The effect of NSAIDs on tumor response and prognosis of stage IV colorectal cancer

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ABSTRACT

The effect of NSAIDs on tumor response and prognosis of stage IV colorectal cancer

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Background: Colorectal cancer (CRC) is the third most frequent cancer in Korea, and it is continuously increasing in prevalence. Despite improved survival rates, the five-year survival in stage IV CRC is less than 10%. There have been many studies which have suggested that there is a protective and adjuvant therapeutic effect on CRC from the regular use of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin. However, recently accumulating data suggest that CRCs have different responses to NSAIDs, depending on the timing of initiation, duration of therapy or target groups. In particular, the data about the effect of NSAIDs on stage IV CRC patients have been limited. The aim of this study was to evaluate the effect of NSAIDs on tumor response and prognosis of stage IV CRC.

Methods: From January 2005 to December 2010, patients who were diagnosed

with stage IV CRC and received chemotherapy at Severance Hospital and who had underlying hypertension (HTN), coronary artery disease (CAD), angina or rheumatoid arthritis (RA) (diseases associated with NSAID use) were recruited, and their medical records were retrospectively analyzed. The NSAIDs non-user group was defined as never having used NSAIDs or patients who took NSAIDs for less than one month, and the prediagnostic NSAID-user group was defined as patients who took NSAIDs over the 12 consecutive months before diagnosis with stage IV CRC. The two groups were compared in terms of baseline characteristics, tumor response, overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS) and disease-free survival (DFS).

Results: Compared with the NSAID non-user group (N=137), the prediagnostic NSAID-user group (N=29) was not different in terms of baseline characteristics, except for CAD prevalence, which was higher in the prediagnostic NSAID-user group (p=0.004). There was no significant difference in tumor response between the NSAID non-user group and the prediagnostic NSAID-user group based on use of NSAIDs during chemotherapy (p=0.304). The OS, PFS and DFS were significantly different in univariate analysis between the NSAID non-user group and the prediagnostic NSAID-user group (OS: 20.48 months vs. 27.03 months, p=0.035, PFS: 8.55 months vs. 13.26 months, p=0.048, DFS: 11.20 months vs. 25.60 months, p=0.031). In multivariate analysis, the OS and CSS of the NSAID non-user group were better than those of the prediagnostic NSAID-user group (overall mortality: HR, 0.478; 95% CI 0.234-0.974; p=0.042,

cancer-specific mortality: HR, 0.386; 95% CI 0.163-0.910; p=0.030).

Conclusion: Long-term NSAID use before diagnosis with stage IV CRC could be a negative prognostic factor.

Key Words: Colorectal cancer stage IV, Non-steroidal anti-inflammatory drugs, Tumor response to chemotherapy, Prognosis

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I. INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in Korea, and the incidence of CRC is increasing continuously[1]. Despite improved survival rates due to the development of novel anticancer drugs and new targeted agents, the five-year survival rate of stage IV colorectal cancer estimated by the American Joint Committee on Cancer was only 8.1%[2].

To improve cancer survival, the use of tumor-suppressing substances as an adjunct to conventional chemotherapy has been a focus of investigation, as has the potential uses of these substances in prevention. Many observational and randomized, controlled studies have suggested a protective effect of regular aspiring use against colorectal neoplasms[3-6]. The favorable outcomes associated with aspirin use after the diagnosis of colorectal cancer suggest that aspirin may

be a promising agent for adjuvant therapy[7,8].

These phenomena are explained by several mechanisms. One is that NSAIDs may increase the rate of apoptosis in colon cancer cells in part via a dramatic increase in arachidonic acid, a prostaglandin precursor[9]. Another possible mechanism by which NSAIDs might prevent colon cancer is inhibition of cyclooxygenase enzymes, which catalyze prostaglandin production. Prostaglandins have been associated with tumor angiogenesis, cell proliferation, and inhibition of immune surveillance and apoptosis[10]. Much experimental evidence on the mechanisms of aspirin and NSAIDs has focused on blockade of COX-2 in colorectal cancer carcinogenesis. In addition, aspirin may mediate additional anti-cancer mechanisms through inhibition of COX-1 present in platelets[11].

In recent studies in which NSAID use and survival after colorectal cancer diagnosis were evaluated, a greater reduction in colorectal cancer mortality was found in patients who used aspirin only after diagnosis[12,13]. Furthermore, there was a large prospective cohort study about aspirin use and survival in stage I, II, or III colorectal cancer. In this study, compared with non-users, participants who regularly used aspirin after diagnosis had a better prognosis. In contrast to aspirin use after diagnosis, aspirin use prior to cancer diagnosis did not appear to be associated with any benefit in either colorectal cancer-specific mortality or overall mortality[7].

This suggests the possibility that tumors that initially developed despite exposure to aspirin may be less susceptible to any potential effect of NSAIDs on tumor progression and may have a different prognosis compared to tumors that have never been exposed to NSAIDs.

However, in stage IV colorectal cancer, there have been no data about tumor response in NSAID users treated with conventional chemotherapy or survival benefit in NSAID users based on duration and time of initiation of NSAIDs.

Focusing on these points, we investigated the effect of NSAIDs on tumor response to chemotherapy and prognosis of stage IV colorectal cancer.

