# Comparative Study of Postoperative Inflammation and Tumor Stimulation Factors between Open and Laparoscopically Assisted Anterior Resection for Sigmoid Colon Cancer

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# Comparative Study of Postoperative Inflammation and Tumor Stimulation Factors between Open and Laparoscopically Assisted Anterior Resection for Sigmoid Colon Cancer

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<ABSTRACT>

Comparative Study of Postoperative Inflammation and Tumor Stimulation Factors between Open and Laparoscopically Assisted Anterior Resection for Sigmoid Colon Cancer

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Laparoscopic colectomy has clinical benefits such as short hospital stay, less postoperative pain, and early return of bowel function. However, objective evidence of its immunologic and oncologic benefits is scarce. Systemic cytokines are used to reflect surgical tissue trauma. Additionally, vascular endothelial growth factor (VEGF) and insulin-like growth factor binding protein-3 (IGFBP-3) levels may affect tumor growth. The aim of this study was to compare functional recovery after open versus

laparoscopic anterior resection and investigate the effect of open versus laparoscopic surgery on acute inflammation as well as tumor stimulation. A total of 57 patients who diagnosed with sigmoid colon cancer were randomized for elective conventional or laparoscopically assisted anterior resection. Demographic, perioperative, and pathologic data were reviewed and analyzed. Serum samples were obtained preoperatively and on postoperative day 1 (POD1). C-reactive protein (CRP) and interleukin-6 (IL-6) were measured for inflammation markers, and VEGF and IGFBP-3 were used as tumor stimulation factors. All serum markers were determined by enzyme-linked immunoassay (ELISA). Clinical parameters and serum markers were compared. The mean operation time ($P$ = 0.011) was significantly longer for the laparoscopic surgery group. Postoperative hospital stay ($P$ = 0.031), the first day of gas out ($P$ = 0.016), and the first day of soft diet ($P < 0.001$) were significantly shorter in laparoscopic surgery group than the open surgery group. The level of CRP, IL-6, and VEGF rose significantly, and the concentration of IGFBP-3 fell significantly after both open and laparoscopic surgery. However, there were no significant differences in the preoperative and postoperative levels of CRP, IL-6, VEGF, and IGFBP-3 between the two groups. There was a significant correlation between the POD1 IL-6 and

ratio of POD1/preoperative VEGF (r = 0.293; *P* = 0.027) as well as between the POD1 IL-6 and ratio of preoperative/POD1 IGFBP-3 (r = 0.354; *P* = 0.007). Our data suggest that both open and laparoscopic surgery are accompanied by significant changes in IL-6, CRP, IGFBP-3, and VEGF levels although recovery from surgical trauma is better in patients with laparoscopic surgery than those with open surgery. Postoperative changes of VEGF and IGFBP-3 levels were correlated with postoperative IL-6 level. Inflammation markers and tumor stimulating factors may not reflect clinical benefits of laparoscopic surgery although these markers are correlated with surgical trauma.

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Key words : colon cancer, laparoscopic surgery, acute inflammation, tumor stimulation

# Comparative Study of Postoperative Inflammation and Tumor Stimulation Factors between Open and Laparoscopically Assisted Anterior Resection for Sigmoid Colon Cancer

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## I. INTRODUCTION

Since the first report of a laparoscopic colectomy by Jacobs *et al.*[1] in 1991, several prospective studies have reported that laparoscopic surgery was similar to conventional open surgery in terms of oncologic safety.[2-4] Moreover, laparoscopic colectomy has benefits like shorter hospital stay, less postoperative pain, and early return of bowel function. These favorable early outcomes of laparoscopic colectomy have been reported in a number of studies.[5-7] As a result, laparoscopic colectomy has been widely accepted for resectable carcinoma. However, these early outcomes of laparoscopic surgery were based on clinical observations. Some

investigators have compared patterns of postoperative cytokine and stress responses with laparoscopic assisted colectomy to conventional open colectomy.[8-13] However, results of these studies have been proved inconsistent. This inconsistency has been attributed to inhomogenous operation type, different sampling timing, and enrollment of immunocompromized patients. Therefore, the impact of laparoscopic colectomy for carcinoma on acute inflammation has not yet been established.

Recently, Belizon *et al.*[14] reported that vascular endothelial growth factor (VEGF) which is important inducer of angiogenesis was significantly higher in open surgery than in laparoscopic surgery. Angiogenesis plays a critical role in the growth and development of tumor.[15] So, a high level of VEGF may influence the growth of tumor.[16] It is possible that open surgery stimulates residual tumor cells more than laparoscopic surgery does.

