의학석사 학위논문

간이식 환자에서 대장 용종 및 대장암의 유병률 및 특성

Prevalence of Advanced Colorectal Neoplasm in Liver Transplant Recipients

2016년 10월

서울대학교 대학원

임상의과학과 전공

강 은 애

A thesis of the Degree of Master of Science in Clinical Medical Sciences

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October 2016

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이 논문을 의학석사 학위논문으로 제출함

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강은애의 의학석사 학위논문을 인준함

2017년 1월

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Abstract

Background and Aim: Liver transplant patients are in high risk of malignancy because of the prolonged immunosuppression after transplantation. The aim of this study was to determine whether the prevalence of advanced colorectal neoplasia increased in liver transplant recipients and to define the effect of immunosuppression on the advanced colorectal neoplasia.

Method: Our study consisted of 348 liver transplant patients who underwent a colonoscopy at Seoul National University Hospital from 1991 to 2012. Age- and sex-matched controls were identified from a population of asymptomatic individuals.

Results: Of the 348 patients (Median age, 58; male gender, 79.9%), seventeen (4.9%) patients had advanced colorectal neoplasms including colorectal cancers (9 patients, 2.6%) after liver transplantation. The odds of advanced colorectal neoplasia occurring in transplant patients were 3.6 times greater than in controls (OR 3.578; 95% CI 1.578-8.115; P = 0.001). The risk of developing colon cancer in transplant patients was 8.4 times greater than in controls (OR 8.416; 95% CI 1.808-39.172; P = 0.001). However, there was no significant difference in the prevalence of non-advanced adenoma between the two groups.

Conclusions: Liver transplant patients were in high risk of colorectal cancer.

Therefore, colonoscopy surveillance after liver transplantation is recommended. Immunosuppressive therapy could facilitate colorectal cancer carcinogenesis.

Key words: Liver transplantation, colon cancer, adenoma

Student number: 2015-22239

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer death in the United States.(1) Trends in age-standardized incidences of CRC have been increasing in Korea and CRC becomes the second most common cancer in male, the third most common cancer in female and the fourth leading cause of cancer death in 2012 in Korea.(2) The current guidelines for CRC screening in asymptomatic, average-risk individuals over the age of 50 are the options of annual fecal occult blood testing with or without flexible sigmoidoscopy every 5 years, or screening colonoscopy every 10 years.(3) It is important to determine appropriate screening or surveillance interval of CRC in high risk patients based on the likelihood of developing advanced colorectal neoplasm because of concerns about the interval cancer.(4)

Liver transplantation (LT) is regarded as a definite treatment of end-stage of liver disease with various etiologies.(5) However, post-transplant patients are at higher risk for developing new malignancies and the risk of skin cancer and lymphoid malignancies has been reported in LT.(6, 7) Increasing risk of cancer is primarily a consequence of the immunosuppressive agents after LT. Furthermore, the improved survival of post-transplant patients and the increasing tendency of patients' age to receive transplantation have added

further risks of new malignancies because cancer, in general, is more common in the elderly.(8) However, only a few studies have investigated CRC in LT patients and these studies have shown conflicting results.(9-13) Many studies have shown that CRC was more common in patients who received LT owing to primary sclerosing cholangitis (PSC) with or without inflammatory bowel disease (IBD) than in healthy controls.(12, 14, 15) Nevertheless, PSC is not a common etiology of end-stage of liver disease in Korea, it is important to determine whether the overall incidence of advanced colorectal neoplasms including CRC increases in LT patients. In addition, it is important to demonstrate the necessity of frequent colonoscopy surveillance among LT patients.

The aim of the study was to determine whether the prevalence of advanced colorectal neoplasm increased in liver transplant recipients and to define the effect of immunosuppressive therapy on the development of advanced colorectal neoplasia.

MATERIALS AND METHODS

Patients and control group

The study was retrospective, case-control study and was approved by the Institutional Review Board (IRB) of Seoul National University Hospital and IRB approval number was H 1304-012-477. We reviewed 1496 patients who had received liver transplantation at Seoul National University Hospital between January 1991 and December 2012. Patients with a prior history of colorectal cancer (n = 2) or major colorectal surgery (n = 3) were excluded. Patients who lacked medical records (n = 234) or who had not received a colonoscopy (n = 909) were also excluded. A total of 348 patients who underwent at least one colonoscopy after transplantation were ultimately investigated in the analysis. Clinical data were acquired by reviewing the information in our electronic medical recording system. The data included age, gender, body mass index (BMI), smoking, etiology of liver failure, donor type, Child-Pugh class, present of esophageal varix, ascites, hepatic encephalopathy, hepatocellular carcinoma, Model For End-Stage Liver Disease (MELD) score, total bilirubin level in blood, prothrombin time level, albumin level and type of immunosuppressive agents after LT.

