

Comparison of Compliance of Adjuvant Chemotherapy Between Laparoscopic and Open Surgery in Patients With Colon Cancer

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Purpose: Many studies have shown that the completion of adjuvant chemotherapy improves the survival rate. Recently, laparoscopic surgery has been used to treat patients with colon cancer. We analyzed the relationship between the completion of adjuvant chemotherapy and the operation method.

Methods: We retrospectively analyzed the medical records of 147 patients diagnosed with colon cancer from January 1, 2009, to May 31, 2012. The numbers of patients who underwent laparoscopic and open surgery were 91 and 56, respectively. We analyzed the relationship between the operation method and various factors such as the completion rate of chemotherapy, the patient's age, gender, and physical activity, the postoperative hospital stay, the start time of chemotherapy, and the patient's body mass index (BMI), TNM stage, and type of health insurance.

Results: In the laparoscopic surgery group, the postoperative hospital stay (13.5 ± 14.82 days vs. 19.6 ± 11.38 days, $P = 0.001$) and start time of chemotherapy (17.7 ± 17.48 days vs. 23.0 ± 15.00 days, $P = 0.044$) were shorter, but the percent complete of chemotherapy ($71/91$ [78.0%] vs. $38/56$ [67.8%], $P = 0.121$), and survival rate ($88/91$ [96.7%], $47/56$ [83.9%], $P = 0.007$) were higher than they were in the open surgery group. Patients who were elderly, had a low BMI, and a high American Society of Anesthesiologists score were less likely to complete adjuvant chemotherapy than other patients were.

Conclusion: Laparoscopic surgery shows a shorter postoperative hospital stay, a shorter start time of chemotherapy, and a higher survival rate. Laparoscopic surgery may be expected to increase compliance of chemotherapy and to improve survival rate.

Keywords: Adjuvant chemotherapy; Colon neoplasms; Percent complete; Laparoscopy

INTRODUCTION

According to 2011 statistical data from the National Cancer Center, a total of 28,112 colon cancer cases occurred, and its crude incidence rate was 39 per 100,000 population. These data show that colon cancer is the third most common cancer diagnosed in Ko-

rea. Also, colon cancer accounts for 11.1% of all cancer deaths and represents the fourth highest mortality rate. The colon cancer five-year survival rate has been gradually increasing over the last 15 years, with a 54.8% increase from 1993 to 1995 and a 73.8% increase from 2007 to 2011 [1]. Such improvements in the survival rate are thought to be mainly due to advances in adjuvant chemotherapy and surgical techniques [2]. Large-scale clinical studies on laparoscopic surgery for treating patients with colon cancer have consistently shown that patients who undergo laparoscopic surgery have some advantages, including shorter hospital stay and recovery period, early postoperative ambulation and physical activity, and reduced postoperative pain [3-5]. We have hypothesized that these advantages might help patients receive their postoperative adjuvant chemotherapy on schedule, so we investigated whether or not the type of surgical procedure had any effect on the compliance with adjuvant chemotherapy in patients who un-

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derwent colon cancer surgery. Moreover, we hypothesized that various clinical and pathological factors might also have an effect on the compliance with adjuvant chemotherapy. Therefore, we analyzed the dependences of the differences in the timing to initiate adjuvant chemotherapy and in its completion rate on clinical and pathological variables, and we investigated the survival rate.

METHODS

We retrospectively analyzed the medical records of 147 patients who were diagnosed with colon cancer and underwent surgery at Sanggye Paik Hospital between July 1, 2009, and May 31, 2012. In this study, there were no strict criteria to determine the preferable surgery method between laparoscopic and open surgery. However, in 2009, laparoscopic surgery was mostly offered to patients with tumors equal to or less than 5 cm in size or with body mass indices (BMIs) less than 23. However, since 2012, it has been offered to patients who underwent a colonic stent placement for large bowel obstruction, but enough decompression had to have been achieved before the surgery. Of patients diagnosed with stage II or III colon cancer on a postoperative biopsy test, the patients who were thought to be at high risk based on the American Joint Committee on Cancer (AJCC), 7th edition TNM classification received adjuvant chemotherapy. With the patient's consent, the adjuvant chemotherapy was initiated when the patient was able to eat solid food and it did not disturb the bowel movement. A total of 147 patients were classified into two groups: 91 patients underwent laparoscopic surgery, and 56 patients underwent open surgery.