Another tumor stimulation factor whose level changed after surgery and may consequently impact tumor growth is insulin-like growth factor binding protein-3 (IGFBP-3). Matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinase (TIMP-1) may also impact tumor growth.[17] Kirman *et al.*[18] demonstrated that postoperative plasma with a low level of IGFBP-3 withdrawn from patients who had undergone major operation stimulated *in vitro* tumor growth compared with preoperative plasma. This postoperative reduction of IGFBP-3 was shown to be more dramatic in open surgery than in laparoscopic surgery.[19] Although it is not clinically proven that a high level of VEGF and a low

level of IGFBP-3 may have an impact on tumor growth, open surgery has stronger association with tumor stimulation factors than laparoscopic surgery dose. Interestingly, inflammatory cytokines including interleukin-6 (IL-6) have been reported to be associated with tumor stimulating factors such as VEGF and IGFBP-3.[20, 21]

However, few studies have compared both acute inflammation and tumor stimulating factors in homogenous patients undergoing open and laparoscopic surgery. The aim of the current study was to compare functional recovery after open versus laparoscopic anterior resection and investigate the effect of open versus laparoscopic surgery on acute inflammation as well as tumor stimulation. In addition, the relationship between the postoperative elevation of IL-6 and changes of VEGF and IGFBP-3 was examined, assuming that this alteration might have effect for the tumor growth.

## II. MATERIALS AND METHODS

### 1. Patients

From October 2008 to June 2009, 80 patients with the diagnosis of resectable sigmoid or rectosigmoid colon cancer were included in this study. Patients were randomized for elective conventional or laparoscopically assisted anterior resection using random numbers. Preoperative evaluations were consisted of

history taking, physical examination, carcinoembryonic antigen (CEA) level, peripheral blood test, colonoscopy, and computed tomography. Exclusion criteria were as follows: distant metastasis, blood transfusion, immunosuppressant medication, and history of chemotherapy or radiotherapy treatment. Informed consent was obtained from each patient. The study was approved by the Institutional Review Board.

2. Anesthesia and surgical procedure

All patients were treated with premedication and had standard anesthesia. The operations were performed by experienced surgeon (NK Kim) in both open and laparoscopically assisted technique. All open surgeries were performed through a midline skin incision. After mobilizing the mesocolon, the inferior mesenteric artery and vein were doubly ligated and divided. End-to-end anastomosis was performed using a circular stapler after transection of proximal and distal bowel resection.

In the laparoscopically assisted anterior resection, patients were placed in a modified lithotomy, right side down, Trendelenburg position. An initial 12-mm port placement was carried out using the open technique and pneumoperitoneum was accomplished using carbon dioxide. A standard 10-mm laparoscope was inserted through the 12-mm trocar. Then, two 5-mm ports were inserted in the upper right and left abdominal quadrants and two more 12-mm ports were placed in the lower right and left abdominal quadrants under laparoscopic guidance. The

left colon was mobilized using the open surgical technique. After dissecting the mesocolon, the inferior mesenteric artery and vein were divided using endoscopic clips, and were introduced using the 12-mm trocar in the right lower quadrant. A small incision was made in the left lower quadrant port to extract the specimen, and the wound was covered with a protector. End-to-end anastomosis was performed intracorporeally using a circular stapler. In both surgical techniques, a Jackson-Pratt drain was placed in the pelvis for drainage.

3. Postoperative treatment and data collection

After both open and laparoscopic surgeries, a clear liquid diet was started one day after patients passed flatus. Patients were given 1mg/kg of pethidine every six hours until postoperative day 1 (POD1) or upon their request after surgery. Patients were discharged if following discharge criteria was met: (1) passing stool, (2) tolerating soft diet, (3) being comfortable on oral analgesia, (4) white blood cell count within the normal range, (5) being happy to be discharged with full ambulation.

Clinical data including operation time, transfusion, time of the first passing flatus, time when start soft diet began, duration of postoperative hospital stay, complications, and pathologic report.

4. Blood sampling and processing

Blood was taken before surgery and the POD1. Seven milliliters of blood was

withdrawn from all patients by peripheral venipuncture. The specimens were centrifuged within 4 hours after withdrawal. The serum was collected and stored at -70°C until enzyme-linked immunosorbent assay (ELISA) was performed. C-reactive protein (CRP), IL-6, VEGF, and IGFBP-3 level were determined in duplicate using an ELISA test (Millipore, Billerica, MA, USA for CRP; BD Biosciences, San Jose, CA, USA for IL-6; RayBiotech, Inc., Norcross, GA, USA for IGFBP-3 and VEGF). Each sample was dispensed into their designated wells from ELISA kit, and the plate was incubated at room temperatures for 30 minutes. Conjugate solution which was provided from each ELISA kit was added into wells after 5 times wash procedure. Substrate reagent was added after incubation of diluted conjugate solution. The plate which was covered with aluminum foil was incubated again at room temperature for 30 minutes and stop solution which was provided from each ELISA kit was added into wells. Procedure-completed plate was inserted into an automated microplate reader (SpectraMax Plus$^{384}$, Sunnyvale, CA, USA) and read absorbance at 450 nm. The results of ELISA were calculated with software program (SoftMax Pro, Sunnyvale, CA, USA).

