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ARID3A Positivity Correlated With Favorable Prognosis in Patients With Residual Rectal Cancer After Neoadjuvant Chemoradiotherapy

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Abstract. *Background/Aim: Recent studies have shown a marked increase of AT-rich interactive domain 3A (ARID3A) in colon cancer tissue compared to normal colon mucosa. However, the role of ARID3A has not yet been determined in rectal cancer. We, therefore, investigated the clinical relevance of ARID3A expression in patients with residual rectal cancer after neoadjuvant chemoradiotherapy (NACRT). Materials and Methods: One hundred thirty-four patients who underwent surgical resection for residual rectal cancer after NACRT were analyzed. ARID3A expression was evaluated using immunohistochemistry on whole-tissue sections. KRAS exon 2 (codons 12 and 13) and BRAF V600E mutation status were determined using polymerase chain reaction. Results: ARID3A positivity was found in 91 cases (64.5%), and it correlated with absence of perineural invasion (p=0.031), longer disease-free survival (DFS) (p=0.048) and cancer-specific survival (CSS) (p=0.006). However, ARID3A positivity was not correlated with KRAS (p=0.231) or BRAF mutation status (p=0.577). In multivariate analysis, ARID3A positivity was independently associated with a favorable CSS (p=0.035), but not DFS (p=0.051). Conclusion: ARID3A positivity can predict favorable prognosis in patients with residual rectal cancer after NACRT.*

Despite early diagnosis, advancement in surgical techniques, and improved adjuvant chemotherapeutic regimens, colorectal cancer (CRC) remains one of the major leading causes of cancer-related deaths worldwide (1). An increasing body of evidence indicates that rectal cancer is a distinct form of colon cancer with different aetiology, risk factors, and genetic and epigenetic alterations (2). The incidence of rectal cancer is approximately 35% of the total CRC incidence (2). Neoadjuvant chemoradiotherapy (NACRT) followed by total mesorectal excision (TME) is the standard treatment for locally advanced stage II/III rectal cancer (3, 4). The pathological complete response (pCR) of NACRT is associated with low rates of local and distant recurrence (2, 5). However, to the best of our knowledge, there are no known surrogate markers that can predict patient response to radiotherapy (RT) or chemoradiotherapy (CRT) (2). Furthermore, in clinical practice, the majority of patients with rectal cancer treated with NACRT fail to achieve a pCR (2, 5). In this context, identification of novel prognostic genes and/or downstream pathways controlling the tumor growth is pivotal for the development of treatment strategies for patients with residual rectal cancer treated with NACRT.

In 2012, Kang *et al.* identified the AT-rich interactive domain 3A (ARID3A) in the protein expression profiling of microsatellite-stable (MSS) CRC using proteomic techniques

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(6). Of the differentially expressed proteins in normal and cancer tissues, ARID3A expression level was approximately 14.29-fold higher in cancer tissues than in paired normal tissues. In 2017, Liu *et al.* found that ARID3A was up-regulated in CRC, by performing integrated analysis of microarray studies and verified it using The Cancer Genome Atlas (TCGA) data sets and quantitative real-time polymerase chain reaction (qRT-PCR) (7). ARID3A encodes a member of the ARID family of DNA-binding proteins known as B-cell regulator of immunoglobulin heavy-chain transcription (BRIGHT)/DRIL1/E2FBP1 (8-11), and it is homologous to the *Drosophila* dead ringer gene, which is important for normal embryogenesis (11). ARID3A is expressed ubiquitously in various tissues, playing a role in various biological processes (8-11). However, to date, the clinical relevance of ARID3A in human disease has not been fully elucidated. In particular, very few studies have reported the role of ARID3A in CRC. Recently, Song *et al.* demonstrated that ARID3A overexpression was an independent prognostic factor for favorable overall survival (OS) in 690 patients with CRC (8). Interestingly, they also performed survival analysis according to tumor location (colon versus rectum), separately, and showed that ARID3A overexpression was significantly correlated with favorable OS in patients with colon cancer but not in patients with rectal cancer (8). However, in their study, patients with rectal cancer were preoperative chemo- or radiotherapy-naïve. Thus, whether ARID3A overexpression is associated with the outcomes of patients with locally advanced mid or low rectal cancer treated with NACRT ought to be examined.

