand, Cobas 6000 model (Tokyo, Japan) immunological autoanalyzer system with test kits manufactured in polystyrene wells suitable for chemiluminescent method.

Statistical Analysis

All data were evaluated using the SPSS software for Windows (v21.0; IBM, Armonk, NY, USA) program. All data were evaluated on the basis of mean, standard derivation, median (minimum-maximum), distribution frequencies, and percentages. The normalization of data distribution was evaluated by Kolmogorov-Smirnov test The Mann-Whitney U and Kruskal-Wallis tests were used to compare non-normal distribution variables. The chi-square test was used to evaluate categorizable variables. Results were considered statistically significant when the p value was <0.05.

Results

In the study group, 60.7% (n=37) of the patients were 45 years of age or older and 39.3% (n=24) were under 45 years of age. When histological variants are examined, classical PTCa with a ratio of 31.1% (n=19) is observed most frequently, while other common subgroups are 27.9% (n=17) multiple variant types, 14.8% (n=9) follicular TCa, and 11.5% (n=7) oncocytic PTCa. All subtypes of other tumors are presented in Table 1.

The average diameter of the largest tumor was 1.8±1.3 (range: 0.5-7.0) cm, 67.2% of lesions (n=41) are multicentric. 31.1% (n=19) were right lobes, 31.1% (n=19) were left lobes, and 37.7% (n=23) were bilateral placement. The thyroid capsule invasion was observed in 49.2% (n=30) and LN metastasis was observed in 16.4% (n=10). Three months after RAI in the postoperative period, the mean ± SD Tg levels were 79.9±469.7 (distribution range: 0.0-3649.0) ng/mL.

Integrin α3 expression was found to be 50.8% (n=31) in normal tissue, 67.2% (n=41) in tumor tissue (Figure 1, 2) and 9.8% (n=6) in metastatic LN. The expression of integrin β1 was evaluated in 4.9% (n=3) of normal tissue, 57.4% (n=35) of tumor tissue (Figure 3) and 16.4% (n=10) of metastatic LN. No statistically significant difference was observed in classic type PTCa (57.9%) and other poor differential variants (57.1%) when the expression of integrin β1 in tumor tissue was compared with clinical features (p=0.956). When the tumor diameters were less than 4 cm (n=57, 93.4%) and more 4 cm (n=4, 6.6%), no statistically significant difference was detected in terms of the presence of integrin β1 expression (p=0.203). Integrin β1 expression (25.7%) in primary tumors of patients with LN metastasis was found to be statistically significantly higher (p=0.022). Significantly higher integrin β1 expression [62.9% (positive) & 37.1% (negative)] was detected in the primary tumor of the patients with capsule invasion (p=0.014). The increase in postoperative Tg levels in the presence of integrin β1 expression was not statistically significant (p=0.555) (Table 2).

Table 1. Distribution of TCa tumor variants in the cases

Tumor variants	n (%)
Classic PTCa	19 (31.1)
Multiple variants	17 (27.9)
Follicular TCa	9 (14.8)
Oncocytic PTCa	7 (11.5)
Tall cell variant PTCa	3 (4.9)
Solid variant of PTCa	3 (4.9)
Warthin-like PTCa	2 (3.3)
Clear cell PTCa	1 (1.6)
Total	61 (100)