5. Statistical analysis

On the basis of our institute's data base over the last five years, the mean difference of hospital stay between open and laparoscopically assisted anterior resections was 4.53 days. Assuming a pooled standard deviation of 4.8 days, and assigning $\alpha = 0.05$, $\beta = 0.15$, 10% of dropout rate, and 1:2 allocation, at least 57

patients were needed. We decided to apply 1:2 allocation of recruits because patients preferred to receive laparoscopic surgery.

Statistical analysis was carried out using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Mann-Whitney test for continuous variables and Fisher's exact tests for categorical variables were used for statistical comparison of clinical characteristics. Differences within each groups was tested with the Wilcoxon matched pairs test. A Spearman correlation coefficient was performed to correlate changes in VEGF and IGFBP-3 levels with postoperative IL-6 levels, respectively. A value of $P < 0.05$ was considered significant.

## III. RESULTS

### 1. Patients

A total of 81 patients were recruited in this study. Nine patients with immunosuppressant, distant metastasis, and transfusion were excluded. Fourteen patients were excluded because samples were found to be inappropriate for ELISA test during the collection process. Patients with anastomotic leakage and tumor perforation which could influence acute-phase response were also excluded. As a result, 57 patients were enrolled in the study. A flow chart of patient selection was described in the Figure 1.

### 2. Clinical characteristics

Nineteen patients received open surgery and 38 patients received laparoscopic surgery. The two groups were comparable in terms of age, sex, body mass index which was devided kilograms of patient's weight by square meters of one's height, preoperative peripheral neutrophil count, preoperative CEA level, preoperative morbidity, and the American Society of Anesthesiologists score. However, the mean operation time was significantly longer in the laparoscopic surgery group (199.6±74.0 minutes vs. 222.7±45.6 minutes; $P = 0.011$). Whereas, postoperative hospital stay (12.5±4.7 days vs. 10.2±3.4 days; $P = 0.031$), the first day of gas out (3.6±2.5 days vs. 2.5±1.0 days; $P = 0.016$), and the first day of soft diet (6.7±2.5 days vs. 4.9±1.8 days; $P < 0.001$) were significantly shorter and earlier in the laparoscopic surgery group compared to the open surgery group. Stage III disease was more common in the open surgery group than in the laparoscopic surgery group although statistical difference was not significant. A summary of patient characteristics comparing open and laparoscopic surgeries is shown in Table 1.

3. Comparison of acute inflammation and tumor stimulating factors

No differences were observed between the two groups in serum concentrations of preoperative and postoperative CRP, IL-6, IGFBP-3, and VEGF (Table 2). Median value of preoperative CRP, IL-6, VEGF, and IGFBP-3 in the open surgery group was 9.4 ng/ml, 12.4 pg/ml, 1462.9 pg/ml, and 20.6 ng/ml. Whereas, median value of preoperative CRP, IL-6, VEGF, and IGFBP-3 in the laparoscopic surgery group was 9.3 ng/ml, 6.5 pg/ml, 1070.4 pg/ml, and 20.4 ng/ml. However, the level of

CRP, IL-6, and VEGF rose significantly after both open and laparoscopic surgeries ($P < 0.001$ for the each group; Fig. 2 to 4). The median value of postoperative CRP, IL-6, and VEGF in the open surgery group rose as 17.8 ng/ml, 119.5 pg/ml, and 2284.7 pg/ml, and postoperative CRP, IL-6, and VEGF in the laparoscopic surgery group elevated as 16.9 ng/ml, 49.2 pg/ml, and 2078.8 pg/ml. In contrast, the concentration of IGFBP-3 decreased significantly after open and laparoscopic surgeries ($P = 0.03$ for the open surgery group and $P = 0.003$ for the laparoscopic surgery group; Fig. 5). The median value of postoperative IGFBP-3 in the open surgery group decreased as 17.5 ng/ml and in the laparoscopic surgery group reduced as 18.3 ng/ml.