Colonoscopy

Colonoscopy was performed at the Endoscopy Center at Seoul National University Hospital. All colonoscopies were performed by board-certified gastroenterologists using CF-240L and CF-H260 colonoscopies (Olympus, Tokyo, Japan). All procedures accomplished the status of complete examination. A complete examination was defined when 1) the insertion to cecum could be done, 2) colonoscopy was withdrawn for at least 7 minutes, and 3) bowel preparation was adequate to visualize a minimum of 90% of the mucosa. All abnormal mucosal lesions were biopsied or resected by endoscopic mucosal resection. The size of lesions was measured using biopsy forceps or was measured after endoscopic resection or surgery. Advanced colorectal adenomas were defined as one with a size larger than 1 cm, a villous component, or a high degree of dysplasia. Serrated adenomas of 1 cm or more were also classified as advanced adenomas. Carcinoma *in situ* or intramucosal carcinoma was classified as high-grade adenoma.(16, 17) Advanced neoplasia was defined as either advanced adenomas or invasive carcinomas. In cases of multiple lesions, the most advanced pathology was selected as the definitive lesion. Non-advanced adenoma was defined as an adenoma < 10 mm in size with low-grade dysplastic changes with < 25% villous components. Nonspecific inflammation or hyperplastic lesions were classified as normal.

Case control study

We performed a case-control study to determine whether LT patients had an increased risk of advanced colorectal neoplasia compared to the general population. For each patient, two or more age- (± 5 years), sex-, BMI- (± 5 kg/m^2), and smoking-matched controls were randomly identified from a population of asymptomatic individuals who had undergone colonoscopy screening for colorectal cancer in our health promotion center between January 1991 and December 2012. Subjects who underwent colonoscopy because of bowel habit changes, positive fecal occult blood test or gastrointestinal bleeding were excluded. Furthermore, subjects with inflammatory bowel disease, history of colorectal cancer, major bowel surgery were also excluded. In this analysis, we attempted to measure the odds of advanced neoplasia in LT patients compared to that in the general population at average risk for CRC. The primary outcome was a comparison of the prevalence of advanced colorectal neoplasia.

Statistical analysis

The Pearson Chi-square test and Fischer's exact test were used to calculate odd ratios (ORs) for advanced colorectal neoplasms with 95% confidential intervals (CI). Univariate analysis was performed using Logistic regression methods and multivariate analysis was performed using Cox proportional hazard model. Kaplan-Meier analysis and log-rank test were used to estimate the time to detect colorectal neoplasms according to the prior colonoscopy findings before LT. Statistical significance was defined as a P value < 0.050. All statistical analyses were performed using SPSS software for Windows, version 22.0 (IBM, New York, USA).

RESULTS

Demographics and clinical characteristics of the TPL patients

A total of 348 patients who had received LT at Seoul National University of Hospital from January 1991 to December 2012 were investigated in our analysis. Among the patients, one hundred patients had received colonoscopy before LT. The baseline characteristics of the LT patients are presented in Table 1. Median age was 58 years old and male patients comprised 79.9% of the patients. Hepatitis B virus was the most common cause of liver failure in LT patients. Mean interval from LT to colonoscopy was 11.4 months. Patients who received LT from cadaveric donor were 264 (75.9%). One hundred and eighty-three (52.6%) patients had liver cirrhosis with Child-Pugh class A. Tacrolimus-based therapy was the most commonly used immunosuppressant after LT.

Table 1. Demographic and clinical characteristics of liver transplant patients (*n* = 348)

Variables	TPL patients
Age (years)	58.44 ± 8.8
Gender (M/F)	278 (79.9%) /70 (20.1%)
BMI (kg/m^2)	22.65 ± 3.06
Smoking	
Never smoker	319 (91.7)
Ex-smoker	10 (2.9)
Current smoker	19 (5.5)
Etiology of liver failure	
HBV (%)	296 (85.1)
HCV (%)	17 (4.9)
Alcoholic (%)	13 (3.7)
Others* (%)	22 (6.3)
Donor	
Cadaveric	264 (75.9)
Living	84 (24.1)
Child-Pugh class	
A (%)	183 (52.6)
B (%)	139 (39.9)
C (%)	26 (7.5)
Esophageal varix	
Yes (%)	97 (27.9)
No (%)	251 (72.1)
Ascites	
Yes (%)	97 (27.9)
No (%)	251 (72.1)
Hepatic encephalopathy	
Yes (%)	149 (42.8)
No (%)	199 (57.2)
HCC	
Yes (%)	98 (28.2)
No (%)	250 (71.8)
MELD score	13.24 ± 6.33
Total bilirubin	2.98 ± 4.83
PT INR	1.31 ± 0.44
Albumin	3.677 ± 1.94
Creatinine	1.243 ± 1.06
Type of immunosuppressant	
TAC (%)	253 (72.7)
CSA (%)	13 (3.7)