We investigated the length of a hospital stay after the surgery, the timing to initiate chemotherapy, and the percent complete of chemotherapy to evaluate the compliance of adjuvant chemotherapy according to the surgery method. In addition, we analyzed the relationships between factors such as gender, age, BMI, physical activity levels, and the completion rate of chemotherapy in order to identify the correlations with the biological characteristics of the patients. The 2013 registration data on overall survival rates of subjects were provided by the National Cancer Center upon our request. The length of a postoperative hospital stay was defined as the number of days from surgery (day 0) until discharge from the hospital. The timing to initiate chemotherapy was defined as the number of days from surgery (day 0) until the first day of adjuvant chemotherapy. Based on BMI values, underweight patients (20 kg/m² or less) were assigned to the first group, and normal-weight or overweight patients than 20 kg/m²) were assigned to the second group. Large bowel obstruction was defined as the presence of air or fluid levels on plain abdominal radiographs taken 3 days after the surgery. The physical status of each patient was evaluated based on the American Society of Anesthesiologists (ASA) score suggested by the ASA and was used to assess the fitness of each patient before surgery. Healthy patients and subjects with mild systemic disease were assigned 1 point and 2 points, respectively, and they were assigned to the first group. Patients with severe systemic

disease and patients with severe systemic disease that was a constant threat to life were assigned 3 and 4 points, respectively, and they were assigned to the second group. No patient was assigned 5 or 6 points based on the ASA score.

Oxaliplatin in combination with 5-fluorouracil (Folfox), Oxaliplatin in combination with Capecitabine (Xelox), Tegafur+Uracil and Capecitabine were used for adjuvant chemotherapy. If patients received 8 cycles of Folfox, 6 cycles of Xelox, and 6 months of oral chemotherapy, the chemotherapy was regarded as complete. This study used the chi-square test and the student t-test for statistical analysis. If the P-value was equal to or less than 0.05, the results were considered statistically significant.

RESULTS

Of 147 patients with colon cancer, 91 and 56 patients underwent laparoscopic and open surgery, respectively. Their average age was 70.0 ± 10.06 and 69.0 ± 13.00 years, respectively (P = 0.450). The gender ratio was 57:34 and 41:15, respectively (P = 0.127). As a result of classifying the patients based on the AJCC 7th edition TNM classification, the numbers of patients with stages II and III colon cancer in the laparoscopic group were 48 and 43, respectively, and the numbers in the open surgery groups were 35 and 21 (P = 0.162). The numbers of patients covered by Korea's National Health Insurance and medical aid program were 83 and 8 in the laparoscopic group and 50 and 6 in the open surgery group, respectively. No statistically significant differences in the patients' characteristics were noted between the two groups (P = 0.454) (Table 1).

The average lengths of stay in the hospital after the surgery were 13.5 and 19.6 days in the laparoscopic and the open surgery group, respectively. The length of stay in the hospital was shorter in laparoscopic group and this result was statistically significant (P = 0.001). The chemotherapy was started, on average, 17.7 and 23.0 days after the surgery in the laparoscopic and the open surgery group, re-

Table 1. Patients' characteristics according to the operation method

Characteristic	LS	OS	P-value
Age (yr), mean ± SD	70.0 ± 10.06	69.0 ± 13.00	0.450
Gender			0.127
Male:female	57/34	41/15	
BMI (kg/m ²), mean ± SD	23.5 ± 3.84	23.6 ± 3.45	0.361
ASA score			0.258
1,2/3,4	77/13	44/11	
Stage			0.162
II/III	48/43	35/21	
Health insurance			0.454
NHI/medicaid	83/8	50/6	

LS, laparoscopic surgery; OS, open surgery; SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; NHI, National Health Insurance.

