보건학석사 학위논문

The prognosis and outcome of resection surgery of colorectal cancer patients with liver cirrhosis

- Based on nationwide cohort in Korea -

간경변 동반 여부에 따른 대장암 환자의 장 절제수술 예후 및 결과 비교

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2019년 2월

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신 나 리

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지도교수 원 성 호

이 논문을 보건학 석사 학위논문으로 제출함

2018 년 12 월

서울대학교 대학원

보건학과 보건학전공

신나리

신나리의 석사학위논문을 인준함

2018 년 12 월

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Abstract

The prognosis and outcome of resection surgery of colorectal cancer patients with liver cirrhosis

- Based on nationwide cohort in Korea -

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Background: The risk of surgery for colorectal cancer in liver cirrhosis patients has been partially evaluated by previous studies. When resection surgery is performed on patients with cirrhosis, the risk of both surgery and anesthesia increases. The risk of colorectal cancer surgery is higher in patients with cirrhosis than in general patients, because of the deterioration of liver function, blood clotting disorder, susceptibility to

infection, and impaired blood circulation. In particular, among various operations that were performed for patients with cirrhosis, the operation performed on colon has been evaluated as a high-risk operation. Therefore, surgical treatment of patients with cirrhosis should be considered when there is no improvement in further conservative treatment. The expectancy life of liver cirrhosis patient is gradually increasing due to medical level development and liver transplantation. This trend has also increased the risk of exposure to diseases in which patients with cirrhosis need surgery. One of them is colon cancer. However, there are insufficient studies to compare the prognosis and outcome of resection surgery in colorectal cancer patients with cirrhosis. In addition, there is a limitation that the results of previous studies are difficult to generalize because of the small number of subjects.

Purpose: In Korea, the National Health Insurance Service (NHIS) provides health insurance claim data for the period from 2002 to 2017. In particular, customized data for researchers of the NHIS provides medical service usage details for 96% of the national population covered by health insurance. The purpose of this study was to investigate the effect of liver cirrhosis on resection surgery using data of the NHIS, compare and evaluate the complications and burdens of patients with liver cirrhosis after colorectal cancer surgery.

Method: This study performed the survival analysis. Before the survival analysis, age - sex was exactly matched for the liver cirrhosis and non-liver cirrhosis groups and the ratio of the two groups was 1: 5. Survival analysis in this study was conducted using an extended Cox model. The covariates included socioeconomic level, location of

colorectal cancer, stage of colorectal cancer, operation method, CCI and the year of surgery. Also, Kaplan - Meier curves were drawn for each variable.

Results: The postoperative survival rate was lower in the patients with liver cirrhosis. During the 5-year follow-up period, 39% of the cirrhotic patients died and 24% of the non-cirrhotic patients died. The HR of the Cox model was 1.98 times higher in the cirrhosis group (95% C.l: 1.66 - 2.37). This was statistically significant with $p < 0.001$. Also, the incidence of postoperative complications were compared, showing a 2-fold increase in incisional hernia in patients with liver cirrhosis. Finally, hospitalization period for surgery was longer than about 60 days in the cirrhosis group.

Conclusion: The liver cirrhosis had a negative effect on resection surgery for colorectal cancer. Postoperative complications were also more frequent and the socioeconomic burden of surgery was higher in patients with liver cirrhosis.

Keywords: Liver cirrhosis, colorectal cancer, resection surgery, survival analysis, Extended Cox hazard model, Kaplan-Meier curve

***Student Number* : 2017-26410**

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Ⅰ. Introduction

1. Background & necessity

Liver cirrhosis (LC) is a disease in which liver inflammation causes liver fibrosis and liver function is impaired. This disease accompanies various complications such as ascites, coagulopathy, renal failure, brain dysfunction and liver cancer. LC is a disease that is difficult to cure completely[1-3]. However, the life expectancy of patients with LC is increasing due to liver transplant and improved quality of medical care[4].

The problem is that the longer the life expectancy of patients with LC is, the more likely it is that the risk of exposure to a disease that requires surgical treatment has increased naturally[5]. However, patients with LC have a higher risk of surgery and anesthesia [5, 6]. In a previous study, the overall survival for patients with LC after resection surgery is lower than patients without LC (Overall survival 46.7% Vs.76.2%)[2]. This is because the lowering of the liver function causes the coagulopathy, decreases the immune system, increases the infection, decreases the flow of blood flow and increases the stress hormone. Therefore, performing surgery on patients with LC should be considered when the conservative care is no longer meaningful.

Of the various abdominal operations performed on patients with LC, the operations performed on the colon are assessed as a high-risk surgery[7]. There are many

diseases associated with colon-related surgery, but colorectal cancer (CRC) is a disease that necessarily requires surgical treatment. In addition, because the metastatic distance of CRC is the closest to the liver and patients with LC has a higher rate of liver metastasis (HR 95% C.I : 1.04~ 1.28) than the general patients[8], so if LC patients are diagnosed with CRC , surgical treatment and ongoing care are needed. However, in a Denmark cohort study, patients with LC were more likely to have colon cancer than general patients[9]

In Korea, the prevalence of chronic hepatitis and LC is 0.17 per 100,000 population. The prevalence of physician-diagnosed chronic hepatitis and cirrhosis is estimated to be 0.0639 per 100,000 population. Since chronic hepatitis patients develop into LC, the proportion of patients with chronic liver disease in Korea is expected to range from 0.17 to 0.0639 per 100,000. Chronic liver disease including LC is also one of the leading causes of death in Korea[3]. The incidence of CRC in Korea in 2015 is 31.9 per 100,000, and the prevalence is 215 per 100,000[10]. The incidence and prevalence of CRC in Korea is higher than other cancer types.

Because the prevalence of LC in Korea is not small and the prevalence and incidence of CRC are high, it is necessary to investigate the proportion of patients with LC among CRC patients in Korea.. The previous studies represents consistently that survival after colorectal surgery is risky to patients with LC[2, 5], so the postoperative outcome and burden of CRC patients with LC need to be evaluated and investigated in the Korean cohort. In addition, there were few studies which have compared the results

of colorectal surgery according to the presence of LC and the sample of CRC patients with LC was so small and limited[1, 2].

In order to overcome the limitations of previous studies and obtain a sufficient number of CRC patients with LC in Korea, I used the customized data for researchers from Korea National Health Insurance Service (NHIS). About 96% of the total population of Korea joined NHIS, and NHIS provides health insurance claims data between 2002-2017 for research purposes. The customized data for researchers provides health insurance claims data for the population covered by the health insurance and includes information on the entire medical history such as the diagnosed disease, treatment history, health screening, prescription preparation and qualifications.

2. Objectives

The purpose of this study is largely divided into two. The first is to maximize the number of patients with LC among the patients undergoing CRC surgery by using the NHIS DB as the data. The second is to identify the proportion of LC patients undergoing CRC surgery and then evaluate the postoperative outcome of LC patients and generalize the results.

The detail purposes of this study are as follows:

1. To compare 5-year overall survival (OS) after surgery between LC and general (without liver cirrhosis, Non-LC) groups.

2. To assess the burden of CRC surgery with various complications rates:

   Length of stay, medical costs, incidence of incisional hernia and intestinal obstruction, entry of intensive care unit after surgery.

Ⅱ. Materials and Methods

1. Ethics statement

The protocol of this study was approved by the IRB(Institutional Review Board) of Seoul National University and was conducted according to the research ethics(IRB No. E1811/001-011). Also, NHIS (National Health Insurance Service) researchers customized data used in this study was formally provided after get the approve from NHIS research committee (NHIS-2018-1-425).

