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Time Trend and Risk Factors of Initial Surgery for Crohn's Disease in Japan

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Abstract

Objective: It is unclear whether the initial surgical rate for CD in Japan has decreased. The present study investigated time trend of background factors and risk factors of initial surgery for CD patients.

Methods: A total of 424 patients diagnosed with CD in our department over the last 20 years who had not undergone surgery were analyzed. The cumulative initial surgery rate was determined using the Kaplan-Meier method. Patients were analyzed to identify risk factors for initial intestinal surgery. Patients diagnosed between 1992 and 2001 were classified into the pre-biological era group (PRE) (n=248), and those diagnosed between 2002 and 2011 into the post-biological era group (POST) (n=176). The groups were compared regarding background factors and reason for initial surgery.

Results: The patients included 303 men and 121 women and a mean length of follow-up of 5.5 ± 4.8 years. The comparison of background characteristics between the PRE group and the POST group for each factor demonstrated a significant increase in inflammatory Crohn's disease in the POST group (47.6% vs. 61.9%; p=0.007). Cumulative initial surgery rates by era did not differ between the two groups, at 21.0% and 30.5% at 3 and 5 years, respectively, in the PRE group and 26.7% and 38.5% at 3 and 5 years, respectively, in the POST group. However, the surgery rate in patient with biologics treatment such as infliximab and adalimumab was significantly lower than that of patient without biologics at 5 year (8.6% vs. 37.9%; p<0.001).

Conclusions: A significant increase in the proportion of inflammatory type CD was observed in patients diagnosed in 2002 or later. The initial surgery rate for the treatment of CD in Japan has not yet decreased over time. However, CD patients who could undergo biologic maintenance treatment had a better prognosis than their untreated counterparts.

Keywords: Crohn's disease; Biologics; Surgery; Trend; Risk factor; Infliximab; Adalimumab

Introduction

Crohn's disease (CD) is a condition of unknown etiology that involves inflammation of the entire gastrointestinal (GI) tract [1,2]. Despite various medical treatments, CD is sometimes difficult to treat and prone to relapse and remission, with a range of complications including intestinal stenosis and fistulas. It is estimated that 50 to 71% of CD patients undergo their initial intestinal surgery within 10 years of diagnosis [1-3].

While the incidence and prevalence of CD have traditionally been high in Europe and the United States, a recent report by a research committee at the Ministry of Health, Labour and Welfare (MHLW) indicated that the number of registered CD patients in Japan has surpassed 30,000 and is increasing each year. Only a few studies in Japan have examined the long-term prognosis of CD patients [4-7]. Although studies on intestinal surgery have addressed re-operation rates [8,9], there are no recent detailed studies on the risk of initial intestinal resection in patients who underwent long-term follow-up prior to biologic maintenance treatment [10].

The treatment of CD in Japan underwent a major transition from 2002 with the emergence of biologic treatments such as infliximab and adalimumab, and these drugs have proven to be particularly effective in inducing and maintaining remission [11,12]. Over the long-term, however, it remains unclear whether the initial intestinal resection rate has decreased among Japanese CD patients. Previously we reported that the natural history of CD and factors of initial operation. The report had only 12 few use of biologics and wasn't analyzed according to the era, before and after the emergence of biologic treatment [13]. It was incorporated biologics user in this report a lot (n=60) because we extended the investigation period until recently December 2012. At this point it became the patient background different from the previous report [13]. With this in mind, the background factors by era, initial intestinal resection rates and associated risk factors, and effects of presurgery treatment among CD patients undergoing long-term follow-up were investigated, and the findings were compared against those of previous studies.

Methods

This study was a single-center, retrospective, cohort study. A database of all CD patients treated at the Department of Gastroenterology, Fukuoka University Chikushi Hospital was created

and used in this study. Since 1985, our department has operated a CD database for patients treated at our hospital (Chikushi CD database; CCDD).