In the present study, we aimed to evaluate the clinical significance and prognostic impact of ARID3A expression in residual rectal disease after NACRT in patients with surgically resected rectal cancer by pathological assessment and immunohistochemistry.

Patients and Methods

Patient selection. A retrospective series of patients described in previous our studies were analyzed in the present study (12-14). Between January 2006 and December 2011, 134 patients with residual rectal cancer after NACRT who underwent surgical resection at Kyungpook National University Hospital and Chilgok Hospital (Daegu, South Korea) and were diagnosed with mid or low rectal adenocarcinoma were included in the study. Patients showing distant metastasis at initial diagnosis, and patients who achieved pCR were excluded from the study. Clinical information data of patients were obtained by reviewing their medical records and pathologic reports. In addition, one experienced gastrointestinal pathologist (ANS) reviewed the haematoxylin and eosin-stained slides and re-confirmed the pathologic assessment. Tumors were categorised according to the 7th UICC/AJCC TNM cancer classification system (15).

Ethical statement. This study was approved by the Institutional Review Board of Kyungpook National University Medical Center (IRB No: 2014-04-215), and the requirement for obtaining informed consent from patients was waived. This study was carried out according to the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Pre-treatment and surgery. All patients with clinical T3, T4, or node-positive disease were treated with NACRT in accordance with our institutional practice strategy and had regular follow-up (16). In long-course radiotherapy, a total radiation dose of 45 or 50 Gy is delivered in 25 fractions (1.8 or 2 Gy per fraction, respectively) five times per week for 5 weeks. The chemotherapy regimen involved the administration of 5-fluorouracil (5-FU), either as a bolus infusion (425 mg/m^2/day) plus leucovorin (20 mg/m^2/day) or as a continuous infusion, 5 days a week (250 mg/m^2/day) during radiotherapy. Curative surgical resection was performed within 6-8 weeks after the completion of NACRT. TME with autonomic nerve preservation was performed following the standard surgical procedure, which comprised of low anterior, intersphincteric, and abdominoperineal resection. All patients received treatment according to the standard practice guidelines and were followed regularly after surgery.

Pathological assessment. All specimens were fixed in 10% neutral-buffered formalin fluid overnight after inking the periphery of the mesorectum and cutting into transverse sections. For obvious residual primary tumor, initially, at least 6 tissue blocks were obtained from the tumor area. If the tumor was absent or not visible, the whole tumor area was blocked. If the tumor was still absent, each tumor block was thoroughly sectioned. CRM-positivity was defined as a tumor infiltration of ≤1 mm from the dyed fascia recti (17). The pathological tumor response to NACRT was assessed according to a previous report by Rödel *et al.* (5, 18): grade 0=no regression, grade 1=minor regression, grade 2=moderate regression, grade 3=good regression and grade 4=total regression (ypCR). If absence of tumor cells in tumors with acellular mucin pools in the whole tissue was demonstrated by immunohistochemistry (IHC) for cytokeratin, tumors were considered as ypCR and excluded from the study.

This work has been reported in line with the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) criteria (19).

IHC and interpretation. IHC was performed on 4 μm whole-sections of formalin-fixed paraffin-embedded (FFPE) tissues using Ventana Bench Mark® XT Autostainer (Ventana Medical Systems, Tucson, AZ, USA) with the ultraView Universal DAB Kit (Ventana Medical Systems) and antibodies against ARID3A (1:100; ProteinTech Group, Chicago, IL, USA) and p53 (1:800; Dako, Glostrup, Denmark), according to the manufacturer's instructions. Briefly, all tissue sections were deparaffinized and rehydrated, and antigens were retrieved for 40 min in a citrate buffer (pH 6.1) at 95˚C. DAB was used as the chromogen, and the sections were counterstained with haematoxylin.

Two experienced pathologists (ANS and JYP), blinded to the patient clinical information, evaluated ARID3A and p53 expression. Both ARID3A and p53 proteins were expressed in the nuclei of tumor cells. Because there is no consensus for ARID3A staining interpretation in rectal cancer, the quantitation was performed according to the previous report (8). When no ARID3A expression or weak/faint expression was observed in tumor cells, the specimen

was regarded as negative. In contrast, tumor specimens that showed ≥50% immunostaining with moderately/strongly intensity at low power magnification (40-100× objective) were considered as positive. Expression of p53 was measured as the percentage of cells showing definite nuclear staining and scored using a semiquantitative grading. Tumor samples with ≥10% positive nuclear staining were considered positive, as described previously (20).