2. Source of Data

In Korea, NHIS operates the National Health Insurance Sharing Service (NHISS) to support policy and academic research using national health information materials in Korea. NHISS provides details of the use of medical services of people who are covered by the NHIS. In Korea, the health insurance system is operated in such a way that, when the health insurance subscribers use the medical service, the medical institution receives the medical expenses from the NHIS after receiving the examination by the Health Insurance Review & Assesment Service(HIRA). In this process, NHIS was naturally able to accumulate big data on Korea's medical service information, and opened NHISS in 2014, providing health insurance data for 2002-2017 to researchers.

The national health insurance coverage rate is about 96% of the total population,

and 50,763,000 people are registered in 2016. NHISS provides materials to researchers who have passed their own deliberations on NHISS, based on studies approved by IRB. The NHISS provides a wide range of materials ranging from examinees' medical history and health checkups to sample cohort database data. Also, it provides data on NHISS health insurance data in conjunction with government agencies such as the National Statistical Office.

3. Study population

This study is a nationwide cohort study in Korea. When I consider the pre-measurement (2 years) and follow-up (5 years) periods, the total data collection period for this study is from January 2006 to December 2017. The purpose of this study is to investigate the prognosis after CRC surgery according to the presence of LC before surgery. Therefore, I first identified patients undergoing CRC surgery. In order to obtain high quality data at the same time as a sufficient number of samples, patients who were diagnosed with CRC between 2008 and 2013 were selected. NHIS data prior to 2007 was not managed well and the data was not reliable, so we chose 2008 to 2013 as Index date.

I then screened patients who underwent resection surgery among those diagnosed with CRC. From January 2008 to December 2013, there were 105,754 patients who underwent CRC and resection surgery for a total of 6 years. Diagnosis of

CRC was confirmed by KCD codes The KCD codes used to identify CRC diagnosis are shown in Table1. The operation of CRC was confirmed by the operation code of Table 2.

Next, in this study, if the history of any cancer exists within the past 1~2 years from surgery date, then the patients were excluded from this study. Additionally other cancer was diagnosed except CRC within past one year from the date of surgery, the patient was excluded. Plus, patients were excluded if (i) they were unable to identify BFC DB(BFC DB providing basic demographic characteristics)(N=1,206), (ii) where the location of CRC was unclear, and(N=6,826) (iii) if there was a CRC in the child(Age <19) (N=22).

For all 58,538 available patients, the history of LC was identified within 2 years from surgery date. LC was confirmed using KCD codes (Table 3). The extraction process is representing for this study subjects in figure 1 and figure 2.

Of the total 58,538 patients, 453 were diagnosed with LC within past 2 years from the operation date and 58,085 patients not diagnosed. In order to compare two groups accurately: LC and Non-LC, the exact matching of sex-age was performed with the ratio of 1: 5 for LC and Non-LC Of the subjects that matched age and sex exactly, they were randomly matched without replacement with a 1: 5 ratio.

Table 1. List of KCD code of colorectal cancer (CRC)

KCD code	Disease
C180	Malignant neoplasm of caecum
C181	Malignant neoplasm of appendix
C182	Malignant neoplasm of ascending colon
C183	Malignant neoplasm of hepatic flexure
C184	Malignant neoplasm of transverse colon
C185	Malignant neoplasm of splenic flexure
C186	Malignant neoplasm of descending colon
C187	Malignant neoplasm of sigmoid colon
C188	Malignant neoplasm of overlapping lesion of colon
C189	Malignant neoplasm of colon unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum

Table 2. List of operational code of colorectal cancer (CRC)

Operational of code (Resection surgery)	Type of operation
QA671	Right or Left Hemicolectomy
QA673	Colectomy-Segmental Resection
QA921	Rectal And Sigmoid Resection-Anterior Resection
Q2671	Right or Left Hemicolectomy
Q2673	Colectomy-Segmental Resection
Q2921	Rectal And Sigmoid Resection-Anterior Resection
Q1261	Subtotal colectomy
Q1262	Subtotal colectomy
QA672	Total colectomy
Q2672	Total colectomy
QA922	Low anterior resection
QA923	Low anterior resection
QA925	Total colectomy with ileostomy
Q2925	Total colectomy with ileostomy

Table 3. List of KCD code of Liver Cirrhosis (LC)

KCD code	Disease
K702	Alcoholic fibrosis and sclerosis of liver
K7030	Alcoholic cirrhosis of liver, without ascites
K7031	Alcoholic cirrhosis of liver, with ascites
K704	Alcoholic hepatic failure
K74	Hepatic fibrosis
K766	Portal hypertension

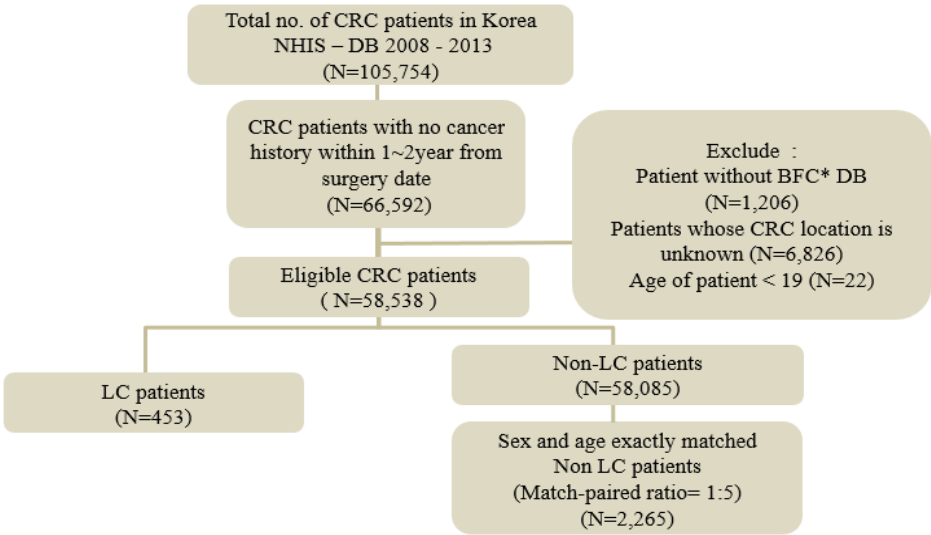

Figure 1. .Study design flowchart.

***BFC DB:** DB containing personal information such as the age, sex, and premium level.

Abbreviations: CRC, Colorectal cancer; LC, Liver cirrhosis

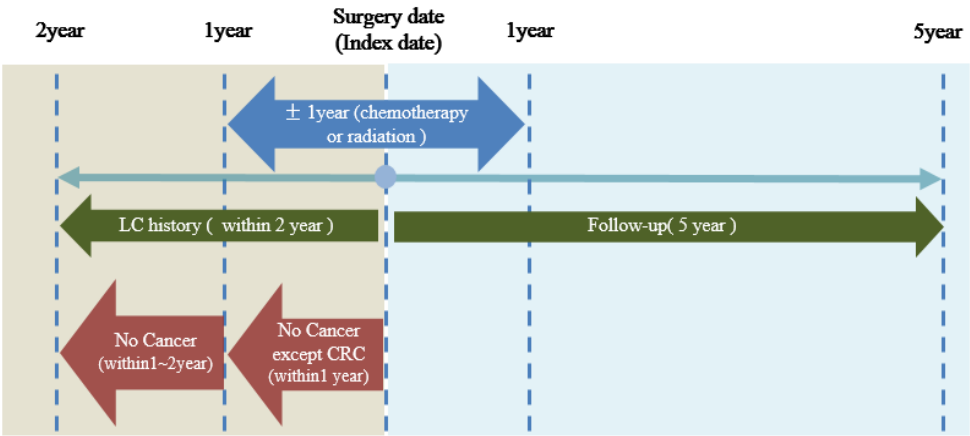

Figure 2. Process for study design and definition of study population.

