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ORIGINAL ARTICLE

Retrospective Study

Annexin A10 expression in colorectal cancers with emphasis on the serrated neoplasia pathway

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Abstract

AIM: To validate the utility of Annexin A10 as a surrogate marker of the serrated neoplasia pathway in invasive colorectal cancers (CRCs).

METHODS: A total of 1133 primary CRC patients who underwent surgical resection at Seoul National University Hospital between January 2004 and December 2007 were enrolled. Expression of Annexin A10 was evaluated by immunohistochemistry using tissue microarray and paired to our findings on clinicopathologic and molecular characteristics of each individual. CpG island methylator phenotype was determined by MethyLight assay and microsatellite instability was determined by high performance liquid chromatography. *KRAS* and *BRAF* mutation status was

evaluated by direct sequencing and allele-specific PCR. Univariate and stage-specific survival analyses were performed to reveal the prognostic value of Annexin A10 expression.

RESULTS: Annexin A10 expression was observed in 66 (5.8%) of the 1133 patients. Annexin A10 expression was more commonly found in females and was associated with proximal location, ulcerative gross type, advanced T category, N category and TNM stage. CRCs with Annexin A10 expression showed an absence of luminal necrosis, luminal serration and mucin production. CRCs with Annexin A10 expression were associated with CpG island methylator phenotype, microsatellite instability and *BRAF* mutation. In survival analysis, Annexin A10 expression was associated with poor overall survival and progression-free survival, especially in stage Ⅳ CRCs.

CONCLUSION: Annexin A10 expression is associated with poor clinical behavior and can be used a supportive surrogate marker of the serrated neoplasia pathway in invasive CRCs.

Key words: Annexin A10; Serrated neoplasia pathway; CpG island methylator phenotype; Colorectal cancer; *BRAF* mutation

Core tip: Annexin A10 is considered a surrogate immunohistochemical marker for sessile serrated adenomas/polyps. We validated the utility of Annexin A10 as a surrogate marker of the serrated neoplasia pathway in invasive colorectal cancers (CRCs). Annexin A10 expression was associated with female sex, proximal location, ulcerative gross type, advanced TNM stage, serration and mucin production. CRCs with Annexin A10 expression were associated with CpG island methylator phenotype, microsatellite instability and *BRAF* mutation. In stage-specific survival analysis, Annexin A10 expression was associated with poor clinical outcome in stage Ⅳ CRCs. Annexin A10 can be used a supportive surrogate marker of the serrated neoplasia pathway.

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INTRODUCTION

Colorectal cancer (CRC) shows heterogeneity in terms of its molecular carcinogenesis, and this heterogeneity contributes to clinical and histomorphological variation[1]. Currently, there are three widely accepted colorectal carcinogenic pathways, the chromosomal instability (CIN) pathway, the microsatellite instability (MSI) pathway, and the epigenetic instability pathway, which corresponds to the CpG island methylator phenotype (CIMP). The CIN pathway is characterized by alterations in the number and structure of chromosomes, as well as by the accumulation of somatic mutations in genes including proto-oncogenes and tumor suppressor genes[2]. MSI is caused by a defective mismatch repair system and is characterized by alterations in the number of repeat nucleotide(s), leading to frame-shift mutations in the corresponding genes[3]. CIMP is characterized by widespread cancer-specific hypermethylation of numerous promoter CpG island loci[4]. Initially, these pathways were considered to be mutually exclusive, but recent comparative studies have reported that molecular alterations in these pathways can partially overlap[5].

CRC is one of the best models for studying multistep carcinogenesis. Virtually all CRCs originate from premalignant polyps, which can be detected by colonoscopy. Colorectal premalignant polyps are divided into two groups: adenomatous polyps (conventional adenomas), which are precursor lesions of CRCs with CIN, and serrated polyps, which are now considered to be precursor lesions of CRCs with CIMP and sporadic MSI[6]. Serrated polyps are series of polyps that share sawtooth-like glandular morphology. Serrated polyps are divided into hyperplastic polyps, sessile serrated adenomas/polyps (SSA/P) and traditional serrated adenomas (TSA). Serrated polyps are highly associated with CIMP, sporadic MSI and the *BRAF* mutation.