II. MATERIALS AND METHODS

1. Patients

From January 2005 to December 2010, patients who were diagnosed with stage IV CRC and received chemotherapy at Severance Hospital and who also had underlying hypertension (HTN), coronary artery occlusive disease (CAD), angina or rheumatoid arthritis (RA) (diseases commonly associated with NSAID use) were recruited. We excluded patients with the following: 1) age less than 18 years, 2) no tumor response evaluation to chemotherapy at Severance Hospital, 3) coexistence of other malignancies, 4) pathology other than adenocarcinoma, 5) 1-5 month duration of NSAID use for investigating tumor response to chemotherapy, and 1-11 month duration of NSAID use for

investigating survival. A total of 181 patients were included in the study sample for investigating survival (Table 2), and a total of 166 patients were included in the study sample for investigating prognosis (Table 6).

2. Study design

This is a retrospective data analysis study based on medical records.

Patient-related factors such as age, sex, BMI (body mass index), smoking history, alcohol history, family history, ECOG (Eastern Cooperative Oncology Group) performance status and comorbidities were investigated. Also, tumor-related factors such as primary site (colon or rectum), initial CEA (carcinoembryonic antigen) level, pathology (adenocarcinoma or mucinous malignancy), pathologic differentiation, MSI (microsatellite instability), and the presence of EGFR (epidermal growth factor receptor), K-ras and BRAF mutations were investigated. NSAID-related factors such as type, dose, duration of NSAIDs and timing in relation to colorectal cancer diagnosis were investigated, and other medications (metformin, thiazolidinediones, insulin and statin) which may affect colorectal cancer prognosis were also surveyed.

3. Evaluation of tumor response to chemotherapy and prognosis

All colorectal cancer staging was determined by AJCC (American Joint

Committee on Cancer) 7th edition, and the evaluation of tumor response to chemotherapy in colorectal cancer was performed using RECIST (Response Evaluation Criteria In Solid Tumors) criteria 1.1 (Table 1). The best tumor response to chemotherapy was used for each patient.

For evaluation of prognosis in colorectal cancer, we used overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), and disease-free survival (DFS).

Table 1. Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Response category	Criteria
Complete response (CR)	Disappearance of all target lesions
	Reduction in short axis of target lymph nodes to < 10 mm
Partial response (PR)	Decrease in target lesion diameter sum ≥ 30%†
Progressive disease (PD)	Increase in target lesion diameter sum ≥ 20%‡
	≥ 5 mm increase in target lesion diameter sum
	New, malignant FDG uptake in the absence of other indications of progressive disease or an anatomically stable lesion, and confirmed on contemporaneous or follow-up CT
	Unequivocal progression of non-target lesions
Stable disease	Does not meet other criteria‡

*Measurements are based on the sum of the uni-dimensional measurement of the greatest diameter of a maximum of five lesions.†Reference standard: baseline sum.‡ Reference standard: smallest recorded sum. Table modified from Eisenhauer et al.[14]

4. Assessment of medication use

In this study, aspirin, non-selective NSAIDs and COX-2 selective NSAIDs were included. If a patient had continuously taken any kind of NSAIDs over the previous 180 days, the patient was defined as an NSAID-user.

5. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Baseline characteristics of the NSAIDs and non-NSAIDs user groups were compared by Student's t-test, ANOVA test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. The logistic regression method was used for multivariate analysis. We used Cox proportional hazards modeling to control for multiple risk factors that have been shown to influence colorectal cancer survival to compute 95% confidence intervals (CIs). Results were considered to be statistically significant when $p < 0.05$. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

III. RESULTS

1. Patient characteristics in investigating tumor response to chemotherapy of stage IV colorectal cancer based on NSAIDs use

To investigate tumor response to chemotherapy between NSAID non-users and NSAID users, we selected stage IV colorectal cancer patients who used NSAIDs over a six month period, because treatment of stage IV colorectal cancer usually involves two or three sessions of response evaluation during chemotherapy within a six month period.

A total of 181 stage IV colorectal cancer patients were selected and divided into three groups. The first group was the NSAID non-users (N=137) who never took NSAIDs or did so for less than one month, the second was postdiagnostic NSAID-users (N=14) who were prescribed NSAIDs over six months only after diagnosis of stage IV colorectal cancer, and the third was prediagnostic NSAID-users (N=30) who started NSAIDs before diagnosis of stage IV colorectal cancer and had used NSAIDs over six months following diagnosis.

The baseline characteristics of the three patient groups are summarized in Table 2. The ages of the three groups did not differ significantly ($P > 0.05$). Comparing the three groups, other patient-related factors (sex, BMI, smoking history, alcohol history, family history, ECOG performance status and comorbidities) also were not significantly different. However, CAD prevalence was higher in the prediagnostic NSAID-user group than in the other two groups

(Table 2).

The baseline medication use, including metformin, TZD, insulin and statin, in the three groups was not significantly different. However, the types of NSAIDs were different between the postdiagnostic NSAIDs-user group and the prediagnostic NSAIDs-user group. In the postdiagnostic NSAIDs-user group, three (20.5%) patients took aspirin, and 11 (82.1%) patients took non-selective NSAIDs. In contrast, in the prediagnostic NSAIDs-user group, 33 (89.2%) patients took aspirin, and three (8.1%) patients took non-selective NSAIDs ($p<0.001$). The period of NSAID use was also significantly different between the postdiagnostic NSAIDs-user group and the prediagnostic NSAIDs-user group (10.21±4.58 months vs. 82.10±68.77 months, $p<0.001$). The tumor characteristics among the three groups were not significantly different including primary site, initial CEA, initial stage, pathology, pathologic differentiation, MSI, and the presence of EGFR, K-RAS and BRAF mutations (Table 3).

Treatment modality among the three groups was also not significantly different in terms of surgery, chemotherapy drugs or use of targeted agents (Table 4).