Notes: In this study, the past two years are set in the pre-measurement period from the surgery date. During the pre-measurement period, patients are examined for history of LC and other cancers. One year before and after surgery, chemotherapy and radiation for CRC were investigated, and patients were followed up for 5 years.

Abbreviations: CRC, Colorectal cancer; LC, Liver cirrhosis

4. Variable definition

In patients with LC, liver function after surgery for CRC may worsen. It determines the prognosis of the operation and affects the survival[5]. Therefore, this study defined the outcome variable as the time to death after surgery. Before conducting the analysis, I defined the covariates that could affect the outcome variable,

time to death.

✓ History of Liver cirrhosis

This is a major group variable of interest in this study. LC group was classified if the diagnosis of LC was made within past 2 years from the date of surgery. Otherwise, the remaining patients were classified as Non-LC group.

✓ Basic demographic characteristics

Age, sex, and the socioeconomic status were considered as variables indicating the basic demographic characteristics of the patient. Level of Insurance premium of NHIS was used as the socioeconomic variables of the patients. It ranges from 0 to 20. The lower the level, the more socioeconomic weakness. Variables representing demographic characteristics are considered together in the analysis because they can act as confounders.

✓ Location of CRC

CRC has a different survival rate depending on the cancer location. The location of CRC can be largely divided into left and right. CRC patients on the left side are known to live longer than CRC patients on the right side. The 5-year survival rates of left and right colon cancer are known as 78.6% and 65.6%, respectively, which differ by more than 10%. This was found to be statistically

significant, and the position of the cancer was used as a covariate in this study[11]. Right CRC refers to cancers that are located in the caecum, appendix, ascending colon, hepatic flexure and transverse colon. Left CRC means splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum cancer.

C185, C186, C187, C19, and C20 codes were classified as left CRC, and C180, C181, C182, C183, and C184 were classified as right CRC.

✓ The stage of CRC

As with all types of cancer, the stage of cancer has a significant impact on survival. The stage of CRC can be classified into four groups from 0 to 4. Stage 0 means polyps in the colon or rectum, and is likely to develop into a tumor later. Stage 1 is a malignant tumor in the inner lining of the colon. From that point on, surgery called resection is needed. With further development in stage 1, the tumor is metastasized to the lymph nodes of the colon, and finally to the other organs of the body (stage 4).

Thus, the cancer stage plays an important role in cancer research. Because the NHIS claim data cannot confirm the exact stage of CRC, this study defined the stage of cancer based on whether chemotherapy or radiation occurred. If the counseling code for chemotherapy or radiation (Supplementary table 1.) is identified in the code of medical behavior for one year before and after the surgery date, it is classified as advanced stage.

✓ Method of operation

There are two methods of CRC surgery: Laparoscopic resection and open resection. This study classified the operation method of CRC as laparoscopic and open and used it as a covariate.

I have defined laparoscopic if the material code for laparoscopic surgery (Supplementary table 2.) occurs in the claim data. If laparoscopic treatment code occurs and more than two different types of resection surgery are performed, on the same day, I defined the operation method was switched from laparoscopic to open and then the case was considered as open surgery.

✓ Year of surgery

This study is a nationwide cohort study and the index date of the study is from 2008 to 2013. In order to adjust the year effect of the cohort, the surgical year was considered as a covariate.

✓ Charlson Comorbidity Index (CCI)

CCI was included as a covariate in order to consider the effect of other diseases except LC on survival. However, in this study, CCI was calculated after excluding the items for LC and cancer in the original CCI disease items, because the purpose of the study is to understand the effect of LC and all of the patients in this study

were diagnosed with cancer.

CCI can be calculated using KCD (Korean Standard Classification of Diseases). I calculated the CCI using the CCI calculation algorithm presented in the manual of the claim data analysis presented to the researcher in HIRA (HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE)[12, 13].

5.Statistical method

The analysis of this study was performed using statistical software R version 3.5. To determine the effect of LC on CRC surgery, this study considers the extended cox model for survival analysis. It has been confirmed that some variables do not satisfy the proportional hazard (PH) assumption and depend on time. The variables that did not satisfy the PH assumption were the stage of cancer and the cancer location. Therefore, extended cox model with the heaviside function(Expression 1.) was used for survival analysis. Heaviside function was constructed with a median value of survival time (=794) which is calculated excluding censored samples. The heaviside function is given as 1 if the survival time is above median 794, as an index variable representing 0 otherwise: I(794≤ t).

$$I(t) = \begin{cases} 1, & \text{median} \leq t \\ 0, & \text{median} > t \end{cases} \quad , \text{median} = 794, \text{t=time}$$

Expression 1. Heaviside function using median

This study considered the stage, location of CRC, year of surgery, socioeconomic status, CCI, and operative method as covariates that may affect the outcome of the surgery. Also, the interaction term of stage and operation method was considered. Sex and age were not considered as covariates because they were exact matching in both groups: LC and Non-LC.

✓ Extended Cox model in this study:

$$\begin{aligned} \mathrm{h}(t, X) = h_0(t) \exp\{ & \beta_1(History\ of\ liver\ cirrhosis) + \beta_2(Method\ of\ operation) \\ & + \beta_3(Stage\ of\ CRC) + \beta_4(Location\ of\ CRC) + \beta_5(CCI) \\ & + \beta_6(Socioeconomic\ Status) + \beta_7(Year\ of\ Surgery) \\ & + \beta_8(Stage\ of\ cancer * Method\ of\ operation) + \gamma_1(HV_1) \\ & + \gamma_2(HV_2) + \gamma_3(HV_3) \} \end{aligned}$$

Expression 2. Extended Cox model of this study.

$(Stage\ of\ CRC$

$* Method\ of\ operation)$: $the\ interaciton\ term\ of\ Stage\ of\ CRC\ and\ Method\ of\ operation.$

$HV_1 = Stage\ of\ CRC * \mathrm{I}(794 \leq \mathrm{t})$,

$HV_2 = Method\ of\ operation * \mathrm{I}(794 \leq \mathrm{t})$,

$HV_3 = Stage\ of\ cancer * Method\ of\ operation * \mathrm{I}(794 \leq \mathrm{t})$,

$\mathrm{I}(794 \leq \mathrm{t})$: $heaviside\ function$

The data on sex - age matched was used to draw the K-M curve for each variable in order to identify the effect of variable for the survival time after surgery.

Finally, t- tests was performed to compare complications rates between the LC group and the Non-LC group.

Ⅲ. Result

1. Characteristics of study population

The characteristics of the subjects of this study were divided into LC group and Non-LC group and summarized in Table 4 and 5. Table 4 shows the distribution of the characteristics of total 58,538 subjects before age and sex matched.

For the categorical variables, the frequencies are summarized and the mean and standard errors for the continuous variables are summarized. The proportion of males was higher than that of females, and age, socioeconomic status and CCI were similar. There were no significant differences between the two groups in the characteristics related with CRC. The proportion of left-sided CRC was higher, non-advanced stage was slightly higher, and the proportion of operation method was almost similar between laparoscopy and open.