Annexin A10 is a member of the annexin family, a large multigene family of calcium- and phospholipid-binding proteins. It plays important roles in physiologic processes including differentiation and proliferation[7-9]. Annexin A10 is expressed in the foveolar cells and glandular cells of the normal antral or body-type gastric mucosa. In addition, Annexin A10 is expressed in Brunner gland cells of the duodenum and urothelial cells of the renal pelvis and urinary bladder[10]. However, aberrant expression of Annexin A10 was found in malignant tumors of other tissue types, including oral cancer, pancreatic cancer, and lung cancer[10,11]. Recently, Gonzalo *et al*[12] proposed Annexin A10 as a marker for the colorectal serrated neoplasia pathway. They observed increased expression of Annexin A10 in SSA/P compared with normal colonic epithelia and microvesicular hyperplastic polyps. However, little is known about Annexin A10 expression in invasive CRCs.

Previously, we reported the correlation of Annexin A10 expression with the serrated neoplasia pathway using 168 microsatellite-unstable CRCs[13]. However, the evaluation of Annexin A10 expression in a large

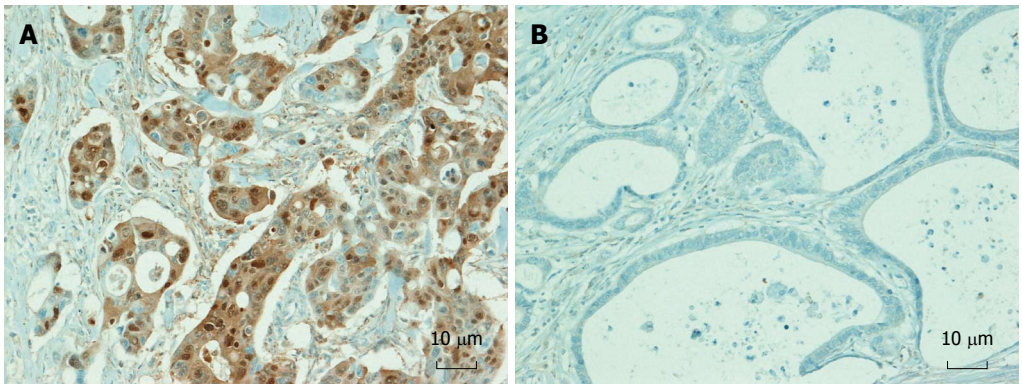

Figure 1 Representative images of immunohistochemical staining for Annexin A10. A: Colorectal cancers (CRCs) with Annexin A10 expression (magnification × 200); B: CRCs without Annexin A10 expression (magnification × 200).

population is required to characterize the clinicopathological and molecular characteristics of Annexin A10, because of its low prevalence in CRCs[10,14]. In this study, we evaluated the clinicopathological characteristics and prognostic value of Annexin A10 expression in 1133 primary CRCs and compared them with molecular profiles including CIMP, MSI, *KRAS* and *BRAF* mutation status. Finally, we evaluated whether Annexin A10 can be used as a surrogate marker for CRCs with CIMP.

MATERIALS AND METHODS

Tissue samples

A total of 1527 patients with CRC underwent curative surgery at Seoul National University Hospital, Seoul, South Korea, from January 2004 to December 2007. After the exclusion of 394 patients with CRC [refusal of molecular study (n = 136), non-invasive cancers (n = 50), familial adenomatous polyposis (n = 13), multiple occurrence (n = 78), neoadjuvant chemo- and/or radiotherapy (n = 89), recurrent tumors (n = 28)], formalin-fixed paraffin-embedded tissue samples from 1133 patients with CRC were selected for this study. This study was approved by the Institutional Review Board.

Clinicopathological analysis

Clinicopathological characteristics including age, sex, tumor location, and TNM stage were obtained from electronic medical records. Through microscopic examination of representative sections of the tumors, we evaluated the following parameters without knowledge of the CIMP, MSI, *KRAS* and *BRAF* mutation status of the specimen: tumor differentiation, luminal necrosis, tumor budding, Crohn-like lymphoid reaction, number of tumor-infiltrating lymphocytes, luminal serration and extraglandular mucin production. Overall survival and progression-free survival data were extracted from the patient's medical records, direct interviews with surviving patients or members of patients' families or death registry offices.