In the present study, 424 surgery-naive non-surgical intervention patients at first visit who were diagnosed with CD at our hospital, which is a referral center for the treatment of inflammatory bowel diseases (IBD), over the 20-year period from 1992 to 2011 were registered in CCDD, and their medical records were analyzed to extract pertinent patient information. In the present study, patients who underwent long-term follow-up for ≥ 3 months were targeted.

Based on sex, age, CD duration, and the Montreal classification, patients were classified according to age at diagnosis (A1: <16 y; A2: 17 ≤ 40 y; A3: ≥ 40 y), CD location (L1: ileal; L2: colonic; L3: ileocolonic), and CD behavior (B1: nonstricturing, nonpenetrating; B2: stricturing; B3: penetrating) [14].

CD has been diagnosed on the basis of clinical, endoscopic, radiographic, and pathological findings that must satisfy the diagnostic criteria proposed by the MHLW in Japan [15].

Patient background characteristics by era, presurgery treatment trends, and reasons for initial surgery

Patients were classified into the following 2 groups in order to compare their background characteristics by era, before and after the emergence of biologic treatment. Specifically, patients diagnosed between 1992 and 2001 were assigned to the pre-biological era group (PRE; n=248), and those diagnosed between 2002 and 2011 were assigned to the post-biological era group (POST; n=176).

Background factors

The PRE and POST group patients were compared by age at CD onset, age at CD diagnosis, sex, CD location and CD behavior at first visit, history of smoking (Y/N), and history of alcohol use (Y/N). Alcohol drinkers were defined as those who drank alcohol almost every day.

Presurgery treatment trends

Treatment prior to surgery was compared between the PRE group and the POST group on the basis of whether patients ate an elemental diet (ED) of ≥ 900 kcal/day or received drug therapy with 5-aminosalicylic acid (5-ASA), prednisolone (PSL), immunomodulators (IM) (azathioprine (AZA), and 6-mercaptopurine hydrate (6-MP)), or biologic treatments such as infliximab and adalimumab, as well as time from CD onset until biologic use.

Reasons for surgery

The main reason for initial surgery was also compared between the PRE group and the POST group.

Cumulative initial surgery rates and risk factors by treatment

The cumulative initial surgery rate was determined using the Kaplan-Meier method. The observation period was regarded as the time from CD diagnosis until the day of initial intestinal surgery or the final day of this study (December 2012). Cumulative initial surgery rates were also calculated by use of biologic maintenance treatment prior to surgery (Y/N), by era (PRE vs. POST), and by era (PRE vs. POST) of the presurgery non-biologic maintenance treatment group (i.e., biologic-nonuse patients or <6 mo biologic patients). Biologic therapy was indicated in patients with fluoroscopic, endoscopic, or other imaging findings of inflammation, perianal lesions, and enterocutaneous fistula. Patients achieved biologic therapy of infliximab 5 mg/kg at weeks 0, 2, and 6 or adalimumab 160 mg at week 0 and 80 mg at week 2, advanced onto a scheduled maintenance regimen of infliximab every 8 weeks or adalimumab 40 mg every other week. In the present study, biologic use was regarded as maintenance treatment for a period of ≥ 6 mo, excluding episodic administration. Moreover, univariate analysis using the log-rank test was performed on the background factors of sex, <22 y at CD onset (Y/N), <22 y at CD diagnosis (Y/N), CD location at first visit, CD behavior at first visit, history of smoking (Y/N), history of alcohol use (Y/N), and treatment prior to surgery (ED>900 kcal/day, 5-ASA, PSL, IM, biologics) (Y/N). Variables that met the cut-off value ($p<0.1$) were then subjected to multivariate analysis using Cox proportional hazard regression analysis to identify risk factors for initial intestinal surgery, and $p<0.05$ was regarded as significant.

Statistical analysis

Patients' background characteristics were compared using the chi-square, Fisher's exact, and Student's t tests. The cumulative initial surgery rate was estimated using the Kaplan–Meier method and compared using the logrank test. Risk factors for initial surgery were evaluated by multivariate analysis using a Cox proportional hazards model. In all statistical analyses, the significance level was set at 0.05.