Table 5 summarizes the characteristics of 2,265 CRC patients obtained after age and sex exactly matched. Because age and sex are matched, the average of age is the same in the two groups and the frequencies of sex is the same and standardized difference of age and sex between LC and Non-LC group is zero after matching. The distribution of other characteristics, except for stage of CRC, is not different from that before matching.

Table 4. Characteristics of CRC patients with LC and Non-LC before matching

Variables	Non-LC(N=58,085)	LC(N=453)
Sex		
Male	35633(0.613)	350(0.773)
Female	22452(0.387)	103(0.227)
Location of CRC		
Right	13294(0.229)	130(0.287)
Left	44791(0.771)	323(0.713)
Stage of CRC		
Non-Advanced	29367(0.506)	286(0.631)
Advanced	28718(0.494)	167(0.369)
Method of operation		
Laparoscopic	34776(0.599)	237(0.523)
Open	23309(0.401)	216(0.477)
Year of surgery		
2008	8180(0.141)	80(0.177)
2009	8911(0.153)	64(0.141)
2010	9065(0.156)	74(0.163)
2011	10458(0.18)	80(0.177)
2012	10846(0.187)	87(0.192)
2013	10625(0.183)	68(0.15)

Age	63.914 ±0.048	63.199 ±0.444
Socioeconomic status	11.546 ±0.026	10.095± 0.316
CCI	0.681±0.004	0.828 ±0.048

Notes: mean (± Standard error**) for Age,** Socioeconomic status and CCI

Abbreviations: CRC, Colorectal cancer; LC, Liver cirrhosis; CCI: charlson comorbidity index

Table 5. Characteristics of CRC patients with LC and Non-LC after matching

Variables	Non-LC(N=2,265)	LC(N=453)
Sex		
Male	1750(0.773)	350(0.773)
Female	515(0.227)	103(0.227)
Location of CRC		
Right	449(0.198)	130(0.287)
Left	1816(0.802)	323(0.713)
Stage of CRC		
Non-Advanced	1093(0.483)	286(0.631)
Advanced	1172(0.517)	167(0.369)
Method of operation		
Laparoscopic	1369(0.604)	237(0.523)
Open	896(0.396)	216(0.477)
Year of surgery		
2008	296(0.131)	80(0.177)
2009	361(0.159)	64(0.141)
2010	345(0.152)	74(0.163)
2011	427(0.189)	80(0.177)
2012	444(0.196)	87(0.192)
2013	392(0.173)	68(0.15)

Age	63.199±0.199	63.199 ±0.444
Socioeconomic status	11.638±0.132	10.095± 0.316
CCI	0.645±0.020	0.828 ±0.048

Notes: mean (± Standard error**) for Age,** Socioeconomic status and CCI

Abbreviations: CRC, Colorectal cancer; LC, Liver cirrhosis; CCI: charlson comorbidity index

2. K-M curve

With age and sex matched data, K-M curves were drawn by the covariates investigated in this study (Figure3). The K-M curve according to the history of LC, which is a variable of interest, shows that the survival function of the LC group is lower than that of the non-LC group. In the K-M curve according to the location of the cancer, the survival rate was significantly lower on the Right side. When the cancer stage was advanced, the survival rate was higher at the beginning than the Non-advanced group, but the survival rate was lower over time. The survival of laparotomy group was higher during the follow-up period of the study than open group, and the gaps in survival rates between the two groups gradually increased over time.

The continuous variables age, CCI, and socioeconomic status are divided into several groups, in order to draw K-M curve(Figure 3.). First, Age was divided into four groups. Age ranged from 40 to 90 years, so it was divided into age ≤55 , 55< age ≤70 , 70< age≤85, and 85<age. The older the group, the survival was lower. Second, CCI was classified into two group ; CCI≤3 and 3<CCI. The survival rate of the group with CCI of 3 or less was higher than that of the group with 3 <CCI Last, the socioeconomic status was divided into 3 groups: socioeconomic status (SC) ≤6, 6 < SC ≤14 and 14< SC considering the range of the socioeconomic status from 0 to 20. The K-M curve shows that the poorer the patient, the lower the survival rate.

Finally, there was no difference in survival rates for sex and year of surgery respectively.

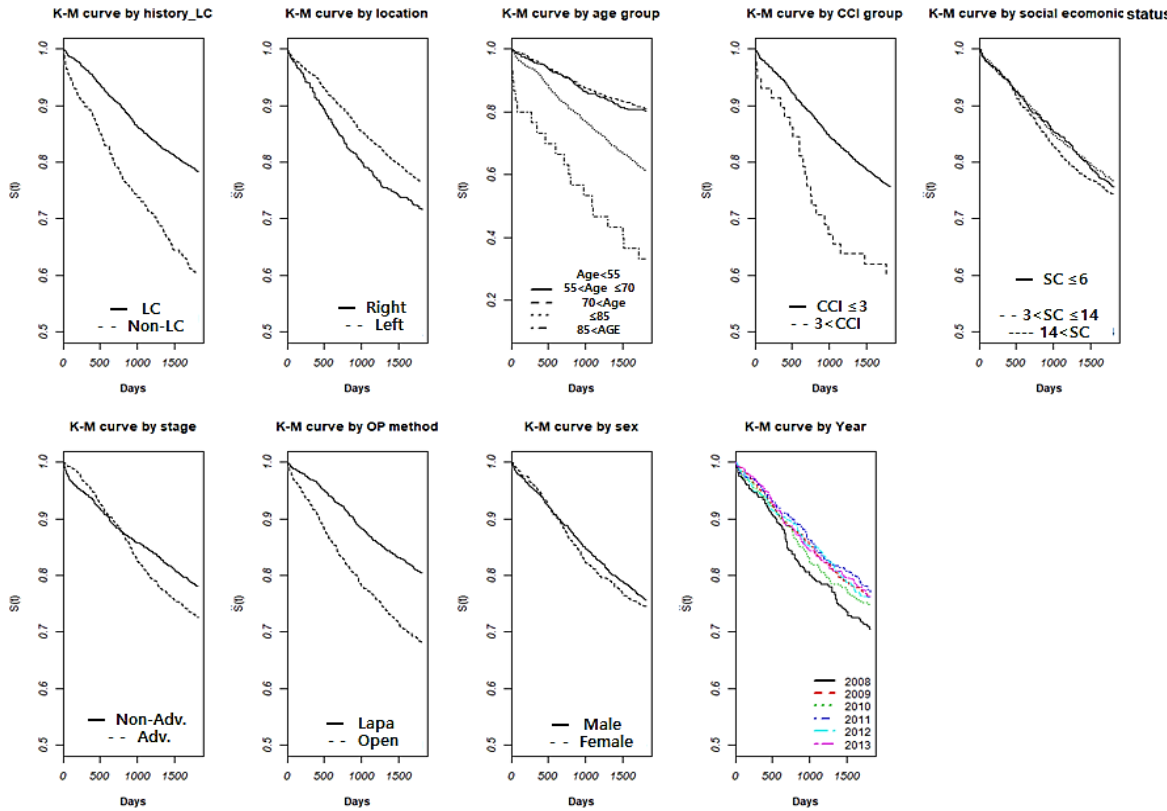

Figure 3. Kaplan-Meier Curve

Abbreviations: s(t), survival time; CRC, Colorectal cancer; LC, Liver cirrhosis; CCI, charlson comorbidity index, SC, socioeconomic status; OP, operation; Lapa, Laparoscopy; Adv., Advanced

3. Risk of LC for resection surgery

To evaluate the risk of LC for resection surgery, first, the mortality rate according to survival time point (30, 60, 90,180 days and 1, 3, 5 year) was compared between 2 group; LC and Non-LC. Before age and sex matched, mortality rates of LC group within 180 days after surgery were 3times than Non-LC group (Table 6). In particular, within 30 days after surgery, the mortality rate was 2.4% for the LC group and 0.6% for the Non-LC group. During the follow-up period of 5 years, the mortality rate of LC group was higher than that of Non-LC group.