Sirolimus (%)	4 (1.1)
Other monotherapy (%)	6 (1.7)
TAC + FK506 (%)	57 (16.4)
Others (%)	15 (4.3)

Continuous variable was presented as mean ± SD, unless otherwise stated

M male, *F* female

HBV hepatitis B, *HCV* hepatitis C, *HCC* hepatocellular carcinoma, *MELD* Model for End Stage Liver Disease, INR international normalized ratio

TAC tacrolimus, CSA cyclosporine A.

*Others included primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, biliary atresia, Wilson's disease, Langerhans cell histiocytosis, and lupus hepatitis

Endoscopic findings in TPL patients and healthy control

Colonoscopy findings in LT patients and healthy controls are presented in Table 2. Among those patients, a hundred patients (28.7%) had undergone screening colonoscopy before LT. Of patients with colonoscopy before transplantation (TPL), two (2.0%) had an adenoma with villous components, thirteen (13.0%) had low-grade tubular adenoma, three (3.0%) had hyperplastic polyp and one (1.0%) had inflammatory polyp. Among transplanted patients who received diagnostic colonoscopy after LT, seventeen (4.9%) had advanced colorectal neoplasms including colorectal cancer (9 patients, 2.6%), adenoma larger than 10 mm in size (1 patient, 0.3%), high-grade dysplasia (4 patients, 1.1%) and tubulovillous or villous adenoma (3 patients, 0.9%). In healthy control group, advanced colorectal neoplasms were detected in nine (1.4%) including two with colorectal cancer (0.3%) by colonoscopy.

Table 2 Colonoscopy findings in liver transplant patients and healthy control

Colonoscopy findings	Patients with Pre-TPL screening (*n* = 100)	Patients with post-TPL screening (*n* = 348)	Healthy control (*n* = 636)
Colorectal cancer (%)	(Exclusion criteria)	9 (2.6)	2 (0.3)
≥ 10mm adenoma (%)	0 (0.0)	1 (0.3)	0 (0)
High-grade dysplasia (%)	0 (0.0)	4 (1.1)	2 (0.3)
Tubulovillous or villous adenoma (%)	2 (2.0)	3 (0.9)	5 (0.8)
Normal (%)	81 (81.0)	253 (72.7)	465 (73.1)
Low-grade tubular adenoma (%)	13 (13.0)	42 (12.1)	122 (19.1)
≥ 3 adenomas (%)	0 (0.0)	6 (1.7)	1 (0.2)
Hyperplastic polyp (%)	3 (3.0)	27 (7.8)	38 (6.0)
Inflammatory polyp (%)	1 (1.0)	3 (0.9)	1 (0.2)
Serrated polyp (%)	0 (0.0)	0 (0.0)	0 (0)

TPL transplantation

Case-control study evaluating the risk of advanced colorectal neoplasms in TPL patients and asymptomatic individuals

As shown in Table 3-1, advanced colorectal neoplasms occurring in transplanted patients were 3.6 times greater than in the age- and gender-matched healthy controls (ORs 3.578; 95% CI 1.578-8.115; $P = 0.001$). The ORs of advanced adenoma in LT patients compared with healthy control is 2.114 but the result was not statistically significant (ORs 2.114; 95% CI 0.760-5.880; $P = 0.142$). Otherwise the ORs of colorectal cancer in LT patients were 8.4 times greater than in healthy controls (ORs 8.416; 95% CI 1.808-39.172; $P = 0.001$). We analyzed subgroups of LT patients who had undergone colonoscopy before LT ($n = 100$) or not ($n = 248$). Similar to previous results, advanced colorectal neoplasms and colorectal cancer occurred more in LT patients than in controls (Table 3-2, Table 3-3).

