Original paper

# Does loss of ARID1A expression affect neoadjuvant chemoradiotherapy response in rectal carcinomas?

Nagehan O. Barisik[1], Sibel Sensu[2], Sevinc H. Keser[1], Yesim S. Gurbuz[2], Ozgul Ozdemir[3], Ramazan O. Yuceer[4], Aylin E. Gul[1], Nusret Erdogan[2]

[1]Department of Pathology, Kartal Dr. Lutfi Kirdar City Hospital, University of Health Sciences, Istanbul, Turkey
[2]Department of Pathology, Medical Faculty, Istinye University, Istanbul, Turkey
[3]Pathology Clinic, Midyat State Hospital, Mardin, Turkey
[4]Pathology Clinic, Batman Training and Research Hospital, Batman, Turkey

This study evaluated the difference of ARID1A protein immunoexpression between responders and non-responders to neoadjuvant chemoradiotherapy in locally advanced rectal cancers.

The biopsies before neoadjuvant chemoradiotherapy and resection materials after mesorectal excision were re-examined for conventional prognostic parameters, tumour regression score was determined, and survival data were evaluated. All parameters were statistically compared.

Of the 117 cases, most (93%) were adenocarcinoma, 88% were moderately differentiated and no response was seen in 28%. Before neoadjuvant therapy, low nuclear expression of ARID1A was noted in 49 (41.9%), while high expression was observed in 68 cases (58.1%). After neoadjuvant therapy, low expression was observed in 12 (10.7%) cases, while high expression was seen in 90 cases (80.3%). After neoadjuvant therapy a statistically lower ARID1A expression was noted in the absence of distant organ metastasis ($p = 0.033$). No statistically significant relationship was observed between ARID1A expression and overall survival or progression-free survival. ARID1A expression before neoadjuvant treatment had no statistically significant effect on response to neoadjuvant treatment and was not significantly associated with survival.

More patients had significantly higher ARID1A expression in the post-treatment period than the pretreatment period. This may suggest that tumour cells with low ARID1A expression are more sensitive to neoadjuvant therapy.

**Key words:** ARID1A, neoadjuvant, chemoradiotherapy, rectal carcinoma.

## Introduction

Rectal cancer, which constitutes up to 30% of all colorectal tumours, is found between the anal orifice and 15 cm distal. Due to its bony pelvis, blood supply, lymphatic drainage, and neural innervation, it is considered a distinct and specific entity in terms of invasive growth pattern, surgical approach, and treatment outcomes. Its stage II (clinical stage T3 or T4 and node-negative) or stage III subtype is called locally advanced rectal cancer (LARC). In 2023, approximately 400,000 new cases of LARC were detected worldwide [1, 2]. Currently, total mesorectal excision (TME) is performed after the completion of neoadjuvant chemoradiotherapy (NCRT) in locally advanced rectal cancers. The effect of neoadjuvant

treatment is evaluated by regression scoring systems. However, the prognosis varies between patients even at the same stage [2].

NCRT leads to side effects, complications, and toxicities in some patients, which may severely impair the quality of life. In addition, neoadjuvant radiotherapy may lead to tissue oedema and loss of surgical plans, making the surgical procedure more difficult [2]. For these reasons, it is important to carefully determine which patients are candidates for NCRT in the preoperative period. A marker with the potential to differentiate the candidates would help to reduce the morbidity and cost of NCRT.

ARID1A is a subunit of the switch/sucrose nonfermenting (SWI/SNF) family [3–7]. The SWI/SNF family is one of the complexes responsible for chromatin remodeling, first distinguished in *Saccharomyces cerevisiae*. It is present in all eukaryotes and is specifically involved in the activation of transcription. During chromatin remodeling, this complex mobilises nucleosomes using ATP hydrolysis energy. Thus, it increases DNA accessibility and can regulate transcription [7]. The SWI/SNF complex consists of 2 subcomplexes called BAF and PBAF. The *ARID1A* gene, one of the subunits forming these complexes, is a large 250 kDa nucleocytoplasmic protein localised on chromosome 1p36.11, and it is present in almost all tissues. *ARID1A* is the largest noncatalytic BAF subunit and is a crucial gene that provides target specificity and directs ATPase activity. The ARID1A protein interacts with transcription proteins, hormone nuclear receptors, p53, p21 (CDKN1A), and SMAD3 proteins through C-terminal peptide-rich binding *loci* (LXXLL-leucine-rich motifs) on the one hand and mediates the affinity between chromatin and the SWI/SNF complex on the other. According to recent data, it is also involved in histone modification. ARID1A is known to play an important role in mammalian development and mouse embryo experiments, it has been observed that it is abundantly expressed and widely involved in many stages of development, while its loss halts embryonic development [4–6]. Although it is noteworthy that ARID1A leads to cancer in many *in vivo* cancer models, most of the current data suggest that ARID1A acts as a tumour suppressor [4]. It is not known whether loss of ARID1A function in colorectal carcinomas affects the treatment resistance and proliferation rate of cancer cells. This study aims to determine whether it is possible to predict the benefit of ARID1A expression in LARC patients before NCRT.

