TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2023;38(2):127–35
doi: 10.5505/tjo.2023.3607

ORIGINAL ARTICLE

Value of Immunoscore in Thyroid Carcinoma

Ceyhan UĞURLUOĞLU,[1] Süleyman BALDANE,[2] Muslu Kazım KÖREZ,[3] Mesut BAYER[4]

[1]Deparment of Medical Pathology, Selçuk University Faculty of Medicine, Konya-*Türkiye*
[2]Deparment of Endocrine, Selçuk University Faculty of Medicine, Konya-*Türkiye*
[3]Deparment of Biostatistics, Selçuk University Faculty of Medicine, Konya-*Türkiye*
[4]Deparment of Medical Pathology, Selçuk University Faculty of Medicine, Konya-*Türkiye*

OBJECTIVE

Thyroid cancer is the most common endocrine neoplasm. About 10% develop invasive disease and 5% lymph node (LN) metastasis. An alternative immunoscore system to the tumor node metastasis (TNM) classification has been developed to predict the prognosis of solid tumors. The aim of this study is to investigate the potential roles of CD3+, CD8+ T lymphocyte infiltration and programmed death-ligand 1 (PD-L1) expression in immunoscore, the prognostic value of Immunoscore for Papillary thyroid cancer and its support for TNM classification.

METHODS

A total of 164 patients diagnosed with papillary thyroid cancer were included in our study. Immunoscore was evaluated by immunohistochemistry according to CD3+ and CD8+ T lymphocyte density at the tumor center and at the tumor margin. Immunoscore values were calculated. PD-L1 was evaluated by immunohistochemistry according to its density at the tumor center and at the tumor margin. The relationships between the parameters studied were evaluated statistically.

RESULTS

The presence of PD-L1 at the tumor centers in CD8+ T lymphocytes height was also significantly higher ($p<0.001$). There was no significant relationship between PD-L1 expression at the tumor center and LN metastasis and tumor size ($p>0.999$ and $p=0.226$, respectively). In the presence of PD-L1 expression at the tumor margin, LN metastasis ($p<0.001$) and tumor size ($p=0.029$) were higher. PD-L1 expression at the tumor margin was significantly associated with overall survival ($p<0.001$).

CONCLUSION

In particular, immunoscore value can be a good prognostic marker and its significant association with conditions associated with poor prognosis, such as PD-L1 expression, suggests that it may be a parameter that can be used and guided in stage scoring.

Keywords: Immunoscore; papillary thyroid cancer; programmed death-ligand 1; prognosis.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, accounting for 3.4% of all cancers.[1] Its incidence has increased over the past three decades, as epidemiological data show.[2,3] Thyroid cancer includes differentiated thyroid carcinoma (DTC), poorly DTC, anaplastic thyroid carcinoma (ATC), and medullary thyroid carcinoma.[4] Subtypes of DTC are papillary thyroid carcinoma (PTC) and follicular thyroid car-

Received: May 09, 2022
Accepted: January 09, 2023
Online: February 07, 2023

Accessible online at:
www.onkder.org

Dr. Ceyhan UĞURLUOĞLU
Selçuk Üniversitesi Tıp Fakültesi,
Tıbbi Patoloji Anabilim Dalı,
Konya-Türkiye
E-mail: drceyhan@gmail.com

Turk J Oncol 2023;38(2):127–35
doi: 10.5505/tjo.2023.3607

cinoma.[5] DTC is the most common type of thyroid cancer, accounting for 90% of all thyroid cancers. PTC accounts for 80% of this.[4] Although PTC has an overall good prognosis, 10% of patients develop invasive disease and distant metastases. In conclusion, it contributes to an increase in recurrence and mortality.[3,6] American Joint Committee on Cancer/International Association for Cancer Control (AJCC/UICC) staging is a classification system developed to define the extent of disease and estimate mortality based on a tumor node metastasis (TNM) scoring system.[7] It is the most commonly used staging system for thyroid cancer.[8] However, the clinical outcome can be very different among patients at the same stage.[9,10] The predictive accuracy of the traditional staging system assumes that disease progression is a tumor cell autonomous process and does not take into account the effects of the host immune response.[11] Recently, it has been reported that the risk of structural recurrence of patients with low-grade DTC may be overlooked by tumor classification in TNM, and the concept of the newly emerging molecular profile in prognosis is still lacking.[12] Evidence that tumor cells and immune cells have an important relationship in the tumor microenvironment is accepted worldwide.[13] The interaction between cancer and immune cells is an important determinant in cancer progression, and tumor infiltrating lymphocytes (TILs) are emerging as a powerful prognostic marker and therapeutic target in oncology.[14]