Table 3-1 Prevalence of colorectal neoplasm between liver transplant patients and age- and gender-matched healthy controls (*n* = 984)

	TPL patients (*n* = 348)	Healthy controls (*n* = 636)	Odds ratio (95% CI)	*P* values
Advanced neoplasm (%)	17 (4.89)	9 (1.42)	3.578 (1.578-8.115)	0.001
Advanced adenoma (%)	8 (2.30)	7 (1.10)	2.114 (0.760-5.880)	0.142
Colorectal cancer (%)	9 (2.59)	2 (0.31)	8.416 (1.808-39.172)	0.001
Non-advanced neoplasm (%)	78 (22.41)	162 (25.47)	0.845 (0.621-1.151)	0.286
Total adenomatous neoplasm (%)	95 (27.30)	171 (26.89)	1.021 (0.761-1.370)	0.889

Table 3-2 Prevalence of colorectal neoplasm between liver transplant patients with pre TPL colonoscopy findings and age- and gender-matched healthy controls (*n* = 736)

	TPL patients (*n* = 100)	Healthy controls (*n* = 636)	Odds ratio (95% CI)	*P* values
Advanced neoplasm (%)	6 (6.00)	9 (1.42)	4.447 (1.548-12.777)	0.003
Advanced adenoma (%)	2 (2.00)	7 (1.10)	1.834 (0.376-8.955)	0.447
Colorectal cancer (%)	4 (4.00)	2 (0.31)	13.208 (2.387-73.094)	0.000
Non-advanced neoplasm (%)	22 (22.00)	162 (25.47)	0.825 (0.498-1.368)	0.456
Total adenomatous neoplasm (%)	28 (28.00)	171 (26.89)	1.058 (0.661-1.693)	0.816

Table 3-3 Prevalence of colorectal neoplasm between liver transplant patients without pre TPL colonoscopy findings and age- and gender-matched healthy controls (*n* = 884)

	TPL patients (*n* = 248)	Healthy controls (*n* = 636)	Odds ratio (95% CI)	*P* values
Advanced neoplasm (%)	11 (4.40)	9 (1.42)	3.233 (1.323-7.902)	0.007
Advanced adenoma (%)	6 (2.40)	7 (1.10)	2.228 (0.741-6.696)	0.143
Colorectal cancer (%)	5 (2.00)	2 (0.31)	6.523 (1.257-33.844)	0.010
Non-advanced neoplasm (%)	56 (22.60)	162 (25.47)	0.853 (0.603-1.207)	0.370
Total adenomatous neoplasm (%)	67 (27.00)	171 (26.89)	1.007 (0.723-1.401)	0.969

TPL transplantation, *CI* confidence interval

Advanced neoplasm includes advanced adenoma or colorectal cancer

Advanced adenoma was defined as ≥ 10 mm in diameter and/or containing > 25% villous or tubulovillous histologic characteristics and/or high-grade dysplasia

Non-advanced neoplasm was defined as adenoma smaller than 10 mm in size with low-grade dysplasia and/or containing ≤ 25% villous component

Regardless of transplantation, screening colonoscopy is recommended at least 50 years of age for detecting colorectal cancer. Therefore, the prevalence of advanced colorectal neoplasm was analyzed according to age in transplanted patients and healthy controls. LT Patients aged 50 years or older had more advanced colorectal neoplasms than healthy controls had. (ORs 2.883; 95% CI 1.257-6.609, $P = 0.009$) (Table 4-1, 4-2, 4-3).

Table 4-1 Prevalence of colorectal neoplasm between liver transplant patients and age- and gender-matched healthy controls over the age of 50 (*n* = 780)

	TPL patients, Age ≥ 50 (*n* = 304)	Healthy controls, Age ≥ 50 (*n* = 476)	Odds ratio (95% CI)	*P* values
Advanced neoplasm (%)	16 (5.26)	9 (1.89)	2.883 (1.257-6.609)	0.009
Advanced adenoma (%)	7 (2.30)	7 (1.47)	1.579 (0.548-4.547)	0.393
Colorectal cancer (%)	9 (2.96)	2 (0.42)	7.231 (1.552-33.695)	0.003
Non-advanced neoplasm (%)	74 (24.34)	141 (29.62)	0.764 (0.551-1.061)	0.108
Total adenomatous neoplasm (%)	90 (29.61)	150 (31.51)	0.914 (0.668-1.250)	0.574

CI confidence interval

Table 4-2 Prevalence of colorectal neoplasm between liver transplant patients with pre TPL colonoscopy findings and age- and gender-matched healthy controls over the age of 50 (*n* = 568)

	TPL patients, Age ≥ 50 (*n* = 92)	Healthy controls, Age ≥ 50 (*n* = 476)	Odds ratio (95% CI)	*P* values
Advanced neoplasm (%)	5 (5.40)	9 (1.89)	2.982 (0.976-9.112)	0.060
Advanced adenoma (%)	1 (1.10)	7 (1.47)	0.736 (0.090-6.056)	0.775
Colorectal cancer (%)	4 (4.30)	2 (0.42)	10.773 (1.943-59.714)	0.001
Non-advanced neoplasm (%)	21 (22.80)	141 (29.62)	0.703 (0.416-1.188)	0.186
Total adenomatous neoplasm (%)	26 (28.30)	150 (31.51)	0.856 (0.523-1.402)	0.537