Table 2. Comparison of baseline characteristics between NSAID non-users and users for investigating tumor response to chemotherapy

	NSAID non-users N=137	NSAID users (≥6 month)		P value
		Postdiagnostic N=14	Prediagnostic N=30	
Age (mean±SD, yr)	62.23±9.33	63.14±10.82	66.10±7.42	0.114
Sex M/F	84(61.3%) /53(38.7%)	7(50.0%) /7(50.0%)	17(56.7%) /13(43.3%)	0.667
BMI (mean±SD, kg/m^2)	23.45±3.76	24.31±3.47	22.77±3.12	0.414
Smoker				
Never /former /current	83(60.6) /26(19%) /28(20.4%)	12(85.7%) /0(0.0%) /2(14.3%)	19(63.3%) /5(16.7%) /6(20.0%)	0.616
Smoking history (py)	14.69±21.96	2.86±7.26	13.72±21.12	0.139
Alcohol				
Never /<1bottle/1day />1bottle/1day	74(54.0%) /42(30.7%) /21(15.3%)	12(85.7%) /2(14.3%) /0(0.0%)	20(66.7%) /8(26.7%) /2(6.7%)	0.058
Colorectal ca. Family Hx	8(5.8%)	1(7.1%)	3(10.0%)	0.401
ECOG 0~1/2	136/1	14/0	30/0	-
Comorbidity				
HTN	109(79.6%)	12(85.7%)	26(86.7%)	0.602
DM	32(20.6%)	9(23.1%)	9(24.3%)	0.863
CAD	7(5.1%)	0(0.0%)	7(23.3%)	0.002
CVA	2(1.5%)	1(7.1%)	1(3.3%)	0.363
Renal failure	6(4.4%)	1(7.1%)	4(13.3%)	0.065
Hepatitis	2(1.5%)	0(0.0%)	1(3.3%)	0.553
Hx of TBc	8(5.8%)	0(0.0%)	3(10.0%)	0.538
RA	3(2.2%)	1(7.1%)	1(3.3%)	0.630

Variables are expressed as mean±SD or n (%)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; BMI, body mass index; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CVA, cerebrovascular accident; TBc, tuberculosis; RA, rheumatoid arthritis

Table 3. Comparison of baseline medications and tumor characteristics between NSAID non-users and users for investigating tumor response to chemotherapy

	NSAID non-users N=137	NSAID users (≥6 month)		P value
		Postdiagnostic N=14	Prediagnostic N=30	
NSAIDs				
Aspirin		3(20.5%)	33(89.2%)	<0.001
Cox 2-selective		0(0.0%)	2(5.4%)	0.007
Non selective		11(82.1%)	3(8.1%)	<0.001
NSAID duration (Mean±SD, months)		10.21±4.58	82.10±68.77	<0.001
Prediagnostic NSAID Duration (Mean±SD, months)		0	69.40±64.28	
Postdiagnostic NSAID duration (Mean±SD, months)		10.21±4.58	12.70±12.48	<0.001
Metformin	17(12.4%)	4(28.6%)	5(16.7%)	0.347
TZD	4(2.9%)	0	0	0.276
Insulin	6(4.4%)	0	4(13.3%)	0.094
Statin	17(12.4%)	3(21.4%)	7(23.3%)	0.101
Site Colon/Rectum	96(70.1%) /41(29.9%)	8(57.1%) /6(42.9%)	23(76.7%) /7(23.3%)	0.419
Initial CEA	179.81±518.42	233.07±544.43	392.76±1107.8	0.272
Initial stage I/II/III/IV	1(0.6%)/7(4.5%)/10(6.5%) /137(88.4%)	0(0.0%)/2(5.1%)/4(10.3%) /33(84.6%)	0(0.0%)/2(5.4%)/3(8.1%)/ 32(86.5%)	0.974
Pathology adeno/mucous	134(97.8%) /3(2.2%)	13(92.9%) /1(7.1%)	30(100%) /0(0.0%)	0.672
Differentiation WD/MD/PD	10(7.6%) /113(86.3%) /8(6.1%)	0(0.0%) /11(84.6%) /2(15.4%)	5(19.2%) /18(69.2%) /3(11.5%)	0.752

MSI(MSS and MSI-H/MSI-L)	54(93.1%))/4(6.9%)	4(100.0%)/0(0.0%)	12(92.3%)/1(7.7%)	0.749
EGFR (-/+)	14(51.9%)/13(48.1%)	0(0.0%)/2(100.0%)	1(16.7%)/5(83.3%)	0.082
K-ras (Wild/Mutant)	24(58.5%)/17(41.5%)	3(75.0%)/1(25.0%)	8(61.5%)/5(38.5%)	0.871
BRAF (Wild/Mutant)	4(80%)/1(20%)	0/0	3(75%)/1(25%)	0.858

Variables are expressed as mean±SD or n (%)
Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; TZD, thiazolidinediones; CEA, carcinoembryonic antigen; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; MSI, microsatellite instability; MSS, microsatellite stable; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; EGFR, epidermal growth factor receptor;

Table 4. Comparison of treatment modality between NSAID non-users and users for investigating tumor response to chemotherapy