Contrary to the infiltration of cells responsible for chronic inflammation, it has been reported that the presence of a high number of T lymphocyte in cancers such as colon cancer, melanoma, lung cancer, pancreatic cancer, hepatocellular carcinoma, breast cancer is an indicator of good prognosis.[15] These findings highlight the relationship between endogenous antitumor immunity and cancer, and further highlight the potential role of patients immune system for the management of malignant disease. Indeed, there is a relationship between prognosis and immune cell infiltration in many types of cancer. This relationship validates the immune system's capacity to influence clinical outcome and predicts therapeutic responses.[16] Immune classification based on the degree of invasion of tumor tissue by immune cells (termed Immunoscore [IS]) has been found to increase the prognostic accuracy of tumor staging in colorectal cancer.[17] An international consortium has been initiated to validate and promote IS in routine clinical settings. The results of this international consortium resulted in the application of immunocorrection as a new component for cancer classification called TNM-Immune.[12] Studies in the field of thyroid cancer immunology support the importance of the immune system in thyroid cancer. The microenvironment of thyroid cancer is very important for prognosis and treatment.[9] However, its importance in PTC is not known enough.[18] The tumor microenvironment provides important prognostic and predictive information that has value in clinical management.[19] The discovery that intratumoral cytotoxic T lymphocytes (CTLs) have strong prognostic value provided the basis for the development of IS. IS evaluates the density of CD3+ and CD8+ T lymphocytes at the tumor center and at the tumor margin.[14] These parameters provide a scoring system ranging from IS 0 (I0), which has low densities of both cell types in both regions, to IS 4 (I4), which is characterized by high densities of both cell populations in both regions.[12] This test is a reproducible, quantitative, and standard immunologic test with high prognostic performance independent of all prognostic markers.[20] For colorectal cancer, the densities and type of CD8+ TILs were found to be correlated with tumor progression regardless of tumor stage in patients, making the IS an important pognostic factor.[21]

The immune checkpoint is of great importance in the recognition of CTLs by the tumor. Programmed death-ligand 1 (PD-L1) is expressed by B and T cells, monocytes, macrophages, and dendritic cells and plays an important role in the regulation of immune responses.[22] Overexpression of PD-L1 in various tumors and *in vitro* experimental models indicates compromised immune surveillance mechanism.[23] Tumor cells containing PD-L1 can induce T cell apoptosis, ınterleukin-10 production, and protect tumor cells from lysis by CTLs.[24] As a result, it leads to tumor cell resistance and immune escape of tumor cells, leading to a poor prognosis.[25] Blocking of immune checkpoints using monoclonal antibodies targeting the PD-L1 pathway has shown very promising results.[26] PD-L1 overexpression has been reported in a variety of human cancers, including head and neck, breast, ovarian, kidney, pancreatic, esophageal, non-small cell lung cancer, melanoma, and glioblastoma.[27] PD-L1 is associated with poor prognosis and increased resistance to anticancer treatments.[28] Therefore, the search for a predictive biomarker is imperative to identify patients likely to respond to anti-PD-L1 immunotherapy.

The relationship between IS and PD-L1 expression in PTC, clinical features and prognosis of PTC remain unclear. In this study, the relationship between IS and PD-L1 expression in PTC, clinical features, overall survival and prognostic value was investigated.

