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Risk Factors for Post-operative Recurrence in Korean Patients with Crohn's disease



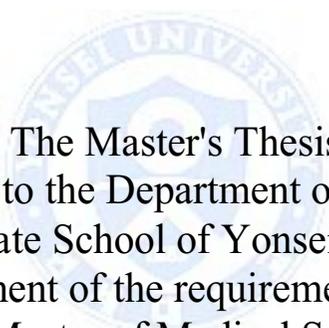
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Risk Factors for Post-operative Recurrence in Korean Patients with Crohn's disease

Directed by Professor Jae Hee Cheon



The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

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December 2015

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ABSTRACT

Risk Factors for Post-operative Recurrence in Korean Patients with Crohn's disease

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Despite the advances in medical treatments, a considerable number of patients with Crohn's disease (CD) ultimately need surgery. However, postoperative recurrence is common and factors that predict postoperative recurrence are still unclear, especially in East Asian countries. We investigated postoperative outcomes and identified the risk factors associated with postoperative recurrence after intestinal resective surgery in patients with CD. We retrospectively reviewed 173 CD patients who underwent intestinal resection due to CD between January 2005 and August 2014. Clinical recurrence was defined as occurrence of CD-related symptoms with any of the followings: medication step up, requiring systemic corticosteroid use, or CD activity index over 150 points. Forty-three (24.9%) patients received a follow-up colonoscopy within 1 year after surgery and endoscopic recurrence was 65.1%. Six year-cumulative clinical recurrence and surgical recurrence rate were 91.1% and 48.0%, respectively. In univariate analysis, young age at diagnosis (<16 years), and perianal disease were associated with clinical recurrence. Multivariate analysis showed that early maintenance of thiopurine medication after surgery within 3 months ($p=0.04$) was independently associated with a lower clinical recurrence rate, whereas perianal disease ($p=0.02$) was associated with a higher clinical recurrence. Moreover, current smoking at surgery ($p=0.02$) was significantly related to higher surgical recurrence rate. Post-operative recurrence rate in Korean CD patients showed the similar outcome compared with that in Caucasians, despite considerably different disease phenotypes and managing strategies. More intensive management strategies will be required in patients with perianal disease, young age onset, and smoking history. Maintenance of immunomodulatory medications after bowel resection in high-risk patients with CD might be an effective preventive strategy for clinical recurrence.

Key words: Crohn's disease, Postoperative recurrence, Azathioprine, 6-mercaptopurine, Surgery

Risk Factors for Post-operative Recurrence in Korean Patients with Crohn's disease

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I. INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease that can affect any part of the gastrointestinal tract with systemic manifestations.^{1,2} Despite the advances in medical treatments, such as immunomodulators and anti-tumor necrosis factor (TNF) agents, a considerable number of patients with CD ultimately need surgery.³⁻⁶ Besides, postoperative recurrence is common and more than half of the patients experience clinical recurrence within 5 years and surgical recurrence within 10 years.^{7,8} Therefore, appropriate follow-up management and medications are important after intestinal resection.

Smoking, perforating disease, and previous intestinal resection have been suggested from retrospective studies as factors that predict earlier postoperative recurrence.^{9,10} Some experts proposed different management and medication algorithms after surgery according to patient's risk factors.^{7,11} Actually, one recent prospective study showed a treatment strategy stratified to the clinical risk of recurrence with selective immune suppression and adjusted for early recurrence is better than conventional drug therapy alone for the prevention of postoperative CD recurrence.⁸

However, most of previous studies regarding postoperative recurrence in CD were conducted in Western nations and mainly Caucasians. Either clinical characteristics such as diagnosed age, cigarette smoking, disease location, behavior, and treatment strategy showed differences between Eastern and Western

in recent studies.^{4,12-15} Indeed, factors that predict postoperative recurrence are still unclear and the data are lacking, especially in East Asian countries.^{1,13} Previous studies were limited in terms of the small patient number, single hospital patients, or lack of clinical and medication data.^{16,17} Consequently, research of postoperative recurrence is needed to target Eastern Asian patients with CD.