	NSAID non-users N=137	NSAID users (≥6 months)		P value
		Postdiagnostic N=14	Prediagnostic N=30	
Surgical op. none/curative /palliative	43(31.4%)/53(38.7%)/41(29.9%)	7(50.0%)/6(42.9%)/1(7.1%)	16(53.3%)/7(23.3%)/7(23.3%)	0.078
CTx adju/neo/palliative	32(23.4%)/21(15.3%)/84(61.3%)	2(14.3%)/3(21.4%)/9(64.3%)	6(20.0%)/2(6.7%)/22(73.3%)	0.572
Type of CTx				
FOLFOX	95(69.3%)	6(42.9%)	21(70.0%)	0.223
FOLFIRI	29(21.2%)	4(28.6%)	6(20.0%)	
FL	2(1.5%)	1(7.1%)	1(3.3%)	
Xeloda	8(5.8%)	1(7.1%)	2(6.7%)	
Other	3(2.2%)	2(14.2%)	0(0.0%)	
Target agent				
Avastin/ Erbitux/Both	21(15.3%)/5(3.6%)/10(7.3%)	2(14.3%/0(0.0%)/2(14.3%)	5(16.7%)/1(3.3%)/1(3.3%)	0.585

Variables are expressed as n (%)
Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; CTx, chemotherapy

2. Relationship between NSAIDs use and tumor response to chemotherapy or prognosis in stage IV colorectal cancer patients

In comparison of the three groups, the tumor response to chemotherapy, progression and recurrence were not different by univariate analysis. However, mortality was much higher in the two NSAID-user groups than in the non-user group. OS, PFS, and DFS did not show any difference in either univariate or multivariate analysis.

Table 5. Comparison of tumor response to chemotherapy and prognosis by univariate analysis between NSAID non-users and users

	NSAID non-users N=137	NSAID users (≥6 months)		P value
		Postdiagnostic N=14	Prediagnostic N=30	
Best tumor response to CTx				
NED	30 (21.9%))	3 (21.4%)	3 (10.0%)	0.304
CR	1 (0.7%)	0 (0.0%)	1 (3.3%)	
PR	43 (31.4%)	6 (42.9%)	11 (36.7%)	
SD	39 (28.5%)	3 (21.4%)	9 (30.0%)	
PD	24 (17.5%)	2 (14.3%)	6 (20.0%)	
Type CTx adju/ neo /palliative	32(23.4%)/21(15.3%)/84(61.3%)	2(14.3%)/3(21.4%)/9(64.3%)	6(20.0%)/2(6.7%)/22(73.3%)	0.572
Mortality	56	13	22	0.023
Progression	126	30	31	0.735
Recurrence	31(n=54)	6(n=15)	8(n=11)	0.240
DFS (mean±SD, months)	26.43±21.40	21.67±21.15	11.20±6.46	0.282
PFS (mean±SD, months)	13.26±16.50	13.50±16.223	8.47±9.83	0.313
OS (mean±SD, months)	27.19±19.56	29.21±15.19	19.70±13.72	0.109

Variables are expressed as mean±SD or n (%)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; CTx, chemotherapy; NED, no evidence of disease; CR, complete response; PR, partial response; SD, stable disease; PD progressive disease; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival

Even though they were not significantly different, we found a trend toward a relatively shorter survival in the prediagnostic NSAID-user group compared to the other two groups. However, due to the short duration of NSAID use and the

small number of patients (N=14), we were unable to determine statistical significance.

3. Patient characteristics in investigating prognosis of stage IV colorectal cancer based on NSAID use

To evaluate prognostic differences between NSAID users and non-users, we selected stage IV colorectal cancer patients who used NSAIDs over the past 12 months. In this group, because there were only four postdiagnostic NSAID-users, we excluded this group from further analysis.

For survival analysis, a total of 166 stage IV colorectal cancer patients were selected and divided into two groups. The first group was NSAID non-users (N=137) who never took NSAIDs or who took them for no more than one month, and the second was prediagnostic NSAID-users (N=29) who took NSAIDs over 12 consecutive months before diagnosis of stage IV colorectal cancer.

The baseline characteristics of each patient group are summarized in Table 6. In comparison between the two groups, patient-related factors such as age, sex, BMI, smoking history, alcohol history, family history, ECOG performance status and comorbidities were not statistically significantly different. However, CAD prevalence was higher in the prediagnostic NSAID-user group than the non-user group (p=0.004) (Table 6).

The baseline medications, including metformin, TZD, insulin and statins, were not significantly different. In the prediagnostic NSAID-user group, 27 (93.1%) patients took aspirin. The average duration of NSAID use in the prediagnostic NSAID-user group was 84.72±68.45 months (prediagnostic duration: 71.59±64.28 months, postdiagnostic duration 13.14±11.43 months). The tumor characteristics between the two groups were not significantly different including primary site, initial stage, pathology, pathologic differentiation, MSI, and the presence of EGFR, K-RAS and BRAF mutations. Only the initial CEA was significantly higher in the prediagnostic NSAID-user group than the NSAID non-user group (179.81±218.42 ng/mL vs. 406.19±1124.94 ng/mL, p=0.005) (Table 7).

Treatment modality between the two groups was also not significantly different in terms of chemotherapy drugs and use of targeted agents. Only the total rate of surgical procedures was higher in the NSAID non-user group than in the prediagnostic NSAID-user group (Table 8).