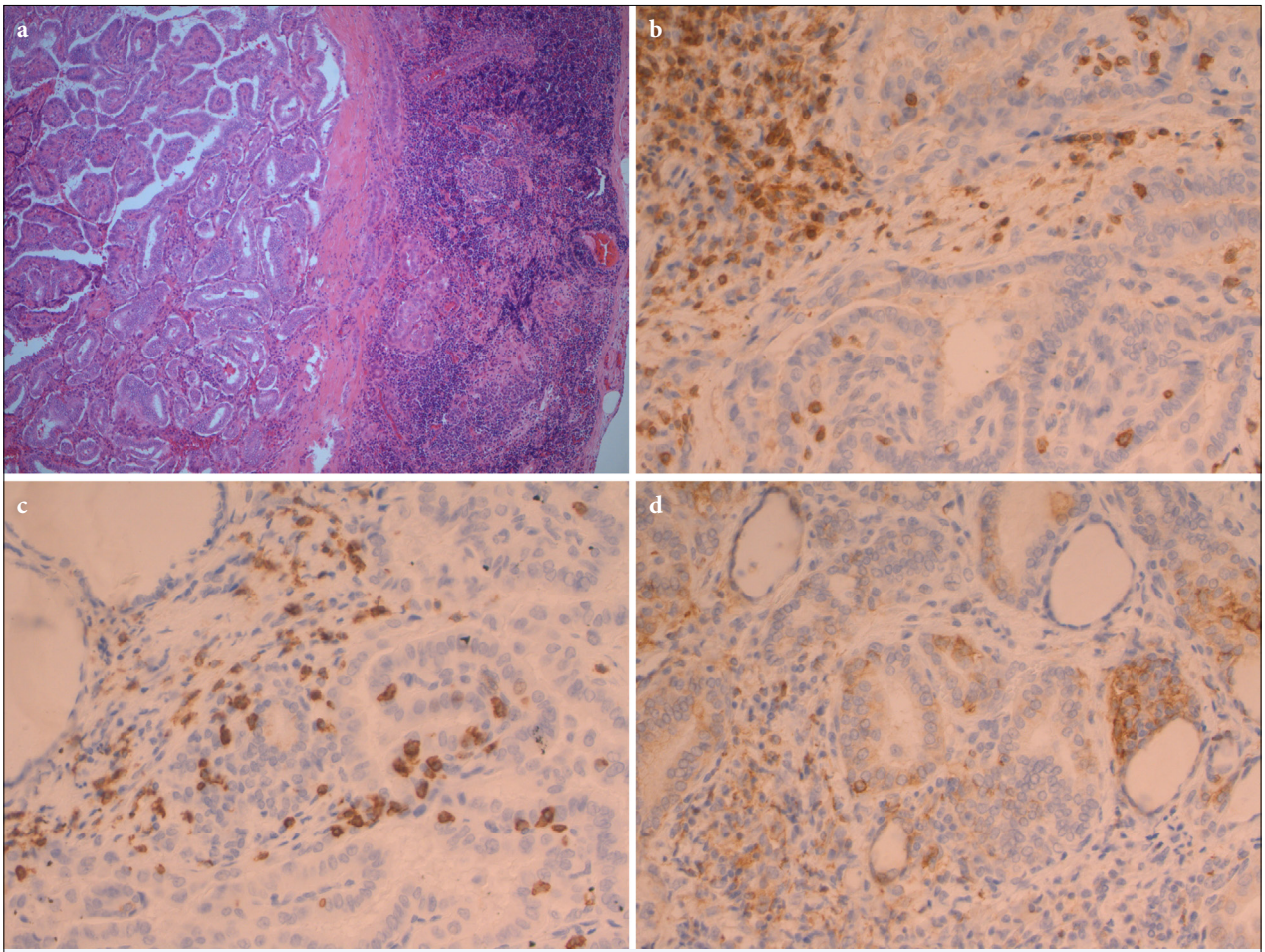

Fig. 1. (a) PTC, H&E ×100. (b) CD3+ immunohistochemical staining, ×200. (c) CD8+ immunohistochemical staining ×200. (d) PD-L1 immunohistochemical staining ×200.
PTC: Papillary thyroid carcinoma.

MATERIALS AND METHODS

A total of 164 patients who underwent total thyroidectomy in our institution between 2012 and 2021 and were diagnosed with PTC were included in the study. Tumor-registered selected blocks prepared from the surgical material were cut with a Leica RM2255 microtome at a thickness of 4 µm. IHC staining was done with the Dako Omnis automated IHC staining device. Immunohistochemically, CD 3 (Dako clone: polyclonal) and CD 8 (Dako clone: 1443) and PD-L1 (Dako clone: 22C3) staining were performed. Stained slides were individually scored from 0 to 2 under the light microscope (Zeiss Imager A1), and the scores both at the tumor center and tumor margin, and tumor center, and margin were summed to find IS values ranging from 0 to 4 (4). The data obtained were accepted as 0–2 points low and 3–4 points high.[29] In the evaluation of PD-L1 expression, cases with >1% tumor cell staining at the tumor center and at the tumor margin were considered positive, and cases without staining were considered negative[30] (Fig. 1a-d).

Statistical Analysis

All statistical analyses were performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Numerical variables such as age were expressed as mean ± standard deviation, and categorical variables were expressed as numbers (n) and percent (%). Yates continuity correction Chi-square and Fisher's exact test were performed to determine whether there was a statistically significant relationship between CD3+ and CD8+ T lymphocytes, PD-L1 expression, and tumor size and lymph node (LN) involvement. In addition, significant relationships with phi (ϕ) coefficients as effect size and

Turk J Oncol 2023;38(2):127–35
doi: 10.5505/tjo.2023.3607

odds ratio were expressed with 95% confidence interval over 2×2 cross tables. OS was defined as the time from diagnosis to date of death from any cause. The survival curves of CD3+, CD8+, and PD-L1 were estimated using the Kaplan–Meier method and Log-rank tests were used to compare the difference. Bipolar p<0.05 was considered statistically significant.