Therefore, we investigated postoperative endoscopic, clinical, and surgical recurrence outcomes and identified the risk factors associated with postoperative recurrence after intestinal resective surgery in Korean patients with CD through a multicenter study.

II. MATERIALS AND METHODS

1. Patients

Clinical data of 208 patients with CD who underwent intestinal resection due to CD between January 2005 and August 2014 at 5 hospitals in Korea were retrospectively reviewed. The diagnosis of CD was based on standard clinical, imaging, and laboratory criteria.¹⁸

Patients with the following were excluded: follow-up period less than 1 year after intestinal resection surgery, operations limited in appendectomy, perianal procedure, and strictureplasty, misdiagnosed other diseases such as intestinal tuberculosis, ulcerative colitis, and intestinal Behcet's disease. Patients with insufficient clinical, biochemical, surgical information were also excluded. After excluding 35 patients based on our exclusion criteria, a total of 173 patients were finally selected (Figure. 1).

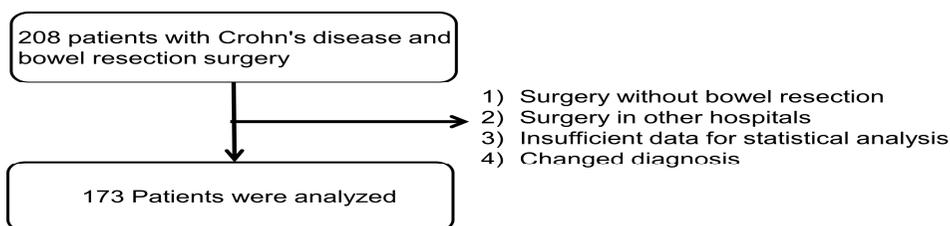


Figure 1. Selection of the study population. After excluding 35 patients according to our exclusion criteria, 173 patients with Crohn's disease who underwent intestinal resection surgery remained.

2. Definition

Clinical recurrence was defined as fulfillment more than one of the following: CD Activity Index (CDAI) score >150 points with increased more than 100-point compared to previous values, corticosteroid use or medication step up 3 months after surgery, re-admission or surgery due to recurrent CD-related symptoms.¹⁸ Endoscopic recurrence was defined as Rutgeerts score of i2-i4 that assesses postoperative mucosal recurrence at anastomosis and neoterminal ileum during colonoscopy by an endoscopist.¹⁹ Surgical recurrence was defined as additional intestinal resection owing to CD per se, except surgery related complications.

3. Clinical data

Clinical, laboratory tests, imaging study, and medication records analyzed at the time point of first diagnosed CD and intestinal resection surgery separately. Clinical characteristics were classified based on the 'Montreal classification' of CD.²⁰ CDAI, erythrocyte sedimentation rate (normal value <15 mm/hr), C-reactive protein level (CRP, normal value <8 mg/L), and hematocrit level (normal value: 40.4~52%) were regularly monitored during the follow-up period.

4. Primary and secondary outcomes

The primary outcome was to investigate the risk factors of post-operative clinical and surgical recurrences in Korean patients with CD. The secondary outcome was to evaluate clinical, endoscopic, and surgical recurrence rates after intestinal resection surgery.

5. Statistical analysis

Data are expressed as the median (interquartile range), n, or n (%), as appropriate. Factors associated with clinical and surgical recurrences were investigated using Kaplan-Meier analysis and cox regression. Any variables identified as significant ($P<0.05$) in univariate analysis were included in the multivariate analysis.

For comparison of cumulative probability of clinical and surgical recurrences,

Kaplan-Meier estimator survival analysis was used. For comparing outcomes, chi-square test or Fisher's exact test was used for categorical data, and Mann-Whitney U test was used for continuous variables. Data analysis was performed using SPSS software version 18.0 (SPSS, Chicago, IL, USA). A two-sided $P < 0.05$ was considered statistically significant.

III. RESULTS

1. Baseline characteristics

Baseline characteristics of the study participants are shown in Table 1. The median ages at diagnosis and at surgery were 23.0 years and 30.0 years, respectively. One hundred and twelve (64.7%) patients were male.