Results

The background characteristics of CD patients who participated in this study are shown in Table 1. All of the CD patients were Asian; 303 were men and 121 were women.

Men : Women	303 : 121	
Age at onset CD (year)	25.7 ± 10.6 (9-76)	
Follow-up (year) *	5.5 ± 4.8 (0.3-19.9)	
Age at diagnosis CD		
below 16 y	(A1)	57 (13.4%)
between 17 and 40 y	(A2)	329 (77.6%)
above 40 y	(A3)	38 (9.0%)
Location (at the initial visit)		
Ileal	(L1)	138 (32.5%)
Colonic	(L2)	78 (18.4%)
Ileocolonic	(L3)	208 (49.1%)
Behavior (at the initial visit)		
non-stricturing non-penetrating	(B1)	227 (53.5%)
Structuring	(B2)	135 (31.9%)
Penetrating	(B3)	62 (14.6%)
* Time from diagnosis CD	according to the Montreal classification	

Table 1: Clinical background of patients with Crohn's disease diagnosed at Fukuoka University Chikushi Hospital from 1992 to 2011.

Their mean age at CD onset was 25.7 y (range: 9-76 y), and the mean observation period was 5.5 ± 4.8 y (range: 0.3-19.9 y). In terms of age at diagnosis, 57 patients (13.4%) were <16 y (A1), 329 patients (77.6%) were 17 ≤ 40 y (A2), and 38 patients (9.0%) were ≥ 40 y (A3). By CD location, 138 patients (32.5%) had ileal CD (L1), 78 patients (18.4%) had colonic CD (L2), and 208 patients (49.1%) had ileocolonic CD (L3). By final CD behavior, 227 patients (53.5%) had nonstricturing, nonpenetrating CD (B1), 135 patients (31.9%) had stricturing CD (B2), and 62 patients (14.6%) had penetrating CD (B3).

Patient background characteristics by era, presurgery treatment trends (Table 2), and reasons for initial surgery (Table 3)

Background factor trends by era (Table 2): There were no significant differences in the ratio of men to women, at 177:71 in the PRE group and 126:50 in the POST group.

		PRE	POST	
		1992-2001(n=248)	2002-2011 (n=176)	p value
Age at diagnosis CD				
below 16 y	(A1)	38	19	
between 17 and 40 y	(A2)	194	135	0.056
above 40 y	(A3)	16	22	
Location (At first visit)				
Ileal	(L1)	88	50	
Colonic	(L2)	39	39	0.142
Ileocolonic	(L3)	121	87	
Behavior (At first visit)				
non-stricturing non-penetrating	(B1)	118	109	0.007**
Structuring	(B2)	93	42	
Penetrating	(B3)	37	25	
Smoking	(n/y)	145:103	121:55:00	0.031*
Drinking	(n/y)	154:94	148:28:00	0.001**
Preoperative medication (n/y)				
Elemental diet (γ 900kcal/day)		120:128	114:62	0.001**
5-ASA		129:119	45:131	0.001**
PSL		209:39:00	136:40:00	0.068*
IM		196:52:00	131:45:00	0.267
Bio***		229:19:00	135:41:00	0.001**
Time from CD onset to Bio start (year) (n=60)		10.4 ± 4.5	3.3 ± 3.2	0.001**
Student's t-test or χ^2test **:p<0.01,*:p<0.05				***Bio; Biologics such as infliximab and adalimumab

Table 2: Comparison between PRE and POST (clinical background and preoperative medication).

