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ORIGINAL ARTICLE

The effect of preferentially expressed antigen in melanoma (PRAME) expression status on survival in stage II and stage III colon cancer

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Summary

Purpose: *There are no studies showing PRAME expression in stage II and III colon adenocarcinoma. In this study, we aimed to determine the frequency of PRAME expression and the relationship with survival and clinicopathological data in stage II and III colon adenocarcinoma that need adjuvant therapy.*

Methods: *Included were 81 patients with stage II and III colon cancer with adjuvant therapy without a second malignancy and systemic inflammatory diseases.*

Results: *A statistically significant relationship was detected between PRAME expression and disease progression and survival (p=0.01 and p=0.003, respectively). Shorter disease-free survival (DFS) and overall survival (OS) were detected in right colon tumors in patients with lymph node metastasis, metastatic lymph node >3, N1 or N2 according to the TNM staging system, with lymphovascular invasion, perineural invasion and PRAME expression (p=0.004, p=0.023, p=0.002, p=0.004, p=0.001, p=0.006, p=0.01, respectively and p=0.009, p=0.037, p=0.001, p=0.004, p=0.003, p=0.004, p=0.006, respectively). In multivariate analysis, it was determined that right colon tumor (HR: 0.488, 95% CI, 0.201-0.998, p=0.049) and PRAME expression (HR: 0.423, 95% CI, 0.170-1.052, p=0.046) were independent risk factors for short DFS. For the OS, only the presence of PRAME expression was determined as an independent risk factor. (HR:0.332, 95%CI, 0.129-0.856, p=0.022).*

Conclusion: *PRAME can be a potential target in immunotherapy in colon cancer treatment.*

Key words: *colon cancer, cancer testis antigen, targeted therapy*

Introduction

Colorectal cancer is the third most common cancer in males and females, and 70% originates from the colon. In the USA, 104,610 colon cancer diagnoses are made annually [1]. Although its incidence varies regionally, the highest incidence is observed in economically developed societies, while it is lower in less developed societies [2]. Mortality rates in colorectal cancers have decreased gradually over the last 40 years thanks to early diagnosis methods [3]. Most patients are diagnosed at stage II or higher, and despite the increase in targeted treatments, the 5-year survival rate is 57% [4].

Preferentially Expressed Antigen in Melanoma (PRAME), also known as Melanoma Antigen Pref-

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erentially Expressed in Tumors (MAPE), CT130 or Opa-Interacting Protein 4 (OIP4), is encoded from a 12-kilobase region in the 22q11.22 locus of chromosome 22. It was first described as a member of the cancer testis antigens (CTA) family recognized by T cells in metastatic malignant melanoma [5]. PRAME expression is regulated primarily by DNA demethylation [6].

In structural analysis, PRAME was found to be similar to toll-like receptors 3 and 4, which play a role in the recognition of molecules related to the pathogen in immune response. It has also been shown that PRAME is upregulated in response to the molecule related to the pathogen and IFN-gamma, and then localized to the ligase complex of Elongin / Cullin E3 ubiquitin by translocation to the Golgi network [7]. PRAME has been shown to support tumor development and progression through different mechanisms [8]. PRAME is the main suppressor of the retinoic acid signaling pathways, thereby playing a role in cell differentiation, proliferation arrest, and apoptosis [9].

PRAME is also lowly expressed from healthy adrenal, endometrial, and ovarian tissue [10]. PRAME expression has been shown in different types of malignancy and is expressed in malignant melanoma by 88-95%, in non-small cell lung cancer by 46-78%, in breast cancer by 27% and in renal cell cancer by 21% [11]. PRAME expression has been shown in many types of cancer, such as malignant melanoma, neuroblastoma, sarcoma, breast cancer, and non-small cell lung cancer, and is associated with poor prognosis [8]. Among the CTA family melanoma associated antigen-A3 (MAGE-A3), New York esophageal squamous cell carcinoma 1 (NY-ESO-1) and PRAME have been shown to be a prognostic biomarker in various types of cancer and may have great potential as a target in immunotherapy [12]. The limited expression of CTAs in somatic tissue has been recognized as promising targets for T cell therapy due to its expression in different cancer types and immunogenic nature. Since CTAs are intracellular proteins, efforts to develop CTA-based immunotherapy are based on the isolation of CTA-specific T cells [13].

