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Prognostic Significance of ARID1A, PTEN and PD-L1 Expressions and MMR Status in Colorectal Cancer Tissue

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ABSTRACT

Objective: Studies on the clinical significance and frequency of adenine-thymine-rich interactive domaincontaining protein 1A (ARID1A) mutation or protein expression and the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) protein expression in colorectal cancer (CRC) are conflicting. In this study, we investigated the relationships between ARID1A and PTEN expression, programmed death ligand 1 (PD-L1) expression, mismatch repair (MMR) status, and prognosis in patients with metastatic CRC.

Material and Methods: Archival CRC formalin-fixed paraffin-embedded tissues were evaluated. The protein expression levels of ARID1A, PTEN and PD-L1 were investigated using immunohistochemistry (IHC). The MMR proteins were determined by the IHC analysis. The associations between clinical and pathological parameters and survival were investigated.

Results: The median duration of follow-up was 43.4 months [95% confidence interval (CI), 39.7-47.15)]. The median overall survival (OS) was 33 months (95% CI, 25.8-40.2), and the median progression-free survival was 17.25 months (95% CI, 11-23.4). The microsatellite stable status, human epidermal growth factor receptor type 2 positivity, and strong ARID1A expression were found to be significantly associated with poor survival, but no significant relationship was found between PD-L1 or PTEN expression and survival.

Conclusion: Comprehensive studies on the molecular basis of the role and significance of ARID1A mutations and expression in mCRC may provide valuable information. The limited number of patients included in this study and the variations in the evaluation and interpretation of the studied biomarker parameters are factors that may hinder the precision of the results obtained.

Keywords: AT-rich interactive domain 1A; phosphatase and tensin homolog deleted on chromosome 10; metastatic colorectal cancer; mismatch repair; prognosis

INTRODUCTION

Adenine-thymine (AT)-rich interactive domaincontaining protein 1A (ARID1A) is a type of chromatin remodeling gene; it was 1st identified as a tumor suppressor gene in gynecological cancers.[1,2] In the modern genomic era, recurrent inactivating ARID1A mutations in various types of cancer, including colorectal cancer (CRC), have been demonstrated using various sequencing methods.[3,4] Studies on the clinical significance and frequency of ARID1A mutations or protein expression status in CRC are limited, and the findings are controversial.[5-8]

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a tumor suppressor protein with phosphatase activity and acts as a negative regulator of the phosphoinositol-3-kinase (PI3K)/AKT signaling pathway.[9] Loss of expression of the PTEN protein may contribute to various processes related

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to tumorigenesis, cell metabolism, proliferation, and survival. In CRC, the expression of the PTEN protein may be associated with survival and response to treatment in patients receiving cetuximab therapy.[10,11] The mitogen-activated protein kinase (MAPK) and PI3K pathways are signaling pathways downstream of the epidermal growth factor receptor (EGFR) and have been demonstrated to be dysregulated in the majority of CRCs.[12] However, the clinical significance of the loss of PTEN expression in CRC remains incompletely established. The lack of an optimal method to assess the loss of PTEN expression, the lack of a standardized method for evaluation by immunohistochemistry (IHC), and the fact that PTEN mutations may not lead to loss of protein expression despite being easily detected may be considered reasons for this uncertainty.

Patients with deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) CRC have a good prognosis compared to their counterparts with proficient mismatch repair/microsatellite stable (pMMR/MSS) tumors.[13] Immune checkpoint inhibitors (ICPIs) provide a significantly stronger and longer-term survival benefit in advanced stages compared to chemotherapy. Therefore, ICPIs have taken their place in the primary care arsenal of advanced MSI-H CRC.[14]

Programmed death ligand 1 (PD-L1) is an immune checkpoint molecule; although PD-L1 can predict the response of many solid tumors (lung, breast, head, and neck cancer) to immunotherapy, its optimal predictive role for treating CRC has not been demonstrated. Data regarding the prognostic role of PD-L1 expression in the context of CRC are also conflicting.[15,16] However, many studies have reported that PD-L1 expression is an important prognostic factor.[16]

Information on the relationships of the abovementioned genes, proteins, and molecules that play a role in CRC pathogenesis with each other and with clinical factors is limited and controversial. Considering that CRC is the 3rd most common cancer type worldwide and is a significant public health problem, studies on the etiopathogenesis of this disease and possible treatment targets are valuable. In this study, we investigated the relationships between the expression status of ARID1A and PTEN, PD-L1 expression, MMR status, and prognosis in patients with metastatic CRC.

MATERIAL AND METHODS

This study was conducted as part of the Ankara Yıldırım Beyazıt University Scientific Research Project (BAP). The Ankara Bilkent City Hospital Ethics Committee approved the study protocol (date: September 9, 2021; no: E2-21-670). The ethics committee waived the requirement for informed consent because of its retrospective and non-invasive nature and evaluation of archival tissues. The study was conducted following ethical standards and the Declaration of Helsinki.