**Table I.** Modified Ryan scheme for tumour regression score [9, 10]

| Score | |
|---|---|
| 0 | No viable cancer cells (complete response) |
| 1 | Single cancer cells or rare cancer cells forming small groups (near-complete response) |
| 2 | Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response) |
| 3 | Extensive residual cancer with no evidence of tumour regression (poor response/no response) |

## Material and methods

This retrospective two-centre study included LARC cases diagnosed in the Pathology Clinic of the University of Health Sciences Kartal Dr. Lutfi Kirdar City Hospital between January 2010 and November 2022, who underwent total mesorectal excision after NCRT. In all cases, paraffin blocks, slides, and reports of biopsies before NCRT and resection materials after mesorectal excision were retrieved from the archives and re-examined (NOB, SHK). Conventional prognostic parameters [8] such as tumour size, depth of invasion, lymph node involvement, surgical margin, vascular and perineural invasion, and lymphocytic response to the tumour were reviewed on haematoxylin-eosin (HE) stained slides. After NCRT, HE stained slides were examined, and the tumour regression score was determined according to the Ryan scheme [9, 10] (Table I). Survival data were extracted from the hospital data system.

After reviewing the slides, the paraffin blocks with the most representative tumour tissues were selected and immunohistochemically stained with ARID1A. For immunohistochemical (IHC) examination, 4-mm-thick sections prepared from formalin-fixed paraffin-embedded tissues were mounted on electrostatically charged slides (isotherm) and kept in an oven at 70°C for at least one hour. The entire IHC staining process including deparaffinisation and antigen retrieval was performed on a fully automated IHC stainer (Ventana Benchmark XT, Ventana Medical Systems, Tucson, AZ). An instrument-compatible, biotin-free, HRP multimer-based kit containing hydrogen peroxide substrate and 3,3'-diaminobenzidine tetrahydrochloride (DAB) chromogen was used (UltraView™ Universal DAB Detection Kit, Catalogue Number 760-500, Ventana Medical Systems, Tucson, AZ). An immunohistochemical study was performed by using ARID1A (CellMarque ARID1A (EP303) Conc. 0.5 ml (1 : 50–200), Merck KGaA, Darmstadt, Germany). The sections were counterstained with haematoxylin and bluing reagent in the staining device, dehydrated, cleared with xylene, and covered with coverslips, manually. Homogeneous strong nuclear staining in fibroblasts, lymphocytes, and endothelial cells was considered a positive internal control.

The evaluation results of all cases were compared and discussed. At least 100 cells were analysed on each slide. Nuclear immunoreactivity was accepted as a positive expression. Immunohistochemical evaluation was performed with our modification of the literature [11–13]. The proportion of immunopositive cells (0 if ≤ 10%, 1 if > 10% to ≤ 25%, 2 if > 25% to ≤ 50%, 3 if > 50% to ≤ 75%, and 4 if > 75%) and the staining intensity (0 if staining is negative, 1 if staining is weak, 2 if staining is moderate, and 3 if staining is strong) were evaluated, and the total score was obtained by multiplying the 2 values. According to the total score, patients were divided into low expression (total score 1 and ≤ 4) and high expression (total score > 4) subgroups.

### Statistical analysis

Statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences) 27.0 software. The normal distribution of variables was assessed through visual and analytical methods, including the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics, comprising numbers, percentages, mean, and standard deviation, were employed. The relationship between clinicopathological data and ARID1A expressions before and after neoadjuvant treatment was assessed using ANOVA, Mann-Whitney U, $\chi^2$ test, and Kruskal-Wallis tests. The correlation between categorical variables was examined using the Pearson correlation test. For survival analysis, Kaplan-Meier analysis was applied, and significance was determined using the log-rank test. Results with a *p*-value below 0.05 were considered statistically significant.