Evaluation of Annexin A10 expression

Tissue microarray (TMA) construction using formalin-fixed, paraffin-embedded (FFPE) tissues from 1133 CRCs was performed. Three different tumor areas in the FFPE tissue of individual CRCs were extracted as three tissue cores (2mm in diameter) for each case and were transferred to TMA blocks. Immunohistochemical analysis was performed with commercially available antibodies against Annexin A10 (1:300, NBP1-90156, Novus Biologicals). Expression of Annexin A10 was assessed independently by two pathologists (Bae JM and Kang GH). The presence of Annexin A10 nuclear staining in more than 5% of the tumor area in any TMA core was classified as expression of Annexin A10[13]. Tumors showing less than 5% nuclear staining of the tumor area or cytoplasmic staining without nuclear staining were classified as exhibiting no-expression of Annexin A10 (Figure 1).

KRAS, BRAF mutation and MSI analyses

Through histological examination, representative tumor portions were marked and then subjected to manual microdissection. Dissected tissues were collected into microtubes containing lysis buffer and proteinase K and were incubated at 55 ℃ for 2 d. DNA from paraffin-embedded tissue was extracted, and polymerase chain reaction (PCR) was performed. Direct sequencing of *KRAS* codons 12 and 13, and allele-specific PCR for *BRAF* codon 600 were performed as previously described[15]. MSI status was determined by 5 NCI markers including BAT25, BAT26, D2S123, D5S346 and D17S250. MSI was defined when two or more markers were unstable, and microsatellite stable (MSS) was defined when only one marker was unstable or when all five markers were stable.

Analysis of CpG island methylator phenotype

Bisulfite DNA modification and real-time methylation specific PCR (MethyLight) assays were performed as described previously[16]. We quantified methylation of eight CIMP-specific markers (*CACNA1G*, *CDKN2A*,

Table 1 Clinicopathologic and histologic features of Annexin A10 expression in colorectal cancers *n* (%)

Parameter	Annexin A10 no-expression (*n* = 1067, 94.2%)	Annexin A10 expression (*n* = 66, 5.8%)	*P* value
Age (mean ± SD)	61.0 ± 11.1	58.1 ± 12.6	0.038[1]
Sex			< 0.001
Male	650 (60.9)	27 (40.9)	
Female	417 (39.1)	39 (59.1)	
Location			< 0.001
Proximal colon	237 (22.2)	42 (63.6)	
Distal colon	430 (40.3)	11 (16.7)	
Rectum	400 (37.5)	13 (19.7)	
Gross type			0.027
Fungating	708 (66.3)	35 (53.0)	
Ulcerative	359 (33.7)	31 (47.0)	
T category			< 0.001[2]
1	47 (4.4)	1 (1.5)	
2	164 (15.4)	0 (0.0)	
3	756 (70.8)	52 (78.8)	
4	100 (9.4)	13 (19.7)	
N category			< 0.001[2]
0	558 (52.3)	16 (24.2)	
1	290 (27.2)	23 (34.9)	
2	219 (20.5)	27 (40.9)	
M category			0.049
0	892 (83.6)	49 (74.2)	
1	175 (16.4)	17 (25.8)	
Stage			< 0.001[2]
Ⅰ	173 (16.2)	0 (0.0)	
Ⅱ	351 (32.9)	15 (22.7)	
Ⅲ	368 (34.5)	34 (51.5)	
Ⅳ	175 (16.4)	17 (25.7)	
Differentiation			0.002
Well	64 (6.0)	2 (3.0)	
Differentiated Moderately	970 (90.9)	56 (84.9)	
Differentiated Poorly	33 (3.1)	8 (12.1)	
Differentiated Luminal necrosis			< 0.001
Absent	83 (7.8)	18 (27.3)	
Present	984 (92.2)	48 (72.7)	
Tumor budding			0.264[3]
Absent	36 (3.4)	0 (0.0)	
Present	1031 (96.6)	66 (100.0)	
Tumor-infiltrating Lymphocytes			0.316
Low TILs (< 8/HPF)	802 (75.2)	39 (59.1)	
High TILs (≥ 8/HPF)	265 (24.8)	27 (40.9)	
Crohn's-like Lymphoid reaction			0.470
Absent	908 (85.1)	54 (81.8)	
Present	159 (14.9)	12 (18.2)	
Luminal serration			< 0.001[3]
Absent	1039 (97.4)	50 (75.8)	
Present	28 (2.6)	16 (24.2)	
Mucin production			
Absent	958 (89.8)	43 (65.1)	< 0.001
Present	109 (10.2)	23 (34.9)	

1Student's *t*-test; [2]Wilcoxon rank-sum test; [3]Fisher's exact test. S.D: Standard deviation; HPF: High power field.