RESULTS

A total of 164 patients with PTC were included in our study. The mean age was 52.43±13.44 years and ranged from 20 to 79 years, and 126 (76.8%) of 164 patients were female and 38 (23.2%) were male. Of 164 patients, 49 (29.9%) were in the right lobe, 47 (28.7%) were in the left lobe, 13 (7.9%) were in the isthmus lobe, and 44 (26.8%) were multilobe. In addition, the location of 11 tumors (6.7%) could not be determined. Tumor size distribution was 40.5% for <1 cm and 59.5% for ≥1 cm. High CD3+ T lymphocyte infiltration was observed in 75 (45.7%) cases and high CD8+ T lymphocyte infiltration was observed in 70 (42.7%) cases. Twenty-two patients showed positive immunostaining for PD-L1 at the tumor center. Eleven patients showed positive immunostaining for PD-L1 at the tumor margin. Of 75 samples with high CD3+ T lymphocyte infiltration, 17 (22.7%) showed positive PD-L1 expression at the tumor center, and 5 (5.6%) of 89 samples with low CD3+ T lymphocyte infiltration showed positive PD-L1 expression at the tumor center. The rate of positive immunostaining for PD-L1 expression at the tumor center was approximately 5-fold higher in cases with high CD3+ T lymphocytes compared with low CD3+ T lymphocytes (22.7% vs. 5.6%, p=0.003). Of 75 samples with high CD3+ T lymphocyte infiltration, 51 (68%) showed high CD8+ T lymphocyte infiltration, and 19 (21.3%) of 89 samples with low CD3+ T lymphocyte infiltration showed high CD8+ T lymphocyte infiltration. The high infiltration rate of CD8+ T-lymphocytes was approximately three-fold higher in cases with high CD3+ T lymphocytes compared with low CD3+ T lymphocytes (68% vs. 21.3%, p<0.001). Eighteen (25.7%) of 70 samples with high CD8+ T lymphocyte infiltration showed positive PD-L1 expression at the tumor center and 4 (4.3%) of 94 samples with low CD8+ T lymphocyte infiltration showed positive PD-L1 expression at the tumor center. The rate of positive immunostaining for PD-L1 expression at the tumor center was approximately 6-fold higher in cases with high CD8+ T lymphocytes compared with low CD8+ T lymphocytes (25.7% vs. 4.3%, p<0.001). There was no statistically significant correlation between CD3+ and CD8+ T lymphocyte levels and tumor size (p=0.330 and p=0.190, respectively). LN involvement was observed in 11 (14.9%) of 74 patients with high CD3+ T lymphocyte levels and 5 (5.6%) of 86 patients with low CD3+ T lymphocyte levels. The difference between these two ratios was not statistically significant (p=0.101). LN involvement was observed in 9 (13.2%) of 68 patients with high CD8+ T lymphocyte levels and 7 (7.6%) of 92 patients with low CD8+ T lymphocyte levels. The difference between these two ratios was not statistically significant (p=0.365) (Table 1).

LN involvement was observed in 2 (9.0%) of 22 patients with PD-L1 positive at the tumor center and 14 (10.1%) of 138 patients who were negative. LN involvement was lower in patients with PD-L1 expression at the tumor center. The difference between these two ratios was not statistically significant (p>0.999). Furthermore, there was no statistically significant correlation between PD-L1 at the tumor center and tumor size (p=0.226). LN involvement was observed in 11 (100%) of 11 patients with positive PD-L1 tumor margin. The difference between these two ratios was statistically significant (p<0.001) (Table 2).

Of the 164 PTC patients, 10 (7.2%) died during the follow-up period. Median follow- up was 1065 days (range: 78–3890 days). In Kaplan–Meier analysis, CD3+ and CD8+ T lymphocyte levels and PD-L1 expression at the tumor center did not show a significant association with OS (Log-rank $\chi 2$=0.921, p=0.337; Log-rank χ^2=2.451, p=0.117; and Log-rank $\chi 2$=0.001, p=0.987; respectively) (Fig. 2a-c). No progression was observed in any of the 164 PTC patients. However, PD-L1 expression at the tumor margin was significantly associated with OS (Log-rank χ^2=18.008, p< 0.001; HR=10.41, 95% CI=2.75–39.36) (Fig. 2d).

DISCUSSION

Despite standard treatments, 5–10% of patients with PTC develop invasive and/or distant metastatic disease.[22] In addition, 1% of patients develop ATC. The prognosis of these patients is poor, survival is 3–5 months despite current treatment strategies.[31] Recurrent metastatic LN disease is common in patients with PTC.[32] The Joint International American Committee on Cancer/International Association for Cancer Control (AJCC/UICC) TNM staging system provides current guidelines for cancer classification.[7] However, the clinical outcome can be very different among patients at the same stage.[9] In addition, it has been

Table 1 Comparisons of CD3+ and CD8+ T-lymphocyte, and PD-L1 expression, lymph node and tumor size

	CD3+					CD8+				
	Low		High		p	Low		High		p
	n	%	n	%		n	%	n	%	
Tumor size					0.330[2]					0.190[2]
< 1 cm (n=66, 40.5%)	33	37.1	33	44.6		34	36.2	32	46.4	
≥ 1 cm (n=97, 59.5%)	56	62.9	41	55.4		60	63.8	37	53.6	
Total (n=163)	89	55.2	74	45.4		94	57.7	69	42.3	
CD8+					<0.001[2]					
Low (n=94, 57.3%)	70	78.7	24	32						
High (n=70, 42.7%)	19	21.3	51	68						
Total (n=164)	89	54.3	75	45.7						
Lymph node (LN)					0.101[1]					0.365[1]
No (n=144, 90%)	81	94.2	63	85.1		85	92.4	59	86.8	
Yes (n=16, 10%)	5	5.8	11	14.9		7	7.6	9	13.2	
Total (n=160)	86	53.8	74	46.3		92	57.5	68	42.5	
PD-L1 at center					0.003[1]					<0.001[1]
No (n=142, 86.6%)	84	94.4	58	77.3		90	95.7	52	74.3	
Yes (n=22, 13.4%)	5	5.6	17	22.7		4	4.3	18	25.7	
Total (n=164)	89	54.3	75	45.7		94	57.3	70	42.7	
PD-L1 at margin					0.030[1]					0.531[3]
No (n=153, 93.3%)	87	97.8	66	88		89	94.7	64	91.4	
Yes (n=11, 6.7%)	2	2.2	9	12		5	5.3	6	8.6	
Total (n=164)	89	54.3	75	45.7		94	57.3	70	42.7	

