

ORIGINAL RESEARCH ARTICLE

Cross-national analysis about the difference of histopathological management in Tis and T1 colorectal cancer between Japan and Korea

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Abstract:

Objectives: There are differences in each country with regards to histopathological managements of colorectal cancer (CRC), such as definition of Tis and lymphatic and venous invasion. In this study, we compared Tis and T1 CRC in Japan and Korea. **Methods:** We retrospectively compared various clinical characteristics of consecutive patients who had Tis and T1 CRCs and who were newly diagnosed between 2010 and 2014 at the Kyoto Prefectural University of Medicine (Japan) and the Konkuk University (Korea). **Results:** Three hundred and sixty-five cases of T1 cancer and 510 cases of Tis cancer from 726 Japanese and 149 Korean patients were included. The rate of Tis in Japan was higher than in Korea (59.8% vs. 51.0%, $P = 0.047$), according to the difference of definition of Tis. In the analyses of 365 T1 CRCs, median age was higher in Japan than Korea (67.8 ± 10.6 vs. 62.2 ± 10.1 , $P < 0.001$). Right-sided lesions were more frequent in Japan than they were in Korea (38.7% vs. 22.2%, $P < 0.001$). The rates of venous and lymphatic invasion were higher in Japan than they were in Korea (venous: 18.6% vs. 1.4%, $P < 0.001$, lymphatic: 25.3% vs. 13.7%, $P = 0.042$), according to the different methods of immunohistochemical examinations used (Japan: E-HE and D2-40, Korea: ERG). **Conclusions:** Our study of T1 CRC showed that there were differences between Japan and Korea in tumor location, elderly incidence, and histopathological lymphatic and venous invasion. Additionally, rates of Tis were different between the two countries. In this international study for CRC, it is considered that we have to pay attention regarding the difference of histopathological definition and method in each country.

Keywords:

T1 cancer, colorectal cancer, Korea, Japan

J Anus Rectum Colon 2019; 3(1): 18-26

Introduction

In East Asia, including in Japan and Korea, incidence of colorectal cancer (CRC) is rapidly increasing, and in 2012 Korea had the highest incidence rate of CRC in the world^{1,2)}. In Japan, CRC in 2017 was the first leading cause of cancer

incidence (149,500 out of 124 million people) and the second leading cause of death to cancer (53,000 people)³⁾. However, in Korea, CRC was the third leading cause of death due to cancer in 2014 (26,978 out of 51 million people), and thyroid cancer and gastric cancer were the first and the second⁴⁾. Generally, CRC incidence increases with age,

and population aging is proceeding rapidly in Japan and Korea. In 2015, more than 33 million Japanese people were more than 65 years old, indicating an increase in the incidence of CRC in elderly people (26.8% of the total population) compared with 14.5% of the total population in 1995⁵⁾. On the other hand, in Korea, 13.1% of people were more than 65 years old in 2015, compared with 5.0% in 1995⁶⁾. Therefore, an overall aging population could be one reason for both countries for the increased incidence of CRC. However, there are lots of differences about the factors related to CRC in each country. For example, there are differences in food preferences, culture, CRC screening method and response rate, endoscopic diagnosis, and histopathological evaluations. Over recent decades, Korean and Japanese food has changed from a traditional rice-based diet to a Westernized one. In Korea, people seem to prefer consuming meat more than Japan. According to the 2015 Korea National Health and Nutrition Examination Survey, the average Korean consumes approximately 109.4 g of red meat per day, which is nearly three times higher than rates seen 30 years ago⁷⁾. On the other hand, a Japanese study showed that average red meat consumptions of Japanese people were 51.5-68.4 g/day for men and 19.8-28.1 g/day for women⁸⁾. Red meat and processed meat were reported to be associated with an increased risk of CRC⁹⁾. Additionally, method of CRC screening in both countries is done by fecal immunochemical test (FIT). However, the starting age for screening is older in Korea (at least 50 years old) compared with Japan (at least 40 years old). The response rate for FIT is higher in Korea (44.7% in 2012) than it is in Japan (Male: 41.4%, Female: 34.5% in 2013)^{1,10)}.