The study was ethically approved by the Human Research Ethics Committee of our University (Date: 08.04.2022, Protocol No. 22-51).

## Results

A total of 117 cases (80 [68.4%] male, and 37 [31.6%] female) were examined. The age range of the cases was 21–84 years, with an average age of 61.23 ±11.08 years. Nonspecific adenocarcinoma (adenocarcinoma, NOS) was observed in 109 cases (93.2%), while 8 cases (6.8%) exhibited a mucinous adenocarcinoma. Histologically, 12 cases (10.3%) were well-differentiated, 103 (88%) were moderately differentiated, and 2 (1.7%) – poorly differentiated. In terms of the response to neoadjuvant treatment, 15 cases (12.8%) showed complete response and were not evaluated for *ARID1A*. Of the remaining 102 cases, 33 (28.2%) had no response (regression score 3). The staging was available for 102 cases, 73 of which were stage 1 and 2 (71.6%) and 29 were stage 3 and 4 (18.4%). A summary of the clinicopathological findings is presented in Table II.

Before neoadjuvant therapy, low nuclear expression of ARID1A was noted in 49 cases (41.9%), while

**Table II.** Clinical and pathological features

| Clinical feature | Frequency *N* (%) |
|---|---|
| Age (years) | |
| < 60 | 51 (43.6) |
| ≥ 60 | 66 (56.4) |
| Gender | |
| Female | 80 (68.4) |
| Male | 37 (31.6) |
| Histological type | |
| NOS | 109 (93.2) |
| Mucinous | 8 (6.8) |
| Histologic grade | |
| Well-differentiated (G1) | 12 (10.3) |
| Moderately differentiated (G2) | 103 (88) |
| Poorly differentiated (G3) | 2 (1.7) |
| Treatment response | |
| No | 15 (12.8) |
| Yes | 102 (87.2) |
| Tumour regression score* | |
| 1 | 15 (12.8) |
| 2 | 20 (17.1) |
| 3 | 49 (41.9) |
| 4 | 33 (28.2) |
| Lymphovascular invasion | |
| No | 80 (78.4) |
| Yes | 22 (21.6) |
| Perineural invasion | |
| No | 68 (66.7) |
| Yes | 34 (33.3) |
| Nodal metastasis | |
| No | 88 (75.2) |
| Yes | 29 (24.8) |
| Distant metastasis | |
| No | 105 (89.7) |
| Yes | 12 (10.3) |
| Stage | |
| 1–2 | 73 (71.6) |
| 3–4 | 29 (28.4) |
| Death | |
| No | 88 (75.2) |
| Yes | 29 (24.8) |