There were also no significant differences in age at CD diagnosis, with 38 patients (15.3%) aged <16 y (A1), 194 patients (78.2%) aged 17 ≤ 40 y (A2), and 16 patients (6.5%) aged ≥ 40 y (A3) in the PRE group, and 19 patients (10.8%) aged <16 y (A1), 135 patients (76.7%) aged 17 ≤ 40 y (A2), and 22 patients (12.5%) aged ≥ 40 y (A3) in the POST group. Similarly, CD location at first visit did not differ between the groups, with ileal CD (L1) observed in 88 patients (35.5%), colonic CD (L2) in 39 patients (15.7%), and ileocolonic CD (L3) in 121 patients (48.8%) in the PRE group versus ileal CD (L1) in 50 patients (28.4%), colonic CD (L2) in 39 patients (22.2%), and ileocolonic CD (L3) in 87 patients (49.4%) in the POST group. In terms of CD behavior at diagnosis, nonstricturing, nonpenetrating CD (B1) was very common, occurring in 118 patients (47.6%) in the PRE group and 109 patients (61.9%) in the POST group, while stricturing CD (B2) was present in 93 patients (37.5%) in the PRE group and 42 patients (23.9%) in the POST group, and penetrating CD (B3) was seen in 37 patients in the PRE group (14.9%) and 25 patients in the POST group (14.2%) (p=0.007).

The ratio of non-smokers to smokers was significantly lower in the POST group at 121:55 (31.3%) compared to 145:103 (41.5%) in the PRE group. The ratio of non-drinkers to drinkers was also significantly lower in the POST group at 148:28 (15.9%) versus 154:94 (37.9%) in the PRE group.

Presurgery treatment trends by era (Table 2): In terms of presurgery treatment history, the ratio of non-treatment to treatment for elemental diet (ED; ≥ 900 kcal/day) was significantly lower in the POST group at 114:62 (35.2%) than in the PRE group at 120:128 (51.6%).

Conversely, the ratio of non-treatment to 5-ASA treatment was significantly higher in the POST group at 45:131 (74.4%) versus 129:119 (48.0%) in the PRE group. There were no intergroup differences for the ratios of either non-treatment to PSL treatment, at 209:39 (15.7%) in the PRE group versus 136:40 (22.7%) in the POST group, or non-treatment to IM treatment at 196:52 (21.0%) in the PRE group versus 131:45 (25.6%) in the POST group.

	PRE	POST	p value
	1992-2001 (n=138)	2002-2011 (n=61)	
Stenosis	60.9%	76.2%	0.042*
Fistula	24.6%	12.7%	0.063
Abscess	8.7%	7.9%	0.908
Perforation	4.3%	1.6%	0.339
Hemorrahage	1.5%	1.6%	0.919
χ^2 test or Fisher's exact test *:p < 0.05			

Table 3: The main reasons for initial surgery for PRE vs. POST.

The ratio of non-treatment to biologic treatment was significantly higher in the POST group at 135:41 (23.3%) versus 229:19 (7.7%) in the PRE group. Time from CD onset to biologic use was significantly shorter in the POST group at 3.3 ± 3.2 y than in the PRE group at 10.4 ± 4.5 y.

Trends in reasons for initial surgery by era (Table 3): During the study period, 199 patients (46.9%) underwent initial intestinal surgery. The main reasons for initial surgery for the PRE group and the POST group were as follows: stenosis, 60.9% and 76.2%; fistula, 24.6% and 12.7%; abscess, 8.7% and 7.9%; perforation, 4.3% and 1.6%; and hemorrhage, 1.5% and 1.6%, respectively (Table 3).

The results indicate that the percentage of patients undergoing initial intestinal surgery primarily due to stenosis had increased in the POST group.

Cumulative initial surgery rates and risk factors (Table 4)

The overall cumulative primary surgery rate (when starting the observation period from the time of CD diagnosis) was 11.0% at 1 y, 33.6% at 5 y, 56.7% at 10 y, and 73.1% at 15 y (Figure 1a).

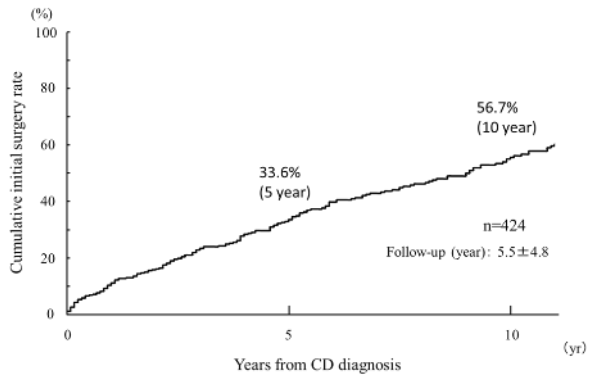

Figure 1a: The cumulative initial surgery rate of CD. The overall cumulative initial surgery rates at 1, 5, and 10 years were 11.0%, 33.6%, and 56.7%, respectively.