Table 6. Comparison of baseline characteristics between NSAID non-users and users in terms of prognosis of stage IV colorectal cancer

	NSAID non-users N=137	Prediagnostic NSAID-users (≥12 months) N=29	P value
Age (mean±SD, age)	62.23±9.33	65.69±7.19	0.234
Sex M/F	84(61.3%)/53(38.7%)	17(58.6%)/12(41.4%)	0.787
BMI (mean±SD, kg/m2)	23.45±3.76	22.68±3.13	0.706
Smoker Never/former/current	83(60.6%)/26(19%)/28(20.4%)	18(62.1%)/5(17.2%)/6(20.7%)	0.976
Smoking history (py)	14.69±21.86	14.21±21.33	0.898
Alcohol Never/<1bottle/day/>1 bottle/day	74(54%)/42(30.7%)/21(15.3%)	19(65.5%)/8(27.6%)/2(6.9%)	0.393
Colorectal ca. Familial Hx	8 (5.8%)	3 (10.3%)	0.409
ECOG 0~1/2	136(99.3%)/1(0.7%)	29(100.0%)/0(0.0%)	0.899
Comorbidity			
HTN	109 (79.6%)	25 (86.2%)	0.410
DM	28 (20.4%)	8 (27.6%)	0.396
CAD	7 (5.1%)	7 (24.1%)	0.004
CVA	2 (1.5%)	1 (3.4%)	0.440
Renal failure	6 (4.4%)	3 (10.3%)	0.193
Hepatitis	2 (1.5%)	1 (3.4%)	0.440
Hx of TBc	8 (5.8%)	3 (10.3%)	0.409
RA	3 (2.2%)	1 (3.4%)	0.540

Variables are expressed as mean±SD or n (%)
Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; BMI, body mass index; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CVA, cerebrovascular accident; TBc, tuberculosis; RA, rheumatoid arthritis

Table 7. Comparison of baseline medication and tumor characteristics between NSAID non-users and prediagnostic NSAID-users for investigating prognosis of stage IV colorectal cancer

	NSAID non-users N=137	Prediagnostic NSAID-users (≥12 months) N=29	P value
NSAIDs			
Aspirin	0	27 (93.1%)	
Cox 2-selective	0	1 (3.4%)	
Non selective	0	2 (6.9%)	
NSAIDs duration (Mean±SD, months)	-	84.72±68.45	
Prediagnostic duration (Mean±SD, months)	-	71.59±64.28	
Postdiagnostic duration (Mean±SD, months)	-	13.14±11.43	
Metformin	17 (12.4%)	5 (17.2%)	0.546
TZD	4 (2.9%)	0 (0.0%)	0.825
Insulin	6 (4.4%)	4 (13.8%)	0.074
Statin	12 (12.4%)	7 (24.1%)	0.142
Site Colon/Rectum	96(70.1%)/41(29.9%)	22(75.2%)/7(24.1%)	0.532
Initial CEA	179.81±218.42	406.19±1124.94	0.005
Pathology adeno/mucous	134(97.8%)/3(2.2%)	29(100%)/0(0.0%)	0.560
Differentiation WD/MD/PD	10(7.6%)/113(86.3%)/8(6.1%)	5(19.2%)/18(69.2%)/3(11.5%)	0.094
MSI (N=58,N=13)			
MSS/MSI-L	54(93.1%)/4(6.9%)	14(92.3%)/1(7.7%)	0.648
EGFR (N=27,N=6)			
Neg/Pos	14(51.9%)/13(48.1%)	1(16.7%)/5(83.3%)	0.186
K-ras (N=41,N=13)			
Wild/Mutant	24(58.5%)/17(41.5%)	8(61.5%)/5(38.5%)	0.848
BRAF (N=58,N=13)			
Wild/Mutant	4(80.0%)/1(20.0%)	3(75.0%)/1(25.0%)	0.722

Variables are expressed as mean±SD or n (%)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; TZD, thiazolidinediones; CEA, carcinoembryonic antigen; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; MSI, microsatellite instability; MSS, microsatellite stable; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; EGFR, epidermal growth factor receptor; K-ras; W, women; M, men

Table 8. Comparison of treatment modality between NSAID non-users and prediagnostic NSAID-users for investigating prognosis of stage IV colorectal cancer

	NSAID non-users N=137	Prediagnostic NSAID-users (≥12 months) N=29	P value
Surgical op. none /curative /palliative	43(31.4%)/53(38.7%)/ 41(29.9%)	15(51.7%)/7(24.1%)/7(24.1%)	0.105
All cause operation	97(68.6%)	14(48.3%)	0.037
RTx on primary site	6(4.4%)	1(3.4%)	0.647
CTx adju/neo/palliative	32(23.4%)/21(15.3%)/ 84(61.3%)	6(20.7%)/2(6.9%)/21(72.4%)	0.413
Type of CTx			
FOLFOX	95 (69.3%)	21 (72.4%)	0.428
FOLFIRI	29 (21.2%)	6 (20.7%)	
FL	2 (1.5%)	1 (3.4%)	
Xeloda	8 (5.8%))	1 (3.4%)	
Other	3 (2.2%)	0 (0.0%)	
Target agent None/Avastin/Erbitux/Both	101(73.7%)/21(15.3%)/5(3.6%)/10(7.3%)	22(75.9%)/5(17.2%) /1(3.4%)/1(3.4%)	0.894

Variables are expressed as n (%)

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; RTx, radiotherapy; CTx, chemotherapy

4. Prognostic differences between prediagnostic NSAID-users and NSAID non-users in stage IV colorectal cancer

Long-term NSAID use effected prognosis of stage IV colorectal cancer in both univariate analysis and multivariate analysis (Table 9, Table 10). Even though there was no difference in tumor response to chemotherapy or progression and recurrence between the two groups, the prediagnostic NSAID-user group had lower mortality and higher CFS, PFS, and OS in univariate analysis than the non-user group (Mortality: 16% vs. 34.3%, p=0.031, DFS: 11.20±6.46 month vs. 25.60±21.33 months, p=0.031, PFS: 8.55±999 months vs. 13.26±16.72 months, p=0.048, OS: 20.48±13.42 months vs. 27.03±19.66 months, p=0.035) (Table 9).