Table 4-3 Prevalence of colorectal neoplasm between liver transplant patients without pre TPL colonoscopy findings and age- and gender-matched healthy controls over the age of 50 (*n* = 688)

	TPL patients, Age ≥ 50 (*n* = 212)	Healthy controls, Age ≥ 50 (*n* = 476)	Odds ratio (95% CI)	*P* values
Advanced neoplasm (%)	11 (5.20)	9 (1.89)	2.840 (1.159-6.959)	0.017
Advanced adenoma (%)	6 (2.80)	7 (1.47)	1.951 (0.648-5.878)	0.227
Colorectal cancer (%)	5 (2.40)	2 (0.42)	5.725 (1.102-29.747)	0.032
Non-advanced neoplasm (%)	53 (25.00)	141 (29.62)	0.792 (0.548-1.144)	0.214
Total adenomatous neoplasm (%)	64 (30.20)	150 (31.51)	0.940 (0.661-1.335)	0.729

Risk factors associated with the development of advanced neoplasms in TPL patients

We identified the risk factors of advanced colorectal neoplasms after LT. In a univariate analysis with Logistic regression analysis, there were no risk factors which had significant impacts on the development of advanced neoplasm after LT. Type of immunosuppressant and duration of immunosuppression had no significant impact on advanced colorectal neoplasm. Furthermore, there were no risk factor which had significant impact in a multivariate analysis (Table 5). On the other hand, univariate and multivariate analysis of overall colorectal neoplasms in LT patients showed that age, male gender and presence of previous advanced neoplasm were risk factors of developing colorectal neoplasms. (Table 6)

Table 5 Univariate and multivariate analysis for risk factors of advanced colorectal neoplasm in liver transplant patients

	Univariate analysis HR (95 % CI)	*P* value	Multivariate analysis HR (95 % CI)	*P* value
Age (≥ 50 years)	1.052 (0.986-1.122)	0.128	1.029 (0.921-1.150)	0.616
BMI (kg/m^2)	0.904 (0.764-1.070)	0.240	1.012 (0.829-1.235)	0.909
Immunosuppressant	2.337 (0.767-7.122)	0.136	2.204 (0.601-8.082)	0.233
Duration of immunosuppression				
< 3 years				
3-5 years	1.288 (0.382-4.339)	0.683	1.086 (0.313-3.776)	0.896
> 5 years	0.752 (0.226-2.506)	0.643	0.708 (0.199-2.516)	0.594
Gender (female)	0.844 (0.236-3.023)	0.795		
Presence of HCC	0.932 (0.346-2.508)	0.889		
Previous advanced neoplasm	1.661 (0.203-13.580)	0.636		

Table 6 Univariate and multivariate analysis for risk factors of overall colorectal neoplasm in liver transplant patients

	Univariate analysis HR (95 % CI)	*P* value	Multivariate analysis HR (95 % CI)	*P* value
Age (≥ 50 years)	1.034 (1.004-1.064)	0.027	0.920 (0.817-1.037)	0.173
BMI (kg/m^2)	1.059 (0.980-1.145)	0.146	1.077 (0.790-1.469)	0.638
Immunosuppressant	1.360 (0.734-2.521)	0.328	1.286 (0.177-9.337)	0.803
Duration of immunosuppression				
< 3 years				
3-5 years	1.376 (0.727-2.604)	0.327	1.199 (0.615-2.340)	0.595
> 5 years	1.460 (0.855-2.495)	0.166	1.381 (0.777-2.457)	0.271
Gender (female)	0.486 (0.248-0.952)	0.036	0.451 (0.216-0.942)	0.034
Presence of HCC	0.905 (0.561-1.461)	0.684		
Previous advanced neoplasm	4.543 (1.447-14.257)	0.009	3.971 (1.220-12.926)	0.022

HR hazard ratio*, CI* confidence interval

BMI body mass index, *HCC* hepatocellular carcinoma

Cumulative incidence of colorectal neoplasm after liver TPL

The time to detect colorectal neoplasms was analyzed in 98 patients who had non-advanced neoplasms or normal colonoscopy findings before LT. (Table 7) Colorectal cancers were detected in 3 of 77 patients (3.90%) less than 5 years and in 1 of 21 patients (4.76%) over 5 years after LT. Advanced adenoma was detected in 1 patient (1.30%) less than 5 years and 1 patient (4.76%) over 5 years after LT. Using the Kaplan-Meier method and log-rank test, the cumulative incidence between patients who had normal findings (normal group) and non-advanced neoplasms (low risk group) by colonoscopy before LT were not statistically different ($P = 0.953$) (Fig. 1). The differences of cumulative incidence of overall colorectal neoplasms were also not significant between normal and low-risk group ($P = 0.066$) (Fig. 2).