Surgery rates were significantly lower in the group that received biologic treatment prior to surgery than among their non-treated counterparts, at 8.6% at 5 y and 12.7% at 10 y versus 37.9% at 5 y and 61.9% at 10 y (p<0.001) (Figure 1b).

There were no significant differences in overall cumulative initial surgery rates by era, at 8.6%, 21.0%, and 30.5% at 1, 3, and 5 y in the PRE group (diagnosed between 1992 and 2001) versus 14.8%, 26.7%, and 38.5% at 1, 3, and 5 y in the POST group (diagnosed between 2002 and 2011) (Figure 2a).

In the presurgery non-biologic maintenance treatment group (biologic- nonuse patients or <6 mo biologic patients), cumulative initial surgery rates were significantly lower in the PRE group at 9.4%, 23.0%, and 33.4% at 1, 3, and 5 y than in the POST group at 18.9%, 35.1%, and 46.7% at the same time points (p=0.014) (Figure 2b).

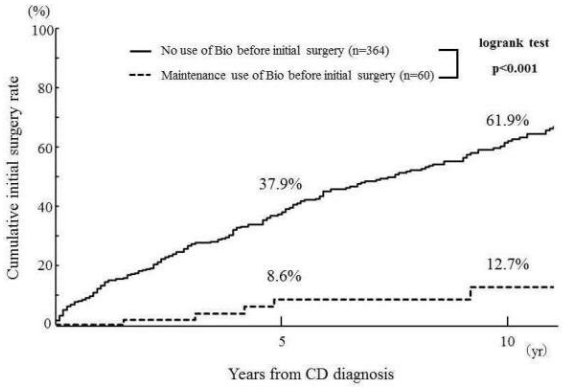

Figure 1b: The cumulative initial surgery rate with Biologics. The group that were given biological products preoperatively had significantly lower initial surgery rates at 5 and 10 years, compared to the group that were not given (8.6% and 12.7% vs. 37.9% and 61.9% respectively; p<0.001 logrank test).

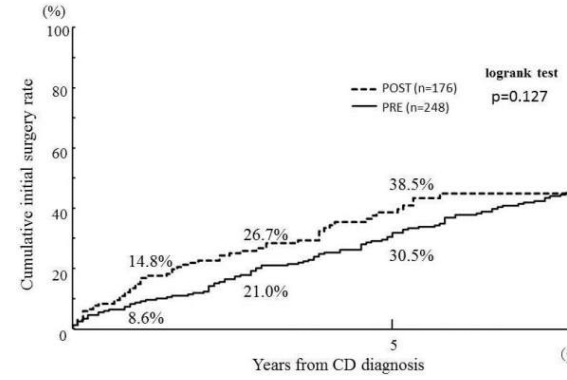

Figure 2a: Comparison of initial surgery rates (overall) in the PRE and POST groups. There were no significant differences in overall cumulative initial surgery rates by era, at 8.6%, 21.0%, and 30.5% at 1, 3, and 5 y in the PRE group (diagnosed between 1992 and 2001) versus 14.8%, 26.7%, and 38.5% at 1, 3, and 5 y in the POST group (diagnosed between 2002 and 2011).