PTCa: Papillary thyroid cancer, TCa: Thyroid cancer

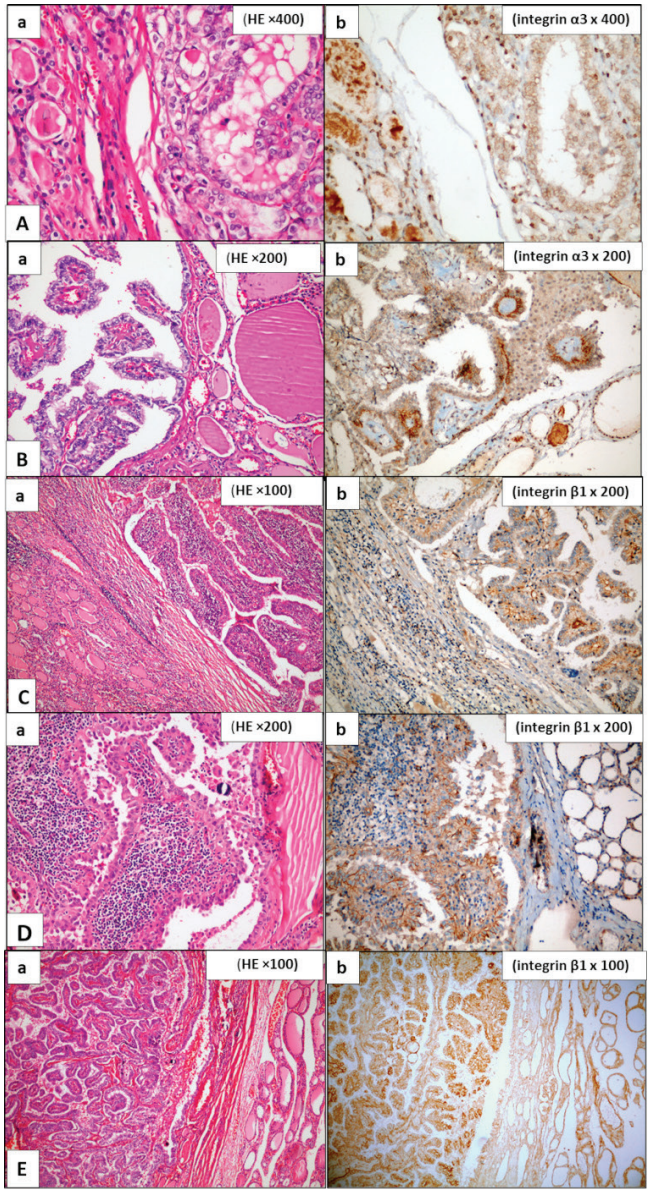

Figure 1. (A) a. Thyroid papillary carcinoma, classic variant (HE × 400). b. Poor cytoplasmic and membranous staining with integrin α3 in carcinoma cells (score 1) (integrin α3 x 400). (B) a. Thyroid papillary carcinoma, classic variant (HE × 200). b. Cytoplasmic membranous staining with integrin α3 in carcinoma cells compared to surrounding non-neoplastic thyroid tissue (score 2) (integrin α3 x 200). (C) a. Warthin-like variant of papiller thyroid carcinoma (HE × 100). b. Membranous staining with integrin β1 (4B7R) in a small number of carcinoma cells (score 1) [integrin β1 (4B7R) x 200]. (D) a. Warthin-like variant of papiller thyroid carcinoma (HE × 200). b. Significant membranous staining with integrin β1 (4B7R) in carcinoma cells compared to surrounding non-neoplastic thyroid tissue (score 2) [integrin β1 (4B7R) x 200]. (E) a. Thyroid papillary carcinoma, classic variant (HE × 100). b. Strong membranous staining with integrin β1 (4B7R) in most carcinoma cells (score 3) [integrin β1 (4B7R) x 100]
HE: Hematoxylin and eosin

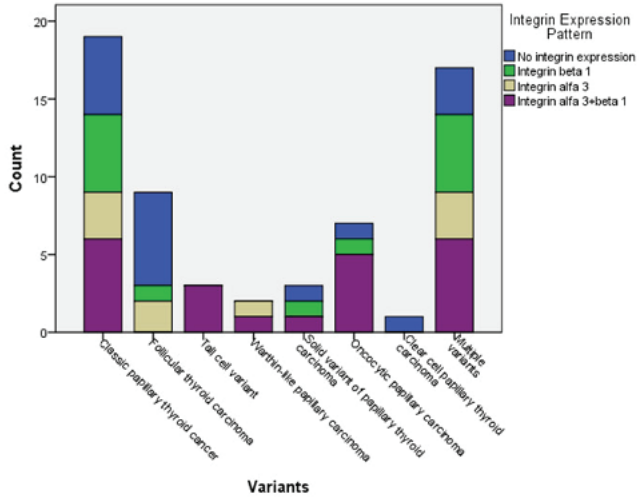

Figure 2. Integrin α3 and β1 expression distribution between all variants

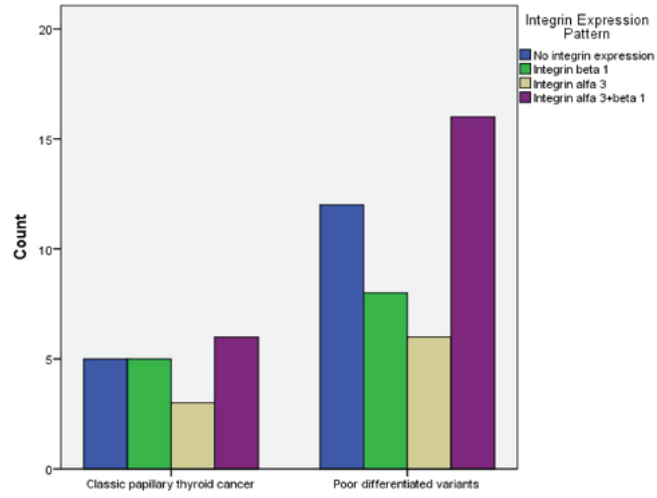

Figure 3. Distribution of integrin α3 and β1 expression between classic PTCa and poor differentiated variants
PTCa: Papillary thyroid cancer