In recent years, immunotherapy and vaccination studies have been initiated for different types of cancer to limit PRAME expression [8,14]. There are no studies in the literature showing PRAME expression in stage II and III colon cancer. In this study, we aimed to determine the frequency of PRAME expression in stage II and III colon cancer with adjuvant treatment needs, and the relationship between expression levels and survival and clinicopathological data.

Methods

Study population

Our retrospective study included 81 patients from Cukurova University School of Medicine who were diagnosed between 2003-2012 with stage II and III disease according to American Joint Committee on Cancer (AJCC) TNM Staging Classification for Colon Cancer 8th ed.; 2017. According to the NCCN (National Comprehensive Cancer Network) guideline version 4.2020, stage II with high risk factors for recurrence (high risk factors are poorly differentiated/undifferentiated histology, lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, undetermined, or positive margins) and all stage III patients received adjuvant chemotherapy. Patients with a second malignancy, systemic inflammatory disease and uncontrolled chronic systemic disease (e.g., diabetes mellitus, chronic obstructive pulmonary disease, renal failure, heart failure and cirrhosis) were excluded from the study.

Age, gender, date of diagnosis, date of progression, date of death, tumor size, presence of lymph node metastasis, number of metastatic lymph nodes, N status according to the TNM staging system, tumor localization, tumor differentiation, presence of additional components in the tumor, lymphovascular invasion (LVI), perineural invasion (PNI) statuses of the patients were recorded. Overall survival (OS) is defined as the time from the date of diagnosis to death and from the date of disease free survival (DFS) diagnosis to the date of the first recurrence or the date when metastatic disease was detected. Patients with disease in the transverse colon were recorded as right colon.

Immunohistochemical analysis

Four-micrometer thick tissue sections were cut from formalin-fixed and paraffin-embedded tissue blocks. All cases were reviewed under microscope and one adequate sample was selected for every patient. Antibody to PRAME (MAb EPR20330; Abcam, #219650) was used on a Ventana-Benchmark automated strainer platform. The percentage of immunoreactive cells and staining intensity were evaluated in the most representative areas.

The staining result was recorded as the percentage of immunoreactive tumor cells with nuclear labeling per total number of tumor cells. The proportion of immunoreactive cells was scored from 0 to 4 as follows: 0, <5%; 1, %5 to <25%; 2, 25% to <50%; 3, 50% to <75%; 4, ≥75% (Figure 1A, Figure 1B, Figure 1C, Figure 1D and Figure 1E). The intensity was scored from 0 to 3 as follows: 0, negative; 1, weak staining; 2 moderate staining; 3, strong staining. The total score (proportion score + intensity score) were evaluated, and cases with a total score >3 were judged as positive. Tissues showing immunehistochemically staining had an intensity score of at least 1. Density score was accepted as zero in patients who did not show tissue staining by immunohistochemistry. Paraffin embedded tissue blocks were evaluated blindly by two experts.

Statistics

After the suitability of the data to the normal distribution is tested; those that showed normal distribution of the continuous variables were analyzed with the *t*-test and those without normal distribution were analyzed using the Mann-Whitney U test. X^2 test was used in the analysis of categorical variables. Kaplan-Meier method and log-rank test were used to determine OS and PFS. Cox regression analysis was used to analyze univariate and multivariate data. The results were expressed as mean ± standard deviation, median (lower limit and upper limit), number and percentage; $p<0.05$ was considered as statistically significant. Statistical analysis of the data was performed using SPSS 21.0 software.

Results

Clinicopathological data and PRAME

42 (52%) of the 81 patients included in the study were male. The median age was 55 years and the age range was 26-89 years. According to the TNM staging system at the time of diagnosis, 43 (53%) had stage III and 38 (47%) had stage II disease. While 74 (91%) of the patients had T4 tumors, 42 patients (52%) had lymph node metastasis. There were LVI and PNI in 27 (33%) patients and 20 (25%) patients, respectively. In approximately two-thirds of the patients, the tumor was localized in the left colon (64%). While 71 (88%) of the patients had differentiated tumors, 16 (12%) had a mucinous component in the tumor. Progression was detected in 28 (35%) of the patients during the follow-up period, while 27 (33%) died.