Table 9. Comparison of tumor response to chemotherapy and prognosis by univariate analysis between NSAID non-users and prediagnostic NSAID-users

	NSAID non-users N=137	Prediagnostic NSAID-users (≥12 months) N=29	P value
Tumor response to chemotherapy			
NED	30 (21.9%)	3 (10.3%)	0.503
CR	1 (0.7%)	1 (3.4%)	
PR	43 (31.4%)	10 (34.5%)	
SD	39 (28.5%)	9 (31.0%)	
PD	24 (17.5%)	6 (20.7%)	
Type CTx adju/neo /palliative	53 (38.7%)	17 (58.6%)	0.048
Mortality	47 (34.3%)	16 (55.2%)	0.035
Progression	112 (81.8%)	26 (89.7%)	0.230
Recurrence (N=48, N=5)	30 (62.5%)	4 (80.0%)	0.643
DFS (mean±SD, months)	25.60±21.33	11.20±6.46	0.031
PFS (mean±SD, months)	13.26±16.72	8.55±9.99	0.048
OS (mean±SD, months)	27.03±19.66	20.48±13.42	0.035

Variables are expressed as mean±SD or n (%)
Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; CTx, chemotherapy; NED, no evidence of disease; CR, complete response; PR, partial response; SD, stable disease; PD progressive disease; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival

However, in multivariate analysis, there was a trend toward higher mortality in the prediagnostic NSAID-user group compared to the NSAID non-user group, although the trend was not statistically significant (p=0.054). Hypertension, pathologic differentiation and primary cancer site affected mortality in

multivariate analysis (OR, 3.821; 95% CI 1.212-12.044; p=0.022, OR, 0.052; 95% CI 0.005-0.602; p=0.018, HR, 4.148; 95% CI 1.376-12.505; p=0.009) (Table 10).

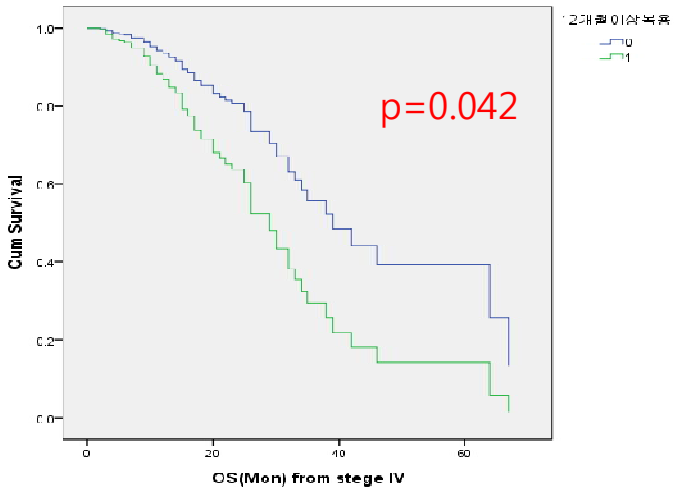
Table 10. The factors related to mortality in stage IV colorectal cancer in multivariate analysis

		Odds Ratio (95% CI)	P value
Age (mean±SD, age)		-	0.275
Sex		-	0.278
Comorbidity	HTN	3.821 (1.212-12.044)	0.022
	DM	-	0.976
	CAD	-	0.657
	Hx of TBc	-	0.866
Alcohol		-	0.799
Smoking		-	0.573
Colorectal cancer FHx		-	0.241
NSAID user (vs. non-user)		3.523(0.977-12.142)	0.054
Statin		-	0.725
Pathologic differentiation (WD vs. PD)		0.052(0.005-0.602)	0.018
Cancer primary site (colon vs. rectum)		4.148(1.376-12.505)	0.009
Radiotherapy		-	0.775
Surgical operation		-	0.134
Target agent		-	0.444
Tumor response to chemotherapy		-	0.978
Initial CEA		-	0.384

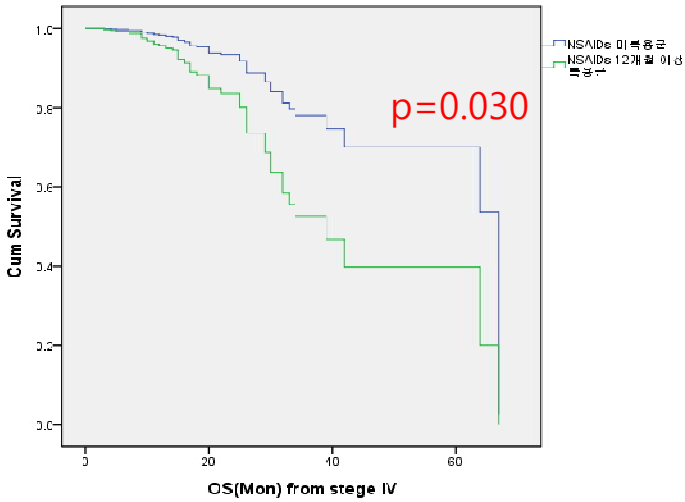
Abbreviations: CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; TBc, tuberculosis; RA, rheumatoid arthritis; WD, well differentiated; PD, poorly differentiated; CEA, carcinoembryonic antigen

For analyzing survival, we used Cox proportional hazards modeling to control for multiple risk factors, showing that OS and CSS were significantly worse in the prediagnostic NSAID-user group than the non-user group (OS: HR, 2.102; 95% CI 1.067-4.142; p=0.042, CSS: HR, 2.422; 95% CI 1.105-5.308; p=0.030) (Figures 1 (A),(B)). However, PFS and DFS were not significantly different between the prediagnostic NSAID-user group and the non-user group (p=0.083, p=0.057) (Figures 1 (C),(D)).