KRAS and BRAF mutation detection. KRAS exon 2 (codons 12 and 13) and BRAF V600E mutation status was confirmed by PNA-mediated real-time polymerase chain reaction using the PNAClamp™ *KRAS* and PNAClamp™ *BRAF* Mutation Detection Kit (Panagene, Daejeon, Korea) according to the manufacturer's procedure (21). *KRAS* and *BRAF* mutation status has already been analyzed previously (12, 13).

Statistical analyses. Statistical analyses were carried out using IBM SPSS version 19.0 (IBM Co., Armonk, NY, USA). The association between ARID3A and p53 expression and clinicopathological data was determined using the χ^2 or Fisher's exact test for categorical variables, as appropriate. Pearson correlation (R) test was used to evaluate the correlation between ARID3A and p53 expression. Two survival end points were evaluated: (1) disease-free survival (DFS), defined as the time interval between surgery and the date of disease relapse or death, and (2) cancer-specific survival (CSS), defined as the time interval between surgery and death caused by the disease. The Kaplan–Meier method was used to estimate DFS and CSS curves, and the log-rank test was used to compare between groups. A multivariate Cox regression analysis was performed, including all variables that were significantly associated with prognosis in the univariate analysis. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated for each factor. Statistical significance was considered as $p<0.05$.

Results

Patient characteristics. The demographic characteristics of the study cohort are summarised in Table I. The patient group included 93 males (69.4%) and 41 females (30.6%), with a median age of 60 years (range=29-85). At the time of surgical resection after NACRT, 27 (20.1%) tumors were ystage I, 64 (47.8%) were ystage II, and 43 (32.1%) were ystage III, according to the 7th UICC/AJCC. Among 100 patients with *KRAS* and *BRAF* mutation results available, 29 patients (29.0%) harboured a *KRAS* mutation, whereas 4 (4.0%) harboured a *BRAF* mutation.

Correlations between ARID3A and clinicopathological data. Figure 1 shows representative images of tumor specimens with positive expression of ARID3A and p53. ARID3A expression was evaluated in all the cases (n=134), whereas p53 expression was not evaluable in 4 of the 134 cases, because of the loss of tissues. ARID3A positivity was found in 91 of 134 (67.9%) patients, whereas p53 positivity was observed in 99 of 130 (76.2%) patients. No statistically significant correlation between ARID3A positivity and p53 positivity was found (R=0.077, $p=0.386$). As shown in Table

Table I. *Patient characteristics*.

Characteristics	n (%)
Age at diagnosis, years*	60.0 (29-85)
Gender	
Male	93 (69.4)
Female	41 (30.6)
Tumor distance from anal verge	
<5	102 (76.1)
≥5	32 (23.9)
Tumor size*	6.0 (2.3-10.0)
Clinical T category	
cT2	8 (6.0)
cT3	109 (81.3)
cT4	17 (12.7)
Clinical N category	
cN0	15 (11.2)
cN1-3	119 (88.8)
Pathologic T category	
ypT1	2 (1.5)
ypT2	31 (23.1)
ypT3	92 (68.7)
ypT4	9 (6.7)
Pathologic N category	
ypN0	91 (67.9)
ypN1-3	43 (32.1)
Pathologic TNM stage (7th UICC/AJCC)	
I	27 (20.1)
II	64 (47.8)
III	43 (32.1)
CRM status	
Negative	105 (78.4)
Positive	29 (21.6)
Preoperative CEA[a]	
<5	86 (68.8)
≥5	39 (31.2)
Tumor regression grade[b]	
0	4 (3.0)
1	21 (15.7)
2	54 (40.3)
3	55 (41.0)
Downstage after neoadjuvant chemoradiotherapy	
No	49 (36.6)
Yes	85 (63.4)
KRAS mutation[c]	
Wild	71 (71.0)
Mutant	29 (29.0)
BRAF mutation[c]	
Wild	96 (96.0)
Mutant	4 (4.0)

TNM, Tumor-node-metastasis; UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer; CRM, circumferential resection margin; CEA, carcinoembryonic antigen. *Data presented as median (range). [a]Patients who had pathologic complete remission (tumor regression grade 4) were excluded in this study. [b]Missing value was included. [c]*KRAS* and *BRAF* mutations were assessed in 100 patients.