Table 2. Compliance of chemotherapy according to the operation method

Variable	LS	OS	P-value
Hospital stay (day)	13.5 ± 7.27	19.6 ± 11.38	0.001
Starting day of chemotherapy (day)	17.7 ± 17.48	23.0 ± 15.00	0.044
Completion rate of chemotherapy	71/91 (78.0)	38/56 (67.8)	0.121
Overall survival rate	88/91 (96.7)	47/56 (83.9)	0.007

Values are presented as mean ± standard deviation or number (%).
LS, laparoscopic surgery; OS, open surgery.

spectively. This result showed that the laparoscopic group started their chemotherapy earlier, and this difference between the two groups was statistically significant ($P = 0.044$). Of the 91 patients who received laparoscopic surgery, 71 patients (78%) completed their adjuvant chemotherapy. In addition, of the 56 patients who received open surgery, 38 patients (67.8%) completed their adjuvant chemotherapy. The completion rate was higher in the laparoscopic group, but this difference was not statistically significant ($P = 0.121$). Based on the 2013 registration data provided by the National Cancer Center upon our request, the overall survival rates of patients were 96.7% (88 of 91) and 85.7% (48 of 56) in the laparoscopic and the open surgery group, respectively ($P = 0.007$) (Table 2).

As a result of analyzing the causes of prolonged hospital stay after surgery, surgical wound infection was more common in the open surgery group, and this result was statistically significant ($P = 0.043$). Other possible causes of prolonged hospital stay, such as bowel obstruction, urinary tract complications, including dysuria, hematuria, and urinary tract infections, and anastomotic leaks, were not found to be statistically significant. Patients who experienced surgical complications started their chemotherapy later than patients who did not experience such complications (28.2 ± 18.00 vs. 17.1 ± 15.40 , $P = 0.002$). In addition to these complications, the hospital stays of 26 patients in the laparoscopic group and 12 patients in the open surgery group were prolonged because they received their first postoperative adjuvant chemotherapy before they were discharged (Table 3).

We also investigated causes for patients not being able to complete their adjuvant chemotherapy. Five patients in the laparoscopic group and 3 patients in the open surgery group failed to complete their adjuvant chemotherapy due to nausea, diarrhea, dizziness, etc. ($P = 0.641$). In addition, 4 patients in the laparoscopic group and 5 patients in the open surgery group discontinued their chemotherapy due to sepsis, pneumonia, neutropenia, and bowel obstruction ($P = 0.221$). Eleven patients in the laparoscopic group and 10 patients in open surgery group voluntarily discontinued their adjuvant chemotherapy ($P = 0.232$).

As a result of analyzing the relationship between clinical and pathological factors and the completion rate of adjuvant chemotherapy regardless of the surgical method, the completion rate

Table 3. Causes of long hospital stay

Variable	LS	OS	P-value
Wound infection	3 (3.3)	7 (12.5)	0.043
Anastomotic leak	2 (2.2)	1 (1.8)	1.000
Urinary complication	7 (7.6)	1 (1.8)	0.156
Ileus	13 (14.3)	11 (19.6)	0.507
Chemotherapy	26 (28.6)	12 (21.4)	0.483

Values are presented as number (%).
LS, laparoscopic surgery; OS, open surgery.

was statistically significantly higher for patients with ASA scores of 1 or 2 points ($P = 0.004$), for patients whose ages were less than 70 years ($P = 0.058$), and for patients whose BMIs were equal to or more than 20 ($P = 0.051$); however, the results were not statistically significant. In addition, patient's gender, stage of cancer, and types of insurance were not correlated to the completion rate of adjuvant chemotherapy (Table 4).

We also analyze results for each group, laparoscopic and open surgery. In the laparoscopic group, the completion rate of adjuvant chemotherapy was not correlated to patient's age ($P = 0.316$) or BMI ($P = 0.231$). On the other hand, 64 of 77 patients with ASA scores of 1 or 2 points and 7 of 13 patients with ASA scores 3 or 4 points completed their adjuvant chemotherapy. These results were statistically significant (81.8% vs. 53.4%; $P = 0.035$). In the open surgery group, the completion rate of adjuvant chemotherapy was higher for patients whose ages were less than 70 years ($P = 0.010$), but it was not related to the ASA score with any statistical significance ($P = 0.066$). Also, its relationship with the BMI was not statistically significant ($P = 0.115$).