**According to Modified Ryan Scheme.*

*NOS – not other specified type*

**Table III**. The relationship between the clinical and pathological data of the cases and *ARID1A* expression

| Categorical features | *ARID1A* expression before neoadjuvant | | *p*-value | *ARID1A* expression after neoadjuvant | | *p*-value |
|---|---|---|---|---|---|---|
| | Low (*n* = 49) | High (*n* = 68) | | Low (*n* = 12) | High (*n* = 90) | |
| Age (year) | | | | | | |
| < 60 | 25 (51) | 26 (38.2) | 0.118 | 6 (50.0) | 40 (44.4) | 0.359 |
| ≥ 60 | 24 (49) | 42 (61.8) | | 6 (50.0) | 50 (55.6) | |
| Gender | | | | | | |
| Female | 14 (28.6) | 23 (33.8) | 0.346 | 11 (91.7) | 59 (65.6) | 0.059 |
| Male | 35 (71.4) | 45 (66.2) | | 1 (8.3) | 31 (34.4) | |
| Histological type | | | | | | |
| NOS | 47 (95.9) | 62 (91.2) | 0.269 | 12 (100.0) | 82 (91.1) | 0.353 |
| Mucinous | 2 (4.1) | 6 (8.2) | | 0 (0.0) | 8 (8.9) | |
| Histologic grade | | | | | | |
| Well (G1) | 4 (8.2) | 8 (11.8) | 0.508 | 1 (8.3) | 6 (6.7) | 0.670 |
| Moderate (G2) | 44 (89.8) | 59 (86.8) | | 11 (91.7) | 82 (91.1) | |
| Poorly (G3) | 1 (2) | 1 (1.4) | | 0 (0.0) | 2 (2.2) | |
| Tumour regression | | | | | | |
| 0 | 6 (12.2) | **9 (13.2)** | 0.718 | 0 (0.0) | 0 (0.0) | 0.512 |
| 1 | 12 (24.5) | 8 (11.8) | | 2 (16.7) | 18 (20.0) | |
| 2 | 16 (32.7) | 33 (48.5) | | 8 (66.6) | 41 (45.6) | |
| 3 | 15 (30.6) | 18 (26.5) | | 2 (16.7) | 31 (34.4) | |
| Lymphovascular invasion | | | | | | |
| No | 6 (14.0) | 16 (27.1) | 0.087 | 2 (16.7) | 20 (22.2) | 0.497 |
| Yes | 37 (86.0) | 43 (72.9) | | 10 (83.3) | 70 (77.8) | |
| Perineural invasion | | | | | | |
| No | 8 (18.6) | 26 (44.1) | **0.006** | 3 (25) | 31 (34.4) | 0.383 |
| Yes | 35 (81.4) | 33 (55.9) | | 9 (75) | 59 (65.6) | |
| Nodal metastasis | | | | | | |
| No | 36 (73.5) | 52 (76.5) | 0.437 | 7 (58.3) | 66 (73.3) | 0.224 |
| Yes | 13 (26.5) | 16 (23.5) | | 5 (41.7) | 24 (26.7) | |
| Distant metastasis | | | | | | |
| No | 45 (91.8) | 60 (88.2) | 0.378 | 8 (66.7) | 82 (91.1) | **0.033** |
| Yes | 4 (8.2) | 8 (11.8) | | 4 (33.3) | 8 (8.9) | |
| Stage | | | | | | |
| 1–2 | 28 (65.1) | 38 (64.4) | 0.881 | 5 (41.7) | 61 (67.8) | 0.077 |
| 3–4 | 15 (34.9) | 21 (35.6) | | 7 (58.3) | 29 (32.2) | |
| Death | | | | | | |
| No | 35 (71.4) | 53 (77.9) | 0.277 | 10 (83.3) | 67 (74.4) | 0.394 |
| Yes | 14 (28.6) | 15 (22.1) | | 2 (16.7) | 23 (25.6) | |

**According to Modified Ryan Scheme*

*NOS – not other specified type*

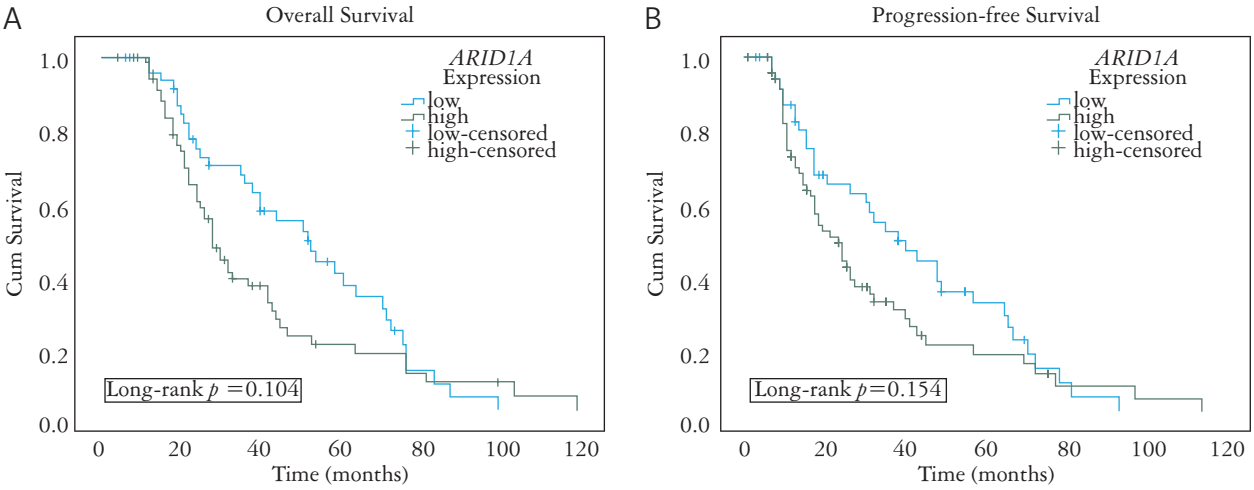


**Fig. 1.** Relationship of *ARID1A* expression before the neoadjuvant treatment with overall survival **(A)** and progression-free survival **(B)**

high expression was observed in 68 cases (58.1%). After neoadjuvant therapy, low expression was observed in 12 cases (10.7%) while high expression in 90 cases (80.3%). Though not statistically significant, higher expression was detected after treatment compared to the pre-treatment period ($p = 0.185$). Before neoadjuvant therapy, perineural invasion was significantly more often detected in the low-expression subgroup (81.4%, $p = 0.006$). No significant relationship was found between the other prognostic parameters and *ARID1A* expression ($p > 0.05$). Table III provides a summary of the relationship between the clinical and pathological data of the cases and *ARID1A* expression. All the parameters were examined also in the post-neoadjuvant therapy materials and only distant metastasis showed a statistically significant difference; thus, a lower *ARID1A* expression was noted in the absence of distant organ metastasis ($p = 0.033$).