There were 38 patients (47%) with PRAME expression. When PRAME expression and clinicopathological data were examined, a statistically significant relationship was found between PRAME expression and disease progression and survival (p=0.01 and p=0.003, respectively). When PRAME expression and standard prognostic variables were examined, no statistically significant relationship was found between PRAME expression and tumor localization, tumor depth, N status, stage, lymph node metastasis, lymph node metastasis count, LVI, PNI, tumor differentia-

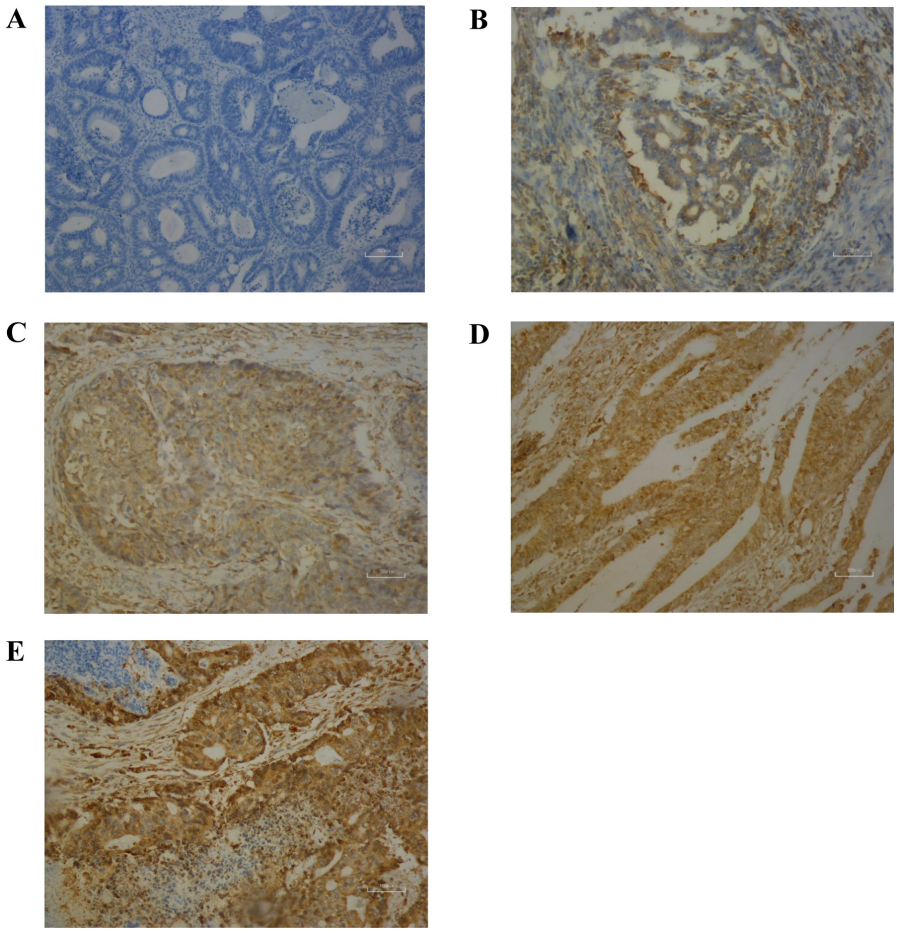

Figure 1. Demonstration of PRAME expression by immunohistochemical method. **A:** Immunoreactive cells score 0 (The proportion of <5%. IHCx100). **B:** Immunoreactive cells score 1 (The proportion of 5 to <25%. IHCx100). **C:** Immunoreactive cells score 2 (The proportion of 25 to <50%. IHCx100). **D:** Immunoreactive cells score 3 (The proportion of 50 to <75%. IHCx100). **E:** Immunoreactive cells score 4 (The proportion of ≥75%. IHCx100).