Table 7 Time intervals between liver transplantation and detection of colorectal neoplasms from patients with normal or non-advanced neoplasm in pre-TPL colonoscopy (*n* = 98)

Interval between TPL and detection of lesion	Colorectal cancer *n* (%)	Advanced adenoma *n* (%)	Non-advanced neoplasm *n* (%)
<5 years (n = 77)	3 (3.90)	1 (1.30)	15 (19.50)
>5 years (n = 21)	1 (4.76)	1 (4.76))	6 (28.57)

TPL transplantation, *CI* confidence interval

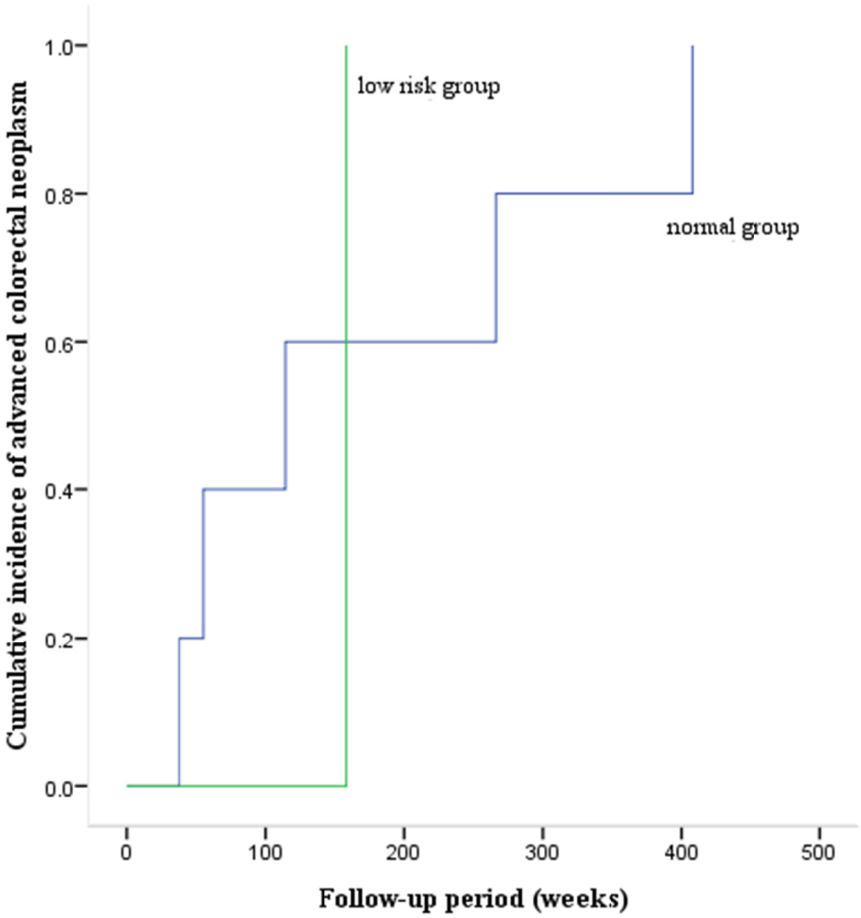

Fig. 1 Kaplan-Meier analysis on the cumulative incidence of advanced colorectal neoplasms according to the risk stratification based on the pre-TPL colonoscopy findings (*P* = 0.953 by Log-rank test)