After matching age and sex (Table 7.), mortality rates were calculated in a similar pattern compared with data before matching.

Table 6.Comparison of mortality rates by survival time before matching.

Time point	Group	
Days*	Non LC(N=58,085)	LC(N=453)
Days < 30	354(0.006)	11(0.024)
Days <60	714(0.012)	18(0.04)
Days <90	970(0.017)	21(0.046)
Days <180	1651(0.028)	33(0.073)
Days <1year	3322(0.057)	48(0.106)
Days <3year	9811(0.169)	124(0.274)
Days <5year	14055(0.242)	179(0.395)

***Days :** Days counted from surgery date . , **Abbreviations:** LC, Liver cirrhosis

Table 7.Comparison of mortality rates by survival time after matching

Time point	Group	
Days*	Non LC(N=2,265)	LC(N=453)
Days < 30	7(0.003)	11(0.024)
Days <60	20(0.009)	18(0.04)
Days <90	31(0.014)	21(0.046)
Days <180	46(0.02)	33(0.073)
Days <1year	96(0.042)	48(0.106)
Days <3year	335(0.148)	124(0.274)
Days <5year	490(0.216)	179(0.395)

***Days :** Days counted from surgery date . , **Abbreviations:** LC, Liver cirrhosis

Next, this study compared the hazard ratio(HR) between the LC and Non- LC groups after adjusting the covariates that may affect survival after surgery. Using the extended cox regression model, the 1.98-fold HR was higher in the LC group compared to the Non-LC group. This is statistically the significant result (P-value <0.001). That is, when the other conditions are the same, it means that the postoperative OS is from 1.666 to 2.37 times higher in the LC group than in the Non-LC group (HR 95% C.I : 1.666 ~ 2.37).

The HRs of the covariates used in this model found to be relatively high when the operation method was open, when the stage of CRC was advanced, when the location of CRC was right , and when CCI was high if the other covariates are fixed. This result is consistent with the results of previous studies.

In the HRs compared using the extended cox model, the variables that had the greatest influence on the postoperative survival rate were operation method and history of LC

Table 8.Hazard ratio of 5 year Overall Survival (OS)

Variable	Hazard Ratio (95% C.I)	P-value
History of LC(LC)	1.987(1.666 - 2.37)	<0.001***
Method of operation(Open)	2.171(1.593 - 2.959)	<0.001***
Stage of CRC (Advanced)	1.118(0.8 - 1.563)	0.514
Location of CRC(Left)	0.846(0.708 - 1.011)	0.07
CCI	1.111(1.031 - 1.197)	0.008
Socioeconomic status	1.004(0.992 - 1.016)	0.446
Year of surgery (2009)	0.861(0.657 - 1.128)	0.282
Year of surgery (2010)	0.938(0.717 - 1.227)	0.643
Year of surgery (2011)	0.85(0.655 - 1.103)	0.227
Year of surgery (2012)	0.915(0.708 - 1.183)	0.498
Year of surgery (2013)	0.947(0.724 - 1.239)	0.695
Stage of CRC *I(794≤ t)	1.957(1.244 - 3.078)	0.004
Method of operation *I(794≤ t)	0.857(0.543 - 1.353)	0.507
Stage of CRC * Method of operation *I(794≤ t)	0.632(0.34 - 1.174)	0.145
Stage of CRC * Method of operation	0.94(0.607 - 1.455)	0.781

Notes :

CCI and Socioeconomic status ; continuous variables

Level of LC; LC and Non-LC; Level of Method of operation, Open and Laparoscopic; Level of Stage of CRC , Advanced and Non- Advanced; Level of Location of CRC, Left and Right ; Level of Location of Year of Surgery= (2008,2009,2010,2011,2012,2013), I(797≤ t); Heaviside function

Abbreviations: CRC, Colorectal cancer; LC, Liver cirrhosis; CCI: charlson comorbidity index

4. Comparison of complication rate

To assess post-operative burden in LC and non-LC groups, the incidence of complications after resection surgery was compared. Also, by comparing the hospitalization period, medical service total cost and intensive care unit entry after surgery within hospitalization period, socioeconomic burden was also evaluated.

Complications that frequently occur in CRC patients after surgery include incisional hernias and post-operative ileus. When the KCD codes presented in tables 9 and 10 were diagnosed and the surgery associated with incisional hernias and post-operative ileus, I count the case of complication. These two complications can be divided into early complications and late complications. Therefore, the complication rates were compared between LC and non-LC by dividing into 30 days, 1 year, 2 year and the entire follow-up period of 5 years.

Table 11 and Table 12 distinguish incisional hernia and obstruction in the LC and non-LC groups, respectively, before and after the matching. First, the complication rates for incisional hernia were compared. Incisional hernia was found to occur more frequently in the LC group, regardless of matching. The total incidence rate of incisional hernia in the matching data was 3.5% for the LC group and 1.7% for the non-LC group (Table 12.)

But, post-operative ileus was observed almost similarly between 2 groups.

Table 9.KCD code and operation code for incisional hernia

KCD code for incisional hernia	Disease
K430	Incisional hernia with obstruction, without gangrene
K431	Incisional hernia with gangrene
K432	Incisional hernia without obstruction or gangrene
K436	Other and unspecified ventral hernia with obstruction, without gangrene
K437	Other and unspecified ventral hernia with gangrene
K439	Ventral hernia
Operational code for incisional hernia	**Operational code for incisional hernia**
Q2731	Operation of Incisional Hernia-With Resection of Intestine
Q2732	Operation of Incisional Hernia-Others

Table 10.KCD code and operation code for ileus

KCD code for ileus	Disease
K91.3	Postoperative intestinal obstruction
Operational code for ileus	Operational code for ileus
Q2621	Nasogastric Tube Insertion
Q2622	Nasoenteral Tube Insertion
Q2691	Operation for Intestinal Obstruction-Including Resection of Intestine
Q2692	Operation for Intestinal Obstruction-Entero-Enterostomy
Q2693	Operation for Intestinal Obstruction-Adhesiolysis

Table 11.Complication rate of incisional hernia & ileus before matching

Incisional hernia after colon surgery	Non-LC	LC
Days* ≤30	330(0.006)	8(0.018)
30< Days ≤1year	128(0.002)	4(0.009)
1year < Days ≤2year	143(0.002)	1(0.002)
2year < Days ≤5year	263(0.005)	3(0.007)
Total	864(0.015)	16(0.035)
Ileus after colon surgery	**Non-LC**	**LC**
Days ≤30	639(0.011)	4(0.009)
30< Days ≤1year	281(0.005)	1(0.002)
1year < Days ≤2year	278(0.005)	2(0.004)
2year < Days ≤5year	442(0.008)	2(0.004)
Total	1640(0.028)	8(0.02)

***Days :** Days counted from surgery date . , **Abbreviations:** LC, Liver cirrhosis

Table 12.Complication rate of incisional hernia & ileus after matching

Incisional hernia after colon surgery	Non-LC	LC
Days*≤30	16(0.007)	8(0.018)
30< Day ≤1year	2(0.001)	4(0.009)
1year < Day ≤2year	6(0.003)	1(0.002)
2year < Day ≤5year	15(0.007)	3(0.007)
Total	39(0.017)	16(0.035)
Ileus after colon surgery	**Non-LC**	**LC**
Day ≤30	21(0.009)	4(0.009)
30< Day ≤1year	12(0.005)	1(0.002)
1year < Day ≤2year	13(0.006)	2(0.004)
2year < Day ≤5year	22(0.01)	2(0.004)
Total	38(0.03)	8(0.02)