CRABP1, *IGF2*, *MLH1*, *NEUROG1*, *RUNX3* and *SOCS1*). CIMP-positive (CIMP-P) was defined by a tumor showing methylation in ≥ five markers of the 8-marker CIMP panel and CIMP-negative (CIMP-N) as tumors showing methylation in ≤ 4 markers (0 to 4 of 8 promoters).

Statistical analysis

SAS system (version 9.3, SAS Institute, Cary, NC, United States) and R software were used for statistical analyses. The age of each group was compared using Student's *t*-test. The other clinicopathological characteristics between groups were compared using χ^2 test or Fisher's exact test for categorical variables and Wilcoxon's rank-sum test for ordinal variables. The survival curves after surgery were estimated by Kaplan-Meier method and the differences in the survival curves were tested by log-rank test. Cox proportional hazards models were used to estimate hazard ratios and corresponding 95% confidence intervals (CIs) for the overall survival. The assumption of proportional hazards was checked by plotting the log[-log[S(t)]] against time on study. All statistical tests were two-sided, and statistical significance was defined as $P < 0.05$.

The statistical methods of this study were reviewed by Myoung Jin Jang from Medical Research Collaborating Center, Seoul National University Hospital.

RESULTS

Clinicopathological characteristics of Annexin A10 expression

Detailed clinicopathological features and histological features according to Annexin A10 expression are summarized in Table 1. A total of 1133 patients with CRC (mean age ± SD, 60.8 ± 11.2) were included in the immunohistochemical analysis. The male to female ratio was 1.48:1 (677 males and 456 females). Tumor location was proximal colon (proximal to the splenic flexure) in 279 patients, distal colon in 441 patients and rectum in 413 patients. Median follow-up duration was 58.1 mo (0.3-89.8 mo). 785 patients received 5-fluorouracil based adjuvant chemotherapy.

Annexin A10 expression was observed in 66 (5.8%) patients. Annexin A10 expression was associated with lower age at diagnosis ($P = 0.038$), female sex ($P < 0.001$), proximal tumor location ($P < 0.001$), advanced T category ($P < 0.001$), N category ($P < 0.001$), M category ($P = 0.049$) and more advanced TNM stage ($P < 0.001$). As shown with microscopic examination, Annexin A10 expression was associated with absence of luminal necrosis ($P < 0.001$), increased number of tumor-infiltrating lymphocytes ($P = 0.003$), luminal

Table 2 Comparison of Annexin A10 expression with other molecular characteristics in colorectal cancers *n* (%)

Parameter	Annexin A10 no-expression (*n* = 1067, 94.2%)	Annexin A10 expression (*n* = 66, 5.8%)	*P* value
CIMP			< 0.001[1]
CIMP-N	1029 (96.4)	41 (62.1)	
CIMP-P	38 (3.6)	25 (37.9)	
MSI			< 0.001[1]
MSS	995 (93.2)	49 (74.2)	
MSI	72 (6.8)	17 (25.8)	
KRAS mutation (*n* = 1071)			0.399
Wild type	745 (73.8)	42 (68.8)	
Mutant type	265 (26.2)	19 (31.2)	
BRAF mutation (*n* = 1005)			< 0.001[1]
Wild type	912 (96.4)	50 (84.7)	
Mutant type	34 (3.6)	9 (15.3)	

[1]Fisher's exact test. CIMP: CpG island methylator phenotype; MSI: Microsatellite instability.

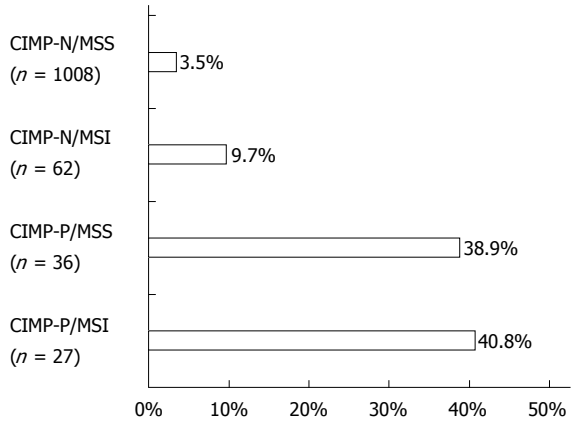

Figure 2 Frequency of Annexin A10 expression according to four molecular subtypes. CIMP-N: CpG island methylator phenotype-negative; CIMP-P: CpG island methylator phenotype-positive; MSS: Microsatellite stable; MSI: Microsatellite instability.