Based on Montreal classification, L3 (53.2%) and B3 (67.6%) were the most common disease phenotype at surgery. At diagnosis, 38 patients (22.0%) were current smokers and 13 patients stopped smoking before their intestinal resection surgery. Perianal disease was present in 65 (37.6%) patients before surgery.

Twenty four patients (13.9%) were diagnosed CD after intestinal resection surgery. Median time of diagnosis to surgery was 37.0 months and median follow-up duration after intestinal resection was 40.0 months. Patients medication histories before and after surgery within 3 months are described in Table 2. Among the study participants, 74 (42.8%) patients received thiopurines (azathioprine or 6-mercaptopurine) and 12 (6.9%) patients continued anti-TNF agents (infliximab or adalimumab).

Table 1. Baseline Characteristics at diagnosis and surgery

| Variables | Diagnosis | Surgery |
|-------------------------------------|------------------------|--------------------|
| Age | 23.0 (19.0 - 31.0) | 30.0 (22.5 - 36.5) |
| Sex (M : F) | 112 (64.7) : 61 (35.1) | |
| Age at diagnosis or surgery (years) | | |
| ≤16 | 25 (14.5) | |
| 17-40 | 131 (75.7) | |
| ≥41 | 17 (9.8) | |
| Disease location ^a | | |
| L1 (ileal) | 69 (39.9) | 66 (38.2) |
| L2 (colonic) | 10 (5.8) | 7 (4.0) |
| L3 (ileocolonic) | 83 (48.0) | 92 (53.2) |
| L4 (isolated upper disease) | 11 (6.4) | 8 (4.6) |
| Disease behavior ^b | | |
| B1 (inflammatory) | 71 (41.0) | 5 (2.9) |
| B2 (stricturing) | 55 (31.8) | 51 (29.5) |
| B3 (penetrating) | 47 (27.2) | 117 (67.6) |
| P (perianal disease) | 50 (28.9) | 65 (37.6) |
| Current smoking | 38 (22.0) | 25 (14.5) |
| Previous surgery history | | 28 (16.2) |
| Diagnosis after surgery | 24 (13.9) | |
| CRP level | | 27.2 (6.1 - 82.2) |
| CDAI classification | | n= 122 |
| < 150 | | 12 (9.8) |
| 150 – 220 | | 19 (15.6) |
| 220 – 450 | | 88 (72.1) |
| > 450 | | 3 (2.5) |

Variables are expressed as n (%).

CRP, c-reactive protein; CDAI, Crohn's disease activity index

Disease location^a and behavior^b classified based on 'Montreal classification' of Crohn's disease

Table 2. Medication history during follow-up

| Variables | Before surgery | After surgery |
|--------------------------------|----------------|----------------|
| Medication history | | |
| 5-aminosalicylic acids (5-ASA) | 150/173 (86.1) | 161/172 (93.1) |
| Corticosteroids | 113/173 (65.3) | |
| Thiopurines | 120/173 (59.0) | 74/173 (42.8) |
| Anti-TNFs | 47/173 (27.2) | 12/173 (6.9) |
| Infliximab | 44/173 (25.4) | 9/173 (5.2) |
| Adalimumab | 10/173 (5.8) | 3/173 (1.7) |
| Infliximab and adalimumab | 7/173 (4.0) | 0/173 (0.0) |

2. Postoperative clinical and surgical outcomes

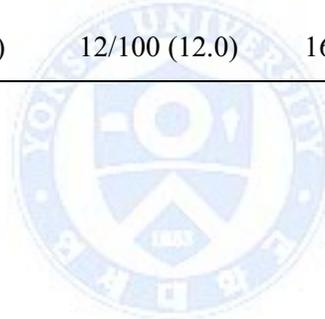
Postoperative recurrence outcomes are summarized in Table 3. Endoscopic recurrence rate was calculated in a total of 107 (59.5%) patients who underwent colonoscopy after intestinal resection, except for those with failure to reach anastomosis site or neoterminal ileum due to stricture. Colonoscopy was done in 43 (24.9%) patients within 12 months after surgery and endoscopic recurrence rate was 65.1%.