This retrospective, cross-sectional study included 81 archived formalin-fixed, paraffin-embedded primary or metastatic CRC tissues from patients whose clinical information was already known to indicate stage 4 disease according to the American Joint Committee on Cancer TNM staging system between June 2012 and May 2023. Two pathologists who were blinded to the clinical information of the patients performed immunostaining and scored the tissue sections. The protein expression levels of ARID1A were investigated using IHC with a rabbit monoclonal antibody (BAF250A/D2A8U). PTEN IHC was performed on tissue blocks with a rabbit monoclonal antibody (D4.3) (Figure 1). PD-L1 expression was detected by conducting the 22C3-IHC assay and reported as the TPS and combined positive score (CPS). The MMR status was determined by IHC with the expression of PMS2, MLH1, MSH2, and MSH6.

The associations between clinical and pathological parameters and survival were investigated. Progression-free survival (PFS) was defined as the time from 1st-line systemic treatment initiation to disease progression or death, whichever occurred earlier. Overall survival (OS) was defined as the time interval between the date of diagnosis of a metastatic disease and the date of death from any cause.

Statistical Analysis

Kaplan-Meier analysis was conducted to calculate mPFS and mOS and to perform univariate analysis in IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp; United States of America. The chi-square test was performed to evaluate differences in categorical variables between the groups. Multivariate analysis was performed with the Cox regression model. All results were considered to be statistically significant at $p \leq 0.05$.

RESULTS

In total, 81 patients had metastatic disease. Among them, 59 had *de novo* metastatic disease, and 22 patients had progressed to the metastatic stage. The median age of the patients was 63 years (range 39-84). A loss of ARID1A expression was recorded in 43 patients (57.3%), and a loss of PTEN expression was recorded in 23 patients (28.4%). The tissues of 6 patients were dMMR (8.1%), and the tissues of 11 patients (14.9%) were PD-L1 positive (TPS or CPS >1). The baseline patient and pathological characteristics are listed in Table 1.

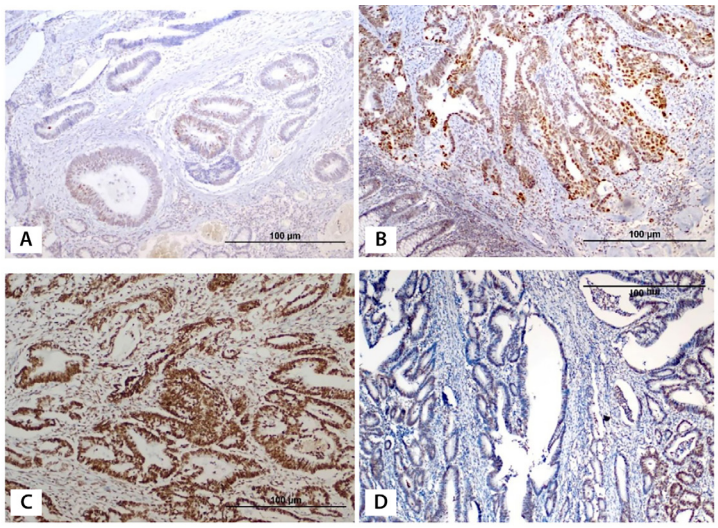

FIGURE 1: Immunohistochemical staining of ARID1A and PTEN.

A. Immunohistochemical staining of AT-rich interactive domain 1A (x100); weak nuclear staining and focal loss of expression, B. Immunohistochemical staining of AT-rich interactive domain 1A (x100); strong nuclear staining (3 positive score), C. Immunohistochemical staining of phosphatase and tensin homolog deleted on chromosome 10 (x100); diffuse and strong nuclear PTEN staining, D. Immunohistochemical staining of phosphatase and tensin homolog deleted on chromosome 10 (x100); focal and weak PTEN staining.

ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A; PTEN: Phosphatase and tensin homolog deleted on chromosome 10

TABLE 1: Clinicopathological characteristics of the patients.	
Clinicopathological characteristics	**n=81 (%)**
Age, years (median, range)	63 (39-84)
Gender	
Female	30 (37%)
Male	51 (63%)
Histological type	
Adenocarcinoma	70 (86%)
Signet cell	2 (2.7%)
Mucinous	7 (8.6%)
Other	2 (2.7%)
Tumor differentiation	
Well differentiated	15 (19.5%)
Moderately differentiated	54 (70.1%)
Poorly differentiated	8 (10.4%)
LVI	
No	22 (27.2%)
Yes	59 (72.8%)
PNI	
No	40 (51.3%)
Yes	38 (48.7%)
Tumor location	
Right colon	16 (19.7%)
Left colon	44 (54.3%)
Rectum	21 (26%)
Metastasis status	
De novo	59 (72.8%)
Progressed during follow-up	22 (27.2%)

TABLE 1: Continued	
Clinicopathological characteristics	**n=81 (%)**
MMR status	
Proficient	68 (91.9%)
Deficient	6 (8.1%)
Ras mutant subgroup	27 (33.3%)
BRAF mutant subgroup	3 (3.7%)
HER2 positive subgroup	10 (12.3%)
Biological treatment of metastatic disease	
Anti-VEGF	26 (32.1%)
Anti-EGFR	27 (33.3%)
Unknown	28 (34.6%)
ARID1A IHC status	
Loss present (0-1 positive)	43 (57.3%)
2 positive	23 (30.7%)
3 positive	9 (1.2%)
PTEN IHC status	
Negative	23 (28.4%)
Positive	52 (64.2%)
PD-L1 IHC status	
Negative	63 (85.14%)
≥%1 (TPS or CPS)	11 (14.86%)

LVI: Lymphovascular invasion; PNI: Perineural invasion; MMR: Mismatch repair; VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A; IHC: Immunohistochemistry; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; PD-L1: Programmed death ligand 1; TPS: Tumor proportion score; CPS: Combined positive score; HER2: Human epidermal growth factor receptor 2.