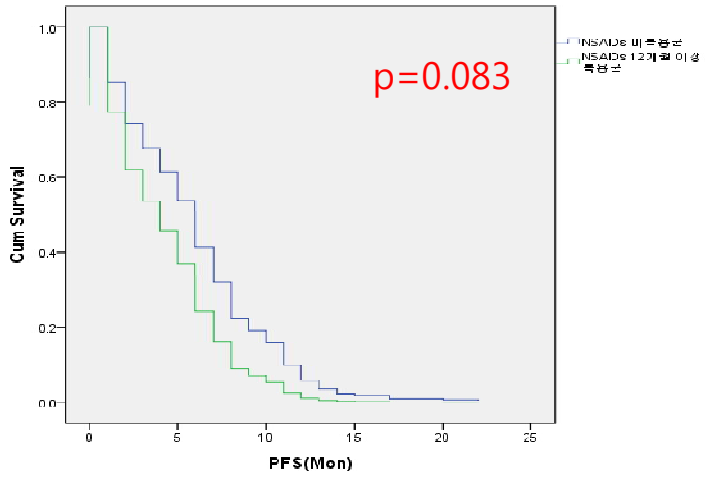
A.



B.



C.



D.

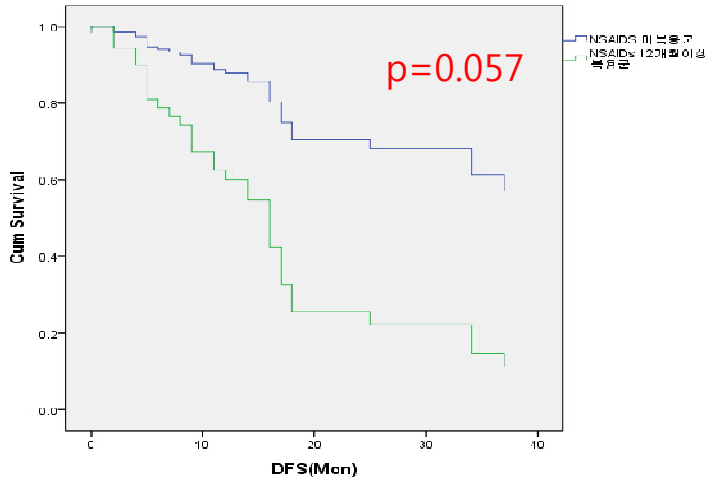


Fig. 1 Overall survival and cancer-specific survival were significantly different between the prediagnostic NSAID-user group and the NSAID non-user group in stage IV colorectal cancer. (A) Overall survival (OS) was significantly poorer in the prediagnostic NSAID-user group than in the non-user group (HR, 2.102; 95% CI 1.067-4.142; p=0.042). (B) Cancer-specific survival (CSS) was significantly poorer in the prediagnostic NSAID-user group than in the non-user group (HR, 2.422; 95% CI 1.105-5.308; p=0.030). (C)(D) Progression-free survival (PFS) and disease-free survival (DFS) were not significantly different between the prediagnostic NSAID-user group and the non-user group (p=0.083 and p=0.057, respectively).
Cox proportional hazard model, adjusted for age, sex, comorbidity, alcohol history, smoking history, colorectal cancer family history, statin use, cancer site, pathology, radiotherapy, operation and initial CEA.

IV. DISCUSSION

We found that long-term use of NSAIDs before diagnosis of stage IV colorectal cancer is associated with poor prognosis. This result was consistent even after adjusting for other variables in OS and CSS. In contrast, many reports have shown that NSAIDs extend the life of patients with colorectal cancer[7,15-17], but these studies showed benefit only in postdiagnostic NSAID-users, not those who were taking NSAIDs regularly prior to diagnosis.

As for this limited effect of NSAIDs, there were some studies that suggested that only patients with limited colorectal cancer could benefit from NSAIDs, related to specific factors such as COX-2 overexpression or specific genetic mutation like *SMAD7*[7,18,19]. Chan et al. reported that, among patients with colorectal cancer participating in a large cohort study, aspirin users had a 29% lower cancer-specific mortality and a 21% lower overall mortality than non-users. The reduction in mortality was even greater among patients who initiated aspirin use after cancer diagnosis than among those who used it before, and the benefit was limited to those with tumors that overexpressed COX-2[7].

In addition, a large case-control study undertaken to extend the Genome-Wide Association Study (GWAS) findings noted a statistically significant interaction between *SMAD7* variants and use of NSAIDs two years prior to diagnosis of colorectal cancer[20]. Inspired by this, there was a study that

showed CRC-specific survival differed by genotype of *SMAD7* variants (each minor allele of rs4939827 was associated with worse survival, and each minor allele of rs4464148 was associated with better survival)[21]. This indicates that prognosis varies in colorectal cancer patients using NSAIDs based on genetic factors.

Recently, accumulating data suggest that colorectal cancers are a heterogeneous group of diseases that potentially have different responses to treatment[22]. As prolonged exposure to specific chemotherapy induces resistance to that agent in tumor cells, prolonged exposure to NSAIDs can induce resistance to NSAIDs in carcinogenesis. Furthermore, higher cyclooxygenase 2 (COX-2) expression, which is associated with the action mechanism of NSAIDs, is often observed in aggressive colorectal cancers[23,24]. This suggests that colorectal cancer that becomes resistant by prolonged NSAIDs exposure before diagnosis could have poor prognosis.