During the follow-up period, overall clinical and surgical recurrences occurred in 95 (54.9%), and 26 (15.0%) patients, respectively. The cumulative clinical recurrence rate increased from 25.4% at 1 year to 91.1% at 6 years. Similarly, the cumulative surgical recurrence rate also increased from 2.9% at 1 year to 48.0% after 6 years of treatment.

Table 3. Outcome of endoscopic, clinical and surgical recurrences

| Variables | Time after bowel resection surgery (years) | | | | | |
|-----------------------|--|---------------|---------------|--------------|--------------|--------------|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Endoscopic recurrence | 28/43 (65.1) | 43/66 (65.2) | | | | |
| Clinical recurrence | 44/173 (25.4) | 38/119 (31.9) | 44/100 (44.0) | 35/73 (47.9) | 32/53 (60.4) | 27/36 (75.0) |
| Surgical recurrence | 5/173 (2.9) | 6/119 (5.0) | 12/100 (12.0) | 16/73 (21.9) | 12/53 (22.6) | 10/36 (27.8) |

Variables are expressed as n (%).



3. Independent factors associated with recurrence after intestinal resection

Disease phenotype at the time of diagnosis CD and surgery, preoperative CDAI scores, CRP level, and postoperative prophylactic medications were analyzed to determine independent factors associated with recurrence after surgery. Among the variables, age at diagnosis ($p=0.043$) and perianal disease at the time of surgery ($p=0.008$) were associated with clinical recurrence in univariate analysis. Subsequent multivariate analysis included the significant variables in the univariate analysis and additional factors including previous intestinal resection history, current smoking at surgery, and postoperative prophylactic thiopurine use that were reported to be factors predictive of recurrence after surgery in previous investigations.^{8,10} The multivariate analysis revealed that perianal disease at surgery ($p=0.02$; odds ratio, 1.629; 95% confidence interval, 1.080 - 2.458) and thiopurine use ($p=0.042$; odds ratio, 0.636; 95% confidence interval, 0.412 - 0.983) were independent risk factors associated with clinical recurrence. In sequence, current smoking at surgery was the significant factor associated with surgical recurrence in univariate analysis. Also, in multivariate analysis incorporating the same variables in clinical recurrence, current smoking at surgery was the only meaningful factors associated with surgical recurrence ($p=0.024$; odds ratio, 3.116; 95% confidence interval, 1.215 - 7.987). (Table 4, 5)

Table 4. Independent factors associated with postoperative clinical recurrence (n=173)

| Variables | Univariate | Multivariate | | |
|------------------------------|------------|--------------|------------|---------------|
| | P-value | P-value | Odds ratio | 95% CI |
| Age (diagnosis) | 0.043 | NS | | |
| Age (surgery) | 0.412 | | | |
| Gender | 0.119 | | | |
| Previous surgery history | 0.490 | | | |
| Disease location (diagnosis) | 0.861 | | | |
| Disease location (surgery) | 0.959 | | | |
| Disease behavior (diagnosis) | 0.842 | | | |
| B1 (inflammatory) | | | | |
| B2 (stricturing) | 0.406 | | | |
| B3 (penetrating) | 0.900 | | | |
| Disease behavior (surgery) | 0.095 | NS | | |
| B1 (inflammatory) | | | | |
| B2 (stricturing) | 0.165 | | | |
| B3 (penetrating) | 0.259 | | | |
| Perianal disease (diagnosis) | 0.261 | | | |
| Perianal disease (surgery) | 0.008 | 0.020 | 1.629 | 1.080 - 2.458 |
| Current smoking (diagnosis) | 0.435 | | | |
| Current smoking (surgery) | 0.444 | NS | | |
| CDAI Score (surgery) | 0.126 | | | |
| CRP (surgery) | 0.653 | | | |
| Preoperative Medications | | | | |
| 5-ASA | 0.718 | | | |
| Thiopurines | 0.382 | | | |
| Anti-TNFs | 0.099 | | | |
| Postoperative Medications | | | | |
| 5-ASA | 0.852 | | | |
| Thiopurines | 0.061 | 0.042 | 0.636 | 0.412 - 0.983 |
| Anti-TNFs | 0.599 | | | |