Improvements in endoscopic diagnosis, such as narrow band imaging (Olympus Co.), blue laser imaging (Fujifilm), and pit pattern observation enable us to diagnose CRC accurately¹¹⁻¹³⁾. Additionally, endoscopic resections such as endoscopic submucosal dissection and endoscopic mucosal resection for Tis and part of T1 cancer have also improved significantly such that we can now resect large tumors without surgical operation^{14,15)}. Because of these improvements, initial therapeutic methods for early colorectal cancer (CRC) have shifted to endoscopic resection, especially for the elderly, because endoscopic resection is less invasive than traditional surgical operation¹⁶⁾. However, these endoscopic diagnoses and therapies vary in each country. Additionally, there are differences regarding histopathological managements of CRC, such as definition of Tis and lymphatic and venous invasion in each country. In order to decrease CRC deaths in the world, analysis of characteristic differences of CRC in more than two countries is necessary. However, limited cross-national studies about CRC have been performed. In this study, we compared Tis and T1 CRC characteristics in two countries, Korea and Japan, with a particular focus on histopathological management of T1 CRCs.

Methods

This study was a multicenter retrospective study that assessed 875 consecutive patients (726 Japanese cases and 149 Korean cases) with Tis and T1 cancer between January 2010 and December 2014 at the Kyoto Prefectural University of Medicine (Kyoto, Japan) and the Konkuk University (Seoul, Korea), which included Tis and T1 cancers, and who were newly diagnosed with adenocarcinoma. The inclusion criteria were tumors that were resected by endoscopic resection or surgical operation and were histopathologically diagnosed as Tis or T1 CRCs at each institution.

By reviewing medical records, we analyzed in both countries overall various clinical factors and outcomes of Tis and T1 CRCs, including age, rate of elderly people (≥ 65 years old), rate of number of people ≥ 75 years old, sex, tumor size, tumor location, rate of antithrombotic use, initial therapeutic method (surgery or endoscopy), histological type (cell type), invasion depth (Tis or T1), and complications. With respect to the difference between Tis and T1 CRCs, the various clinical characteristics in both countries were also analyzed in Tis and T1 CRCs, respectively. Regarding T1 cancer receiving endoscopic surgery, the rates of additional surgery were analyzed in both countries. The indications of the additional surgery were poor histology, lymphatic and venous invasion, deeper submucosal invasion, and grade 2 \geq budding, according to Japanese guidelines in both countries¹⁴⁾. Additionally, detailed analysis of tumor location of T1 CRCs in the elderly and the non-elderly in the two countries were analyzed. Moreover, multivariate analysis was performed to analyze related factors of right-sided colon location compared to other locations in T1 CRCs.

Tumor location was classified using three segments, which included the right-sided colon (from the cecum to the transverse colon), the left-sided colon (from the descending colon to the sigmoid colon), and the rectum. Complications, which included postoperative hemorrhage, perforation, infection, anastomotic leak, pancreatic fistula, and pulmonary dysfunction, were examined both after endoscopic resection and after surgical operation. Perforation was detected using endoscopy or abdominal computed tomography. Postoperative hemorrhage was defined as the occurrence of hematochezia requiring endoscopic and radiologic treatment to stop bleeding.

Histopathological diagnoses were performed by two clinical pathologists (A.Y. and M.K.) in Japan and one pathologist (H.S.) in Korea. In Korea, these diagnoses were performed according to the World Health Organization classification, and in Japan it was performed according to the Japanese Classification of Colorectal Carcinoma proposed by the Japanese Society for Cancer of the Colon and Rectum^{17,18)}. All tumors were classified as Tis or T1 CRCs. The definition for Tis was severe cytologic dysplasia, structural atypia,