***Days :** Days counted from surgery date . , **Abbreviations:** LC, Liver cirrhosis

Table 13.Cost and Length of stay before matching

Cost*	Mean	Std.error	Min	Max	P value (t-test)
Total	₩ 8,589,983	26760.14	₩1,443,910	₩253,607,260	<0.0001
LC	₩ 10,578,226	40659	₩2,568,080	₩99,793,360	
Non-LC	₩ 8,574,477	26772.19	₩1,443,910	₩253,607,260	

Length of stay*	Mean	Std.error	Min	Max	P value (t-test)
Total	123.73	0.919142	2	3052	<0.0001
LC	172.075	13.08719	3	2239	
Non-LC	113.275	0.920433	2	3052	

***Cost :** total cost of medical service , ***Length of stay** : the hospitalization period for surgery,

Std.error= Standard error., **Abbreviations:** LC, Liver cirrhosis

Table 14.Cost and Length of stay after matching

Cost*	Mean	Std.error	Min	Max	P value (t-test)
Total	₩8,817,450	26960.29	₩2,010,550	₩175,088,790	<0.0001
LC	₩10,578,226	406591.3	₩2,568,080	₩99,793,360	
Non-LC	₩8,559,001	28401.46	₩2,010,550	₩175,088,790	

Length of stay*	Mean	Std.error	Min	Max	P value (t-test)
Total	123.492	1.024575	3	2982	<0.0001
LC	172.0751	13.08719	3	2239	
Non-LC	113.775	0.996584	4	2982	

***Cost :** total cost of medical service , ***Length of stay** : the hospitalization period for surgery,

Std.error= Standard error., **Abbreviations:** LC, Liver cirrhosis

Table 15. Intensive care unit entry after surgery before and After Matching

Before Matching		
Intensive care unit entry*	LC	Non-LC
Y	136(0.3)	9817(0.169)
N	317(0.7)	48268(0.831)
After Matching		
Intensive care unit entry*	LC	Non-LC
Y	136(0.3)	339(0.151)
N	317(0.7)	1907(0.849)

*Intensive care unit entry: intensive care unit entry after surgery within hospitalization period, **Abbreviations:** LC, Liver cirrhosis

T-test was performed to compare the cost and length of stay .mean, standard error, and range of hospital stay and cost for CRC surgery are presented in Tables 13 and 14. The average length of stay for the LC group is 172 days, which is longer than about 60 days, compared to 113 for the non-LC group in Table 13 using before matching data. Plus, there was a significant difference in average hospitalization costs. Comparisons between the two groups were performed using both data before and after matching, and the t-test result was significantly lower (p.value <0.0001) . Intensive care unit entry after

surgery the hospitalization period of LC group is about twice that of the non-LC group (Table15). Therefore, it can be confirmed that resection surgery for LC patients is not only burdensome to the body but also socioeconomically.

IV. Discussion

The purpose of this study was to evaluate the postoperative outcome and burden of patients with LC among CRC patients. In order to understand the effect of LC exactly, matching was performed. One of the frequently used matching methods, exact matching[14], was performed for age and sex, and the remaining covariates were corrected for the cox model.

In this study, it reveals that LC had a significant effect on 5 year OS after resection surgery for CRC. The HR of the LC group was 1.66 ~ 2.37 (95% C.I of HR) times higher than Non-LC using matched data, which was a statistically significant value. In addition, a comparison of various complication rates suggests that LC acts as a burden in CRC surgery. Postoperative complications in CRC patients are known to affect survival. In this regard, the complication rate of intestinal obstruction and incisional hernia after surgery was compared between the two groups. Early and late complications of incisional hernia were more frequent in LC group. However, the rate of postoperative ileus complications was slightly higher in the non-LC group and the socio-economic burden of CRC surgery was significantly higher in the LC group. The results of this study suggest that prognosis after resection surgery of CRC patients with LC are poorer compared with non-LC patients.

The results of this study show the directions that are consistent with the existing studies. However, the 5-year OS of the LC group among the CRC patients was higher than the previous studies[2]. In this study, the OS of the LC group was 62% and the OS of the non-LC group was 73%. In a previous study of similar subjects, 5-year OS of LC group was 46.7%. However, the study has limitation that the number of LC groups (N = 55) is too small and subject are collected in only one clinic center, so it is difficult to interpret and generalize the results. However, this study uses the entire population of Korea (about 96% of population), so the number of samples is at least 2 to 5 times higher than the previous studies[2, 5].

LC transforms liver into fibrotic tissues of hepatocytes, causing liver function loss in the body. Liver is the organ that is responsible for protein synthesis and detoxification and bile synthesis necessary for our body. When liver function is lowered by LC, protein synthesis becomes difficult and hemostasis is not done well. Therefore, when cirrhosis progresses, the pressure of the portal vein entering the liver increases, and as the blood flow becomes congested[6]. When LC patients with these clinical features are operated, the risk of surgery increases and the mortality rate increases. For this reason, other chronic liver disease, including LC, are high mortality after surgery[15].

Although it is advantageous to have a large number of samples, but there are some limitations in interpreting this study and caution is needed in interpreting the results. This study has the disadvantage that specific and accurate information about the stage of CRC cannot be obtained because NHIS insurance claims data are used instead of clinical

data or lab data. To overcome this problem, this study defined the stage of CRC depending on whether patients had a treatment of chemotherapy. Chemotherapy or radiation can be performed even when the stage of CRC develops. Therefore, the stage of CRC defined in this study has definite limit. In particular, I can see the two groups by stages in the K-M curve crossed, which is not the case in the preceding studies. This suggests that even though the P-value of the HR of the stage is significant in this study, but it requires special attention to interpretation.

Second, there is no variable in this study that can identify the degree of LC. Previous studies have been able to confirm the degree of cirrhosis[16] in clinical data and symptom of LC[17]. However, this study uses the claim data of health insurance, so it is difficult to grasp the liver function exactly and clinical symptom. Therefore, within the LC group, it is difficult to judge the difference in the results of surgery. For these reasons, it is not clear exactly how much postoperative liver function deteriorated and how aggravated liver function affected the survival rate.

Finally, the effect of LC itself on the OS was not adjusted. In this study, 5-year OS after surgery was compared between the LC group and the non-LC group. There is a limitation to interpret this result, that is the cause of low OS after surgery in LC patients cannot be precisely confirmed whether the effect of LC itself on OS or the effect of surgery on OS due to LC. Severity of cirrhosis can generally be classified by Child- pugh score. The Child-pugh score has values of A, B and C, and C means worst cirrhosis. Patients with a Child-pugh score C have a lower survival rate[18]. In the general, Patients

who underwent surgery among patients with LC are mild LC patients having Child-pugh score A or B[2]. The status of patients in the LC group of this study is not expected to be very severe. However, even in the case of mild LC, attention has to be paid to the interpretation of the results since it has not been adjusted in this study.

Although large sample sizes cannot complement all of the above limitations of the present study, the 5 year OS of patients with LC and non-LC among CRC patients can be grasped and the tendency of complication rates can be ascertained in Korea. Yet patients with LC are still unfamiliar with surgeons [2], and the researches on CRC surgery in patients with LC have been limited. Continuous research on this subject will be needed focusing on the fact that the survival rate increases[4].