CDAI, Crohn's disease activity index; CRP, c-reactive protein; 5-ASA, 5-aminosalicylic acids; TNF, tumor necrosis factor

Table 5. Independent factors associated with postoperative surgical recurrence (n=173)

| Variables | Univariate | Multivariate | | |
|------------------------------|------------|--------------|------------|---------------|
| | P-value | P-value | Odds ratio | 95% CI |
| Age (diagnosis) | 0.373 | NS | | |
| Age (surgery) | 0.359 | | | |
| Gender | 0.269 | | | |
| Previous surgery history | 0.535 | NS | | |
| Disease location (diagnosis) | 0.497 | | | |
| Disease location (surgery) | 0.083 | | | |
| Disease behavior (diagnosis) | 0.646 | | | |
| B1 (inflammatory) | | | | |
| B2 (stricturing) | 0.526 | | | |
| B3 (penetrating) | 0.600 | | | |
| Disease behavior (surgery) | 0.406 | NS | | |
| B1 (inflammatory) | | | | |
| B2 (stricturing) | 0.915 | | | |
| B3 (penetrating) | 0.676 | | | |
| Perianal disease (diagnosis) | 0.945 | | | |
| Perianal disease (surgery) | 0.642 | NS | | |
| Current smoking (diagnosis) | 0.139 | | | |
| Current smoking (surgery) | 0.024 | 0.018 | 3.116 | 1.215 - 7.987 |
| CDAI Score (surgery) | 0.465 | | | |
| CRP (surgery) | 0.967 | | | |
| Preoperative Medications | | | | |
| 5-ASA | 0.237 | | | |
| Thiopurines | 0.757 | | | |
| Anti-TNFs | 0.599 | | | |
| Postoperative Medications | | | | |
| 5-ASA | 0.124 | | | |
| Thiopurines | 0.326 | NS | | |
| Anti-TNFs | 0.786 | | | |

CDAI, Crohn's disease activity index; CRP, c-reactive protein; 5-ASA, 5-aminosalicylic acids; TNF, tumor necrosis factor

4. Outcomes according to risk factors

Risk groups were stratified according to univariate analysis results. Age at diagnosis and existence of perianal disease before surgery which were significant in terms of clinical recurrence and current smoking at surgery that was associated with surgical recurrence were included. Among these factors, patients with two or more risk factors were considered high risk group. Clinical and surgical recurrence results are described in Table 6. Patients in high risk group showed significantly short clinical recurrence interval compared to those in low risk group ($p < 0.001$). Statistical differences of surgical recurrence were not proven, but the tendency was similar to clinical recurrence results.

Effectiveness of post-operative thiopurine use according to risk group is shown in Figure 2. In patients in high risk group, thiopurine use within 3 months after surgery revealed longer clinical recurrence free interval, compared to the patients who did not use thiopurines