4. Correlation between IL-6 and postoperative changes in VEGF and IGFBP-3

There was a significant correlation between the POD1 IL-6 level and a drop in VEGF calculated as a ratio between POD1/preoperative VEGF ($r = 0.293$; $P = 0.027$; Fig. 6). In addition, a drop in IGFBP-3 calculated as a ratio between preoperative/POD1 IGFBP-3 also had significant correlation with POD1 IL-6 ($r = 0.354$; $P = 0.007$; Fig. 7).

Table 1. Clinical characteristics

| | OS | LS | *P* value |
|---|---|---|---|
| | *n* = 19 (%) | *n* = 38 (%) | |
| Age, years | | | 1.000 |
| ≤ 60 | 7 (36.8) | 14 (36.8) | |
| > 60 | 12 (63.2) | 24 (63.2) | |
| Sex | | | 0.775 |
| Male | 13 (68.4) | 24 (63.2) | |
| Female | 6 (31.6) | 14 (36.8) | |
| CEA level, ng/ml | | | 0.541 |
| ≤ 5 | 12 (63.2) | 28 (73.7) | |
| > 5 | 7 (36.8) | 10 (26.3) | |
| Comorbidity | | | 1.000 |
| No | 10 (52.6) | 20 (52.6) | |
| Yes | 9 (47.4) | 18 (47.4) | |
| ASA | | | 0.763 |
| 1 | 14 (73.7) | 25 (65.8) | |
| 2 | 5 (26.3) | 13 (34.2) | |
| Mean BMI, kg/m$^2$ | 23.1±3.3 | 23.6±2.8 | 0.537 |
| Mean operation time, min | 199.6±74.0 | 222.7±45.6 | 0.011 |
| Mean preoperative neutrophil count, 10$^3$/ml | 5.7±3.1 | 4.5±1.5 | 0.257 |
| Mean postoperative neutrophil count, 10$^3$/ml | 9.8±3.1 | 10.5±3.1 | 0.446 |
| Mean postoperative hospital stay, day | 12.5±4.7 | 10.2±3.4 | 0.031 |
| First day of gas out, day | 3.6±2.5 | 2.5±1.0 | 0.016 |
| First day of soft diet, day | 6.7±2.5 | 4.9±1.8 | < 0.001 |
| Stage | | | 0.159 |
| II | 6 (31.6) | 21 (55.3) | |
| III | 13 (68.4) | 17 (44.7) | |

OS, open surgery; LS, laparoscopic surgery; CEA, carcinoembryonic antigen; BMI, body mass index, ASA, American Society of Anesthesiologists.

Table 2. Comparison of acute phase responses and tumor stimulating factors.

| | OS (n = 19) | LS (n = 38) | *P* value |
|---|---|---|---|
| Preoperative CRP (ng/ml, median) | 9.4 (5.2-13.1) | 9.3 (3.7-14.5) | 0.260 |
| Postoperative CRP (ng/ml, median) | 17.8 (9.6-80.1) | 16.9 (9.4-21.8) | 0.229 |
| Preoperative IL-6 (pg/ml, median) | 12.4 (0.5-81.6) | 6.5 (0.1-360.3) | 0.176 |
| Postoperative IL-6 (pg/ml, median) | 119.5 (1.78-298.7) | 49.2 (2.3-407.7) | 0.407 |
| Preoperative VEGF (pg/ml, median) | 1462.9 (91.6-2240.7) | 1070.4 (19.2-4949.1) | 0.243 |
| Postoperative VEGF (pg/ml, median) | 2284.7 (922.7-6752.1) | 2078.8 (311.0-8275.5) | 0.388 |
| Preoperative IGFBP-3 (ng/ml, median) | 20.6 (16.9-22.6) | 20.4 (13.7-24.0) | 0.761 |
| Postoperative IGFBP-3 (ng/ml, median) | 17.5 (13.4-22.5) | 18.3 (9.7-23.4) | 0.919 |