Looking at background factors, patients with ileal CD (L1), stricturing CD (B2), and a history of smoking were at a significantly higher risk for initial intestinal surgery. On the other hand, patients with colonic CD (L2) and nonstricturing, nonpenetrating CD (B1) had a significantly lower risk for initial intestinal surgery. The initial surgery rate did not differ according to whether patients were treated with ED>900 kcal/day, 5-ASA, PSL, or IM prior to surgery, and presurgery biologic use was the only treatment modality that reduced the initial surgery rate (p<0.05). Multivariate analysis revealed a significantly higher risk for initial surgery among patients initially diagnosed with stricturing CD (B2) (hazard ratio [HR]=1.82; 95% confidence interval [CI]: 1.37-2.42), and a significantly lower risk among patients initially diagnosed with colonic CD (L2), in other words, cases in which lesions were localized in the colon (HR=0.57; 95% CI: 0.37-0.89).

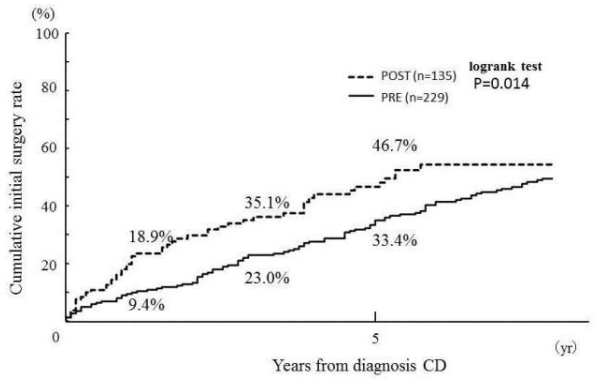

Figure 2b: Comparison of initial surgery rates in the PRE and POST groups (biologic-nonuse or <6 m biologic patients only). In the presurgery non-biologic maintenance treatment group (biologic-nonuse patients or <6 mo biologic patients), cumulative initial surgery rates were significantly lower in the PRE group at 9.4%, 23.0%, and 33.4% at 1, 3, and 5 y than in the POST group at 18.9%, 35.1%, and 46.7% at the same time points (p=0.014) loglank test.

There was also a significantly reduced risk of initial surgery in presurgery biologic-treated patients (HR=0.23; 95% CI: 0.12-0.41).

		Univariate	Multivariate		
Variable	n=424	P Value	Hazard ratio	(95%CI)	P Value
Gender					
Men	303	0.148			
Women	121				
Age at onset					
<22	228	0.418			
γ 22	196				
Age at diagnosis					
<22	173	0.085	1.176	(0.881-1.572)	0.27
γ 22#	251				
Location (At first visit)					
ileal (L1)	138	0.04			
colonic (L2)#	78	0.002	0.569	(0.365-0.890)	0.013*
ileocolonic (L3)	208	0.538			
Behavior (At first visit)					
non-stricturing non-penetrating (B1)	227	<0.001			
stricturing (B2)#	135	<0.001	1.821	(1.370-2.421)	<0.001*
penetrating (B3)	62	0.218			
Smoking					
Yes#	158	0.003	1.302	(0.970-1.751)	0.079
No	266				
Drinking					
Yes#	122	0.058	1.325	(0.969-1.808)	0.078
No	302				
Preoperative medication (n/y)					
Elemental diet (γ 900kcal/day)					
Yes	190	0.621			
No	234				
5-ASA					
Yes	250	0.918			
No	174				
PSL					
Yes#	79	0.053	0.982	(0.660-1.406)	0.929
No	345				
IM					
Yes	97	0.762			
No	327				
Biologics					
Yes#	60	<0.001	0.225	(0.124-0.406)	<0.001*
No	364				
#Reference group in multivariate analysis HR, hazard ratio; CI, confidence interval			Cox proportional hazard regression analysis *:p<0.05		

Table 4: Hazard ratio for initial intestinal resection in Crohn's disease.

Discussion

Since the start of the 21st century, biologic treatments have been widely used in the treatment of CD. However, there are few long-term, large-cohort studies examining the rates of recent initial intestinal surgery in Asia [10,16].

With this in mind, a long-term follow-up study of CD patients at our hospital, which is a referral center for the treatment of inflammatory bowel diseases, was performed to investigate the background factors by era, initial intestinal surgery rates and associated risk factors, and effects of preoperative treatment, and then the findings were compared to those of previous studies.