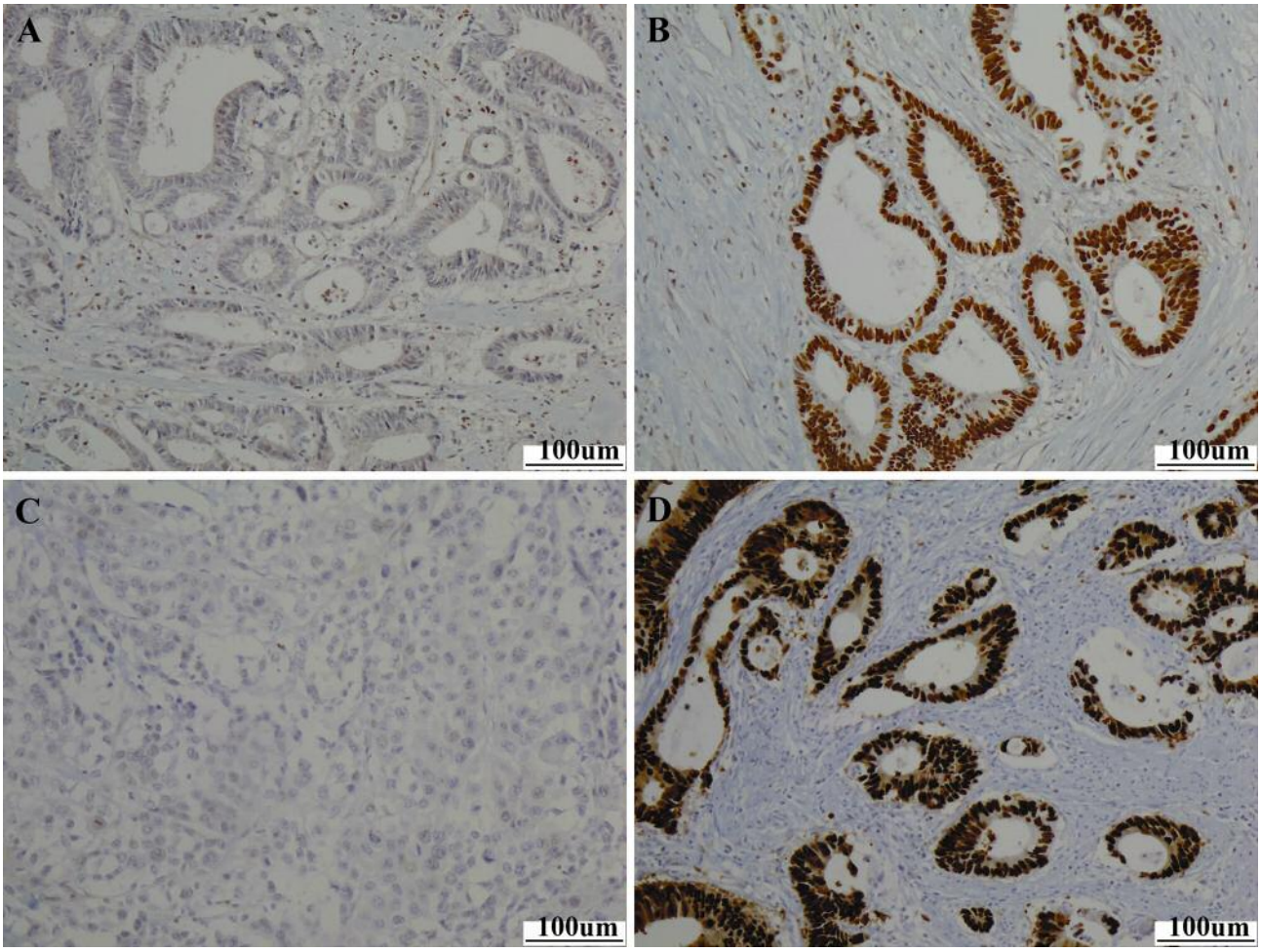

Figure 1. *The expression of ARID3A and p53 proteins in rectal cancer specimens was assessed by immunohistochemistry. Representative images of negative (A) and positive (B) staining for ARID3A, as well as negative (C) and positive for p53 (D) are shown. 200× magnification; Scale bar 100 μm.*

II, ARID3A positivity inversely correlated with perineural invasion (p=0.031), whereas p53 positivity had no association with any clinicopathological parameters. Neither ARID3A nor p53 positivity was related to *KRAS* or *BRAF* mutations (Table II).