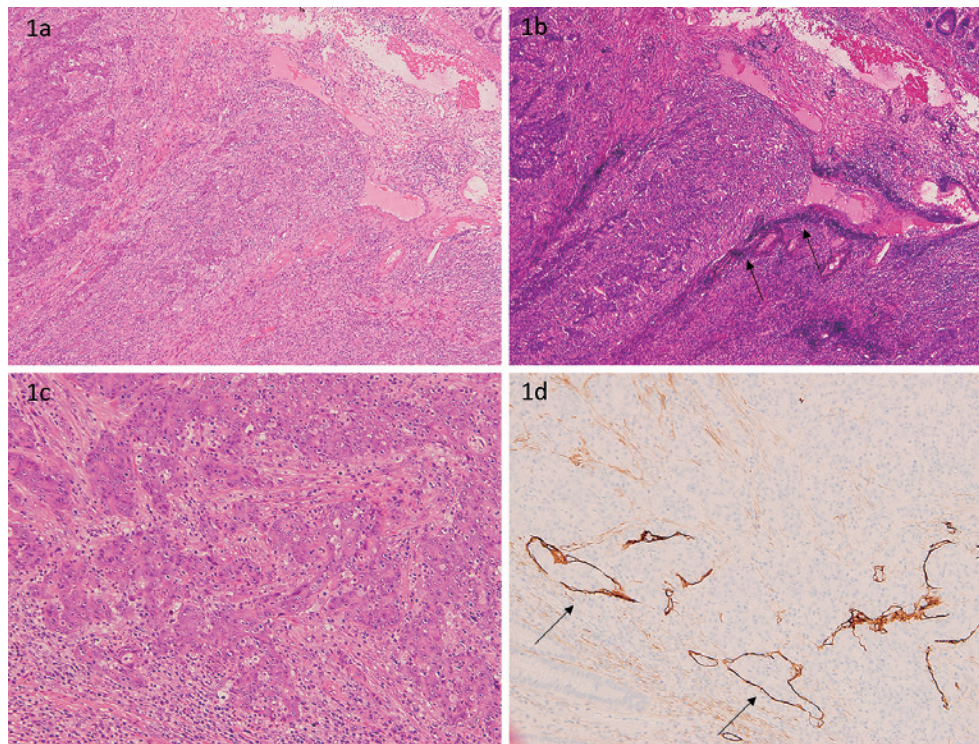


Figure 1. Immunohistochemical examination of lymphatic and venous invasion.

1a. Hematoxylin and eosin (HE) staining did not show venous invasion clearly in a T1 cancer case.

1b. Venous invasion was detected clearly with E-HE. 1c. HE staining did not show lymphatic invasion clearly in a T1 cancer case.

1d. Lymphatic invasion was detected clearly with D2-40 in the T1 cancer case.

and nuclei atypia, regardless of invasion to the lamina propria in Japan, whereas it was dysplastic cells invading the lamina propria in Korea. Regarding the definition of T1 cancer, depth of invasion was provided in Japan as the level of cancer cell infiltration or lymphatic and venous invasion, whereas in Korea it was provided as the level of cancer cell infiltration regardless of the depth of lymphatic and venous invasion. Histological types of tumors were classified as follows: well; moderately; or poorly-differentiated adenocarcinoma. Poorly-differentiated adenocarcinoma also included mucinous adenocarcinoma and signet ring cell carcinoma in this study. Lymphatic and venous invasion was examined using hematoxylin and eosin (HE) staining. Immunohistochemical examinations such as E-HE (elastic HE stain) for venous invasion and D2-40 for lymphatic invasion were performed in Japan (Figure 1). On the other hand, immunohistochemical examination such as ERG (ETS [erythroblast transformation-specific]-related gene) was performed for lymphatic and venous invasion in Korea. This study was a part of the subgroup analysis of a study approved by the Institutional Review Board of Kyoto Prefectural University of Medicine (IRB approval No. ERB-C-838-2) and the Konkuk University (IRB approval No. KUH1010644). This study was registered with the clinical trial registration sites in Ja-

pan (<http://umin.co.jp>) as UMIN000019935 and in Korea (<http://cris.nih.go.kr>) as KCT0001490.

Statistical Analysis

Statistical analyses were performed using the Mann-Whitney-*U* and the chi-squared tests (SPSS version 22.0 for windows, IBM Japan, Ltd., Tokyo, Japan). Continuous variables, such as patient age and tumor size, were analyzed using the Mann-Whitney-*U* test. Multivariate logistic regression analyses of the right-sided colon in T1 cancer were performed for related factors with a *P*-value=0.1 in univariate analysis. A *P*-value <0.05 was considered statistically significant.

Results

The differences of clinical characteristics in 726 Japanese cases and 149 Korean cases of early CRC are shown in Table 1. Median age was significantly higher in Japan than it was in Korea (67.8 ± 10.6 years vs. 62.2 ± 10.1 years, *P* < 0.001). The right-sided colon incidence (38.7% vs. 22.1%, *P* < 0.001) was higher in Japan than it was in Korea. The rate of Tis in Japan was higher than that in Korea (59.8% vs.

Table 1. Differences in Characteristics of Tis and T1 CRCs between Two Countries.