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VI. Supplementary Contents

Supplementary Table1.Laparoscopic Material Code

Laparoscopic Material Code	Name of materials
M2050003	GAIA BLADE TROCAR
M2050008	DILATING TIP TROCAR
M2050009	VERSAPORT(RPF)
M2050010	SINGLE-USE TROCAR W/INTERNAL SHIELD
M2050012	APPLIED PREMIUM TROCAR
M2050015	AUTO SHIELD TROCAR
M2050020	INNO SAFE PORT TROCAR-K SET
M2050022	CLEAR PORT(BLADE TYPE)
M2050029	LAGIS BLADE TROCAR
M2050030	UNIMAX AUTOLOCKING TROCAR
M2050033	BLADE TROCAR
M2050037	ENDO-PORT BLADE TROCAR
M2050039	KII ACRCESS SYSTEMS BLADED
M2050046	PROPORT
M2050060	PASSPORT SMART TIP TROCAR
M2050085	CROWN TROCAR(BLADE TYPE)
M2050108	XCEL DILATING TIP TROCAR

M2050109	VERSAPORT(V2)
M2050110	SINGLE-USE TROCAR WITH UNIVERSAL CONVETER
M2050111	LAPORT
M2050185	OPTCLA TROCAR(BLADE TYPE)
M2050209	MINIPORT
M2050211	DRG PORT SAFETY TYPE
M2050309	DEXIDE 5MM THREADED TROCAR
M2050409	MINISITE MINIPORT
M2051008	BLUNT TIP TROCAR
M2051009	BLUNT TIP TROCAR (BALLOON TYPE)
M2051011	LAPORT(BLUNT TYPE)
M2051015	HASSON TROCAR
M2051030	UNIMAX HASSON TROCAR
M2051032	SINGLE USE TROCAR SOLUTION
M2051033	BLADELESS TROCAR
M2051034	WECK VISTA PORT
M2051039	KII BALLOON BLUNT TIP SYSTEM
M2051092	VECTEC BLUNT
M2051109	BLUNT PORT PLUS
M2051134	WECK VISTA BALLOON ACRCESS PORT
M2051209	VERSASTEP
M2051309	VERSAONE BLUNT TROCAR

M2052003	GAIA BLADELESS TROCAR
M2052008	XCEL BLADELESS TROCAR
M2052009	VISIPORT
M2052010	ONEPORT DILATING TYPE
M2052011	LAPORT(BLADELESS TYPE)
M2052012	SEPARATOR ACRCESS SYSTEM
M2052014	VAXCON BLADELESS TROCAR
M2052015	DILATING TIP TROCAR
M2052016	ULTIMATE DILATING TIP TROCAR
M2052019	LEADERS PORT
M2052020	INNO SAFE PORT TROCAR-S SET
M2052022	CLEAR PORT(BLADELESS TYPE)
M2052023	TRANSPORT
M2052024	ENPOLE
M2052025	GENICON
M2052027	FEMCARE NIKOMED TROCAR
M2052028	POMO BLADELESS LAPAROSCOPY TROCAR
M2052029	LAGIS TROCAR
M2052030	UNIMAX BLADELESS TROCAR
M2052031	R5 TROCAR
M2052037	ENDO-PORT BLADELESS TROCAR
M2052039	KII ACRCESS SYSTEMS
M2052053	ANCHORPORT

M2052060	PASSPORT TROCAR
M2052081	S PORT TROCAR
M2052082	TROPIAN
M2052083	ASE PLUS TROCAR
M2052084	CONCORD
M2052085	OPTCLA TROCAR(BLADELESS TYPE)
M2052091	BIOCUBE PORT
M2052092	VECTEC BLADELESS
M2052108	BLADELESS TROCAR
M2052109	VERSAPORT PLUS BLADELESS TROCAR
M2052111	DRG PORT(BLADELESS TYPE)
M2052112	OPTICAL SEPARATOR
M2052114	SAFEPASS NGS
M2052123	TPORT
M2052124	ENPOLE
M2052125	NEX PORT
M2052129	LAGIS TROCAR
M2052130	UNIMAX VISIBLE TROCAR
M2052139	KII BALLOON OPTICAL SYSTEM
M2052182	TROPIAN(F)
M2052183	ASE OPTIC-FIX TROCAR
M2052185	CROWN TROCAR(BLADELESS TYPE)
M2052208	BASX BLADELESS TROCAR

M2052209	VERSAPORT BLADELESS LOWPROFILE TROCAR
M2052211	LAPORT MINI UNIVERSAL OPTICAL
M2052212	GELPORT SEPARATOR BALLOON SYSTEM
M2052224	SAFEPASS GENERAL
M2052229	LAGIS TROCAR
M2052282	TROPIAN(T)
M2052283	ASE TROCAR
M2052308	BASX BLADELESS TROCAR 5LT SET
M2052309	VERSAPORT BLADELESS OPTICAL TROCAR
M2052311	DRG PORT BLADELESS PACK
M2052324	ENPOLE PRO (TROCAR)
M2052408	BASX BLADELESS TROCAR 5ST SET
M2052411	DRG PORT OPTICAL PACK
M2052508	BASX BLADELESS TROCAR 12LT SET
M2052511	DRG PORT SAFETY PACK
M2052608	BASX BLADELESS TROCAR 11LT SET
M2053009	PDB BALLOON TROCAR
M2053209	BLUNT TIP TROCAR WITH DISSECTION BALLOON
M2053309	STRUCTURE BALLOON TROCAR WITH DISSECTION BALLOON
M2054008	THORACIC TROCAR SLEEVE
M2054009	THORACOPORT

M2054011	LAPORT-CS(SOFT)
M2054012	THORACIC SEPARATOR
M2054024	T-PORT
M2054030	UNIMAX THORACIC TROCAR
M2054031	H5 TROCA
M2054038	SURGIPORT
M2054082	TROPIAN
M2054108	FLEXIPATH TROCAR
M2054109	THORACIC THORACOPORT
M2054111	LAPORT-CS(HARD)
M2054114	SAFEPASS NCS
M2054124	VAXCON BLADELESS TROCAR CS
M2054211	BIOCUBE THORAPORT
M2054224	SAFEPASS CS
M2054324	T-PORT(SINGLE)

Supplementary Table 2.Code for chemotherapy

Code for chemotherapy	contents
AP602	injection of anticancer agent
AP603	counseling of chemotherapy
AZ200	counseling of chemotherapy
AZ200001	re-counseling of chemotherapy
J0041	injection of anticancer agent
KK151	injection of anticancer agent
KK152	injection of anticancer agent
KK153	injection of anticancer agent
KK154	injection of anticancer agent
KK155	injection of anticancer agent
KK156	injection of anticancer agent
KK158	antitumor drug

국문 초록

간경변 동반 여부에 따른 대장암 환자의 장 절제수술 예후 및 결과 비교

- 한국의 건강보험청구자료를 활용한 전국기반 코호트 분석 -

신 나 리

서울대학교 보건대학원

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연구 배경: 간경변 환자에서의 대장암 수술의 위험성은 선행연구들에 의하여 일정 부분 밝혀져 있다. 간경변을 동반한 대장암 환자에게 장 절제술을 시행할 경우, 수술과 마취에 대한 자체 위험이 모두 증가하게 된다. 간경변환자의 경우 간기능의 악화로 인하여 혈액응고장애, 감염에 취약성 그리고 혈액순환의 장애를 겪기 때문에 대장암 수술로 인한 위험성이 일반 대장암 환자군에서 보다 높다. 특히, 간경변 환장에게 행해질 수 있는 여러 수술 중 대장 부위에 시행되는 수술은 고위험 수술로 평가되어 왔다. 따라서, 간경변 환자에게 수술적 처치를 시행할 때는 더 이상의 보전적 치료로 호전이 없을 때 고려되어야 한다. 의료 수준의 발전과 간이식 수술로 인하여 간경변 환자의 생존율이 점차 증가하고 있다.