DISCUSSION

Over the last 10 years, laparoscopic surgery for colon cancer has drastically increased. Many factors have contributed to this increase. The dissemination and implantation of cancer cells at the port site can be successfully prevented during the surgical procedure. Also, many studies have reported on the short- and the long-term follow-up results of laparoscopic and open surgery, and those results have consistently shown the oncological outcome of laparoscopic surgery not to be inferior to outcome of open surgery. This is the major reason laparoscopic surgery is recognized as a safe surgical method nowadays. Moreover, advances in surgical techniques and development of various laparoscopic surgical instruments are other causes for this increase [6].

The stage of cancer, its histologic grade, lymphovascular invasion, and adjuvant chemotherapy have been reported to be factors that influence the survival rate of colon cancer patients [7, 8]. Adjuvant chemotherapy has improved the survival rate of patients with various solid tumors. However, it is difficult to expect an improved survival rate due to adjuvant chemotherapy if the compliance with

Table 4. Completion rate of chemotherapy according to the patient's clinico-pathologic characteristics

Variable	LS	P-value	OS	P-value	Overall	P-value
Age (yr)		0.316		0.010		0.058
>70	29/39 (74.3)		20/23 (87.0)		16/22 (72.2)	
≤70	42/52 (80.7)		18/33 (54.5)		16/29 (55.2)	
Sex		0.489		0.139		0.230
Male	45/57 (78.9)		30/41 (73.2)		75/98 (76.5)	
Female	26/34 (76.5)		8/15 (53.3)		34/49 (69.4)	
Stage		0.316		0.090		0.061
II	36/48 (75.0)		21/35 (60.0)		57/83 (68.7)	
III	35/43 (81.4)		17/21 (81.0)		52/64 (81.2)	
ASA score		0.035		0.066		0.004
1,2	63/77 (81.8)		33/44 (75.0)		96/121 (79.3)	
3,4	7/13 (53.8)		5/11 (45.5)		12/24 (50.0)	
Health insurance		0.438		0.085		0.079
NHI	64/83 (77.1)		32/50 (64.0)		96/133 (72.2)	
Medicaid	7/8 (87.5)		6/6 (100)		13/14 (92.9)	
Chemotherapy		0.489		0.078		0.193
Intravenous	33/43 (76.7)		15/18 (83.3)		48/61 (78.7)	
Oral	38/48 (79.2)		23/38 (60.5)		61/86 (70.9)	
BMI (kg/m ²)		0.231		0.115		0.051
≥20	8/12 (66.7)		4/9 (44.4)		12/21 (57.1)	
<20	62/77 (80.5)		33/46 (71.7)		95/123 (77.2)	
Operation type		0.220		1.000		0.451
Elective	71/90 (78.8)		37/55 (67.3)		108/145(74.5)	
Emergency	0/1 (0)		1/1 (100)		1/2 (50.0)	
Postoperative complication		0.237		0.558		0.246
X	60/70 (85.7)		31/41 (75.6)		91/111 (82.0)	
0	16/21 (76.2)		11/15 (73.3)		27/36 (75.0)	

Values are presented as number/total number (%).

LS, laparoscopic surgery; OS, open surgery; ASA, American Society of Anesthesiologists; BMI, body mass index; NHI, National Health Insurance.

adjuvant chemotherapy in patients is poor due to its side effects [9]. Many studies have reported that age, gender, postoperative complications, the severity of the side effects of chemotherapy, and patients' socioeconomic status are factors that have an influence on the completion of adjuvant chemotherapy [10-13].

In this study, the hospital stay was shorter, and the adjuvant chemotherapy started earlier in the laparoscopic group; these differences were statistically significant. In addition, the completion rate of adjuvant chemotherapy and the survival rate were higher. Many other studies have also reported mostly shorter hospital stays in laparoscopic groups [14, 15], which is consistent with the results of this study ($P = 0.001$). However, the hospital stay in this study was longer than it was in previous studies. This seems to be due to the facts that many patients received their first postoperative adjuvant chemotherapy before their discharge, that some pa-

tients experienced postoperative complications, and that some patients resided location far from the hospital. Therefore, the average length of the hospital stay was prolonged in this study.