	Japan	Korea	P-value
Case number	726	149	
Age, mean±SD	67.8±10.6	62.2±10.1	<0.001
The rate of the elderly and the non-elderly, % (n)	66.4/33.6 (482/244)	43.0/57.1 (64/85)	<0.001
The rate of patients ≥75 y.o., % (n)	27.8 (202)	8.8 (13)	<0.001
Sex, Male/Female, % (n)	62.4/37.6 (453/273)	64.4/35.6 (96/53)	0.710
Tumor size (mm), mean±SD	24.6±16.9	21.9±13.8	0.066
Tumor location, right-sided/left-sided/rectum, % (n)	38.7/31.3/30.0 (280/226/217)	22.2/45.0/32.9 (33/67/49)	<0.001
Antithrombotics, % (n)	12.8 (38/296)	6.6 (5/76)	0.160
Initial therapeutic method, Surgery/Endoscopy, % (n)	23.3/76.7 (169/557)	21.5/78.5 (32/117)	0.670
Histological type, well+mod/por, % (n)	99.2/0.7/ 0.1 (720/5/1)	96.6/2.7/ 0.7 (144/4/1)	0.050
Invasion depth, Tis/T1, % (n)	59.8/40.2 (434/292)	51.0/49.0 (76/73)	0.047
Complications, % (n)			
Overall	5.4 (39)	8.7 (13)	0.114
Surgery	12.4 (21)	6.3 (2)	0.314
Endoscopy	3.2 (18)	9.4 (11)	0.002

y.o.: years old, right-sided: cecum to transverse colon, left-sided: descending colon to sigmoid colon, well: well differentiated adenocarcinoma, mod: moderately differentiated adenocarcinoma, por: poorly-differentiated adenocarcinoma

Table 2. Characteristic Differences of 510 Tis CRCs between Two Countries.

	Japan	Korea	P-value
Case number	434	76	
Age, mean ± SD	68.8±10.2	61.8±9.3	<0.001
Initial therapeutic method, Surgery/Endoscopy, % (n)	5.8/94.2 (25/409)	14.5/85.5 (11/65)	0.013
Tumor size (mm), mean ± SD	26.1±18.3	21.5±14.9	0.036
Tumor location, right-sided/left-sided/rectum, % (n)	41.8/29.3/28.9 (181/127/125)	26.3/40.8/32.9 (20/31/25)	0.026
Histological type, well+mod/por, % (n)	99.8/0.2 (433/1)	97.4/2.6 (74/2)	0.059
Venous invasion, % (n)	0	0	n.c.
Lymphatic invasion, % (n)	0	0	n.c.
Lymph node metastasis, % (n)	0 (0/25)	0 (0/11)	n.c.

right-sided: cecum to transverse colon, left-sided: descending colon to sigmoid colon, well: well differentiated adenocarcinoma, mod: moderately differentiated adenocarcinoma, por: poorly-differentiated adenocarcinoma, n.c.: not calculated

51.0%, $P = 0.047$), according to the difference of Tis definition. Regarding complications, the rate of complication due to endoscopy in Japan was lower than it was in Korea (3.2% vs. 9.4%, $P = 0.002$).

Differences in cancer characteristics of Tis for the 510 patients from Japan and Korea are shown in Table 2. The mean age was higher in Japan than it was in Korea (68.8 ± 10.2 years vs. 61.8 ± 9.3 years, $P < 0.001$). The rate of endoscopic resection as an initial therapeutic method was also significantly higher in Japan than it was in Korea (94.2% vs. 85.5%, $P = 0.013$). The rate of right-sided colon lesions was higher in Japan than it was in Korea (41.8% vs. 26.3%, $P = 0.026$).

Differences in T1 cancer characteristics for the 365 patients from the two countries are shown in Table 3. The mean age was higher in Japan than it was in Korea (66.4 ± 11.0 years vs. 62.6 ± 11.0 years, $P = 0.007$). However, the