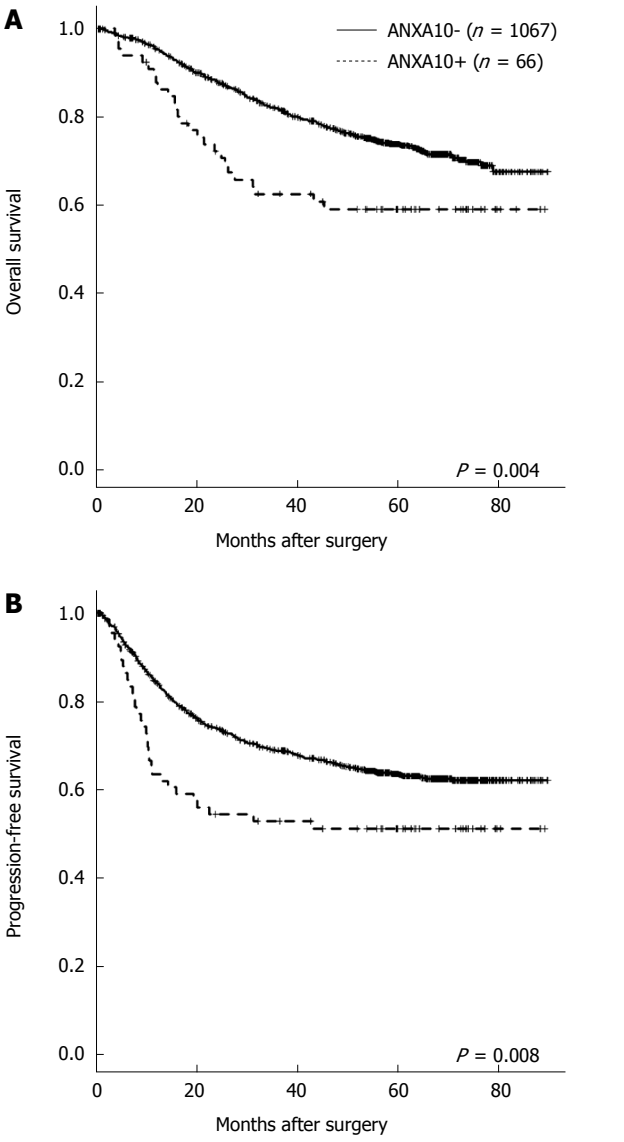

Figure 3 Univariate survival analysis in colorectal cancers according to Annexin A10 expression status. A: Overall survival; B: Progression-free survival. ANXA10-; Annexin A10 no-expression, ANXA10+: Annexin A10 expression.

serration ($P < 0.001$) and mucin production ($P < 0.001$).

Molecular characteristics of Annexin A10 expression

Table 2 shows molecular characteristics of CRCs according to Annexin A10 expression. Among the 1133 CRCs, CIMP-P CRCs were detected in 63 (5.6%) patients and MSI CRCs were found in 88 (7.8%) patients. Annexin A10 expression was associated with CIMP-P CRCs ($P < 0.001$) and MSI CRCs ($P < 0.001$). Sensitivity and specificity of Annexin A10 expression for detection of CIMP-P CRCs were 39.7% and 96.2%, respectively. Positive predictive value (PPV) and negative predictive value (NPV) of Annexin A10 expression for detection of CIMP-P CRCs were 0.38 and 0.96, respectively. In four molecular subtypes which were generated by the combined status of CIMP and MSI, Annexin A10 expression was observed in 3.5% of CIMP-N/MSS CRCs, 9.7% of CIMP-N/MSI CRCs, 38.9% of CIMP-P/MSS CRCs and 40.8% of CIMP-P/MSI CRCs (Figure 2). In the mutation studies, CRCs with Annexin A10 expression showed a higher frequency of the *BRAF* mutation than did CRCs with Annexin A10 no-expression ($P < 0.001$).