Data were described as n, %. [1]: Yates continuity correction χ^2 test; [2]: Pearson χ^2 test; [3]: Fisher's exact test.

Table 2 Comparisons of PD-L1 expression and lymph node metastasis and tumor size

	PD-L1 center					PD-L1 çevresi				
	0		1		p	0		1		p
	n	%	n	%		n	%	n	%	
Lymph node (LN)					>0.999[1]					<0.001[1]
No (n=144, 90%)	124	89.8	20	90.9		144	96.6	0	0	
Yes (n=16, 10%)	14	10.1	2	9.1		5	3.4	11	100	
Total (n=160)	138	86.3	22	13.7		149	93.1	11	6.9	
Tumor size					0.226[2]					0.029[1]
< 1 cm (n=66, 40.5%)	54	38.3	12	54.5		65	42.8	1	9.1	
≥ 1 cm (n=97, 59.5%)	87	61.7	10	45.5		87	57.2	10	90.9	
Total (n=163)	141	86.5	22	13.5		152	93.3	11	6.7	

Data were described as n, %. [1]: Fisher exact test; [2]: Yates continuity correction χ^2 test

recently reported that the risk of structural recurrence in patients with low-grade PTC may be overlooked by tumor classification in TNM-8.[33] The recently emerged concept of molecular profile in determining prognosis is still incomplete.[12] New prognostic markers may guide a therapeutic approach. Developing an effective antitumor immune response reduces the likelihood of tumor recurrence and metastasis. Thus, it positively affects the outcome of the disease.[4] Gallon developed an IS system that shows useful prognostic value for colorectal cancer.[11] Similarly, it has been discussed that IS may be superior to TNM classification in terms of prognosis in other malignancies such as pancreatic, liver, and breast cancer, as was ob-

Turk J Oncol 2023;38(2):127–35
doi: 10.5505/tjo.2023.3607

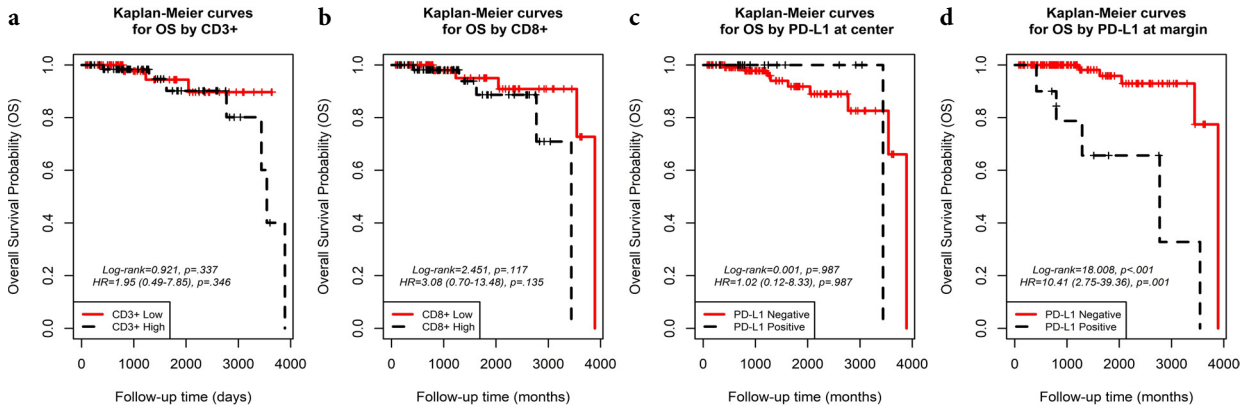

Fig. 2. Kaplan–Meier analysis of the overall survival of patients with PTC. (a) High or low CD8+ tumor-infiltrated lymphocyte count. (b) High or low CD8+ tumor-infiltrated lymphocyte count. (c) Programmed death ligand (PD-L1)+ or PD-L1– tumor cells at center. (d) Programmed death ligand (PD-L1)+ or PD-L1– tumor cells at margin.
PTC: Papillary thyroid carcinoma

served in colorectal cancer, and it was mentioned that a new cancer classification system might exist.[15,34,35]