TPL transplantation

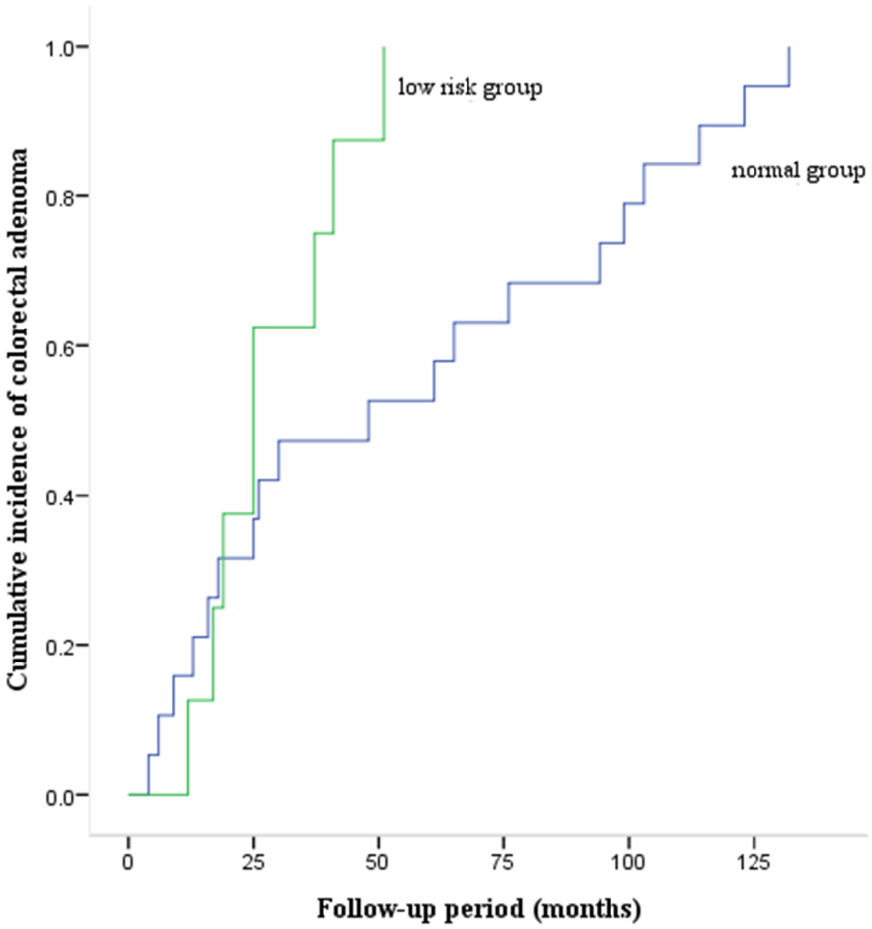

Fig. 2 Kaplan-Meier analysis on the cumulative incidence of colorectal neoplasms according to the risk stratification based on the pre-TPL colonoscopy findings (*P* = 0.066 by Log-rank test)

TPL transplantation

DISCUSSION

The study was conducted to investigate the prevalence of advanced colorectal neoplasm in liver transplant recipients compared with healthy controls and to establish the effect of immunosuppressive therapy on the development of advanced colorectal neoplasia. In this study, LT patients were in high risk of advanced colorectal neoplasia especially colorectal cancer compared with healthy controls. LT patients who had undergone colonoscopy before LT and known the outcomes (n = 100) also had more advanced colorectal neoplasms than controls had. According to this study, we can recommend a surveillance colonoscopy to LT patients because of higher risk of developing colorectal cancer in patients than in normal population. Patients with normal colonoscopy findings proven by colonoscopy before LT (n = 81) also had higher risk of developing colorectal cancer than controls. It suggests that colorectal cancer in LT patients was affected by post-transplant circumstances. However, it is unclear what facilitates carcinogenesis in LT patients.

Several studies have investigated whether the secondary cancer risk is higher or not in LT patients, but the results of studies were controversial. As mentioned in introduction, PSC with or without IBD was known to relate to increasing relative risk of colorectal cancer after LT. In this study, however,

we had only two cases of PSC and PSC patients did not have advanced colorectal neoplasms. Therefore, PSC had no significant impact on the results. The results of the present study correspond well with those found in the earlier studies.(6, 8, 10, 11, 13, 18) Indeed, increasing relative risk of colorectal cancer after LT was related to post-transplant situation including immunosuppression. One hypothesis is that long-standing immunosuppressive therapies after LT cause immune tolerance of malignant cells and weaken antitumor response. A report of cancer risk following organ transplantation in Swedish cohort suggested that immune modulation was most important factor on cancer development, especially on oncogenic viral associated malignancies.(19) Another report showed cases of Epstein-Barr virus associated cecal post-transplant lymphoproliferative tumor and Human papilloma virus associated anal tumors after liver transplantation.(20) Selgrad M *et al.*(21) have reported that JC virus infection may undergo reactivation by immunosuppressive agents and implicate in colorectal carcinogenesis after LT.

Another hypothesis is that de novo CRC in LT patients is characterized by rapid growing and aggressive features. Unlike the prevalence of advanced colorectal neoplasm in LT patients, there were no statistical differences of prevalence of non-advanced colorectal neoplasm between LT patients and controls. It implied that post-transplant situation could increase risk of colorectal cancer by promoting carcinogenesis from non-advanced neoplasm to cancer rather than initiating carcinogenesis. According the table 6, three

patients (3.90%) with normal or non-advanced colorectal neoplasm before LT developed colorectal cancer less than 5 years after LT. Although the number of cases was small, there was possibility of different biologic characteristics of tumor growth among transplanted patients. Furthermore, rapid growth or aggressive nature could be facilitated synergistically by immunosuppressive therapy regardless of oncogenic viruses. An in vivo study reported the impact of cyclosporine on cancer progression by a direct cellular effect.(22) It suggested that cyclosporine played a direct role in tumor growth by cyclosporine-induced transforming growth factor-β (TGF- β) production.