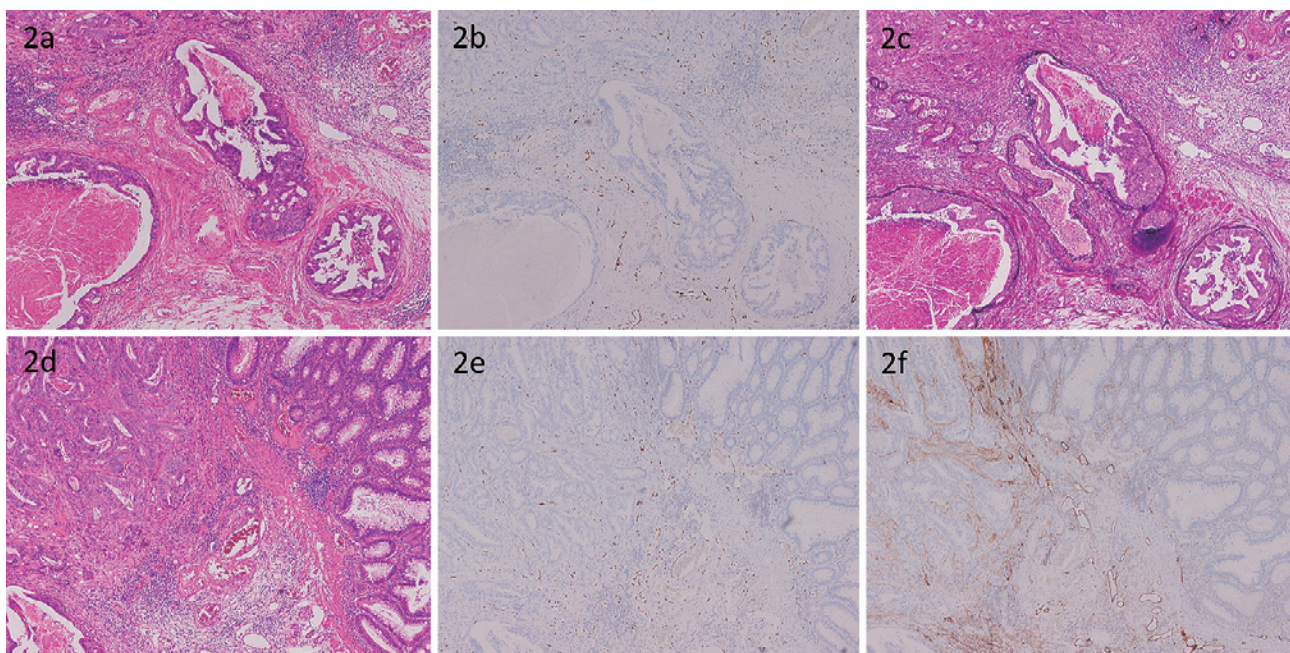
rate of endoscopic resection as an initial therapeutic method was significantly lower in Japan than it was in Korea (50.7% vs. 71.2%, $P = 0.002$). There was no significant difference regarding the rate of additional surgery after endoscopic resections between Japan and Korea. The rates of right-sided colon lesions (34.1% vs. 17.8%, $P = 0.011$) were higher in Japan than they were in Korea. With respect to histopathological evaluation, both venous invasion (18.6% vs. 1.4%, $P < 0.001$) and lymphatic invasion (25.3% vs. 13.7%, $P = 0.042$) were higher in Japan than Korea (Figure 2). However, there was no significant difference between Japan and Korea in the rate of lymph node metastasis in surgical cases (11.8% vs. 10.0%, $P = 0.999$).

The difference between Japan and Korea of locations of tumors for T1 cancer in the elderly and the non-elderly are shown in Figure 3. In Japan, there was a significant difference in rate of right-sided lesions between the non-elderly

Table 3. Characteristic Differences of 365 T1 CRCs in Two Countries.

	Japan	Korea	P-value
Case number	292	73	
Age, mean \pm SD	66.4 \pm 11.0	62.6 \pm 11.0	0.007
Initial therapeutic method Surgery/Endoscopy, % (n)	49.3/50.7 (144/148)	28.8/71.2 (21/52)	0.002
The rate of additional surgery after endoscopic resection, % (n)	11.5 (17/148)	17.3 (9/52)	0.338
Tumor size (mm), mean \pm SD	22.1 \pm 14.1	22.3 \pm 12.6	0.890
Tumor location, right-sided/left-sided/rectum, % (n)	34.1/34.1/31.7 (99/99/92)	17.8/49.3/32.9 (13/36/24)	0.011
Histological type, well+mod/por, % (n)	98.3/1.4/0.3 (287/4/1)	95.9/2.7/1.4 (70/2/1)	0.212
Venous invasion, % (n)	18.6 (52)	1.4 (1)	<0.001
Lymphatic invasion, % (n)	25.3 (71)	13.7 (10)	0.042
Lymph node metastasis, % (n)	11.8 (19/161)	10.0 (3/30)	0.999

right-sided: cecum to transverse colon, left-sided: descending colon to sigmoid colon, well: well differentiated adenocarcinoma, mod: moderately differentiated adenocarcinoma, por: poorly-differentiated adenocarcinoma