Table 1. Association between expression of PRAME and clinicopathological parameters in 81 patients

Variables	*Patients n (%)*	*PRAME expression positive in CC tissue n (%)*	*PRAME expression negative in CC tissue n (%)*	*p value*
Age, years				0.270
<65	54 (67)	23 (28)	31 (38)	
≥65	27 (33)	15 (19)	12 (15)	
Gender				0.564
Male	42 (52)	21 (26)	21 (26)	
Female	39 (48)	17 (21)	22 (27)	
Survival status				0.003
Alive	54 (67)	19 (23)	35 (44)	
Deceased	27 (33)	19 (23)	8 (10)	
Progression status				0.01
Yes	28 (35)	19 (23)	9 (11)	
No	53 (65)	19 (23)	34 (43)	
Tumor localization				0.115
Right colon	29 (36)	17 (21)	12 (15)	
Left colon	52 (64)	21 (26)	31 (38)	
Tumor depth				0.309
pT3	7 (9)	2 (3)	5 (6)	
pT4	74 (91)	36 (44)	38 (47)	
N status				0.203
pN0	39 (48)	19 (23)	20 (25)	
pN1a-b-c	26 (32)	9 (11)	17 (21)	
pN2a-b	16 (20)	10 (12)	6 (8)	
Stage				0.578
IIA-B-C	38 (47)	18 (21)	20 (25)	
IIIA-B-C	43 (53)	20 (25)	23 (29)	
Lymph node metastasis				0.754
Absent	39 (48)	19 (23)	20 (25)	
Present	42 (52)	19 (23)	23 (29)	
Lymph node metastasis count				0.164
≤3	65 (80)	28 (34)	37 (46)	
>3	16 (20)	11 (14)	5 (6)	
Lymphovascular invasion				0.875
Absent	54 (67)	25 (31)	29 (36)	
Present	27 (33)	13 (16)	14 (17)	
Perineural invasion				0.843
Absent	61 (75)	29 (36)	32 (39)	
Present	20 (25)	9 (11)	11 (14)	
Tumor differentiation				0.425
Differentiated	71 (88)	34 (42)	37 (46)	
Undifferentiated	10 (12)	4 (5)	6 (7)	
Tumor mucinous component				0.777
Absent	65 (80)	31 (38)	34 (42)	
Present	16 (20)	7 (9)	9 (11)	

PRAME: preferentially expressed antigen in melanoma, CC: colon cancer

Table 2. Comparison of disease free survival data of the patients according to clinicopathological features

Features	*n*	*DFS Median (95% CI)*	*5-year DFS (%)*	10-year DFS (%)	p
Total	81	129 (113-146)	69.1	66.7	
Age,years					0.165
<65	54	138 (118-157)	74.1	70.4	
≥65	27	95 (70-120)	59.3	59.3	
Gender					0.575
Male	42	134 (110-157)	69	69	
Female	39	105 (86-125)	69.2	64.1	
Tumor localization					0.004
Right colon	29	79 (57-100)	51.7	44.8	
Left colon	52	147 (128-166)	78.8	78.8	
Tumor depth					0.288
pT3	7	124 (90-158)	85.7	85.7	
pT4	74	126 (109-144)	67.6	64.9	
N status					0.004
pN0	39	150 (130-170)	82.1	76.9	
pN1a-b-c	26	108 (84-132)	65.4	65.4	
pN2a-b	16	59 (32-86)	43.8	43.8	
Stage					0.015
IIA-B-C	40	151 (131-170)	82.5	77.5	
IIIA-B-C	41	91 (113-146)	56.1	56.1	
Lymph node metastasis					0.023
Absent	39	150 (130-170)	82.1	76.9	
Present	42	93 (73-13)	57.1	57.1	
Lymph node metastasis count					0.002
≤3	61	144 (126-161)	77	73.8	
>3	20	69 (42-96)	45	45	
Lymphovascular invasion					0.001
Absent	54	148 (131-166)	79.6	75.9	
Present	27	68 (46-90)	48.1	48.1	
Perineural invasion					0.006
Absent	61	141 (124-159)	75.4	72.1	
Present	20	68 (43-94)	50	50	
Tumor differentiation					0.544
Differentiated	72	131 (113-149)	69.4	68.1	
Undifferentiated	9	88 (53-123)	66.7	55.6	
Tumor mucinous component					0.367
Absent	65	125 (106-144)	66.2	64.6	
Present	16	108 (85-130)	81.3	75	
PRAME expression					0.01
Negative	43	149 (129-170)	79.1	79.1	
Positive	38	91 (71-112)	57.9	52.6	