The median duration of follow-up was 43.4 months [confidence interval (CI) (95%, 39.7-47.15)]. The median OS was 33 months (95% CI, 25.8-40.2) (Figure 2), and the median PFS was 17.25 months (95% CI, 11-23.4) (Figure 3). Among the patients who received biologics (65.4%), half received anti-vascular endothelial growth factor receptor (VEGF) therapy, and the remaining half received anti-epidermal growth factor receptor (EGFR) therapy. Although the survival outcomes with anti- EGFR treatment were better, the difference was not statistically significant (Figures 4A and 4B).

No difference in mOS was found according to the PTEN expression status in patients treated with anti-EGFR. The mOS for patients with loss of expression was 32.5 months and for those with PTEN positivity, the mOS was 33 months (p=0.76). However, patients with PTEN-positive tumors had a shorter mPFS than patients with loss of expression; however, this difference was not statistically significant (for patients who were lost to follow-up, the mPFS was 32.2 months; for those who were PTENpositive, the mPFS was 15.1 months; p=0.61).

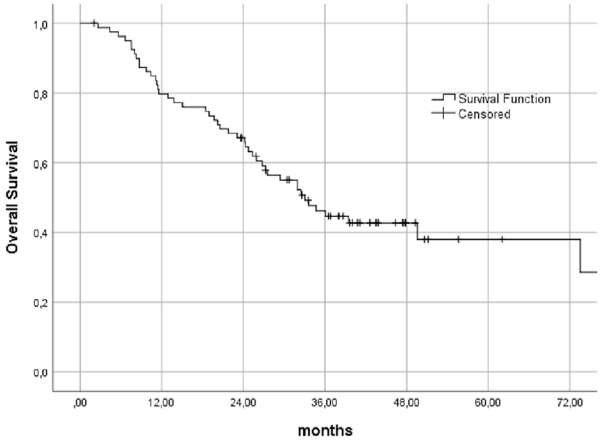

FIGURE 2: Median overall survival.

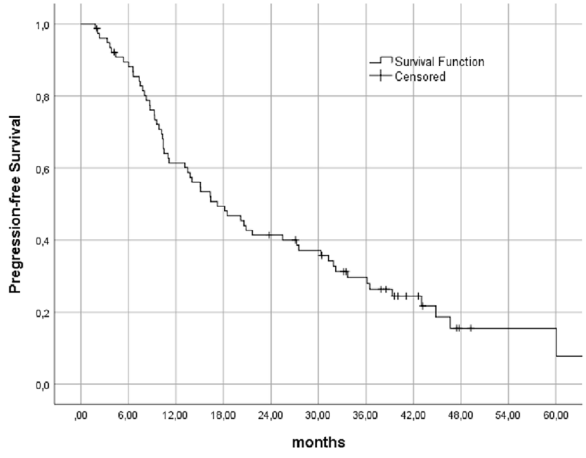

FIGURE 3: Median progression-free survival.

This effect was not found with anti-VEGF treatment (p=0.23) (Figures 5A and 5B).

When ARID1A was evaluated, while no difference was found between patients with loss of expression and patients with ARID1A positivity (2 positive scores by IHC), patients with strong expression (3 positive scores by IHC) had significantly shorter mOS (32 months, 34.7 months and 10.4 months, respectively; p=0.02) (Figure 6). Among the nine ARID1A strongly positive patients, all were PD-L1 negative, 8 were MSI stable (MSS), and 7 had metastatic disease at diagnosis. No significant relationship was found between PD-L1 status and OS (p=0.29).

The results of the multivariate analysis showed that while MSS status (p=0.014), human epidermal growth factor receptor