When clinical features and expression of integrin α3 in primary tumor tissue were compared, no statistically significant difference was observed in the classic PTCa and poor differential variants (p=0.717). However, integrin α3 expression (25.8%) was found to be statistically significantly higher in primary tumor in LN metastases (p=0.045). The increase in postoperative Tg levels was not statistically significant in the presence of Integrin α3 expression (p=0.655) (Table 3).

In 27.9% (n=17) of the cases, both types of integrin expression were not observed, while in 21.3% (n=13) only integrin β1, in 14.8% (n=9) only integrin α3 and in 36.1% (n=22) integrin α3 and β1 expression were both observed.

However, the distributions of these groups on variants were not statistically significant (p=0.764) (Figure 2, 3). In primary tumor and lymph node metastasis, both integrin β1 and integrin α3 receptors were negative in 9 patients. The subtype distribution of these patients was as follows; 2 follicular (Tg: 0.43-2.38), 1 tall cell + classic (Tg: 3.85), 1 oncocytic (Tg: 3.51), 1 clear cell (Tg: 8.85) and 4 classical variants of papillary cancer (Tg: 0.39-213.24). There were multiple bone metastases in one of the patients with a classical variant with a serum Tg value of 213.24.

Discussion

Integrins regulate complex cellular behavior, such as intracellular signaling, survival, proliferation, migration, and transition. To date, pancreatic cancer, melanoma, prostate cancer, ovarian cancer, and many other cancer types including ECM signal TCa through provocation, especially in regulation; tumor progression, invasion, metastasis E-cadherin plays an important role in the processes is known (9). Integrins are formed in various combinations of α and β subunits and are expressed at varying rates in both normal and tumoral tissues. In normal thyroid tissue, especially α3β1 and αvβ3 integrin expression is restricted rates and their expression increases when cell-cell signaling intensifies and tumor transformation (10). While integrin α1β1 and α6β1 subunits are expressed in both normal and tumor tissues; integrin α6β4 subunit has never been observed in normal and adenomatous follicular cells of the thyroid, only intense expression of the thyroid in malignant forms such as follicular and PTCa has been reported and integrin α6β4 expression has been associated with aggressive tumoral behavior and poor prognosis (11). Liu et al. (12) in a study conducted with 150 TCa patients, integrin αvβ6 expression was never found in normal thyroid tissue; they reported its expression in tumor tissue and metastatic LN and determined the sensitivity of integrin αvβ6 expression to separating normal tissue from TCa at 78.9% and specificity at 62%. In our study, integrin β1 was expressed 4.9% in normal tissue, 57.4% in tumor tissue and 16.4% in metastatic LN. However, the expression of integrin α3 was found to be 50.8% in normal tissue, 67.2% in tumor tissue and 9.8% in metastatic LN. Integrin β1 was observed in 21.3% of cases, integrin α3 in 14.8% and integrin α3 + β1 expression in 36.1%.

Integrin αvβ3 is also known to be expressed at different rates in tumor cells and dividing vascular cells. The role of the thyroid hormone-tetrac (tetra-iodo-thyro-acetic-acid) receptor site on this molecule was determined by angiogenesis, cancer cell proliferation, metastasis and cancer cell resistance pathways (13). Chernaya et al. (14) investigated integrin expression in 70 TCa patients and showed a statistically significant increase in integrin α2 (p=0.037), integrin α3 (p=0.041) and integrin α5 (p=0.048) expression in PTC. Increased expression of integrin α3

Table 2. Relation between integrin β1 expression in tumor tissue and clinical, histopathological features of the patients