CD trends over time

In the present study, the rate of nonstricturing, nonpenetrating CD (B1) at diagnosis was higher in the POST group (62%) than in the PRE group (48%). This finding suggests that CD in Japan is both widely recognized and diagnosed in the early stages.

Conversely, the rates of history of smoking and history of alcohol use are declining significantly. Smoking is a known risk factor for exacerbating CD [17-19]. Peyrin-Biroulet et al. reported on the effects of smoking on abdominal surgery in CD patients, and they found that current smokers were at a significantly higher risk (1.7 times) for abdominal surgery [20]. Increased awareness of the benefits of not smoking in Japanese society was also partly responsible for the decline in smoking rates among POST group patients [21].

Presurgery treatment trends

The proportion of patients undergoing ED therapy declined in the POST group. ED is widely recognized in Japan, but the emergence of new drug therapies has led to low patient tolerance for ED; this is why we believe the rate of ED therapy decreased in the POST group of the present study. Nevertheless, ED has been found to be effective in maintaining CD remission [22,23] and, therefore, represents a possible viable treatment option for patients with drug intolerance.

Meanwhile, there was a significant increase in the percentage of patients using 5-ASA and biologics prior to surgery. The time from CD onset to commencement of biologic use also showed a significant decrease. Biologic administration reportedly reduces hospitalization and surgery rates [24-26], and endoscopic mucosal healing has also been found to bring down CD surgery rates [27,28]. Early treatment with potent biologics has also proven to be effective [29,30]. Biologics should therefore ideally be administered before lesions can organize within the intestinal tract or, in other words, before the formation of irreversible changes such as stenosis and fistulae.

Reasons for initial surgery

Examining the reasons for initial surgery among the PRE- and POST-biologic patients, the POST group patients had a higher rate of stenosis and lower rates of fistula, perforation, and hemorrhage than their PRE group counterparts. While there are concerns that biologic use causes ulcers to heal and stenosis to worsen, endoscopic balloon dilatation for the treatment of intestinal stenosis has been described as a useful means for avoiding surgery [31,32].

Initial surgery rates

Table 5 summarizes the initial intestinal surgery rates in various regions according to time of CD diagnosis year [10,16,20,33-38].

Compared to the older study findings, surgery rates in Europe and North America are gradually declining [33,35,36,39] (Bernell & Jess). In the present study, overall initial surgery rates at 1, 5, and 10 years were 11.0%, 33.6%, and 56.7%, respectively. Although this appears to be slightly higher compared to recent results in Europe and the U.S., the studies in these regions were conducted using population-based cohorts, whereas the present study was conducted at our hospital, which is a referral center for CD patients, which is why we believe our population contained a larger percentage of severe cases. If we compare the literature originating from referral centers in Japan over the past decade and earlier, we can see that surgery rates at our hospital have actually declined.

Region/Country	Author	Year	Diagnosed Year	n	observation period(yr)	Operation rate (%)		
						1yr	5yr	10yr
Europe								
Sweden	Bernell [33]	2000	1955-1989	1936	14.9	44	61	71
Norway	Solberg [34]	2007	1990-1994	237	10.3	14	27	38
Denmark	Jess [35]	2007	1964-1987	374	17	35		63
			1991-1993	58	10	28		65
			2003-2004	209	11	12		
UK	Ramadas [36]	2010	1986-1991	105	14	32	59	
			1992-1997	99	9.3	25	37	
			1998-2003	137	6.1	19	25	
Hungary	Golovics [37]	2013	1977-2008	506	11.4 ± 7.8	15	30	52
North America								
US	Peyrin-Biroulet [20]	2012	1990-2003	310	12		38	48
Canada	Nguyen [38]	2011	1988-2008	3403		13	24	32
			1988-1996	1364	15.8	16	30	38

			1996-2000	920	9.6	13	22	29
			2001-2008	1119	3.7	10	18	
Asia								
Japan	Oriuchi [10]	2003	1965-1998	276	9.9 ± 7.5		49	66
South Korea	Ye [16]	2010	1991-2007	278	5.9	16	25	33
Japan	This study	2015	1992-2011	424	5.5 ± 4.8	11	34	57

Table 5: Summary of reported initial operation rate in Crohn's disease after diagnosis.