**Figure 2.** A case presentation of T1 cancer using immunohistochemical examination of EHE, D2-40, and ERG.

2a. Hematoxylin and eosin (HE) staining showed venous invasion. 2b. Venous invasion was detected clearly with ERG. It looked like accumulation of dots. 2c. E-HE staining showed venous invasion clearly. 2d. HE staining did not show lymphatic duct clearly. 2e. The existence of lymphatic duct was suspected with ERG; it looked like accumulation of dots. 2f. D2-40 staining clearly showed multiple lymphatic ducts without invasion. Lymphatic duct looked like a continuous circular line with D2-40.

and the elderly (26.0% vs. 40.5%, $P = 0.010$). However, there was no significant difference in this rate in Korea (10.8% vs. 25.0%, $P = 0.201$).

Multivariate analysis showed that the factors related with the location of right-sided colon among 365 T1 CRCs were Japan (OR: 2.222, 95%CI: 1.131-4.366, $P = 0.021$) and older age (OR: 1.028, 95%CI: 1.005-1.052, $P = 0.015$) (Table 4).

Discussion

In the current study, we analyzed Tis and T1 CRC characteristics in both Japan and Korea, especially focusing on histopathological managements such as definition of Tis and lymphatic and venous invasion. With respect to T1 cancer, the mean age, the right-sided colon incidence, and the rate of lymphatic and venous invasion were higher in Japan than they were in Korea.

Generally, previous studies regarding CRC have reported an increased proportion in Western countries in right-sided

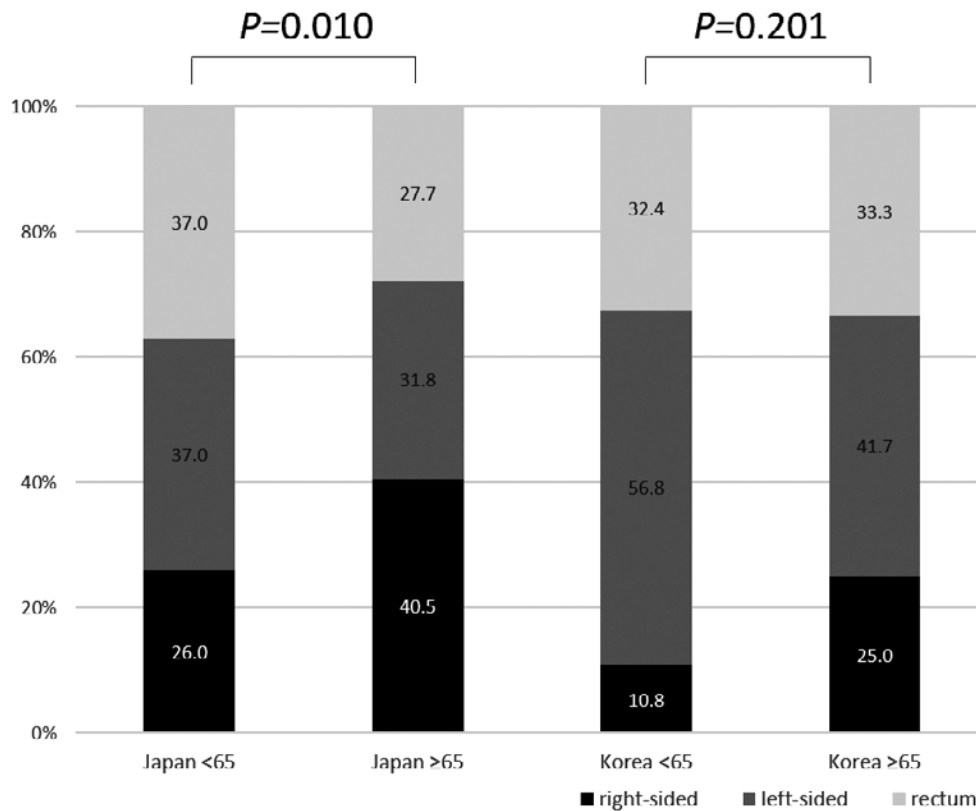


Figure 3. Analysis of tumor location of T1 CRCs between Japan and Korea for the elderly and the non-elderly.