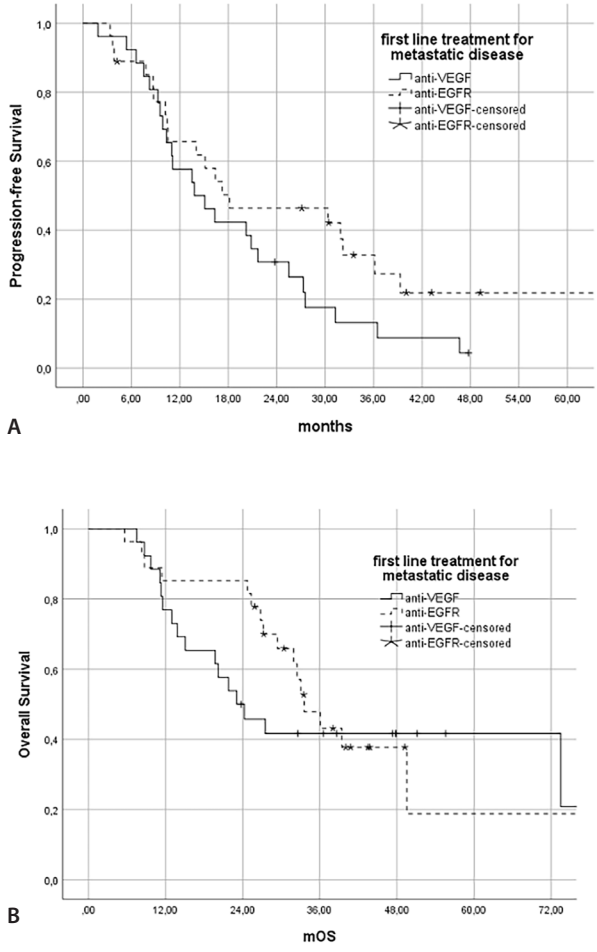

FIGURE 4: mPFS according to the biological agent (p=0.11). 18.17 (95% CI: 0.1-36.5) months for anti-EGFR and 13.8 (95% CI: 7.3-20.32) for anti-VEGF B: mOS accordeng to the biological agend (p=0.43). 33.6 (95% CI: 28.4-38.7) months for anti-EGFR and 23.1 (95% CI: 14.35-31.84) for anti-VEGF

VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; CI: Confidence interval; mOS: Median overall survival

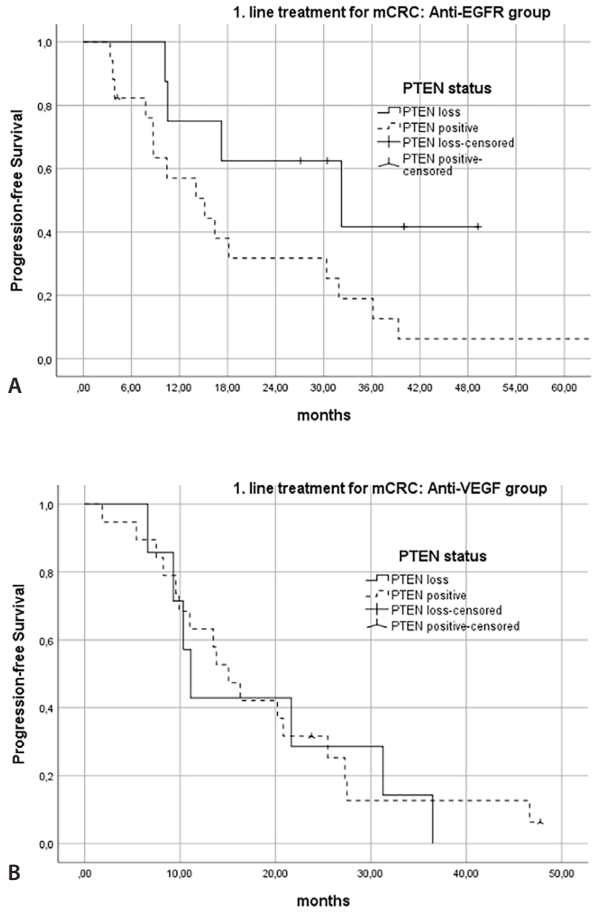

FIGURE 5A: mPFS according to PTEN expression status (anti-EGFR received), B: mPFS according to PTEN expression status (anti-VEGF received).

VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; mPFS: Median progression-free survival

type 2 (HER2) positivity (p≤0.001), and ARID1A 3 positivity (p=0.03) were significantly associated with poor prognosis and inferior mOS, no significant relationship was found between the expression of PD-L1 or PTEN and survival (Table 2).

When the relationships between clinicopathological factors and ARID1A were assessed by conducting the chi-square test, only the relationship with sex was found to be statistically significant (Table 3). ARID1A negativity or loss was significantly more likely to occur in females than in males [odds ratio for females/males 3.74 (95% CI, 1.33-10.47), p=0.019].

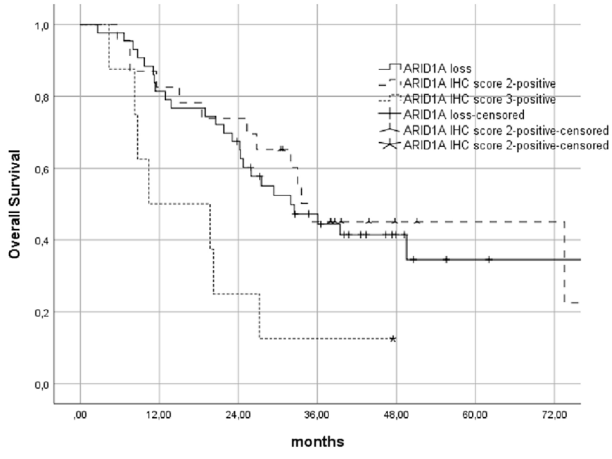

FIGURE 6: mOS according to ARID1A expression status.

mOS: Median overall survival; ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A

TABLE 2: Univariate and multivariate analysis of parameters associated with survival.