	Clinical variables	Integrin β1 expression		p value
		Negative n (%)	Positive n (%)	
Gender	Female Male	20 (76.9%) 6 (23.1%)	28 (80.0%) 7 (20.0%)	0.772
Age	<45 year ≥45 year	9 (34.6%) 17 (65.4%)	15 (42.9%) 20 (57.1%)	0.515
Variant	Classic PTC Poor differentiated variants	8 (42.1%) 18 (42.9%)	11 (57.9%) 24 (57.1%)	0.956
Tumor size	<4 cm ≥4 cm	23 (88.5%) 3 (11.5%)	34 (97.1%) 1 (2.9%)	0.203
Multicentric	Absent Present	9 (34.6%) 17 (65.4%)	11 (31.4%) 24 (68.6%)	0.793
Lobe	Unilateral Bilateral	17 (65.4%) 9 (34.6%)	21 (60.0%) 14 (40.0%)	0.668
LN involvement	Absent Present	25 (96.2%) 1 (3.8%)	26 (74.3%) 9 (25.7%)	0.022*
Thyroid capsular invasion	Absent Present	18 (69.2%) 8 (30.8%)	13 (37.1%) 22 (62.9%)	0.014*
Postoperative thyroglobulin levels	Mean ± SD	12.39±41.24	130.11±618.08	0.555

*p<0.05 statistically significant. PTCa: Papillary thyroid cancer, LN: Lymph node, SD: Standard deviation

Table 3. Relation between integrin α3 expression in tumor tissue and clinical, histopathological features of the patients

	Clinical variables	Integrin α3 expression		
		Negative n (%)	Positive n (%)	p value
Gender	Female Male	24 (80.0%) 6 (20.0%)	24 (77.4%) 7 (22.6%)	0.806
Age	<45 year ≥45 year	10 (33.3%) 20 (66.7%)	14 (45.2%) 17 (54.8%)	0.344
Variant	Classic PTC Poor differentiated variants	0 (52.6%) 20 (47.6%)	9 (47.4%) 22 (52.4%)	0.717
Tumor size	<4 cm ≥4 cm	27 (90.0%) 3 (10.0%)	30 (96.8%) 1 (3.2%)	0.294
Multicentric	Absent Present	11 (36.7%) 19 (63.3%)	9 (29.0%) 22 (71.0%)	0.525
Lobe	Unilateral Bilateral	19 (63.3%) 11 (36.7%)	19 (61.3%) 12 (38.7%)	0.869
LN involvement	Absent Present	28 (93.3%) 2 (6.7%)	23 (74.2%) 8 (25.8%)	0.045*
Thyroid capsular invasion	Absent Present	17 (56.7%) 13 (43.3%)	14 (45.2%) 17 (54.8%)	0.369
Postoperative thyroglobulin levels	Mean ± SD	32.40±97.42	25.94±653.95	0.655

*p<0.05 statistically significant. PTCa: Papillary thyroid cancer, LN: Lymph node, SD: Standard deviation

(p=0.017), integrin α6 (p=0.028) and integrin α9 (p=0.026) was also reported to be statistically significantly higher in patients with T3-T4 stages compared with T1-T2 stages. He et al. (15) in a study conducted with 181 patients with PTCa diagnosis, it was reported that integrin α3 expression showed 96.5% sensitivity and 77.3% specificity. Although the postoperative serum Tg levels were significantly higher in both integrin β1 and α3 expression positive patients than in patients with negative, no statistically significant differences were found in our study (respectively p=0.555, p=0.655). We think that these results are due to the small number of the study groups, as well as large SD values. In our study, we observed a statistically significant increase in integrin β1 expression in the presence of LN metastasis and capsular invasion, and a statistically significant increase in integrin α3 expression in the presence of LN metastasis.

Conclusion

In conclusion, in addition to the increase in integrin α3 and β1 expression in TCa primary tumor tissue, significantly increased expression of integrins in the presence of LN metastasis and capsular invasion was demonstrated. Thus, we think that the expression of integrin α3 and β1 in TCa can be used as diagnostic and prognostic biomarkers.

Ethics

Ethics Committee Approval: Approval from the Institutional Review Board, University of Health and Sciences Turkey, Istanbul Training and Research Hospital Ethics Committee of our hospital was obtained (2670/2021).

Informed Consent: Written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.C.Ş., D.C.T., A.V.S., Concept: E.A., T.F.Ç., Design: E.A., T.A., T.C.Ş., D.C.T., A.V.S., T.F.Ç., Data Collection or Processing: E.A., T.A., Analysis or Interpretation: E.A., T.A., Literature Search: E.A., T.A., Writing: E.A., T.A., T.F.Ç.

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

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