Patients over the age of 50 was analyzed because the screening colonoscopy is recommended over that age. The relative risk of colorectal cancer is still high in LT patients over 50 years old compared with controls. Therefore, we can suggest more frequent colonoscopy especially to the LT patients aged 50 years or older. However, the relatively smaller number of cases of advanced colorectal neoplasm was reported in healthy controls than known prevalence on the average; 1.42% versus 5.6%.(23) The reason for the low prevalence of advanced neoplasia can be explained by younger median age (55.89 ± 11.10) and smaller portion of male (62.3%) in control group.

We analyzed possible confounding factors including age, gender, BMI, type of immunosuppressive agents, duration of immunosuppression after LT, presence of hepatocellular carcinoma (HCC) and presence of advanced colorectal neoplasm before LT by univariate and multivariate analysis. There

were no significant risk factors of advanced colorectal neoplasm. On the other hand, older age could be a risk factor of development of overall colorectal neoplasms in univariate analysis and male gender or presence of previous advanced neoplasm also could be risk factors of colorectal neoplasms in univariate and multivariate analysis. Tacrolimus based immunosuppressant regimen was the main treatment method in our center (89.1%) and had no statistically significant impact on prevalence of CRC compared with other regimen. It was demonstrated that type of immunosuppressant and duration of therapy did not play a significant role in the development of CRC after LT. We emphasized that physicians should consider such risk factors among LT patients to recommend more frequent colonoscopy surveillance to them after transplantation. Indeed, compliance of screening colonoscopy over the age of 50 was not high because of the discomfort of colonoscopy examination and bowel preparation. Therefore, colonoscopy should be encouraged more strongly to transplant patients with risk factors. Except for patients with previous advanced colorectal neoplasm before LT (n = 2), a total of 98 patients were investigated by Kaplan-Meier analysis and log-rank test to determine appropriate interval of colonoscopy after LT. We divided patients whether they had non-advanced colorectal neoplasms before transplantation; low-risk group or not; normal group. As a result, advanced colorectal neoplasms occurred earlier in low- risk group than in normal group but the results were not statistically significant due to very small numbers of cases. Cumulative incidence of overall colorectal neoplasms is also higher in low-

risk group even though statistically insignificant. Prospective study is warranted to define needs of frequent surveillance colonoscopy after LT. Nevertheless, it is significant that our study proposed necessity for early screening after LT especially to patients with previous colorectal adenoma.

There were several limitations in our study. It was retrospective study and all databases were obtained by electronic medical records. A large portion of LT patients was missing owing to lack of records or not undergoing colonoscopy. Furthermore, recall and selection bias could affect the results because LT patients tends to have more concerns for diseases and have chances of colonoscopy more frequently than normal population.

In summary, the prevalence of advanced colorectal neoplasm including CRC was higher in LT patients than in healthy controls. Type of immunosuppressant and duration of therapy did not affect the development of CRC after LT. Physicians should recognize risk factors of developing colorectal neoplasm and recommend colonoscopy more strongly to LT patients after transplantation.

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국문 초록

배경: 장기 이식 환자는 이식 후 장기간의 면역 억제제 사용으로 인해 이식 후 악성 종양 발생의 위험도가 높다. 본 연구는 간 이식 환자에서 이식 후 진행성 대장 종양 및 대장암의 유병률이 증가하는지의 여부와 면역 억제제가 미치는 영향을 평가하기 위하여 시행되었다.

방법: 1991년 1월부터 2012년 12월까지 간 이식을 시행한 환자 중 이식 후 대장 내시경을 시행한 총 348명을 대상으로 하였다. 연령, 성별이 일치하는 대조군을 선정하여 양 군의 진행성 대장 종양 및 대장암의 발생률을 비교하였다.

결과: 간 이식 후 대장 내시경을 시행한 총 348명 중 17명 (4.9%)에서 진행성 대장종양이 확인되었고, 그 중 9명 (2.6%) 은 대장암이었다. 대조군에 비해 진행성 대장 종양의 유병률은 3.6배 높았으며 (승산 비, 3.578; 95% 신뢰구간, 1.578-8.115; P = 0.001) 대장암의 유병률은 간 이식 환자군에서 대조군에 비해 8.4배 더 높았다 (승산 비, 8.416; 95% 신뢰구간, 1.808-39.172; P = 0.001).

결론: 간 이식 환자에서 진행성 대장 종양의 유병률은 대조군에 비해 높았다. 그러므로 본 연구진은 간 이식 후 대장 내시경을 이용한

감시를 권장하며 면역 억제제 치료가 대장암으로의 악성화를 촉진할 가능성이 있음을 제시한다.

주요어: 간 이식, 대장암, 선종

학 번: 2015-22239