DFS: disease free survival; PRAME: preferentially expressed antigen in melanoma

Table 3. Comparison of overall survival data of the patients according to clinicopathological features

Features	*n*	*OS Median (95% CI)*	*5-year OS (%)*	10-year OS (%)	p
Total	81	131 (114-148)	74.1	67.9	
Age,years					0.125
<65	54	140 (121-159)	77.8	72.2	
≥65	27	95 (70-120)	66.7	59.3	
Gender					0.711
Male	42	134 (110-157)	73.8	69	
Female	39	108 (89-128)	74.4	66.7	
Tumor localization					0.009
Right colon	29	82 (60-104)	58.6	48.3	
Left colon	52	147 (128-166)	82.7	78.8	
Tumor depth					0.310
pT3	7	124 (90-158)	85.7	85.7	
pT4	74	128 (111-146)	73	66.2	
N status					0.004
pN0	39	150 (130-170)	84.6	76.9	
pN1a-b-c	26	112 (89-136)	73.1	69.2	
pN2a-b	16	59 (32-86)	50	43.8	
Stage					0.025
IIA-B-C	40	151 (131-170)	85	77.5	
IIIA-B-C	41	94 (73-115)	63.4	58.5	
Lymph node metastasis					0.037
Absent	39	150 (130-170)	84.6	76.9	
Present	42	96 (75-116)	64.3	59.5	
Lymph node metastasis count					0.001
≤3	61	146 (114-148)	80.3	75.4	
>3	20	69 (42-96)	55	45	
Lymphovascular invasion					0.003
Absent	54	148 (131-166)	83.3	75.9	
Present	27	72 (49-94)	55.6	51.9	
Perineural invasion					0.004
Absent	61	144 (126-161)	80.3	73.8	
Present	20	68 (43-94)	55	50	
Tumor differentiation					0.496
Differentiated	72	133 (115-150)	73.6	69.4	
Undifferentiated	9	88 (53-123)	77.8	55.6	
Tumor mucinous component					0.415
Absent	65	127 (108-146)	70.8	66.2	
Present	16	108 (85-130)	85.7	75	
PRAME expression					0.006
Negative	43	153 ((133-173)	83.7	81.4	
Positive	38	91 (71-112)	63.2	52.6	

OS: overall survival, PRAME: preferentially expressed antigen in melanoma

tion and tumor mucinous component (p>0.05). Table 1 shows the relationship between PRAME expression and clinicopathological data.

Disease-free survival and overall survival

The median follow-up period was 92 months out of a total range of 14-185 months. The median DFS was 129 (95% CI, 113-146) months, 5-year DFS was 69.1% and 10-year DFS was 66.7%. In the univariate analysis performed with the Cox regression model, DFS was shorter in patients with lymph node metastasis, metastatic lymph node number >3, N stage N1 or N2 according to the TNM staging system, detected LVI and PNI and PRAME expression in their right colon tumors. (p=0.004, p=0.023, p=0.002, p=0.004, p=0.001, p=0.006, p=0.01, respectively) (Table 2, Figure 2).

The median OS was 131 months (95% CI, 114-148), the 5-year OS was 74.1% and the 10-year OS was 67.9%. In the univariate analysis performed with the Cox regression model, in patients with lymph node metastasis, metastatic lymph node number >3, N stage, N1 or N2 according to the TNM staging system, showed LVI and PNI and PRAME expression in their right colon tumors had much shorter OS (p=0.009, p=0.037, p=0.001, p=0.004, p=0.003, p=0.004, p=0.006, respectively) (Table 3, Figure 3).