Clinicopathological characteristics	n=81 (%)	Univariate analysis p-value	Multivariate analysis HR (95% CI)	p
Age, years (median, range)				
≤55 years	63 (39-84)	0.40		
>55 years				
Gender				
Female	30 (37%)	0.135		
Male	51 (63%)			
Histological type				
Adenocarcinoma	70 (86%)	0.64		
Signet cell	2 (2.7%)			
Mucinous	7 (8.6%)			
Other	2 (2.7%)			

TABLE 2: Continued				
Clinicopathological characteristics	**n=81 (%)**	**Univariate analysis p-value**	**Multivariate analysis HR (95% CI)**	**p**
Tumor differentiation				
Well differentiated	15 (19.5%)	0.83		
Moderately differentiated	54 (70.1%)			
Poorly differentiated	8 (10.4%)			
Tumor location				
Right colon	16 (19.7%)	0.40		
Left colon	44 (54.3%)			
Rectum	21 (26%)			
Metastasis status				
De novo	59 (72.8%)	0.29		
Progressed during follow-up	22 (27.2%)			
MMR Status				
Proficient	68 (91.9%)	0.20	**7.36 (1.48-36.43)**	**0.014**
Deficient	6 (8.1%)			
Ras mutant	27 (33.3%)	0.82	**8.58 (3.32-22.20)**	**<0.001**
BRAF mutant	3 (3.7%)	0.42		
HER2 positive	10 (12.3%)	**<0.001**		
Biological treatment of metastatic disease (known)				
Anti-VEGF	26 (32%)	0.43		
Anti-EGFR	27 (33.3%)			
ARID1A status				
Loss present (0-1 positive)	43 (57.3%)	**0.020**	**2.67 (1.1-6.5)**	**0.03**
2 positive	23 (30.7%)			
3 positive	9 (1.2%)			
PTEN status				
Negative	23 (28.4%)	0.92		
Positive	52 (64.2%)			
PD-L1 negative	63 (85.14%)	0.29		
PD-L1≥ %1	11 (14.86%)			

MMR: Mismatch repair; VEGFR: Vascular endothelial growth factor receptor; EGFR: Epidermal growth factor receptor; ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; PD-L1: Programmed death ligand 1; HR: Hazard ratio; CI: Confidence interval.

TABLE 3: The clinicopathological relevance of ARID1A.				
Clinicopathological characteristics	**ARID1A negative/loss (IHC 0-1 score)**	**ARID1A positive (IHC 2 positive score)**	**ARID1A strong positive (IHC 3 positive score)**	**p-value**
Age, years				
≤55 years	9 (21.4%)	6 (26%)	1 (11%)	0.65
>55 years	33 (78.6%)	17 (74%)	8 (89%)	
Gender				
Female	22 (51%)	5 (22%)	2 (22 %)	**0.036**
Male	21 (49%)	18 (78%)	7 (78%)	
Gender	ARID1A negative	ARID1A positive		

TABLE 3: Continued

Clinicopathological characteristics	ARID1A negative/loss (IHC 0-1 score)	ARID1A positive (IHC 2 positive score)	ARID1A strong positive (IHC 3 positive score)	p-value
Female	22 (51%)	7 (22%)		**0.019**
Male	21 (49%)	25 (78%)		
Histological type				
Adenocarcinoma	40 (93%)	17 (74%)	7 (78%)	0.19
Signet cell	1 (0.23%)	1 (4%)	0	
Mucinous	2 (0.47%)	3 (13%)	2 (22%)	
Other	0	2 (9%)	0	
Tumor differentiation				
Well differentiated	9 (22%)	2 (9.5%)	2 (22%)	0.21
Moderately differentiated	29 (71%)	14 (66.5%)	7 (78%)	
Poorly differentiated	3 (7%)	5 (24%)	0	
Tumor location				
Right colon	5 (%)	8 (%)	3 (%)	0.050
Left colon	27 (%)	12 (%)	2 (%)	
Rectum	11 (%)	3 (%)	4 (%)	
MMR status				
Proficient	38 (97.5%)	16 (80%)	8 (89%)	0.080
Deficient	1 (2.5%)	4 (20%)	1 (11%)	
PTEN status				
Negative	17 (%)	3 (13%)	3 (33%)	0.080
Positive	26 (%)	20 (87%)	6 (67%)	
PD-L1 status				
Negative	38 (88%)	17 (74%)	9	0.12
≥%1	5 (12%)	6 (26%)	0	

MMR: Mismatch repair; ARID1A: Adenine-thymine (AT)-rich interactive domain-containing protein 1A; PTEN: Phosphatase and tensin homolog deleted on chromosome 10; PD-L1: Programmed death ligand 1.

DISCUSSION

CRC is the third most common cancer and the second leading cause of cancer-related death globally.[17] Therefore, identifying the factors related to disease prognosis, pathogenesis, and treatment pathways is an ongoing process. In this study, we revealed the clinical implications of primarily ARID1A and PTEN in CRC tissue and suggested that shorter survival is associated with ARID1A-3 positivity, MSS status, and HER2 positivity.

The ARID1A protein (BAF250a) is a member of the switching defective/sucrose non-fermenting (SWI/SNF) complex that remodels nucleosomes and modulates transcription.[18,19] SWI/SNF chromatin remodeling complexes serve as epigenetic regulators and can alter cell function as a result of molecular changes.[20-22] Subunits of these complexes have various mutations in different types of carcinomas.[5,23] In a mouse model, researchers reported findings that matched the role of ARID1A as a tumor suppressor and a novel pathway involved in colon tumorigenesis. A lack of adenomatous polyposis coli (APC)/β-catenin deregulation was reported in this study. Therefore, the loss of ARID1A is considered to cause invasive colon cancer through a mechanism independent of the inactivation of APC.[24] Here, we presented data obtained from the tissues of 81 patients with CRC in the metastatic stage with known clinical information.