Most studies have shown that high density of CD3+ and CD8+ T lymphocytes are associated with longer disease-free survival (DFS) and/or improved OS.[24] In PTC, CD8+ T lymphocytes were associated with lower tumor aggressiveness and a more favorable patient outcome.[21,36] Infiltration of CD8+ T cells was associated with increased DFS.[37] Positive expression of PD-L1 in PTC is associated with a higher risk of relapse and shortened DFS.[23,28] In another study, they found that PD-L1 expression was associated with lower survival in patients with thyroid cancer.[17] In our study, high CD3+ and CD8+ T lymphocytes infiltration may be associated with DFS. CD3+, CD8+ T lymphocytes, and PD-L1 expression at the tumor center did not show a significant association with OS (p=0.337, p=0.117, p=0.987, respectively). However, PD-L1 expression at the margin was significantly associated with OS (p<0.001).

In some studies, they did not find a significant relationship between CD8+ T lymphocytes infiltration and tumor size.[38] In our study, no statistically significant correlation was found between CD3+ and CD8+ T-lymphocyte levels and tumor size (p=0.330 and p=0.190, respectively). In PTCs, expression of PD-L1 was significantly associated with increased tumor size and multifocality.[39] In this study, they found a relationship between PD-L1 expiration and tumor size in advanced thyroid cancer.[17] In our study, no statistically significant correlation was found between PD-L1 expiration at the tumor center and tumor size (p=0.226). However, A significant correlation was found between PD-L1 expiration at the tumor margin and tumor size (p=0.029).

However, besides the relationship between PD-L1 expression and PTC, the clinical features and prognosis of PTC still remain unclear. In our study, the rate of positive immunostaining for PD-L1 expression at the tumor center was approximately six-fold higher in cases with elevated CD8+ T lymphocytes (p<0.001). The high infiltration rate of CD8+ T lymphocytes was approximately three-fold higher in subjects with high CD3+ T lymphocytes (p<0.001). These ratios show that CD8+ T lymphocytes are more valuable in determining the IS. It also supports that the IS is a strong prognostic marker. The IS can add additional power to the TNM classification, prognosis, and follow-up of patients. This information supports that CD3+ and CD8+ T lymphocytes are associated with progression and survival of thyroid cancer patients.

In our study, we examined whether there is a statistically significant relationship between CD3+ and CD8+ T lymphocytes, PD-L1 expression, and LN involvement. LN involvement was observed in 2 (9.5%) of 22 positive patients and 14 (10.1%) of 138 negative patients in the PD-L1 at the tumor center. The difference between these two ratios was not statistically significant (p>0.999). LN involvement was observed in 11 (100%) of 11 patients who were positive at the PD-L1 expression at the tumor margin. The difference between these two ratios is statistically significant (p<0.001). LN involvement was observed in 11 (14.9%) of 74 patients with high CD3+ T lymphocyte levels and 5 (5.8%) of 86 patients with low CD3+ T lymphocyte levels. The difference between these two ratios was not statistically significant (p=0.101). LN involvement was observed in 9 (13.2%) of 68 patients with high CD8+ T lymphocyte levels and 7 (7.6%) of 92 pa-

tients with low CD8+ T lymphocyte levels. The difference between these two ratios was not statistically significant (p=0.365). In our study, there was no statistically significant relationship between CD3+ and CD8+ T lymphocyte infiltrations, PD-L1 expression, and LN involvement. This shows us that LN metastasis develops independently of these parameters in early stage PTC. One study found that patients who were PD-L1 expression negative at the tumor center had a significantly longer survival than patients who were positive for PD-L1 at the tumor margin. [40] In our study, we found that LN involvement was less in patients with PD-L1 expression tumor center and LN involvement was higher in patients with PD-L1 expression at the tumor margin. This suggests that it is associated with shortened survival and shortened DFS. This information suggests that PD-L1 may be a biomarker for LN involvement in cases with PD-L1 expression at the tumor margin. As a biomarker, it can be used to monitor the survival and prognosis of cases.

Immune checkpoint inhibitors have made major contributions to the treatment of malignancies. [4,15,26] Our research may provide potential value for immunotherapy of PTC. At present, we think that effective biomarkers for predicting the prognosis of thyroid cancer are still lacking. Therefore, more studies should be conducted on IS, other factors in the microenvironment, and immune checkpoints in patients with PTC.

CONCLUSION

In our study, the correlation between IS levels, which is accepted as a prognostic biomarker in PTC, and PD-L1 levels, which acts as an immune checkpoint receptor ligand, among themselves and with other prognostic data was investigated. In particular, the IS value may be a good prognostic marker, and its significant association with conditions associated with poor prognosis, such as PD-L1 expression, suggests that it may be a parameter that can be used and guided in stage scoring. Similarly, considering the high cost of treatment protocols and the level of side effects, it was thought that it could be used in the selection of patients to be treated. In our study, no significant correlation was found between IS value and OS and tumor size. However, a significant correlation was found between the presence of PD-L1 expression at the tumor border and LN involvement and OS. Considering that these data are the parameters of the TNM system, the high IS value and PD-L1 expression at the tumor margin, which have a significant relationship with the prognosis, can be evaluated within the TNM staging system.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Selçuk University Faculty of Medicine Local Ethics Committee (no: 2022/190, date: 12/04/2022).