Multivariate analysis showed that the existence of right colon tumor (HR:0.488, 95%CI,

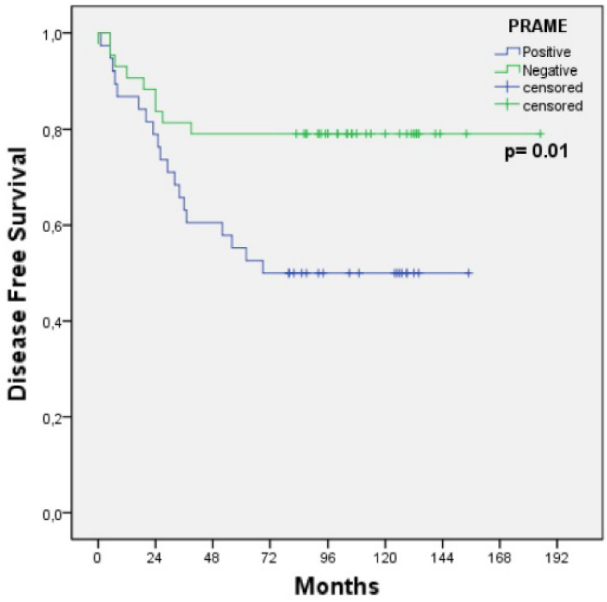

Figure 2. Kaplan-Meier plots for disease free survival for all patients (n=81) categorised by PRAME status. P values were calculated by using log rank test (p=0.01).

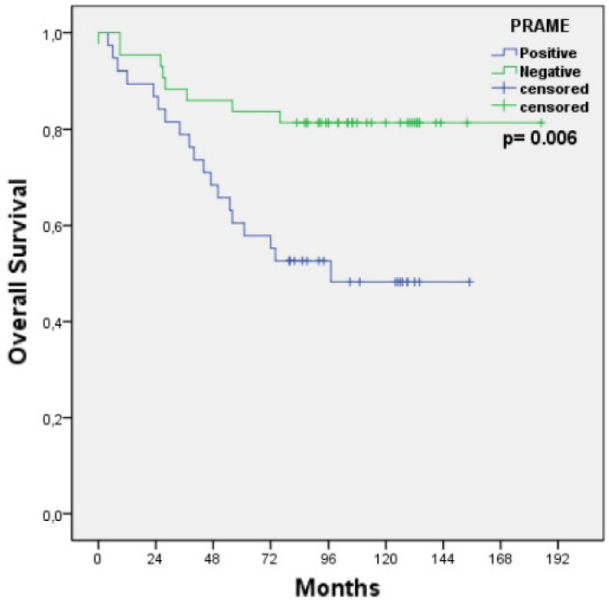

Figure 3. Kaplan-Meier plots for overall survival for all patients (n=81) categorised by PRAME status. P values were calculated by using log rank test (p=0.006).

Table 4. Multivariate Cox regression model of disease free survival and overall survival

	DFS			*OS*		
	HR	*CI (95%)*	*p*	*HR*	*CI (95%)*	*p*
Tumor localization (Right colon)	0.488	0.201-0.998	0.049	0.525	0.234-1.176	0.117
N status (pN2)	0.850	0.155-4.652	0.851	0.946	0.169-5.291	0.949
Stage (III)	0.832	0.124-5.573	0.933	1.118	0.158-3.087	0.934
Lymph node metastasis (Present)	0.924	0.258-1.343	0.937	1.018	0.267-3.663	0.937
Lymph node metastasis count (> 3)	0.672	0.127-3.557	0.640	0.620	0.114-3.377	0.580
Lymphovascular invasion (Present)	0.425	0.155-1.161	0.095	0.528	0.188-1.487	0.227
Perineural invasion (Present)	0.964	0.313-2.969	0.949	0.794	0.245-2.568	0.700
PRAME expression positive	0.423	0.170-1.052	0.046	0.332	0.129-0.856	0.022

DFS: disease-free survival, OS: overall survival, PRAME: preferentially expressed antigen in melanoma

0.201-0.998, p=0.049) and PRAME expression (HR:0.423, 95%CI, 0.170-1.052, p=0.046) were independent risk factors for short DFS. For OS, only PRAME expression was an independent risk factor (HR: 0.332, 95% CI, 0.129-0.856, p=0.022) (Table 4).

Discussion

In this study, we investigated the presence of PRAME expression in the tissues of patients with stage II-III colon adenocarcinoma who needed adjuvant therapy and its relationship with survival. As a result of the study, we found that patients with colon adenocarcinoma who needed adjuvant therapy with the presence of PRAME expression had shorter DFS and OS.