Values in parentheses are ranges. OS, open surgery; LS, laparoscopic surgery

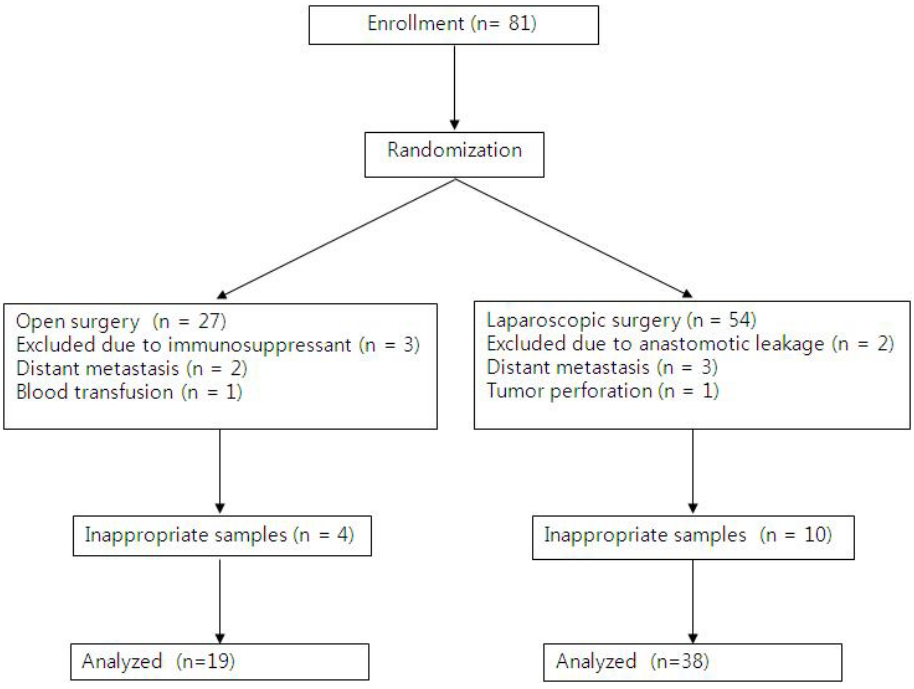


Figure 1. The flow chart of patient selection process.

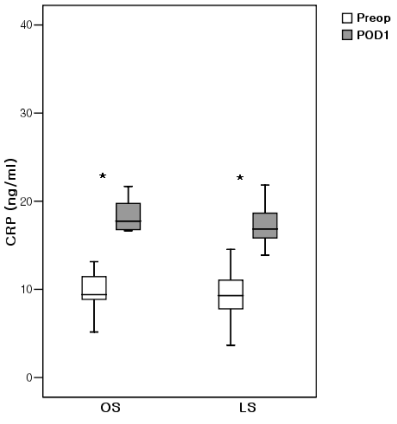


Figure 2. Changes in the serum concentration of C-reactive protein (CRP) in

patients undergoing open or laparoscopic surgery for sigmoid colon cancer. No significant differences were found between the open and laparoscopic surgery groups.

*$P < 0.001$ Preoperative (Preop) value versus the first postoperative day (POD1)

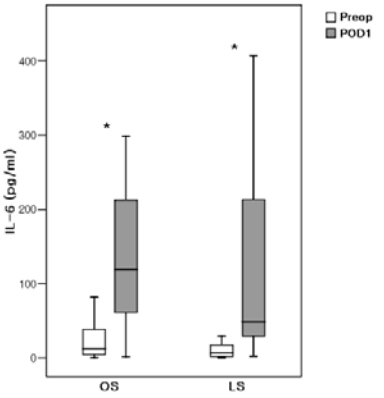


Figure 3. Changes in the serum concentration of interleukin-6 (IL-6) in patients undergoing open or laparoscopic surgery for sigmoid colon cancer. No significant differences were found between the open and laparoscopic surgery groups.

*$P < 0.001$ Preoperative (Preop) value versus the first postoperative day (POD1)

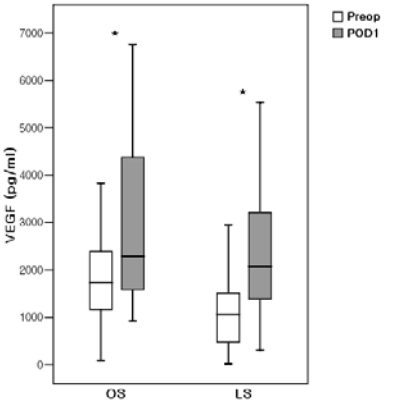


Figure 4. Changes in the serum concentration of vascular endothelial growth factor (VEGF) in patients undergoing open or laparoscopic surgery for sigmoid colon cancer. No significant differences were found between the open and laparoscopic surgery groups.

*$P < 0.001$ Preoperative (Preop) value versus the first postoperative day (POD1)

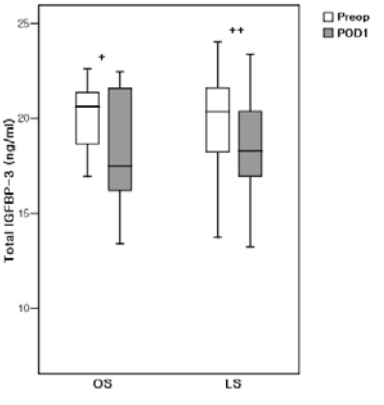


Figure 5. Changes in the serum concentration of insulin-like growth factor binding

protein-3 (IGFBP-3) in patients undergoing open or laparoscopic surgery for sigmoid colon cancer. No significant differences were found between the open and laparoscopic surgery groups.