Survival outcomes. At the time of analysis, the median follow-up durations for DFS and CSS were 47.7 (range=2.2-111.0) and 48.3 (range=3.2-111.0) months, respectively. During follow-up period, 53 (39.6%) experienced recurrence and 22 (16.4%) died of rectal cancer. Patients with ARID3A positivity showed a significantly longer DFS (p=0.048; Figure 2A) and CSS (p=0.006; Figure 2B) than those with ARID3A negativity. In contrast, p53 positivity was not significantly associated with DFS (p=0.493; Figure 2C) or CSS (p=0.354; Figure 2D). In a Cox proportional hazard model adjusted for ypT category, ypN category, lymphatic invasion, perineural invasion, venous invasion, and CRM status, ARID3A positivity was an independent prognostic factor for favorable CSS (HR=2.655, 95% CI=1.072-6.576, p=0.035; Table III). There was no statistical significance between DFS and ARID3A expression (HR=1.778, 95% CI=0.998-3.166, p=0.051; Table III).

Discussion

In patients with rectal cancer, after NACRT, the goals of care include decreasing the risk of recurrence and optimizing the length of life. As previously mentioned, a pCR after NACRT is associated with low rates of local recurrence and distant metastasis. However, because the majority of patients with residual disease do not achieve pCR, the use of surrogate markers that can predict patient outcomes is necessary. Herein, we evaluated whether ARID3A expression could

Table II. *The association between clinicopathologic parameters and AT-rich interactive domain 3A (ARID3A) and p53 protein expressions.*

Clinicopathologic characteristics	ARID3A expression (n=134)		*p*-Value	p53 expression[a] (n=130)		*p*-Value
	Negative n (%)	Positive n (%)		Negative n (%)	Positive n (%)	
Age at diagnosis, years						
<60	17 (39.5)	47 (51.6)	0.201	14 (45.2)	46 (46.5)	1.000
≥60	26 (60.5)	44 (48.4)		17 (54.8)	53 (53.5)	
Gender						
Male	26 (60.5)	67 (73.6)	0.160	24 (77.4)	66 (66.7)	0.277
Female	17 (39.5)	24 (26.4)		7 (22.6)	33 (33.3)	
Tumor distance from anal verge, cm						
<5	33 (76.7)	69 (75.8)	1.000	21 (67.7)	78 (78.8)	0.231
≥5	10 (23.3)	22 (24.2)		10 (32.3)	21 (21.2)	
Preoperative CEA, ng/m[b]						
<5	28 (70.0)	58 (68.2)	1.000	19 (67.9)	64 (68.8)	1.000
≥5	12 (30.0)	27 (31.8)		9 (32.1)	29 (31.2)	
Tumor size, cm						
<6	23 (53.5)	44 (48.4)	0.712	17 (54.8)	47 (47.5)	0.540
≥6	20 (46.5)	47 (51.6)		14 (45.2)	52 (52.5)	
Pathologic T category						
ypT1-T2	11 (25.6)	22 (24.2)	1.000	1 (3.2)	7 (7.1)	0.679
ypT3-T4	32 (74.4)	69 (75.8)		30 (96.8)	92 (92.9)	
Pathologic N category						
ypN0	25 (58.1)	66 (72.5)	0.114	2 (6.5)	13 (13.1)	0.520
ypN1-3	18 (41.9)	25 (27.5)		29 (93.5)	86 (86.9)	
Pathologic TNM stage						
I & II	25 (58.1)	66 (72.5)	0.114	23 (74.2)	66 (66.7)	0.511
III	18 (41.9)	25 (27.5)		8 (25.8)	33 (33.3)	
Downstage after neoadjuvant chemoradiotherapy						
No	20 (46.5)	29 (31.9)	0.125	9 (29.0)	38 (38.4)	0.397
Yes	23 (53.5)	62 (68.1)		22 (71.0)	61 (61.6)	
CRM status						
Negative	35 (81.4)	70 (76.9)	0.656	27 (87.1)	76 (76.8)	0.311
Positive	8 (18.6)	21 (23.1)		4 (12.9)	23 (23.2)	
Tumor regression grade[c]						
0	2 (4.7)	2 (2.2)	0.181	2 (6.5)	2 (2.0)	0.592
1	8 (18.6)	13 (14.3)		5 (16.1)	16 (16.2)	
2	12 (27.9)	42 (46.2)		11 (35.5)	41 (41.4)	
3	21 (48.8)	34 (37.4)		13 (41.9)	40 (40.4)	
Lymphatic invasion						
Negative	29 (67.4)	73 (80.2)	0.130	24 (77.4)	75 (75.8)	1.000
Positive	14 (32.6)	18 (19.8)		7 (22.6)	24 (24.2)	
Venous invasion						
Negative	40 (93.0)	89 (97.8)	0.327	29 (93.5)	96 (97.0)	0.592
Positive	3 (7.0)	2 (2.2)		2 (6.5)	3 (3.0)	
Perineural invasion						
Negative	27 (62.8)	74 (81.3)	0.031	22 (71.0)	77 (77.8)	0.473
Positive	16 (37.2)	17 (18.7)		9 (29.0)	22 (22.2)	
KRAS mutation[d]						
Wild	18 (62.1)	53 (74.6)	0.231	20 (80.0)	49 (68.1)	0.313
Mutant	11 (37.9)	18 (25.4)		5 (20.0)	23 (31.9)	
BRAF mutation[d]						
Wild	27 (93.1)	69 (97.2)	0.577	24 (96.0)	69 (95.8)	1.000
Mutant	2 (6.9)	2 (2.8)		1 (4.0)	3 (4.2)	