Survival analysis

As shown using univariate survival analysis with Kaplan-Meier survival curves, patients with Annexin A10 expression showed worse overall survival ($P = 0.004$) and progression-free survival ($P = 0.008$) than patients with Annexin A10 no-expression (Figure 3). Although sample size did not get enough power to predict clinical outcome, in stage Ⅳ CRCs, the Annexin A10 expression group showed shorter median overall survival (OS) (17.0 mo *vs* 25.3 mo, $P < 0.001$) and shorter progression-free survival (PFS) (7.5 mo *vs*

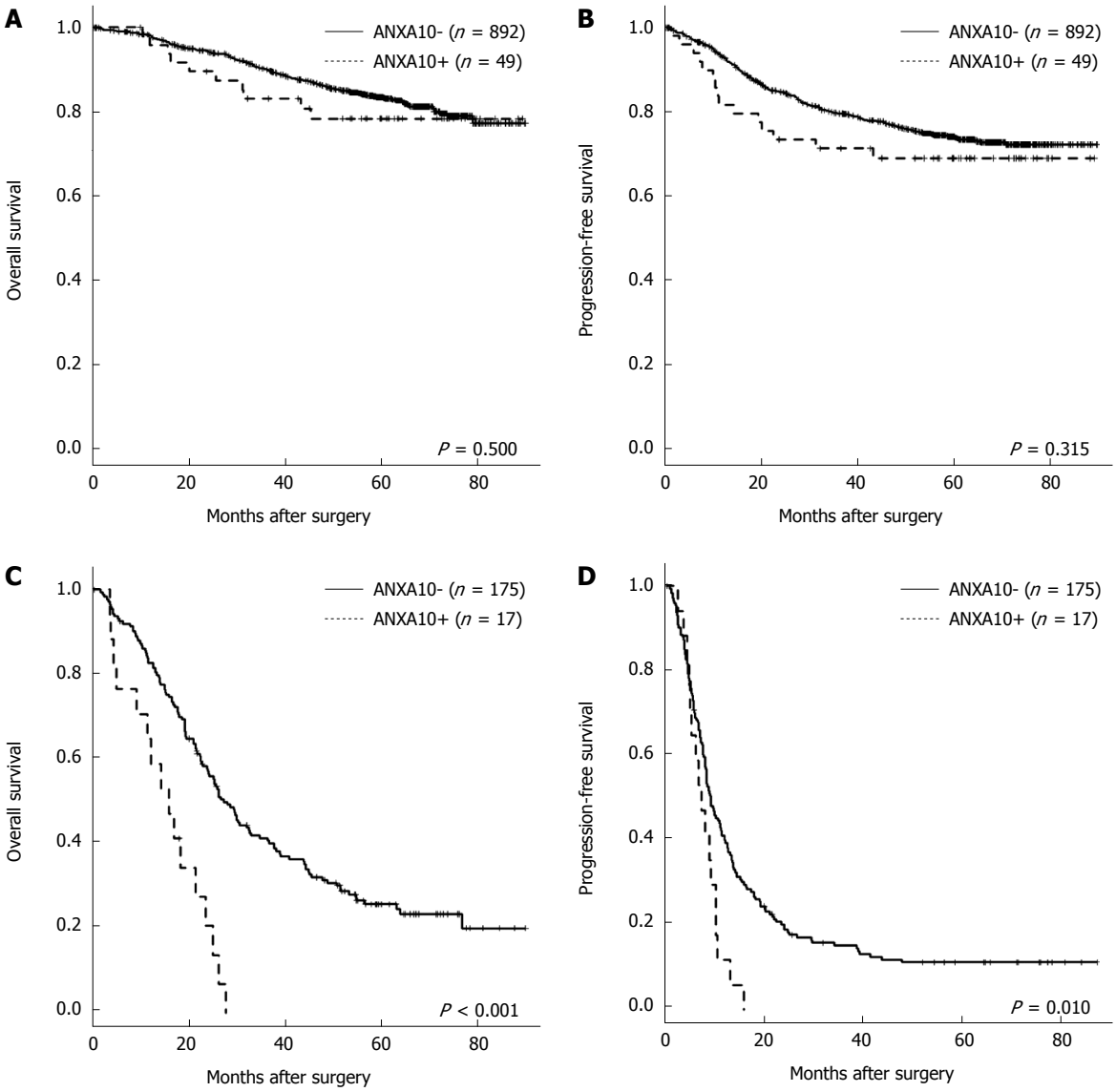

Figure 4 Stage-specific survival analysis according to Annexin A10 expression status. A: Overall survival for Stages Ⅰ-Ⅲ colorectal cancers (CRCs); B: Progression-free survival of Stages Ⅰ-Ⅲ CRCs; C: Overall survival of Stage Ⅳ CRCs; D: Progression-free survival of Stage Ⅳ CRCs. ANXA10-; Annexin A10 no-expression, ANXA10+: Annexin A10 expression.