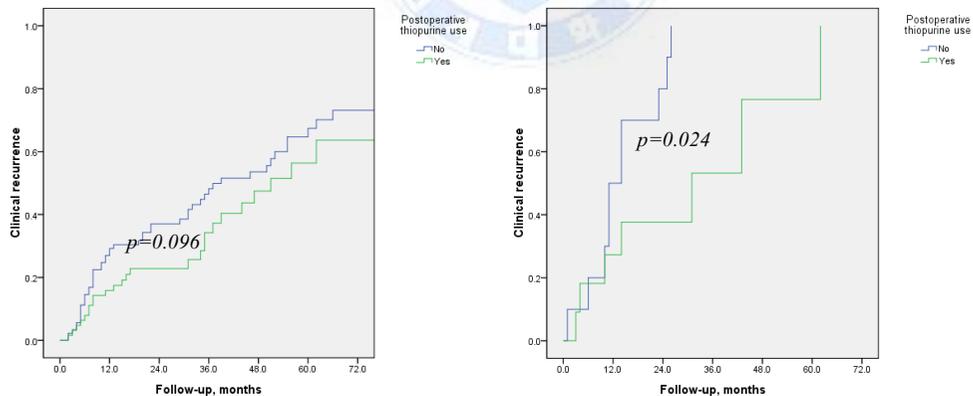


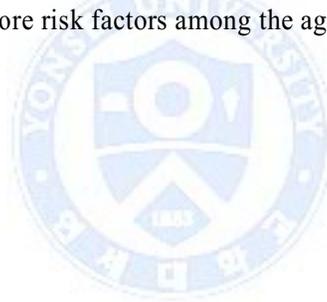
Fig. 2. Cumulative clinical recurrence among patients with low-risk group (A) and high-risk group (B). Comparisons of clinical recurrence rates between patients with postoperative prophylactic thiopurine use and those without.

Table 6. Clinical and surgical recurrence outcomes according to risk factors

| Variables | Low risk group (n=152, 87.9%, 0 or 1 risk factors) | High risk group ^a (n=21, 12.1%, 2 or 3 risk factors) | <i>P</i> value |
|-----------------------------|---|--|----------------|
| Follow-up duration (month) | 41 (21.0-65.8) | 26 (15.5 - 81.5) | 0.206 |
| Time to clinical recurrence | 51.7 ± 3.9 | 22.2 ± 4.3 | <0.001 |
| Time to surgical recurrence | 96.5 ± 4.0 | 66.1 ± 8.6 | 0.096 |

Variables are expressed as n (%) or median (interquartile range) or mean ± standard deviation.

High risk group^a defined as patients with two or more risk factors among the age at diagnosis under 16 years, perianal disease before surgery, and current smoker at surgery



IV. DISCUSSION

Although CD is still more prevalent in North America and Europe, the importance of CD in Asia is worthy of notice by its rapidly increasing incidence.^{1,21} Several studies reported that East Asian patients are different in natural course with lower intestinal resection and higher survival rates and have different clinical and disease phenotypes compared with Western patients.^{4,13} In the way of postoperative recurrence is still a crucial problem in CD management, it is important to recognize the risk factors after intestinal resection in Korean patients with CD to tailor prophylactic postoperative management for those in selective high risk group.

A few studies have investigated the postoperative recurrence in Korea. In one retrospective single center study including 34 patients who underwent intestinal resection, clinical recurrence rate was 8.8% and 33.5% at 12 months and 48 months. The additive use of immunomodulators was the only predictor of clinical recurrence in univariate analysis.¹⁷ Another retrospective multicenter study, including 708 patients, young age onset, stricturing behavior, intra-abdominal abscess, emergency surgery, and delayed diagnosis after surgery were the risk factors for repeated abdominal surgeries.¹⁶ However, these studies were limited by the small number of patients, included only surgical recurrence, or had insufficient clinical data.

In our study, baseline characteristics at diagnosis and surgery were similar with the previous studies conducted in East Asian countries. Only 10 patients (5.8%) were diagnosed CD after 50 years with male predominance (1.83: 1). Low proportion of current smokers was notable compared to Western data and these findings were also compatible with recent Asian reports. Relatively high proportion of perianal fistula (37.6%) compared to Western patients was also observed in previous Asian studies.^{13,21} In contrast, clinical recurrence rate (80.7% at 5 years) was higher than previous Korean studies, because our clinical recurrence definition that included any of CD related CDAI elevation, admission, or systemic steroid use or upgrade of medications.

Disease phenotype and smoking history changed between the time of diagnosis and surgery, we used these variables (Montreal classification,

smoking) at both time points separately to identify independent risk factors of recurrence. Although previous surgery, disease behavior, and postoperative prophylactic thiopurine use were not significant in the univariate analysis, we included these factors in multivariate analysis in addition to those significant in univariate analysis because these variables were suggested as absolute risk factors in Western studies.⁸⁻¹⁰ Finally, perianal disease and postoperative prophylactic thiopurine use were significantly associated with clinical recurrence and current smoking at surgery was associated with surgical recurrence in multivariate analysis.