The strength of this study is that this is the first to investigate a relationship between NSAID use and prognosis of stage IV colorectal cancer.

Previous research has shown that there is a reduction in all-cause mortality in colorectal cancer patients who take aspirin for the year following diagnosis. However, the benefit was observed only in the period up to five years after diagnosis, after which point aspirin users had a higher mortality[25]. In our study, because the postdiagnostic NSAID-user group had only a mean of 10.21 months

of NSAID use, and all patients had stage IV colorectal cancer, the follow-up period might not have been sufficient to show prognostic differences between the postdiagnostic NSAID-user group and NSAID non-user group.

In addition, the heterogeneity of NSAIDs in the users in our study could also be important, as other studies about NSAIDs and cancers were usually restricted to only one type of NSAID. However, most NSAID users in our study used aspirin (93.1%). Thus, we had some homogeneity in terms of the type of medication used.

The weakest points in our study are the small number of patients and the retrospective nature. Due to insufficiency in record-keeping, the medication information could be inaccurate, and the loss to follow-up was fairly significant, up to 38%. Therefore, a prospective study of a large number of patients is needed to identify the effect of NSAIDs on prognosis of stage IV colorectal cancer when used over a certain period of time before or after cancer diagnosis. In a recent phase II study targeted to 51 colorectal cancer patients, NSAID use as an adjuvant drug combined with chemotherapy showed that time to progression and overall survival were longer in the high COX-2 expression group than in the low COX-2 expression group even though there was no statistical significance[19]. This implies that specific subgroups of colorectal cancer which have different responses to NSAIDs might exist.

Nevertheless, this is the only study of stage IV colorectal cancer patients

examining the relationship between NSAIDs and cancer, and the results suggest that if a particular tumor-suppressing agent is used for a significant duration during tumor development, resistance might occur, and the tumor could evade the anticancer effects of that agent.

V. CONCLUSION

In conclusion, our results showed that long-term NSAID use before diagnosis of stage IV colorectal cancer could be a negative prognostic factor. In order to confirm and further elucidate the mechanism of this, a prospective study with a large number of patients is needed. Furthermore, to identify molecules related to this phenomenon, genetic and molecular studies using colorectal cancer tissues of NSAID users or an *in vitro* study using NSAID-resistant cells is needed in the future.

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ABSTRACT(IN KOREAN)

4기 대장암 환자에서 NSAIDs 복용 여부에 따른 항암약물요법 반응 및 질병의 예후

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배경: 대장직장암은 대한민국에서 발생분률이 남녀 공히 3위에 해당하는 주요 암이여 지속적으로 증가하는 추세이다. 생존률의 향상에도 불구하고 4기 대장직장암의 5년 생존률은 10% 미만에 불과하다. 정기적 NSAIDs의 복용이 대장직장암의 예방 및 보조적 치료와 연관성의 효과를 가질 수 있음을 보여주는 많은 연구들이 있었다. 하지만 최근의 연구 결과들은 NSAIDs의 사용 시작 시점 및 사용 기간, 사용 대상 군에 따라서 NSAIDs가 대장직장암에 끼치는 영향이 다르게 나타날 수 있음을 보여주고 있다. 특히, 4기 대장직장암에서의 NSAIDs의 효과에 대한 연구는 매우 드물다. 따라서 본 연구의 목적은 이러한 4기 대장직장암에서의 항암제 반응성 및 예후에 NSAIDs가 끼치는 영향을 알아보는 것이다.

방법: 2005년 1월부터 2010년 12월까지 4기 대장직장암으로 세브란스 병원에서 항암화학약물 치료를 받은 환자 중 고혈압, 관상동맥질환, 협심증, 류마티스 관절염의 진단명을 가진 환자를 대상으로 의무기록을 후향적 분석 하여 NSAIDs 복용 여부에 따라 항암제 반응성 및 예후 (전체생존률 (overall survival; OS),

질병진행생존률 (progression free survival; PFS), 무병생존률 (disease free survival; DFS), 암특이생존률 (cancer specific survival; CSS))를 통계적으로 비교 분석 하였다.

결과: 최종 대상 환자 166명을 암 진단 후부터 12개월 이상 NSAIDs를 복용한 29명 및 미복용한 137명으로 나누어 양군간의 항암제 반응성 및 예후의 차이를 분석하였다. 양군은 관상동맥질환의 빈도가 NSAIDs 복용군에서 유의하게 많았던 것을 제외하고는 임상적, 종양적, 치료적 특징에서 차이를 보이지 않았다. NSAIDs 복용 여부에 따라 항암약물요법의 최대 반응은 차이가 없었으나 예후는 단변량 분석상 양군간 의미 있게 차이가 있었다 (OS: 20.48±13.42달 vs. 27.03±19.66달, p=0.035, PFS: 8.55±9.99달 vs. 13.26±16.72달, p=0.048, DFS: 11.20±6.46달 vs. 25.60±21.33달, p=0.031). 다변량 생존 분석을 시행하였을 때에도 12개월 이상의 NSAIDs 복용군이 NSAIDs 미복용 군에 비하여 불량한 예후를 보였다 (OS: HR, 2.102; 95% CI 1.067-4.142; p=0.042, CSS: HR, 2.422; 95% CI 1.105-5.308; p=0.030).

결론: 본 연구는 4기 대장직장암으로 진단된 환자에서 진단 전 aspirin를 포함한 NSAIDs의 지속적 복용력이 환자의 불량한 종양 관련 예후를 예측하는 인자일 가능성이 있음을 시사한다.

핵심되는 말: 대장직장암 4기, NSAIDs, 항암약물반응 및 생존률