CRC with increasing age¹⁹⁻²³). Cooper et al. found in their study that the proportions of right-sided CRC were 36%, 40%, 43%, 46%, and 49%, respectively, in patients 65-69, 70-74, 75-79, 80-84, and ≥ 85 years old²¹). In Japan, the study by Okamoto et al. analyzed 196 CRCs, and reported that 15%, 21%, 32%, 42%, and 57% of patients were <50, 50-59, 60-69, 70-79, and ≥ 80 years old²⁴). In Korea, right-sided colon incidence of CRC also increased with aging²⁵). Most data in these studies were obtained from surgical operations in a single country. In our study, we showed that right-sided colon lesion proportions of T1 cancers were higher in Japan than they were in Korea. Additionally, a significant increase of right-sided colon lesion proportions between the non-elderly and the elderly was observed in Japan. However, this tendency was not observed in Korea. The different relationships between tumor location and aging for each country might be reasons for this difference. One of these possible reasons is that Japan has a larger elderly population than Korea; these Japanese data possibly enable us to predict future changes in Korea, although there are differences in histopathological evaluation, as described below. The other possible reason is that the differences of food habit, lifestyle and race might cause this increase in right-sided CRC in the elderly. However, there is a lack of Korean cases and this study was performed in only two institu-

tions. Thus, further analyses should be performed for this.

Right-sided colon tumor has a relationship with a kind of cancer pathway. Two pathways have been suggested for sporadic CRC carcinogenesis: chromosomal instability (CIN); and microsatellite instability (MSI)²⁶). CIN is predominantly associated with the adenoma to carcinoma sequence. On the other hand, MSI is associated with the serrated neoplastic pathway²⁷). CIN is more frequent in cancers originating from the left-sided colon and rectum than in those originating from the right-sided colon²⁶). By contrast, most sporadic MSI high CRCs tend to occur in the right-sided colon in the elderly²⁸). Thus, the increase in right-sided early CRC in the elderly may be due to genetic changes in the population in Japan. On the other hand, those changes may not be detected in Korean elderly populations.

As shown by the higher prevalence of Tis cancer in Japan (59.8%) as opposed to in Korea (51.0%) in our study findings, the small number of Korean cases might be due to the lower prevalence of Tis cancer based on the different histopathological definitions of Tis between the countries. In Korea, most of the endoscopically resected colorectal neoplasms are finally diagnosed as tubular adenoma with either high-grade or low-grade dysplasia instead of Tis cancer, according to the WHO criteria. Thus, "enlarged nuclei and prominent nucleoli regardless of invasion" is diagnosed as

Table 4. Multivariate Analysis of Related Factors for Right-sided Colon of 365 T1 CRCs.

	Location		Logistic regression analysis (right-sided colon = 1, Other = 0)								
			Univariate			Multivariate					
	right-sided colon	Other	OR	95%CI	P-value	OR	95%CI	P-value			
Case number	112	253									
Country											
Japan	99, 88.39%	193, 76.28%	2.369	1.240, 4.524	0.009	2.222	1.131, 4.366	0.021			
Korea	13, 11.61%	60, 23.72%	ref.								
Sex											
Male	68, 60.71%	158, 62.45%	ref.								
Female	44, 39.29%	95, 37.55%	1.076	0.682, 1.699	0.753	-					
Age											
mean ± SD	68.3±9.6	64.5±11.4	1.035	1.012, 1.058	0.002	1.028	1.005, 1.052	0.015			
median [IQR]	70.0 [62.00, 75.00]	65.0 [58.50, 72.00]									
Tumor size											
mean ± SD	22.9±13.4	21.7±13.9	1.006	0.990, 1.023	0.465	-					
median [IQR]	20.0 [12.00, 30.00]	20.0 [12.00, 26.50]									
Histological type											
Well	108, 96.43%	249, 98.42%	ref.			ref.					
Por	4, 3.57%	2, 0.79%	4.611	0.832, 25.554	0.080	6.081	0.829, 44.621	0.076			
Others	0, 0.00%	2, 0.79%	n.c.			n.c.					
Lymph.node metastasis											
1	107, 97.27%	231, 92.40%	ref.			ref.					
2	3, 2.73%	18, 7.20%	0.360	0.104, 1.248	0.107	0.253	0.060, 1.068	0.061			
3	0, 0.00%	1, 0.40%	n.c.			n.c.					
Lymphatic invasion											
0	188, 76.73%	85, 77.98%	ref.								
1	44, 17.96%	17, 15.60%	0.855	0.462, 1.581	0.617	-					
2, 3	13, 5.31%	7, 6.42%	1.191	0.459, 3.091	0.720	-					
Venous invasion											
0	209, 85.31%	90, 84.11%	ref.								
1	36, 14.69%	17, 15.89%	1.097	0.586, 2.054	0.773	-					

right-sided: cecum to transverse colon, IQR: interquartile range, well: well differentiated adenocarcinoma, por: poorly-differentiated adenocarcinoma, carcinoma, ref.: reference, n.c.: not calculated