+*P* = 0.03 for the open surgery group

++*P* = 0.003 for the laparoscopic surgery group

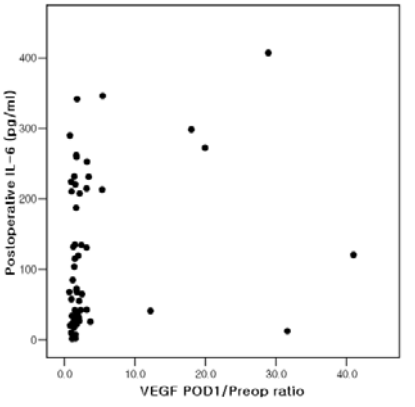


Figure 6. A postoperative increase in vascular endothelial growth factor (VEGF) correlates with a concentration of the first postoperative day (POD1) interleukin-6 (r = 0.293, *P* = 0.027). The ratio between the values of the POD1 versus preoperative (Preop) VEGF was used to analyze a postoperative increase of concentration.

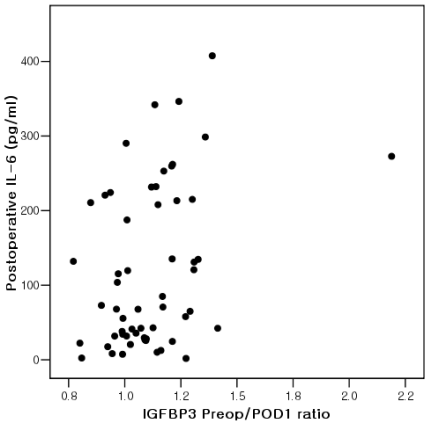


Figure 7. A postoperative decrease in insulin-like growth factor binding protein-3 (IGFBP-3) correlated with a concentration of the first postoperative day (POD1) interleukin-6 (r = 0.354, *P* = 0.007). The ratio between the values of preoperative (Preop) versus the POD1 IGFBP-3 was used to analyze a postoperative loss of the protein.

## IV. DISCUSSION

In several prospective studies, laparoscopic colectomy has been reported to have similar oncologic outcomes compared with open colectomy.[2-4] Laparoscopic surgery is also known to be associated with short hospital stay, less postoperative pain, and early resumption of normal diet. This favorable early outcome has been regarded to be related to the reduced bowel injury, surgical metabolic stress, and immunosuppressive response.[22] CRP is a key marker of acute-phase proteins as its

level increases in proportion to the degree of inflammation. Plasma concentration of CRP serves as a reliable screening test for acute-phase response. The CRP level usually rises 4 to 12 hours after surgery and peak at 24 hours. An elevated CRP level may remain for approximately 2 weeks.[23] The acute-phase response consists of a series of hormonal, metabolic, and immunologic changes in response to surgery, trauma, or sepsis.[24] Tumor necrosis factor-α (TNF-α), IL-1β, and IL-6 are major components of the acute-phase response in humans. Among these mediators, IL-6 is primarily responsible for the hepatic component of the response, resulting in the synthesis of acute-phase proteins. IL-6 usually peaks at 4 to 48 hours after surgery and rapidly falls afterwards. The levels of the cytokines and CRP were identified to correspond with the severity of surgery and the presence of complications. Thus, these markers have been used to reflect surgical tissue trauma.[24]

Previous studies on acute-phase response after laparoscopic colorectal surgery were inconclusive.[8-13] Leung *et al.*[8] and Delgado *et al.*[13] demonstrated that acute-phase response was less in the laparoscopic surgery group than in the open surgery group. Therefore, they suggested that the difference in the systemic cytokine response may have effect on anti-inflammation and immunosuppression. In contrast, Tang *et al.*,[9] Fukushima *et al.*,[11] and Dunker *et al.*[12] described that no differences in the acute-phase response were noted in patients receiving conventional open surgery and those who had laparoscopic surgery for colorectal cancer. Interestingly, Stage et al.[10] showed that the CRP and IL-6 peak levels were

higher in the laparoscopic than in the open group. These studies were relatively uniform and conducted with randomized fashion. However, some of studies included metastatic disease, immunocompromized patients, and inconstant surgical procedure. In this study, homogenous group of patients with sigmoid colon cancer were enrolled, and patients with metastatic disease, use of immunosuppressant, and intraoperative transfusion were excluded. In addition, patients with anastomotic leakage and tumor perforation at the time of surgery were also excluded because these factors could influence acute-phase response after operation.