During a mean follow-up period of 58.8 months, 24.8% ($n = 29$) of the patients died. For those with low expression before neoadjuvant treatment, the median overall survival (OS) was 52.0 ±9.7 months (95% confidence interval [CI]: 34.2–69.8), and the median progression-free survival (PFS) was 38.0 ±6.7 months (95% CI: 24.3–51.7). In the high-expression group, the median OS was 28.0 ±2.1 months (95% confidence interval: 23.8–32.2), and the median PFS was 21.0 ±3.3 months (95% confidence interval: 14.5–25.5). No statistically significant relationship was observed between *ARID1A* expression and overall survival or progression-free survival ($p > 0.05$) (Fig. 1).

## Discussion

Today, the TNM (tumour diameter – lymph node involvement status – distant metastasis) staging system of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) is a widely used clinical prognostic factor in colorectal cancer [14]. The European Society of Medical Oncology (ESMO) recommends the use of neoadjuvant therapy in advanced rectal adenocarcinomas, whose clinical stage is determined as T3 or T4 by transrectal endoscopic ultrasound (EUS) or pelvic magnetic resonance imaging (MRI) if there is lymph node involvement on imaging and the adequacy of surgical procedure is doubtful [2]. Neoadjuvant therapy is either radiotherapy alone or radiotherapy in combination with chemotherapy [2]. However, probably due to molecular differences, the prognosis of patients varies even at the same stage, and 5-year survival ranges between 10% and 90% [14]. It is an accepted current view that to practice precision medicine, it is necessary to know the genetic and molecular characteristics of tumours as well as their pathological features. This information, which will be added to the TNM stage, is thought to be useful for more specific prognosis determination and for tailoring treatment protocols specific to each tumour. Currently, total mesorectal excision (TME) is performed after completion of NCRT in locally advanced rectal cancers. This procedure aims to remove the tumour and resisting lymph nodes within the intact mesenteric package and to achieve negative surgical margins to reduce local recurrence rates. In 15–38% of the cases, a complete response to neoadjuvant therapy is achieved and fibrous tissue replaces the tumour tissue [15–17].

The effect of NCRT is evaluated by regression scoring systems. During scoring, the tumour regression grade (TRG) is determined by looking at the amount of viable cancer cells in the remaining carcinoma sections. The most commonly used regression scoring system is the modified Ryan scheme [18,

19–21]. According to studies, higher complete cure rates have been reported with neoadjuvant therapy, the need for ileostomy has been delayed, resection has become easier, and completion rates of chemotherapy have increased [15]. According to a 2017 National Cancer Database analysis, a 13% pathologic complete response rate was achieved in a cohort of 27,532 patients. There was a significant difference in the 5-year local recurrence rates between those who received preoperative chemoradiotherapy and those who received only postoperative treatment (6% and 13%, respectively) [2].

Although the benefits of NCRT have been demonstrated, it is important to carefully determine whether patients are candidates for NCRT in the preoperative period. A marker that helps in this regard would help reduce the morbidity and cost of NCRT [2, 3, 22]. Randomised trials have shown that the response to NCRT in rectal cancers varies between individuals. Up to 20% of rectal tumours show complete resistance, and overall disease-free survival is low in these patients. It seems likely that tumour response to neoadjuvant therapy depends on multiple variables and that tumour biology plays an important role. Molecular biomarkers are thought to be useful in predicting tumour response [4].

In recent years, the association of *ARID1A* mutation with carcinogenesis has been demonstrated in various studies [3–6]. It has been found that insufficient function of *ARID1A* decreases mismatch repair (MMR) protein capacity, is associated with programmed cell death ligand-1 (PD-L1) expression and regulation of the immune environment, and influences steroid receptor modulation, DNA damage checkpoints, p53, and KRAS signalling regulation [3, 6]. ARID1A deficiency in gastric cancer has been shown to activate phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signalling [6]. A significant correlation was found between *ARID1A* loss and hormone receptor negativity ($p < 0.05$) and the presence of lymph node metastasis ($p = 0.001$) in breast carcinomas [23]. *ARID1A* mutations have been shown in clear cell carcinomas of the ovary (46–57%), high- and low-grade endometrioid adenocarcinomas (60% and 47%), and hepatocellular carcinomas (17%) [3, 4].