In this study, ARID1A IHC scores of 0-1 and 2 positivity did not translate to any clinical difference, whereas 3 positivity was closely associated with poor OS. Similar to this study, another study, which included 209 patients, of which 71 had stage 4 disease, reported the association of ARID1A positivity with poor prognosis. In stage 4 CRC patients, a significant association between unfavorable survival and ARID1A expression rather than loss of ARID1A expression was reported [hazard ratios (HR)=2.49]. Similar findings were obtained in both studies. However, both studies presented

data on a limited number of patients. Therefore, the statistical data may not be robust, and further studies with larger samples are required.

The data in published studies regarding the relationships between ARID1A status (loss, mutation) and prognosis and clinicopathological factors in the presence of early and metastatic disease in CRC are not consistent. Drawing a definitive conclusion is difficult as most studies have limited sample sizes and are retrospective.[5-7,25] Lee et al.[25] reported that the frequency of ARID1A loss is greater in late-stage tumors than in stage 1 tumors in early-stage CRC and suggested that ARID1A loss may play a role in tumor progression. Besides playing a role in pathogenesis, ARID1A may activate downstream MAPK, PI3K, and mTOR pathways, which should be further evaluated as therapeutic options.

The expression of ARID1A was only associated with sex in this study but not with MMR, PTEN status, or other clinicopathological factors (i.e., sidedness). A study evaluating the expression of ARID1A mRNAs in hepatocellular carcinoma tissue and neighboring normal hepatic samples reported a significant association between sex and ARID1A overexpression.[26] Female patients were shown to have greater expression of ARID1A. On the other hand, there was a greater probability of loss of ARID1A expression in women in our study. ARID1A assessment differed between the 2 studies, but the possibility of sex-based differences is also acceptable. Another study reported that the meiotic spermatocytes of mice require ARID1A.[27] ARID1A was enriched in male sex chromosomes during meiosis and may play a role in meiotic sex chromosome gene regulation and DNA repair. The researchers interpreted the findings of their study as a topic worth investigating regarding the effects of the relationship between the ARID1A gene and sex on human reproductive development or biological processes.

Although a significant relationship between ARID1A loss and microsatellite instability has been reported in several studies, we could not demonstrate any association in our study.[5,7,25] These association data may be obscured by the small number of patients. In a study on gene expression profiling of CRC, 6.7% of the patients had ARID1A mutations. A significant correlation was found between ARID1A and immunological features in MSS tumors.[28] One limitation of this study is that the expression status of ARID1A could not be evaluated by gene profiling in our patient group, whose tumors were mostly MSS.

The clinical relevance of PD-L1 and PTEN in CRC has not been revealed. In this study, no significant relationship was found between PD-L1 expression and survival. A comprehensive meta-analysis on the prognostic significance of PD-L1 expression in CRC revealed its potential to predict poor outcomes.[29] The pooled analysis included studies with sufficient numbers of patients and PD-L1 positivity. We found a lower proportion of PD-L1-positive tissue from relatively smaller numbers of patients. Uniform assessment in a large series with methods using validated antibodies and standardized cutoff values for PD-L1 may help resolve the discrepancy. A distinction may also be made based on whether tumor tissue or the immune environment is being examined.

The frequency of somatic PTEN-inactivating mutations is low (8-9%) in CRC, and their effect on the nature of the tumor is not fully understood.[30] An extended cohort analysis by the same research group showed that PTEN deletions predict a negative prognosis in MSS tumors, whereas PTEN mutations predict a positive prognosis in MSI tumors.[31] These findings highlighted the need to identify clinically important PTEN mutations and expression patterns in CRC. Given that drugs targeting EGFR, which operates upstream of PI3K/PTEN, represent the backbone therapy in mCRC, researchers may investigate whether preserved PTEN expression leads to resistance to anti-EGFR therapy. We did not find a significant association between PTEN expression and survival. On the other hand, a significant difference was found in mPFS according to the PTEN expression status in patients treated with anti-EGFR therapy.

Our results were consistent with the data that PTEN-positive tumors may benefit less from anti EGFR treatment. When interpreting the result, researchers should consider that the determination and optimal interpretation of tumor PTEN status can be a challenge. A semiquantitative scoring system was used to obtain a better IHC scoring method than the intensity score. However, tumors can exhibit intratumor heterogeneity, and PTEN-positive tumors may display impaired PTEN function.[32] Although our study had some biases, the numerical difference we found may be a significant finding. In this study, the MSS status and HER2 positivity were shown to be poor prognostic factors.