These findings are consistent with previous Western studies in which smoking and perianal disease were suggested as potential risk factors and perianal disease as a poor prognostic factor. In fact, smoking not at diagnosis but at the time of surgery was associated with recurrence. Penetrating phenotype and previous surgery effect were insignificant in this study, different from previous Western reports.^{9,22,23} However, two previous Korean studies had shown that penetrating phenotype was insignificant to surgical recurrence, rather stricture phenotype was suggested as a risk factor for surgical recurrence.^{16,24} Different results in behavior phenotype might have come from distinctive disease nature between the Western and Eastern countries, but a larger scaled study is needed.

The patients who fulfilled more than two factors among the young age onset (<16 years), perianal disease, and current smoking were considered high risk group. According to definition, there were 21 (12.1%) high-risk patients in this study. The number is small compared to another high-risk definition that requires more than one of factors out of smoking, penetrating phenotype, and previous surgery.¹⁰ Although surgical recurrence was not statistically different between the high and low-risk groups, the tendency to early surgical recurrence and significant early clinical recurrence were shown in patients at high risk.

With postoperative prophylactic thiopurine use, high-risk group showed a better outcome in clinical recurrence than low-risk group. Therefore, routine prophylactic thiopurine use in selective high-risk group patients might be effective as a preventive strategy.

Our study has several limitations. First, endoscopic follow-up was

recommended within 6 to 12 months after surgery in several Western guidelines, but it was performed in only small number of patients in this study. However, in patients who underwent follow-up colonoscopy, 65.1% had endoscopic recurrence within 1 year, comparable to previous studies.^{8,17} Second, follow-up duration was relatively shorter than previous Western studies. Nevertheless, our result has an important meaning since this is the first Korean multicenter study about postoperative endoscopic, clinical and surgical recurrences.

V. CONCLUSION

Post-operative recurrence rate in this study showed the similar outcomes compared with that in Caucasians, despite considerably different disease phenotypes and managing strategies. More intensive management strategies will be required in patients with young age onset, perianal disease, and current smokers. Since smoking at the time of surgery is related to surgical recurrence and is a modifiable risk factor, it is important to educate patients about smoking cessation at the time of diagnosis. Also, the maintenance of thiopurine medications (azathioprine, 6-mercaptopurine) after intestinal resection surgery in selective high-risk patients with CD might be an effective preventive strategy for clinical recurrence.

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ABSTRACT(IN KOREAN)

한국인 크론병 환자의 수술 후 재발 위험 인자

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김성배

약물치료의 발전에도 불구하고, 많은 수의 크론병 환자는 여전히 수술적 치료를 받게 된다. 하지만, 수술 후 재발률은 여전히 높으며 어떠한 요인이 영향을 미치는지에 대한 연구는 동아시아 환자에서 특히 부족한 실정이다. 본 연구는 국내 크론병 환자의 수술 후 재발률과 위험인자에 대해 분석하였다. 대기관 후향적 연구로 2005년 1월에서 2014년 8월까지 크론병으로 인한 장 절제 수술을 진행한 173명의 환자를 대상으로 연구를 시행하였다. 총 43명 (24.9%) 환자에서 수술 후 1년 이내 추적 내시경 검사를 진행하였으며, 내시경적 재발률은 65.1% 이었다. 6년 누적 임상재발률과 수술재발률은 각각 91.1%, 48.0%로 나타났다. 다변량 분석에서 수술 후 예방적 thiopurine 약제 사용 ($P=0.04$), 수술 전 항문 주위 병변 진단($P=0.02$)이 임상재발의 예측 인자, 수술 시 흡연 ($P=0.02$)은 수술재발의 예측 인자로 나타났다. 결론으로, 한국인 크론병 환자에서 수술 후 재발률은 질환의 표현형과 치료 전략이 다름에도 불구하고 서양인과 유사한 결과를 보였다. 항문 주위 병변, 젊은 나이 진단, 흡연력이 있는 환자에서는 보다 적극적인 치료 전략이 필요하며 고위험군에서 수술 후 thiopurine 약제의 사용은 임상재발에 예방할 수 있는 효과적인 방법으로 생각된다.

핵심되는 말 : 크론병, 수술 후 재발, 수술, 면역조절제