Risk factors for initial surgery

On multivariate analysis, there was a significant increase in initial surgery rates among patients initially diagnosed with stricturing CD (B2), patients not treated with biologics prior to surgery, and patients not diagnosed with colonic CD (L2), in other words, patients in whom lesions were not localized in the colon.

Peyrin-Biroulet et al. reported that patients with ileal CD (L1) and colonic CD (L2), in which lesions were not localized in the colon, were at 3-4 times higher risk of surgery [20]. Similarly, Bernell et al. described L1 as a surgery risk, and Solberg et al. described distal ileal lesions and stenosis as surgery risks [33,34], which are all consistent with the findings of the present study.

Effect of presurgery biologic treatment on the initial surgery rate

Upon comparing cumulative initial surgery rates on the basis of whether patients were treated with biologics prior to surgery, one can see that the biologic-treated patients had a significantly lower 5-year cumulative rate than their non-biologic-treated counterparts, at 10.2% versus 26.5%. Multivariate analysis also showed that presurgery biologic treatment significantly reduced the risk of initial intestinal surgery by 0.23 times (95% CI: 0.12-0.41).

Sakatani et al. reported that time to initial surgery was prolonged by administering infliximab to CD patients prior to initial surgery [40]. In a U.S.-based study using the Nationwide Inpatient Sample, Jones et al. reported that, during the period of adoption of infliximab as a novel CD treatment, the overall rate of bowel resection either remained relatively stable or decreased moderately [41]. Meanwhile, Domènech et al. reviewed the clinical outcomes of newly diagnosed CD patients before and after infliximab availability in a retrospective study and concluded that infliximab availability did not reduce the need for surgery [42].

However, in the present study, initial surgery rates were examined before and after the introduction of biologics (PRE vs. POST), but there was no clear decrease in the surgery rate by era. This may be due to bias, given that the study was conducted at a referral center. Moreover, several previous studies also reported that there were almost no changes in surgery rates over time [20,41,43-45].

While we well understand that CD patients who can receive biologic maintenance treatment tend to have a good prognosis, not all CD patients can use biologics. Within the so-called 'biologic failure' group in the present study, which consisted of biologic-nonuse patients and those who were treated for <6 mo, the POST group patients had a significantly worse prognosis. The diminished rate of ED therapy among POST group patients may have played a part in this result. Put simply, improving the prognosis of CD patients will require the optimization of biologic treatment through the development of strategies to reduce this so-called biologic failure. Measures to achieve this could include early introduction of biologic treatment, refraining from ill-considered switching of biologics in order to prevent antibodies from forming, and appropriate monitoring of drug levels in the blood. The appropriate use of ED and other existing treatment modalities in addition to biologics, and the addition of novel therapies might also be essential for improving treatment outcomes. Nguyen et al. conducted a meta-analysis to assess the effect of specialized enteral nutrition therapy with infliximab versus infliximab monotherapy in patients with CD. The use of specialized enteral nutrition therapy in combination with infliximab appears to be more effective at inducing and maintaining clinical remission among patients with Crohn's disease than infliximab monotherapy [46].

More prospective studies involving the long-term follow-up of a large patient cohort are needed in the future to investigate how presurgery biologic treatment can affect and improve initial intestinal surgery rates.

Conclusions

A significant increase in the proportion of inflammatory type CD was observed in patients diagnosed in 2002 or later, compared to those diagnosed in 2001 or earlier. This finding can be attributed to the recent availability of early diagnosis of CD in Japan. Furthermore, the initial surgery rate for CD in Japan did not yet decrease over time. However, CD patients who could undergo biologic maintenance treatment had a better prognosis than their untreated counterparts. Strategies to deal with biologic- nonuse and intractable CD patients are needed in the future to improve the long-term prognosis of CD.

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