Tis-staged CRC in Japan, but only as “adenoma with dysplasia” in Korea and the West, unless there is an invasion²⁹). Although there are WHO criteria for unifying histopathological evaluation in the world, each country has its own histopathological evaluation system. Yao et al. reported the international exchange like our study and the molecular analysis might be useful for the establishment of standardized diagnostic criteria of CRC²⁹). However, there is no reported detailed information about the difference between carcinoma *in situ* and intramucosal invasive cancer. In any future bilateral studies, the same histopathological evaluation should be performed.

There is one more histopathological finding about lymphatic and venous invasions. Previous reports revealed that histopathological evaluation of lymphatic invasion and venous invasion showed lower inter-observer variability^{30,31}). Because recognizing veins and lymphatic channels using HE staining alone is difficult, immunohistochemical staining

with the monoclonal D2-40 antibody reacts with the O-linked sialoglycoprotein (MW: 40 kDa) on the lymphatic endothelial surface and is used to distinguish lymphatic channels from small vessels³²). Similarly, to identify venous walls, Elastica van Gieson (EVG), E-HE, or Victoria blue staining is used to stain and identify the venous wall elastic fibers, which stain dark violet using these techniques³³). Suzuki et al. reported when evaluating T1 cancer histology that immunohistochemical staining techniques reduced inter-observer variability³⁴). Additionally, EVG staining significantly increased the rate of positive T1 cancer venous invasion (33.1%) as compared with HE staining (17.7%). In our study, there was a significant difference in the rates of lymphatic and venous invasion between Japan and Korea (venous invasion: 18.6% vs. 1.4% and lymphatic invasion: 25.3% vs. 13.7%). This might be due to the difference of types of immunohistochemical staining. Thus, E-HE and D2-40 were used in Japan. On the other hand, ERG was

performed for all Korean cases. However, our study also showed that rates of lymph node metastasis were similar for both countries. It indicated that immunohistochemical staining might detect too many minor lymphatic and venous invasions in Japan. Generally, ERG stains the nucleus of endothelial cells and lymphatics and it looks like dots. The weak point of ERG is that it is considered not to be able to distinguish lymphatic and venous invasion from minute granulation tissue. On the other hand, D2-40 stains the cytoplasm of lymphatics and it looks like a continuous circular line. The weak point of D2-40 is to stain nervous tissue and desmoplastic reaction and increase false positive of lymphatic invasion. These differences with regard to histopathological evaluation in each country confuse international discussion about CRC in the world. A unified evaluation should be established in the future and further analysis should be performed to address this issue.

There were some limitations in this study. This was a retrospective study performed only in two institutions. Thus, it may include a bias and a standardized study examining our results should be performed in the future. Additionally, the Korean sample size was small due to the differences of histopathological evaluation, and there was the possibility of bias. Regarding histopathological evaluation, specimens in Korea and Japan were examined according to pathologic criteria in each country and by one or two pathologists in each country although all specimens should be pathologically examined according to the same pathologic criteria and by the same pathologist. It may influence the real difference in CRC between Japan and Korea.

In conclusion, our cross-national study showed several differences in Tis and T1 CRCs characteristics and histopathological evaluation in Korea and Japan. Additionally, researchers can know the difference of histopathological evaluation about intramucosal cancer and lymphatic and venous invasion in Japan and Korea, especially the difference between Japanese criteria and WHO criteria. We suggest close attention has to be paid to this kind of difference in a cross-national study. This kind of international study is thought to be useful to learn more about CRC features and decrease the incidence of colorectal cancer death.

Acknowledgments

We thank Dr. Takaaki Murakami, Dr. Ryohei Hirose, Dr. Kiyoshi Ogiso, Dr. Osamu Dohi, and all other members of the Department of Molecular Gastroenterology and Hepatology at the Kyoto Prefectural University of Medicine and the Department of Internal Medicine at Konkuk University School of Medicine for helping with this study.

Conflicts of Interest

There are no conflicts of interest.

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