Most mCRC patients have MSS tumors and, unfortunately, unlike patients with MSI-H tumors, they do not respond well to immunotherapy. Effective alternative treatment strategies and the identification of new predictive targets for MSS tumors are urgently required. Our study was not primarily intended to investigate the effect of HER2; it was mentioned as a significant finding of this study. We found that HER2 positivity is associated with a poor prognosis. The prognostic role of the overexpression of the HER2 gene in patients with CRC is controversial; however, other studies have mostly suggested poor survival outcomes.[33,34] In a large sample retrospective series, HER2-positivity was found to be an

independent prognostic risk factor indicating poor prognosis for stage III and IV CRC patients.[35] In this study, HER2 positivity was assessed via IHC of the tumor tissue. All 10 patients were IHC 3+, and no confirmatory FISH test was needed. Our results reflected HER2 protein overexpression in tumor tissue.

In this study, biomarkers were evaluated using known optimal methods in CRC tissue samples. However, these results reflected the immunoreactivity in stored tissue slides. Correlations between metastatic tissue and primary tissue were not evaluated. Additionally, the composition of the heterogeneous patient cohort and the small number of patients included were other limitations of the study. HRs and 95% CIs from multivariate analysis determined for parameters associated with survival were relatively wide. This finding of our study may be attributed to retrospective studies and related to the small number of cases and events, which provides power in statistical analysis. New prognostic mutations are being detected in the pathogenesis of mCRC, and studies on targeted treatment strategies are ongoing. We argue that prospective studies that simultaneously assess gene amplification and activating mutations in large numbers of CRC tissues and liquid biopsies are needed.

CONCLUSION

We found that the MSS status, HER2 positivity, and ARID1A-positivity were significantly associated with poor prognosis in patients with mCRC. However, these three factors were not related to each other. The only significant association found between ARID1A loss and clinicopathological parameters was sex. Evaluating the role of ARID1A expression and its importance for mCRC through comprehensive studies and on a molecular basis may be valuable.

Ethics

Ethics Committee Approval: Our study was conducted as part of Ankara Yıldırım Beyazıt University Scientific Research Project (BAP). Ankara Bilkent City Hospital Ethics Committee approved the study protocol (approval number: E2-21-670, date: 29.09.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., H.T.D., B.Y., Concept: S.K., H.T.D., B.Y., Design: S.K., B.Y., Data Collection or Processing: S.K., S.N.Ö.Ç., A.D.K., İ.K., D.Ş.D., M.A.N.Ş., M.B.A., C.E., M.H., B.B., Y.E., F.T.K., H.T.D., B.Y., Analysis or Interpretation: S.K., Y.E., Literature Search: S.K., H.T.D., Writing: S.K., Critical Review: H.T.D., B.Y.

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REFERENCES

1. Guan B, Wang TL, Shih IeM. ARID1A, a factor that promotes formation of SWI/SNF-mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. Cancer Res. 2011;71(21):6718-6727. Erratum in: Cancer Res. 2012;72(12):3116. [Crossref] [PubMed] [PMC]
2. Jones S, Wang TL, Shih IeM, et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. Science. 2010;330(6001):228-231. [Crossref] [PubMed] [PMC]
3. Jones S, Li M, Parsons DW, et al. Somatic mutations in the chromatin remodeling gene ARID1A occur in several tumor types. Hum Mutat. 2012;33(1):100-103. [Crossref] [PubMed] [PMC]
4. Wu JN, Roberts CW. ARID1A mutations in cancer: another epigenetic tumor suppressor? Cancer Discov. 2013;3(1):35-43. [Crossref] [PubMed] [PMC]
5. Wei XL, Wang DS, Xi SY, et al. Clinicopathologic and prognostic relevance of ARID1A protein loss in colorectal cancer. World J Gastroenterol. 2014;20(48):18404-18412. [Crossref] [PubMed] [PMC]
6. Chou A, Toon CW, Clarkson A, et al. Loss of ARID1A expression in colorectal carcinoma is strongly associated with mismatch repair deficiency. Hum Pathol. 2014;45(8):1697-1703. [Crossref] [PubMed]
7. Ye J, Zhou Y, Weiser MR, et al. Immunohistochemical detection of ARID1A in colorectal carcinoma: loss of staining is associated with sporadic microsatellite unstable tumors with medullary histology and high TNM stage. Hum Pathol. 2014;45(12):2430-2436. [Crossref] [PubMed]
8. Putra J, Suriawinata AA. Clinical significance of loss of ARID1A expression in colorectal and small intestinal carcinoma. Clin Transl Gastroenterol. 2015;6(12):e131. [Crossref] [PubMed] [PMC]
9. Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem. 1998;273(22):13375-133758. [Crossref] [PubMed]
10. Frattini M, Saletti P, Romagnani E, et al. PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients. Br J Cancer. 2007;97(8):1139-1145. [Crossref] [PubMed] [PMC]
11. Park JH, Han SW, Oh DY, et al. Analysis of KRAS, BRAF, PTEN, IGF1R, EGFR intron 1 CA status in both primary tumors and paired metastases in determining benefit from cetuximab therapy in colon cancer. Cancer Chemother Pharmacol. 2011;68(4):1045-1055. [Crossref] [PubMed]
12. Koveitypour Z, Panahi F, Vakilian M, et al. Signaling pathways involved in colorectal cancer progression. Cell Biosci. 2019;9:97. [Crossref] [PubMed] [PMC]
13. Sinicrope FA, Sargent DJ. Molecular pathways: microsatellite instability in colorectal cancer: prognostic, predictive, and therapeutic implications. Clin Cancer Res. 2012;18(6):1506-1512. [Crossref] [PubMed] [PMC]
14. Diaz LA Jr, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2022;23(5):659-670. [Crossref] [PubMed] [PMC]