9.2 mo, p=0.010) compared with the Annexin A10 no-expression group (Figure 4). However, stages Ⅰ-Ⅲ CRCs did not show a significant difference in clinical outcome according to Annexin A10 expression status (P = 0.500 for OS and P = 0.315 for PFS, median survival: not reached) (Figure 4). Multivariate survival analysis using Cox proportional hazard model in stage Ⅳ CRCs suggested that Annexin A10 expression could be an independent prognostic marker for overall survival in stage Ⅳ CRCs, despite limitation of insufficient sample size (Table 3).

DISCUSSION

CIMP is one of the molecular subtypes of CRC and is characterized by concurrent hypermethylation of promoter CpG islands in tumor-suppressor genes and tumor-associated genes. To characterize CIMP, we must measure the methylation status of several panels of multiple genes using methylation-specific PCR or the MethyLight assay[17-19]. However, these assays are not easily used in daily clinical practice because these assays require complicated work and show low cost-effectiveness and inconsistent results[20]. Therefore, an easily applicable strong surrogate marker is required to characterize CIMP clinically. Clear association of the *BRAF* mutation and CIMP led us to consider a recently developed BRAF V600E-specific antibody (clone VE1)[21]. Some studies showed excellent concordance of immunohistochemical staining results of clone VE1 and the *BRAF* mutation determined by sequence analysis[22-24]. However, other studies reported poor sensitivity of clone VE1 immunostaining owing to its vulnerability to pretreatment conditions[25,26].

In a recent study, Annexin A10 was proposed as a surrogate marker for SSA/P[12] and found to be

Table 3 Univariate and multivariate Cox proportional hazards models for overall survival of stage Ⅳ colorectal cancers

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Differentiation (undifferentiated/differentiated)	2.20 (1.31-3.72)	0.003	1.95 (1.07-3.56)	0.030
Tumor location (proximal colon/distal colon, rectum)	1.66 (1.16-2.38)	0.005	1.60 (1.06-2.42)	0.025
Adjuvant chemotherapy (treatment/no-treatment)	0.42 (0.27-0.66)	< 0.001	0.47 (0.27-0.81)	0.006
Annexin A10 (expression/no-expression)	3.13 (1.83-5.38)	< 0.001	2.38 (1.18-4.83)	0.016
Age (yr) (≥ 65/< 65)	1.54 (1.10-2.15)	0.012	1.37 (0.92-2.03)	0.123
Gross pattern (ulcerative/fungating)	1.41 (1.01-1.96)	0.042	1.18 (0.81-1.71)	0.387
CIMP (CIMP-P/CIMP-N)	2.24 (1.24-4.06)	0.008	1.13 (0.44-2.89)	0.801
MSI (MSI/MSS)	2.46 (1.08-5.63)	0.033	1.46 (0.44-4.86)	0.540
BRAF mutation (Mt/Wt)	2.42 (1.12-5.19)	0.024	1.67 (0.71-3.91)	0.239
Sex (male/female)	1.03 (0.74-1.45)	0.858	-	-
KRAS mutation (Mt/Wt)	1.09 (0.75-1.58)	0.653	-	-

HR: Hazard ratio; CI: Confidence interval; CIMP-P: CpG island methylator phenotype-positive; CIMP-N: CpG island methylator phenotype-negative; MSI: Microsatellite instability; MSS: Microsatellite stable; Mt: Mutant type; Wt: Wild type.

expressed even in traditional serrated adenomas[27]. Because SSA/P or traditional serrated adenomas are considered to be precursor lesions of CIMP-P CRCs, Annexin A10 expression could be another surrogate marker for CIMP-P CRCs. In a study by Tsai *et al*[28], Annexin A10 was found to be expressed in 28% of CIMP-P/MSI CRCs and 67% of CIMP-P/MSS CRCs. Our present study showed that Annexin A10 was expressed in 40.8% of CIMP-P/MSI CRCs and 38.9% of CIMP-P/MSS CRCs. These results imply that nuclear expression of Annexin A10 might be lost or reduced during multistep carcinogenesis of some SSA/P or another carcinogenic pathway can contribute to the development of CIMP-P CRCs.