Preclinical findings suggest that alterations in SWI/SNF complex subgroup genes may enhance antitumour immune response and response to chemo/radiotherapy. The relationship between *ARID1A* loss and chemoradiotherapy sensitivity remains open for further investigation. Various compounds such as immune checkpoint blockade, mTOR inhibitors, EZH2, histone demethylases, ATR, and/or PARP are thought to be useful in the treatment of cancers with *ARID1A* mutation [17]. Furthermore, it has been suggested that changes in *ARID1A* may be associated with resistance to platinum chemotherapy, and *ARID1A* may increase platinum sensitivity [3, 24]. Likewise, it has also been reported that *ARID1A* may be associated with resistance to oestrogen receptor modulators [3]. Recent studies have also suggested that the sensitivity of cancer cells to radiation and chemotherapy can be increased by targeting the *ARID1A* gene. The relationship between *ARID1A* mutation and chemo/radiotherapy sensitivity is a subject that awaits elucidation and may help to develop a personalised approach.

There are few studies on ARID1A in colorectal carcinomas, and in these studies, mutations were reported in 13% of cases and ARID1A loss in 12% of cases [4, 5]. In one study, in rectal carcinomas, a predisposition to respond to neoadjuvant therapy was suggested with *ARID1A* gene mutation [25]. One of the most interesting findings in our study was the significant difference between *ARID1A* expression before and after neoadjuvant therapy. During the pre-neoadjuvant therapy period, low *ARID1A* expression was observed in 42% of the cases, and the rate of low *ARID1A* expression decreased to 11% after neoadjuvant therapy. Similarly, the proportion of cases with high *ARID1A* expression increased from 58% to 80% after neoadjuvant therapy. In one of the 2 cases that had no staining, a complete regression was developed. We think that the cells with problematic *ARID1A* expression may be more sensitive to neoadjuvant treatment and suggest further research on this subject.

So far, few publications have demonstrated a positive association between inadequate *ARID1A* function and distant metastasis, poor prognosis, advanced TNM stage, and high grade [5, 18]. Erfani *et al.* reported that *ARID1A* expression decreased in colorectal carcinomas and that there was a correlation between low expression and lymphatic invasion [26]. In our study, low *ARID1A* expression was observed in 86% of cases with lymphovascular invasion and 81% of cases with perineural invasion. Cases with perineural invasion before neoadjuvant therapy were associated with lower *ARID1A* expression, in line with the literature.

## Conclusions

Our study is one of the few studies in the literature investigating the effect of *ARID1A* on response to neoadjuvant treatment in rectal carcinomas. According to our findings, low or high levels of *ARID1A* expression before neoadjuvant treatment were not associated with tumour regression score, meaning that it had no statistically significant effect on response to neoadjuvant treatment. In addition, contrary to some data in the literature [5, 18, 23, 25, 27], *ARID1A* expression level was not significantly associated with conventional prognostic pa-

rameters other than PNI and not with survival. In addition, contrary to the literature [18], the rate of distant metastasis was found to be higher in patients with high expression after neoadjuvant therapy. Our noteworthy finding is that significantly higher *ARID1A* expression was observed in our patients who received neoadjuvant therapy compared to the pretreatment period. This may suggest that tumour cells with problematic *ARID1A* expression are more sensitive to neoadjuvant therapy. These results support the hypothesis that *ARID1A* expression in colorectal carcinomas may be handled differently from other cancers [27]. However, in our study, ARID1A protein immunoexpression was examined, but gene mutation was not analysed. The effect of *ARID1A* gene mutations on the regression score after neoadjuvant treatment should be investigated in further studies and compared with immunohistochemical data.

## Disclosures

1. The study was ethically approved by the Human Research Ethics Committee of University of Health Sciences in Istanbul (Date: 8.04.2022, Protocol No. 22-51).
2. Assistance with the article: None.
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4. Conflicts of interest: None.

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## Address for correspondence


**Sibel Sensu**
Department of Pathology,
Medical Faculty,
Istinye University,
Istanbul, Turkey
e-mail: sibel.sensu@istinye.edu.tr