In the current study, CRP and IL-6 levels increased significantly after both open and laparoscopic anterior resection ($P < 0.001$; Figs. 2 and 3), which indicates significant activation of the inflammatory response. There were no significant differences in the postoperative CRP and IL-6 levels between the open and laparoscopic surgery groups. This phenomenon could be explained by surgical bowel injury, which was comparable in both surgical techniques. The IL-6 level after laparoscopic surgery may vary greatly because of the surgical technique and patient selection. Technique of laparoscopic surgery is influenced by the surgeon's experience, patient factor, and tumor factor. In contrast, open surgery is well established and gives similar results. According to current data, the level of postoperative IL-6 level was more variable in the laparoscopic than in the surgery group. There was a problem of the current study that deserves mention. Time interval from the end of surgery to POD1 varied in each patient because sampling

of POD1 was performed at the same time regardless of end time of surgery. Therefore, this study was limited by the bias inherent to quantitative analysis of this nature.

The early outcome of the laparoscopic surgery group was remarkable. There was significant difference in longer operation time, shorter postoperative hospital stay, and earlier return of bowel function in the laparoscopic surgery group. Clinical outcome after laparoscopic surgery was better than after open surgery although laparoscopic surgery needed longer operation time. Despite of randomization, pathologic report revealed that stage III disease was more common in the open surgery group than in the laparoscopic surgery group (68.4% vs. 44.7%; $P$ = 0.159). In addition, median value of preoperative IL-6 and VEGF were higher in the open surgery group than laparoscopic surgery group. These results might be attributable to inaccuracy of nodal prediction of computed tomography for colon cancer. The exact extent of involved lymph nodes could be informed only after surgical resection because currently available imaging modalities lack accuracy for preoperative nodal status for colorectal cancer.[25] However, level of postoperative acute inflammation markers and tumor stimulating factors were higher in the open surgery group than laparoscopic surgery group in this study. This data suggested that surgical trauma might be more invasive in the open surgery than laparoscopic surgery.

A recent study evaluated plasma VEGF levels preoperatively and on days 1 and 3 after open and laparoscopic colorectal resections for benign and malignant

diseases as well as after gastric bypass for morbid obesity.[14] This study demonstrated that the mean values of VEGF significantly increased on POD 1 and 3 after colorectal resection and gastric bypass, and the extent of elevation at postoperative time was significantly greater for the open surgery group. An elevated VEGF level may remain unchanged for approximately 3 weeks after curative surgery.[16]

A high level of VEGF may stimulate the development and growth of metastases.[26] Major surgery has been associated with IGFBP-3 depletion and increased plasma MMP-9 levels, which were related with tumor stimulation.[17, 18] In this study, the VEGF level increased, and the IGFBP-3 level decreased significantly after both open and laparoscopic anterior resections ($P < 0.001$ for VEGF in both open and laparoscopic surgery; $P = 0.03$ for IGFBP-3 in open surgery, $P = 0.003$ for IGFBP-3 in laparoscopic surgery; Figs. 4 and 5). However, there were no significant differences in the postoperative VEGF and IGFBP-3 levels between the open and laparoscopic surgery groups. Do increased VEGF and decreased IGFBP-3 levels after both open and laparoscopic surgeries affect tumor growth? Should clinicians start anti-tumor chemotherapy in early postoperative time? It is not clear that such therapy would be safe or effective in early time of post-operation. Moreover, plasma VEGF levels did not increase in all patients after surgery and varied broadly from patient to patient.[16] Therefore, clinical importance of these findings is unclear.

The current study demonstrated that a rise in the VEGF concentration and

reduction in the IGFBP-3 concentration after surgery were associated with the postoperative IL-6 level. Proteases are thought to be responsible for the depletion of IGFBP-3 in plasma and numerous molecules have IGFBP-3 proteolytic activity. Plasmin, thrombin, kallikrein, prostate-specific antigen, matirix metalloproteinases, cathepsins, elastase, and several unidentified proteases present in serum are able to cleave IGFBP-3.[27, 28] It is likely that proteolysis generates inactive IGFBP-3 fragments. IL-6 is a factor that has been shown to induce IGFBP-3 proteolytic activity.[29] Kirman *et al.*[21] showed that the IL-6 level on POD1 was found to be significantly correlated with a decrease in plasma IGFBP-3 after open surgery ($r = 0.81$, $P < 0.0001$). Several investigators have reported that IL-6 induced gene expression of various proteases such as cathepsins and metalloproteinase-13, and enhanced IGFBP-3 proteolysis.[30-32] In addition, it has been found that IL-6 upregulates VEGF expression using various molecular pathways.[20] It is not known how exactly IL-6 affects IGFBP-3 and VEGF balance. However, results of current study suggest that an acute inflammatory response may be correlated with IGFBP-3 and VEGF which are associated with tumor stimulation. It is postulated that minimally invasive procedure may have oncologic benefit in patient with colon cancer. Knowledge of inflammatory response mediated pathway of VEGF production and IGFBP-3 depletion may bring novel therapeutic strategies for colon cancer patients undergoing surgery. The relationship of inflammation and tumor stimulation after surgery should be taken into consideration and requires further evaluation in the future.