이와 같은 경향은 간경변 환자가 수술적 처치를 반드시 필요로 하는 질병에 대한 노출 위험도 함께 증가시켰다. 그 중 하나가 대장암이다. 하지만, 간경변을 동반한 대장암 환자에서의 장 절제술 예후 및 결과를 비교하는 연구는 부족한 실정이다. 또한, 기존의 선행연구의 결과는 연구대상자의 수가 적어 결과의 일반화가 어렵다는 한계점이 존재한다.

연구 목적: 우리나라의 경우, 건강보험공단에서 2002~2017 년도의 건강보험 청구 자료를 연구목적용으로 제공하고 있다. 특히, 건강보험공단의 연구자 맞춤형자료는 건강보험에 가입되어 있는 국내 인구의 96%에 대한 의료서비스 이용내역을 제공한다. 따라서, 본 연구는 건강보험공단의 자료를 이용하여 간경변을 동반한 대장암 환자의 수를 충분히 얻어 간경변 동반 여부가 대장함 수술에 미치는 영향을 파악하는 것을 주요 목적으로 하고 있다. . 또한, 대장암 수술 후 발생할 수 합병증 및 부담을 간경변 그룹과 비간경변 그룹으로 나누어 비교・평가하는 것을 목적으로 하였다.

연구 방법: 본 연구는 대장암 수술 후 예후를 사망으로 두고, 장 절제술부터 사망까지 소요된 시간에 대해 생존 분석을 진행하였다. 생존 분석 실시 전, 간경변 집단과 비 간경변집단에 대해서 나이-성별을 정확히 매칭하여 두 개 집단의 비율을 1:5 로 하였다. 생존 분석은 확장된(익스텐디드) 콕스 모형을 사용하여 진행되었다. 일반 콕스 비례 위험 모형의 비례위험 가정이 만족하지 않아, 헤비사이드 함수를 사용한 확장된 콕스 모형을 고려하였다. 공변량으로는 보험료분위수(사회경제적 지표), 대장암의 위치, 대장암의 기수, 장 절제 수술 방법, 찰슨 동반질환 지수

그리고 수술을 시행한 년도를 고려하였다. 나이와 성별은 정확히 매칭이 되었기 때문에 공변량에서 제외하였다. 또한, 각 변수 별로 카플란 마이어 곡선을 그려 각 공변량이 생존에 미치는 영향을 확인하였다.

연구 결과: 간경변 집단에서 수술 후 생존율이 더 낮은 것으로 나타났다. 우선, 5 년의 추적관찰 기간 동안 간경변 환자 집단은 38.9%가 사망하였고, 비간경변 집단은 24%가 사망하였다. 추적 관찰 기간의 시점을 수술 후 30 일, 60 일, 90 일, 180 일,1 년 그리고 5 년으로 나누어 비교한 결과 초기 사망률은 3 배 가량 차이가 났으나 최종 5 년 추적관찰 기간에는 1.6 배 차이가 나타났다. 콕스 모형의 위험도비에서도 간경변 집단이 약 1.98 배 위험률(신뢰구간 :1.66 – 2.37)이 높았다. 이는 유의 수준이 0.001 미만으로 통계적으로 유의한 결과였다. 간경변 수술 후 발생할 수 있는 절개 탈장과 장 폐색의 발생률의 경우 간경변 그룹이 절개탈장이 2 배이상 더 많이 발생했다. 장 폐색의 발생률은 비슷하였다. 마지막으로, 수술에 대한 병원 재원기간은 간경변 그룹이 약 60 일이상 긴 것으로 나타났다.

결론: 본 연구에서는 대장암치료를 목적으로 하는 장 절제술에서, 간경변이 수술 후 예후에 중요한 요인으로 나타났다. 또한, 간경변 그룹이 수술 후 합병증도 더 자주 관찰되었고 수술에 대한 사회경제적 부담도 큰 것으로 나타났다.

주요어: 간경변, 대장암, 장 절제술, 확장된 콕스 위험 모형, 카플란 마이어 생존 곡선

학번 : 2017-26410

감사의 글

이 논문이 나오기 까지 많은 분들의 응원과 은혜가 있었습니다.

우선, 나의 사랑하는 가족. 항상 저를 믿어주고, 묵묵히 지켜주었기에 제가 다사다난했던, 석사 과정을 무탈하게 마무리 할 수 있었습니다. 내가 가장 사랑하는 차미숙 여사, 내 인생의 가장 단단한 버팀목인 신승기 사장님, 그리고 미안함이 더 큰 내 하나뿐인 동생 동훈이. 지금은 비록 힘든 시기를 지나고 있고 또 그 중 몇몇은 잘 넘겼습니다. 남은 어려움도 우리 모두 함께 헤쳐갈 수 있으리라 저는 믿습니다.

그리고 김남곤 선생님. 갓 대학원에 입학해서 철없고 방황하던 시절을 이해해 주고 옳은 선택을 하도록 인도해 주셨기에, 이 겨울 대학원을 무사히 졸업합니다. 항상 감사합니다.

다음으로, 대학원 생활에서 나의 기쁨과 슬픔을 같이 나눠준 옥천아리. 대학원 2 년동안 처음 겪는 일들 앞에서, 희로애락의 모든 감정들이 교차하는 순간하는 나날 속에서 같이 공감해준 것은 저에게 큰 응원이 되었습니다.

또한, 무엇보다 잊지 못할 연구실 선배와 동기들에게 감사 인사 전합니다. 잊지 못할 코코아 동지 뚱허, 이젠 정말 갓인 강진선배, ggplot2 장인 재훈선배, 사려 깊은 경택선배, 그리고 논문에 대해 깊은 고민을 같이 해준 건우선배. 포기의 순간 구세주가 되어 주었던 나의 동기, 주희언니와 남은언니. 마지막으로 문서 출력 요정인 깜찍한 윤환오빠. 차분한 금경언니, 팀뷰어 요정 아라 언니, %in%장인 문규선배. 저에게 이렇게나 많은 따뜻한 사람들, 요정들, 장인들 그리고 갓까지 만날 수 있었던 것은 큰 행운이었습니다. 손이 많이 가는 저를 열린 마음으로 이해해주신 것을 잘 알고 있습니다. 여기 모두를 쓰지는 못했지만 속 깊이 감사함을 기억할 것 입니다.

마지막으로 원성호 교수님. 학부를 졸업하고 철없던 저를 이해해주시고, 성심껏 지도해 주셔서 감사합니다. 2 년 전과 지금 이 감사의 글을 쓰는 저를 비교해보면, 참 많은 것이 달라졌습니다. 돌이켜 생각해보면, 위기의 순간순간 교수님의 큰 가르침이 있었기 이전보다 성숙한 사람이 될 수 있었던 것 같습니다. 교수님이 제게 주신 인생의 가르침과 통계학의 지식은, 저의 인생에 오랫동안 남으리라 믿습니다. 교수님, 감사합니다.

많은 분들의 손길 속에서, 보탬을 받아 제가 여기까지 올 수 있었습니다. 모두들 감사합니다.

신나리 올림