Financial Support: None declared.

Authorship contributions: Concept – C.U., S.B., M.K.K., M.B.; Design – C.U., S.B., M.K.K., M.B.; Supervision – C.U., S.B., M.K.K., M.B.; Funding – C.U., S.B., M.K.K., M.B.; Materials – C.U., S.B., M.K.K., M.B.; Data collection and/or processing – C.U., S.B., M.K.K., M.B.; Data analysis and/or interpretation – C.U., S.B., M.K.K., M.B.; Literature search – C.U., S.B., M.K.K., M.B.; Writing – C.U., S.B., M.K.K., M.B.; Critical review – C.U., S.B., M.K.K., M.B.

REFERENCES

1. Prete A, Souza PB, Censi S, Muzza M, Nucci N, Sponziello M. Update on fundamental mechanisms of thyroid cancer. Front Endocrinol (Lausanne) 2020;13;11:102.
2. Joong Na K, Choi H. Immune landscape of papillary thyroid cancer and immunotherapeutic implications. Endocr Relat Cancer 2018;25(5):523–31.
3. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, et al. Thyroid cancer mortality and incidence. Int J Cancer 2015;136(9):2187–95.
4. Nguyen QT, Lee EJ, Huang MG, Park YI, Khullar A, Plodkowski RA. Diagnosis and treatment of patients with thyroid cancer. Am Health Drug Benefits 2015;8(1):30–40.
5. Seib CD, Sosa JA. Evolving understanding of the epidemiology of thyroid cancer. Endocrinol Metab Clin North Am 2019;48(1):23–35.
6. Bai Y, Kakudo K, Jung CK. Updates in the pathologic classification of thyroid neoplasms: a review of the World Health Organization Classification. Endocrinol Metab 2020;35(4):696–715.
7. Onoda N, Sugitani I, Ito KI, Suzuki A, Higashiyama T, Fukumori T, et al. Evaluation of the 8th edition TNM classification for anaplastic thyroid carcinoma. Cancers 2020;27;12(3):552.
8. Park J, Lee S, Kim K, Park H, Ki CS, Oh YL, et al. TERT promoter mutations and the 8th edition TNM classification in predicting the survival of thyroid cancer patients. Cancers. 2021;5;13(4):648.
9. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. Nat Rev Cancer 2020;20(11):662–80.
10. Paulsen EE, Kilvaer TK, Rakaee M, Richardsen E, Hald SM, Andersen S, et al. CTLA-4 expression in the

Turk J Oncol 2023;38(2):127–35
doi: 10.5505/tjo.2023.3607

non-small cell lung cancer patient tumor microenvironment: diverging prognostic impact in primary tumors and lymph node metastases. Cancer Immunol Immunother 2017;66(11):1449–61.