TNM, Tumor-node-metastasis; UICC/AJCC, Union for International Cancer Control/American Joint Committee on Cancer; CRM, circumferential resection margin; CEA, carcinoembryonic antigen. [a]p53 protein expression was evaluated in 130 patients. [b]Missing value was included. [c]Patients who had pathological complete remission (tumor regression grade 4) were excluded in this study. [d]*KRAS* and *BRAF* mutations were assessed in 100 patients.

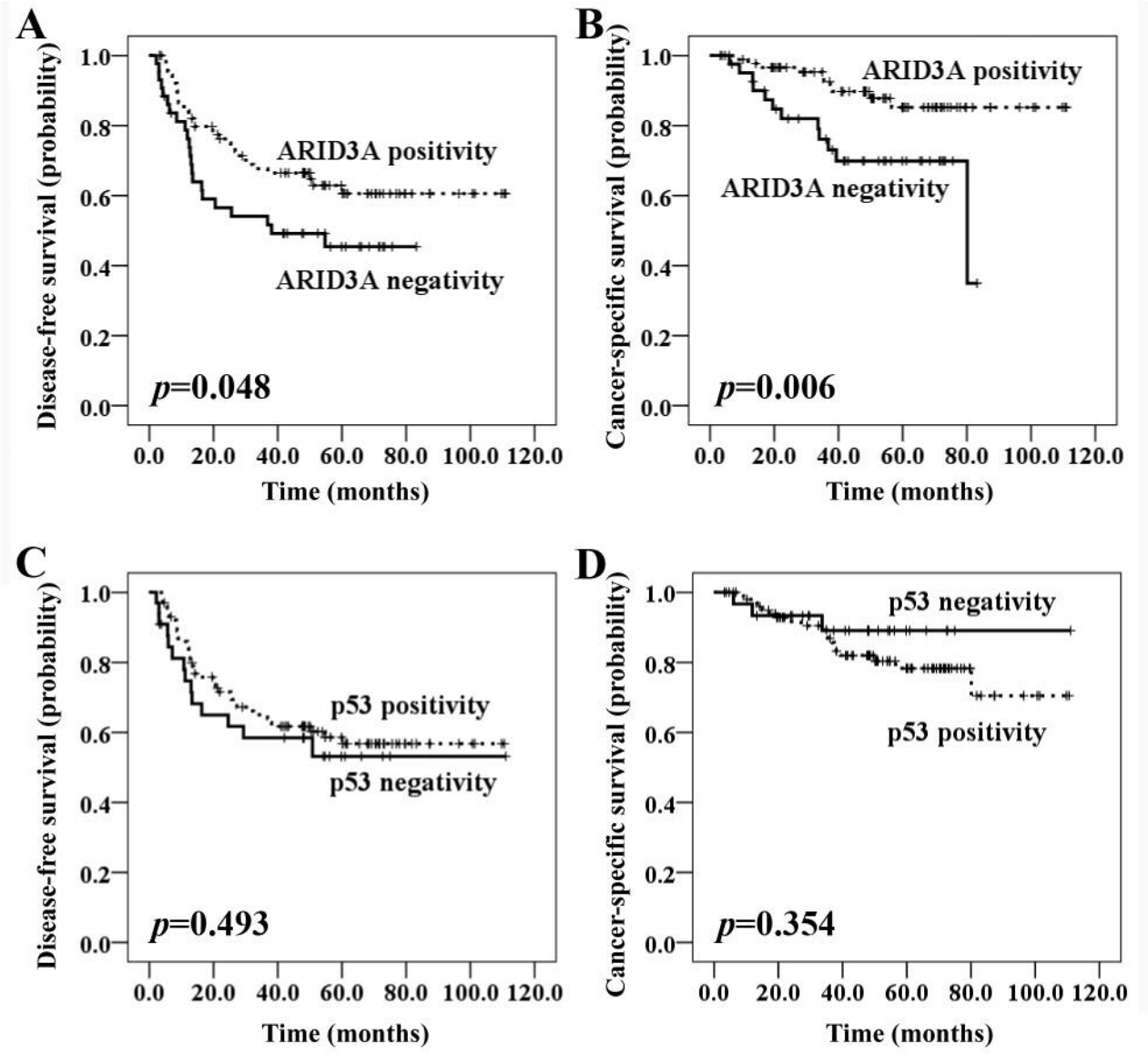

Figure 2. *Kaplan–Meier survival curves for disease-free survival (DFS) (A) and cancer-specific survival (CSS) (B) according to the expression of ARID3A. Kaplan–Meier survival curves for DFS (C) and CSS (D) according to the expression of p53.*

predict prognosis of patients who developed residual rectal cancer after NACRT. The rationale was supported by the study by Song *et al*., which showed that strong nuclear expression of ARID3A can independently predict favorable OS in patients with CRC (8). We also found that strong nuclear expression of ARID3A was significantly associated with improved CSS in patients with residual rectal cancer after NACRT, independent of the standard prognostic and predictive factors (ypT category, ypN category, lymphatic invasion, venous invasion, perineural invasion, and CRM). To the best of our knowledge, there have been no studies investigating the prognostic significance of ARID3A