## V. CONCLUSION

This study demonstrated that early outcome after laparoscopic surgery was better than that after open surgery despite longer operation time. Thus, laparoscopic anterior resection is an acceptable and safe procedure for sigmoid or rectosigmoid cancer. This study did not identify any difference in preoperative and postoperative CRP, IL-6, VEGF, and IGFBP-3 levels between the open and laparoscopic surgery groups. However, the levels of these markers significantly changed after both open and laparoscopic surgeries. Postoperative increase of the VEGF level and decrease of IGFBP-3 level were correlated with the postoperative IL-6 level. Inflammation markers and tumor stimulating factors may not reflect clinical benefit of laparoscopic surgery.

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< ABSTRACT(IN KOREAN)>

# 전방절제술에서 개복술과 복강경 수술간 염증반응인자 및 종양성장관련인자의 비교연구

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복강경 대장절제술은 개복술에 비해 짧은 재원기간, 수술 후 동통의 감소, 빠른 장의 기능 회복 등 많은 임상적 장점을 가지기 때문에 환자 및 외과의사에게 모두 선호되고 있다. 그러나 복강경 수술의 이러한 장점은 면역학적 또는 종양학적 관점으로 측정할 수 있는 객관적인 증거는 불충분하다. 수술 후 환자에게 가해지는 자극의 정도를 측정하기 위해 여러 연구에서 cytokine을 포함한 염증반응인자가 제시되고 있다. 또한 vascular

endothelial growth factor (VEGF) 및 insulin-like growth factor binding protein-3 (IGFBP-3) 등 종양성장 및 억제인자의 변화는 수술 후 종양의 성장을 촉진하는 것으로 알려져 있다. 본 연구는 에스자결장암에서 시행하고 있는 전방절제술의 개복술과 복강경 수술 후 임상적 차이를 비교하고 수술 후 급성 염증반응 및 종양성장과 관련된 인자를 비교 분석함으로서 복강경 수술이 갖는 임상적 장점에 대한 객관적인 근거를 수립하고자 하였다.

에스자결장암으로 진단받은 57명의 환자를 무작위 추출하여 개복술 군과 복강경 수술 군으로 나누고 수술 전 및 수술 후 1일째 환자로부터 채혈 한 후 enzyme-linked immunoassay (ELISA) 검사를 시행하였다. ELISA 검사는 C-reactive protein (CRP), interleukin-6 (IL-6), VEGF, IGFBP-3에 대하여 시행하였다. 환자가 수술 후 퇴원할 시에 임상자료를 모아 임상적 차이를 분석하였다. 평균 수술시간 ($P = 0.011$), 평균재원기간 ($P = 0.031$), 첫 방귀배출일($P = 0.016$), 첫 연식시작일 ($P < 0.001$)에서 두 군간 차이를 보였다. CRP, IL-6, VEGF, IGFBP-3 값은 양 군에서 수술 전후 모두 통계적으로 의미 있는 차이를 보였으나 양 군간의 차이는 보이지 않았다. 그러나 수술 전 후의 VEGF (r = 0.293, $P$ =

0.027), IGFBP-3 (r = 0.354, *P* = 0.007) 값의 비율과 수술 후 IL-6 값에는 상관관계를 보였다.

본 연구에서는 수술 후 회복이 복강경 수술 군에서 더 나은 결과를 보였으나 염증인자 및 종양 성장관련 인자의 객관적으로 측정된 값에서는 개복술 및 복강경 수술 군 모두 차이를 보이지 않았다. 그러나 VEGF, IGFBP-3 의 수술 전후 값의 변화는 수술 후 IL-6 값과 상관관계를 보였다. 염증인자 및 종양 성장관련 인자는 수술 후 증가하는 양상을 보이지만 복강경 수술의 빠른 회복과는 상관관계가 없을 것으로 사료된다.

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핵심되는 말 : 대장암, 복강경 수술, 급성 염증반응, 종양성장인자