Although PRAME, which was first described as a surface antigen produced by autologous cytotoxic T lymphocytes by Ikeda et al, has a function in the retinoic acid signal pathway, and its role in carcinogenesis is not clear. Right and left-sided colon tumors show different molecular and histological features, as well as their treatment benefits from cytotoxic therapy or targeted therapy. Patients with right-sided colon cancer do not respond well to traditional cytotoxic therapy. However, since the right-sided colon tumors have high antigenic load, the immunotherapy option shows more promising results [15]. In our study, there was no statistically significant difference between the right and left-sided colon tumors in terms of PRAME expression, but there was a higher rate of PRAME expression in patients with right-sided colon cancer than in patients with left-sided colon cancer (58 *vs.* 40%). Although there is no statistically difference due to the non-homogeneous distribution of the number of patients compared to tumor localizations, it can be said that PRAME expression is more common in the right colon. This supports the opinion that the right colon has more antigenic load.

Increased PRAME expression is associated with an increased risk of metastasis in various tumors and an increase in tumor invasion ability [16-18]. PRAME has been found to induce epithelial mesenchymal transition (EMT) in triple negative breast cancer [8]. In our study, tumor depth, N status according to TNM staging system, presence of lymph node metastasis, number of metastatic lymph nodes, presence of LVI and PNI were not found to be related to PRAME expression. Similarly, in the study of Baba et al, the presence of PRAME expression in patients with esophageal cancer was not associated with tumor depth, presence of lymph node metastasis, and presence of vascular invasion [19]. However, in another study conducted by Baba et al it was stated that in patients with gastric cancer, the presence of tumor depth and PRAME expression was not related, while vascular invasion, lymphatic invasion and regional lymph node metastasis increased with increased PRAME expression [20]. Considering these two studies conducted by Baba et al, the majority of patients with esophageal cancer have a differentiated tumor (84 *vs.* 16%), while the majority of patients with gastric cancer have undifferentiated tumor (53 *vs.* 47%). Similar to the study with patients with esophageal cancer, the number of patients with differentiated tumors was higher in our study (82 *vs.* 18%). Therefore, it may be determined in our study that tumor depth, N status according to the TNM staging system, presence of lymph node metastasis, number of metastatic lymph nodes, presence of LVI and PNI are not related to PRAME expression. On the other hand, this indicates that tumor differentiation is impaired by increased PRAME expression.

LVI and PNI are poor prognostic factors in colon cancer and therefore chemotherapy is recommended in stage II colon cancer when present [21]. Similarly, detection of lymph node metastasis in colon cancer is accepted as stage III disease and it is a poor prognostic factor for survival. In a study conducted by Gleisner et al, lymph node metastasis or more than three metastatic lymph nodes (N2 disease according to TNM staging system) in patients with colon cancer has been shown as a poor prognostic factor for survival [22]. Presence of PRAME expression has been shown to be associated with shorter survival in esophageal cancer, gastric cancer and breast cancer [19,20,23]. Similarly, a study conducted by Ercolak et al stated that in the presence of PRAME expression, patients with Hodgkin lymphoma had shorter relapse time, shorter DFS and OS [24]. In our study, PRAME expression positivity in addition to tumor localization, N stage, stage, presence of lymph node metastasis, number of lymph node metastases, LVI and PNI were also associated with shorter DFS and OS in patients with colon cancer (91 months *vs.* 149 months, p=0.01 and 91 months *vs.* 153 months, p=0.006, respectively).

In addition, in the multivariate Cox regression analysis performed to detect independent risk factors, we found that the presence of PRAME expression alone was an independent risk factor for OS (p=0.022), while tumor localization and PRAME expression were independent risk factors for DFS (p=0.049, p=0.046). In our study, the presence of PRAME expression in living and deceased patients was statistically significant. Similarly, the presence of PRAME expression was observed

more frequently in patients who had disease progression.

In conclusion, this study showed for the first time that the presence of PRAME expression in stage II and stage III colon adenocarcinoma needs administration of adjuvant therapy and was associated with short DFS and OS. PRAME can be a potential target in immunotherapy in the treatment of colon cancer.

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Ethical conduct of research

This article was approved by the Cukurova University Medical Faculty Non-interventional Clinical Research Ethics Committee dated 10.06.2016 with the ID of 54. The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the *Declaration of Helsinki* for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Conflict of interests

The authors declare no conflict of interests.

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