in rectal cancer after NACRT. Interestingly, we found ARID3A positivity in 69.4% of residual rectal cancer after NACRT, whereas Song *et al*. observed in 30% of rectal cancer with preoperative chemotherapy or radiotherapy naïve (8). This difference of frequency might be due to tumor location (mid- or low- rectum versus upper rectum) and/or NACRT.

Although ARID3A/BRIGHT expression in adults was originally thought to be limited to cells of the B lymphocyte lineage, studies have revealed that ARID3A is expressed in multiple foetal, embryonic, and placental

Table III. *Multivariate analyses for disease-free survival (DFS) and cancer-specific survival (CSS).*

Variable	Category	DFS			CSS		
		Multivariate analysis			Multivariate analysis		
		HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
ypT category	ypT1-T2 *vs*. ypT3-T4	2.567	0.962-6.849	0.060	95104.564	0.000-1.06E172	0.953
ypN category	ypN0 *vs*. ypN1-3	1.788	0.878-3.639	0.109	3.991	1.255-12.692	0.019
Venous invasion	Absent *vs*. Present	17.577	4.759-64.918	<0.001	2.631	0.666-10.393	0.168
Lymphatic invasion	Absent *vs*. Present	1.272	0.638-2.535	0.495	1.971	0.702-5.533	0.197
Perineural invasion	Absent *vs*. Present	1.362	0.724-2.563	0.338	3.493	1.278-9.544	0.015
CRM	Negative *vs*. Positive	3.391	1.840-6.250	<0.001	6.849	2.540-18.465	<0.001
ARID3A expression	Negative *vs*. Positive	1.778	0.998-3.166	0.051	2.655	1.072-6.576	0.035