The clinicopathological characteristics of CRCs in which Annexin A10 is expressed are not well known. In this study, Annexin A10 expression was observed in 5.8% of 1133 primary surgically resected CRCs. This result is similar to a previous study which reported that Annexin A10 was expressed in 6% of CRCs[10]. Tsai *et al*[28] reported that Annexin A10 expression is associated with right-side tumor location, moderate to poor differentiation, Crohn-like lymphoid reaction and lack of dirty necrosis, but there was no correlation with mucinous differentiation, medullary histology or tumor-infiltrating lymphocytes. Sajanti *et al*[29] reported that Annexin A10 expression was associated with proximal tumor location, mucin production and serrated histology, but there was no correlation with stage and grade. In our present study, CRCs with Annexin A10 expression were associated with lower age at diagnosis, female sex, proximal tumor location, advanced T, N, M category, advanced TNM stage, absence of luminal necrosis, increased number of tumor-infiltrating lymphocytes, luminal serration and mucin production. Ethnic difference and different proportion of molecular subtypes such as CIMP and MSI might contribute to discrepancies in clinicopathologic characteristics of Annexin A10 expression between studies. However, previous studies had several limitations. The study of Tsai *et al*[28] might have selection bias because they included entire CRCs which had CIMP, MSI and *BRAF* mutation as a case group, however CRCs with conventional pathway were randomly selected as a control group. The study of Sajanti *et al*[29] analyzed only 42.4% (146/344) of patients who underwent surgical resection in the enrollment period. Our present study showed clinicopathologic characteristics of Annexin A10 expression in a large and consecutively collected CRC patient population.

The prognostic value of Annexin A10 expression in CRCs has not yet been reported. However, association of Annexin A10 with poor prognostic molecular features such as CIMP and the *BRAF* mutation led us to assume that Annexin A10 was a poor prognostic indicator[30-32]. In this study, stage-specific survival analysis results showed that Annexin A10 expression is associated with poor OS and PFS in stage Ⅳ CRCs. Multivariate survival analysis confined to stage Ⅳ CRCs suggested that Annexin A10 expression could be an independent prognostic marker in advanced stage CRCs.

This study has several limitations. First, Annexin A10 expression was measured using TMA. Regional heterogeneity of Annexin A10 expression was reported, so we could not exclude the possibility of false-negativity in Annexin A10 expression[28]. Second, exclusivity of Annexin A10 for sporadic MSI CRCs is inconclusive, but we could not evaluate germline mutation status of MMR genes (*hMLH1*, *hMSH2*, *hMSH6* and *hPMS2*)[28,33,34]. Third, the proportion of CIMP-P, MSI and *BRAF* mutations in this study was low compared to Western population[31,35] .

In conclusion, Annexin A10 expression has a supportive but inconclusive role as a surrogate marker of CIMP-P CRCs. Further studies focusing on the molecular mechanisms of Annexin A10 expression and its oncogenic functions in CRCs are required.

COMMENTS

Background

The serrated neoplasia pathway is an explanatory model of multistep

carcinogenesis in CRC displaying the CpG island methylator phenotype (CIMP). Recently, Annexin A10, a eukaryotic calcium- and phospholipid-binding protein, was proposed to be a surrogate marker for sessile serrated adenomas/polyps.

Research frontiers

In this study, the authors attempted to validate the utility of Annexin A10 as a surrogate marker of the serrated neoplasia pathway in invasive CRCs.

Innovations and breakthroughs

Annexin A10 expression was observed in 66 (5.8%) patients. CRCs with Annexin A10 expression were associated with CIMP, microsatellite instability and *BRAF* mutation. Annexin A10 expression was associated with poor overall survival and progression-free survival in stage Ⅳ CRCs.

Applications

The study results suggest that Annexin A10 expression has a supportive but inconclusive role as a surrogate marker of CIMP-P CRCs

Terminology

Annexin A10 is a member of the annexin family, a large multigene family of calcium- and phospholipid-binding proteins and plays important roles in physiologic processes including differentiation and proliferation. Serrated neoplasia pathway is a model of multistep carcinogenesis for CRCs which share serrated morphology, CIMP and *BRAF* mutation.

Peer-review

This is an interesting study investigating the association between Annexin A10 expression and clinical behavior in CRC.

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