Some studies have reported that delayed adjuvant chemotherapy leads to a lower overall survival rate [16, 17]. In this study, the chemotherapy was started, on average, 17.7 days after surgery in laparoscopic group, which was earlier than the open surgery group, the difference being statistically significant ($P = 0.044$). This is thought to have been due to patients in the laparoscopic group experiencing less pain and having a lower incidence of surgical wound infection, one of the complications.

The laparoscopic and the open surgery groups showed 78% and 67.8% completion rates of adjuvant chemotherapy, respectively. The result was higher in the laparoscopic group, but this results had no statistical significance ($P = 0.121$). The completion rate of

adjuvant chemotherapy was, with statistical significance, related to the group with the shorter hospital stay after surgery ($P = 0.020$) and to the group with an earlier initiation of adjuvant chemotherapy ($P = 0.029$). Because the laparoscopic surgery group has the advantages of shorter hospital stay and earlier initiation of adjuvant chemotherapy, the choice of laparoscopic surgery is thought to have an indirect effect on the completion of adjuvant chemotherapy, but further studies with more patients are required.

In this study, factors, including BMI and ASA score, had an influence on the completion of adjuvant chemotherapy. Frank et al. [14], reported that BMI affected the survival rate of patients. They investigated patients who received 5-FU-based adjuvant chemotherapy and found that the mortality was higher in obese and underweight patients than it was in patients of normal weight group and that the disease-free survival was shorter in the underweight group.

This study found the completion rate of adjuvant chemotherapy to be 57.1% (12/21) for patients who were underweight, which was lower than the 77.2% (95/123) for patients of normal weight or patients who were overweight ($P = 0.051$). However, our sample size was very small; thus, further studies should include more patients in order to give statistical significance to this result.

Previous studies reported that the completion rate of adjuvant chemotherapy was lower in older patients [12, 13]. In this study, the patients whose ages were less than 70 years showed a higher completion rate than the patients whose ages were over 70. Especially, in the open surgery group, the completion rate of adjuvant chemotherapy was significantly different, depending on age ($P = 0.002$). On the other hand, no difference in the completion rates was found in the laparoscopic group. Therefore, we can conclude that laparoscopic surgery leads to an improvement in the completion rate of adjuvant chemotherapy, even in elderly patients.

In this study, the ASA score was also, with statistical significance, related to the completion rate of adjuvant chemotherapy. In the laparoscopic group, the completion rate of adjuvant chemotherapy was higher in patients with ASA scores of 1 or 2 than it was in patients with ASA scores of 3 or 4; however, no such difference was observed in the open surgery group. These results show that the preoperative physical status of patients is associated with the completion rate of adjuvant chemotherapy and, especially in the laparoscopic group, underlying diseases and low physical activity levels are thought to be factors that may decrease the completion rate.

Sharon et al. [10], studied the completion rate of adjuvant chemotherapy in 3,193 patients with stage III colon cancer. They reported no statistically significant difference based on gender, even though it was higher for male patients, which is consistent with the observation in this study. In our case, statistical significance may not have been proven due to the small sample size. Cathy et al. [17], reported that patients who were supported by the medical aid program usually started their adjuvant chemotherapy late, and its completion rate was low. However, in this study, no statistically significant difference was noted between patients covered by Ko-

rea's National Health Insurance and patients covered by the medical aid program. These differences in results are thought to be due to differences in the medical insurance systems between Korea and the USA.

According to many previous studies, no statistically significant differences in the overall survival rate of patients with colorectal cancer between laparoscopic and open surgery groups were found [18, 19]. However, in this study, the laparoscopic group showed a 96.7% (88 of 91) survival rate compared to 85.7% (48 of 56) in the open surgery group ($P = 0.007$). However, many patients with a high ASA score were included in the open surgery group, and accompanying diseases were not analyzed in this study. In addition, the follow-up term was short. Therefore, a long-term follow-up and survival analysis are required to give statistical significance to this result.

In conclusion, the completion rate of adjuvant chemotherapy was lower in patients with a low ASA score in this study. Also, the hospital stay was shorter and adjuvant chemotherapy started earlier in the patients who underwent laparoscopic surgery than in the patients who underwent open surgery for colon cancer. We conclude that laparoscopic surgery contributes to improved compliance with adjuvant chemotherapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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