15. Chung BS, Liao IC, Lin PC, et al. PD-L1 expression in high-risk early-stage colorectal cancer-its clinical and biological significance in immune microenvironment. Int J Mol Sci. 2022;23(21):13277. [Crossref] [PubMed] [PMC]
16. Li Y, He M, Zhou Y, et al. The prognostic and clinicopathological roles of PD-L1 expression in colorectal cancer: a systematic review and meta-analysis. Front Pharmacol. 2019;10:139. [Crossref] [PubMed] [PMC]
17. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. [Crossref] [PubMed]
18. Wang X, Nagl NG, Wilsker D, et al. Two related ARID family proteins are alternative subunits of human SWI/SNF complexes. Biochem J. 2004;383(Pt 2):319-325. [Crossref] [PubMed] [PMC]
19. Nagl NG Jr, Patsialou A, Haines DS, Dallas PB, Beck GR Jr, Moran E. The p270 (ARID1A/SMARCF1) subunit of mammalian SWI/SNF-related complexes is essential for normal cell cycle arrest. Cancer Res. 2005;65(20):9236-9244. [Crossref] [PubMed] [PMC]
20. Varela I, Tarpey P, Raine K, et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. Nature. 2011;469(7331):539-542. [Crossref] [PubMed] [PMC]
21. Wiegand KC, Shah SP, Al-Agha OM, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med. 2010;363(16):1532-1543. [Crossref] [PubMed] [PMC]
22. Wong AK, Shanahan F, Chen Y, et al. BRG1, a component of the SWI-SNF complex, is mutated in multiple human tumor cell lines. Cancer Res. 2000;60(21):6171-7. [Crossref] [PubMed]
23. Wilson BG, Roberts CW. SWI/SNF nucleosome remodellers and cancer. Nat Rev Cancer. 2011;11(7):481-492. [Crossref] [PubMed]
24. Mathur R, Alver BH, San Roman AK, et al. ARID1A loss impairs enhancer-mediated gene regulation and drives colon cancer in mice. Nat Genet. 2017;49(2):296-302. [Crossref] [PubMed] [PMC]
25. Lee LH, Sadot E, Ivelja S, et al. ARID1A expression in early stage colorectal adenocarcinoma: an exploration of its prognostic significance. Hum Pathol. 2016;53:97-104. [Crossref] [PubMed] [PMC]
26. Feng Y, Tang X, Li C, et al. ARID1A is a prognostic biomarker and associated with immune infiltrates in hepatocellular carcinoma. Can J Gastroenterol Hepatol. 2022;2022:3163955. [Crossref] [PubMed] [PMC]
27. Menon DU, Chakraborty P, Murcia N, Magnuson T. ARID1A governs the silencing of sex-linked transcription during male meiosis in the mouse. Elife. 2024;12:RP88024. [Crossref] [PubMed] [PMC]
28. Mehrvarz Sarshekeh A, Alshenaifi J, Roszik J, et al. ARID1A mutation may define an immunologically active subgroup in patients with microsatellite stable colorectal cancer. Clin Cancer Res. 2021;27(6):1663-1670. [Crossref] [PubMed] [PMC]
29. Azizi M, Mokhtari Z, Tavana S, et al. A comprehensive study on the prognostic value and clinicopathological significance of different immune checkpoints in patients with colorectal cancer: a systematic review and meta-analysis. Curr Ther Res Clin Exp. 2024;101:100760. [Crossref] [PubMed] [PMC]
30. Serebriiskii IG, Pavlov V, Tricarico R, et al. Comprehensive characterization of PTEN mutational profile in a series of 34,129 colorectal cancers. Nat Commun. 2022;13(1):1618. [Crossref] [PubMed] [PMC]
31. Serebriiskii IG, Pavlov VA, Andrianov GV, et al. Source, co-occurrence, and prognostic value of PTEN mutations or loss in colorectal cancer. NPJ Genom Med. 2023;8(1):40. [Crossref] [PubMed] [PMC]
32. Ferraldeschi R, Nava Rodrigues D, Riisnaes R, et al. PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. Eur Urol. 2015;67(4):795-802. [Crossref] [PubMed] [PMC]
33. Ahcene Djaballah S, Daniel F, Milani A, Ricagno G, Lonardi S. HER2 in colorectal cancer: the long and winding road from negative predictive factor to positive actionable target. Am Soc Clin Oncol Educ Book. 2022;42:1-14. [Crossref] [PubMed]
34. Babkoff A, Zick A, Hubert A, Tarantino P, Grinshpun A. Unleashing the power of anti-HER2 therapies in metastatic colorectal cancer: paving the way for a brighter future. ESMO Gastrointestinal Oncology. 2024;3:100032. [Crossref]
35. Huang W, Chen Y, Chang W, et al. HER2 positivity as a biomarker for poor prognosis and unresponsiveness to anti-EGFR therapy in colorectal cancer. J Cancer Res Clin Oncol. 2022;148(4):993-1002. [Crossref] [PubMed]