11. Galon J, Mlecnik B, Bindea G, Angell HK, Berger A, Lagorce C, et al. Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. J Pathol 2014;232(2):199–209.
12. Manzardo OA, Cellini M, Indirli R, Dolci A, Colombo P, Carrone F, et al. TNM 8th edition in thyroid cancer staging: is there an improvement in predicting recurrence? Endocr Relat Cancer 2020;27(6):325–36.
13. Rakaee M, Kilvaer T, Jamaly S, Berg T, Paulsen EE, Berglund M, et al. Tertiary lymphoid structure score: a promising approach to refine the TNM staging in resected non-small cell lung cancer. Br J Cancer 2021;124(10):1680–9.
14. Trabelsi M, Farah F, Zouari B, Jaafoura MH, Kharrat M. An immunoscore system based on CD3 + And CD8 + infiltrating lymphocytes densities to predict the outcome of patients with colorectal adenocarcinoma. Onco Targets Ther 2019;12:8663–73.
15. Ros-Martínez S, Navas-Carrillo D, Alonso-Romero JL, Orenes-Piñero E. Immunoscore: a novel prognostic tool. Association with clinical outcome, response to treatment and survival in several malignancies. Crit Rev Clin Lab Sci 2020;57(7):432–43.
16. Fridman WH, Zitvogel L, Sautès-Fridman C, Kroemer G. The immune contexture in cancer prognosis and treatment. Nat Rev Clin Oncol 2017;14(12):717–34.
17. Wan B, Deng P, Dai W, Wang P, Dong Z, Yang C, et al. Association between programmed cell death ligand 1 expression and thyroid cancer: A meta-analysis. Medicine 2021;100(14):e25315.
18. Menicali E, Guzzetti M, Morelli S, Moretti S, Puxeddu E. Immune landscape of thyroid cancers: New insights. Front Endocrinol 2021;27;11:637826
19. Yang Z, Wei X, Pan Y, Xu J, Si Y, Min Z, et al. A new risk factor indicator for papillary thyroid cancer based on immune infiltration. Cell Death Dis 2021;12(1):51.
20. Marliot F, Pagès F, Galon J. Usefulness and robustness of Immunoscore for personalized management of cancer patients. Oncoimmunology 2020;9(1):1832324.
21. Church SE, Galon J. Regulation of CTL infiltration within the tumor microenvironment. In: Advances in Experimental Medicine and Biology. Cham: Springer; 2017. p. 33–49.
22. Chowdhury S, Veyhl J, Jessa F, Polyakova O, Alenzi A, MacMillan C, et al. Programmed death-ligand 1 overexpression is a prognostic marker for aggressive papillary thyroid cancer and its variants. Oncotarget 2016;7(22):32318–28.
23. Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. Clin Ther 2015;37(4):764–82.
24. Angell H, Galon J. From the immune contexture to the Immunoscore: the role of prognostic and predictive immune markers in cancer. Curr Opin Immunol 2013;25(2):261–7.
25. Uhercik M, Sanders AJ, Owen S, Davies EL, Sharma AK, Jiang WG, et al. Clinical significance of PD1 and PDL1 in human breast cancer. Anticancer Res 2017;37(8):4249–54.
26. Ascierto PA, Capone M, Urba WJ, Bifulco CB, Botti G, Lugli A, et al. The additional facet of immunoscore: immunoprofiling as a possible predictive tool for cancer treatment. J Transl Med 2013;11:54.
27. Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. Clin Cancer Res 2005;11(8):2947–53.
28. Seliger B. Basis of PD1/PD-L1 Therapies. J Clin Med 2019;8(12):2168.
29. Kwak Y, Koh J, Kim DW, Kang SB, Kim WH, Lee HS. Immunoscore encompassing CD3+ and CD8+ T cell densities in distant metastasis is a robust prognostic marker for advanced colorectal cancer. Oncotarget 2016;7(49):81778–90.
30. McLemore LE, Janakiram M, Albanese J, Shapiro N, Lo Y, Zang X, et al. An ımmunoscore using PD-L1, CD68, and tumor-infiltrating lymphocytes (TILs) to predict response to neoadjuvant chemotherapy in invasive breast cancer. Appl Immunohistochem Mol Morphol 2018;26(9):611–9.
31. Bastman JJ, Serracino HS, Zhu Y, Koenig MR, Mateescu V, Sams SB, et al. Tumor-infiltrating T cells and the PD-1 checkpoint pathway in advanced differentiated and anaplastic thyroid cancer. J Clin Endocrinol Metab 2016;101(7):2863–73.
32. An HJ, Ko GH, Lee JH, Lee JS, Kim DC, Yang JW, et al. Programmed death-ligand 1 expression and its correlation with lymph node metastasis in papillary thyroid carcinoma. J Pathol Transl Med 2018;52(1):9–13.
33. Ito Y, Miyauchi A, Jikuzono T, Higashiyama T, Takamura Y, Miya A, et al. Risk factors contributing to a poor prognosis of papillary thyroid carcinoma: validity of UICC/AJCC TNM classification and stage grouping. World J Surg 2007;31(4):838–48.
34. Mlecnik B, Van den Eynde M, Bindea G, Church SE, Vasaturo A, Fredriksen T, et al. Comprehensive intrametastatic immune quantification and major impact of immunoscore on survival. J Natl Cancer Inst 2018;110(1).
35. Mlecnik B, Tosolini M, Kirilovsky A, Berger A, Bindea G, Meatchi T, et al. Histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction. J Clin Oncol 2011;29(6):610–8.

36. Cunha LL, Morari EC, Guihen AC, Razolli D, Gerhard R, Nonogaki S, et al. Infiltration of a mixture of immune cells may be related to good prognosis in patients with differentiated thyroid carcinoma. Clin Endocrinol (Oxf) 2012;77(6):918–25.
37. Kuo CY, Liu TP, Yang PS, Cheng SP. Characteristics of lymphocyte-infiltrating papillary thyroid cancer. J Cancer Res Pract 2017;4:95–9.
38. Peng GL, Li L, Guo YW, Yu P, Yin XJ, Wang S, et al. CD8+ cytotoxic and FoxP3+ regulatory T lymphocytes serve as prognostic factors in breast cancer. Am J Transl Res 2019;11(8):5039–53.
39. Ferrari SM, Fallahi P, Galdiero MR, Ruffilli I, Elia G, Ragusa F, et al. Immune and ınflammatory cells in thyroid cancer microenvironment. Int J Mol Sci 2019;20(18):4413.
40. Zhou Z, Mu D, Zhang D, Zhang X, Ding X, Yang J, et al. PD-L1 in combination with CD8+TIL and HIF-1α are promising prognosis predictors of head and neck squamous cell carcinoma. Cancer Manag Res 2020;12:13233–9.