HR, Hazard ratio; CI, confidence interval; CRM, circumferential resection margin; ARID3A, AT-rich interactive domain 3A.

tissues, as well as in adult hematopoietic stem cells (22-27). Of note, abnormal ARID3A expression is associated with increased proliferative capacity and malignancy; however, ARID3A may play distinct regulatory roles in different types of cells (25). In CRC, Liu *et al*. demonstrated that REGEL, CA1, ANGPTL7, TMEFF2, and ZNF354C were downregulated, whereas ARID3A was upregulated among the differentially expressed genes (DEGs) and their transcription factors (TFs) in CRC. In the light of previous studies, ARID3A might be a potential oncogenic factor (6, 7). ARID3A is an upstream TF of ESM1 and could be involved in CRC by regulating ESM1 (7). However, high ARID3A expression was associated with favorable prognosis in the present study as well as in the study published by Song *et al*. (8). Thus, the mechanisms that regulate ARID3A expression in tumor cells remain unknown. ARID3A is known to repress the formation of promyelocytic leukaemia (PML) nuclear bodies (28). PML can actively promote Ras-induced senescence and modify the tumor-suppressor effects of the retinoblastoma protein (Rb) and p53 pathways (29). Oncogenic Ras can upregulate PML expression, which, in turn, induces senescence in a p53-dependent manner (30). Contrastingly, other studies have reported the function of ARID3A as a tumor suppressor (9, 31). Ma *et al*. suggested that ARID3A expression can be activated by p53 and, in parallel, can increase endogenous p53 levels in a dose-dependent manner after DNA damage (9, 10). They also showed that ARID3A could inhibit tumor cell growth in cells with wild-type p53, but not in cells lacking p53 (9). Lestari *et al*. demonstrated that ARID3A plays important roles in p53-mediated p21Waf1 transactivation and that modulation of ARID3A levels affects p53 protein stability, providing interdependent and cooperative roles for ARID3A and p53 proteins in transcriptional activation of p21Waf1 in response to DNA damage (31). This means that ARID3A may play a key role in p53-mediated tumor growth suppression (8, 9). However, in the present study, we found no significant association between ARID3A and p53 protein expression. In addition, we did not found any correlation between p53 expression and TRG as well as prognosis. Terzi *et al*. suggested that IHC assessment of p53 in pre-treatment biopsy specimens does not predict TRG and prognosis (32). In contrast, Chen *et al*. demonstrated that wild-type form of p53 status was associated with good response rates to neoadjuvant radiation-based treatment by performing meta-analysis of 30 studies (33).

Thus far, whether ARID3A acts as an oncogene or as a tumor suppressor remains controversial. This is because of the distinct roles influenced by ARID3A during the cell cycle in different cell types that result from different interactions with different cooperating factors or maturation states (25). Therefore, further comprehensive studies taking into account these findings are necessary.

One limitation of our study is selection bias due to the retrospective design from a single institution, the relatively small number of patients with residual rectal cancer after NACRT, and the lack of comparison of ARID3A expression between pre-treatment biopsy and post-treatment surgical tissues. Hence, our findings should be interpreted with caution, and further large-scale studies should be carried out to validate these results in other ethnic groups.

In summary, we demonstrated that ARID3A overexpression is an independent prognostic factor for CSS in patients with surgically resected residual rectal cancer after NACRT. Although the underlying mechanism requires further research, our results indicate that ARID3A plays an important role in rectal cancer. These findings would be helpful in uncovering the biological mechanism and develop novel therapeutic targets in patients with residual rectal cancer after NACRT.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

A.N. Seo had substantial contributions to the conception or design of the work. G. Yoon and A.N. Seo wrote the first draft and the revised draft, and then reviewed the final article. J.Y. Park and A.N. Seo performed the experiments. A.N. Seo performed the statistical analyses. H.J. Kim, G.S. Choi, J.G. Kim, B.W. Kang, and M.K. Kang collected and interpreted the clinical data and specimens. All authors approved the final version and agreed to be accountable for all aspects of the work.

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